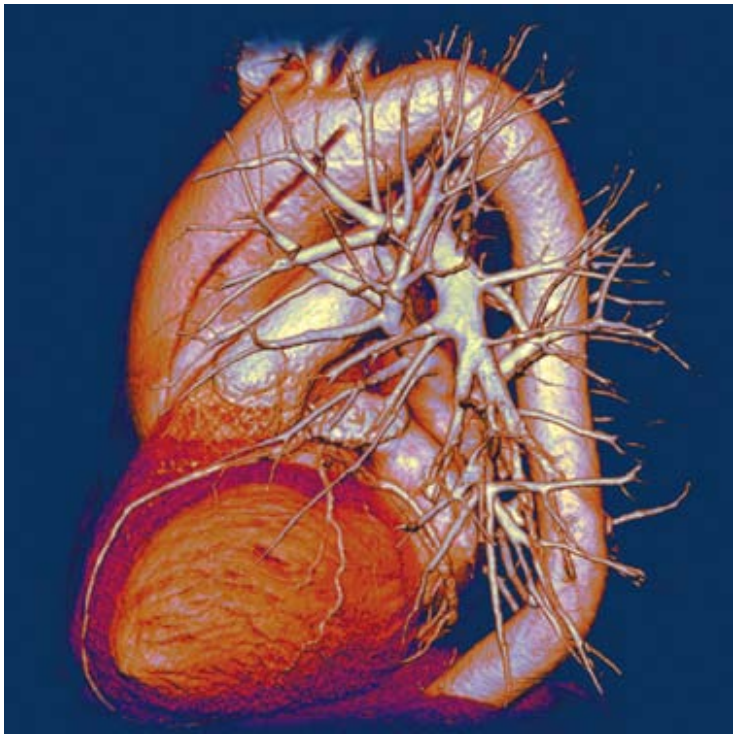
The ESC Textbook of

Cardiovascular Medicine



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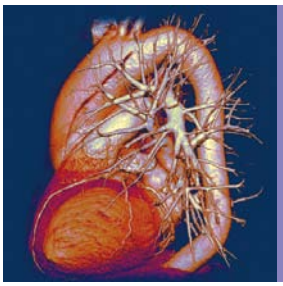

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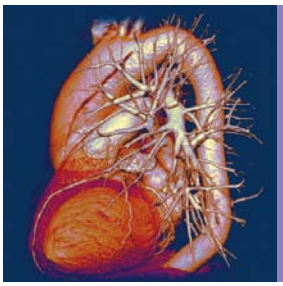

Foreword

Cardiovascular disease has become the foremost cause of death and permanent disability in western countries, and is set to become the foremost cause of death and permanent disability worldwide by the year 2020. We are confronting a pandemic that will be a heavy burden on the population and that will cause much human suffering. The burden on health systems is also considerable in terms of healthcare expenditure, which looks set to continue growing. Cardiovascular disease is becoming increasingly common, in particular all types of atherothrombosis. This is driven by the rapid increase in the prevalence of risk factors among the world's population, such as the increasing frequency of obesity, type 2 diabetes, smoking, physical inactivity and psychological stress combined with a gradual increase in consumption of energy-dense foods and lower consumption of fruit and vegetables. In this context, the burden of cardiovascular disease will continue to increase with a gradual increase in life expectancy in the population.

Despite major progress in this field over the last 50 years, there is still much to learn about the progression of cardiovascular disease, particularly in understanding the mechanism of disease, the pathophysiology and evolution of diagnostic methods. The explosion of imaging techniques combined with ever more refined biological assays, particularly those based on genomics and proteomics, have all helped to make the diagnosis of cardiovascular diseases considerably more accurate and rapid. This exponential progress is the result of very active research and heavy investment in this field. This exciting progress has been translated from basic research into clinical management, thanks to active clinical research in cardiovascular disease. A large number of clinical trials, surveys and registries have helped us to understand both the impact of cardiovascular disease on the population and the impact of new strategies for diagnosis and management. European cardiologists have played an active part in advancing research in cardiovascular disease in basic, clinical and population sciences. The overall result is an improvement in diagnostic and therapeutic potential, as well as better prevention measures. Patients now benefit from a greater diversity of therapeutic options than ever before. The dissemination of this increased knowledge base is of paramount importance because physicians need to be aware of the best evidence concerning the most suitable treatment strategies for a particular disease. They need to implement this information in their daily routine practice, and keep abreast of changes and improvements in the management of cardiovascular disease. The ESC mission statement is to improve the quality of life of the European population by reducing the burden of cardiovascular disease. To fulfil its mission, the ESC has taken on the responsibility of training cardiologists and disseminating knowledge through congress activity, writing and publication of guidelines and, now, publication of The *ESC Textbook of Cardiovascular Medicine*. This is the first textbook to be proposed by an international society of

cardiology. More specifically, the goals of the textbook are to address the knowledge requirements specified in the ESC Core Syllabus, to be consistent with ESC Guidelines and best practice and to produce a clinically focused resource for cardiologists and trainees. In all, The ESC Textbook of Cardiovascular Medicine is set to become the new benchmark for cardiologists in Europe and beyond. The textbook is available in traditional printed format, as well as an online edition complete with CME-accredited self-assessment programmes. The online edition will be regularly updated, and it is hoped that translations will be available in the future. A large number of prominent European cardiologists have contributed to this comprehensive textbook that covers all aspects of cardiovascular disease from diagnosis to management and prevention. As a teaching text, this textbook covers knowledge that every general cardiologist needs to know and keep current, but does not address all the information needs of subspecialists. The concise and practical style was deliberately chosen to make this textbook easy to use. We would like to take this opportunity to thank all those who have contributed so generously their experience, and time, in order to produce this work, most particularly the authors and the co-editors. The wealth of their experience will be invaluable in bringing the most pertinent information to our colleagues throughout Europe and around the world. We are confident that this textbook will enjoy wide recognition, and hope that it will become a reference work for cardiologists around the globe.

Jean-Pierre Bassand President European Society of Cardiology 2002–2004

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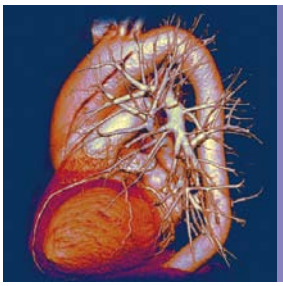

Preface

The goal of every good medical textbook is to teach excellence in medicine. This is the main purpose of this new *ESC Textbook of Cardiovascular Medicine*. This book specifically attempts to draw together all up-to-date strands of relevant information and use all appropriate modern educational methods to ensure good and comprehensive learning. It is not merely a treatise on theory but a practical compendium on cardiac and vascular disease. Yogi Berra, the great Yankee baseball player, once said 'theory and practice are in theory the same, but in practice they are not!' It is the editors' intention to harmonize theory and practice in this new teaching text. The *ESC Textbook of Cardiovascular Medicine* is the first ever cardiovascular textbook to be published in partnership with an international medical society, and is set to become the standard text in Europe and beyond. Initiated by the ESC Board and strongly supported by the President, it represents a major undertaking and long-term commitment from the ESC.

Everything a trainee or practising cardiologist needs to know

As a teaching or training text structured around the ESC Core Syllabus, The *ESC Textbook of Cardiovascular Medicine* contains the knowledge that every general cardiologist should strive to attain and keep current. It does not try to contain everything a subspecialist should know about the field. The textbook is consistent with the ESC Guidelines and with best practice. The book has 120 contributors from 12 European countries who were chosen as much for their ability as writers as for their knowledge. The result is a balanced, expert and comprehensive review of each topic. It covers the entire field of cardiovascular medicine and, unlike other texts, the first six chapters are dedicated to diagnostic imaging. Imaging modalities are also discussed within the subsequent chapters on different disorders and diseases and referenced back to the first chapters.

Easy to navigate and lavishly illustrated

All chapters follow the same format so that there are no inconsistencies in style or content. Each chapter opens with a brief 'Summary' box detailing the scope of the chapter and ends with a 'Personal perspectives' box in which the author outlines state-of-the-art and future directions for the area. The ESC Textbook of Cardiovascular Medicine is succinct, focused and practical to use. Only key references are included so that readability is not inhibited by overly dense text. It is also visually appealing, with an image on every two-page spread. There are over 700 full colour images and over 230 informative tables. All of the illustrations (and many of the ECG traces too) have been

redrawn to ensure consistency of style and quality. This truly outstanding art programme means that techniques and concepts are easy to grasp.

Accompanying online version and CME accreditation

An online version of The ESC Textbook of Cardiovascular Medicine is provided with each printed copy. A card with the website address and a unique access number is bound into every book. The unique access number is used when registering, at which point a user name and password can be chosen. Using the website is straightforward and technical help is available if needed. The online version contains all the text and images from The *ESC Textbook of Cardiovascular Medicine* as well as: l an excellent full text search facility; l downloadable PDF chapter files; l links from reference lists to PubMed; l a database of video clips supplied by the authors; l chapter-based CME multiple choice questions. The provision of high-quality CME for cardiologists and trainees in Europe is a key priority of the ESC. In line with this aim, accreditation of chapters in The ESC Textbook of Cardiovascular Medicine is awarded by EBAC (The European Board for Accreditation in Cardiology). Having read a chapter, you are required to submit your answers to a set of multiple choice questions relating to the chapter's content. Your score is then displayed and feedback is given on the correctly answered questions. Feedback is not given on incorrect answers so that the test may be attempted again. Having successfully completed a chapter (achieving a pass mark of 60% or above), you can download an EBAC certificate from the website. The editors wish to acknowledge the great help provided to them by the editorial staff at Blackwell Publishing. Gina Almond and Julie Elliott, in particular, have been engaged and involved in the production of this book from start to finish.

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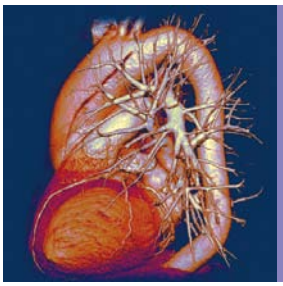

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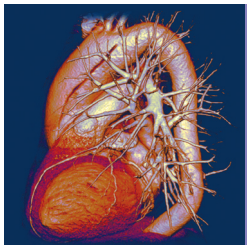


1 The Morphology of the Electrocardiogram

Antoni Bayés de Luna, Velislav N. Batchvarov and Marek Malik

Summary

The 12-lead electrocardiogram (ECG) is the single most commonly performed investigation. Almost every hospitalized patient will undergo electrocardiography, and patients with known cardiovascular disease will do so many times. In addition, innumerable ECGs recorded are made for life insurance, occupational fitness and routine purposes. Most ECG machines are now able to read the tracing; many of the reports are accurate but some are not. However, an accurate interpretation of the ECG requires not only the trace but also clinical details relating to the patient. Thus, every cardiologist and physician/cardiologist should be able to understand and interpret the 12-lead ECG. Nowadays, many other groups, for example accident and emergency physicians, anaesthetists, junior medical staff, coronary care, cardiac service and chest pain nurses, also need a good grounding in this skill. In the last several decades a variety of new electrocardiographic techniques, such as short- and long-term ambulatory ECG monitoring using wearable or implantable devices, event ECG monitoring, single averaged ECGs in the time, frequency and spatial domains and a variety of stress recoding methods, have been devised. The cardiologist, at least, must understand the application and value of these important clinical investigations. This chapter deals comprehensively with 12-lead electrocardiography and the major pathophysiological conditions that can be revealed using this technique. Cardiac arrhythmias and other information from ambulatory and averaging techniques are explained only briefly but are more fully covered in other chapters, for example those devoted to specific cardiac arrhythmias.

Introduction

Broadly speaking, electrocardiography, i.e. the science and practice of making and interpreting recordings of cardiac electrical activity, can be divided into morphology and arrhythmology. While electrocardiographic morphology deals with interpretation of the shape (amplitude, width and contour) of the electrocardiographic signals, arrhythmology is devoted to the study of the rhythm (sequence and frequency) of the heart. Although these two parts of electrocardiography are closely interlinked, their methodological distinction is appropriate. Intentionally, this chapter covers only electrocardiographic morphology since rhythm abnormalities are dealt with elsewhere in this book.

Morphology of the ECG

The electrocardiogram (ECG), introduced into clinical practice more than 100 years ago by Einthoven, comprises a linear recording of cardiac electrical activity as it occurs over time. An atrial depolarization wave (P wave), a ventricular depolarization wave (QRS complex) and a ventricular repolarization wave (T wave) are successively

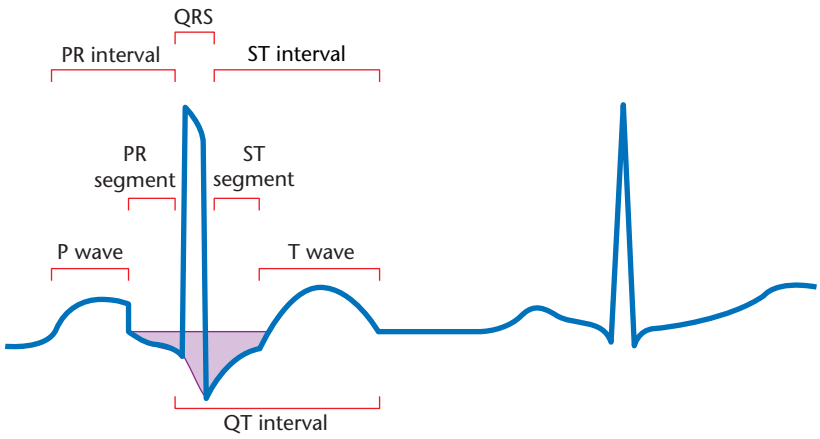


Figure 1.1 ECG morphology recorded in a lead facing the left ventricular free wall showing the different waves and intervals. Shading, atrial repolarization wave.

recorded for each cardiac cycle (Fig. 1.1). During normal sinus rhythm the sequence is always P–QRS–T. Depending on heart rate and rhythm, the interval between waves of one cycle and another is variable.

Electrophysiological principles [1–6]

The origin of ECG morphology may be explained by the dipole-vector theory, which states that the ECG is an expression of the electro-ionic changes generated during myocardial depolarization and repolarization. A pair of electrical charges, termed a dipole, is formed during both depolarization and repolarization processes (Fig. 1.2). These dipoles have a vectorial expression, with the head of the vector located at the positive pole of a dipole. An electrode that faces the head of the vector records a positive deflection.

To ascertain the direction of a wavefront, the ECG is recorded from different sites, termed 'leads'. When recording the 12-lead ECG six frontal leads (I, II, III, aVR, aVL, aVF) and six horizontal leads (V1–V6) are used. There are three bipolar leads in the frontal plane that connect the left to right arm (I), the left leg to right arm (II) and the left leg to left arm (III). According to Einthoven's law, the voltage in each lead should fit the equation II = I + III. These three leads form Einthoven's triangle (Fig. 1.3A). Bailey obtained a reference figure (Bailey's triaxial system) by shifting the three leads towards the centre.

There are also three augmented bipolar leads (aVR, aVL and aVF) in the frontal plane (Fig. 1.3B). These are de-

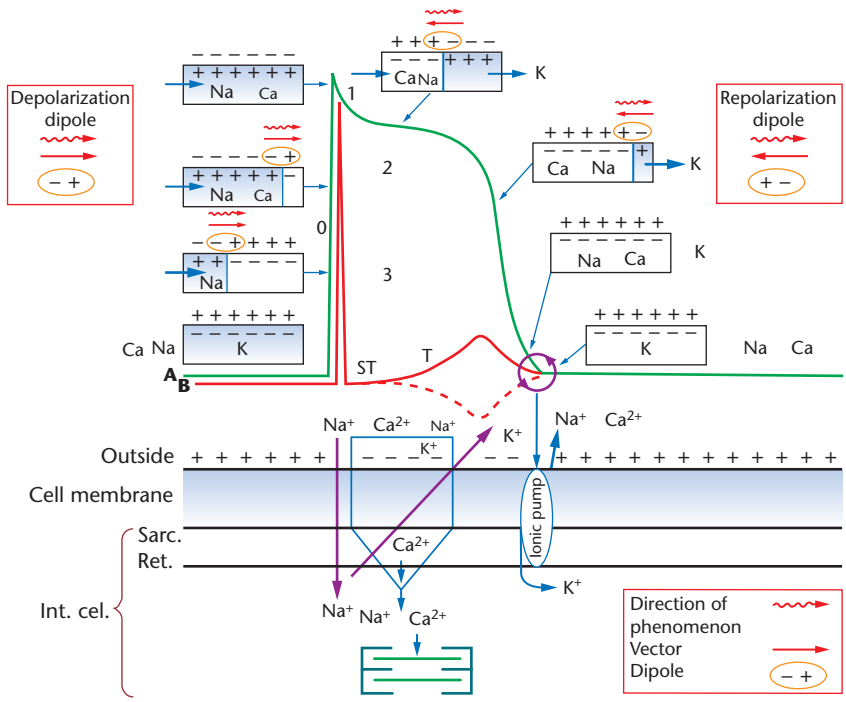


Figure 1.2 Scheme of electro-ionic changes that occur in the cellular depolarization and repolarization in the contractile myocardium. (A) Curve of action potential. (B) Curve of the electrogram of a single cell (repolarization with a dotted line) or left ventricle (normal curve of ECG with a positive continuous line). In phase 0 of action potential coinciding with the Na^+ entrance, the depolarization dipole (–+) and, in phase 2 with the K^+ exit, the repolarization dipole (+–), are originated. At the end of phase 3 of the action potential an electrical but not ionic balance is obtained. For ionic balance an active mechanism (ionic pump) is necessary.

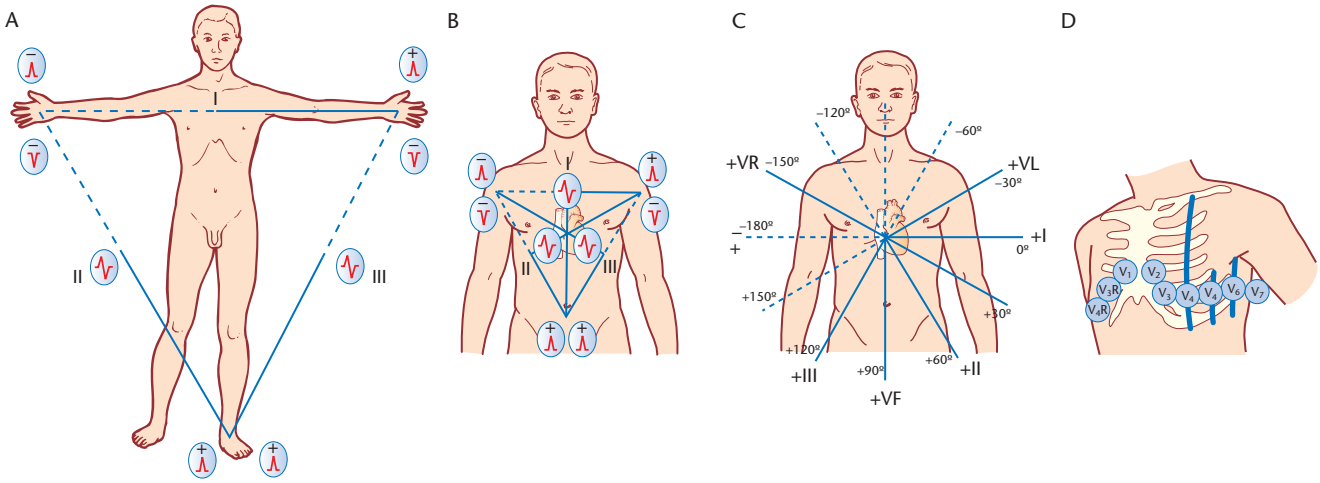


Figure 1.3 (A) Einthoven's triangle. (B) Einthoven's triangle superimposed on a human thorax. Note the positive (continuous line) and negative (dotted line) part of each lead. (C) Bailey's hexaxial system. (D) Sites where positive poles of the six precordial leads are located.

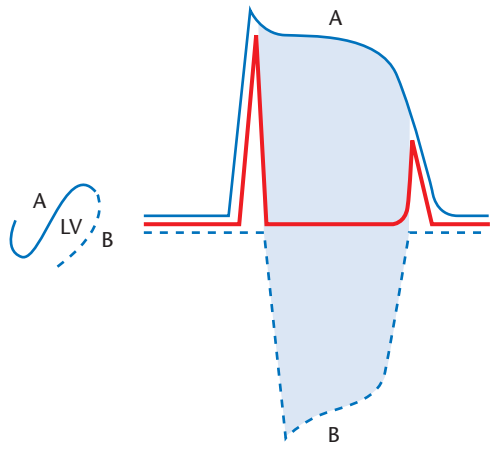


Figure 1.4 Correlation between global action potential, i.e. the sum of all relevant action potentials, of the subendocardial (A) and subepicardial (B) parts of the left ventricle and the ECG waveform. Depolarization starts first in the furthest zone (subendocardium) and repolarization ends last in the furthest zone (subendocardium). When the global action potential of the nearest zone is 'subtracted' from that of the furthest zone, the ECG pattern results. (LV = left ventricle.)

scribed as 'augmented' because, according to Einthoven's law, their voltage is higher than that of the simple bipolar leads. By adding these three leads to Bailey's triaxial system, Bailey's hexaxial system is obtained (Fig. 1.3C). In the horizontal plane, there are six unipolar leads (V1–V6) (Fig. 1.3D).

One approach to understanding ECG morphology is based on the concept that the action potential of a cell or the left ventricle (considered as a huge cell that contributes to the human ECG) is equal to the sum of subendocardial and subepicardial action potentials. How this occurs is shown in Fig. 1.4. This concept is useful for understanding how the ECG patterns of ischaemia and injury are generated (see Fig. 1.17).

Normal characteristics

Heart rate

Normal sinus rhythm at rest is usually said to range from 60 to 100 b.p.m. but the nocturnal sleeping heart rate may fall to about 50 b.p.m. and the normal daytime resting heart rate rarely exceeds 90 b.p.m. Several methods exist to assess heart rate from the ECG. With the standard recording speed of 25 mm/s, the most common method is to divide 300 by the number of 5-mm spaces (the graph paper is divided into 1- and 5-mm squares) between two consecutive R waves (two spaces represents 150 b.p.m., three spaces 100 b.p.m., four spaces 75 b.p.m., five spaces 60 b.p.m., etc.).

Rhythm

The cardiac rhythm can be normal sinus rhythm (emanating from the sinus node) or an ectopic rhythm (from a site other than the sinus node). Sinus rhythm is considered to be present when the P wave is positive in I, II, aVF and V2–V6, positive or biphasic (+/–) in III and V1, positive or –/+ in aVL, and negative in aVR.

PR interval and segment

The PR interval is the distance from the beginning of the P wave to the beginning of the QRS complex (Fig. 1.1). The normal PR interval in adult individuals ranges from

0.12 to 0.2 s (up to 0.22 s in the elderly and as short as 0.1 s in the newborn). Longer PR intervals are seen in cases of atrioventricular (AV) block and shorter PR intervals in pre-excitation syndromes and various arrhythmias. The PR segment is the distance from the end of the P wave to QRS onset and is usually isoelectric. Sympathetic overdrive may explain the down-sloping PR segment that forms part of an arc with the ascending nature of the ST segment. In pericarditis and other diseases affecting the atrial myocardium, as in atrial infarction, a displaced and sloping PR segment may be seen.

QT interval

The QT interval represents the sum of depolarization (QRS complex) and repolarization (ST segment and T wave) (Fig. 1.1). Very often, particularly in cases of a flat T wave or in the presence of a U wave, it is difficult to measure the QT interval accurately. It is usual to perform this measurement using a consistent method in order to ensure accuracy if the QT interval is studied sequentially. The recommended method is to consider the end of repolarization as the point where a tangent drawn along the descending slope of the T wave crosses the isoelectric line. The best result may be obtained by measuring the median duration of QT simultaneously in 12 leads. Automatic measurement may not be accurate but is often used clinically [7].

It is necessary to correct the QT interval for heart rate (QTc). Different heart rate correction formulae exist. The most frequently used are those of Bazett and Fridericia:

$$\text{Bazett (square root) correction: QT corrected} = \text{QT measured}/\text{RR interval (s)}^{0.5}$$

$$\text{Fridericia (cube root) correction: QT corrected} = \text{QT measured}/\text{RR interval (s)}^{0.33}$$

Although these correction methods are not accurate and are highly problematic in cases when a very precise QTc value is needed, their results are satisfactory in standard clinical practice. Because of its better accuracy the Fridericia formula is preferred to that of Bazett.

A long QT interval may occur in the congenital long QT syndromes or can be associated with sudden death [8], heart failure, ischaemic heart disease, bradycardia, some electrolyte disorders (e.g. hypokalaemia and hypocalcaemia) and following the intake of different drugs. Generally, it is believed that if a drug increases the QTc by more than 60 ms, torsade de pointes and sudden cardiac death might result. However, torsade de pointes rarely occurs unless the QTc exceeds 500 ms [9]. A short QT interval can be found in cases of early repolarization, in association with digitalis and, rarely, in a genetic disorder associated with sudden death [10].

P wave

This is the atrial depolarization wave (Fig. 1.1). In general, its height should not exceed 2.5 mm and its width should not be greater than 0.1 s. It is rounded and positive but may be biphasic in V1 and III and –/+ in aVL. The atrial repolarization wave is of low amplitude and usually masked by coincident ventricular depolarization (QRS complex) (see shading in Fig. 1.1).

QRS complex

This results from ventricular depolarization (Figs 1.1 and 1.5). According to Durrer *et al*. [11], ventricular depolarization begins in three different sites in the left ventricle and occurs in three consecutive phases that give rise to the generation of three vectors [6].

The ventricular depolarization signal is often described generically as a QRS complex. Usually the deflection is triphasic and, provided that the initial wave is negative (down-going), the three waves are sequentially known as Q, R and S. If the first part of the complex is up-going the deflection is codified as an R wave, etc. If the R or S wave is large in amplitude, upper case letters (R, S) are used, but if small in amplitude, lower case letters (r, s) are used. A normal or physiological initial negative wave of the ventricular depolarization waveform is called a q wave. It must be narrow (< 0.04 s) and should not usually exceed 25% of the amplitude of the following R wave, though some exceptions exist mainly in leads III, aVL and aVF. If the initial deflection is wider or deeper, it is known as a Q wave. Different morphologies are presented in Fig. 1.5.

The QRS width should not exceed 0.095 s and the R wave height should not exceed 25 mm in leads V5 and V6 or 20 mm in leads I and aVL, although a height greater than 15 mm in aVL is usually abnormal.

ST segment and T wave

The T wave, together with the preceding ST segment, is formed during ventricular repolarization (Fig. 1.1). The T wave is generally positive in all leads except aVR, but may be negative, flattened or only slightly positive in V1, and flattened or slightly negative in V2, III and aVF. The T wave presents an ascending slope with slower inscription than the descending slope. In children, a negative T wave is normal when seen in the right precordial leads (paediatric repolarization pattern) (Fig. 1.6F). Under normal conditions, the ST segment is isoelectric or shows only a slight down-slope (< 0.5 mm). Examples of normal ST–T wave variants are displayed in Fig. 1.6 (the figure caption provides comment on these patterns). Occasion-

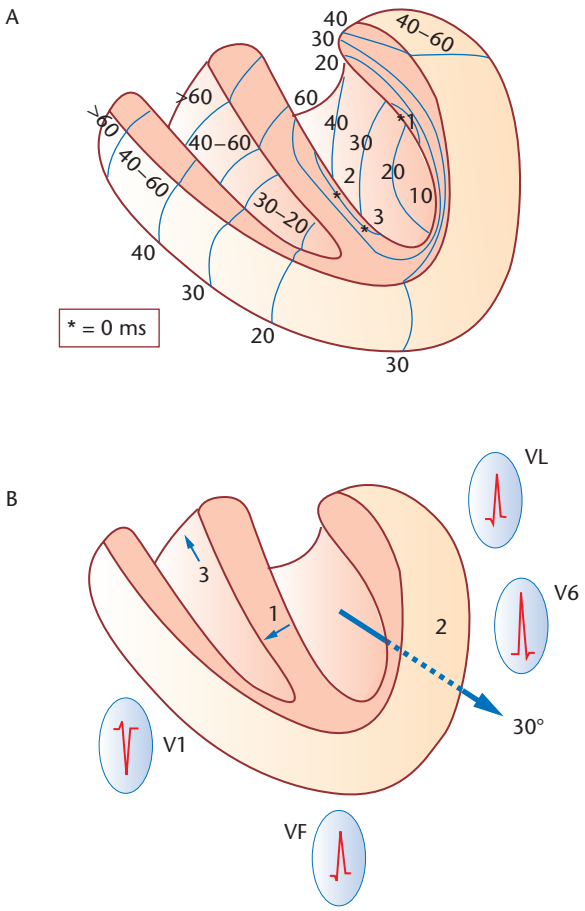


Figure 1.5 (A) The three initial points (1, 2, 3) of ventricular depolarization are marked by asterisks. The isochrone lines of the depolarization sequence can also be seen (time shown in ms). (B) The first vector corresponds to the sum of depolarization of the three points indicated in (A) and because it is more potent than the forces of the right vector, the global direction of vector 1 will be from left to right. The second vector corresponds to depolarization of the majority of the left ventricle and usually is directed to the left, downward and backward. The third vector represents the depolarization of basal parts of the septum and right ventricle.

ally, after a T wave, a small U wave can be observed, usually showing the same polarity as the T wave (Fig. 1.1).

Electrocardiographic morphological abnormalities

Electrocardiography can be considered the test of choice or the gold standard for the diagnosis of AV blocks, abnormal intra-atrial and intraventricular conduction, ventricular pre-excitation, most cardiac arrhythmias and, to some extent, acute myocardial infarction. However, in other cases, such as atrial and ventricular enlargement, abnormalities secondary to chronic coronary artery disease (ECG pattern of ischaemia, injury or necrosis), other repolarization abnormalities and certain arrhythmias, electrocardiography provides useful information and may suggest the diagnosis based on predetermined electrocardiographic criteria. However, these criteria have lesser diagnostic potential compared with other electrocardiology or imaging techniques (e.g. echocardiography in atrial or ventricular enlargement). In some circumstances, electrocardiography is the technique of choice and the electrocardiographic criteria in use are diagnostic for those conditions (e.g. bundle branch block), while for other conditions (e.g. cavity enlargement) the criteria are only indicative. In order to know the real value of the ECG criteria in these cases, it is important to understand the concepts of sensitivity, specificity and predictive accuracy [1].

Atrial abnormalities

Electrocardiographic patterns observed in patients with atrial hypertrophy and atrial dilation (atrial enlargement) and with atrial conduction block are encompassed by this term (Fig. 1.7).

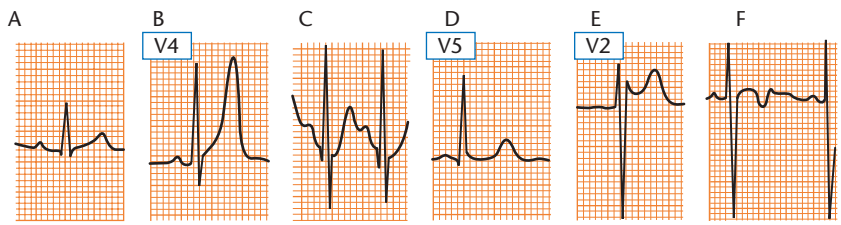


Figure 1.6 Different morphologies of normal variants of the ST segment and T wave in the absence of heart disease. (A) Normal ST/T wave. (B) Vagotonia and early repolarization. (C) Sympathetic overdrive. ECG of a 22-year-old male obtained with continuous Holter monitoring during a parachute jump. (D) Straightening of ST with symmetric T wave in a healthy 75-year-old man without heart disease. (E) Normal variant of ST ascent (saddle morphology) in a 20-year-old man with pectus excavatum. (F) Normal repolarization in a 3-year-old child.

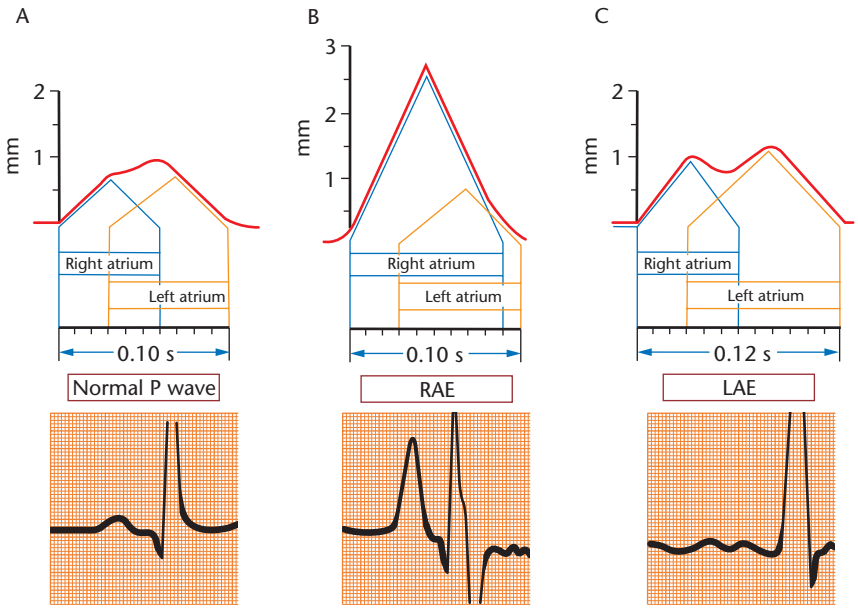


Figure 1.7 Schematic diagrams of atrial depolarization in (A) normal P wave, (B) right atrial enlargement (RAE) and (C) left atrial enlargement (LAE) with interatrial conduction block. An example of each of these P waves is shown beneath each diagram.

Right atrial enlargement (Fig. 1.7B)

Right atrial enlargement is usually present in patients with congenital and valvular heart diseases affecting the right side of the heart and in cor pulmonale.

Diagnostic criteria

The diagnostic criteria of right atrial abnormality are based on P-wave amplitude abnormalities (≥ 2.5 mm in II and/or 1.5 mm in V1) and ECG features of associated right ventricular abnormalities.

Left atrial enlargement (Fig. 1.7C)

Left atrial enlargement is seen in patients with mitral and aortic valve disease, ischaemic heart disease, hypertension and some cardiomyopathies.

Diagnostic criteria

1. P wave with duration ≥ 0.12 s especially seen in leads I or II, generally bimodal, but with a normal amplitude.
2. Biphasic P wave in V1 with a terminal negative component of at least 0.04 s. Criteria 1 and 2 have good specificity (close to 90%) but less sensitivity (< 60%).
3. P wave with biphasic (±) morphology in II, III and aVF with duration ≥ 0.12 s, which is very specific (100% in valvular heart disease and cardiomyopathies) but has low sensitivity for left atrial abnormality [12,13].

Interatrial block

PARTIAL BLOCK

P-wave morphology is very similar to that seen with left atrial abnormality. Usually the negative part in V1 may be less prominent than in atrial hypertrophy or dilation, although it is not surprising that the morphology of left atrial abnormality and atrial block are similar because the features of left atrial abnormality are more dependent on delayed interatrial conduction than on atrial dilation.

ADVANCED INTERATRIAL BLOCK WITH LEFT ATRIAL RETROGRADE ACTIVATION

This is characterized by a P wave with duration ≥ 0.12 s and with biphasic (±) morphology in II, III and aVF. A biphasic P-wave morphology in V1 to V3/V4 is also frequent (see below). This morphology is a marker for paroxysmal supra-ventricular tachyarrhythmias [12,13] and is very specific (100%) for left atrial enlargement.

Ventricular enlargement

The electrocardiographic concept of enlargement of the right and left ventricle encompasses both hypertrophy and dilation and, of course, the combination. The diagnostic criteria for ventricular enlargement when QRS duration is less than 120 ms are set out below. The criteria for the diagnosis of right and/or left ventricular enlargement combined with intraventricular block (QRS duration ≥ 120 ms) are defined elsewhere [1,5,14,15].

Right ventricular enlargement

Right ventricular enlargement (RVE) is found particularly in cases of congenital heart disease, valvular heart disease and cor pulmonale. Figure 1.8 shows that

Table 1.1 Electrocardiographic criteria of right ventricular enlargement

	Criterion	Sensitivity (%)	Specificity (%)
V1	R/S V1 ≥ 1	6	98
	R V1 ≥ 7 mm	2	99
	qR in V1	5	99
	S in V1 < 2 mm	6	98
	IDT in V1 ≥ 0.35 s	8	98
V5-V6	R/S V5–V6 ≤ 1	16	93
	R V5–V6 < 5 mm	13	87
	S V5–V6 ≥ 7 mm	26	90
V1 + V6	RV1 + SV5-V6 > 10.5 mm	18	94
ÂQRS	ÂQRS ≥ 110°	15	96
	SI, SII, SIII	24	87

IDT, intrinsicoid deflection (time from QRS onset to R wave peak).

Table 1.2 Morphologies with dominant R or R′ (r′) in V1

Clinical setting	QRS width	P-wave morphology in V1
No heart disease		
Incorrect electrode placement	< 0.12 s	Various changes
Normal variant (post-term infants, scant Purkinje fibres in anteroseptal zone)	< 0.12 s	Normal
Chest anomalies	< 0.12 s	Normal
Typical right bundle branch block	From < 0.12 to ≥ 0.12 s	Normal
Atypical right bundle branch block		
Ebstein's disease	Often ≥ 0.12 s	Often tall, peaked and + or ±
Arrhythmogenic right ventricular dysplasia	Often ≥ 0.12 s	Often abnormal
Brugada's syndrome	Sometimes ≥ 0.12 s	Normal
Right ventricular or biventricular enlargement (hypertrophy)	< 0.12 s	Often tall and peaked
Wolff–Parkinson–White syndrome	From < 0.12 to ≥ 0.12 s	Normal P, short PR
Lateral myocardial infarction	< 0.12 s	Normal P

the ECG pattern in V1 (prominent R wave) is related more to the degree of RVE than to its aetiology.

Diagnostic criteria

The electrocardiographic criteria most frequently used for the diagnosis of RVE are shown in Table 1.1, along with their sensitivities (low) and specificities (high). The differential diagnosis of an exclusive or dominant R wave in V1 (R, Rs or rSR′ pattern) is given in Table 1.2.

1 Morphology in V1: morphologies with a dominant or exclusive R wave in V1 are very specific, but not so sensitive (< 10%) for the diagnosis of RVE. Nevertheless, other causes that may cause a dominant R pattern in V1 must be excluded (see Table 1.2). An rS or even QS morphology in V1, together with RS in V6, may often be observed in chronic cor pulmonale, even in advanced stages or in the early stages of RVE of other aetiologies (Fig. 1.8).

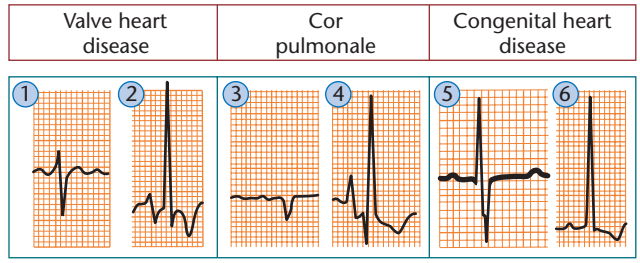


Figure 1.8 ECG pattern of right ventricular enlargement: note that QRS in V1 depends more on the severity of right ventricular enlargement than on aetiology of the disease. 1, 3 and 5 represent examples of mild mitral stenosis, cor pulmonale and congenital pulmonary stenosis respectively, while 2, 4 and 6 are cases of severe and long-standing mitral stenosis, cor pulmonale with severe pulmonary hypertension, and congenital pulmonary stenosis respectively.

2 Morphology in V6: the presence of forces directed to the right expressed as an S wave in V5–V6 is one of the most important ECG criteria.
3 Frontal plane QRS electrical axis (ÂQRS): ÂQRS ≥ 110° is a criterion with low sensitivity but high specificity (95%) provided that left posterior hemiblock, an extremely vertical heart position and lateral left ventricular wall infarction have been excluded.
4 SI, SII, SIII: an S wave in the three bipolar limb leads is frequently seen in chronic cor pulmonale with a QS or rS pattern in V1 and an RS pattern in V6. The possibility of this pattern being secondary to a positional change or simply to peripheral right ventricular block must be excluded [16].

The combination of more than one of these criteria increases the diagnostic likelihood. Horan and Flowers [15] have published a scoring system based on the most frequently used ECG criteria for right ventricular enlargement.

Left ventricular enlargement

Left ventricular enlargement, or ischaemic heart disease, is found particularly in hypertension, valvular heart disease, cardiomyopathies and in some congenital heart diseases.

In general, in patients with left ventricular enlargement, the QRS voltage is increased and is directed more posteriorly than normal. This explains why negative QRS complexes predominate in the right precordial leads. Occasionally, probably related to significant cardiac laevorotation or with more significant hypertrophy of the left ventricular septal area than of the left ventricular free wall, as occurs in some cases of apical hypertrophic cardiomyopathy, the maximum QRS is not directed posteriorly. In this situation a tall R wave may be seen even in V2.

The normal q wave in V6 may not persist if hypertrophy is associated with fibrosis and/or partial left bundle branch block. In Fig. 1.9, the ECG from a case of aortic valvular disease without septal fibrosis shows a q wave in V6 and a positive T wave, whereas the ECG from another case with fibrosis does not have a q wave in V6 [17,18]. The ECG pattern is more related to disease evolution than to the haemodynamic overload (Fig. 1.10), although a q wave in V5–V6 remains more frequently in long-standing aortic regurgitation than in aortic stenosis. The pattern of left ventricular enlargement is usually fixed but may be partially resolved with medical treatment of hypertension or surgery for aortic valvular disease.

Diagnostic criteria

Various diagnostic criteria exist (Table 1.3). Those with good specificity (≥ 95%) and acceptable sensitivity (40–50%) include the Cornell voltage criteria and the Romhilt and Estes scoring system.

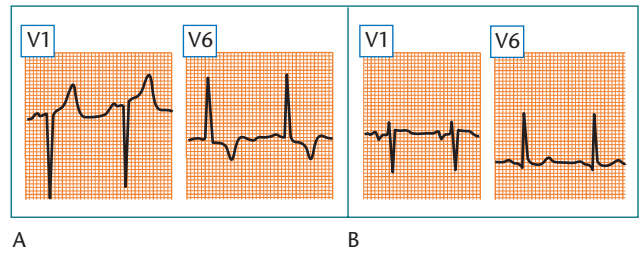


Figure 1.9 The most characteristic ECG feature of left ventricular enlargement is tall R waves in V5–6 and deep S waves in V1–2. The presence of a normal septal q wave depends on whether septal fibrosis is present. This figure shows two examples of aortic valvular disease both with left ventricular enlargement: (A) no fibrosis and a normal septal q wave; (B) abnormal ECG (ST/T with strain pattern) and no septal q wave due to extensive fibrosis.

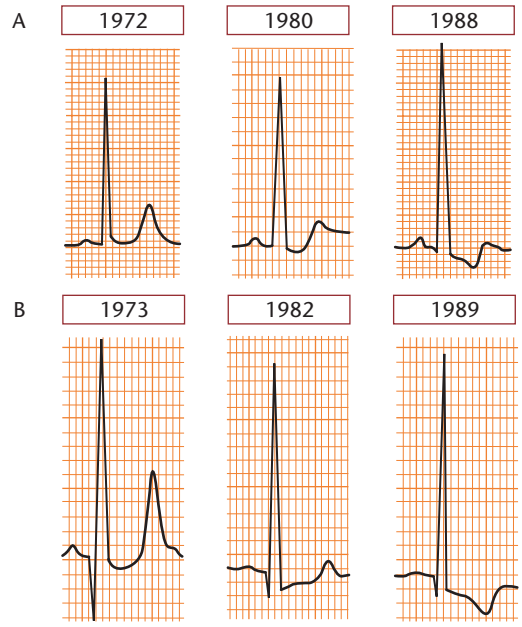


Figure 1.10 Examples of different ECG morphologies seen during the evolution of aortic stenosis (A) and aortic regurgitation (B).

Intraventricular conduction blocks

Ventricular conduction disturbances or blocks can occur on the right side or on the left. They can affect an entire ventricle or only part of it (divisional block). The block of conduction may be first degree (partial block or conduction delay) when the stimulus conducts but with

Table 1.3 Electrocardiographic criteria of left ventricular enlargement

Voltage criteria	Sensitivity (%)	Specificity (%)
RI + SIII > 25 mm	10.6	100
R aVL > 11 mm	11	100
R aVL > 7.5 mm	22	96
SV1 + RV5–6 ≥ 35 mm (Sokolow–Lyon)	22	100
RV5–6 > 26 mm	25	98
Cornell voltage criterion: R aVL + SV3 > 28 mm (men) or 20 mm (women)	42	96
Cornell voltage duration: QRS duration × Cornell voltage > 2436 mm/seg	51	95
In V1–V6, deepest S + tallest R > 45 mm	45	93
Rohmilt–Estes score > 4 points	55	85
Rohmilt–Estes score > 5 points	35	95

delay, third degree (advanced block) when passage of the wavefront is completely blocked, and second degree when the stimulus sometimes passes and sometimes does not.

Advanced or third-degree right bundle branch block (Fig. 1.11)

Advanced right bundle branch block (RBBB) represents complete block of stimulus in the right bundle or within the right ventricular Purkinje network. In this situation, activation of the right ventricle is initiated by condution through the septum from the left-sided Purkinje system.

Diagnostic criteria

1. QRS ≥ 0.12 s with slurring in the mid-final portion of the QRS.
2. V1: rsR′ pattern with a slurred R wave and a negative T wave.
3. V6: qRs pattern with S-wave slurring and a positive T wave.
4. aVR: QR with evident R-wave slurring and a negative T wave.
5. T wave with polarity opposite to that of the slurred component of the QRS.

Partial or first-degree RBBB

In this case, activation delay of the ventricle is less delayed. The QRS complex is 0.1–0.12 s in duration, but V1 morphology is rsR′ or rsr′.

Advanced (third degree) left bundle branch block (Fig. 1.12)

Advanced left bundle branch block (LBBB) represents complete block of stimulus in the left bundle or within the left ventricular Purkinje network. In this situation, activation of the left ventricle is initiated by conduction through the septum from the right-sided Purkinje system.

Diagnostic criteria

1. QRS ≥ 0.12 s, sometimes over 0.16 s, especially with slurring in the mid-portion of the QRS.
2. V1: QS or rS pattern with a small r wave and a positive T wave.
3. I and V6: a single R wave with its peak after the initial 0.06 s (delayed intrinsicoid deflection).
4. aVR: a QS pattern with a positive T wave.
5. T waves with their polarity usually opposite to the slurred component of the QRS complex.

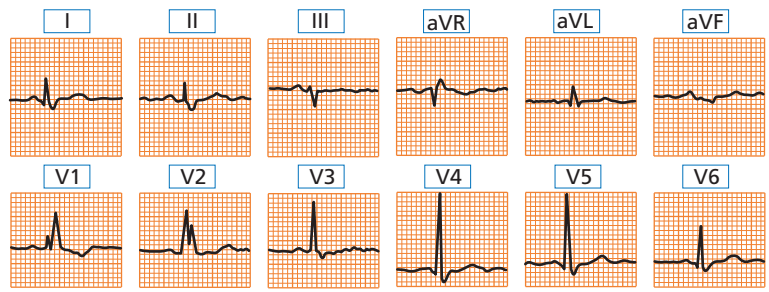


Figure 1.11 ECG in a case of advanced right bundle branch block.

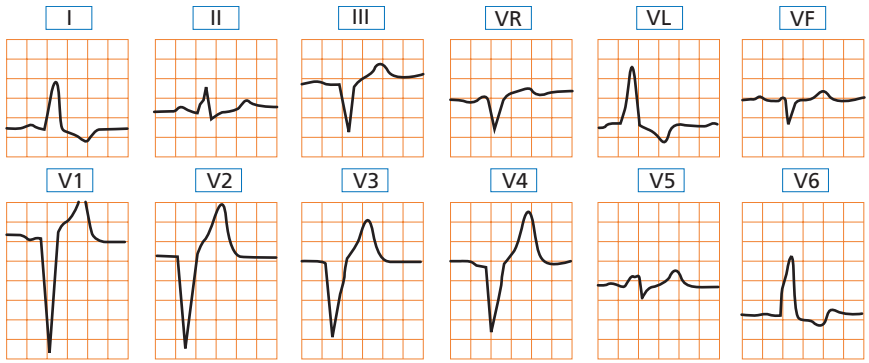


Figure 1.12 ECG in a case of complete left bundle branch block.

Partial or first-degree LBBB

In this case, left ventricular activation is less delayed. The QRS complex is 0.1–0.12 s in duration and presents as a QS complex or a small r wave in V1 and a single R wave in I and V6. This is explained by the fact that due to the delay in activation the first vector that is responsible for formation of the r wave in V1 and the q wave in V6 is not formed. This pattern is partly explained by the presence of septal fibrosis [17].

Divisional left ventricular block (hemiblocks)

The stimulus is blocked or delayed in either the supero-anterior (left anterior hemiblock) or inferoposterior division (left posterior hemiblock) of the left bundle branch [19].

LEFT ANTERIOR HEMIBLOCK

A typical example of left anterior hemiblock (LAH) is illustrated in Fig. 1.13. The differences between LAH and the SI, SII, SIII pattern can also be seen. Inferior wall myocardial infarction and Wolff–Parkinson–White (WPW) syndrome should also be ruled out.

Diagnostic criteria

1 QRS complex duration < 0.12 s.
2 ÂQRS deviated to the left (mainly between –45° and –75°).
3 I and aVL: qR, in advanced cases with slurring especially of the descending part of R wave.
4 II, III and aVF: rS with SIII > SII and RII > RIII.
5 S wave seen up to V6.

LEFT POSTERIOR HEMIBLOCK

In order to make the diagnosis of left posterior hemiblock (LPH), electrocardiographic and clinical characteristics (mainly RVE and an asthenic habitus) must be absent. It is also helpful if evidence of other left ventricular abnormalities is present. A typical electrocardiographic morphology in the frontal and horizontal planes of LPH is shown in Fig. 1.14b.

Diagnostic criteria

1 QRS complex duration < 0.12 s.
2 ÂQRS shifted to the right (between +90° and +140°).
3 I and aVL: RS or rS pattern.
4 II, III and aVF: qR morphology.
5 Precordial leads: S waves up to V6.

The evidence that the ECG pattern suddenly appears confirms the diagnosis of LPH (see Fig. 1.14).

Bifascicular blocks

The two most characteristic bifascicular blocks are advanced RBBB plus LAH and advanced RBBB plus LPH. On some occasions there is RBBB with alternans

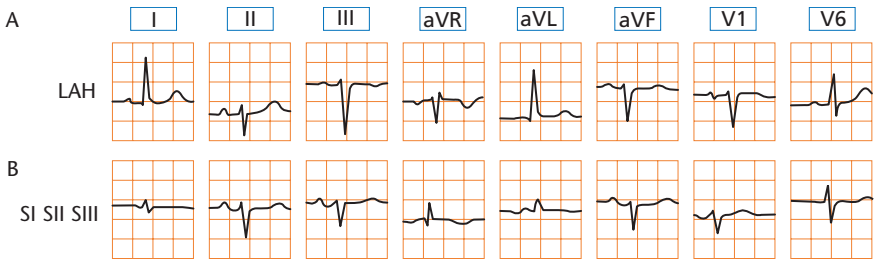


Figure 1.13 (A) An example of left anterior hemiblock. (B) SI SII SIII pattern. See in this case SII > SIII and there is S in lead I.

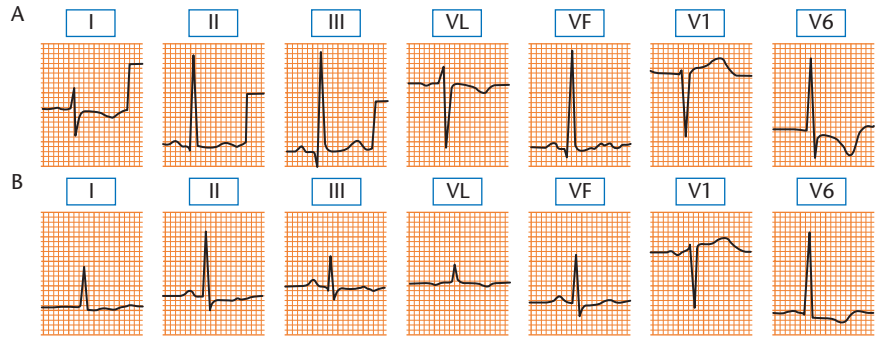


Figure 1.14 (A) An example of left posterior hemiblock. (B) The ECG of same patient some days before. The sudden appeareance of ÂQRS shifted to the right confirms the diagnosis of LPH.

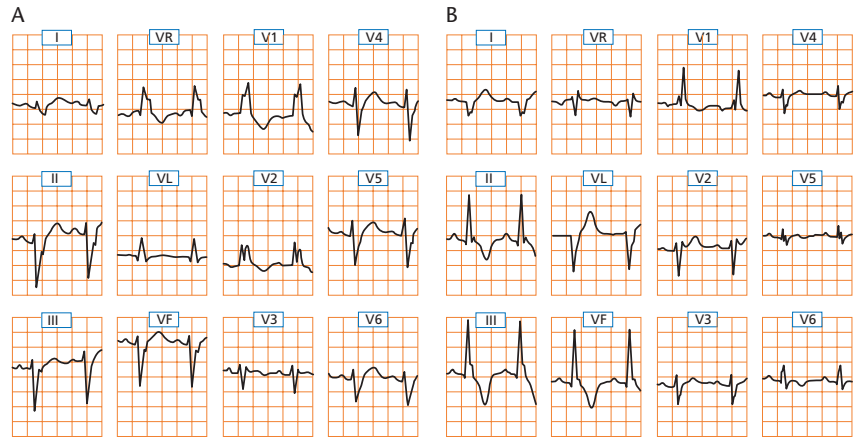


Figure 1.15 (A) Right bundle branch block plus left anterior hemiblock and, the following day, (B) right bundle branch block plus left posterior hemiblock.

of LAH and LPH (one form of trifascicular block) (Fig. 1.15).

ADVANCED RBBB PLUS LAS (Fig. 1.15A)
The diagnostic criteria are as follows.
1 QRS complex duration > 0.12 s.
2 QRS complex morphology: the first portion is directed upwards and to the left as in LAH, while the second portion is directed anteriorly and to the right as in advanced RBBB.

ADVANCED RBBB PLUS LPH (Fig. 1.15B)
The diagnostic criteria are as follows.
1 QRS complex duration > 0.12 s.
2 QRS complex morphology: the first portion of the QRS complex is directed downwards as in isolated LPH, while the second portion is directed anteriorly and to the right similar to advanced RBBB.

Ventricular pre-excitation

Ventricular pre-excitation (early excitation) occurs when the depolarization wavefront reaches the ventricles earlier (via an anomalous pathway) than it would normally (via the AV node/His–Purkinje conduction system). Early excitation is explained by fast conduction through the anomalous pathway that connects the atria with the ventricles, the so-called Kent bundles (WPW-type pre-excitation) [20]. Sometimes, pre-excitation of the His–Purkinje network occurs because of an anomalous atrio-His tract (or simply because of the presence of accelerated AV conduction). This produces short PR-type pre-excitation, called Lown–Ganong–Levine syndrome when associated with junctional tachycardias [21]. Rarely, an anomalous pathway including a section of the normal or accessory AV nodal tissue (Mahaim fibre) produces pre-excitation [22]. The importance of pre-excitation lies in its association with supraventricular tachycardias and sometimes sudden death [23] and the risk of its being mistaken (in the case of WPW pre-excitation) for other pathologies, such as myocardial infarction or hypertrophy. The presence of pre-excitation may also mask other ECG diagnoses.

WPW-type pre-excitation [20,23–25]

The electrocardiographic diagnosis is made by the presence of a short PR interval plus QRS abnormalities characterized by a slurred onset (delta wave) (Fig. 1.16) and T-wave abnormalities.

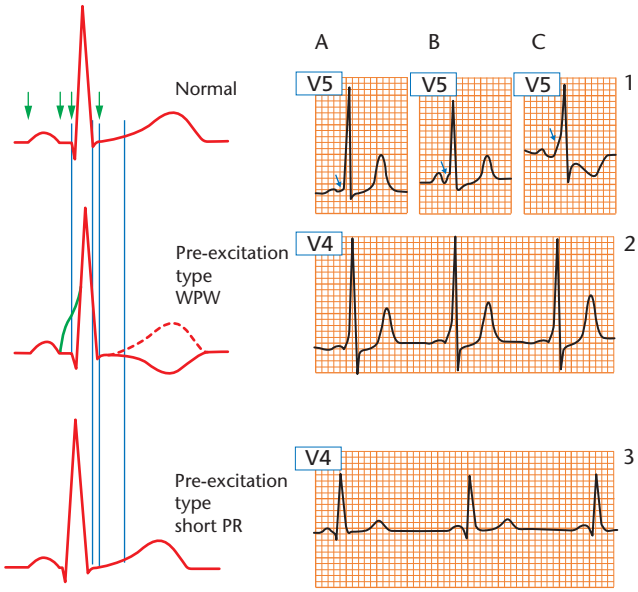


Figure 1.16 *Left*: Comparison of ECGs with normal ventricular activation, Wolff–Parkinson–White (WPW)-type pre-excitation and short PR-type pre-excitation. *Right*: (1) delta waves of different magnitude: (A) minor pre-excitation; (B, C) significant pre-excitation; (2) three consecutive QRS complexes with evident WPW-type pre-excitation; (3) short PR-type pre-excitation.

SHORT PR INTERVAL

In WPW pre-excitation, the PR interval is usually between 0.08 and 0.11 s. However, this form of pre-excitation can also occur with a normal PR interval in the presence of conduction delay within the anomalous pathway or because the anomalous pathway is remotely situated (usually left-sided). Only comparison with a baseline ECG tracing without pre-excitation will confirm whether the PR interval is shorter than usual.

QRS ABNORMALITIES

The QRS complexes are abnormal, i.e. wider than normal (often > 0.11 s) with a characteristic initial slurring (delta wave), caused by early direct activation of the ventricular myocardium as opposed to activation via the His–Purkinje network (Fig. 1.16). Different degrees of pre-excitation (more or less delta wave, QRS widening and T-wave abnormalities; see below) may be observed [1].

QRS complex morphology in the different surface ECG leads depends on the ventricular location of the anomalous pathway. Accordingly, WPW-type pre-excitation may be divided with respect to the location of the pathway [1]. Different algorithms exist to predict the location of the anomalous pathway [25]. However, electrophysiological studies are required to determine the exact location. Precise localization of the anomalous pathway is critical for successful ablation, a procedure performed to destroy the pathway, eliminate pre-excitation and avoid recurrence of paroxysmal supraventricular tachycardias.

REPOLARIZATION ABNORMALITIES

Repolarization is altered (T-wave polarity opposite to that of the pre-excited R wave) except in cases with minor pre-excitation. The changes are secondary to the alteration of depolarization and are more prominent when pre-excitation is greater.

DIFFERENTIAL DIAGNOSIS OF WPW-TYPE PRE-EXCITATION

Right-sided pre-excitation can be mistaken for LBBB; left-sided pre-excitation can be mistaken for RBBB, RVE and various myocardial infarction patterns. In all these cases, a short PR interval and the presence of a delta wave indicate the correct diagnosis of WPW-type pre-excitation.

SPONTANEOUS OR PROVOKED CHANGES IN MORPHOLOGY DUE TO ANOMALOUS CONDUCTION

Changes in the degree of pre-excitation are frequent. Pre-excitation can increase if conduction through the AV node is depressed (vagal manoeuvres, drugs, etc.) and can decrease if AV node conduction is enhanced (adrenaline, physical exercise, etc.).

Short PR-type pre-excitation (Lown–Ganong–Levine syndrome)

This type of pre-excitation is characterized by a short PR interval without changes in QRS morphology [21] (Fig. 1.16). It is impossible to be sure with a surface ECG whether the short PR interval is due to pre-excitation via an atrio-His pathway that bypasses slow conduction in the AV node or whether it is simply due to a rapidly conducting AV node. Associated arrhythmias (atrial, AV nodal and anomalous pathway dependent re-entry) are frequent in Lown–Ganong–Levine syndrome. Sudden death is very uncommon.

Mahaim-type pre-excitation

Mahaim-type pre-excitation usually presents with a normal PR interval, an LBBB-like QRS morphology and often an rS pattern in lead III [22]. A marked delta wave is usually not present. It is due to an accessory AV node connected directly to the right ventricle or is the result of an anomalous pathway linking the normal AV node to the right ventricle.

Electrocardiographic pattern of ischaemia, injury and necrosis [26–53]

The ionic changes, pathological alterations and electrophysiological characteristics that accompany different

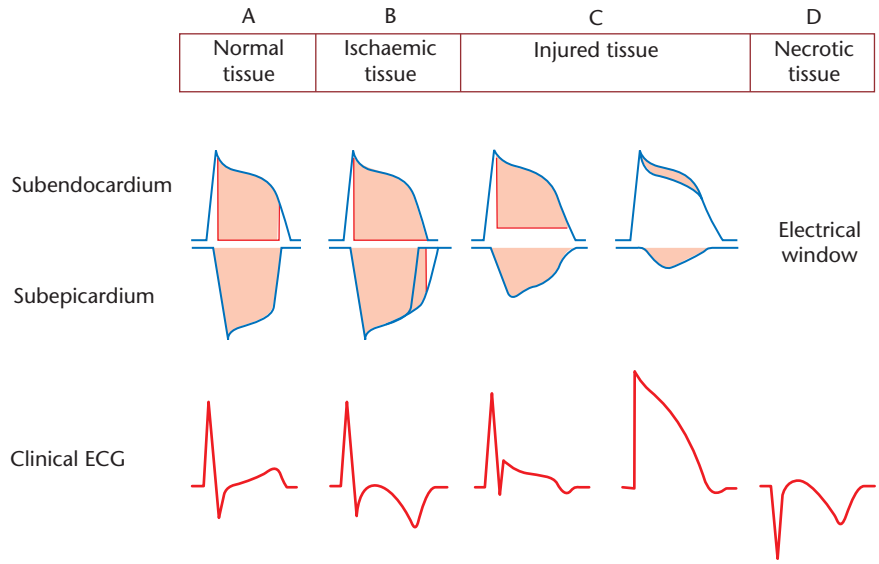


Figure 1.17 Corresponding electrical changes in subepicardial and subendocardial 'global action potentials' and the resulting ECG patterns in normal, ischaemic, injured or necrotic tissue. Correlations for normal tissue (A), subepicardial ischaemia (B), subepicardial injury (C) and necrotic tissue (D) are shown (see also Fig. 1.4).

stages of clinical ischaemia/infarction are illustrated in Fig. 1.17. The classic ECG sequence that appears in cases of complete coronary occlusion is as follows. The ECG pattern of subendocardial ischaemia (increase of T-wave amplitude) appears first. When the degree of clinical ischaemia is more important, the pattern of injury (ST-segment elevation) is present. Finally, necrosis of the myocardium is indicated by the development of a Q-wave pattern.

Electrocardiographic pattern of ischaemia

From an experimental perspective, ischaemia may be subepicardial, subendocardial or transmural. From the clinical point of view, only subendocardial and transmural ischaemia exist and the latter presents the morphology of 'subepicardial' ischaemia owing to the proximity of the subepicardium to the exploring electrode.

Experimentally and clinically, the ECG pattern of ischaemia (changes in the T wave) may be recorded from an area of the left ventricular subendocardium or subepicardium in which ischaemia induces a delay in repolarization. If the ischaemia is subendocardial, a more positive than normal T wave is recorded; in the case of subepicardial ischaemia (in clinical practice transmural), flattened or negative T waves are observed.

Alterations of the T wave due to ischaemic heart disease

The negative T wave of subepicardial ischaemia (clinically transmural) is symmetric, usually with an isoelectric ST segment. It is a common finding, especially in the long term after a Q-wave myocardial infarction (Figs 1.17D and 1.18D). It may also be a manifestation of acute coronary syndrome (ACS).

The electrocardiographic pattern of ischaemia is observed in different leads according to the affected zone. In the case of inferolateral wall involvement, T-wave changes are observed in II, III, aVF (inferior leads) and/or V6, I, aVL (lateral leads). In V1–V2 (inferobasal segment),

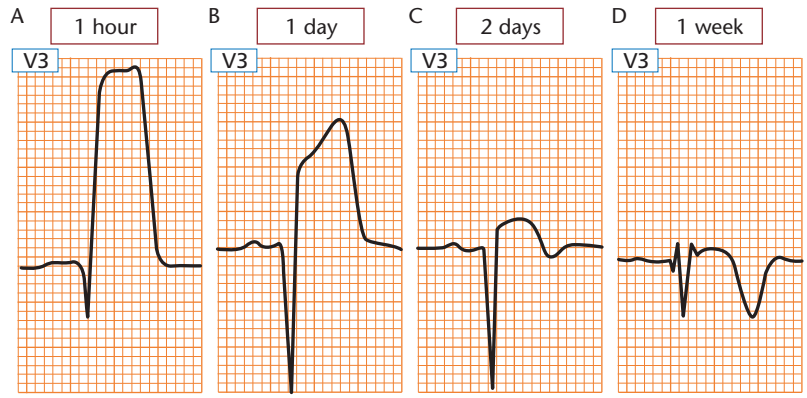


Figure 1.18 Evolutionary pattern of an extensive anterior wall myocardial infarction: (A) 1 h after the onset of pain; (B) 1 day later; (C) 2 days later; (D) 1 week later.

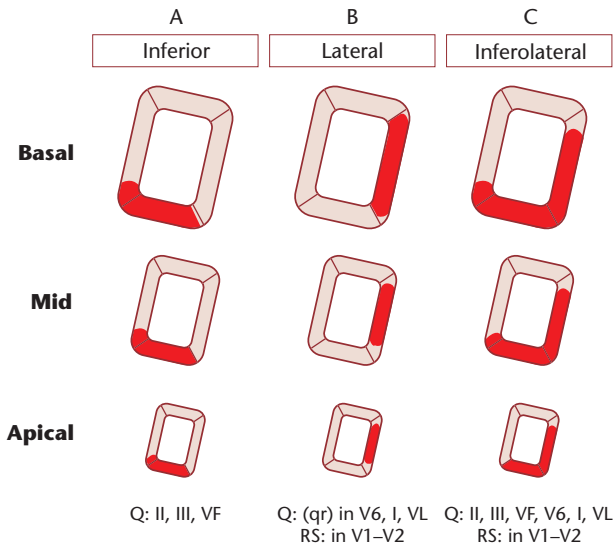


Figure 1.19 Anatomical–ECG correlations in myocardial infarction affecting (A) inferior wall, (B) lateral wall and (C) the entire inferolateral zone.

the T wave is positive instead of negative due to a mirror image (in subepicardial inferobasal injury ST depression instead of elevation, and in the case of necrosis a tall R wave instead of a Q wave) (Fig. 1.19). In anteroseptal involvement, T-wave changes are found from V1–V2 to V4–V5. If recorded in right precordial leads, it may correspond to a proximal occlusion of the left anterior descending (LAD) artery.

In contrast, an increase in T-wave amplitude, a common feature of subendocardial ischaemia, is recognized less frequently and the difficulty of diagnosis is increased because of its transient nature. It is observed in the initial phase of an attack of Prinzmetal angina (Fig. 1.20A) and occasionally in the hyperacute phase of ACS (Fig. 1.20B). Sometimes, it is not easy to be sure when a positive T wave may be considered abnormal. Therefore, sequential changes should be evaluated.

Table 1.4 Causes of a more-positive-than-normal T wave (other than ischaemic heart disease)

Normal variants: vagotonia, athletes, elderly
Alcoholism
Moderate left ventricular hypertrophy in heart diseases with diastolic overload
Stroke
Hyperkalaemia
Advanced AV block (tall and peaked T wave in the narrow QRS complex escape rhythm)

ALTERATIONS OF THE T WAVE IN VARIOUS CONDITIONS OTHER THAN ISCHAEMIC HEART DISEASE

The most frequent causes, apart from ischaemic heart disease, of a negative, flattened or more-positive-than-normal T wave are summarized in Tables 1.4 and 1.5. Examples of some of these T-wave abnormalities not due to ischaemic heart disease are shown in Fig. 1.21. Pericarditis is a very important differential diagnosis of the pattern of subepicardial ischaemia. The ECG in pericarditis shows a pattern of extensive subepicardial ischaemia with less frequent mirror images in the frontal plane, and with less negative T waves.

Electrocardiographic pattern of injury [26–36]

Experimentally and clinically, the ECG pattern of injury (changes in the ST segment) is recorded in the area of myocardial subendocardium or subepicardium where

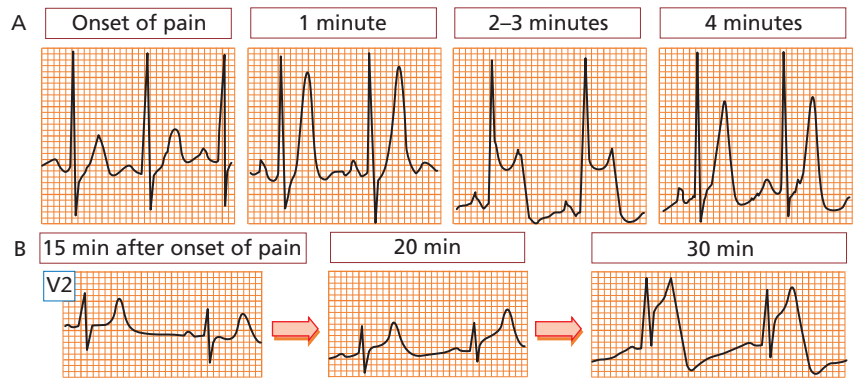


Figure 1.20 (A) Patient with Prinzmetal angina crisis: sequence of Holter ECGs recorded during a 4-min crisis. Note how the T wave becomes peaked (subendocardial ischaemia), with a subepicardial injury morphology appearing later; at the end of the crisis, a subendocardial ischaemia morphology reappears before the basal ECG returns. (B) A 45-year-old patient presenting with acute chest pain with a tall peaked T wave in right precordial leads following a normal ST segment as the only suggestive sign of acute coronary syndrome. A few minutes later, ST-segment elevation appears, followed by an increase in R wave and decrease in S wave.

Table 1.5 Causes of negative or flattened T waves (other than ischaemic heart disease)

Normal variants: children, black race, hyperventilation, females
Pericarditis
Cor pulmonale and pulmonary embolism
Myocarditis and cardiomyopathies
Alcoholism
Stroke
Myxoedema
Athletes
Medication: amiodarone, thioridazine
Hypokalaemia
Post-tachycardia
Left ventricular hypertrophy
Left bundle branch block
Post-intermittent depolarization abnormalities ('electrical memory')
Left bundle branch block
Pacemakers
Wolff–Parkinson–White syndrome

diastolic depolarization occurs as a consequence of a significant decrease in blood supply.

In the leads facing the injured zone, ST depression is recorded if the current of injury is dominant in the subendocardium (ECG pattern of subendocardial injury), while ST elevation is observed if the current of injury is subepicardial (clinically transmural) (ECG pattern of subepicardial injury). Mirror image patterns also exist, for example if subepicardial injury occurs in the posterior part of the lateral wall of the left ventricle, ST-segment elevation will be observed in the leads on the back while ST depression will be seen in V1–V2 as a mirror image. Also, the mirror images, or reciprocal changes, are very useful for locating the culprit artery and the site of the occlusion (Fig. 1.22).

The different morphologies of subepicardial injury in the evolution of acute Q-wave anterior myocardial infarction are shown in Fig. 1.18 and the various subendocardial injury ECG patterns observed in the course of an acute non-Q-wave myocardial infarction are shown in Fig. 1.23.

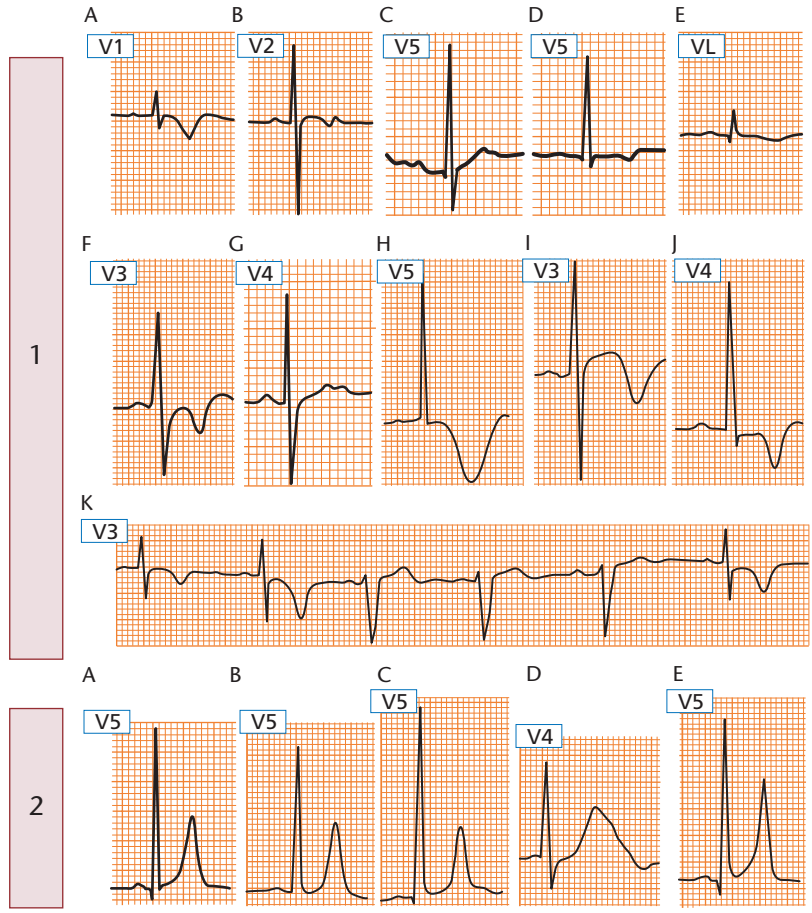


Figure 1.21 T-wave morphologies in conditions other than coronary artery disease. (1) Some morphologies of flattened or negative T waves: (A, B) V1 and V2 of a healthy 1-year-old girl; (C, D) alcoholic cardiomyopathy; (E) myxoedema; (F) negative T wave after paroxysmal tachycardia in a patient with initial phase of cardiomyopathy; (G) bimodal T wave with long QT frequently seen after long-term amiodarone administration; (H) negative T wave with very wide base, sometimes observed in stroke; (I) negative T wave preceded by ST elevation in an apparently healthy tennis player; (J) very negative T wave in a case of apical cardiomyopathy; (K) negative T wave in a case of intermittent left bundle branch block in a patient with no apparent heart disease. (2) Tall peaked T wave in (A) variant of normal (vagotonia with early repolarization), (B) alcoholism, (C) left ventricular enlargement, (D) stroke and (E) hyperkalaemia.

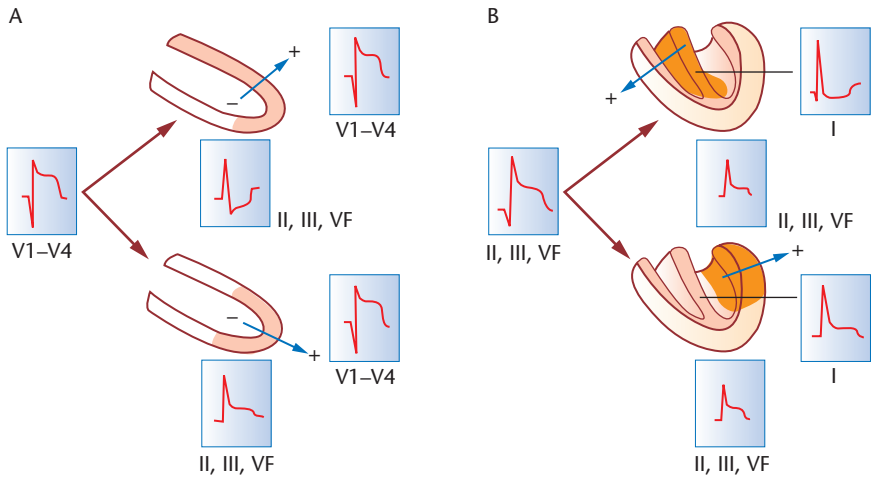


Figure 1.22 (A) ST elevation in precordial leads: as a consequence of occlusion of the left anterior descending artery (LAD), the ST changes in reciprocal leads (II, III, VF) allow identification of the site of occlusion, i.e. proximal LAD (above) shows ST depression or distal LAD (below) shows ST elevation. (B) ST elevation in inferior leads (II, III, aVF): the ST changes in other leads, in this case lead I, provide information on whether the inferior infarction is likely to be due to occlusion of the right coronary artery (above) (ST depression) or left circumflex artery (below) (ST elevation).

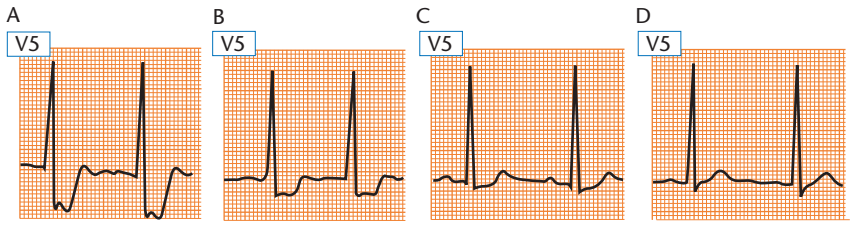


Figure 1.23 A 65-year-old patient with non-Q wave infarction. Note the evolutionary morphologies (A–D) during the first week until normalization of the ST segment.

ECG PATTERNS FOR CLASSIFICATION, OCCLUDED ARTERY IDENTIFICATION AND RISK STRATIFICATION OF ACUTE CORONARY SYNDROMES (ACS)

ACS may be classified into two types according to ECG expression: with or without ST-segment elevation. This classification has clear clinical significance as the former is treated with fibrinolysis and the latter is not. Figure 1.24 shows the different ECG presentations in ACS and their evolution.

ACS WITH ST ELEVATION [26–33]

New occurrence of ST elevation ≥ 2 mm in leads V1–V3 and ≥ 1 mm in other leads is considered abnormal and evidence of acute coronary ischaemia in the clinical setting of ACS. Sometimes minor ST elevation may be seen as a normal variant in V1–V2. Because of modern treatment, some acute coronary syndromes with ST elevation do not lead to Q-wave myocardial infarction and may not provoke a rise in enzymes. Nevertheless, the majority will develop a myocardial infarction, usually of Q-wave type (Fig. 1.24).

LAD artery occlusion leads to ST-segment elevation predominantly in precordial leads, while right coronary artery (RCA) or left circumflex (LCX) artery occlusion gives rise to ST-segment elevation in the inferior leads (Fig. 1.22). The extent of myocardium at risk can be estimated based on the number of leads with ST changes ('ups and downs') [26]. This approach has some limitations, especially related to the pseudo-normalization of ST changes in the right precordial leads that often occurs when the RCA occludes prior to the origin of the right ventricular artery.

Proximal LAD occlusion (before the first diagonal and septal arteries) as well as RCA occlusion proximal to the right ventricular artery have a poor prognosis. It is therefore useful to predict the site of occlusion in the early phase of ACS to enable decisions regarding the need for urgent reperfusion strategies. Careful analysis of ST changes in the 12-lead ECG recorded at admission may predict the culprit artery and the location of the occlusion. ST elevation is found in leads that face the head of an injury vector, while in the opposite leads ST depression can be recorded as a mirror image. Algorithms for the prediction of the sites of arterial occlusion are shown in Figs 1.25 and 1.26.

The right ventricular involvement that usually accompanies proximal RCA occlusion may be shown by ST changes in the right precordial leads (V3R, V4R) [27] (Fig. 1.26). ST-segment changes in these leads, though specific, disappear early during the evolution of myocardial infarction. Furthermore, these leads are often not recorded in emergency rooms. Thus, the real value of these changes is limited and in order to identify the culprit artery (RCA or LCX) in the case of an acute inferior myocardial infarction, we use the algorithm shown in Fig. 1.26 [31].

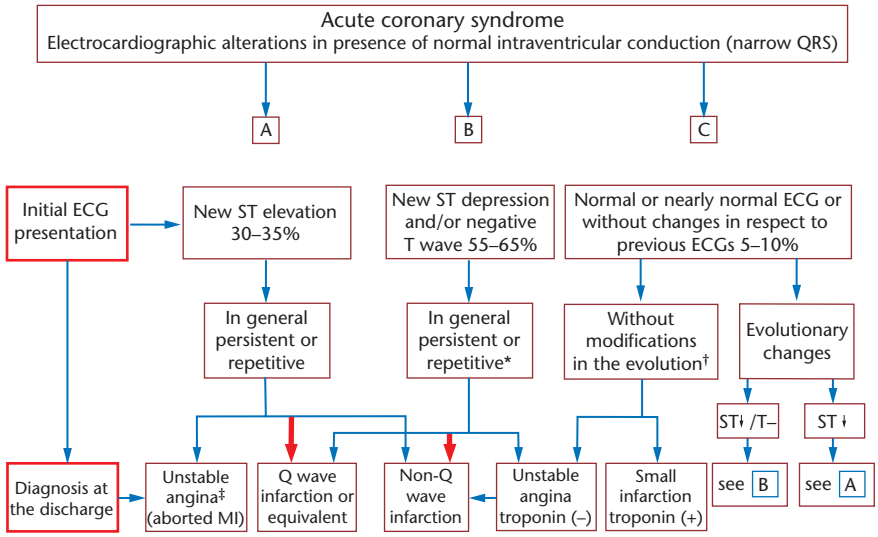


Figure 1.24 ECG alterations observed in patients with acute coronary syndrome (ACS) presenting with narrow QRS complex. Note the initial ECG presentations: (A) new ST elevation; (B) new ST depression/negative T wave; (C) normal or nearly normal ECG T wave or without changes in respect to previous ECGs. The approximate incidence of each presentation and the likely final discharge diagnosis based on both clinical and ECG settings are indicated. *In ACS with ECG pattern of ST depression or negative T waves, troponin levels allow differentiation between unstable angina (troponin negative) and non-Q-wave infarction (troponin positive). Usually, cases with short-duration ECG changes, particularly with negative T waves, present with negative troponin levels and correspond to unstable angina. †According to ESC/ACC guidelines in patients presenting with chest pain or its equivalent suggestive of ACS with accompanying normal ECG, troponin level is a key factor in differentiating between small myocardial infarction (MI) and unstable angina. ‡Sometimes, thanks to quick treatment, patients present with normal troponin levels despite important ST elevation in the initial ECG (aborted MI).

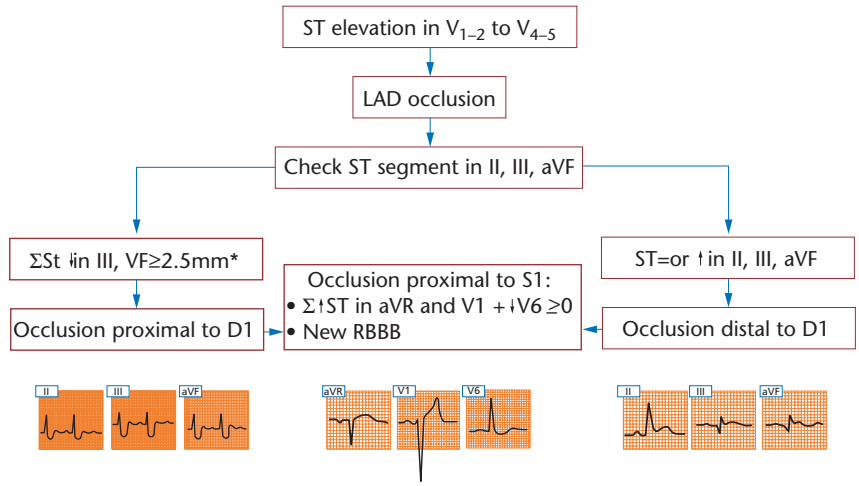


Figure 1.25 Algorithm for locating occlusion of left anterior descending artery (LAD) in evolving myocardial infarction with ST elevation (STEMI) in precordial leads, with ECG examples of the different situations. *Cases with ST depression < 2.5 mm are the most difficult to classify.

Furthermore, the criterion of isoelectric or elevated ST in V1 has the highest accuracy in predicting proximal RCA occlusion [32]. In these cases the ST elevation in V1 may also occur in V2 or V4 but with a V1/V3–4 ratio over 1. This differentiates these cases from cases of antero-inferior infarction [33], in which there is also ST elevation in inferior and precordial leads but the ST elevation V1/V3–4 ratio is less than 1.

ACS WITHOUT ST ELEVATION

ACS with ST depression in eight or more leads has a worse prognosis as it frequently corresponds to a left main artery subocclusion or its equivalent (three-vessel disease). Generally, in these cases ST elevation in aVR can be observed as a mirror image [34] (Fig. 1.27). If, in cases of ACS without ST elevation, ST depression in V4–V5 is followed by a final positive T wave, the prognosis is better

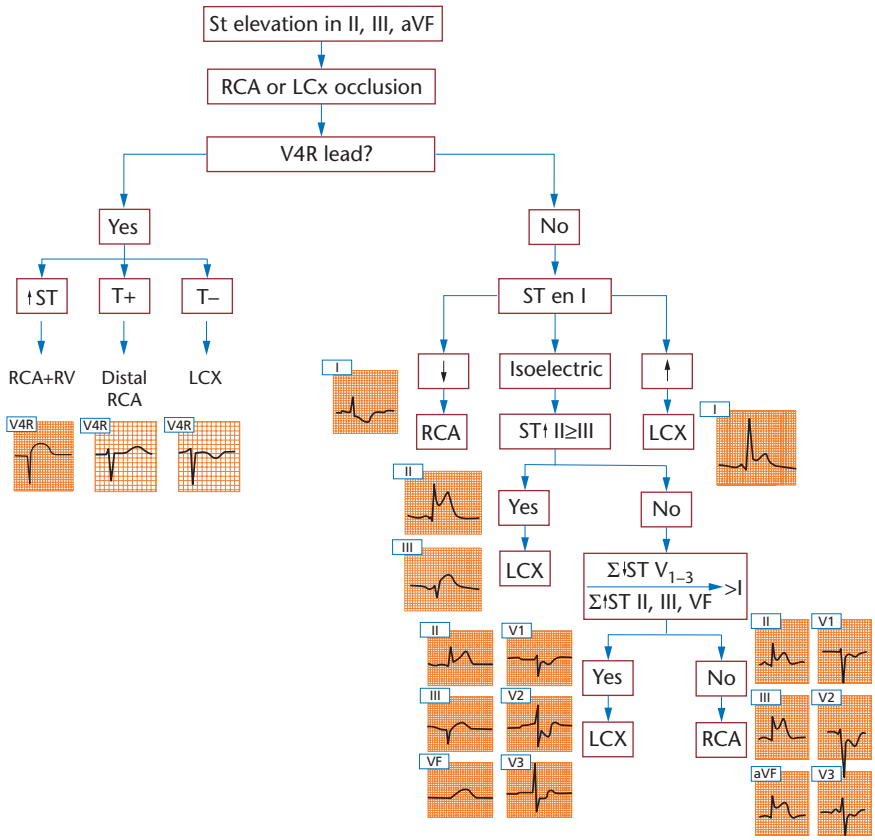


Figure 1.26 Algorithm for locating occlusion of right coronary artery (RCA) or left circumflex artery (LCx) in evolving myocardial infarction with ST elevation (STEMI) in inferior leads, with ECG examples of different situations.

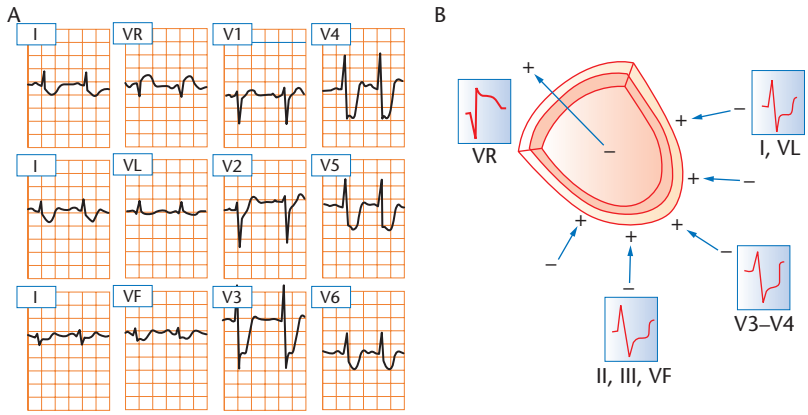


Figure 1.27 (A) ST-segment depression in more than eight leads and ST-segment elevation in VR in a case of non-STEMI due to involvement of the left main coronary artery. Note that the maximum depression occurs in V3–V4 and ST-segment elevation occurs in aVR as a mirror image. (B) Schematic representation that explains how ST-segment depression is seen in all leads, except for aVR and V1, in a case of non-Q-wave infarction secondary to the involvement of the left main coronary artery. The vector of circumferential subendocardial injury is directed from the subepicardium to the subendocardium and is seen as a negative vector in all leads except VR.

and single-vessel (often the proximal LAD) disease may be present [35]. The presence of deep negative T waves from V1 to V4–V5 suggests subocclusion of the proximal LAD. On the other hand, in the group of ACS with ST depression and/or negative T waves, the presence in leads with dominant R waves of mild ST depression usually signifies a worse prognosis than negative T waves.

ST-segment alterations remote from the acute phase of ischaemic heart disease

ST-segment elevation is usually found in association with coronary spasm (Prinzmetal angina) often preceded by peaked and tall T waves [36] (see Fig. 1.20A). Occasionally, upward convex ST elevation may persist after the acute phase of a myocardial infarction. It has been

Table 1.6 Most frequent causes of ST-segment elevation (other than ischaemic heart disease)

Normal variants: chest abnormalities, early repolarization, vagal overdrive. In vagal overdrive, ST-segment elevation is mild and generally accompanies the early repolarization image. T wave is tall and asymmetric
Athletes: sometimes an ST-segment elevation exists that may even mimic an acute coronary syndrome with or without negative T waves, at times prominent. No coronary involvement has been found, although this abnormality has been observed in sportsmen who die suddenly; thus its presence implies the need to exclude hypertrophic cardiomyopathy
Acute pericarditis in its early stage and myopericarditis
Pulmonary embolism
Hyperkalaemia: the presence of a tall peaked T wave is more evident than the accompanying ST-segment elevation, but sometimes it may be evident
Hypothermia
Brugada's syndrome
Arrhythmogenic right ventricular cardiomyopathy
Dissecting aortic aneurysm
Left pneumothorax
Toxicity secondary to cocaine abuse, etc.

classically considered to be related to left ventricular aneurysm. The specificity of this sign is high but its sensitivity is low. On the other hand, slight persistent ST-segment depression is frequently observed in coronary disease due to persistence of ischaemia. An exercise test may increase this pattern.

ST-SEGMENT ALTERATIONS IN CONDITIONS OTHER THAN ISCHAEMIC HEART DISEASE

Different causes of ST-segment elevation, aside from ischaemic heart disease, are shown in Table 1.6. Representative examples are illustrated in Fig. 1.28. The most frequent causes of ST-segment depression in situations other than ischaemic heart disease are shown in Table 1.7.

Electrocardiographic pattern of necrosis [37–53]

Classically, the electrocardiographic pattern of established necrosis is associated with a pathological Q wave, generally accompanied by a negative T wave (necrosis Q wave) [1] (Table 1.8). The specificity of this criterion is high but its sensitivity is low (around 60%) and is even lower with current treatment regimens and the new definition of myocardial infarction (ESC/ACC consensus) [37,38].

Table 1.7 Most frequent causes of ST-segment depression (other than ischaemic heart disease)

Normal variants: sympathetic overdrive, neurocirculatory asthenia, hyperventilation
Medications: diuretics, digitalis
Hypokalaemia
Mitral valve prolapse
Post-tachycardia
Secondary: bundle branch block, ventricular hypertrophy

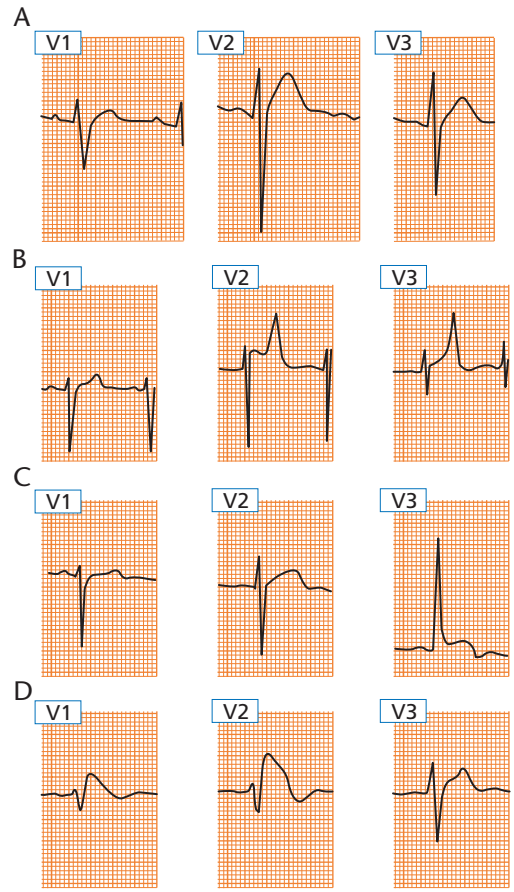


Figure 1.28 The most frequent causes of ST elevation other than ischaemic heart disease: (A) pericarditis; (B) hyperkalaemia; (C) in athletes; (D) Brugada pattern.

Figure 1.18 shows the ECG morphology seen with transmural involvement after total occlusion of a coronary artery. After an initial stage of ST-segment elevation, a Q wave with a negative T wave appears. It was thought that cases of non-Q-wave infarction had a predominantly subendocardial location (electrically 'mute'). Thus, it was considered that Q-wave infarction signified transmural involvement, while non-Q-wave infarction implied subendocardial compromise.

It is now well known that, from a clinical point of view, isolated subendocardial infarctions do not exist [39]. Nevertheless, there are infarctions that compromise a great portion of the wall, but with subendocardial predominance, which may or may not develop a Q wave. Furthermore, there are completely transmural infarctions (such as infarctions of basal parts of the cardiac

Table 1.8 Characteristics of the pathological Q wave, named 'necrosis Q wave' when secondary to myocardial infarction

Characteristics of pathological Q wave

Duration: ≥ 30 ms in I, II, III, aVL and aVF, and in V3–V6. The presence of a Q wave is normal in aVR. In V1–V2, all Q waves are pathological. Usually also in V3, except in cases of extreme laevo-rotation (qRs in V3)

Depth: above the limit considered normal for each lead, i.e. generally 25% of the R wave (frequent exceptions, especially in aVL, III and aVF)

Present even a small Q wave in leads where it does not normally occur (e.g. qrS in V1–V2)

Q wave with decreasing voltage from V3–V4 to V5–V6, especially if accompanied by a decrease of voltage in R wave compared with previous ECG

Criteria for diagnosing location of myocardial infarction

Anteroseptal zone

Q wave, regardless of duration and depth, in V1–V3

Presence of Q wave > 30 ms in duration and over 1 mm in depth in leads I, aVL, V4–V6

Inferolateral zone

Presence of Q wave in II and aVF; lead III is not used due to false-positive cases

Q wave may appear in lateral leads (V6 or V6 and/or I and aVL)

ECG may present equivalent of Q wave (increase in R wave in V1–V2) or be practically normal in cases of involvement of posterior part of lateral wall

walls, especially the posterior part of the lateral wall) that may not develop a Q wave. This assumption has been recently confirmed by magnetic resonance imaging (MRI) [40]. Consequently, the distinction between transmural (Q-wave infarction) and subendocardial (non-Q-wave infarction) can no longer be supported.

Q-wave infarction

Genesis of Q Wave The appearance of the Q wave of necrosis may be explained by the electrical window theory of Wilson (Fig. 1.29). The vector of necrosis is equal in magnitude but opposite in direction to the normal vector that would be generated in the same zone without necrosis. The onset of ventricular depolarization changes when the necrotic area corresponds to a zone that is depolarized within the first 40 ms of ventricular activation, which applies to the majority of the left ventricle except the posterobasal parts.

Location of infarction In everyday practice the nomenclature of the affected myocardial infarction zone is still determined by the presence of Q waves in different leads as proposed more than 50 years ago by Myers *et al.* [41]

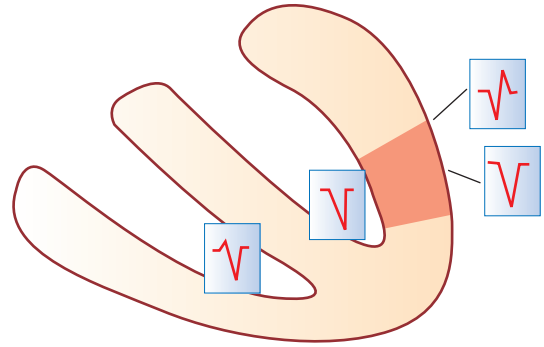


Figure 1.29 According to Wilson the necrotic zone is an electrical window that allows the intraventricular normal QS morphology to be recorded from the opposing necrotic wall of the left ventricle. The lead facing the necrotic myocardium 'looks' into the cavity of the left ventricle.

based on their classical pathological study. According to this classification, the presence of Q waves in V1–V2 represents septal infarction, in V3–V4 anterior infarction, in V1–V4 anteroseptal infarction, in V5–V6 low lateral infarction, in V3–V6 anterolateral infarction, in V1–V6 anteroseptolateral infarction, and in I and aVL high lateral infarction.

However, this classification has some limitations. Correlation with coronary angiography and imaging techniques including MRI [42–46] has revealed the following.

1 The presence of a Q wave in V1–V2 does not imply involvement of the entire septal wall; as a matter of fact the initial vector of ventricular depolarization originates in the mid-low part of the anterior septum. Therefore, the upper part of the septum need not be involved for the appearance of a Q wave in V1–V2.
2 Correlation with cardiovascular magnetic resonance (CE-CMR) [45,46] has demonstrated that: (a) the posterior wall often does not exist, therefore the basal part of the inferior wall should be called the inferobasal segment (segment 4); (b) the necrosis vector (NV) of the inferobasal segment faces V3–V4 and not V2–V1, therefore the RS morphology does not originate in V1; in those cases where the inferobasal segment does not bench upwards (the entire inferior wall is flat), the NV is directed only upwards and contributes to the Q wave in II, III and VF; (c) in cases of isolated lateral infarction, the NV may face V1, explaining the RS morphology seen in this lead.
3 In rare cases, if the LAD is very long, the occlusion of this artery proximal to S1 and D1 may not cause Q waves in I and aVL because the vector of necrosis of the lateral wall may be masked by the vector of necrosis of the inferior wall.
4 Because of new treatments for revascularization given

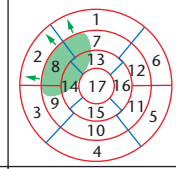
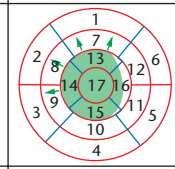
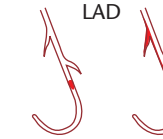
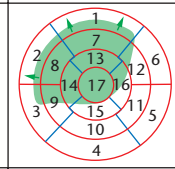
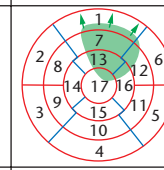
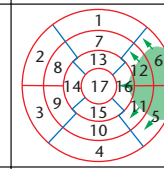
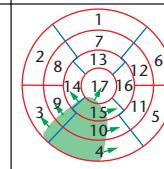
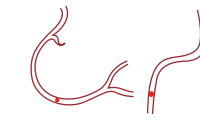
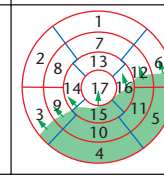
Type of MI		Infarction area (CMR)	ECG pattern	Name given to MI	Most probable place of occlusion
ANTEROSEPTAL ZONE	A1 n=7		Q in V1–2 SE: 86% ES: 98%	Septal	LAD 
	A2 n=7		Q in V1–2 to V4–V6 SE: 86% ES: 98%	Apical/ anteroseptal	LAD 
	A3 n=6		Q in V1–2 to V4–V6 I and VL SE: 83% ES: 98%	Extensive anterior	LAD 
	A4 n=4		Q (qs or r) in VL (I) and sometimes V2–3 SE: 70% ES: 100%	Limited anterior	LAD 
INFEROLATERAL ZONE	B1 n=6		Q (qr or r) in I, VL, V5–6 and/or RS in V1 SE: 50% ES: 98%	Lateral	LCX 
	B2 n=8		Q in II, III, VF SE: 87.5% ES: 98%	Inferior	RCA LCX 
	B3 n=10		Q in II, III, VF (B2) + Q in I, VL, V5, 6 and / or RS in V1 (B1) SE: 70% ES: 100%	Inferolateral	

Figure 1.30 Relationship between infarcted area, ECG pattern, name given to infarction and the most probable culprit artery and place of occlusion. LAD, left anterior descending artery; RCA, right coronary artery; LCX, left circumflex artery.

in the acute phase, the necrotic zone is often very limited compared with the zone at risk in the acute phase.

5 The location of precordial, especially mid-precordial (V3–V5), leads may change from one day to another and therefore it is difficult to make a diagnosis based on the presence or absence of Q waves in these leads.

As a result of these limitations, a study on correlations between ECG patterns and different myocardial areas of necrosis detected by CMR has been undertaken in the chronic phase of myocardial infarction [45,46]. The left ventricle was divided into two zones, anteroseptal and inferolateral. Figure 1.30 shows seven ECG patterns that accurately correlate with seven areas of necrosis detected on CMR (four anteroseptal and three inferolateral) (see also Figs 1.31 and 1.32). Nevertheless, some areas, especially at the base, frequently present with normal ECGs in the chronic phase [46].

Quantification A quantitative QRS score has been developed by Selvester *et al.* [47] to estimate the extent of myocardial necrosis especially in the case of anterior myocardial infarction. Recently, the same group demonstrated that MRI may improve its accuracy [48]. The most significant error was the misinterpretation of Q waves in V1–V2 as indicating basal septal and anterior wall

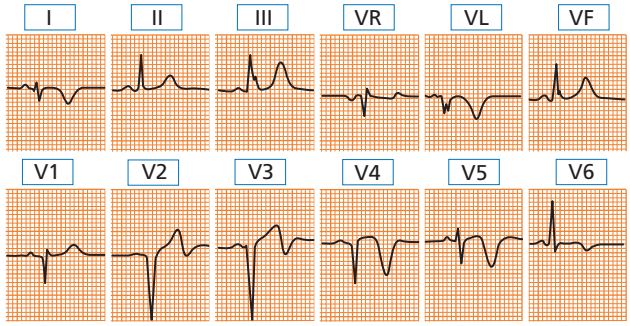


Figure 1.31 ECG of extensive anterior myocardial infarction (A3 type in Fig. 1.30).

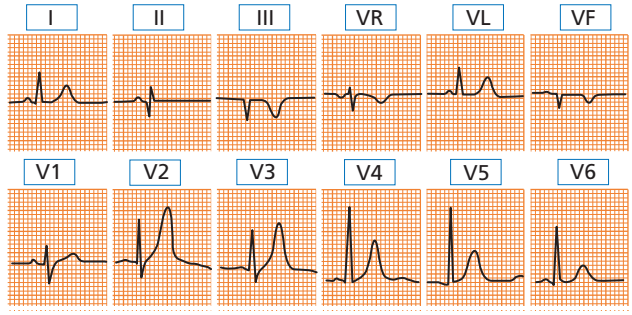


Figure 1.32 ECG of inferolateral myocardial infarction (B3 type in Fig. 1.30).

involvement. As already stated this is incorrect because the first vector (r wave in V1–V2) is generated in the mid-low anterior part of the septum. Also recently, it has been found that pre-discharge scoring in patients with anterior Q waves did not correlate with the amount of myocardial damage as estimated by radionuclide techniques in patients treated with and without thrombolytics [49]. Furthermore, spontaneous changes in the QRS score from discharge to 6 months seem to be of limited value in identifying patients with late improvement of perfusion or left ventricular function.

Differential diagnosis of pathological Q wave

Although the specificity of a pathological Q wave for diagnosing myocardial infarction is high, similar Q waves can be seen in other conditions. The diagnosis of myocardial infarction is based not only on electrocardiographic alterations but also on the clinical evaluation and enzyme changes. The pattern of ischaemia or injury accompanying a pathological Q wave is supportive of the Q wave being secondary to ischaemic heart disease. The main causes of pathological Q waves other than myocardial necrosis are listed in Table 1.9. On the other hand, in 5–25% of Q-wave infarctions (with the highest incidence in inferior wall infarction) the Q wave disappears with time, which explains the relatively poor sensitivity of the Q wave for detecting old myocardial infarction.

Table 1.9 Pathological Q wave not secondary to myocardial infarctioon

During the evolution of an acute disease involving the heart
Acute coronary syndrome with an aborted infarction
Coronary spasm (Prinzmetal angina type)
Acute myocarditis
Presence of transient apical dyskinesia that also shows ST-segment elevation and a transient pathological q wave (Tako-tsubo syndrome) [53]
Pulmonary embolism
Miscellaneous: toxic agents, etc.
Chronic pattern
Recording artefacts
Normal variants: aVL in the vertical heart and III in the dextrorotated and horizontal heart
QS in V1 (hardly ever in V2) in septal fibrosis, emphysema, the elderly, chest abnormalities, etc.
Some types of right ventricular hypertrophy (chronic cor pulmonale) or left ventricular hypertrophy (QS in V1–V2, or slow increase in R wave in precordial leads, or abnormal q wave in hypertrophic cardiomyopathy)
Left bundle branch conduction abnormalities
Infiltrative processes (e.g. amyloidosis, sarcoidosis, tumours, chronic myocarditis, dilated cardiomyopathy)
Wolff–Parkinson–White syndrome
Dextrocardia
Phaeochromocytoma

Diagnosis of necrosis in the presence of ventricular blocks, pre-excitation or ventricular pacemaker

Complete RBBB Since cardiac activation begins normally in RBBB, the presence of a myocardial infarction causes an alteration in the first part of the QRS complex that can generate a Q wave, just as with normal ventricular conduction. Furthermore, in the acute phase the ST–T changes can be seen exactly as with normal activation. Patients with ACS with ST elevation that during its course develops new-onset complete RBBB usually have the LAD occluded before the first septal and first diagonal arteries (Fig. 1.25). This is explained by the fact that the right bundle branch receives its blood supply from the first septal artery.

Complete LBBB In the acute phase, the diagnosis of myocardial infarction in the presence of complete LBBB may be suggested by ST-segment changes [50]. In the chronic phase, detection of underlying myocardial infarction is difficult. Ventricular depolarization starts close to the base of the anterior papillary muscle of the right ventricle. This causes a depolarization vector that is directed forward, downwards and to the left. Trans-septal depolarization of the left ventricle initiates subsequent

vectors. As a result, even if important zones of the left ventricle are necrotic, the overall direction of the initial depolarization vector does not change and it continues to point from right to left, preventing the inscription of a Q wave. Nevertheless, small 'q' waves or tall R waves may occasionally be observed [6]. The correlation of clinical and ECG changes with enzyme changes and radionuclide studies have confirmed that the presence of Q waves in I, aVL, V5 and V6 and R waves in leads V1–V2 are the most specific criteria for diagnosing myocardial infarction in the presence of LBBB in the chronic phase [51].

Diagnosis of Q-wave myocardial infarction in the presence of a hemiblock In general, necrosis associated with LAH may be diagnosed without difficulty. In the case of an ECG with left-axis deviation of the QRS and Q waves in II, III and aVF, the presence of QS without a terminal 'r' wave confirms the association with LAH. In some cases, mainly in small inferior myocardial infarctions, LAH may mask myocardial necrosis. The initial vector is directed more downwards than normal as a result of LAH and masks any necrosis vector due to a small inferior myocardial infarction.

LPH may mask or decrease an inferior necrosis pattern by converting a QS or Qr morphology in II, III and aVF into QR or qR pattern. It may also cause a small positive wave in I and aVL in the case of a lateral myocardial infarction because the initial vector in LPH may be directed more upwards than usual as a result of LPH and mask the necrosis vector of a small lateral infarction.

Pre-excitation and pacemakers It is difficult to diagnose myocardial infarction in the presence of pre-excitation. Sometimes it may be suggested by changes of repolarization especially in the acute phase of ACS. Also, in patients with pacemakers the changes in repolarization, especially ST elevation, may suggest ACS [52]. In the chronic phase of myocardial infarction the presence of a spike qR pattern, especially in V5–V6, is a highly specific but poorly sensitive sign of necrosis.

Value of the ECG in special conditions [1,4,14]

The most characteristic ECG patterns in different clinical conditions, such as electrolyte imbalance, hypothermia and in athletes, are shown in Fig. 1.33.

ECG patterns associated with sudden cardiac death

Figure 1.34 shows the most characteristic ECG patterns in genetically induced conditions that may trigger sudden death, such as long QT syndrome, Brugada's syndrome and arrhythmogenic right ventricular dysplasia. Hypertrophic cardiomyopathy is often associated with an ECG showing left ventricular hypertrophy without clear differentiation from other causes of left ventricular hypertrophy. However, a typical ECG pattern is sometimes present (Fig. 1.34).

ECG of macroscopic electrical alternans [1]

Alternans of ECG morphologies is diagnosed when there are repetitive changes in the morphology of alternate QRS complexes, ST segments or rarely P waves. The presence of definite QRS alternans during sinus rhythm

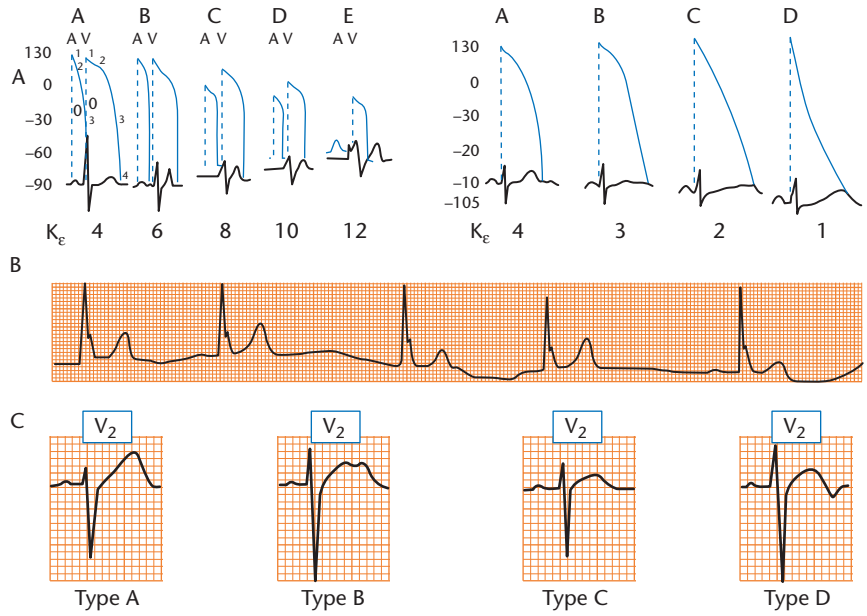


Figure 1.33 ECG patterns in (A) hyperkalaemia and hypokalaemia (see different patterns at different levels of K^+); (B) hypothermia (note the Osborne or 'J' wave at the end of the QRS and bradycardia with different repolarization abnormalities); (C) athletes without evidence of heart disease.

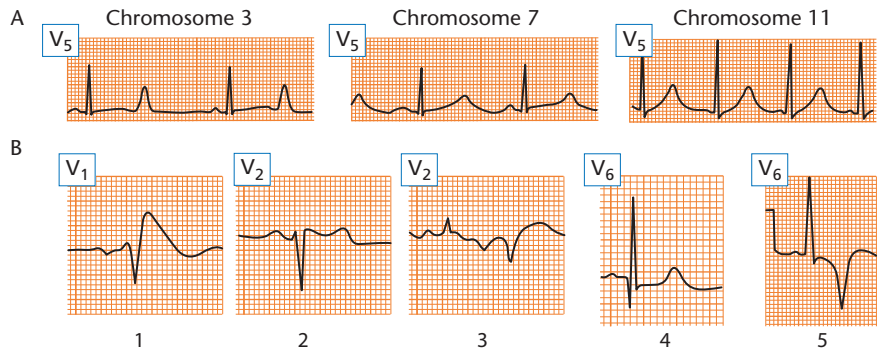


Figure 1.34 Other ECG patterns associated with sudden cardiac death. (A) Long QT syndrome related to genetic abnormalities on chromosomes 3, 7 and 11. (B1,2) The Brugada pattern: (1) typical, with coved ST elevation; (2) atypical, with wide r′ and 'saddleback' ST elevation (also a possible normal variant). (B3) Arrhythmogenic right ventricular cardiomyopathy. Note the atypical complete right bundle block, negative T waves in V1–V4 and premature ventricular impulses from the right ventricle. QRS duration is much longer in V1 than in V6. (B4) Typical pattern of a pathological Q wave in a patient with hypertrophic cardiomyopathy. (B5) Typical ECG pattern from a patient with hypertrophic apical cardiomyopathy.

may occasionally be observed in mid-precordial leads, particularly in very thin subjects during respiration. True alternans of QRS complexes (change in morphology without change of width) is suggestive of a large pericardial effusion and sometimes cardiac tamponade (Fig. 1.35A). Alternans of QRS morphology may also be observed during supraventricular arrhythmias, especially in patients with WPW syndrome. True alternans of

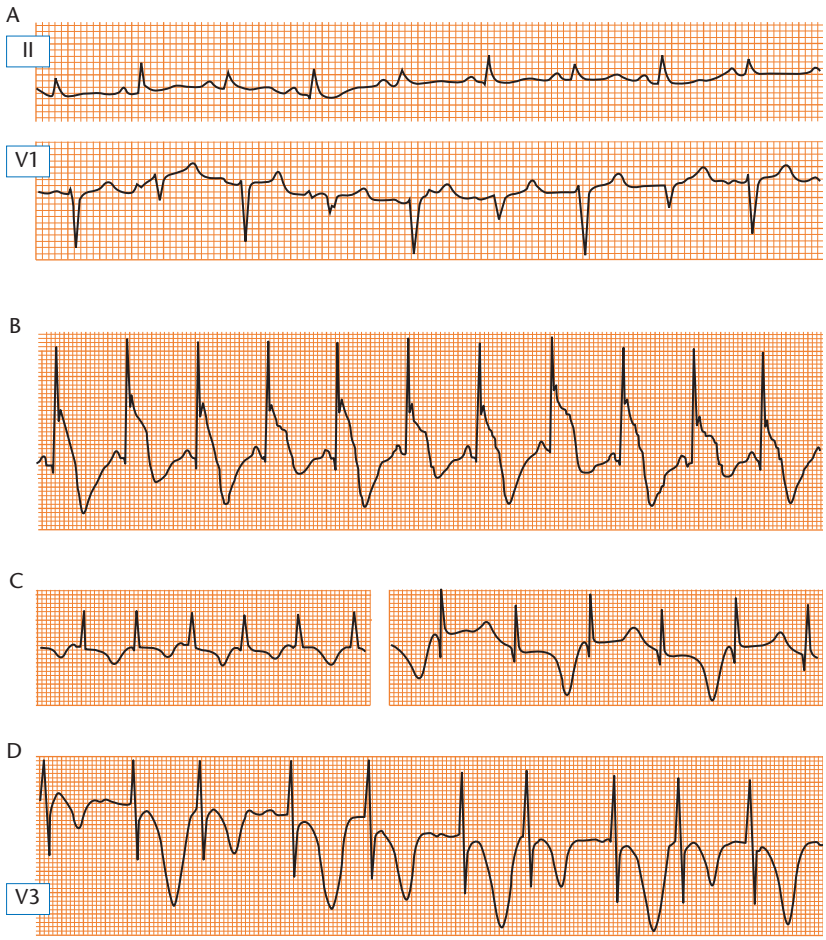


Figure 1.35 Typical examples of electrical alternans: (A) alternans of QRS in a patient with pericardial tamponade; (B) ST–QT alternans in Prinzmetal angina; (C) repolarization alternans in congenital long QT syndrome; (D) repolarization alternans in significant electrolyte imbalance.

QRS complexes can be confused with QRS changes, such as alternating bundle branch block or WPW pattern, with normal conduction. In these situations, two clearly distinct QRS–T morphologies exist with different QRS widths and sometimes with changes in the PR interval.

Alternans of the ST–T components of the ECG may be observed in the hyperacute phase of severe myocardial ischaemia (Fig. 1.35B), in congenital long QT syndrome (Fig. 1.35C) and with significant electrolyte imbalance (Fig. 1.35D). Techniques now exist to detect microvolt T-wave alternans, which are potentially important for risk stratification [54–57].

Incorrect electrode placement and cable connection

Reversal of the left arm, right arm or left leg electrode

The most common technical errors are incorrect cable connections to the peripheral electrodes. Table 1.10 presents the changes in the peripheral leads resulting from incorrect connection of the right arm, left arm and left leg electrode cables.

Most frequently, the left arm and right arm electrode cables are reversed. The mistake is easily recognizable during sinus rhythm by the presence of a negative P wave in lead I in the absence of other ECG signs of dextrocardia, such as mostly negative QRS complexes in leads V3–V6 (Fig. 1.36) [58]. The T wave may or may not be inverted depending on the underlying pathology. In the presence of atrial fibrillation, if the QRS complex in lead I is inverted compared with the QRS in lead V6, the arm electrodes have likely been reversed [59].

Reversal of the right arm and left leg electrode cables produces an ECG pattern that might resemble inferior myocardial infarction as aVF has the appearances of aVR. This technical error can also be suspected from an inverted P wave in aVF.

Reversal of the left arm and left leg electrodes is difficult to recognize, unless a previously recorded ECG is available for comparison [58–60]. In the presence of some ECG abnormalities, this technical error might be more easily suspected than in a normal ECG, e.g. during atrial flutter by the appearance of saw-tooth flutter waves in leads I, III and aVL but not lead II [58].

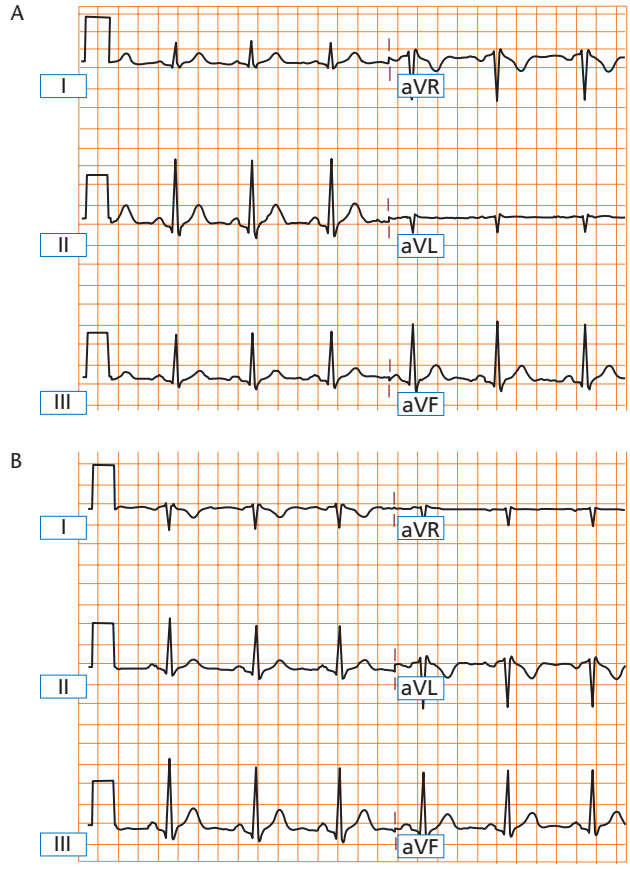


Figure 1.36 Limb leads of a 12-lead ECG recorded with correct cable connections (A) and after intentional reversal of the left arm and right arm electrode cables (B).

Table 1.10 Changes in the six peripheral leads resulting from errors in connecting the right arm, left arm and left leg cables

	Lead*					
Reversal	**'I'**	**'II'**	**'III'**	**'aVR'**	**'aVL'**	**'aVF'**
Left arm–right arm	Inverted I	III	II	aVL	aVR	Unchanged
Left arm–left leg	II	I	Inverted III	Unchanged	aVF	aVL
Right arm–left leg	Inverted III	Inverted II	Inverted I	aVF	Unchanged	aVR

*The leads as they appear in the ECG recorded with wrong connections.

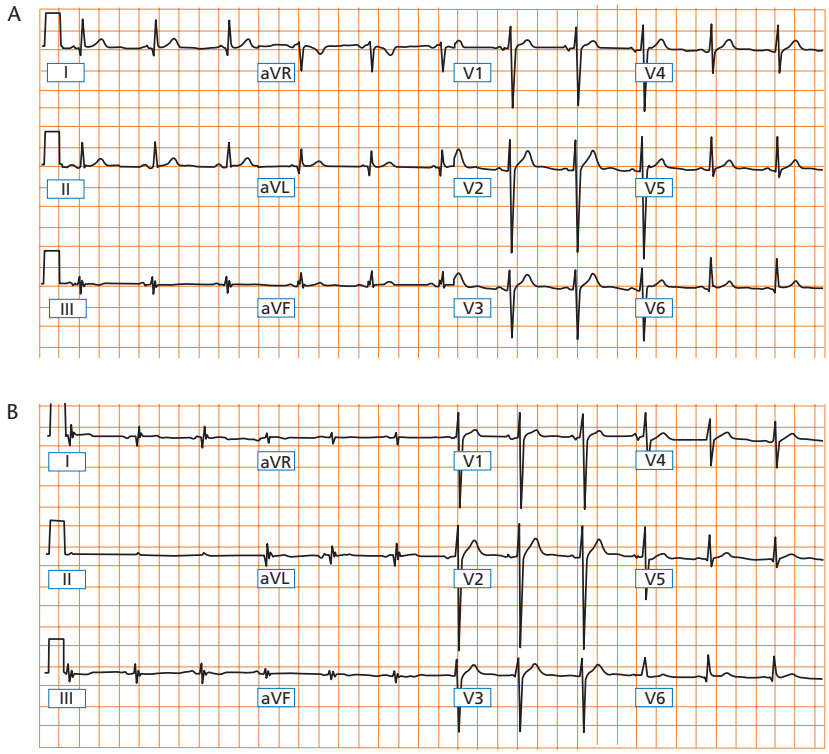


Figure 1.37 Standard 12-lead ECG recorded with correct cable connections (A) and after intentional reversal of the right arm and right leg electrode cables (B).

Incorrect connections of the right leg (ground) electrode

The ground electrode, which is placed on the right leg by convention, can be positioned anywhere on the body without affecting the ECG waveforms. However, when the ground electrode cable is interchanged with the right arm or left arm electrode cables, significant changes occur in both the morphology and amplitude of most peripheral leads [58–61]. Three possible lead reversals are of practical importance: right arm–right leg reversal (the most frequent), left arm–right leg reversal, and interchange of both leg cables with the corresponding arm cables. Reversal of the right and left leg electrodes does not change the ECG noticeably, because the potential at both legs is practically the same.

The hallmark of these misplacements is that one standard lead (I, II or III) shows almost a straight line (potential difference between both legs). When the right arm and right leg cables are reversed, this is seen in lead II (Fig. 1.37), whereas with left arm and right leg cable reversal, it is seen in lead III. Likewise, when both leg electrode cables are switched with the corresponding arm cables, lead I shows a very low potential [61]. Importantly, the central terminal is affected by these three connection errors. This may lead to visible changes in the precordial leads [58].

Errors in connection of precordial electrodes

Interchange of precordial cables is a common technical error that is usually easy to spot. It may be suspected if the transition of the P wave, QRS complex and T wave is unexplainable [58], for example lower amplitude of R wave and deeper S wave in V3 compared with V2 when V2 and V3 cables are reversed, or lack of the normal increase in amplitude of the T wave from V2 to V3 to V4, etc. [59].

Incorrect electrode placement

Incorrect (and hence most likely variable and inconsistent) placement of the precordial electrodes is a well-recognized and important source of inaccuracy [62]. It has been repeatedly shown that a change in the precordial electrode positions by as little as 2 cm can produce diagnostically important differences [63–65]. For example, Herman *et al.* [65] have demonstrated that even a 2-cm vertical displacement of the precordial electrodes produced a greater than 25% change in R-wave amplitude in half of their patients, leading to altered R-wave progression in 20% of patients and a shift in the precordial transition zone in 75%.

Precordial electrode displacement of such magnitude often occurs even when experienced clinicians or ECG

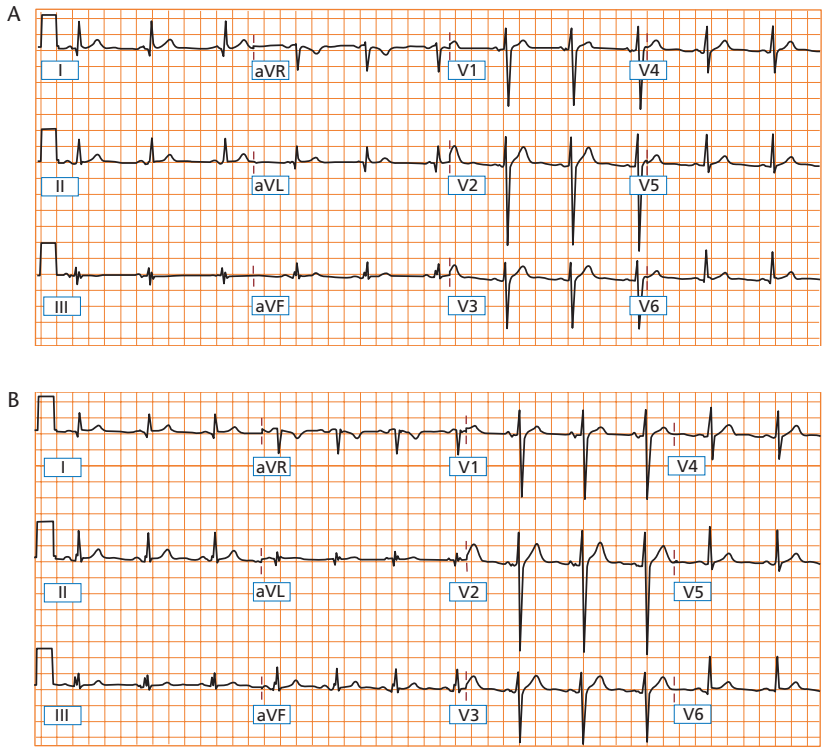


Figure 1.38 Standard 12-lead ECG recorded with the peripheral electrodes in the standard position (A) and positioned according to the Mason–Likar system (B).

technicians are recording the ECG [66,67]. Frequent mistakes include positioning V1 and V2 too high, in the third and even in the second instead of the fourth intercostal space, with resultant vertical misplacement of all precordial leads, excessively wide separation of V1 and V2, and placement of V4 and V5 too low and too lateral [66]. When V1 and V2 are placed one or more intercostal spaces higher, they tend to show an rSr′ configuration with inverted P and T waves, resembling incomplete RBBB.

There is still no universal agreement [68–70] about whether the precordial electrodes in female patients should be placed underneath or on top of the left breast. However, when the electrodes are placed over the left breast instead of beneath it, they are likely vertically displaced. In general submammary placement is recommended.

It is common practice in many centres to attach the arm electrodes above the wrists (forearms, upper arms) or above the ankles, in the belief either that it makes no difference where exactly on the limb they are placed or that it decreases the noise. However, it has been shown that there is a small potential difference between the upper arm and the wrists [59–71], and a similar potential difference is likely to exist between the ankles and the upper leg. However, these differences are hardly noticeable to the naked eye and will not affect the clinical (visual) interpretation of the ECG, hence the recommendation of the American Heart Association that 'the electrodes may be placed on any part of the arms or of the left leg as long as they are below the shoulders in the former and below the inguinal fold anteriorly and the gluteal fold posteriorly in the latter' [72].

In exercise electrocardiography and recently in 12-lead ambulatory (Holter) electrocardiography the Mason–Likar electrode system [73] is used, in which the limb leads are moved onto the torso. There are very significant differences between the conventional 12-lead ECG and one recorded using the Mason–Likar electrode system, including rightward shift of the mean QRS axis, reduction of R-wave amplitude in leads I and aVL and significant increase in R wave in leads II, III and aVF (Fig. 1.38). The precordial leads are also affected because of the altered potential of the central terminal [74].

Ventricular signal-averaged electrocardiography

Signal-averaged electrocardiography (SAECG) is the most widely used method of high-resolution electrocardiography and aims to record cardiac signals from

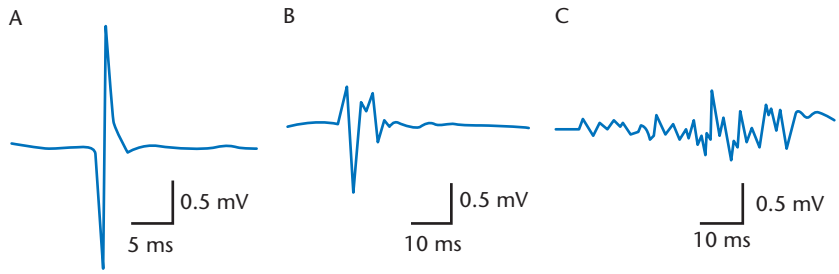


Figure 1.39 Development of low-amplitude fractionated electrograms in experimental models of myocardial infarction in canine hearts. Bipolar subepicardial electrograms are shown recorded from (A) a non-infarcted preparation, (B) 5-day-old infarction and (C) 2-month-old infarction. The low-amplitude fractionated electrograms shown in (C) reflect zones of abnormal conduction, which represent a substrate for the development of re-entrant arrhythmias. These can be recorded as late potentials on the signal-averaged ECG. Reproduced with permission from Gardner *et al*. [80].

the body surface that are not visible or apparent from the standard ECG [75]. In its most popular form, ventricular SAECG uses temporal averaging in order to improve the signal-to-noise ratio and enable the detection of low-amplitude potentials usually outlasting the QRS complex (so-called 'late potentials') [75–77]. Late potentials on SAECG reflect low-amplitude fractionated electrograms generated by surviving myocardial fibres within or surrounding regions of myocardial infarction (less frequently by other forms of ischaemic heart disease or other cardiac diseases) that are activated after a delay and thus create a substrate for re-entrant ventricular arrhythmias (Fig. 1.39) [78–80].

The SAECG is recorded using orthogonal bipolar XYZ ECG leads, which are averaged, filtered and combined into a vector magnitude called the filtered QRS complex. The most frequently used time-domain analysis (Fig. 1.39) of the filtered QRS complex includes:

1 filtered QRS duration;
2 root-mean-square voltage of the terminal 40 ms of the filtered QRS (RMS40);
3 duration that the filtered QRS complex remains < 40 μV (LAS).

The abnormal SAECG recorded with a 40-Hz high-pass filter (i.e. the presence of late potentials) is characterized by a filtered QRS complex > 114 ms, RMS40 < 20 μV and LAS > 38 ms [76,81], of which the most important is the prolonged filtered QRS duration (Figs 1.40 and 1.41) [82].

The ventricular SAECG is most frequently used in patients recovering from myocardial infarction. Studies during the 1980s showed that late potentials are recorded much more frequently (in up to 93%) in patients recovering from myocardial infarction who develop sustained ventricular arrhythmias or sudden cardiac death. Although the presence of late potentials is not a highly specific or sensitive marker of sudden cardiac death, SAECG was considered a useful test, alone or in combination with other risk factors, for prediction of arrhythmic events in patients recovering from myocardial infarction because of its high (up to 97%) negative predictive value despite its very low (about 20%) positive predictive value [75,83].

The widespread use of thrombolysis/revascularization, beta-blockers and other advances in the treatment of myocardial infarction during the 1990s considerably decreased the rate of sudden cardiac death and sustained ventricular arrhythmias [84] and reduced the prevalence of late potentials following myocardial infarction [85]. Recent large studies on patients receiving modern treat-

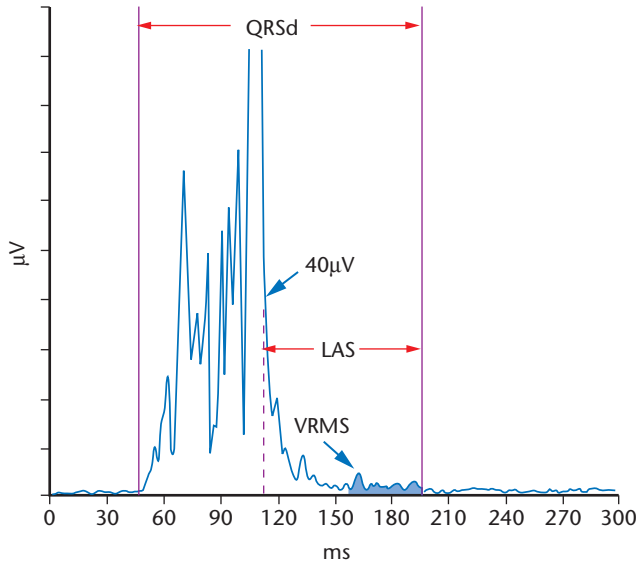


Figure 1.40 Schematic presentation of the three parameters that characterize the filtered QRS complex of the ventricular signal-averaged ECG. Note the low noise level of all three recordings.

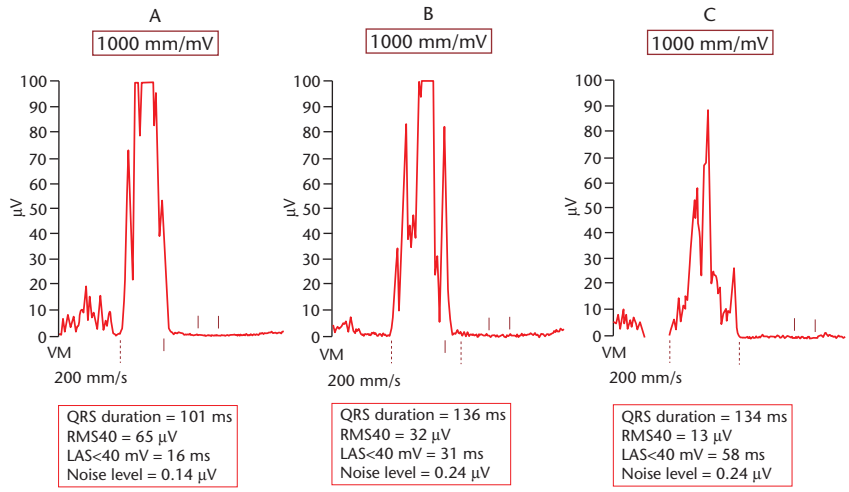


Figure 1.41 Examples of normal and abnormal ventricular signal-averaged ECG (SAECG). (A) Normal SAECG. (B) SAECG recorded in a 67-year-old man with mild heart failure and no history of arrhythmias. Only the filtered QRS duration is prolonged. (C) A clearly abnormal SAECG recorded in a man with severe heart failure. Note that all three parameters of the filtered QRS are abnormal.

ment after myocardial infarction demonstrated greatly reduced predictive power of SAECG for sudden cardiac death following myocardial infarction [86]. Nonetheless, a recently published substudy of the Multicenter Unsustained Tachycardia Trial (MUSTT) [87] demonstrated that in patients with ischaemic heart disease, left ventricular ejection fraction < 40% and non-sustained ventricular tachycardia, a filtered QRS duration > 114 ms was an independent predictor of cardiac and arrhythmic mortality. Because of its high negative predictive value (> 90%), SAECG is considered useful in the management of patients with syncope of unknown cause and ischaemic heart disease [75].

The value of SAECG in non-ischaemic cardiac diseases is less well investigated and established. Late potentials have been shown to independently predict adverse outcome in patients with non-ischaemic dilated cardiomyopathy in some studies [88] but not in others [89]. Although late potentials are more frequently recorded in patients with hypertrophic cardiomyopathy compared with healthy subjects, SAECG does not seem to have practical value for prediction of arrhythmic events in these patients [90]. Due to the localized character of the conduction abnormalities, SAECG can be useful as an additional diagnostic test in arrhythmogenic right ventricular cardiomyopathy [91].

In addition to time-domain analysis, other methods of analysis of the SAECG, such as spectrotemporal analysis [92,93], spectral turbulence analysis [94] and methods of high-resolution electrocardiography not based on temporal averaging (e.g. spatial averaging, which enables beat-to-beat analysis of late potentials [95]), have also been proposed but their clinical applicability is still unknown.

Atrial signal-averaged electrocardiography

Signal-averaged electrocardiography of the P wave (P-SAECG) was developed during the 1990s [96,97] as a result of growing awareness of the enormous clinical and socioeconomic significance of atrial fibrillation (AF) and hence of the need for simple and easily applicable methods for prediction of its occurrence or recurrence. Similarly to ventricular SAECG, the goal of P-SAECG is to detect and quantify intra-atrial conduction defects, one of the main factors for development of AF, which cannot simply be discerned from the shape and duration of the P wave on the standard ECG [98,99].

At present, most clinical studies have been performed using time-domain analysis of the P-SAECG. Similarly to ventricular SAECG, the filtered X, Y and Z leads are combined into a vector magnitude, and the latter is characterized by a set of parameters, such as the filtered P-wave duration, the integral of the P wave and the amplitude (RMS voltage) in different segments (e.g. the last 10, 20 or 30 ms) [96].

Several studies have demonstrated that the preoperatively assessed P-SAECG (mainly increased signal-averaged P-wave duration) independently predicts occurrence of AF following coronary artery bypass surgery [100–104]. P-SAECG has been shown to be useful for identifying patients at risk of transition from paroxysmal to sustained forms of AF [105], for prediction of AF recurrence after cardioversion [106,107], for prediction of paroxysmal AF in patients with congestive heart failure [108] and for assessment of antiarrhythmic drug efficacy for prophylaxis of paroxysmal AF [109].

A limited number of studies suggest that spectral analysis of the P-SAECG can provide additional information to the standard time-domain methods, but its clinical value is still unknown.

Microvolt T-wave alternans

Visible variations of the shape, amplitude or polarity of the T wave on an alternate-beat basis, described as T-wave alternans, have been recognized as a harbinger of ventricular arrhythmias in many clinical conditions, such as congenital long QT syndrome, myocardial ischaemia, electrolyte disturbance and toxic myocarditis [110–112]. In the 1980s, progress in computerized electrocardiography and signal processing led to the discovery, and routine clinical assessment, of microvolt (a few milliseconds) T-wave alternans (MTWA) induced by an increase in heart rate and invisible to the naked eye [113]. Subsequently, experimental studies demonstrated that MTWA is caused by non-uniform alterations (sequential shortening and lengthening) of action potential duration in different parts of the myocardium, which produce repolarization gradients that alternate in magnitude and direction on every other beat and thus create conditions for re-entry [114,115].

The methodology of measurement, the technical aspects and the interpretation of MTWA tests have recently been reviewed in detail (Fig. 1.42) [116]. Whilst early clinical studies used invasive atrial pacing in order to achieve the necessary increase in heart rate [117], currently MTWA is assessed using bicycle or treadmill exercise. Hohnloser *et al*. [118] demonstrated that the two methods were equivalent, both in terms of average heart rate at which MTWA becomes detectable and in terms of diagnostic yield.

During the last decade, a number of clinical studies have demonstrated a strong link between abnormal MTWA and arrhythmic events including sudden cardiac death in different cardiac patient populations [119,120]. Abnormal MTWA has been shown to strongly predict inducibility of ventricular tachycardia or ventricular fibrillation during electrophysiological study [121,122] and all-cause mortality [123] or arrhythmic events in patients recovering after myocardial infarction [124,125] and in those with dilated cardiomyopathy [126,127], Brugada's syndrome [128], non-ischaemic cardiomyopathy [129] or heart failure [130].

Three recent studies have demonstrated that MTWA testing can identify patients at high risk of arrhythmic death who might benefit from an implantable cardioverter-defibrillator (ICD) within the population of patients with left ventricular dysfunction after myocardial infarction (MADIT II type patients). In a meta-analysis of patients drawn from two previously published prospective studies on MTWA, Hohnloser *et al*. [131] reported a 15.6% rate of cardiac arrest or sudden cardiac death during a follow-up of 24 months in patients who tested positive or indeterminate (non-negative) for MTWA compared with no events in MTWA-negative patients ($P = 0.02$). Chow *et al*. [132] followed up similar patients for 18 months and reported an 11.8% rate of arrhythmic events (arrhythmic death, resuscitated cardiac arrest, or appropriate ICD discharge) among MTWA-positive patients compared with 2.0% among those who were MTWA negative (relative risk 6.0, $P = 0.035$). Bloomfield *et al*. [133] reported that the actuarial 2-year all-cause mortality rate of patients with abnormal (positive or indeterminate) MTWA was 17.8% compared with 3.2% of patients with negative MTWA (hazard ratio 4.8, $P = 0.02$). The mortality rate of patients with negative MTWA was only 3.8% (3.5% false-negative tests), which suggests that the test could be used for identifying MADIT II type patients who are at low arrhythmic risk and unlikely to benefit from an ICD.

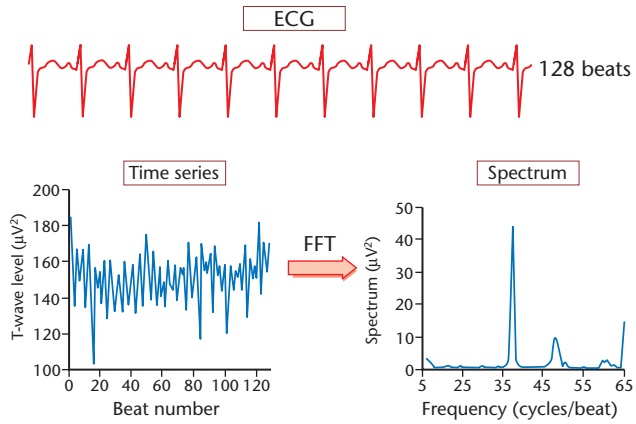


Figure 1.42 Principles of spectral analysis of microvolt T-wave alternans. The amplitudes of the T waves of 128 consecutive beats are measured and a time series consisting of these 128 amplitudes is constructed. The power spectrum of this time series is computed using fast Fourier transform (FFT) analysis. In the power spectrum obtained from recordings during bicycle exercise, peaks corresponding to frequencies of respiration, pedalling and alternans are shown. Microvolt T-wave alternans appears as a peak at half the beat frequency (0.5 cycles/beat). The amplitude of this peak is compared with the mean and standard deviation of the spectrum in a reference 'noise band'. Reprinted with permission from Cohen RJ. TWA and Laplacian imaging. In: Zipes DP, Jalife J (eds) *Cardiac Electrophysiology: From Cell to Bedside*, 2000. Philadelphia: WB Saunders, pp. 781–789.

Personal perspective

It is said by some that the 12-lead ECG could be reduced to a report and the trace itself omitted. For example, in many hospitals it is customary to receive nuclear scintigram reports and even radiography reports without copies of the images themselves. These experiences naturally frustrate most cardiologists, who would like to see the 'raw data' on which others have commented in order that they can make decisions relevant to the life and livelihood of their patients. Analysing the ECG or other images, especially as medical informatics and information technology improves, should not be a technical problem and the cardiologist should insist upon this. Examining the quality of the image, assessing the accuracy and confidence of the report, and assembling multiple images, technical information and patients' details are crucial to modern medicine.

Although electrocardiography is a well-established technique, the refinement of computer interpretation algorithms, improvements in recording technology and the development of completely new techniques (such as T-wave alternans, implantable ECG rhythm and ST-segment surveillance and logging, and very long-term wearable monitoring systems) will continue to evolve. High-resolution electrocardiography, for detecting early disease, discerning the effects of medications on the ECG and the prediction of electrical instability of the heart, will continue to develop. Web-based, ECG-related, patient-accessed systems will become more popular world-wide.

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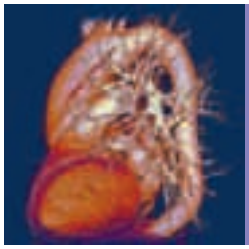

2 Cardiac Ultrasound

Jos Roelandt and Raimund Erbel

Summary

Cardiac ultrasound is a sophisticated imaging modality that has made unique contributions to our understanding of cardiac disease. It allows the cardiologist to observe the heart and to obtain an integrated non-invasive assessment of its structure, function and haemodynamics by simply manipulating a transducer without exposing the patient to any risk. Portability and unprecedented versatility of application are other reasons for its success. Consequently, the method has had an enormous impact on the practice of cardiology. However, the technique is operator-dependent and the performance of an echocardiographic/Doppler examination is therefore related to appropriate training and the cognitive and practical skills of the examiner. Obviously, this relatively short chapter cannot be more than a starting point and is only a frame of reference for learning echocardiography. We provide a cursory description of the physical principles, the instrumentation and the examination using the many diagnostic modalities. The application of echocardiographic/Doppler techniques in specific cardiac conditions and more particularly for myocardial and valve function assessment is also presented. Because of the rapid developments and new applications, for example real-time three-dimensional echocardiography and strain rate imaging, it is mandatory to continuously update knowledge and practical skills.

Principles of echocardiography

Echocardiographic and Doppler examinations require a thorough knowledge of the underlying physical principles, instrumentation and recording techniques. A comprehensive overview of the basic principles pertinent to echocardiographic/Doppler assessment is presented in this chapter. Echocardiography encompasses a group of tests that use ultrasound to examine the heart and obtain diagnostic data in the form of echoes. Ultrasound is a mechanical radiation that requires a medium in order to travel from one point to another by alternate compression and rarefaction. It refers to sound waves of a frequency above the range audible to humans (> 20 000 Hz); in cardiology, frequencies of 2–7 MHz are employed.

Transducers

In order to generate ultrasound waves, piezoelectric crystalline material is used in a transducer that converts electrical energy to mechanical energy (ultrasound) and vice versa [1]. The diagnostic potential of ultrasound waves is the result of their partial reflections when they strike boundaries between media of different acoustic impedances. The difference in density and sound speed is referred to as acoustic impedance mismatch and arises from the difference in structural composition at the boundary. The larger this difference, the stronger the echo reflected from the boundary. Because more than 99% of the ultrasound energy is reflected at the air–tissue boundary, a coupling gel is used between the transducer and skin that causes more than 99% of the energy to be transmitted into the body. Other factors that contribute to the strength of echoes are the angle of incidence, the irregularity of the boundary surface (scattering), the size of the interface relative to the wavelength of the

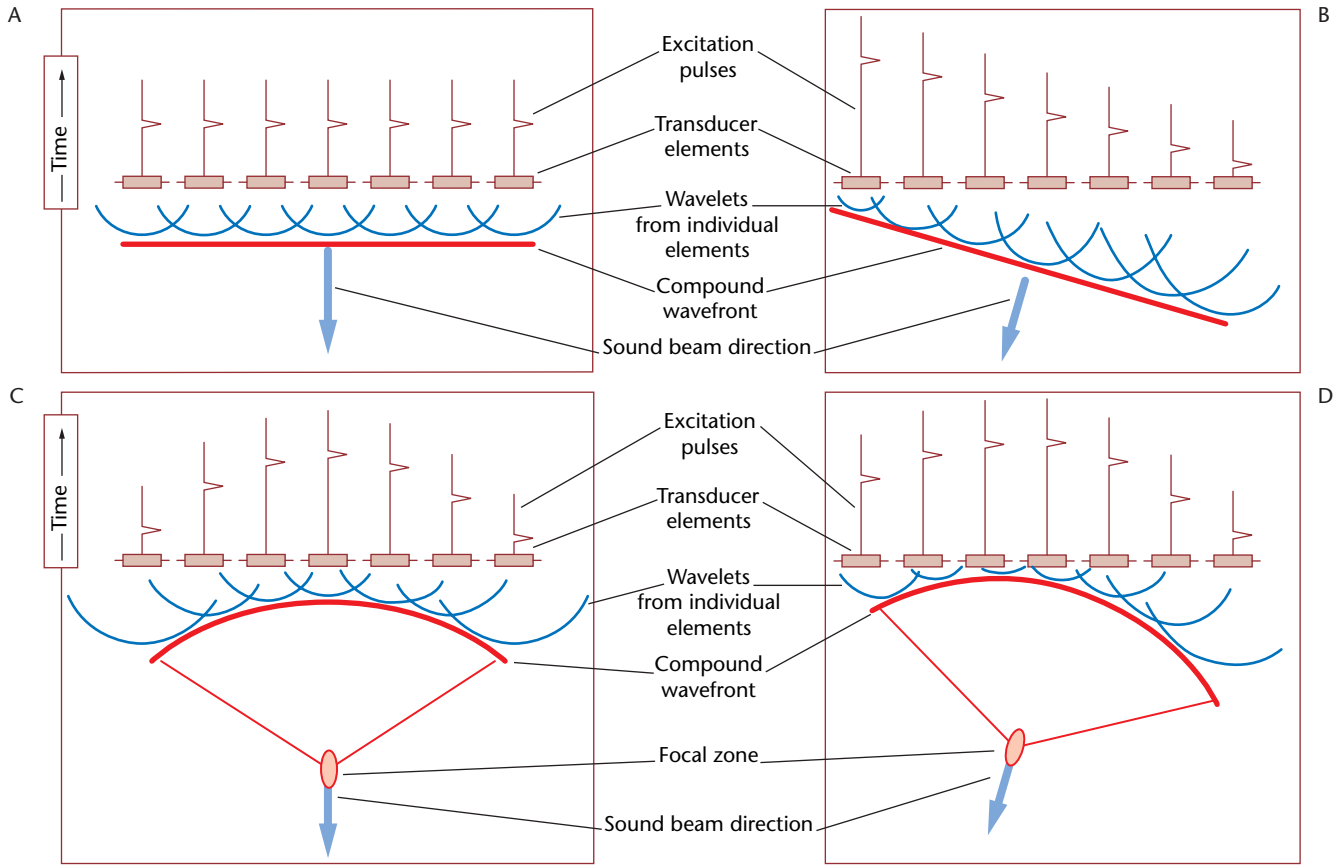

Figure 2.1 The concept of electronic beam steering. (A) Seven elements of a phased-array transducer firing simultaneously. A short distance from the transducer the individual wavelets from each of the elements merge to produce a compound wavefront, which creates a sound beam in the direction perpendicular to the transducer face. (B) The elements are now fired in sequence but are all used to create a single sound beam. When the individual wavelets merge to form a compound wavefront, it is not perpendicular and the sound beam travels away at an angle. Varying the excitation sequence allows rapid steering of a sound beam in any direction through a sector. (C) Electronic beam focusing is realized by exciting the peripheral elements first and the centre element last (cylindrical time-gated excitation). In addition to focusing the transmitted sound beam, it is also possible to focus the returning signals so that at any one instant the transducer array is selectively receiving only those echoes coming from a specified beam direction and depth (dynamic receive focusing). This requires very complicated electronics. (D) The principle of cylindrical time-gated excitation can be used to steer and focus sound beams in any direction during both transmission and reception.

ultrasound and the distance causing attenuation. Therefore, echo signals from deeper structures must be amplified much more than those from nearer structures (time-gain amplification).

Ultrasound waves of relatively low frequency (2 MHz) penetrate to deep structures and are used in adults. In contrast, higher frequencies (5–7 MHz) have less penetration but better axial resolution and are used in paediatric applications. The currently used broadband transducers incorporate multiple frequencies (2–7 MHz), allowing better resolution of structures distant from the transducer. The width of the ultrasound beam is a function of transducer size and operating frequency and determines the lateral resolution or the ability to distinguish two adjacent structures in the direction perpendicular to the sound beam axis. The power density used in diagnostic ultrasound applications is well within accepted limits of safety [2,3].

In ultrasound systems, the level of ultrasound pressure and possible mechanical effects is expressed as the mechanical index (MI) [4].

Phased-array transducers

All modern ultrasound systems make use of phased-array transducers, which create and steer the ultrasound beams [5,6]. These transducers consist of a set of 128 small piezoelectric elements, which have separate electrical connections and are all used at any given time to transmit ultrasound pulses and to receive echoes. The individual elements are electronically excited at a slight different time delay so that the electronic wavefront produced by each

of these elements interferes to synthesize a beam that is directed in a given direction (Fig. 2.1A,B). Hence, the beam is steerable. This approach generates the triangle sector typically seen on the display of ultrasound machines.

Adjusting the time delays allows the ultrasound beam to be dynamically focused during transmission and reception so that at any one instant in time the transducer is selectively receiving only those echoes coming from a specified direction and depth. This is achieved by sequentially firing the outer crystals first and the centre crystals last (Fig. 2.1C and D).

Recently, matrix phased-array transducers have become available with up to 3000 individual elements, which are capable of providing real-time pyramidal volumetric imaging [7].

Parallel processing

Traditionally, sequential single scan lines have created two-dimensional images, which has limited the frame rate. With phased-array transducers it is possible to transmit multiple sound beams simultaneously in different directions by activating the individual crystals in a very complex manner. The echoes from each of these sound beams are independently analysed by a separate signal processing circuitry (parallel processing). Parallel processing allows a significant increase in frame rate for both two- and three-dimensional echocardiography and tissue Doppler imaging.

Harmonic imaging

In harmonic imaging, the ultrasound image is created from echoes that have twice (second harmonic) the frequency of the transmitted ultrasound. Harmonic imaging allows suppression of the near-field artefacts and reduces clutter in the image by suppression of side lobe effects. Its use has now become the standard imaging modality and improves endocardial definition both with and without the addition of echo contrast [8].

Integrated backscatter

Myocardial integrated backscatter is the broadband scattering of a region of interest [9]. Its cyclic variation has been used for tissue characterization and more particularly the identification of ischaemic stunned or hibernating but viable myocardium in infarcted areas, transplant rejection and cardiomyopathies. However, the results are not reproducible with currently available processing software. Integrated backscatter is used for automated endocardial border detection and for tracking its motion and velocity in real time (see Acoustic quantification, below).

Principles of ultrasound imaging

Assuming a constant propagation speed of 1540 m/s for ultrasound in soft tissue, measurement of the time taken from transducer to a boundary allows determination of the distance. In fact, part of the sound energy is reflected from each subsequent tissue boundary along the sound beam pathway and consequently distance measurements to all echo-producing boundaries are available from individual pulses. Most instruments transmit ultrasound pulses for 1 μs and receive echoes over the next 999 μs, yielding a sampling rate of 1000/s. If the pulses are emitted in a constant direction repeatedly, an M-mode display results, showing structure motion along a single 'ice pick' through the heart (Fig. 2.2). In contrast, if the ultrasound beam is moved rapidly at a constant speed across a sector of the heart, a two-dimensional image of the heart is created.

M-mode echocardiography

Echoes returning to the transducer are electronically processed to produce three types of oscilloscope display (Fig. 2.2). In 'A-mode', the height or amplitude represents the intensity of the echoes. The distance of the boundary to the transducer is in practice represented on the oscilloscope display on the vertical axis, and 'B-mode' is an intermediate step where A-mode echoes are converted to dots whose brightness indicates the relative intensity of the echoes. B-mode is well suited to production of a record of echo (structure) motion or 'M-mode' [1,5]. This is obtained by emitting the ultrasound pulse in a constant direction repeatedly and sweeping the dots across the display screen or by moving a recording surface at a constant speed past the B-mode display. M-mode display permits recording of both the depth and motion pattern of intracardiac boundaries or structures. The original M-mode studies were performed using a focused single crystal transducer that was aimed in the desired direction. All systems now use phased-array transducers that allow simultaneous sampling of any of the scan lines and which display both the M-mode and two-dimensional cross-section in real time (Figs 2.3–2.5). Measurements are aided by centimetre depth markers, which are displayed on the oscilloscope at calibrated time intervals of 0.5 s. An electrocardiographic tracing is recorded simultaneously for timing purposes.

M-mode echocardiograms have an excellent time resolution and allow detailed analysis of motion patterns, temporal relationships with physiological parameters and time intervals. They will always remain an integral part of a comprehensive study of a cardiac condition (Fig. 2.6).

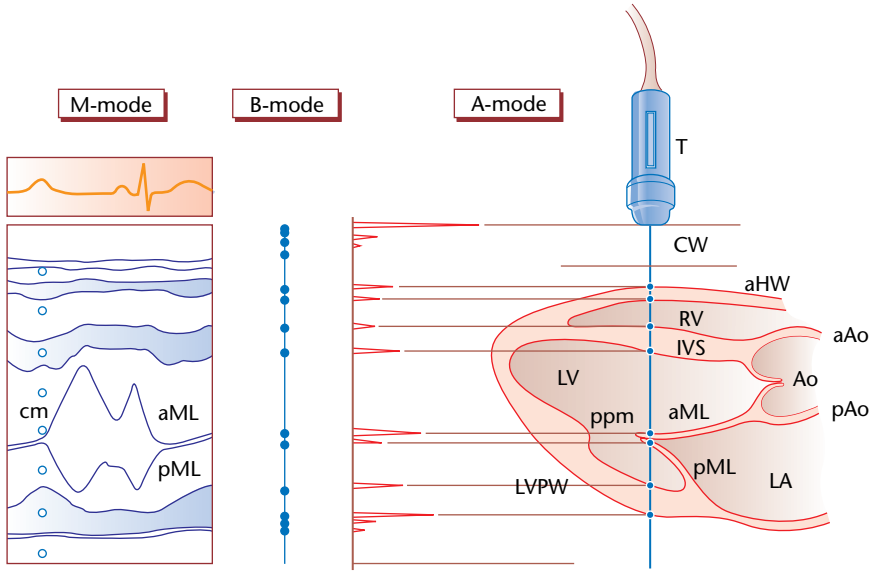

Figure 2.2 Schematic diagram showing the creation of the M-mode echocardiogram. A long-axis cross-section of the heart from base to apex with cardiac structures is shown. The single sound beam produced by the transducer (T) on the chest wall (CW) is aimed so that it traverses from anterior to posterior: anterior heart wall (aHW), right ventricle (RV), interventricular septum (IVS), left ventricular cavity (LV), anterior and posterior mitral valve leaflets (aML and pML) and the posterior wall (LVPW). The echoes originating from the structure boundaries can be represented in three types of oscilloscope display: A-mode, B-mode and M-mode. Ao, aorta; LA, left atrium; aAo and pAo, anterior and posterior aortic wall; ppm, posteromedial papillary muscle.

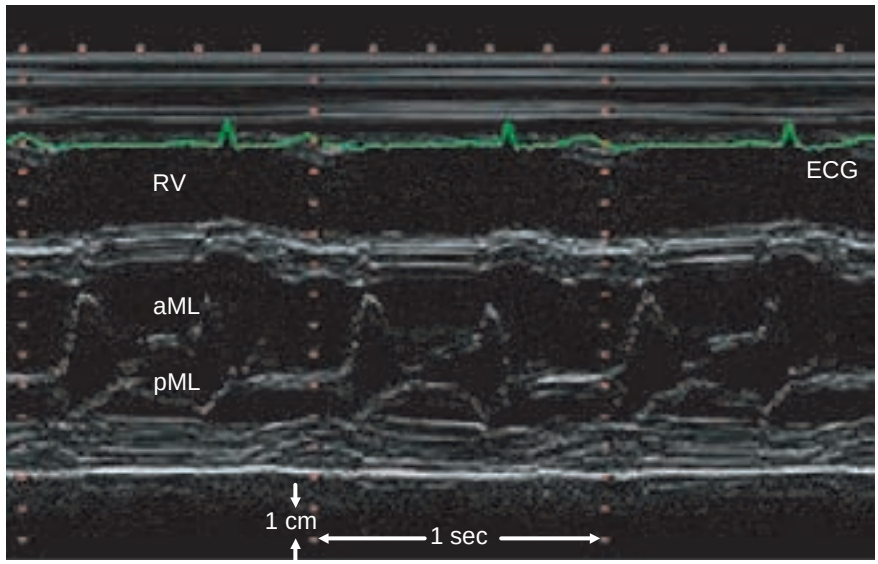

Figure 2.3 M-mode registration of a normal subject showing the structures discussed in Fig. 2.2. The anterior mitral valve leaflet moves anteriorly and the posterior leaflet posteriorly with less excursion but a similar pattern. The recording speed is 50 mm/s. The calibration scale of depth is in centimetres from top to bottom and time in seconds from left to right.

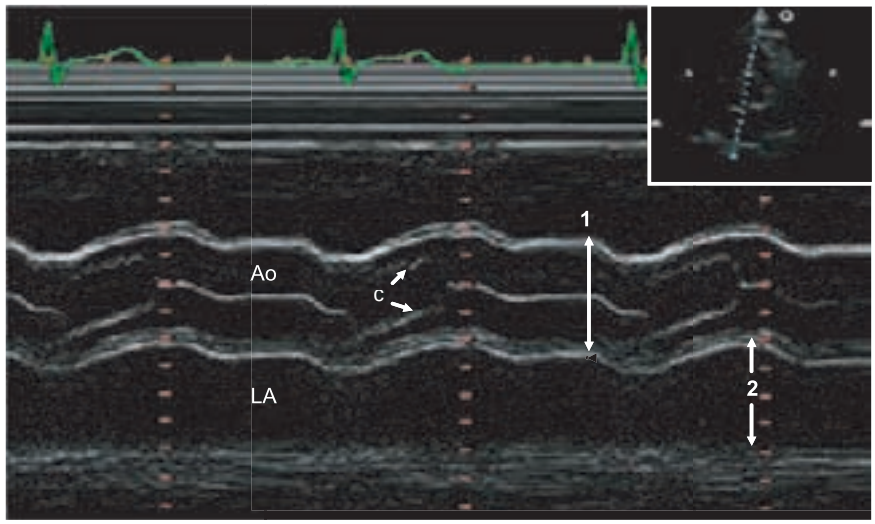

Figure 2.4 Two-dimensional reference image shows the cursor indicating the direction of the sampling sound beam in the short-axis view through the base of the aorta and aortic valve. The aorta (Ao) is seen as two parallel structures moving in an anterior direction in systole. The aortic valve cusps (c) are open in systole and are seen as a single echo when closed in diastole, with the same motion as the aortic walls. The left atrium (LA) is posterior to the aorta. Arrows 1 and 2 indicate the landmarks for diameter measurements (see Table 2.2 and Fig. 2.22).

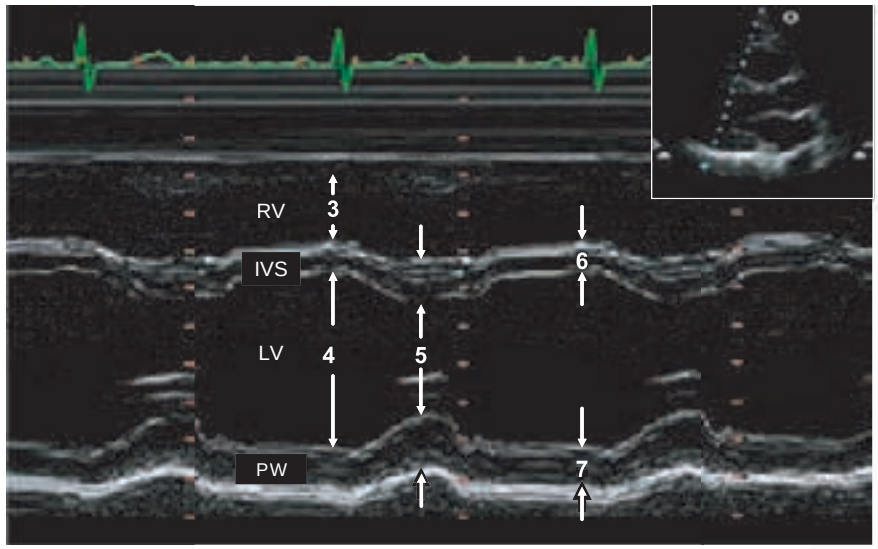

Figure 2.5 M-mode registration of the left ventricle (LV) at the tips of the mitral valve leaflets showing inward motion of the interventricular septum (IVS) and posterior wall (PW) in systole. The cursor in the two-dimensional image shows the direction of the sampling sound beam. The arrows indicate landmarks for diameter measurements of the right ventricle (RV)(3), left ventricular end-diastolic diameter (4), left ventricular end-systolic diameter (5), interventricular septal thickness (6) and posterior wall thickness (7) (see Table 2.2 and Fig. 2.22).

Using the M-scan technique and by sweeping the sound beam from one area of the heart to another while recording, it is possible to derive information concerning the spatial relationship of cardiac structures. However, the need for more accurate spatial information about cardiac structures and function led to the development of real-time two-dimensional imaging systems. Recent digital systems allow M-mode recordings in any direction

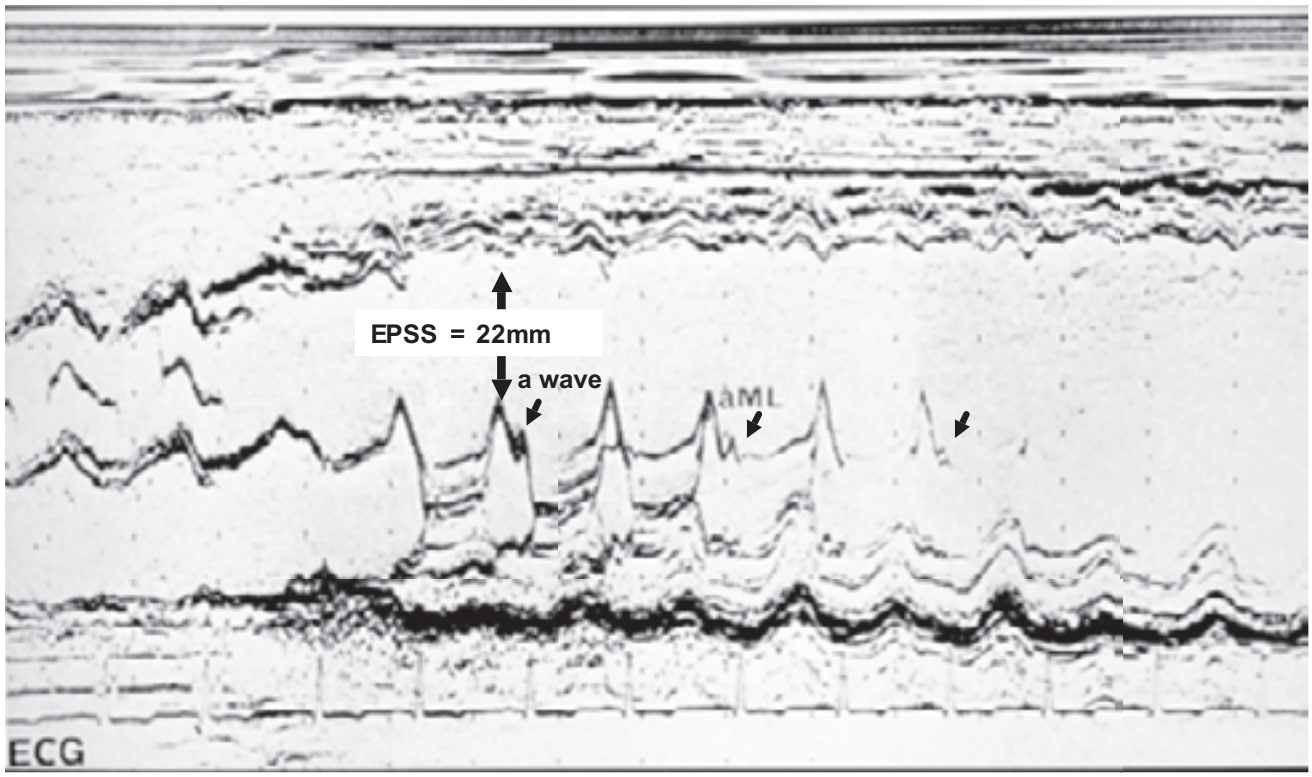

Figure 2.6 M-mode sector scan from aorta towards the left ventricle. The left ventricle is dilated (70 mm). There is an abnormal motion pattern of the interventricular septum and posterior wall showing mechanical alternans. The anterior mitral valve (aML) motion pattern shows alternating presence/absence of the a-wave (arrow) indicating mechanical alternans of the left atrium that is causing the ventricular wall motion abnormality. This detailed analysis requires high temporal resolution and would not be available from two- or three-dimensional echocardiography. Note the mitral E point–septal separation (EPSS) of 22 mm (normal ≤ 7 mm). An increased separation indicates a dilated left ventricle.

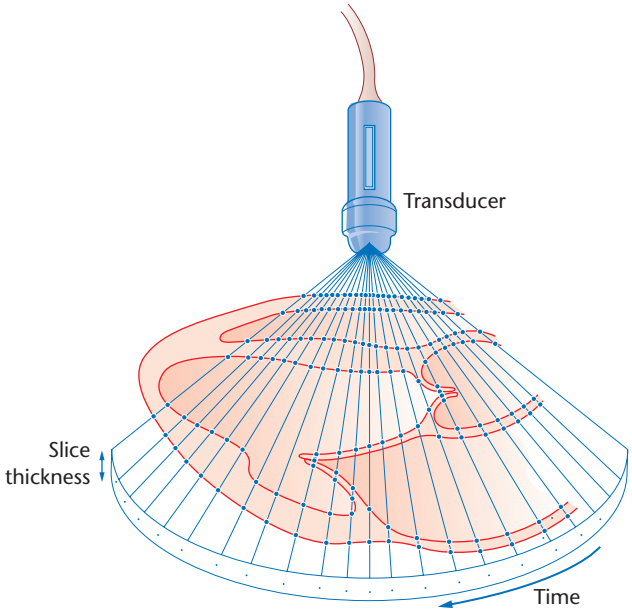

Figure 2.7 How a two-dimensional image of the heart is created. The ultrasound beam is electronically steered through a sector arc of 80° at a uniform speed at an imaging rate of 25/s. The radial scan line data from the transducer are converted into a digital memory matrix (scan converter), which can be frozen and displayed in the horizontal TV/video format. A cursor can be moved over the image to select a scan line to produce an M-mode recording (see Figs 2.2–2.5). The scanning can be stopped either to sample one ultrasound beam direction at a high sampling rate or to intermittently sample for simultaneous M-mode recording at a lower repetition rate and two-dimensional imaging.

independent of transducer orientation to be obtained from the two-dimensional images.

Two-dimensional echocardiography

In modern ultrasound systems the phased-array transducer produces a fan of ultrasound beams, which is used to create a sector-shaped image (Figs 2.7 and 2.8). There is a trade-off between the times taken to create a sector frame, the number of scan lines in the sector frame and the scanning depth because of the limited ultrasound speed of 1540 m/s in tissue. Typically, 25 frames/s are obtained. Parallel processing allows frame rates in excess of 100 frames/s.

Acoustic quantification (colour kinesis)

Acoustic quantification is a real-time automated border detection modality used to identify the blood–endocardial boundary based on their disparate echo signals [10]. It allows continuous real-time display of the endocardial contour of the left ventricle (LV) on a beat-to-beat basis. Colour kinesis allows tracking of endocardial motion velocity in real time (Fig. 2.9). Motion and velocity are captured in a geometric image that shows quantitative information on wall function. Endocardial excursion is mapped in colour schemes on sequential two-dimensional LV images. At a frame rate of 25/s each colour represents a successive 40-ms interval of the contraction period and the thickness of the colour band the endocardial excursion during that interval. This method has advantages for continuous monitoring of regional wall function (e.g. stress echocardiography) but requires excellent image quality and endocardial definition.

Three-dimensional echocardiography

Three-dimensional echocardiography is rapidly becoming an integral part of the echocardiographic examination procedure. The images are more realistic in appearance

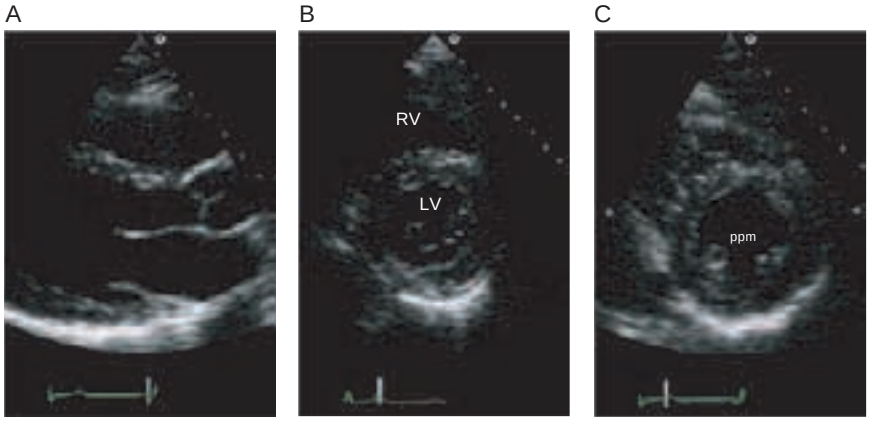

Figure 2.8 (A) Two-dimensional end-diastolic long-axis image of the left ventricle in end-diastole of a normal subject (see Fig. 2.2 for reference). The aortic valve is closed and the mitral leaflets are in an open position. Calibration dots are 1 cm apart. The bar in the ECG indicates the location of the stop frame within the cardiac cycle. Two-dimensional short-axis images of the left ventricle (LV) at mitral valve level (B) and at the level of the papillary muscles (ppm) (C). The left ventricle is circular in shape with discrete structures of the mitral valve in the cavity. The right ventricle (RV) is anterior to the left ventricle.

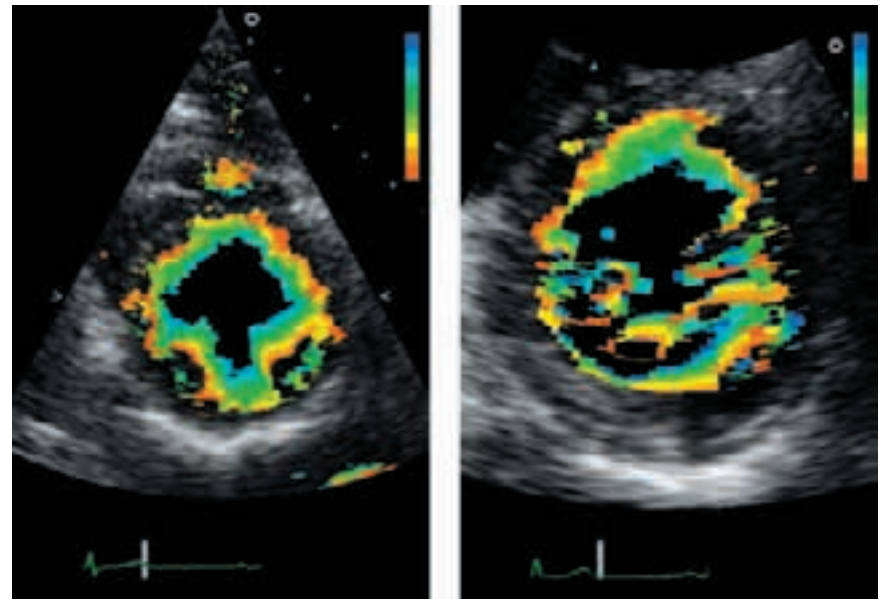

Figure 2.9 (A) Colour kinesis end-systolic image of the left ventricle showing a homogeneous pattern of endocardial inward motion (contraction). There is uniform thickening of the colour bands each indicating a successive interval of 40 ms on a frame-by-frame basis. The thickness of the colour bands represents the degree of endocardial inward motion during that interval. Therefore, this end-systolic frame represents a snapshot of both the amplitude and timing of systolic wall motion. (B) Colour kinesis end-systolic image of a patient with an inferoseptal myocardial infarction. There is thinning of the colour bands in that region indicating decreased wall motion (akinesis) while the increased thickening of the colour bands in the anterior wall indicate compensatory hyperkinesis.

Table 2.1 Three-dimensional echocardiography: the approaches

Off-line reconstruction (spatial and temporal gated image acquisition)
External reference system (freehand scanning)
Mechanical arm
Acoustic (spark gap) locator
Electromagnetic sensor
Internal reference system (predetermined image acquisition)
Linear
Fan-like
Rotational (sequential or continuous)
Real-time volumetric acquisition

and provide spatial information and unique *en face* views, referred to as surgical views. Basically, two approaches have been followed: off-line (gated) reconstruction and real-time volumetric imaging (Table 2.1).

In off-line reconstruction, a volumetric dataset is created by the acquisition of a continuum of two-dimensional images in which both spatial orientation and position in the cardiac cycle are simultaneously registered using either an external (random image acquisition) or internal (sequential image acquisition) coordinate system; a workstation is used to input the images for Cartesian coordinate conversion. It is clear that this process takes time [11].

Over the last 10–15 years, complex matrix-array transducers have been developed that allow real-time acquisition of an entire volumetric dataset. In an earlier system, parallel processing was used where 16 simultaneous receive directions for any given transmit pulse are sampled to allow cardiac motion to be captured in a volumetric dataset [7]. In a recent system, each of the 3000 individual elements of a broadband 2–4 MHz matrix-array transducer is used for both transmission and reception in order to register cardiac motion [12]. This system also provides three-dimensional Doppler flow imaging (Figs 2.10 and 2.11).

Volumetric datasets can be rapidly sliced and rotated to show cardiac anatomy from different viewpoints (Fig. 2.12). These capabilities provide an improved understanding of unpredictable pathomorphology and decrease variability in the interpretation of these abnormalities among investigators. Quantitative methods allow exploitation of the spatial information inherently present in the volumetric dataset for more accurate measurements of surfaces, orifices, volumes of cardiac chambers, masses and shapes than with two-dimensional echocardiography (see Reference values for M-mode and two-dimensional echocardiography, below).

Real-time three-dimensional echocardiography is particularly useful in structural abnormalities such as valvular pathologies and congenital defects and in rapidly changing (patho)physiological states such as transient ischaemic wall motion abnormalities in the setting of stress testing and conditions where short-time examination and rapid results are desirable (e.g. critically ill patients, interventional procedures and small children).

The current limitations of real-time three-dimensional echocardiography systems are their limited spatial and temporal resolution. These limitations will be solved when newer sensitive transducers and the next generation of high-speed processors become available. Three-

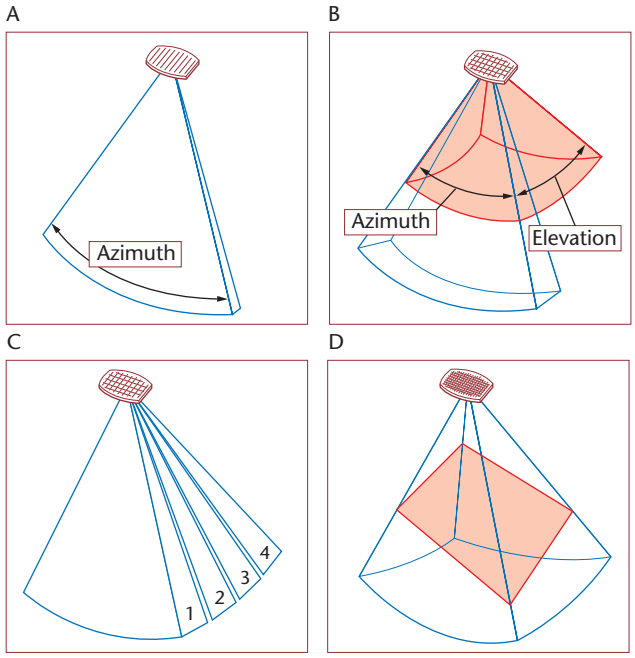

Figure 2.10 Diagrams showing the differences between (A) a single two-dimensional plane obtained with a linear phased-array transducer and (B) a volumetric scan obtained with a matrix phased-array transducer. Because of inherent time limitations of ultrasound speed in tissue, the pyramidal volume is not large enough to acquire the entire volume of the heart or left ventricle in adults. By narrowing the elevation scan angle of the pyramidal volume, a greater depth is achieved (C). Four such subvolumes (1–4) can be acquired using four ECG-triggered heartbeats with respiratory gating or a few seconds of breath-holding. (D) These volumes are then time aligned to render a composite volume encompassing the entire heart or an enlarged left ventricle. This modality is used for left ventricular volume measurement. The volume can be sliced in any direction (C-plane) in addition to perpendicular planes.

dimensional echocardiography, in combination with sophisticated imaging software, data manipulation and new display techniques, will allow unique displays of non-visible dynamic cardiac properties such as elasticity, electrical depolarization, strain and strain rate. These displays are referred to as parametric imaging [13]. Since all imaging information is available in a standardized digital format (DICOM 3.0), it will become possible to exchange clinical data between centres and share expensive facilities for online research between laboratories via ultra-high speed networks.

Another important medical frontier opened by three-dimensional echocardiography is virtual reality, the immersive environment created by a computer. Virtual reality allows the physician to interact with these data and heralds a revolution for medical diagnosis and Internet-based distance learning and treatment, for example by remote robot interventions.

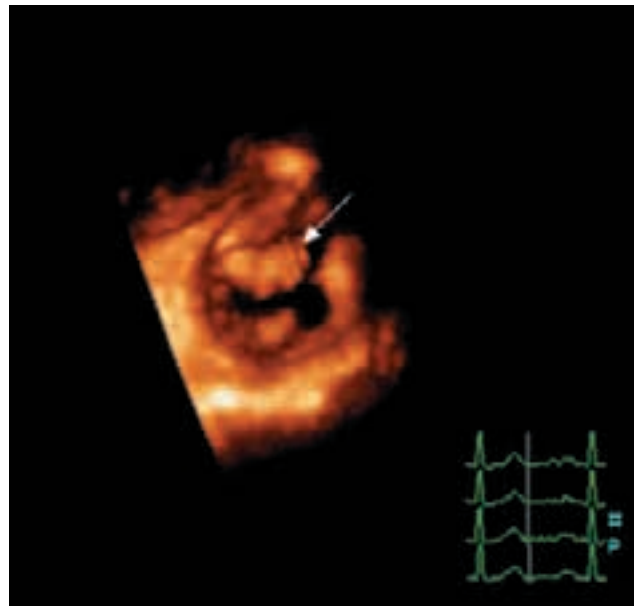

Figure 2.11 Stop-frame image of a patient with mitral valve prolapse seen from a left atrial perspective obtained with a real-time three-dimensional imaging system (surgical view). The arrow indicates the prolapsing anterior mitral valve leaflet.

Hand-held ultrasound systems (ultrasound stethoscopy)

Miniaturization and digital techniques have resulted in the development of high-resolution battery-powered personal imaging devices ranging in size from laptop to almost personal organizer, with excellent grey-scale and colour blood flow imaging capabilities (Fig. 2.13). These devices are appropriately called 'ultrasound stethoscopes' [14]. They extend our physical perception during a clinical examination by 'seeing the invisible pathology', and thus allow assessment of specific clinical problems anywhere and augment the yield of clinical examination at the point of care. In some systems Doppler functions have been integrated to allow basic haemodynamic assessment. Murmurs and abnormal precordial movements can be directly related to cardiac structural, functional and flow abnormalities. A cardiac abnormality (pericardial effusion, dilated heart, valvular disease, mass lesion) is rapidly confirmed during the clinical examination. Often, a specific diagnosis can be made and unsuspected abnormalities found. A major strength is that a limited echocardiographic/Doppler examination may allow exclusion of the cardiac abnormality with great certainty. Overall, they strengthen clinical diagnostic accuracy and

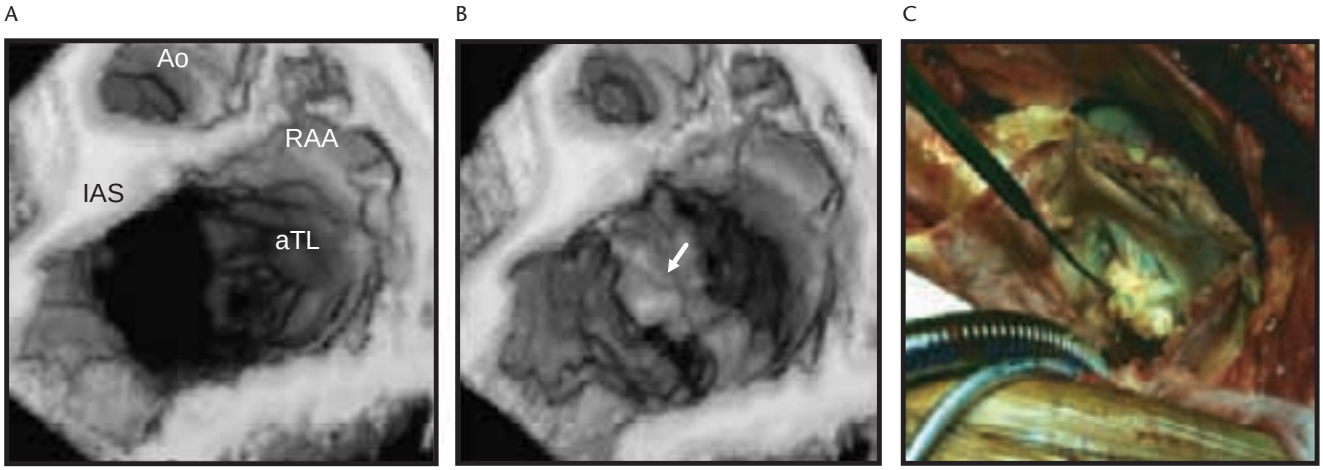

Figure 2.12 Reconstructed three-dimensional images of the tricuspid valve seen from a right atrial perspective. The anterior leaflet (aTL) is flail due to papillary muscle rupture after a car accident. (A) is a diastolic image and (B) shows the anterior leaflet and the flailing papillary muscle (arrow) in the right atrial cavity in systole. (C) is an intraoperative picture showing the flail muscle and leaflet that confirms the three-dimensional findings. Ao, aorta; IAS, interatrial septum; RAA, right atrial appendage.

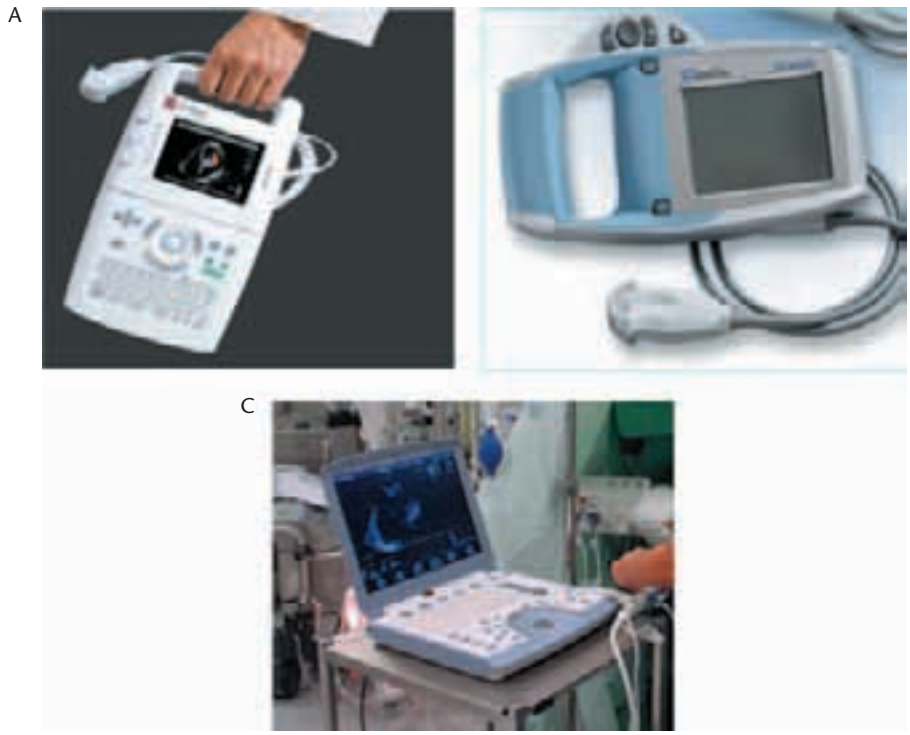

Figure 2.13 Currently available hand-held ultrasonic imaging systems: (A) Sonoheart (Sonosite, Inc.); (B) iLook (Sonosite, Inc.); (C) a recent laptop-based full-featured Vividi (General Electric) system which is available with transthoracic and transoesophageal imaging probes.

add quantitative information. The ultrasound stethoscope is also suitable for a limited 'goal-oriented' examination (e.g. pericardial effusion after pericardiocentesis, ejection fraction, hypertrophy) and can effectively assist in the initial evaluation and rapid diagnosis of potentially life-threatening conditions or situations where quick decision-making is essential (emergent tamponade, low output state, acute valvular pathology, right ventricular involvement, hypovolaemia and mechanical complications of acute myocardial infarction). The ultrasound stethoscope allows rapid screening for occult aortic abdominal aneurysm, LV hypertrophy in patients with hypertension, hypertrophic cardiomyopathy, etc. Ultrasound stethoscopy is a fast-developing field. Micro-miniaturized ultrasound systems have been incorporated in a transducer assembly that connects to a notebook PC and pocket-size

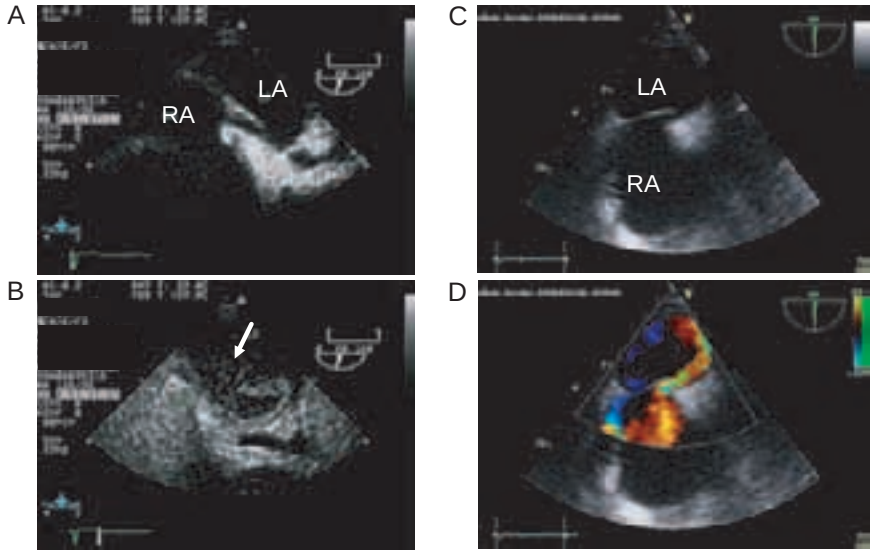

Figure 2.14 Patient with patent foramen ovale (A) before and (B) after intravenous contrast-agitated saline injection. The right atrium (RA) is opacified with contrast, which also appears in the left atrium (LA), proving right-to-left shunting of blood. (C) Patient with a patent foramen ovale and large right-to-left shunting of blood visualized with colour Doppler flow imaging (D).

ultrasound systems based on iPAQ technology are already in use and will soon emerge onto the market.

The small hand-held devices should not be confused with the portable desktop systems, which are full-featured systems with high imaging performance (Fig. 2.13). They integrate most diagnostic functions and are equipped to perform transoesophageal and intracardiac echocardiography. They have considerable digital storage capabilities and connect to the hospital intranet for online consultation and storage. These portable systems will considerably expand the diagnostic applications of cardiac ultrasound in many different clinical scenarios.

Specific applications

Contrast echocardiography

Ultrasound contrast agents (microbubbles containing gas) increase the echogenicity of blood and are used for enhanced endocardial delineation, Doppler signal enhancement and intracardiac shunt detection (Fig. 2.14). In patients with larger-volume shunting and turbulence, colour Doppler flow imaging allows direct visualization of the right-to-left shunt (Fig. 2.14C,D) (see Colour flow imaging, below). Agitation of 5–8 ml of saline with 1 ml of air and a few drops of aspirated blood (stabilizes the microbubbles of air) between two syringes connected by a three-way stopcock provides an excellent contrast medium for right-sided cavity opacification, demonstration of right-to-left shunts and enhancing Doppler signals [15]. Also, other agents such as X-ray contrast, cardiogreen and gelatine produce echo contrast [16].

In the 1990s, important advances were made in microbubble engineering. New ultrasound contrast agents are capable of passing through the pulmonary capillary bed without destruction and behave as red blood cell tracers. At low ultrasound power (low MI), microbubbles scatter ultrasound and generate strong echo signals. At higher MI, they resonate and produce non-linear resonant frequencies, which are detected by harmonic imaging. They produce significant improvement of LV endocardial border identification in patients with poor or suboptimal non-contrast-enhanced echocardiographic images and allow consistent imaging of the coronary microcirculation following peripheral intravenous injection. These agents reside exclusively in the microcirculation, do not pass into the extravascular space and do not penetrate myocardial cells, a major advantage over contrast agents used in other imaging modalities. The method is therefore extremely promising for assessment of myocardial perfusion in various acute and chronic cardiac conditions (Fig. 2.15) [17]. Harmonic imaging is a prerequisite for optimal imaging of the capillary circulation.

Microbubbles can also be targeted specifically to bind unique cell markers and can be used to non-invasively detect incipient disease (e.g. endothelial dysfunction, transplant rejection), thrombi, etc. They can also be engineered for local drug and gene delivery.

Stress echocardiography

Stress echocardiography is a powerful and safe method for diagnosis, localization of the ischaemic wall segment, functional assessment and risk stratification in several

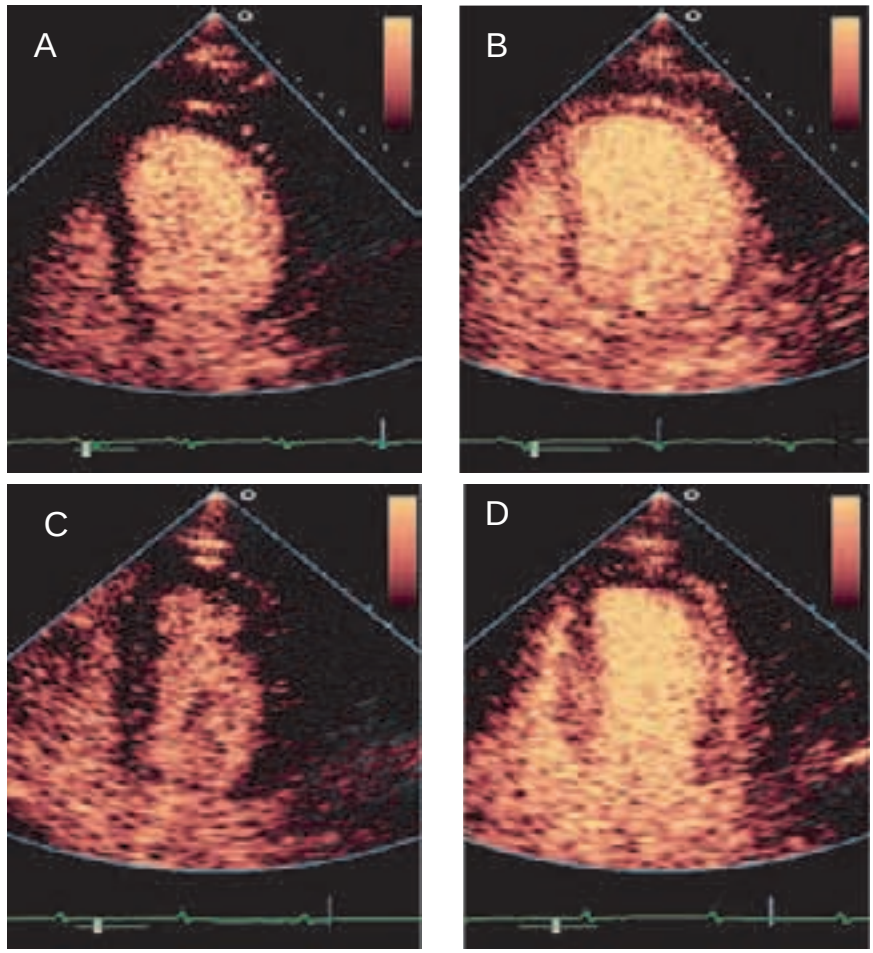

Figure 2.15 Myocardial perfusion imaging (Sonovue Bracco). (A) Four-chamber view in a patient with a dilated left ventricle shows echocontrast in the cavities, which are nicely delineated, but not much in the myocardium; (B) after a few cardiac cycles, the whole myocardium is well opacified indicating normal perfusion. (C) Four-chamber view of a patient with coronary artery disease and opacification of the left ventricular cavity; (D) after a few cardiac cycles, there is a perfusion defect in the apical septal and apical lateral segments.

types of cardiac disease [18]. In patients with coronary artery disease, the increased cardiac workload causes an imbalance in oxygen supply/demand and results in regional ischaemia, with a decrease in myocardial thickening and endocardial inward motion. The indications are similar to those for nuclear perfusion scintigraphy. A variety of stress methods can be used for inducing ischaemia and wall motion abnormality during echocardiographic monitoring. Physical exercise allows a high level of stress but adequate images are difficult to obtain at peak stress [19]. Pharmacological agents are most commonly used. These either increase the heart rate and the inotropic state (dobutamine) or induce maximal coronary vasodilatation (dipyridamole, adenosine), which may induce a 'coronary steal' and induce a wall motion abnormality (Figs 2.16 and 2.17).

The test provides similar sensitivity and specificity as perfusion scintigraphy but requires experienced echocardiographers. Its major advantage over ECG exercise testing is that it has a higher sensitivity (20–25%) and that it is applicable to patients unable to exercise (ageing population). It is less time-consuming, has a greater availability and is less expensive than nuclear studies. Dobutamine stress echocardiography is used to study viability by enhancing wall function in akinetic or hypokinetic segments (low dose) and ischaemia in the same segments (high dose) during the same test in order to plan revascularization procedures in patients after myocardial infarction who received thrombolytic therapy. In fact, dobutamine stress echocardiography has the best sensitivity and specificity of all the available viability tests. Stress echocardiography using specific protocols is also utilized to obtain specific information in valvular heart disease (aortic valve area), cardiomyopathies (outflow obstruction), right ventricular failure and pulmonary hypertension [20] (see Chapters 16, 21 and 25). Digital image technology has made stress echocardiography progressively easier to perform and analyse. However, the analysis is still largely subjective and should become quantitative, which is a major challenge for the immediate future.

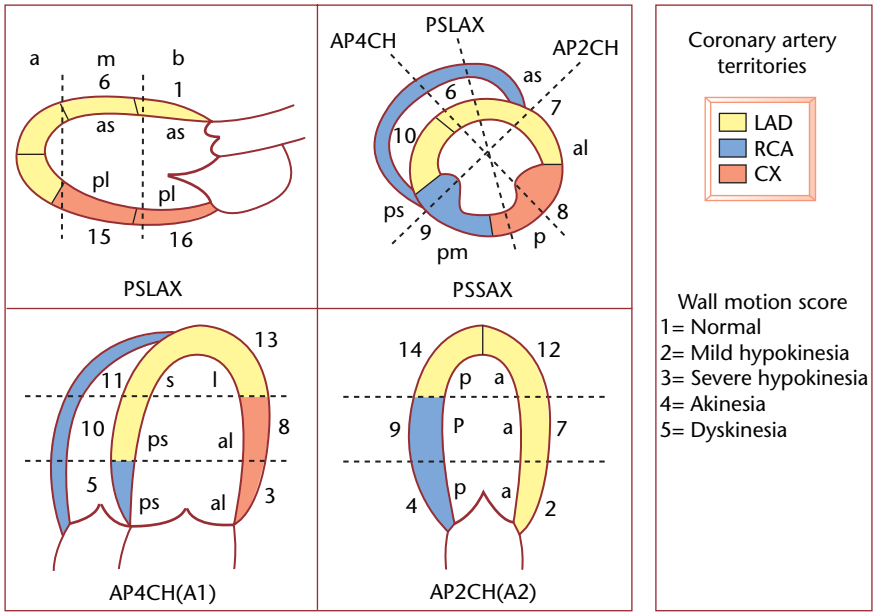

Figure 2.16 Method for standardized qualitative wall function analysis using the 16-segment model. The colour indicates the coronary artery territories supplying the wall segments. Diagrams show the parasternal long-axis (PSLAX), apical four-chamber (AP4CH, corresponding to A_1 in Fig. 2.24), apical two-chamber (AP2CH, corresponding to A_2 in Fig. 2.24) and parasternal short-axis (PSSAX) views. The left ventricular long axis is divided at three levels: apical (a), mid-papillary (m) and basal (b). Some segments are visualized in more than one view (see numbers). In the analysis the motion pattern of the 16 segments is given a wall motion score: normal, hypokinetic (< 25% inward motion), akinetic (25% motion) and dyskinetic (outward motion). a, anterior; as, anteroseptal; al, anterolateral; l, lateral; p, posterior; ps, posteroseptal; pl, posterolateral; pm, posteromedial; s, septal.

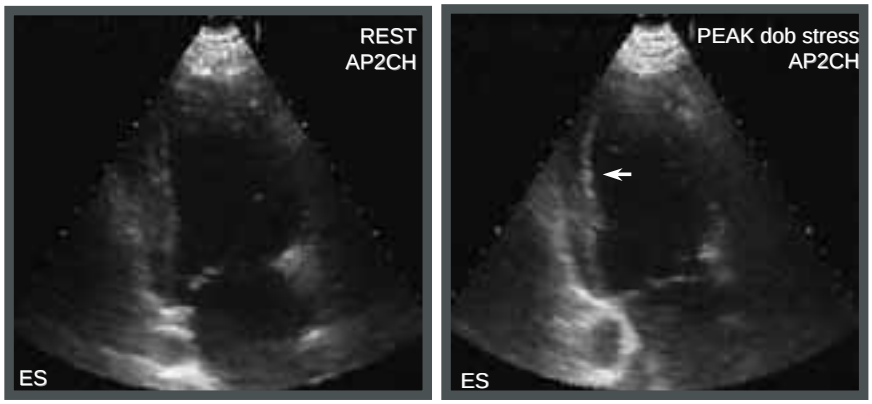

Figure 2.17 Paradoxical outward motion (dyskinesia) of the posterior wall (arrow) visualized in the apical two-chamber view (AP2CH) and induced at peak dobutamine stress. Still frames at rest and peak stress are recorded in end-systole (ES). This is a positive test. The posterior segments are supplied by the right coronary artery (see also Fig. 2.16).

Transoesophageal echocardiography

In transoesophageal echocardiography (TOE), a miniaturized phased-array transducer is incorporated in the tip of a flexible endoscope and can be passed into the oesophagus and stomach. The transducer can be electronically rotated along the long axis of the image sector in a 180° arc and produces an infinite number of transverse and longitudinal images (omniplane or multiplane TOE) combined with all Doppler modalities (Fig. 2.18). The angle of rotation is shown on the display system. The images are of excellent clarity and resolution and provide more detailed information when necessary. The examination involves some discomfort and carries a minimal risk [21], and is used to answer specific clinical questions when precordial images are inadequate either because of the patient's body habitus (obesity, emphysema) or because of shielding of structures of interest by prosthetic components.

The use of TOE has grown explosively in such diverse settings as the out-patient clinic, emergency room and the intensive care unit. It provides a definitive diagnostic modality for a broad range of cardiovascular disease, especially in acute conditions and the critically ill with haemodynamic compromise [22]. This has led to a decline in the use of Swan–Ganz catheters for invasive haemodynamic monitoring. TOE has provided new insights into the pathophysiology of acute aortic syndromes and is now the initial diagnostic method in patients with aortic disease and those suspected of having an acute aortic syndrome (aortic dissection, aortic ulcer, intramural

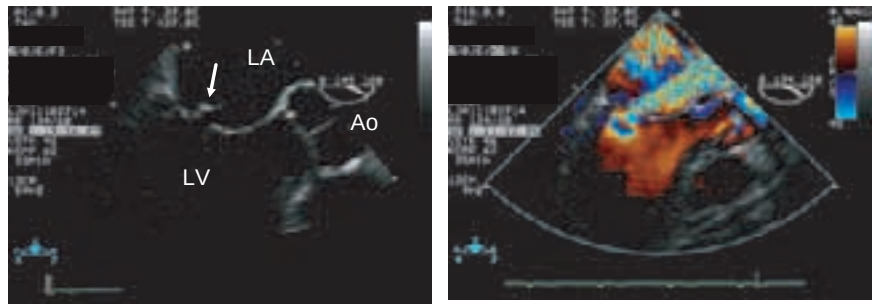

Figure 2.18 Patient with mitral valve prolapse of the posterior leaflet (arrow) seen from a middle-lower oesophageal transducer position with the imaging plane at 140–145°. The colour flow image shows the regurgitant jet directed away from the prolapsing leaflet and striking the posterior aortic wall. This results in an underestimation of the jet size (Coanda effect). The proximal isovelocity surface area is also well seen proximal to the regurgitant orifice. Ao, aorta; LA, left atrium; LV, left ventricle.

haematoma and trauma see p. 87 and Chapter 34). It provides crucial information in these patients and also in those with prosthesis dysfunction, endocarditis and pulmonary embolism [23]. It is also an important tool for cardiac monitoring during anaesthesia and for guiding intracardiac interventions. In patients undergoing surgical interventions, it is the most common and convenient way to obtain echocardiographic data and provides important continuous information on structure and function before and after endovascular aortic repair and cardiopulmonary bypass, does not interfere with the surgical field and influences surgical and haemodynamic management. Transnasal probes for continuous cardiac monitoring are also used [24]. Over the years, TOE has stimulated the collaboration between a wide range of disciplines within hospitals.

Intraoperative echocardiography

Intraoperative echocardiography may be used via the transoesophageal, direct epicardial and epi-aortic routes and has become an integral part of cardiac surgery. It can be adapted to the entire spectrum of cardiac surgical procedures in order to assist both the surgeon and anaesthesiologist [25]. Particularly during minimally invasive port-access surgery and robotic-assisted procedures, it helps to minimize the risk and improves outcome by providing a 'third eye' for guiding surgical manipulations. Epi-aortic imaging is the superior approach for detecting aortic atherosclerosis when manipulations of the aorta are planned.

Substernal (epicardial) echocardiography

A specially constructed mediastinal chest drain tube that allows access to a small TOE probe is used in postoperative intensive care (precordial bandages, ventilation) to evaluate myocardial function and coronary graft flow and allows rapid exclusion of tamponade after chest closure.

Intracardiac echocardiography

Some of the drawbacks of transthoracic and transoesophageal echocardiographic imaging can be overcome with the use of an ultrasound transducer-tipped catheter capable of intracardiac imaging [26]. This has either a mechanically rotating single-element transducer (9 MHz) mounted on a 9F catheter tip or a phased-array transducer (5.5–10 MHz) on a 10F catheter tip. The latter allows spectral Doppler haemodynamic and colour flow information to be obtained as well. The procedure is invasive and allows continuous detailed visualization of endocardial anatomy and is increasingly used for monitoring interventional procedures (device defect closure, valvuloplasty) and electrophysiological procedures, enhancing both success and safety while minimizing radiation exposure [27] (see Chapter 6).

Intravascular/intracoronary echocardiography

Intravascular, and more particularly intracoronary, ultrasound require both a small transducer system mounted on 2–3F catheter tips and a catheter delivery system with optimal steerability and flexibility. Mechanically rotated single-element systems and electronic multielement transducer systems are available with operating frequencies of 30–40 MHz. The method provides detailed information about morphology and pathology of the lumen and vessel wall and has contributed considerably to the understanding of the pathology of atherosclerosis and the mechanisms of intracoronary and pharmacological interventions (see Chapter 6).

Examination techniques

Transthoracic (precordial) echocardiography

To answer a clinical question or solve a diagnostic problem, a standardized examination procedure must be followed. In many situations it may be important to review the patient's file and measure blood pressure; the ECG should always be recorded as a reference trace.

The M-mode registrations are simultaneously sampled from the two-dimensional phased-array transducer. Precise knowledge of the position of the heart in the thorax and intracardiac structure relationships is mandatory and can be found in textbooks [28]. The examination begins with transthoracic two-dimensional scanning from four standard precordial transducer positions: the parasternal and apical views with the patient in the lateral decubitus position and the subcostal and suprasternal views in the supine position (Fig. 2.19). From each position standardized, multiple, cross-sectional images of the heart relative to the perpendicular long and short axes are obtained by angulating and rotating the transducer. An optimal grey-level and gain setting has to be used. The examination procedure is extensively described in textbooks [29–31].

Two-dimensional imaging is also the basis for colour Doppler imaging and guided pulsed- and continuous-wave Doppler interrogation. It is important that the interrogation beam is parallel with the direction of blood flow to avoid underestimation of the maximal frequency shift. Colour flow imaging is used to optimize the alignment of the ultrasound beam with the direction of flow and placing the sample volume.

Transoesophageal echocardiography

Cardiac imaging

The patient is examined in the left lateral decubitus position and the endoscope is introduced after fasting for 4 h, mild sedation and local anaesthesia of the posterior hypopharynx with 10% lidocaine spray. An intravenous line is introduced and heart rate, blood pressure and oxygen saturation are continuously monitored. The procedure is usually well tolerated. Longitudinal, transverse and intermediate images are obtained at three levels (upper transoesophageal, lower-middle transoesophageal

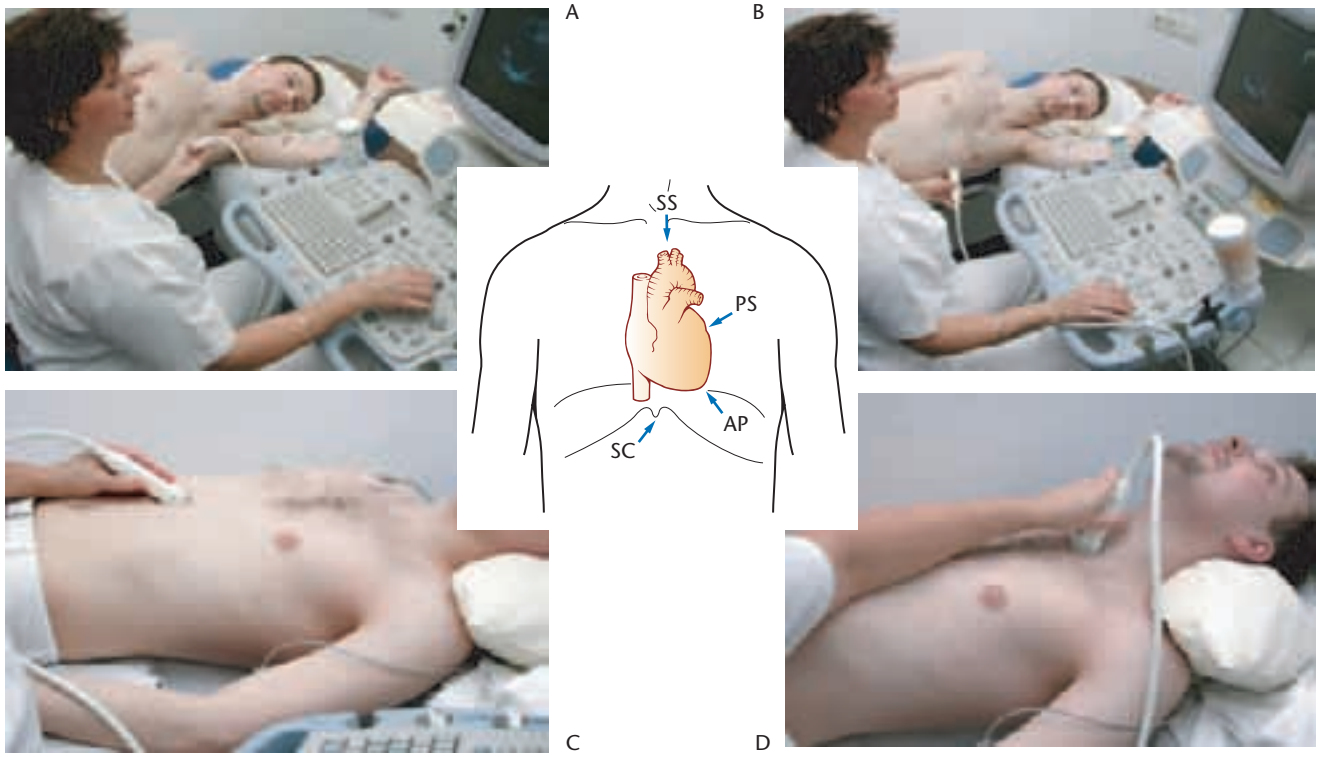

Figure 2.19 The four standard transducer positions for transthoracic two-dimensional echocardiography: (A) left parasternal (PS); (B) apical (AP); (C) subcostal (SC); (D) suprasternal (SS).

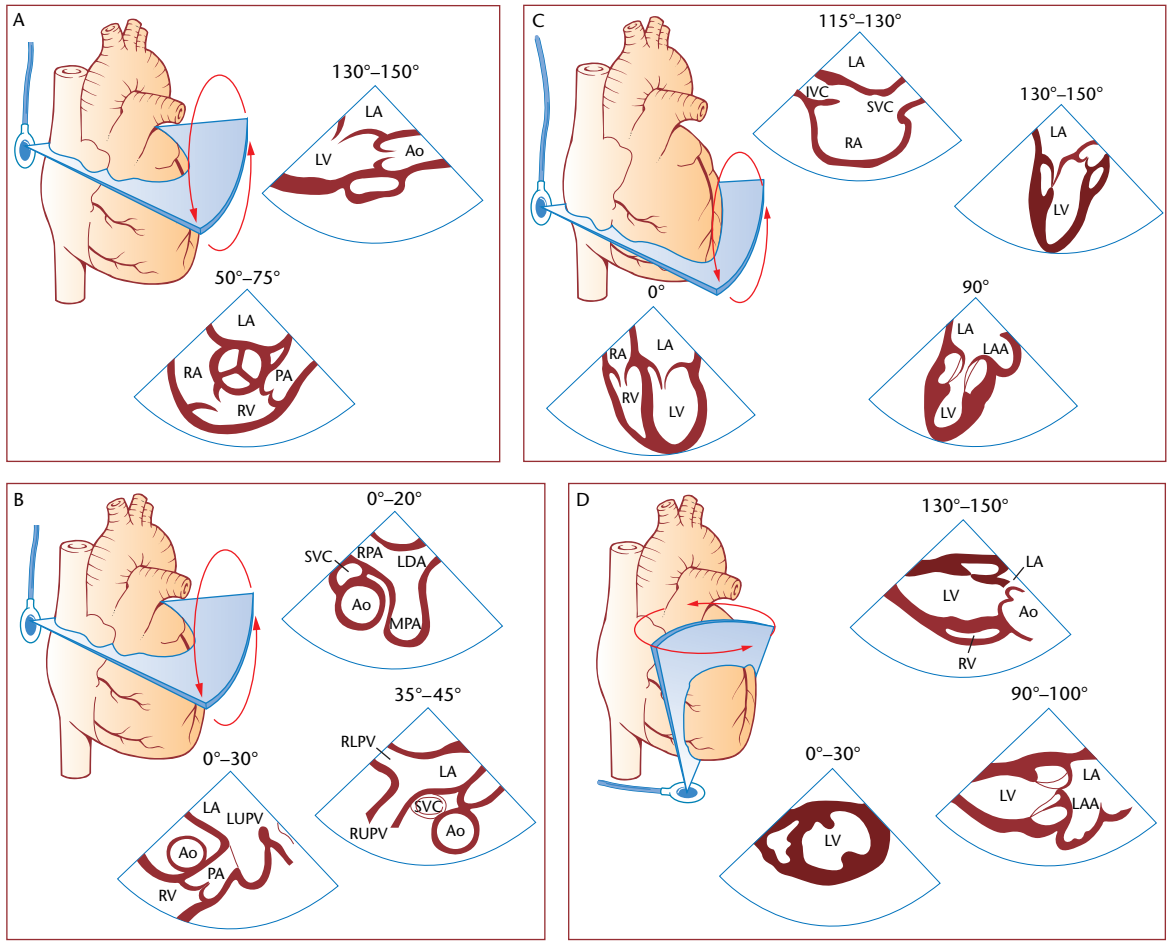

Figure 2.20 Position of the scanning plane is indicated on the display screen: 0° indicates the transverse view, which is orthogonal to the probe, 90° shows a longitudinal view and 180° is the mirror image of 0°. (A) Upper transoesophageal views of the aortic valve in long-axis (130–150°) and short-axis (50–75°) views. (B) Upper transoesophageal views of the great vessels and atrial appendage (counter-clockwise): transverse view of the left atrial appendage and the left upper pulmonary vein (0–30°); intermediate view of ascending aorta, left atrium and right pulmonary veins (35–45°); and, with anterioflexion of the probe, transverse view of the ascending aorta, superior vena cava and main pulmonary artery with its bifurcation are obtained (0–20°). (C) Lower-middle transoesophageal views with exemplary cross-sections corresponding to (counter-clockwise) the four-chamber view of the left ventricle. From this transducer location, right heart structures can be visualized. A right atrial longitudinal view is visualized at 115–130°. (D) Transgastric views with exemplary cross-sections corresponding to (counter-clockwise) transgastric short-axis view at mid-papillary level, transgastric two-chamber view and transgastric long-axis view of the left ventricle after passing the left liver lobe.

and transgastric) by rotating and flexing the transducer tip medially and laterally (Fig. 2.20).

Aortic imaging

The entire thoracic aorta can usually be visualized in horizontal short axis and longitudinal scan planes [32–35] (Fig. 2.21). Standardized imaging sequences have to be used for high-quality examination and optimal diagnostic yield (see also Chapter 34).

Pulmonary artery imaging

Examination of the main, right and left pulmonary artery is important in acute pulmonary hypertension and suspected embolism.

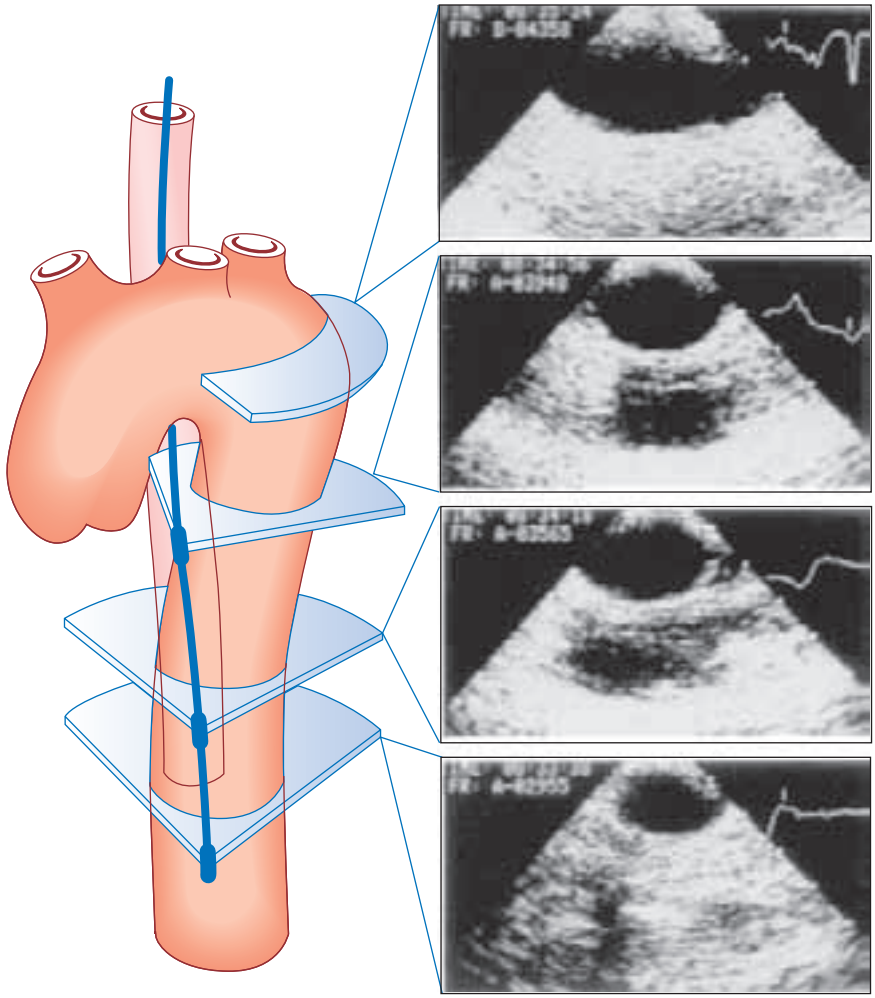

Figure 2.21 Examination of the thoracic aorta in the transverse plane in relation to the oesophagus. The diagram shows the intertwining relationship of the aorta and oesophagus.

Reference values for M-mode and two-dimensional echocardiography

M-mode echocardiography

Echocardiography is a quantitative method and both linear and temporal calibrations are available on each individual recording [36]. M-mode echocardiography provides good structural definition. For rapid assessment, dimensional measurements are made from parasternal M-mode recordings. Landmarks for measurement are given in Figs 2.4 and 2.5 and reference values in Table 2.2. Measurements of structure and cavity dimensions (Fig. 2.22) are more accurate and reproducible when guided by two-dimensional echocardiography. The principles of measurement and reference values corrected for body surface area are given in Fig. 2.22 [37]. Principles are also found in textbooks [30,38].

Despite the availability of three-dimensional echocardiography, which is inherently more accurate, M-mode measurements are still used in most studies to estimate LV myocardial mass and are useful for follow-up of individual patients. An ellipsoid with a long axis (L) twice the length of the short axis is assumed as the geometric model of the LV (Fig. 2.23). The LV end-diastolic short-axis dimension (D) is taken from either the parasternal long-axis or short-axis view.

The volume of a prolate ellipsoid is:

$$V = {}^{1}/_{6}\pi LD^2$$

Since L is assumed to be $2D$, the LV cavity volume is $(1.047)D^3$. The total (epicardial) LV volume includes cavity and myocardium and is calculated by adding interventricular septal thickness (T_{IVS}) and posterior wall thickness (T_{PW}). Consequently:

$$\text{Total LV volume} = 1.047(D + T_{PW} + T_{IVS})^3$$

The myocardial volume is the difference between the epicardial and endocardial volume. Hence:

Table 2.2 Reference values for M-mode diameter measurements

	Men (mm)	Women (mm)
Aortic root	26–36	23–34
Left atrium (end-systole)	30–40	26–38
Right ventricle (end-diastole)	< 30	< 30
Left ventricle		
End-diastole	47–58	43–55
End-systole	28–37	28–40
Fractional (systolic) shortening	> 25%	> 25%
Interventricular septal thickness (T_{IVS})	8–12	7–12
Systolic thickening	> 30%	> 30%
Posterior wall thickness (T_{PW})	7–12	6–11
Systolic thickening	> 30%	> 30%

Ranges represent 90% confidence intervals.

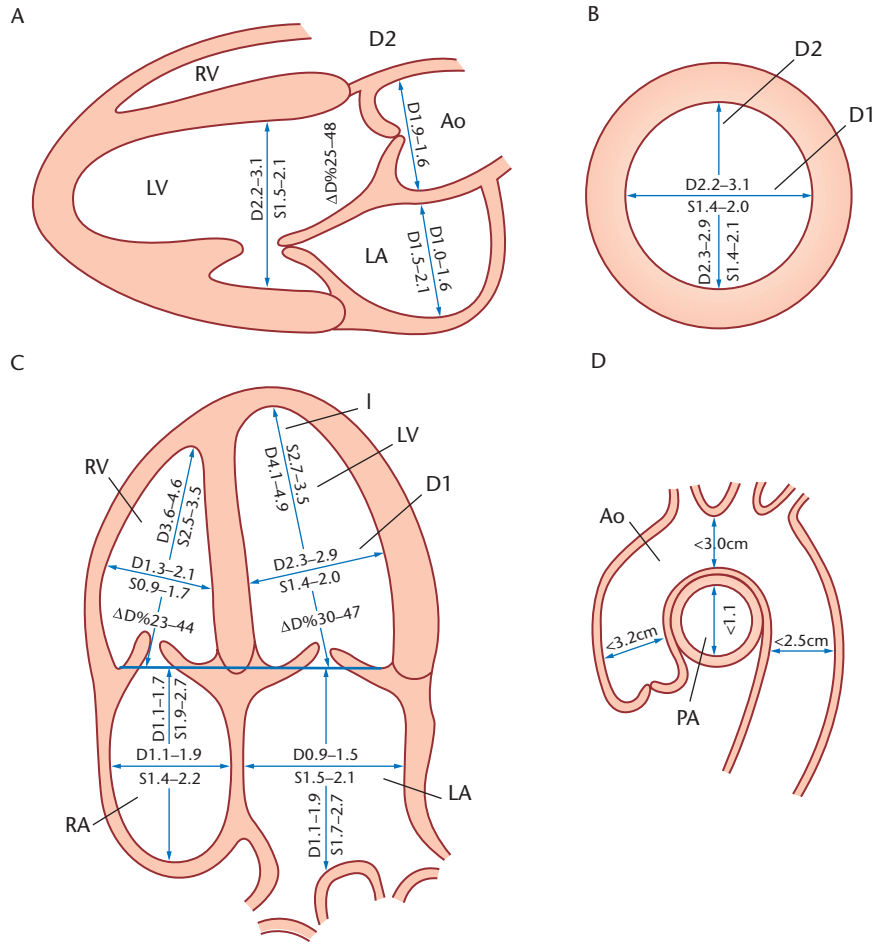

Figure 2.22 Measurements of cardiac structure, cavity dimensions and area can be obtained from three two-dimensional views: (A) parasternal long-axis view; (B) parasternal short-axis view at the chordal level; (C) apical four-chamber views. (D) Long-axis and short-axis view of the aorta and pulmonary artery. Dimensions are given in centimetres corrected for body surface area (m^2) in diastole (D) and systole (S). L, left ventricular long-axis dimension in the apical four-chamber view; D_1, mediolateral left ventricular dimension in the apical four-chamber view; D_2, anteroposterior left ventricular dimension in the parasternal long-axis and short-axis views. Ao, aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

$$\text{Myocardial volume} = 1.047[(D + T_{PW} + T_{IVS})^3 - D^3]$$

Hence LV mass (grams)
= myocardial volume – 13.6 (Penn convention) or
= myocardial volume × 1.04 × 0.8 + 0.6

where 1.04 g/ml is the specific gravity of muscle and 0.8 is a correction factor. Normal values are 93 ± 22 g/m^2 for men and 76 ± 18 g/m^2 for women. Upper limits of LV mass (mean ± 2SD) are 132 g/m^2 for men and 110 g/m^2 for women.

Two-dimensional echocardiography

Two-dimensional echocardiography has become the routine examination for cardiac chamber volume and function assessment. This requires adequate endocardial

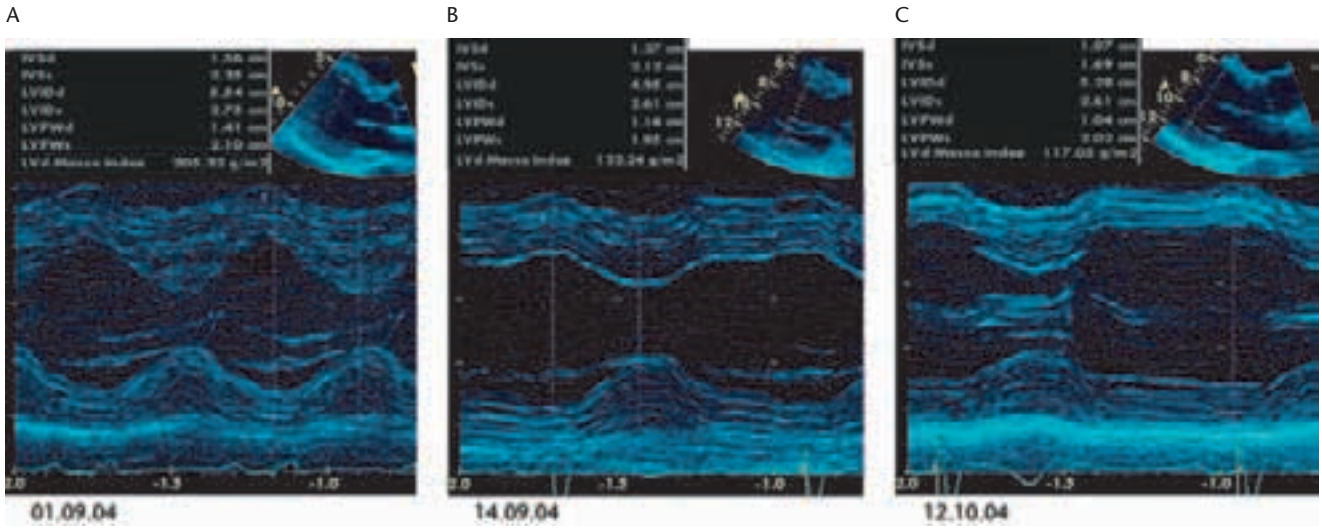

Figure 2.23 (A) M-mode recordings of the left ventricle in a patient with parvovirus B19-induced myocarditis. The admission echo showed thickened interventricular septal and posterior walls of 1.56 and 1.41 cm respectively. The left ventricular mass index was 205 g/m^2. (B) Two weeks later the left ventricular mass index has decreased to 133 g/m^2 and (C) 6 weeks later it was within normal limits (117 g/m^2).

border visualization (contrast LV opacification can be used for better cavity delineation), proper alignment of the imaging planes and careful planimetry. Nevertheless, the ellipsoidal models and the geometric assumptions introduce inaccuracies, especially of the right ventricle (RV) and ventricles with shape abnormalities. Three-dimensional echocardiography is able to overcome these limitations mainly by avoiding both these assumptions and models and has rapidly become the new reference method.

Left ventricular volume

The volume of the LV is calculated from the dimension and area obtained from the orthogonal four-chamber and two-chamber apical views (Fig. 2.24) and a wide range of formulae is used [39]. The biplane disc summation method (also called the modified Simpson's rule) is the most commonly used and also the most accurate [38] (Fig. 2.25). This method should be used whenever possible. Modern equipment has built-in computer software programs for rapid contouring of the LV endocardium (and epicardium, which allows measurement of wall thickening and more accurate mass calculation) and for calculating the cavity area. Volumes are calculated by summating an average of 20 discs (Figs 2.25 and 2.26).

In some patients only an adequate single view can be obtained. In this situation the single plane method of discs can be applied (Figs 2.25 and 2.27). Less accurate

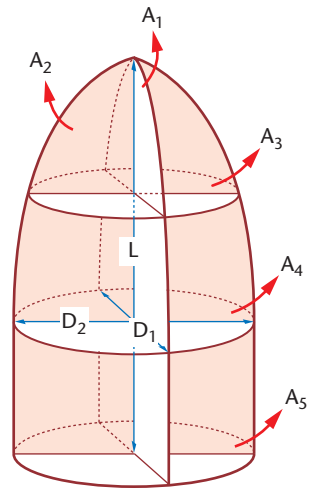

Figure 2.24 Model of the left ventricle and the dimensions and imaging planes used in formulae to calculate cavity volumes from two-dimensional echocardiographic views, assuming a rotation ellipsoid body for which the length and the major and minor axes have to be determined. A_1, cavity area in the four-chamber view; A_2, cavity area in the apical two-chamber view; A_3, cavity area in the parasternal short-axis view at papillary muscle level; A_4, cavity area in the short-axis view at mitral valve level; A_5, basal cavity area in the short-axis view (this surface area is not measured in practice and is taken as A_4). L, left ventricular long axis in either the apical long-axis or four-chamber view; D_1, mediolateral left ventricular dimension in the four-chamber view; D_2, anteroposterior left ventricular dimension in the parasternal short-axis or apical two-chamber view.

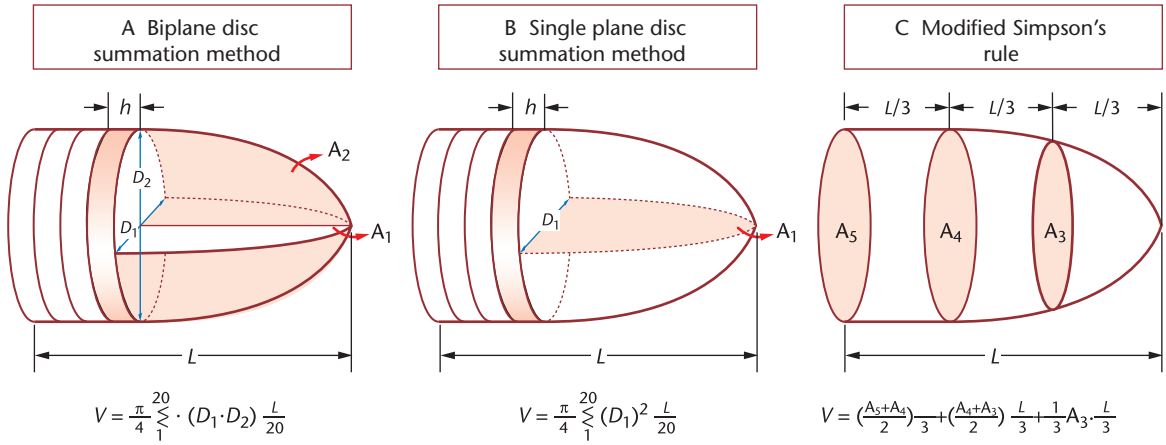

Figure 2.25 Methods for calculating left ventricular volume by the method of discs. (A) Biplane method uses the two orthogonal apical views. The calculation is based on summation of the volumes of discs (calculated from perpendicular diameters D_1 and D_2 and disc thickness) of 20 equal discs, which are summed for calculation of a rotation ellipsoid. (B) In the single plane method, only one diameter is measured in order to calculate the area of volume of each individual disc. (C) In this method the parasternal short-axis views A_4 and A_3 are used ($A_5 = A_4$) for planimetry and the long-axis length (L) is measured from the apical two-chamber view.

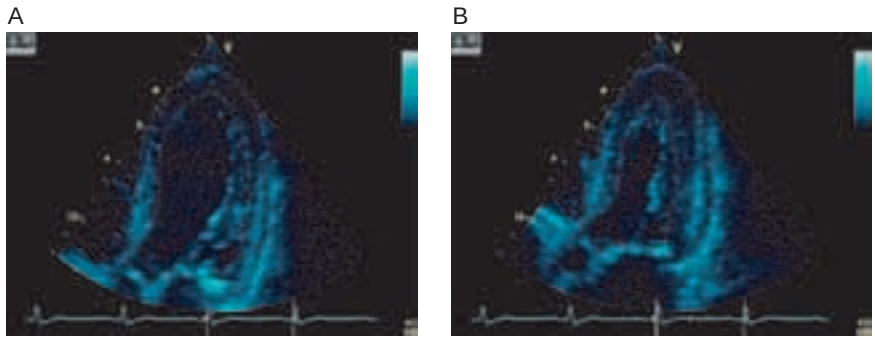

Figure 2.26 (A) End-diastolic and (B) end-systolic apical long-axis views of a normal left ventricle. The endocardial and epicardial contours are traced and the built-in computer software of the ultrasound system allows calculation of volumes, wall thickening and myocardial mass.

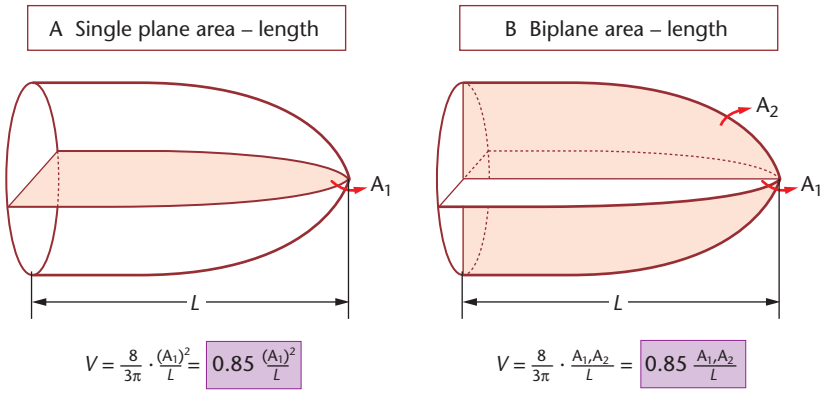

Figure 2.27 The two methods for calculating left ventricular volume assuming a rotation ellipsoid model. (A) Single plane area–length is used when only one apical view is visualized (in this diagram the apical four-chamber view). The area (A_1) is planimetered and the long-axis length (L) is measured. (B) In the biplane area–length method, the areas of the orthogonal four-chamber (A_1) and apical two-chamber (A_2) views are planimetered and the long-axis length (L) measured from either of these views.

is the prolate ellipsoid model, which assumes that the ventricle both in systole and diastole approximates the shape of a prolate ellipse. The area–length method can then be employed in a single plane or in two orthogonal planes. Combined geometric shapes have been proposed to better approximate LV shape for volume calculation (cylinder hemi-ellipse or bullet, cylinder–cone and cylinder truncated cone–cone models). Models based

Table 2.3 Reference values for cavity volumes by two-dimensional echocardiography: methods of areas and discs

Reference	*N*	Method	EDV (ml/m^2)	ESV (ml/m^2)	EF (%)
Triulzi *et al.* [40]	62	A_2/area–length	70 ± 26	25 ± 13	64 ± 10
	55	$A_2 + A_4$/biplane	73 ± 21	28 ± 11	62 ± 8
	39	$A_1 + A_2$/biplane	71 ± 24	23 ± 11	68 ± 8
	52	$A_2 + A_4$/cylinder	84 ± 18	28 ± 9	67 ± 7
Wahr *et al.* [41]	52	Simpson's rule	55 ± 10	18 ± 6	67
Erbel *et al.* [42,43]	55	$A_1 + A_2$/biplane	Men 66 ± 8 Women 60 ± 12	Men 26 ± 5 Women 25 ± 7	Men 59 ± 6 Women 58 ± 6

EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction.

on short-axis views are not practical because adequate views are difficult to obtain. Reference values for cavity volumes using methods of areas and disc summation are presented in Table 2.3.

It must be taken into account that, because of the position of the transducer on the chest wall relative to the apex of the heart, tangential scanning planes are recorded that underestimate the true LV volume [44]. This assumption has been proved by three-dimensional echocardiography.

Right ventricular volume

Volumetric measurements of the RV are problematic because of its complex geometry (the RV chamber poorly approximates to any convenient model), its variable trabeculation causing difficulties in endocardial border detection, and inadequate imaging planes (by its inaccessibility behind the sternum) [45]. However, biplane disc summation is used in most methods. For RV volume calculation the subtraction method has been developed, which takes into account that the RV has a scale shape [46]. Using the method of discs, the volume of the LV and RV including the interventricular septum (IVS) is calculated and the volumes of the LV and IVS are subtracted:

$$\text{RV} = (\text{LV} + \text{IVS} + \text{RV}) - (\text{LV} + \text{IVS})$$

Three-dimensional echocardiography complemented with contrast cavity delineation offers advantages for volume calculation but data are lacking.

Non-volumetric methods provide both qualitative and semi-quantitative information on function that can be used for patient management (anteroposterior M-mode dimension in combination with septal motion, fractional area change, tricuspid annular plane systolic excursion and velocity, MP index, pulmonary artery pressure). The transtricuspid flow pattern provides information on diastolic RV function in combination with annular tissue Doppler imaging.

Left atrial volume

The anteroposterior diameter of the left atrium (LA) measured in the parasternal long-axis view is commonly used to assess LA size. This measurement is insensitive to LA dilation but specific. Therefore the LA volume should be measured [47]. The area–length and disc summation method can be applied using apical two- and four-chamber views (Fig. 2.28). The normal maximal LA volume is ≤ 36 ml/m^2.

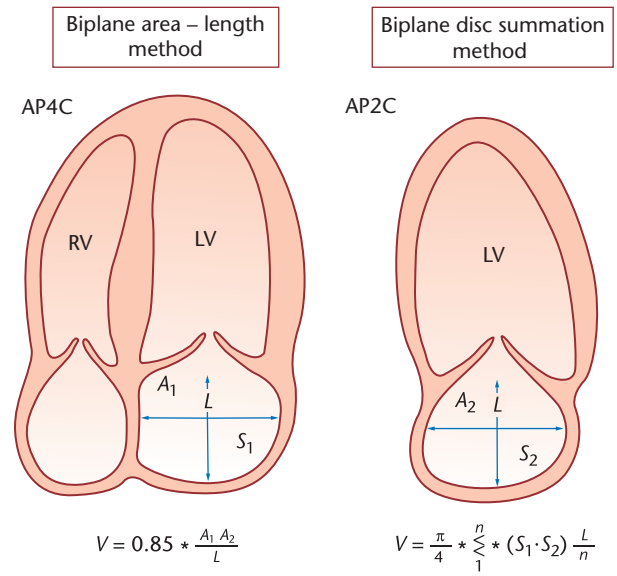

Figure 2.28 Principle of measuring the left atrial volume using the biplane area–length model and biplane disc summation methods at ventricular end-systole. The shortest long-axis (L) dimension from either the AP4C or AP2C view between the posterior wall and the line across the mitral valve hinge points should be taken. S_1, short axis in the AP4C view; S_2, short axis in the AP2C view; A_1 and A_2, surface areas in these views.

Recently, an elliptical model has been proposed that does not require endocardial contour tracing [48]:

$$V = \pi/6 \cdot DLS_1$$

where D is the anteroposterior dimension from M-mode and L and S are measured in the apical long-axis view. Three-dimensional echocardiography provides more accurate and reproducible quantitative data [49].

Principles of Doppler echocardiography

Doppler echocardiography is based on the principle that the echoes reflected from moving red blood cells (or any object) undergo a small shift in frequency. This frequency shift (difference in transmitted versus received frequency) is proportional to the proportion of velocity directed along the ultrasound beam or scan line. Blood cells flowing toward the transmitted ultrasound beam compress the signal frequency (the transducer receives a lower frequency). For blood flow where the direction of the sound beam is not aligned, the shift will be a factor cosine θ less than it would be for on-axis interrogation.

Therefore, the position of the transducer is usually adjusted so that the direction of blood flow is parallel to the sound beam. The frequency shift (Δf) is calculated by knowing the transmitted frequency (f_t), the velocity of the moving object (v), ultrasound speed (c) and the angle of interrogation (θ).

$$\Delta f = \frac{2f_t \cdot v \cdot \cos\theta}{c} \quad \text{and hence} \quad v = \frac{c\Delta f}{2f_t \cos\theta}$$

The 'Nyquist velocity' is the maximum velocity that can be measured without ambiguity (aliasing): it is inversely proportional to the distance and the transmitted frequency. Therefore, to maximize the maximum velocity that can be recorded, it is best to use a low-frequency transducer and bring the transducer as close as possible to the area of interest.

There are five Doppler modalities for cardiac examination: continuous wave, pulsed wave, colour flow mapping, colour M-mode and tissue Doppler velocity imaging.

Pulsed-wave Doppler

Pulsed-wave Doppler can measure velocity at a specific point by intermittently emitting ultrasound pulses and by gating the returning signals to a desired depth (i.e. sample volume at a specific site within the image) (Fig. 2.29A) [50]. However, the maximum measurable velocity is limited by the Nyquist limit. This problem has been overcome to some degree by high-frequency sampling (high pulse repetition frequency). Signals from the receive-transducer contain strong echoes from the relatively slow-moving structures (myocardium, vessel wall) and much weaker signals from the fast-moving red blood cells. By implementation of appropriate thresholding

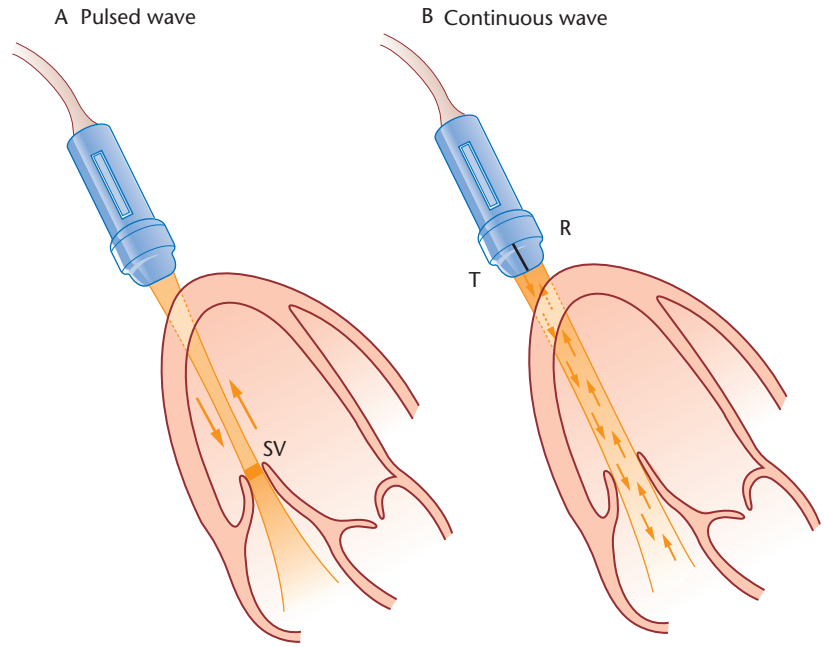

Figure 2.29 (A) In pulsed-wave Doppler there is one transducer that alternately transmits and receives ultrasound information from a single small region or sample volume (SV) within the sound beam. The location of this sample volume is operator-controlled. (B) Continuous-wave Doppler uses two independent transducers, one for constant transmission (T) and one for continuous reception (R) of ultrasound information. This allows recording of the highest velocities within the sound beam but there is no depth information.

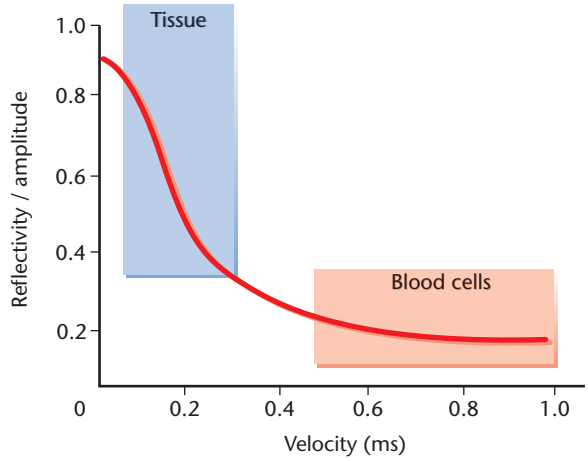

Figure 2.30 Principle of tissue Doppler imaging. Highly reflective slow-moving tissue (myocardium) can be distinguished from poorly reflecting high-velocity blood cells by applying appropriate thresholding and clutter filters.

and clutter filters, the signals can be separated so that high-amplitude/low-velocity information is processed for tissue Doppler velocity imaging and low-amplitude/high-velocity signals for blood flow velocity recording (Fig. 2.30).

Continuous-wave Doppler

Continuous-wave Doppler instruments use two separate transducers, one for transmitting and one for receiving ultrasound signals continuously [50] (Fig. 2.29B). Continuous-wave Doppler is not limited by the Nyquist limit. However, it cannot measure velocity at a specific point but only the maximum velocity along a specific beam direction. It is therefore useful if one knows with a high degree of certainty where the maximum velocity is occurring. Fortunately, high-velocity jets occur only in a few locations in the heart (stenotic and regurgitant lesions and shunts).

Doppler allows study of not only the velocity of the blood flow structures but also the flow period and the direction of flow. Direction is represented as either a positive deflection above the zero baseline (motion towards the transducer) or a negative deflection below the zero baseline (motion away from the transducer). When all velocities (cm/s) during a flow period are added together and divided by the flow duration (s), the result is called the velocity time integral.

Velocity of blood is related to pressure difference through the Bernoulli equation, which is a restatement of the law of conservation of energy in fluids and allows measurement of instantaneous pressure gradients across obstructions and shunts in the cardiovascular system.

Colour flow imaging

A comprehensive cardiovascular ultrasound examination requires blood flow information to be obtained from large segments of blood vessels and cardiac chambers similar to an angiocardiogram. This information must therefore be integrated within the two-dimensional images. This is impossible when using the fast Fourier transform analysis of data from over 100 scan lines to calculate the Doppler shift from a single site because of time constraints. To overcome this problem only mean velocities and their variance are calculated from a few scan lines by autocorrelation techniques. These calculations are relatively simple and rapidly performed on echoes received from each individual sample volume. Each calculation yields information on flow direction, velocity and variance (laminar or turbulent). Flow in the sample volume towards the transducer is encoded in red and brighter colours indicate higher mean velocities. A mosaic of colours indicates increased variance (turbulence). The colour-coded flow parameters are displayed on the screen superimposed on the two-dimensional images in real-time at a frame rate of 25/s (Fig. 2.31). These 'ultrasonic angiograms' allow immediate differentiation between normal and abnormal blood flow and these

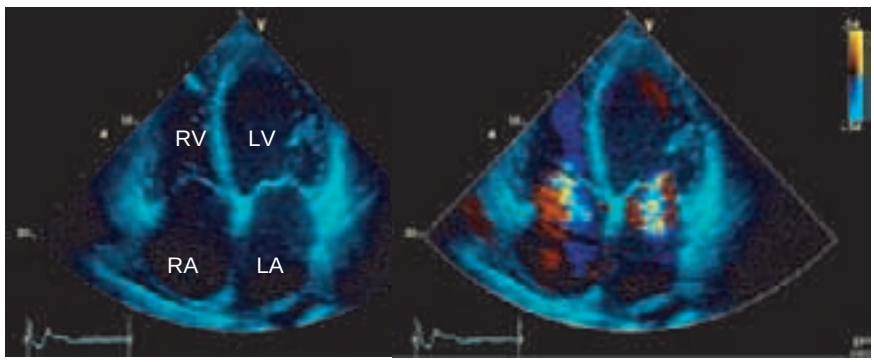

Figure 2.31 Colour flow image of a patient with dilated cardiomyopathy and mitral and tricuspid regurgitation. The apical four-chamber view is shown. The tricuspid regurgitant jet is seen in the right atrium (RA) and a central mitral regurgitant jet in the left atrium (LA) in systole. LV, left ventricle; RV, right ventricle.

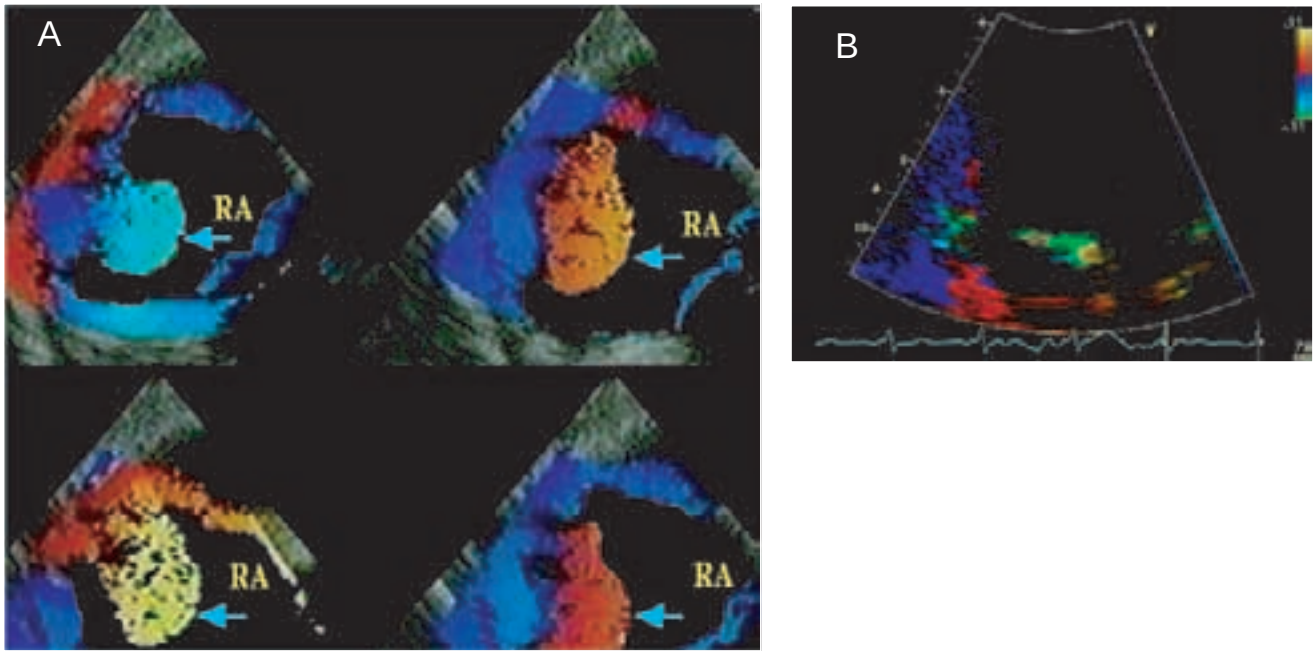

Figure 2.32 Tissue Doppler imaging for structure identification. (A) Lymphoma attached to the right atrial (RA) wall shows coherent motion, seen as a velocity phase shift between the atrial wall and tumour due to Newton's law of inertia of mass. (B) A vegetation on a mitral valve prosthesis shows incoherent motion. This means that the mass lesion is out of phase with cardiac contraction and relaxation, which results in chaotic motion.

areas can then be interrogated with pulsed-wave or continuous-wave Doppler for quantification. Indeed, it must be realized that colour flow imaging is a qualitative method. Colour Doppler flow imaging allows calculation of the flow rate at proximal isovelocity surface areas (PISA method; see Doppler haemodynamics, below) in regurgitant lesions in order to determine the regurgitant volume and valve orifice areas. Pulsed-wave, continuous-wave and colour flow imaging are interdependent but complementary functions for a comprehensive haemodynamic evaluation. Recently, three-dimensional imaging of colour flow Doppler has been introduced, integrating the information of both three-dimensional (patho)anatomy and colour-coded flow and providing spatial and temporal information on the extension, direction, origin and size of intracardiac flow abnormalities.

Colour M-mode Doppler

With colour M-mode both the temporal and spatial propagation of flow is visualized along a single scan line (rather than a single sample volume) selected from a colour flow image over time. This function is used to assess the timing of transient flow events, the length of regurgitant jets and the diastolic propagation of transmitral flow in the LV for diastolic function assessment. Colour M-mode tissue imaging provides myocardial velocities (high amplitude–low velocities, with a low gain filter at different depths of the myocardial wall) and velocity differences across the myocardium (velocity gradients). This requires a perpendicular interrogating beam and basically limits the myocardial segments that can be studied to the anterior septal and posterior walls.

Tissue Doppler imaging

Tissue Doppler imaging (TDI) is an extension of conventional Doppler echocardiography (flow velocities). In this modality the velocity of motion within tissue (tissue velocity imaging) is displayed by eliminating the high-pass wall filter and using a low-gain filter, which eliminates the higher blood flow velocities (see Fig. 2.30). The method allows assessment of regional myocardial function and timing of contraction within the myocardium, assuming that in the normal heart a synchrony is present. Initially, the method provided radial and longitudinal myocardial velocity profiles using pulsed-wave or a spatial colour map of velocities within the myocardium throughout the sector of interest using autocorrelation methods. It should be realized that the method is limited by the angle dependence of the Doppler ultrasound beam.

TDI can also be used for structure identification on the basis of different motion patterns and colour coding [51]:

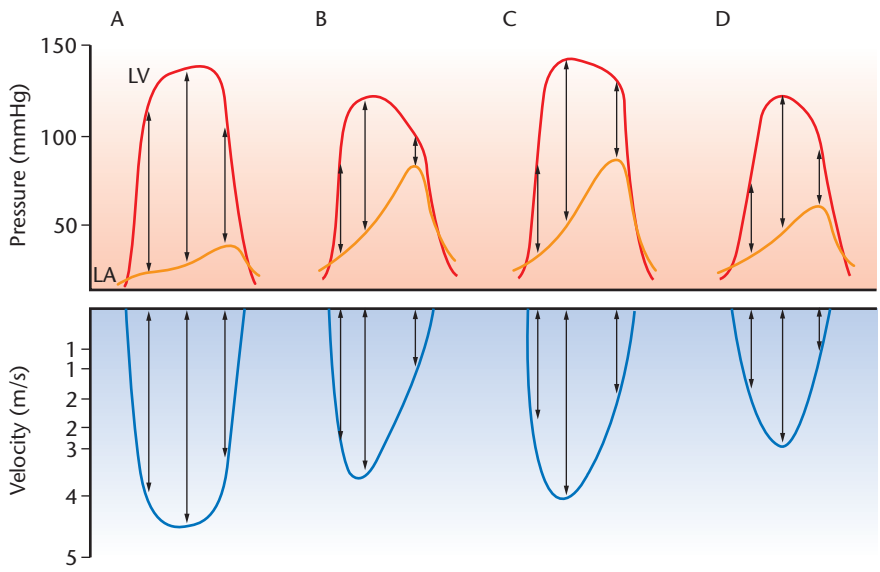

Figure 2.33 Schematic representation of Doppler flow patterns in different forms of mitral regurgitation illustrating the instantaneous interplay of left ventricular (LV) and left atrial (LA) pressures on the resulting waveforms. (A) Mild mitral regurgitation. (B) Severe mitral regurgitation and high compliant left atrium. Because of the high LA compliance in chronic severe mitral regurgitation, the pressure difference falls rapidly resulting in a rapidly decreasing velocity. (C) In acute severe mitral regurgitation, LA compliance is low and the pressure difference remains higher with a higher velocity. (D) In poor LV function, LV pressure rise is decreased (low d*P*/d*t*) and rapidly decreases, resulting in slow rise and rapid decrease of velocities.

- incoherent motion is present in vegetations, free oscillating thrombi and Chiari network (Fig. 2.32);
- coherent motion is observed as a phase difference between tissues, seen in atrial and ventricular thrombi and tumours;
- concordant motion is observed in aortic sclerosis, post-rheumatic valvular lesions and intramural haematoma.

Second-generation tissue Doppler techniques allow transformation of Doppler velocity to an angle-corrected quantitative display or colour-coded wall displacement towards the centre of LV contraction. Subsequently, the method was further developed to measure regional strain and strain rate, which represent local deformation and the rate at which this deformation takes place (time derivative of strain) as a function of stress. Currently, two-dimensional strain and strain-rate calculations are possible based on radiofrequency data analysis from high frame rate imaging using cross-correlation methods [52].

Normal Doppler velocity patterns

Transvalvular velocity patterns

The transmitral blood flow velocity waveforms result from the complex interplay of instantaneous pressure differences (and several other factors) (Figs 2.33 and 2.34). Transmitral pulsed-wave Doppler flow velocities are recorded within the apical four-chamber or apical long-axis views and several measurements can be used to define LV filling haemodynamics. As the mitral valve is funnel-shaped, the velocities increase progressively across the mitral valve apparatus towards the outlet of the mitral funnel. For reasons of reproducibility, all transmitral pulsed-wave Doppler flow measurements must be made with the sample volume in the same position at the outlet of the mitral valve funnel. Figure 2.35 shows the normal transmitral velocity pattern and the parameters that can be measured.

Normal transmitral blood flow is laminar and of relatively low velocity (usually < 1 m/s). There is an early diastolic velocity caused by the continued myocardial relaxation resulting in a LV pressure below LA pressure, which causes the mitral valve to open and rapid LV filling to occur (E wave). E-wave acceleration is directly determined by LA pressure and inversely related to myocardial relaxation. Viscoelastic properties and compliance of the myocardium then come into play, raising LV pressure and resulting in a decreased transmitral flow velocity. The rate of fall in velocity is represented by the deceleration time (DT) and is a measure of how rapidly early diastolic filling stops. DT becomes shorter when LV compliance decreases. There is an inverse relationship between mean LA pressure and DT. Inertia effects may cause continued forward low-velocity flow during mid-diastole. The higher LA pressure during its contraction causes an increase in velocity (A wave) and is an important parameter of diastolic function. Commonly, the E/A ratio is used to assess LV diastolic function and is > 1.

The normal aortic flow velocity pattern is shown in Fig. 2.35. Flow in the left ventricular outflow tract (LVOT) is interrogated with the pulsed-wave sample 1 cm below the aortic valve and the velocities are used in the continuity equation to calculate aortic valve surface area. The reference values in healthy subjects are presented in

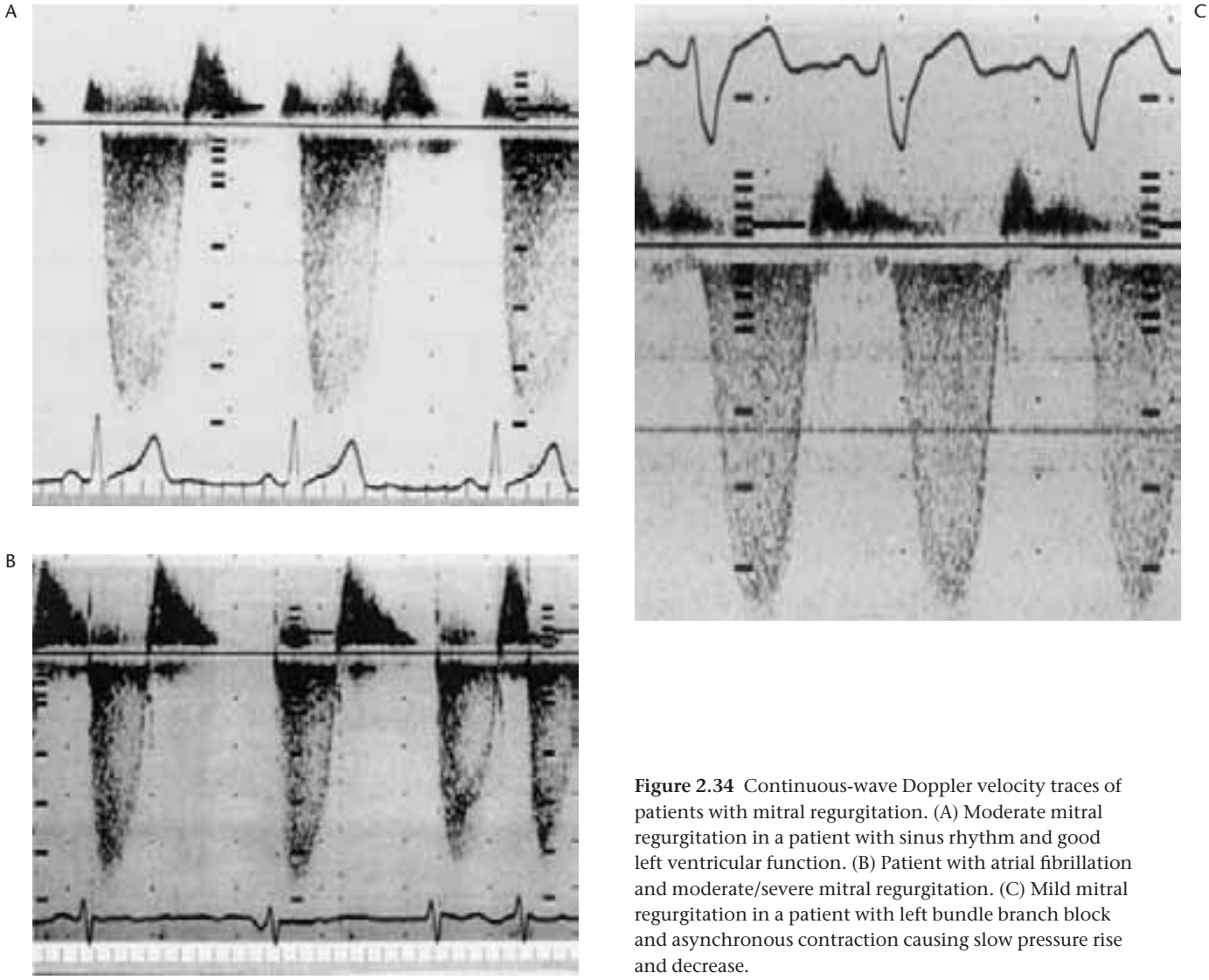

Figure 2.34 Continuous-wave Doppler velocity traces of patients with mitral regurgitation. (A) Moderate mitral regurgitation in a patient with sinus rhythm and good left ventricular function. (B) Patient with atrial fibrillation and moderate/severe mitral regurgitation. (C) Mild mitral regurgitation in a patient with left bundle branch block and asynchronous contraction causing slow pressure rise and decrease.

Table 2.4 Reference values (± 1SD) for transvalvular Doppler velocities (cm/s)

	Adults		Children	
	Mean	Range	Mean	Range
Mitral valve	90	60–130	100	80–130
Tricuspid valve	50	30–70	60	50–80
Pulmonic valve	75	60–90	90	70–110
Aortic valve	135	100–170	150	120–180
Left ventricular outflow tract	100	70–110	100	70–120

Reproduced with permission from Hatle and Angelsen [50].

Table 2.4 [52,53]. The transtricuspid flow velocity pattern is similar in morphology to the transmitral flow pattern but the velocities are lower (Table 2.4). The flow velocity patterns recorded proximal and distal to the pulmonary valve are similar to those obtained from the aortic valve but peak velocities are significantly lower.

Pulmonary vein velocity pattern

In most patients the flow velocity profile of the right upper pulmonary vein can be interrogated from a foreshortened apical cross-section with the Doppler sample volume placed just inside the vein. All pulmonary veins

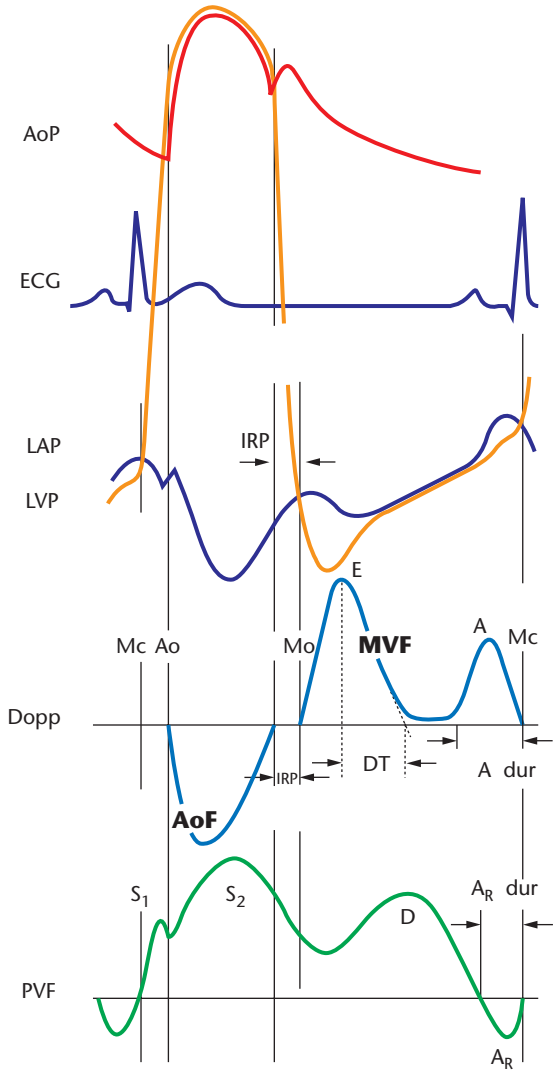

Figure 2.35 Intracardiac pressure tracings from the aorta (AoP), left ventricle (LVP) and left atrium (LAP) with the corresponding Doppler aortic (AoF), mitral (MVF) and pulmonary vein (PVF) flow velocity patterns. The isovolumic relaxation period (IRP) is the interval between aortic valve closure (Ac) and the onset of left ventricular (LV) filling at mitral valve opening (Mo) on the Doppler trace. Ac is best defined on a simultaneously recorded phonocardiogram but a more practical way is by positioning the sample volume of the pulsed-wave Doppler halfway between the anterior mitral leaflet and the outflow tract. AoF and MVF are both recorded as shown on the diagram. The time interval between the end of AoF (aortic valve closure, Ac) and the onset of MVF (mitral valve opening, Mo) represents IRP. During relaxation there is a pressure cross-over between left atrial and LV pressure, which causes the mitral valve to open and rapid filling to occur (E wave). In this part of the cardiac cycle LV relaxation is still ongoing, causing a continuing drop in LV pressure and reflects the speed of the initial part of myocardial relaxation. Prolonged IRP is a sensitive marker of abnormal myocardial relaxation. The area under the E wave is the velocity time integral and reflects the contribution of the rapid filling phase in LV diastolic filling. The deceleration time (DT) is a measure of how rapidly early diastolic filling stops. It is represented by the time interval between the E peak and the point on the baseline where the descending limb crosses the baseline. The A wave is associated with atrial contraction and is an important index of diastolic function. The area under the A wave is the velocity time integral and reflects the contribution of atrial contraction to LV diastolic filling. The normal PVF usually has a biphasic (occasionally triphasic with S_1 wave) flow with a slightly greater systolic (S_2) than diastolic (D) wave and a small retrograde flow wave during atrial contraction (A_R). The A_R wave may become larger with increasing age. A dur, A-wave duration; A_R dur, A_R duration; Ao, aortic valve opening; Mc, mitral valve closure.

are readily imaged via the transoesophageal approach. The normal pulmonary vein flow pattern is shown in Fig. 2.35. It is usually biphasic with a predominant systolic forward flow (S wave) and a less prominent diastolic forward flow wave (D wave). Occasionally, there may be a triphasic flow pattern with two distinct systolic flow waves, of which the initial flow into the LA results from atrial relaxation followed by a further inflow due to the increase in pulmonary venous pressure. The D wave occurs when there is an open conduit between the pulmonary vein, LA and LV and reflects the transmitral E wave. A retrograde flow wave into the pulmonary vein (A_R wave) occurs during atrial contraction and its amplitude and duration are related to LV diastolic pressure, LA compliance and heart rate [8]. In normal subjects, the amplitude of the A_R wave is generally less than 25 cm/s and its duration is shorter than that of the transmitral A wave.

Tissue Doppler velocity imaging

The normal heart shows synchronous contraction and relaxation, with maximum velocities at the base and decreasing towards the apex, which shows an opposite velocity direction. The centre towards contraction of the LV walls lies in an area which is situated 70% down in the LV cavity on a virtual line connecting the anterolateral aortic valve edge to the apex in end-systole [54]. This basic knowledge of the ventricular contraction pattern was obtained with endocardial markers implanted during open heart surgery and is now confirmed by tissue Doppler echocardiography. The maximum velocity is found during the first third of systole and is colour-coded in the four-chamber and five-chamber views in both LV walls [55].

Using M-mode recordings, the timing of contraction and relaxation, including the periods of isovolumic

contraction and relaxation, can be determined in order to assess global and regional wall function [56]. This has been confirmed with invasive measurements [57].

In the absence of gross LV shape abnormalities or severe regional wall motion abnormalities, mitral annulus motion reflects volume changes rather than pressure differences between the LA and the LV and is less load dependent than the transmitral inflow velocity pattern. Mitral annulus velocity can be measured by TDI. The normal mitral annulus velocity pattern is shown in Figs 2.46 and 2.47.

It should be noted that annulus velocities may differ around its circumference and that an average value of septal, anterior, lateral and posterior velocities should be used, especially in patients with regional wall motion abnormalities. In the systolic phase the annulus shows anterior motion, which starts after the isovolumic contraction. The diastolic phase includes the isovolumic relaxation period (IRP), early rapid diastolic filling (E′ wave) followed by diastasis and atrial contraction, which causes the late diastolic A′ wave. The E′ wave is larger than the A′ wave and mirrors the transmitral flow velocity pattern. Peak systolic mitral annulus velocity correlates with the peak rate of LV pressure rise (dP/dt). TDI annulus velocity measurements are used for differentiating pseudo-normal from normal transmitral inflow patterns since early diastolic velocity of the mitral annulus (E′ wave) is relatively preload independent and correlates with LV relaxation [58]. The peak transmitral E′ wave velocity ratio correlates with main pulmonary capillary wedge pressure.

Colour M-mode transmitral flow

The rate of flow propagation from the LA into the LV is determined by the rate of relaxation and diastolic LV suction and is also helpful in differentiating between normal and pseudo-normal transmitral velocity patterns [59]. The colour M-mode method offers a practical means to rapidly screen for a diastolic inflow abnormality during the examination procedure. In practice, an M-mode cursor is placed parallel to the mitral inflow and adjusted so that the longest column of colour flow from mitral valve to apex is recorded (see Figs 2.46 and 2.47). The propagation velocity is measured by the slope along a distinct isovelocity (aliasing) line during early filling from the mitral valve plane up to 4 cm into the LV cavity. The normal value is > 40 cm/s.

Doppler haemodynamics

Both M-mode and two-dimensional echocardiography provide indirect qualitative information on haemodynamic abnormalities (Table 2.5). However, Doppler echocardiography allows accurate quantitative assessment of intracardiac haemodynamics and is currently the preferred method.

Volume flow

Stroke volume and cardiac output

Volume flow across an orifice is the product of its cross-sectional area (CSA) and the blood flow velocity (V). The flow velocity varies during ejection. Therefore, in order to obtain the total volume, the individual velocities during a given ejection period must be integrated (the sum of the individual velocities), i.e. the

Table 2.5 Indirect M-mode and two-dimensional echocardiographic signs of haemodynamic abnormalities

Sign	Abnormality
Mitral valve flutter	Aortic regurgitation
'B' notch on mitral or tricuspid valve	Elevated LA or RA end-diastolic pressure
Systolic anterior motion of mitral valve	Dynamic LVOT obstruction, pseudo-obstruction
Premature mitral valve closure	High LV pressure
Premature aortic valve closure	Fixed (membranous) subaortic stenosis
Mid-systolic aortic valve closure	Dynamic LVOT obstruction
Dilated inferior vena cava: non-collapsing during inspiration	High RA pressure
Absent A wave and systolic W-shape of (mid-systolic closure) pulmonary valve tracing	Pulmonary hypertension
Diastolic RA and RV wall collapse	Cardiac tamponade
Abnormal paradoxical septal motion	See Table 2.7

LA, left atrium; RA, right atrium; RV, right ventricle; LV, left ventricle; LVOT, left ventricular outflow tract.

velocity time integral (VTI). Stroke volume (SV) is then calculated as:

$$SV = CSA \cdot VTI$$

Built-in software allows Doppler velocity waveforms to be traced directly from the screen to obtain VTI. The CSA of the LVOT is most commonly used but can also be measured at other orifices. For practical reasons these are assumed to be circular and only the diameter (D) is measured. CSA is calculated as follows:

$$CSA = \pi(D/2)^2 = 0.785D^2$$

$$SV = 0.785D^2 \cdot VTI$$

Cardiac output (CO) is obtained by the product of SV and heart rate. The cardiac index is CO divided by body surface area.

Regurgitant volume

Two methods can be used: the volumetric and the PISA methods.

VOLUMETRIC METHOD

Total forward flow (Q) across a leaking valve is the sum of SV and regurgitant volume. Consequently:

$$\text{Regurgitant volume} = Q - SV$$

In aortic regurgitation, the regurgitant volume is calculated by subtracting the mitral inflow volume, which in the absence of mitral regurgitation equals SV, from the LVOT (or aortic) forward flow (Q_{Ao}). In mitral regurgitation, the regurgitant volume is calculated as the mitral inflow volume (Q_{MR}) minus the LVOT forward flow, which in the absence of aortic regurgitation equals SV. Mitral inflow volume is calculated from the mitral VTI and its CSA.

Regurgitant fraction is the percentage regurgitant volume of the total flow through the regurgitant valve.

$$\text{Regurgitant fraction (\%)} = (Q - SV/Q) \times 100$$

PISA METHOD

The total volume through a leaking valve is estimated by the product of the effective regurgitant orifice area (EROA) and regurgitant VTI (VTI_{reg}) [60].

$$\text{Regurgitant volume} = EROA \cdot VTI_{reg}$$

EROA is estimated using the PISA method (Fig. 2.36) [61]. On colour Doppler flow images, the region proximal to the regurgitant orifice shows smoothly accelerating blood flow as it rushes into the EROA and forms a series of hemispherically shaped isovelocity contours of decreasing surface area and increasing velocities. All the blood passing through these isovelocity contours must also pass through the EROA (conservation of mass). Flow is estimated by measuring the radial distance (r) from the

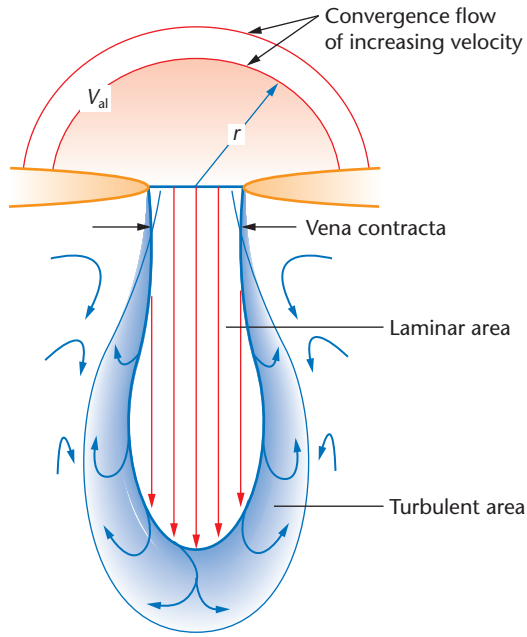

Figure 2.36 The principle of the proximal isovelocity surface area (PISA) method and vena contracta measurement for regurgitant volume measurement. The vena contracta or narrowest extent of the regurgitant jet as it passes through the effective regurgitant orifice correlates well with the severity of mitral regurgitation. This method assumes that the regurgitant orifice does not alter in shape or size during septole and should therefore not be applied to initial valve prolapse. As blood flow accelerates towards the regurgitant orifice, concentric rings of isovelocity regions are produced and are visualized as concentric isovelocity hemispheres with colour Doppler. The smallest hemisphere nearest the regurgitant orifice has the highest velocity. The PISA radius (r) is the radial distance between this nearest aliasing contour (V_{al}) and the centre of the regurgitant orifice. The regurgitant jet area consists of the laminar area with the highest velocities and a turbulent area caused by the high laminar flow jet in the stagnant blood volume.

EROA to the PISA and calculating the surface area of this isovelocity hemisphere or PISA ($2\pi r^2$). The product of that surface area and the aliasing velocity (V_{al}) gives the instantaneous volume flow through the PISA, which equals the flow rate through the EROA.

$$\text{Volume flow} = 2\pi r^2 V_{al}$$

EROA can now be estimated by dividing the volume flow by the regurgitant velocity. For example, in mitral regurgitation the EROA is estimated as follows:

$$EROA = \frac{\text{Volume flow}}{V_{MR}} = 2\pi r^2 \times \frac{V_{al}}{V_{MR}}$$

$$\text{Regurgitant volume} = 2\pi r^2 \frac{V_{al}}{V_{MR}} \times VTI_{MR}$$

The same principle can be used in aortic regurgitation.

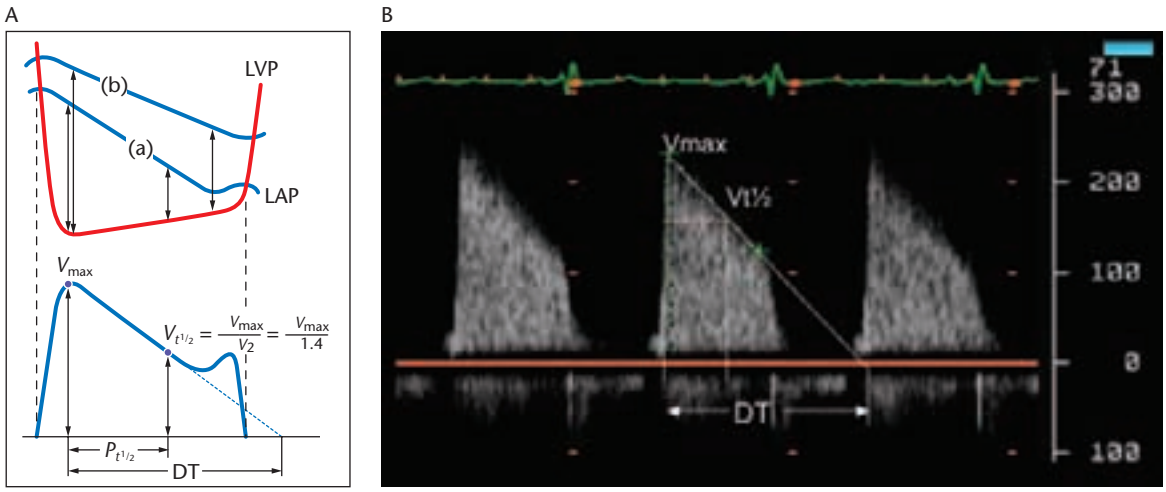

Figure 2.37 Calculation of pressure half-time in mitral stenosis. (A) Diastolic left ventricular (LVP) and left atrial (LAP) pressures are shown with the Doppler velocity trace. The pressure gradient linearly decreases during diastole (a) resulting in a linear decrease of transmitral velocities. In more severe mitral stenosis (b) the transmitral peak gradient is higher, its fall slower and the interval to reach the half-value is prolonged (see arrows). (B) Recording of a patient with mitral stenosis. V_{max} is 2.3 m/s; using the equations in the text $V_{t^1/_2}$ is 2.3/1.4 = 1.64 m/s. The time interval between V_{max} and $V_{t^1/_2}$ on the Doppler trace is 135 ms. The deceleration time (DT) can also be measured and is 480 ms. Using the equations in the text $P_{t^1/_2}$ is 0.29 × 480 = 139 ms. The valve surface area is 220/135 (or 220/139) or 1.63 cm^2 (1.58 cm^2).

Shunts

The magnitude of an intracardiac shunt is expressed as the flow ratio between the pulmonary (Q_p) and systemic (Q_s) circulation. Q_p is measured in the right ventricular outflow tract, i.e. $(CSA \cdot VTI)_{RVOT}$, and Q_s in the left ventricular outflow tract, i.e. $(CSA \cdot VTI)_{LVOT}$.

$$Q_p/Q_s = (CSA \cdot VTI)_{RVOT}/(CSA \cdot VTI)_{LVOT}$$

Pressure gradient

Doppler velocities allow measurement of the instantaneous pressure drop (gradient) across stenotic orifices or restrictive defects. These are calculated by applying the simplified Bernoulli equation, which is based on the principle of conservation of energy (pressure energy vs. kinetic energy) [50].

$$\text{Pressure gradient (in mmHg)} = 4V^2$$

where V is the peak blood flow velocity (m/s) at the stenotic valve (or restrictive defect) measured with continuous-wave Doppler. The Doppler-derived pressure gradient is the maximal instantaneous pressure difference and is always larger than the pressure gradient measured at cardiac catheterization. The mean pressure gradient is an average of the instantaneous pressure gradients during the total flow period and correlates better with catheter measurements.

The Doppler velocity waveforms are interactively traced from the display screen and peak velocity, maximal pressure gradient and mean pressure gradient are calculated by integrated software.

Valve surface area

Three methods can be used: the pressure half-time, the continuity equation and the PISA method.

Pressure half-time

In mitral stenosis, the pressure difference between the LA and LV is maximal at the onset of diastole and decreases linearly after valve opening. The time course of the decrease of pressure fall can be expressed as the time needed to reach half-maximal pressure difference ($P_{t^1/_2}$) and is the same as the time for peak velocity (V_{max}) to fall to a value that equals V_{max} divided by 1.4 (Fig. 2.37).

$$P_{t^1/_2} = {}^1/_2 P_{max} = 4(V_{t^1/_2})^2 - {}^1/_2 4(V_{max})^2$$

$$V_{t^1/_2} = V_{max}/\sqrt{2} \quad \text{or} \quad V_{max}/1.4$$

Pressure half-time (PHT) is also calculated from DT (the time interval for peak velocity to reach zero baseline) and is always 0.29DT (0.29 is an algebraic constant that converts velocity to pressure) (Fig. 2.37). Mitral valve area (MVA) is then estimated using the empiric constant 220.

$$\text{MVA} = 220/\text{PHT} \quad \text{or} \quad 220/0.29\text{DT}$$

In severe aortic regurgitation, the diastolic pressure difference between the aorta and LV decreases rapidly with shortening of the deceleration time. The PHT of the regurgitant jet can be used to estimate the severity of the regurgitation (Fig. 2.38) (see also Chapter 21).

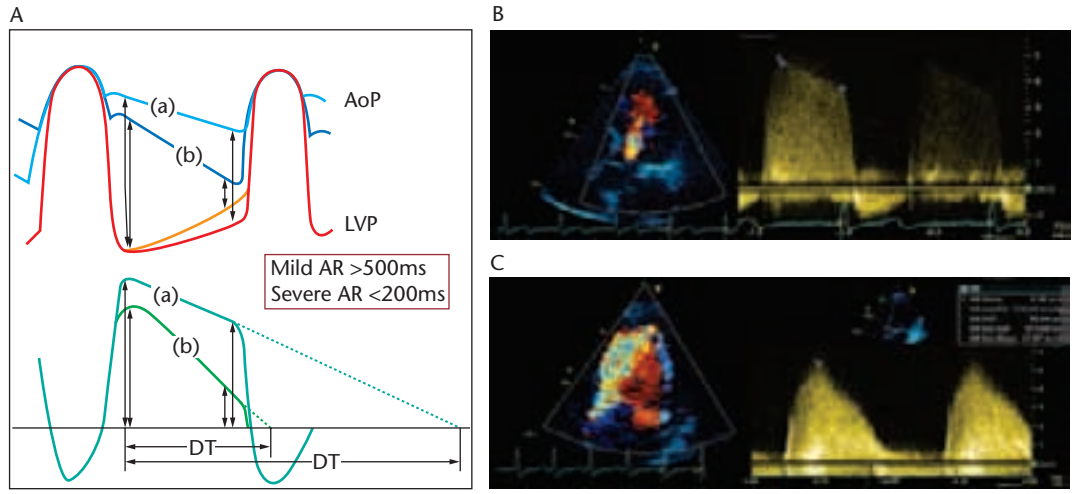

Figure 2.38 (A) In aortic regurgitation (AR) the pressure half-time becomes progressively shorter with severity of disease. The left ventricular (LVP) and aortic (AoP) pressure traces are shown with the corresponding Doppler velocity traces. With more severe AR (b) the pressure decreases more rapidly and is associated with a rapid rise in diastolic LVP. The pressure gradient rapidly becomes lower and the velocity rapidly decreases resulting in a shorter deceleration time (DT) than in mild AR (a). (B) Velocity recording of a patient with a pressure half-time of 470 ms indicating mild/moderate AR. (C) Patient with a pressure half-time of 90 ms indicating severe AR. Pressure half-time is automatically calculated by machine software after marking two points on the slope of velocity trace. The colour Doppler flow images show the moderate jet and the larger jet reaching the apex in severe aortic regurgitation.

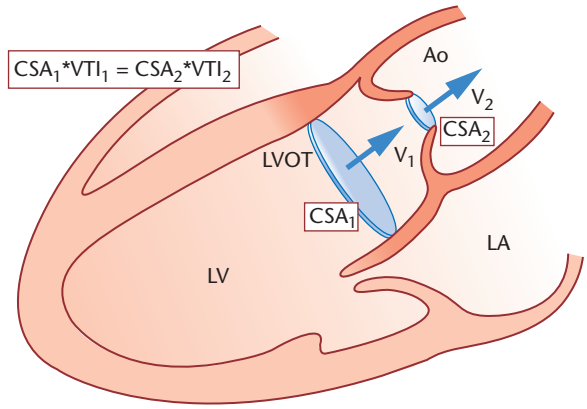

Figure 2.39 Principle of stenotic orifice area calculation based on the continuity equation (see text).

Continuity equation

This is based on the principle of conservation of mass, which states that flow proximal to the stenosis is equal to the flow across the stenosis.

$$CSA_1 \cdot VTI_1 = CSA_2 \cdot VTI_2$$

The flow velocity integral proximal to the stenosis and in the stenosis and the CSA proximal to the stenosis or regurgitant orifice can be calculated (Fig. 2.39). Consequently:

$$CSA_2\ (cm^2) = CSA_1 \cdot VTI_1 / VTI_2 = SV / VTI_2$$

For aortic stenosis, the valve area equals SV/VTI_{Ao} and for mitral stenosis SV/VTI_{MS}. (These equations cannot be used in the presence of aortic and mitral regurgitation.)

PISA method

By measuring the volume flow using the PISA method through the stenotic mitral valve, its surface area (MVA) can be calculated using the continuity equation:

$$MVA = 2\pi r^2 \times \frac{V_{al}}{Peak\ V_{mitr}} \times \alpha/180^\circ$$

When the angle (α) of the mitral leaflets relative to the inflow direction is different, a correction factor (α/180°) should be used.

Intracardiac pressures

Doppler is a reliable alternative to cardiac catheterization for the assessment of intracardiac haemodynamics in most clinical conditions. As shown above, Doppler echocardiography allows non-invasive measurement of pressure gradients across valves or chamber defects. It is fortunate that (trivial) valvular closure-associated regurgitation is commonly present in the normal condition (physiological) and even more so in cardiac disease so that these measurements are possible. Accurate beam alignment is necessary in order to minimize velocity underestimation related to non-parallel beam angles.

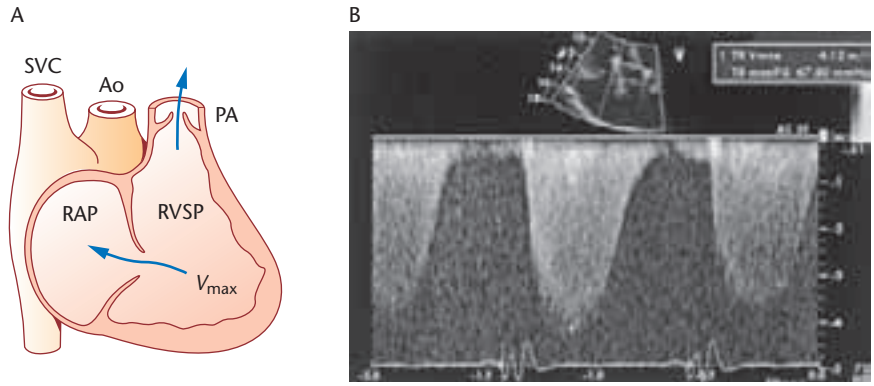

Figure 2.40 Basic principle involved in measuring intracardiac pressures and gradients. (A) This diagram shows the principle of right ventricular systolic pressure (RVSP) measurement. Right atrial pressure (RAP) is estimated from the central venous pressure or imaging of the inferior vena cava and its diameter change during respiration. From V_{max}, the pressure gradient between RV and RA is calculated. (B) Doppler velocity trace of a tricuspid regurgitant jet of 4.12 m/s. The instantaneous pressure gradient is thus 67.8 mmHg. Adding RAP gives an RVSP of 77.8 mmHg.

Table 2.6 Estimation of right atrial pressure (RAP)

Inferior vena cava diameter (cm)	Respiratory change (%)	Estimated RAP (mmHg)
< 1.5	Collapse	0–5
Nl (1.5–2.5)	Decrease > 50	5–10
Nl (1.5–2.5)	< 50	11–15
> 2.5	Decrease < 50	16–20
> 2.5	No change	> 20

Reproduced with permission from Otto [62].

M-mode and two-dimensional echocardiographic signs may provide indirect qualitative evidence of abnormal haemodynamics (see Table 2.5).

Right ventricular systolic pressure (RVSP) is calculated by interrogating the tricuspid regurgitant jet which is commonly present. Its maximal (peak) velocity (V_{max}) is converted to a pressure gradient with the simplified Bernoulli equation. By adding the pressure of the receiving chamber, in this case right atrial pressure (RAP), the RVSP is obtained (Fig. 2.40):

$$RVSP = 4(V_{max})^2 + RAP$$

RAP can be estimated by measuring the diameter of the inferior vena cava and its percentage collapse during respiration (Table 2.6).

This principle is the basis of measuring intracardiac pressures. Echo contrast injection for Doppler signal enhancement may allow more accurate peak velocity measurements in patients with poor Doppler signals. Similarly, in mitral regurgitation, the velocity reflects the pressure difference between the LV and LA. In the absence of LVOT obstruction, the cuff-measured systolic brachial artery pressure (SBP_{cuff}) equals LV systolic pressure. Consequently, left atrial pressure (LAP) is calculated as follows:

$$LAP = SBP_{cuff} - 4(V_{MR})^2$$

In mitral stenosis:

$$LAP = LVEDP + \text{mitral gradient}$$

where LVEDP denotes LV end-diastolic pressure. In aortic regurgitation, the regurgitant velocity reflects the diastolic pressure difference between the aorta and LV. Therefore:

$$LVEDP = SBP_{cuff} - 4(V_{ARend\text{-}diastole})^2$$

In the presence of a ventricular septal defect, the colour Doppler flow identified shunt can be interrogated with continuous-wave Doppler and the LV-to-RV or ventricular septal defect pressure gradient measured from the velocity recordings. SBP_{cuff} represents LV peak systolic pressure in the absence of LVOT obstruction. Hence:

$$RVSP = SBP_{cuff} - 4(V_{LV\text{–}RV})^2$$

In patients with an LVOT outflow gradient:

$$LVSP = SBP_{cuff} + \text{LVOT gradient}$$

The RV diastolic pressure (RVDP) equals RAP in the absence of tricuspid stenosis but can also be estimated as:

$$RVDP = LVEDP - 4(V_{LV\text{–}RV})^2_{diast}$$

When right ventricular outflow tract (RVOT) obstruction is absent, the pulmonary artery systolic pressure (PASP) equals RVSP. Both RVOT and pulmonary valve velocities should always be measured in the presence of elevated RVSP in order to exclude RVOT obstruction. In the presence of pulmonary stenosis (PS):

$$PASP = RVSP - PS_{gradient}$$

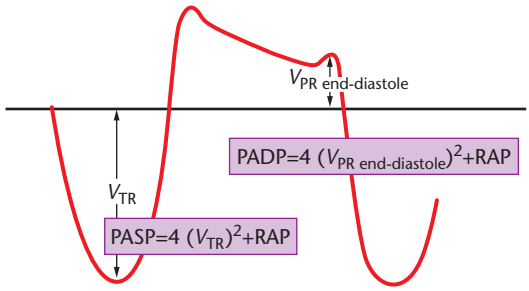

Figure 2.41 The principle involved in measuring systolic (PASP) and end-diastolic pulmonary artery (PADP) pressure. V_{PR} is the end-diastolic regurgitant PA jet velocity and V_{TR} is the systolic tricuspid regurgitant jet velocity. RAP, right atrial pressure.

Pulmonary regurgitation (PR) is common in pulmonary hypertension and allows estimation of the pulmonary artery (PA)-to-RV pressure gradient and pulmonary artery diastolic pressure (PADP). This principle is shown in Fig. 2.41. The end-diastolic PR velocity is measured and the pressure difference between PA and RV is calculated:

$$PADP = 4(V_{PRend\text{-}diastole})^2 + RAP$$

where RAP (right atrial pressure) equals RV end-diastolic pressure. The early (peak PR velocity) diastolic pressure difference between PA and RV closely corresponds to the mean PA pressure and is estimated using the same formula as for PADP. (For estimating LV filling pressures, see Assessment of left ventricular diastolic function, below.)

Assessment of left ventricular systolic function

Assessment of both systolic and diastolic left ventricular function is the most common request for, and an essential part of, the echocardiographic examination. Global systolic function assessment is based on size and volume changes, while the diagnosis of ischaemic myocardial disease is based on segmental wall motion analysis.

Global left ventricular systolic function

M-mode echocardiography: dimensions

Simple M-mode-derived parameters indicating impaired LV function include mitral E point–septal separation (EPSS) greater than 7 mm (dilated left ventricle) (see Fig. 2.6), 'B' bump or AC notch on the mitral valve trace (elevated end-diastolic pressure) and decreased systolic anterior motion of the aortic root (low SV).

LV dimensions are measured in end-systole (ESD) and end-diastole (EDD) at chordal level from two-dimensional guided M-mode tracings in the parasternal long-axis and short-axis views (see Fig. 2.22). Linear cavity dimensions are useful for detecting LV dilatation and can be used for follow-up of patients and for calculating the percentage change in LV dimension during systolic contraction (fractional shortening).

$$\text{Fractional shortening (in \%)} = \frac{EDD - ESD}{EDD} \times 100$$

Interventricular and posterior wall thickness in end-systole (TES) and end-diastole (TED) are used to calculate their systolic thickening.

$$\text{Systolic thickening (in \%)} = \frac{TES - TED}{TES} \times 100$$

For LV mass calculation, see p. 53.

Two-dimensional echocardiography: areas and volumes

When end-diastolic surface area (EDA) and end-systolic surface area (ESA) are measured using planimetry of two-dimensional views of the LV, the fractional area change can be calculated.

$$\text{Fractional area change (in \%)} = \frac{EDA - ASA}{EDA} \times 100$$

Acoustic quantification (see above) allows online computation of LV cavity area changes from the automatically generated endocardial boundaries. These can be displayed as an area vs. time curve synchronized with the ECG.

For determination of ejection fraction one has to calculate both end-diastolic volume (EDV) and end-systolic volume (ESV) (see p. 56). Manual tracing of LV endocardial borders from two-dimensional echocardiograms is time-consuming and tedious. Currently, real-time semi-automated border detection systems (acoustic quantification) are integrated into most ultrasound systems and allow rapid calculation of volumes and ejection fraction.

$$\text{Ejection fraction (in \%)} = \frac{EDV - ESV}{EDV} \times 100$$

Doppler-derived systolic indices

Several Doppler indices have been proposed for assessment of LV systolic function. SV and CO (see p. 64), ejec-

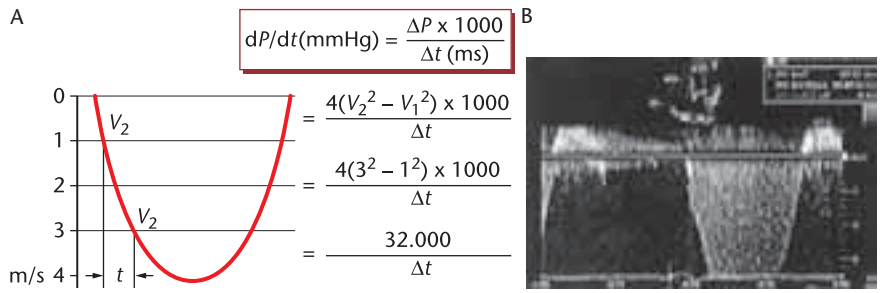

Figure 2.42 Measurement of left ventricular d*P*/d*t* from the mitral regurgitant velocity trace. (A) d*P*/d*t* can be estimated from the rate of rise of velocity of the mitral regurgitant jet. The time interval (d*t* in ms) between regurgitant velocities of 1 and 3 m/s is measured from the velocity waveform (recording speed of 100 mm/s must be used). It is assumed that left atrial pressure does not change significantly in this time interval. (B) In most systems the acceleration slope is automatically calculated after marking the velocity waveform at 1 and 3 m/s. In this patient d*P*/d*t* is 400 mmHg/s.

tion time, myocardial performance index and d*P*/d*t* are used. Peak aortic flow velocity has also been proposed but this index is highly load dependent.

GLOBAL LEFT VENTRICULAR PERFORMANCE

A Doppler-derived myocardial performance index (MPI) or time ejection index, which combines systolic and diastolic time intervals, can be used for the assessment of overall cardiac function. This index is the sum of isovolumic contraction and relaxation time divided by the ejection time [63]. These time intervals are readily obtained with Doppler echocardiography from the mitral closure–mitral opening interval minus ejection time, divided by the ejection time (see Fig. 2.35). This index can also be used for RV function assessment [63,64]. The normal value is 0.40 ± 0.05. It is also helpful in valvular heart disease for discriminating between normal and impaired ventricular function, and for the prediction of prognosis [65–67].

LEFT VENTRICULAR CONTRACTILE FUNCTION (d*P*/d*t*)

d*P*/d*t* represents the rate of rise of LV pressure and reflects systolic contractile function. d*P*/d*t* can be estimated from the rate of rise of velocity of the mitral regurgitant jet [68] (Figs 2.42 and 2.49). The time interval (d*t* in ms) between regurgitant velocities of 1 and 3 m/s is measured from the velocity waveform (recording speed of 100 mm/s must be used). The Bernoulli equation allows calculation of the pressure change during that period, i.e. $4(3^2 - 1^2) = 32$ mmHg. Hence:

$$dP/dt\ (mmHg/s) = 32 \times 1000/dt$$

The normal value is > 1200 mmHg/s.

Similarly, RV contractile function can be estimated from tricuspid velocity signals. The negative d*P*/d*t* is estimated from the dowstroke of the regurgitant velocity waveform.

Table 2.7 Differential diagnosis of paradoxical motion of the interventricular septum (IVS)

Increased right ventricular internal dimension (> 30 mm)
Normal IVS thickening (> 30%)
Right ventricular volume overload
Primary pulmonary hypertension
Reduced IVS thickening (< 30%)
Coronary artery disease
Dilated cardiomyopathy
Normal right ventricular internal dimension (< 30 mm)
Normal IVS thickening (> 30%)
Postoperative patients
Acute right ventricular volume overload
Constrictive pericarditis
Pericardial effusion (large)
Intraventricular conduction abnormalities
Reduced IVS thickening (< 30%)
Coronary artery disease
Left bundle branch block (typical early systolic notch)
Hypertrophic cardiomyopathy (septal hypertrophy)

Segmental left ventricular function

Detailed motion analysis of the interventricular septum from M-mode echocardiography may allow a specific diagnosis (Table 2.7 and Fig. 2.43). For two-dimensional echocardiographic analysis the LV is divided into three levels (basal, mid and apical) and 16 segments for standardized analysis from multiple parasternal and apical views. LV wall function is graded using a scoring scale in which 1 denotes normal function, 2 hypokinesis, 3 akinesis and 4 aneurysmal dyskinesis for each individual segment (Figs 2.16 and 2.44). For quantitative analysis, colour kinesis can be used (see Fig. 2.16). Recently, analytical software has become available for rapid segmental analysis.

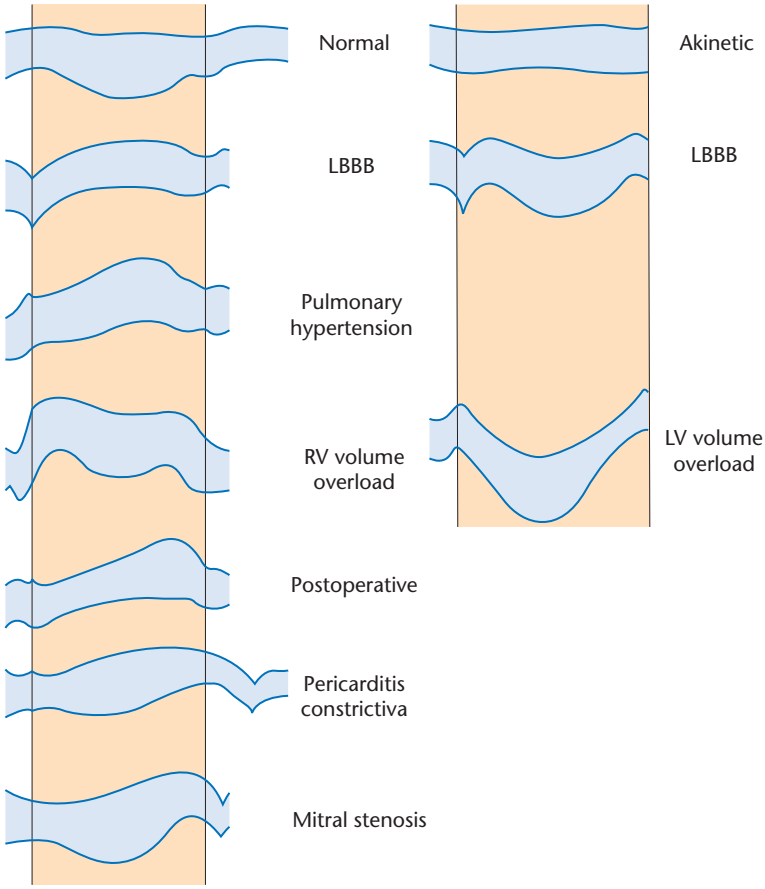

Figure 2.43 Specific diagnostic motion patterns of the interventricular septum on M-mode echocardiography. LBBB, left bundle branch block; LV, left ventricle; RV, right ventricle.

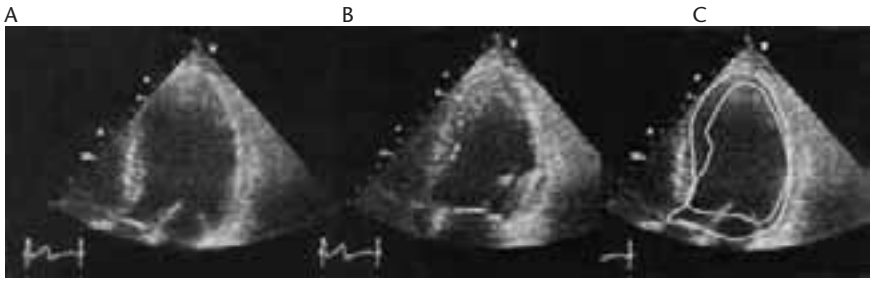

Figure 2.44 Segmental wall function analysis: postinfarct lateral wall hypokinesis shown in the AP4C view. The left ventricle is dilated. Superposition of the traced endocardial contours at end-diastole (A) and end-systole (B) shows the hypokinesis and compensatory hyperkinesis of the interventricular septum. (C) shows the superimposed end-diastolic and end-systolic contours.

Tissue Doppler velocity imaging is now also used for segmental wall function analysis (see Principles of Doppler echocardiography, above).

Right ventricular function

Measurement of RV volume and mass by M-mode and two-dimensional echocardiography remains problematic because the assumptions used for LV volume calculation do not apply (see p. 54). The MPI index can be used to detect RV global dysfunction. Three-dimensional echocardiography provides excellent estimations and will rapidly become the method of choice for volume-based RV function assessment.

Assessment of left ventricular diastolic (dys)function and filling pressure

Assessment of diastolic LV function and estimation of filling pressures is an important part of the management of patients with heart disease. It is well known that symptoms and prognosis are better related to diastolic than systolic function and that physical signs provide limited information. Recent studies have validated Doppler flow and tissue velocity measurements for reliable and non-invasive evaluation of filling dynamics in patients with LV dysfunction and heart failure [69].

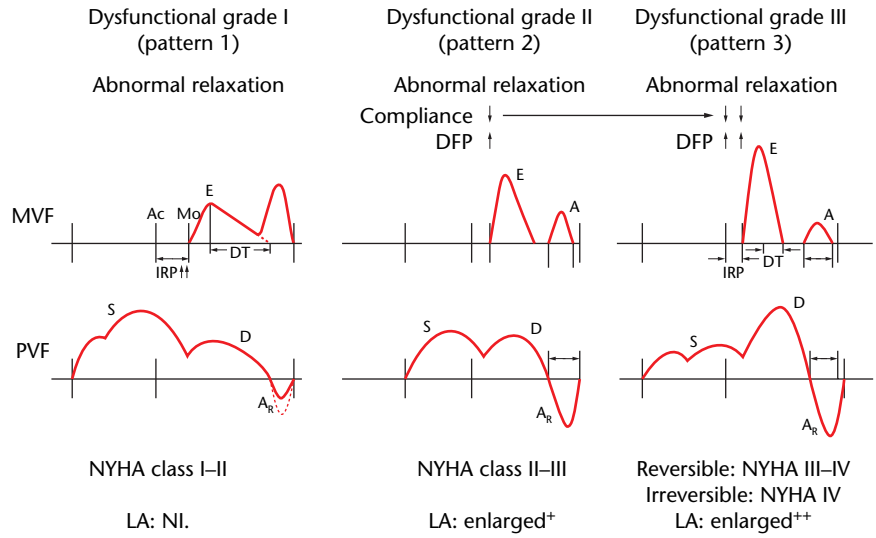

Figure 2.45 Basic abnormal mitral valve (MVF) and pulmonary vein (PVF) Doppler flow velocity patterns corresponding to different grades of left ventricular (LV) dysfunction. Pattern 1 is seen in patients with abnormal relaxation. The isovolumic relaxation period (IRP) is prolonged, the E wave decreased, deceleration time (DT) prolonged and the A wave increased as a result of increased atrial contribution to LV filling. The E/A ratio is < 1 and the D wave on the PVF becomes smaller in proportion to the reduction of the E wave. Pattern 2 shows pseudo-normalization when the decreased LV compliance causes increased diastolic filling pressure (DFP). In these patients, there is increased flow reversal into the pulmonary veins and the amplitude of the A_R wave increases, as well as its duration. Pattern 3 is the typical waveform of restrictive LV filling, when LV compliance further deteriorates causing increased E-wave velocity, shortened DT and low A-wave velocity. Most of the atrial contraction results in flow reversal into the pulmonary veins and A_R duration is much longer than the transmitral A duration.

Table 2.8 Assessment of diastolic (dys)function: transmitral Doppler velocities

		Normal	Abnormal relaxation	Restrictive filling
Isovolumic relaxation period	< 40 years	70 ± 12 ms	> 110 ms	< 60 ms
	> 40 years	80 ± 12 ms	> 110 ms	< 60 ms
Deceleration time		200 ± 32 ms	> 240 ms	< 150 ms
E wave		0.85 ± 0.15 m/s	< 0.50 m/s	> 1.20 m/s
A wave		0.55 ± 0.15 m/s	< 0.80 m/s	30 m/s
E/A ratio		> 1	< 1	> 2

Assessment of left ventricular diastolic dysfunction

Different grades of LV diastolic dysfunction result in different flow velocity patterns. The basic patterns of abnormal transmitral and pulmonary vein Doppler flow velocities are shown diagrammatically in Fig. 2.45 and the transmitral Doppler velocities in Table 2.8.

Pattern 1 is seen in patients with impaired myocardial relaxation and normal diastolic LA and LV pressures. This pattern is characterized by a prolonged IRP, a decrease in E-wave amplitude, prolonged DT and an increase in A-wave amplitude, the latter being a reflection of compensatory increase in atrial contraction to diastolic filling. The E/A ratio is < 1. The pulmonary venous flow velocity pattern may show a diminished D wave as a result of reduced early diastolic filling and an increased A_R wave when LVEDP is elevated. The E' wave on TDI is decreased and the rate of flow propagation in the LV on colour M-mode is decreased. An abnormal relaxation pattern is common in the elderly but represents the earliest manifestation of diastolic dysfunction in younger individuals.

Patients with an abnormal relaxation pattern (grade I diastolic dysfunction) usually do not have symptoms at rest but may experience mild functional impairment (NYHA class I–IIa)

When diastolic function deteriorates, LV compliance progressively decreases with an increase in LA pressure and size. In fact, LA size is a key indicator of LV diastolic dysfunction. The transmitral flow pattern and more particularly the E wave normalize. This pseudo-normal pattern (pattern 2) is a transition pattern from impaired

relaxation to restrictive filling. In certain clinical conditions this pattern may be confusing and must be distinguished from the normal pattern. In patients who are regularly followed, progression of disease and pseudo-normalization is usually recognized. However, it may be a problem in the patient with minimal symptoms who presents with a normal transmitral velocity pattern. A pseudo-normal pattern can be identified as follows.

- The LA is (moderately) enlarged (a normal LA size makes diastolic dysfunction unlikely) [70].
- The A_R wave on the pulmonary venous flow trace has an amplitude > 25 cm/s and its duration is longer than the transmitral A wave [70].
- The E′ wave on TDI is diminished and the transmitral E/E′ ratio is > 15 [54].
- Colour M-mode shows a reduced flow propagation rate (< 40 cm/s) [71].
- Altering loading conditions (induced, for example, by nitroglycerin, nitroprusside or Valsalva manoeuvre) reveals an impaired relaxation pattern.
- The rate of fall of mitral and/or aortic regurgitation velocity (negative d*P*/d*t*) measured from continuous-wave Doppler velocity recordings provides a direct measurement of LV relaxation rate and is decreased [69].

Patients with a pseudo-normal filling pattern (grade II diastolic dysfunction) experience exertional dyspnoea and have moderate functional impairment (NYHA class IIb–III)

With further decrease of LV compliance as a result of the deterioration of diastolic LV function, LAP increases and a restrictive filling pattern develops (pattern 3). The higher LAP causes an earlier opening of the mitral valve and a shortened IRP, and the low compliance of the LV causes a rapid increase in early LV pressure and a shortened inflow and DT. The E/A ratio is > 2. Forward diastolic pulmonary vein flow stops in mid–late diastole and there is a significant flow reversal in the pulmonary veins during atrial contraction resulting in a prolonged A_R. DTI shows a diminished E′ wave and colour M-mode a low flow propagation rate.

Patients with a restrictive filling pattern (grade III dysfunction) have dyspnoea with minimal exertion and severe functional impairment (NYHA class IV)

Patients with restrictive filling can be further classified into those with reversible and those with irreversible restrictive pattern by altering the loading conditions. Decreasing preload with nitroglycerin or nitroprusside will change reversible restriction to an impaired relaxation pattern, whereas the irreversible pattern remains unchanged [71]. The distinction is important for prognostication and management of patients with advanced heart failure. Those with a reversible pattern can still benefit from medical therapy while those with an irreversible pattern are candidates for a device to assist LV function or for cardiac transplantation. Studies have shown that patients with a mitral annulus A′ wave > 5 cm/s on TDI have a reversible restrictive physiology.

Estimation of left ventricular filling pressure

Several parameters, alone or in combination, can be used to identify patients with an elevated LV filling pressure (Figs 2.45, 2.46 and 2.47 and Table 2.9). However, these parameters must be interpreted in the clinical context considering age, symptoms and functional status.

The initial E-wave velocity is mainly determined by LAP at mitral valve opening and its peak acceleration rate correlates with LV filling pressure. In general, a high E-wave amplitude indicates a high mean LAP and a low E-wave amplitude a low mean LAP. In the presence of systolic dysfunction, an E/A ratio > 2 indicates a high LAP, while a low E/A ratio indicates a low LAP. When the mean LAP is high as a result of a diseased non-compliant LV, DT is shortened. A DT of less than 150 ms represents a mean LAP of 20 mmHg. It should be noted that young subjects with fast relaxation, rapid LV suction and a highly compliant LV may have a high E wave and a short DT (they have no symptoms and good exercise tolerance). The TDI mitral annulus velocity in these subjects is elevated whereas it is decreased in patients with diastolic dysfunction. On the other hand, patients with a dilated LA and LV will always have symptoms and an increased filling pressure.

The difficult patient is the one with mild functional impairment and LV systolic dysfunction who has a pseudo-normal transmitral velocity pattern. Indices derived from the pulmonary vein velocity pattern are then helpful for identifying a pseudo-normal pattern. The S/D ratio or the systolic forward flow fraction (in percent) decreases, and when less than 40% indicates a pulmonary artery wedge pressure higher than 18 mmHg [72]. Other parameters are the amplitude and duration of the A_R wave. When the LV becomes more diseased and non-compliant, transmitral flow after atrial contraction rapidly stops and the flow reversal in the pulmonary veins will increase. An A_R-wave velocity > 25 cm/s and an A_R duration 30 ms longer than that of the transmitral A wave indicate an LVEDP of > 15 mmHg. However, pulmonary vein flow parameters are often difficult to measure especially at faster heart rates.

Two indices that aim at correcting the E-wave velocities for the confounding relaxation rate are the mitral annulus velocity (E′ wave) and the colour M-mode LV

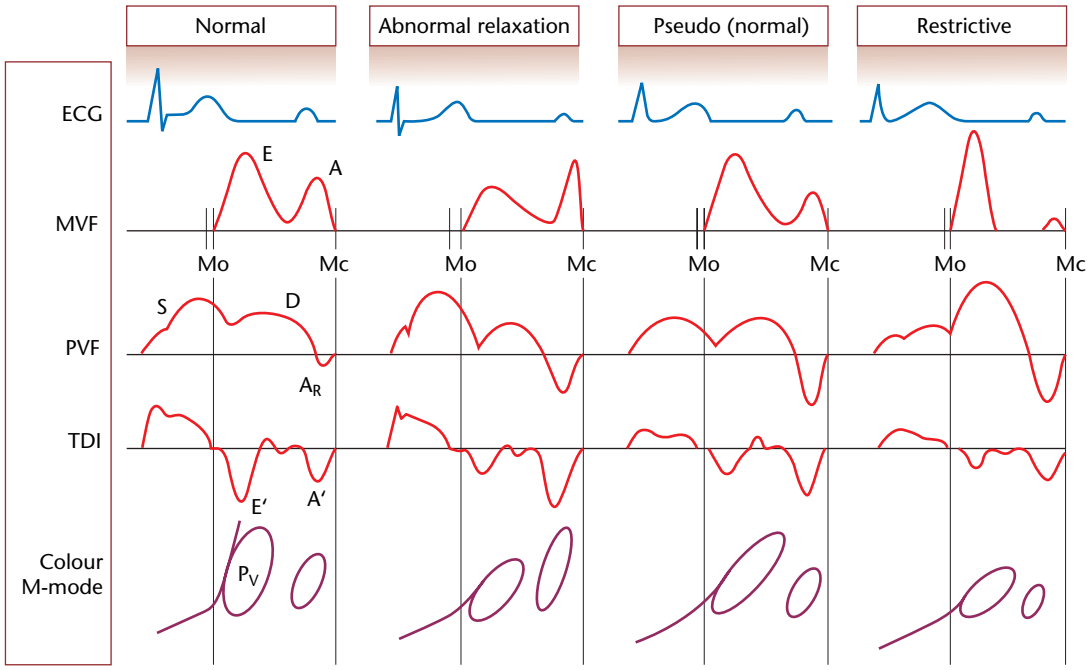

Figure 2.46 Typical mitral valve flow (MVF), pulmonary vein flow (PVF), tissue Doppler mitral annulus velocity (TDI, tissue Doppler imaging) and colour M-mode patterns of the various stages of diastolic dysfunction. Modified with permission from Garcia and Thomas, *Echocardiography* 1999; **16**: 501–508.

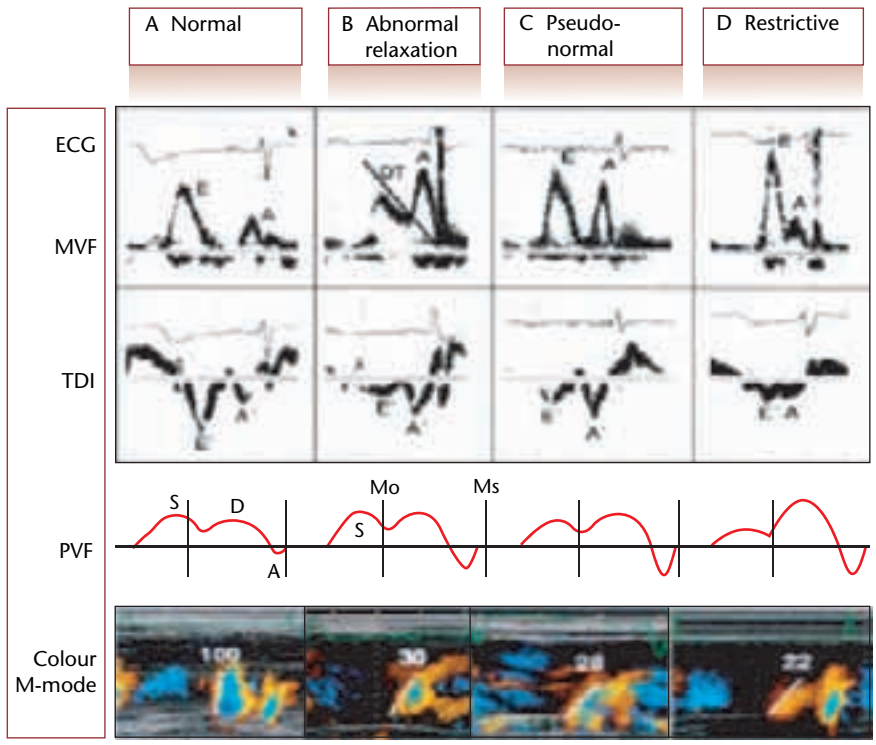

Figure 2.47 Recordings obtained from a normal individual and patients with diastolic dysfunction. (A) Normal individual. (B) Abnormal relaxation in a patient with left ventricular (LV) hypertrophy on haemodialysis. (C) Patient with LV hypertrophy. (D) Patient with end-stage heart failure. See Figs 2.45 and 2.46 for explanation of abbreviations.

Table 2.9 Identification of patients with elevated left ventricular filling pressure

Enlarged left atrial size, decreased function
Left ventricular enlargement and hypertrophy
Transmitral E/A ratio > 2
Deceleration time < 150 ms*
Pulmonary vein flow
S/D < 40%
A_R amplitude > 25 cm/s
A_R duration 30 ms greater than transmitral A duration
E/E′ ratio > 15*
Colour M-mode flow propagation velocity (PV) < 40 cm/s*
E/PV ratio < 2

*Parameters used in atrial fibrillation.

Table 2.10 Formulae for estimation of left ventricular filling pressure

Sinus rhythm
1.9 + 1.24(E/E′)
5.27(E/PV) + 4.66
Sinus rhythm plus (severe left ventricular dysfunction)
1.85DR – 0.15SF + 1.9
Sinus tachycardia
1.55 + 1.47(E/E′)
Atrial fibrillation
6.49 + 0.82(E/E′)

E and DR, E-wave velocity and its deceleration rate of transmitral flow velocity pattern; E′, velocity of mitral annulus TDI; PV, propagation velocity of left ventricular inflow on colour M-mode; SF, systolic fraction of pulmonary vein flow (see also text).

propagation velocity (PV). The E/E′ ratio is a practical index that can be calculated in most patients. A ratio < 8 indicates a normal filling pressure, whereas a ratio > 15 corresponds to a filling pressure in excess of 15 mmHg [73]. The ratio can also be used in patients with sinus tachycardia (fused mitral E and A waves) and atrial fibrillation.

An E/PV ratio < 2 suggests an elevated LV filling pressure. Several formulae that allow the estimation of LV filling pressures have been proposed and are presented in Table 2.10.

Specific conditions

Atrial fibrillation

In atrial fibrillation there is no atrial contraction and consequently no A wave on the transmitral flow velocity pattern, no A_R wave on the pulmonary vein flow and no A′ wave on the TDI mitral annulus velocity recordings. Nonetheless, some parameters can be used to identify patients with an elevated LV filling pressure (Table 2.9). Peak E-wave velocity and DT vary with the length of the cardiac cycle. Peak E-wave acceleration rate correlates with LV filling pressure but is often difficult to measure. DT is shortened when LV filling pressure is elevated but should not be measured from short RR interval cycles because filling stops very early and the DT may become artificially short. Therefore it is practical to select cardiac cycles corresponding to a heart rate of 60–80 b.p.m. The S wave on the pulmonary vein flow is low in amplitude since forward flow to the LA is predominantly diastolic. The E/E′ ratio is a practical parameter for estimating LV filling pressure (Table 2.10). The initial deceleration rate of the D wave and the flow propagation velocity can also be used.

Constrictive pericarditis

This condition can mimic the manifestations of restrictive cardiomyopathy, which are clinically difficult to distinguish. In patients with constrictive pericarditis, an increase in respiratory variation of the early mitral inflow velocity is seen whereas this is not present in restrictive cardiomyopathy. These phasic changes result from exaggerated ventricular interdependence [74]. TDI shows a decreased mitral annulus velocity in restrictive cardiomyopathy whereas the velocity is normal in constrictive pericarditis.

Hypertrophic cardiomyopathy

Prolonged relaxation is the predominant diastolic abnormality in hypertrophic cardiomyopathy (prolonged IRP, low E wave, slow DT and increased A wave). Relaxation can be markedly delayed in some myocardial areas, resulting in a triphasic mitral inflow pattern. When the disease progresses and LAP increases, the early E-wave velocity increases and the DT shortens as a result of diminishing LV compliance. In some patients an intracavitary reversed gradient can be produced by apical relaxation during the IRP, producing flow from base to apex. A formula to estimate the pre A-wave diastolic pressure has been proposed by Nagueh *et al*. [75].

Echocardiography/Doppler in specific cardiac conditions

Echocardiographic/Doppler techniques play an invaluable role in the diagnosis and management of patients with virtually any form of cardiac disease. The relative

Table 2.11 Relative diagnostic information obtained with various echocardiographic/Dopper modalities*

	Morphology	Function	Dimensions	Pressure drop	Regurgitation
M-mode	+	++	+++	−−	−−
Two-dimensional	+++	+++	++	−−	−−
Three-dimensional	+++	+++(+)	+	−−	−−
Doppler	−−	−−	−−	++	+
Pulsed	−−	−−	−−	++++	++
Continuous	−−	−−	−−	+	
Colour	−−	+	−−	−−	++++
Tissue imaging	−−	+++	−−	−−	−−

*Use of echo contrast helps to enhance both image quality and Doppler signals. Qualitative information on myocardial perfusion can also be obtained.

diagnostic information obtained with echocardiographic/Doppler modalities in the different aspects and presentation of cardiac disease are presented in Table 2.11.

It is impossible to describe in detail the salient features and the diagnostic echocardiographic/Doppler criteria of all cardiac conditions in this limited chapter. Some are presented in their respective chapters and are extensively available in specific textbooks [1,30,38,62] and in the ACC/AHA guidelines for the clinical application of echocardiography [76]. The most important referral questions for echo/Doppler examination are for the evaluation and follow-up of cardiac function (heart failure), ischaemic heart disease, myocardial disease (cardiomyopathies), valvular disease, pericardial disease, mass lesions and congenital heart disease. Patients are also often referred for the evaluation of cardiac symptoms, physical signs or abnormal laboratory tests. A diagnostic clue and, more often, a definitive diagnosis is provided (Table 2.12).

The cardiomyopathies (myocardial diseases)

Echocardiography combined with Doppler allows the detection of structural, functional and intracardiac flow abnormalities for the accurate diagnosis and classification of cardiomyopathy [77] (see Chapter 16).

Dilated cardiomyopathy

Dilated cardiomyopathy is characterized by dilatation of the LV (or both LV and RV) without increased wall thickness and a widened outflow tract (increased EPSS) (see Figs 2.6, 2.31 and 2.49). Systolic as well as diastolic function and CO parameters are all decreased (see Assessment of left ventricular systolic function and Assessment of left ventricular diastolic (dys)function and filling pressure, above). Both the amplitude of wall motion (hypokinesis) and its thickening are globally decreased. Doppler techniques provide information about the presence of associated mitral regurgitation (as a result of annulus dilatation and incomplete mitral leaflet coaptation), pulmonary artery pressure and diastolic LV dysfunction (elevated filling pressures).

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is characterized by LV hypertrophy (or both LV and RV) in the absence of other causes. The pattern of hypertrophy is often asymmetric (most often in the interventricular septum, while isolated apical hypertrophy is a rare variant) and its distribution is readily visualized by echocardiography (Fig. 2.50). Subsets of patients have a dynamic LVOT obstruction (hypertrophic obstructive cardiomyopathy) caused by systolic anterior motion of the anterior mitral leaflet produced by a Venturi effect or an intraventricular (mid-cavity) obstruction that causes typical Doppler patterns (Figs 2.51 and 2.52). Systolic function is normal or increased and diastolic filling is always impaired with a characteristic inflow pattern. Patients with dynamic LVOT obstruction have mitral regurgitation (Fig. 2.51).

Restrictive cardiomyopathy

Restrictive cardiomyopathy results from deposition of substances between the myocytes (haemochromatosis, glycogenosis) or within the myocytes (infiltrative, e.g. amyloidosis). It is typically characterized by impaired diastolic filling of either or both ventricles [74]. This causes atrial dilatation. LV size and systolic function may be normal but wall thickness is increased. Restrictive physiology is found in patients with endomyocardial disease (hypereosinophilic syndrome, endomyocardial fibrosis) (Fig. 2.53).

Hypertensive hypertrophic cardiomyopathy

Hypertensive heart disease results from arterial hypertension and manifests with concentric LV hypertrophy and

Table 2.12 Common referral symptoms, signs or laboratory abnormalities for echocardiographic/Doppler evaluation

Referral questions	Differential diagnosis (or exclusion)
Chest pain	Regional wall motion abnormality: ischaemia or infarction? Left ventricular outflow obstruction: aortic stenosis, HOCM? Aortic disease: intramural haematoma, aortic dissection? Pulmonary embolism (Pericarditis)
Dyspnoea	Left ventricular systolic and/or diastolic dysfunction: heart failure? Valvular disease Cardiomyopathy Pulmonary artery pressure: pulmonary hypertension
Heart murmur	No structural abnormality: flow murmur Valvular disease Dynamic left ventricular outflow obstruction Shunt (mainly right-to-left shunt)
Palpitations	Structural cardiac abnormality?
Syncope	Aortic stenosis, cardiomyopathy, intracardiac mass (myxoma)
Hypotension/shock	See Emergency echocardiography
Chest radiography	Enlarged heart shadow: cardiomyopathy, left ventricular dysfunction, pericardial effusion, specific chamber enlargement?
Abnormal ECG	Non-specific ECG changes: regional wall motion abnormality (old silent myocardial infarction, chronic ischaemia), left ventricular hypertrophy, structural heart disease Signs of hypertrophy: specific chamber enlargement, increased mass
Suspicion of endocarditis	See Infective endocarditis
Embolic event(common indication for TOE)	Intracardiac mass lesion Structural and functional abnormalities predisposing to embolic events: atrial septal defect, patent foramen ovale, interatrial septal aneurysm (Fig. 2.48), low LAA velocities Atheroma in aorta

HOCM, hypertrophic obstructive cardiomyopathy; LAA, left atrial appendage; TOE, transoesophageal echocardiography.

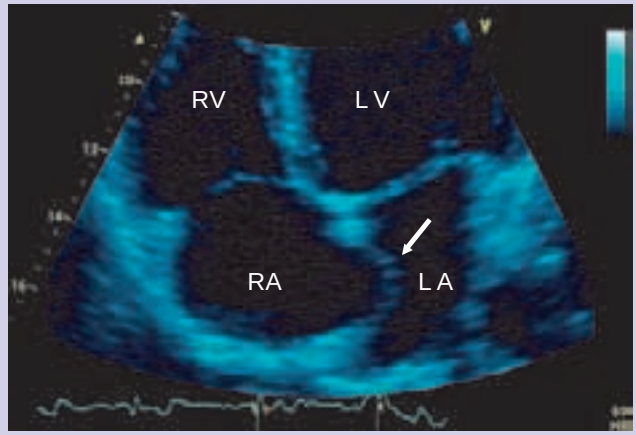

Figure 2.48 Apical four-chamber view showing an interatrial septal (IAS) aneurysm (arrow) with a width and fixed depth of > 2 cm (normal < 1 cm depth deviation). This represents a type I IAS aneurysm and these patients do not usually have an interatrial shunt. In type II IAS aneurysm, there is motion of the interatrial septum in both directions of > 10 mm. These patients often have an interatrial shunt. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

diastolic dysfunction. Both the aortic root and the LA are often dilated and there is a high incidence of aortic valve sclerosis and mitral annulus calcification. Hypertensive hypertrophic cardiomyopathy represents an extreme manifestation of LV hypertrophy, with normal systolic function and signs of heart failure. When long-standing hypertension leads to systolic LV dysfunction, the LV becomes dilated.

Ventricular non-compaction

Non-compaction of the LV myocardium is a rare cardiomyopathy that manifests with typical echocardiographic features. Presence of thin compacted myocardium on the epicardial and a non-compacted myocardium on the endocardial side with prominent trabeculae in the absence of acquired or congenital heart disease are diagnostic (ratio

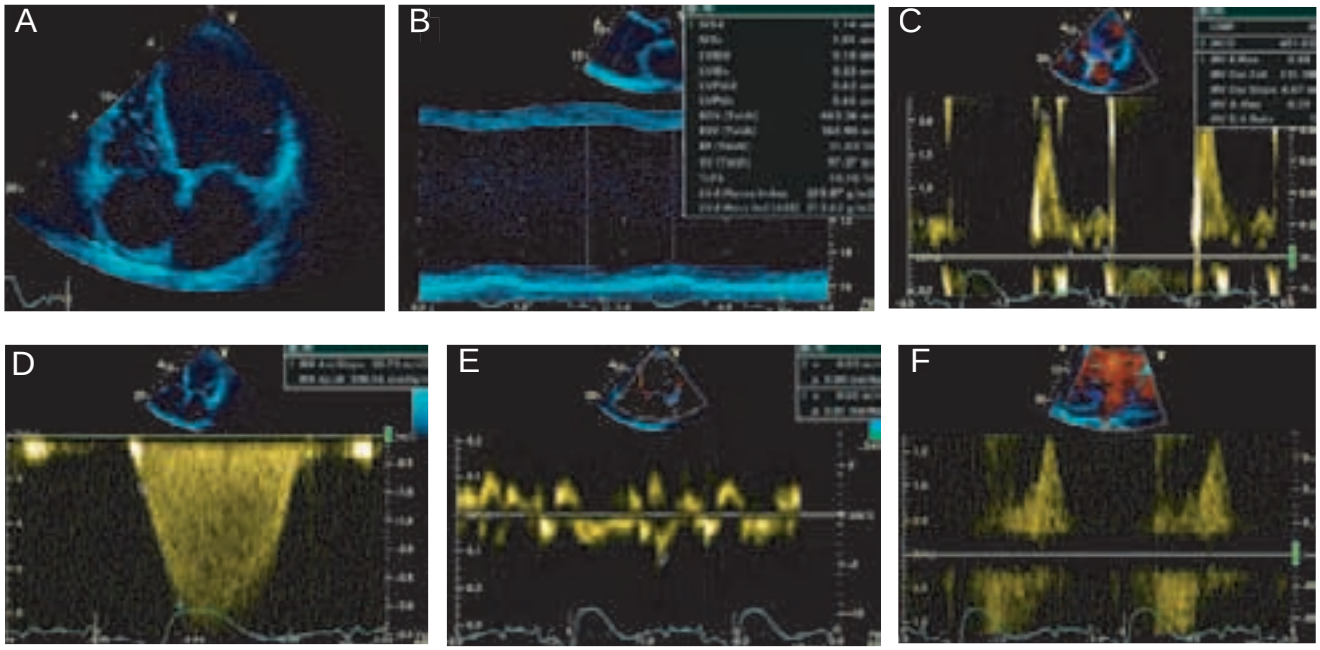

Figure 2.49 A patient with severe dilated cardiomyopathy. (A) Apical four-chamber view shows a severely dilated left ventricle and left atrium. (B) M-mode shows the extremely dilated left ventricle (end-diastolic dimension of 9.14 cm) with a fractional shortening of 10% on the dynamic images. There is also global wall hypokinesis. (C) Transmitral inflow Doppler trace shows a restrictive left ventricular filling pattern (grade 3). (D) Left ventricular d*P*/d*t* is 330 mmHg/s, which is extremely low. (E) Mitral annulus velocities are also very low. (F) Pulmonary vein flow has a high D wave and low S wave, consistent with grade 3 diastolic dysfunction (see Fig. 2.45).

of non-compacted/compacted layers > 2 at end-systole at the thickest LV wall). Deep recesses communicating with the LV cavity are best visualized with colour Doppler or echocardiographic contrast (Fig. 2.54).

Arrhythmogenetic right ventricular cardiomyopathy

In this myopathy the RV myocardium is progressively replaced by fatty and fibrous tissue with outpouching of the free wall. The RV becomes dilated with poor contractility and visible on the echo study. It is one of the most common causes of sudden death in young adults. The limited spatial information of echocardiographic images is a problem for accurate analysis of this cardiomyopathy and is the domain of magnetic resonance imaging (MRI).

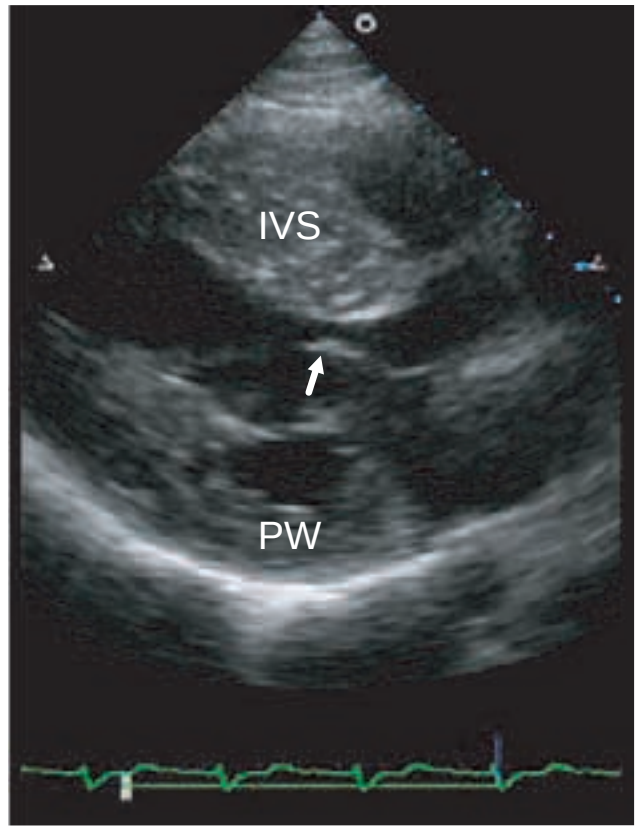

Figure 2.50 Hypertrophic obstructive cardiomyopathy (parasternal long-axis view). The interventricular septum (IVS) is extremely hypertrophic. The posterior wall (PW) is also thickened. The systolic anterior position of the anterior mitral leaflet is nicely shown (arrow) and causes the dynamic obstruction of the left ventricular outflow tract and mitral regurgitation.

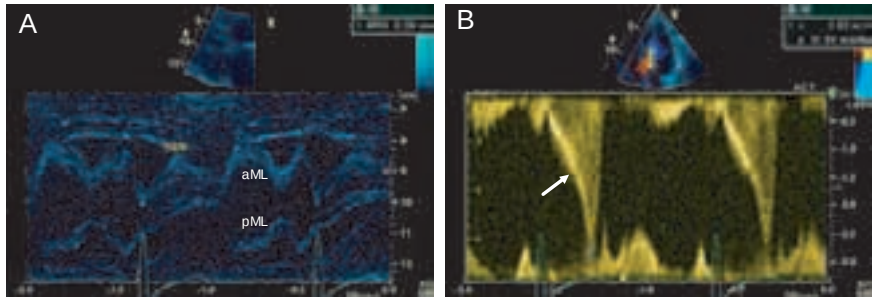

Figure 2.51 Hypertrophic obstructive cardiomyopathy. (A) M-mode echocardiogram showing systolic anterior motion (SAM) of the anterior mitral valve leaflet (aML). pML, posterior mitral valve leaflet. (B) Continuous-wave Doppler velocity recording showing the typical 'dagger-shape' pattern of the outflow obstruction (arrow). The maximum velocity is 2.8 m/s, corresponding to a gradient of 31 mmHg.

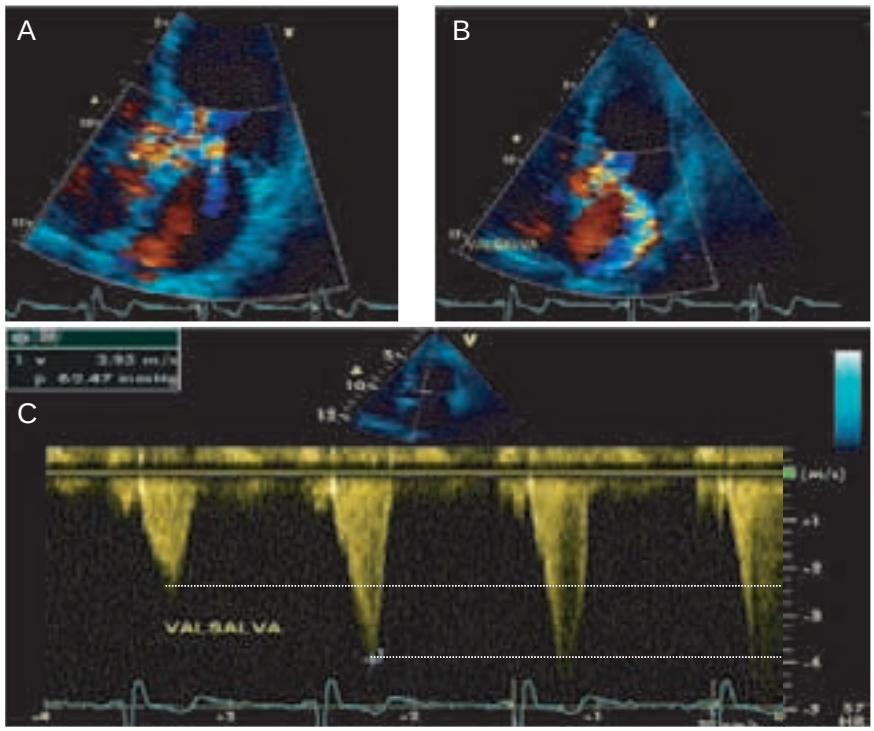

Figure 2.52 Hypertrophic obstructive cardiomyopathy. (A) Colour flow Doppler apical long-axis systolic view shows turbulence in the outflow tract and trivial mitral regurgitation. (B) During the Valsalva manoeuvre the outflow obstruction increases and the mitral regurgitation jet increases. (C) The dynamics of the outflow obstruction is better demonstrated in the spectral Doppler recording during the Valsalva manoeuvre. The peak velocity increases from 2.4 to 3.9 m/s.

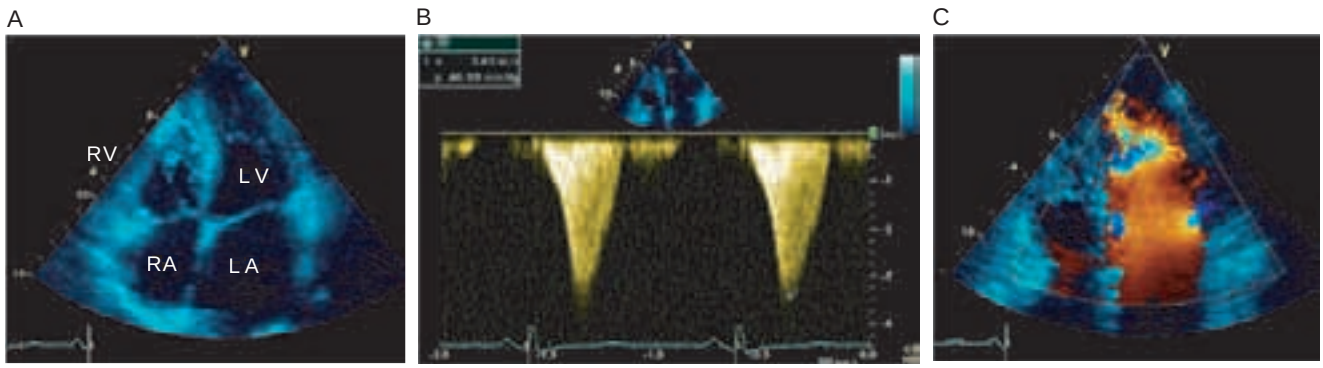

Figure 2.53 Endomyocardial fibrosis. (A) There is apical obliteration of the right ventricle (RV) and involvement of the left ventricle (LV) mid-ventricular endocardium. Both the right atrium (RA) and left atrium (LA) are dilated. (B) This mid-ventricular involvement causes a dynamic mid-cavitary obstruction with a peak pressure gradient of 47 mmHg (see the sample volume in the middle of LV). (C) Colour Doppler inflow shows turbulence in the middle/apical areas of the LV.

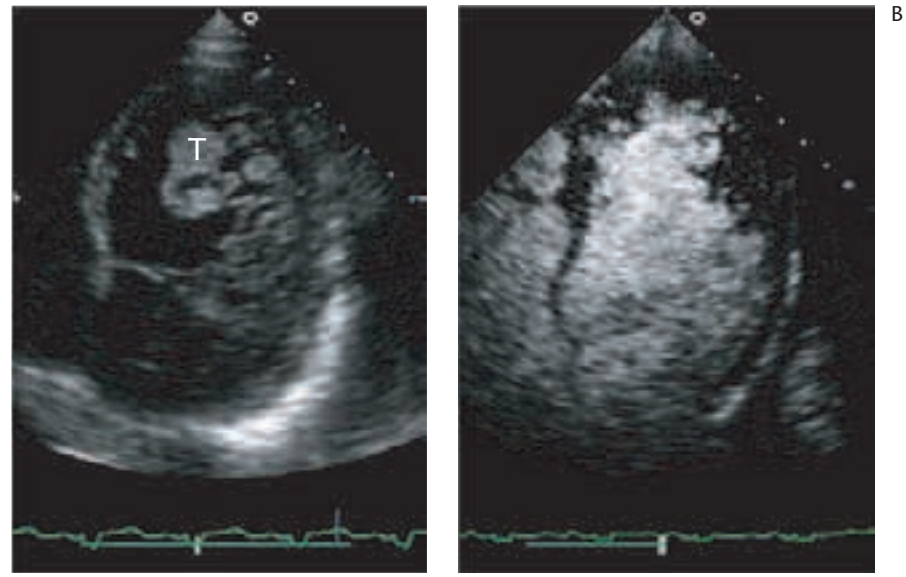

Figure 2.54 Left ventricular non-compaction. Apical four-chamber views (A) without and (B) with left ventricular echo-contrast opacification. Excessive and prominent trabeculation of the left ventricle is visualized. The echo contrast nicely shows the communication between the recesses and left ventricular cavity. A thrombus (T) is present in the apex.

Ischaemic heart disease

Reduction in myocardial blood flow causes ischaemia with decreased wall thickening/function followed by ECG changes and chest pain (see Chapter 12). Echocardiography allows detection of transient regional wall motion abnormalities during episodes of chest pain and has been shown to be extremely helpful for the assessment of patients presenting with chest pain and acute coronary syndrome (see Fig. 2.17). Demonstration of completely normal wall function/motion during such an episode virtually excludes myocardial ischaemia or myocardial infarction. This wall-motion assessment is very useful in patients presenting with chest pain and a non-diagnostic ECG. In addition, echocardiography/Doppler allows diagnosis of most diseases that can mimic ischaemic episodes.

Unstable angina is characterized by transient or permanent wall motion abnormalities. Myocardial infarction results in a permanent reduction in wall thickness (< 6 mm), which is replaced by fibrotic/scar tissue (Fig. 2.55).

Outward systolic motion or bulging results in an abnormal ventricular shape and indicates aneurysm formation. Free-wall rupture after pericarditis with epicardial and pericardial adhesion results in a pseudo or false aneurysm (Fig. 2.56). Both types of aneurysm contain thrombus but a true aneurysm leads more often to systemic embolization. RV infarct involvement is also readily detected (RV dilatation). The detection of complications of a myocardial infarction is the domain of

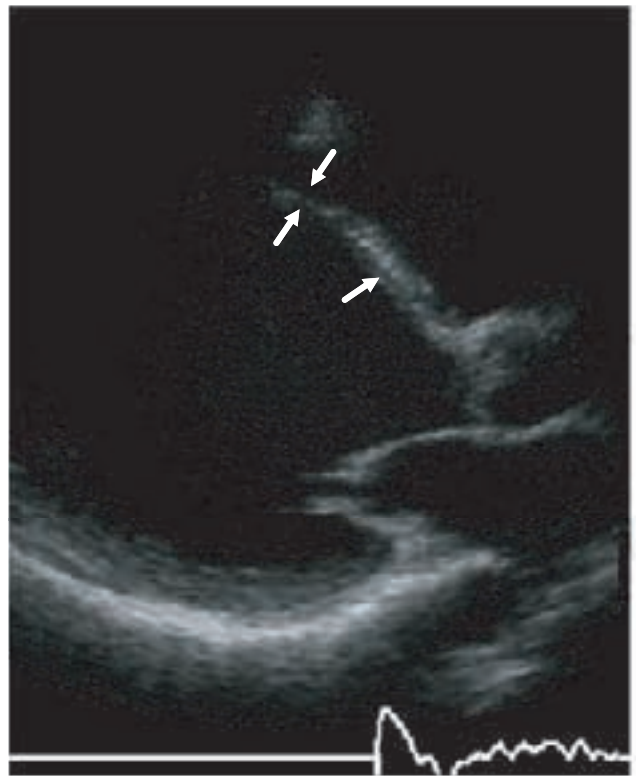

Figure 2.55 Ischaemic cardiomyopathy. The left ventricle is extremely dilated after a large anteroseptal myocardial infarction, which shows outward bulging (aneurysm). The septal myocardium is replaced by scar tissue which is < 6 mm in thickness (see arrows).

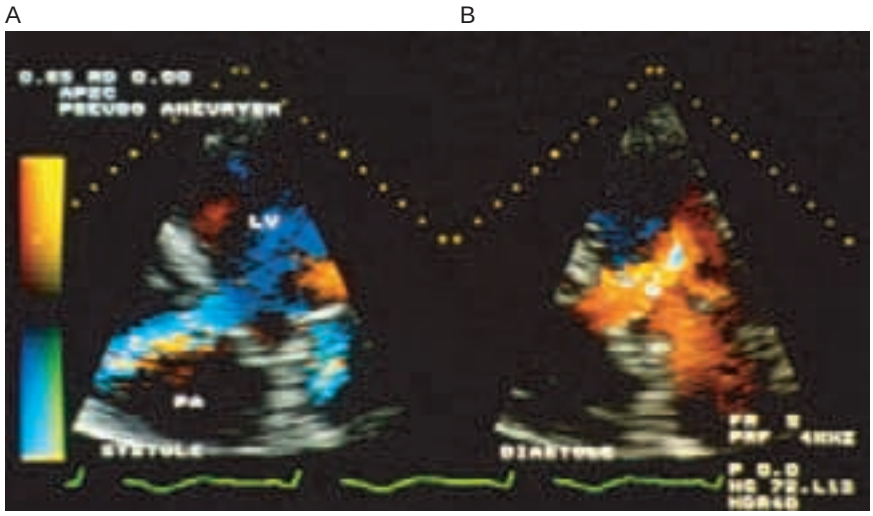

Figure 2.56 Pseudo-aneurysm of the left ventricle. (A) Systolic frame with a jet from the left ventricle into the pseudo-aneurysm. There is also a jet of mitral regurgitation into the left atrium. (B) Diastolic frame: the blood passes from the pseudo-aneurysm into the left ventricle. Note the normal diastolic transmitral and the mild aortic regurgitation jet.

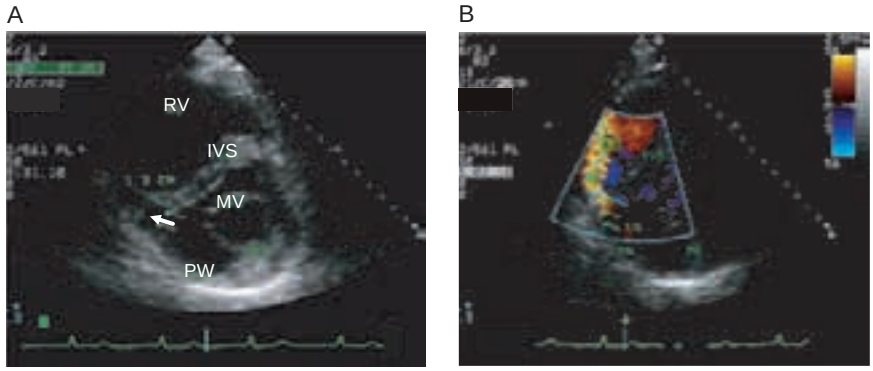

Figure 2.57 Postinfarction interventricular septal (IVS) rupture. (A) Short-axis view at the level of the mitral valve (MV) and the posteriorly located rupture (arrow). Note the dilated right ventricle (RV), flattened IVS and the 'D-shaped' left ventricle (LV) cavity indicating acute RV pressure and volume overload. PW, posterior wall. (B) Colour flow image demonstrates the turbulent shunting blood flow from LV to RV.

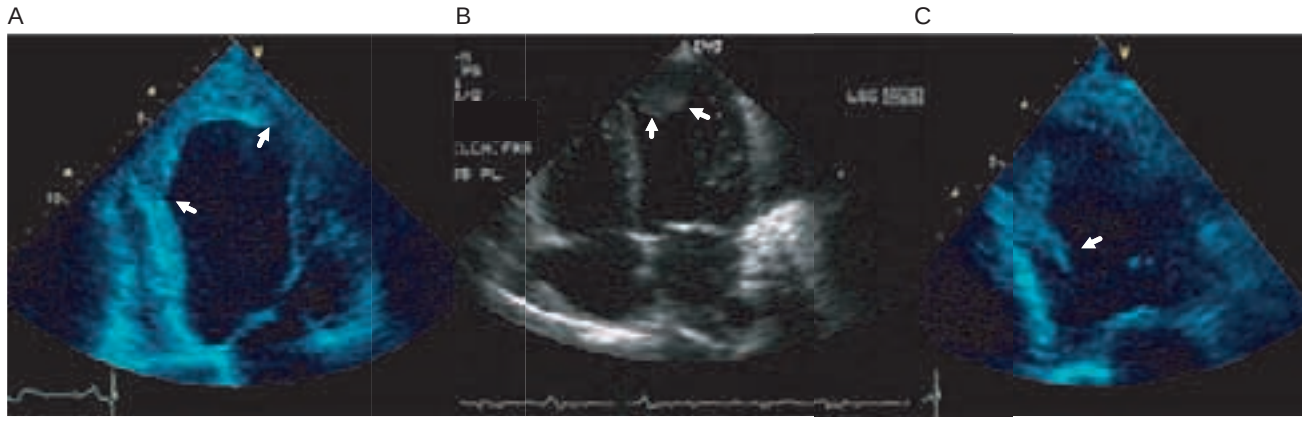

Figure 2.58 (A) Large aneurysm and thrombus formation in a patient after antero-apical myocardial infarction. The thrombus is laminated and smooth. The risk of embolization is low. (B) Protruding thrombus in a patient with antero-apical myocardial infarction. (C) Pedunculated mobile thrombus after anteroseptal infarction. The risk of embolization is high.

bedside echocardiography. Ventricular septal rupture (Fig. 2.57) and papillary muscle rupture are readily diagnosed. Signs of pericardial effusion in the acute phase are a warning sign for rupture of the myocardium and require urgent surgery. Chronic complications include thrombosis (Fig. 2.58), aneurysm formation and remodelling with heart failure, all of which are readily diagnosed by echocardiography.

Heart failure

Echocardiographic/Doppler examination has a crucial role in patients presenting with complaints (dyspnoea, reduced exercise tolerance) and signs (hypervolaemia) suggesting heart failure and is recognized by the European Society of Cardiology as the most important diagnostic test [78].

Evaluation of pericardial and valvular structure and myocardial function can accurately establish the diagnosis and the aetiology of heart failure and identify concomitant relevant disease. In the absence of such abnormalities, a non-cardiac cause mimicking a heart failure syndrome should be investigated. The classification of heart failure as systolic, diastolic [79] (or both) or high-output failure must be made (see Assessment of left ventricular systolic function and Assessment of left ventricular diastolic (dys)-function and filling pressure, above). Quantification of LV systolic and diastolic function is also the basic step in effective management and prognosis (remodelling, ejection fraction). Echocardiographic/Doppler techniques have an important role in resynchronization procedures of the LV (Fig. 2.59) and in guiding and monitoring novel therapies (e.g. LV assist devices, ACORN and Myosplint devices, DOR and Maze procedures, cardiac resynchronization therapy). Stress echocardiography should be considered when the symptoms are suggestive of angina pectoris rather than heart failure.

Valvular heart disease (see Chapter 21)

Native valves

The diagnosis, differentiation and grading of valvular heart disease is one of the important tasks of echocardiographic laboratories. With the addition of colour Doppler echocardiography, not only the diagnosis but also the aetiology and the underlying patho-anatomy of the disease can be described (Fig. 2.60). Only rarely is cardiac catheterization necessary in order to establish cardiac haemodynamics and select the appropriate form of therapy. Using the different algorithms, valvular gradients, orifice areas and regurgitation fraction can be assessed for the four heart valves (see Principles of Doppler echocardiography and Doppler haemodynamics, above) [62,80,81]. Many patients have to be studied by TOE in order to obtain exact information about the valve pathology and to exclude thrombus in patients selected for intervention or valve repair. Echocardiography/Doppler is particularly useful in patients with low gradients and LV dysfunction in which the gradient response to dobutamine helps in the decision-making. If reconstructive methods during surgery are used, intraoperative echocardiography is widely used to monitor the procedure and to prove its success.

Prosthetic valves

Another domain is the follow-up of prosthetic valves (bioprosthesis, homografts and mechanical valves) after surgery. TOE is often necessary because of acoustic shadowing and reverberations. Transvalvular gradients and valve areas can be determined (estimates of these parameters for most common prosthetic valves can be found in ref. 82). Virtually all early and late complications are detected, including vegetative endocarditis (Figs 2.32 and 2.61), paraprosthetic regurgitation (Fig. 2.62), abscess formation, mycotic aneurysm (Fig. 2.63), fistula (Fig. 2.64) and thrombus formation interfering with valve mechanics. Each prosthetic valve has its own haemodynamic characteristics, and these should be established by each echo laboratory based on the product information and the surgeon's information after valve implantation. A discharge echo/Doppler study should always be available after surgery. Also the degenerative process, which often

A

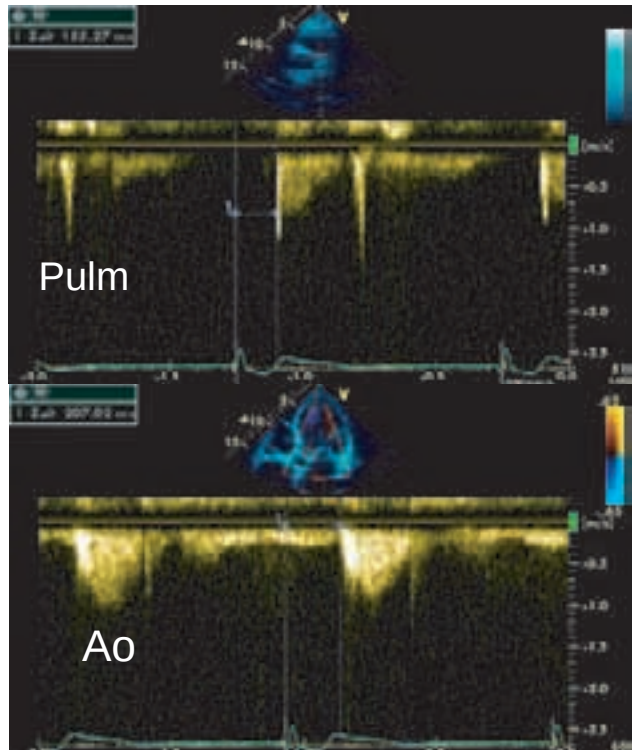

Figure 2.59 (A) Principle of measurement of the interventricular delay of contraction by Doppler echocardiography. The pre-ejection period (PEP) of the right ventricle (RV) is measured from the onset of QRS to the onset of pulmonary outflow (Pulm), and for the left ventricle (LV) from the onset of QRSD to the onset of aortic outflow (Ao). Subtracting RV-PEP from LV-PEP gives the mechanical/contraction delay. In this example the interventricular contraction delay is 52 ms (delay > 40 ms indicates interventricular dyssynchrony). (*Continued* p. 82.)

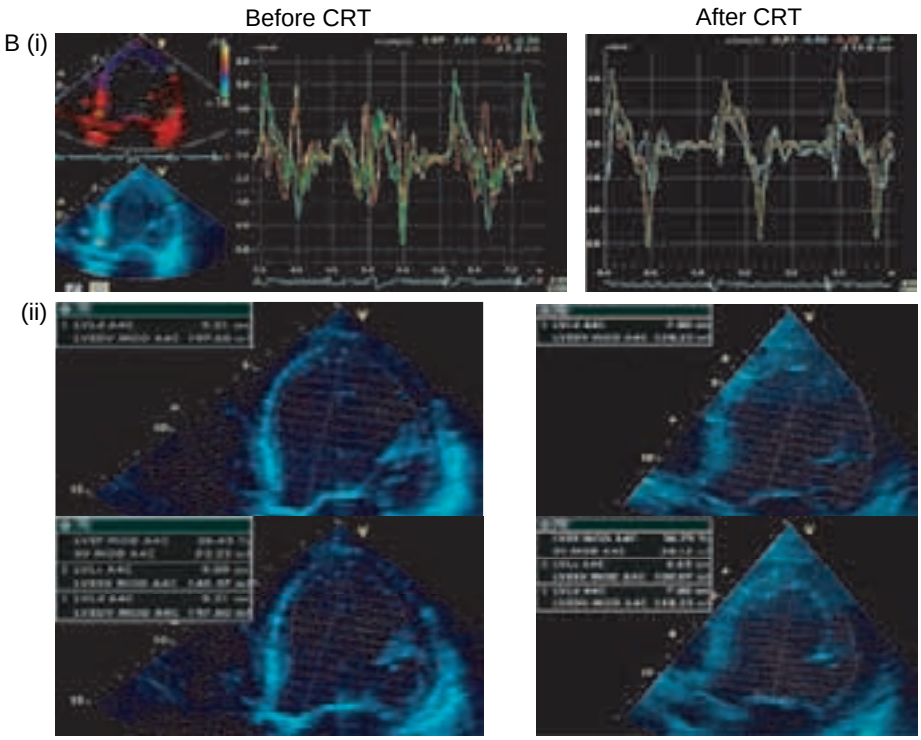

Figure 2.59 (Continued) (B) Tissue Doppler imaging (i) obtained in the basal and middle segments of the interventricular septum and the posterolateral wall of a patient with interventricular dyssynchrony before and after cardiac resynchronisation therapy (CRT). Note the severe dyssynchrony before CRT tracings and normalization of contraction synchrony after implantation of a CRT device. Note also that LV end-diastolic volume has decreased from 197 to 158 ml and that ejection fraction has increased from 20 to 37% (ii).

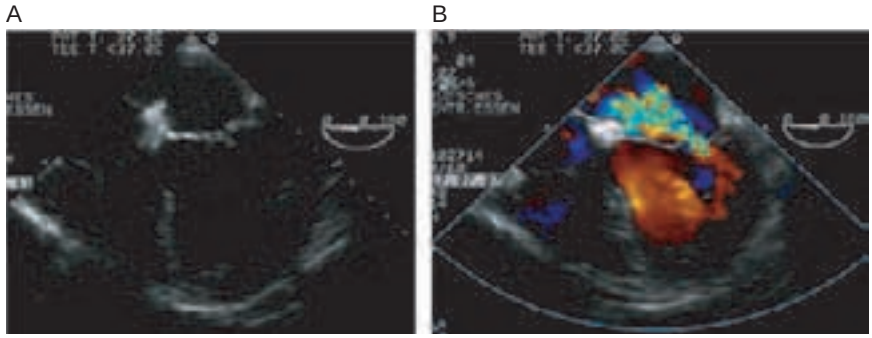

Figure 2.60 (A) Transoesophageal echocardiography obtained at 0° in a patient with mitral valve prolapse of the posterior leaflet. (B) Colour flow Doppler shows the turbulent jet directed towards the interatrial septum indicating severe mitral regurgitation.

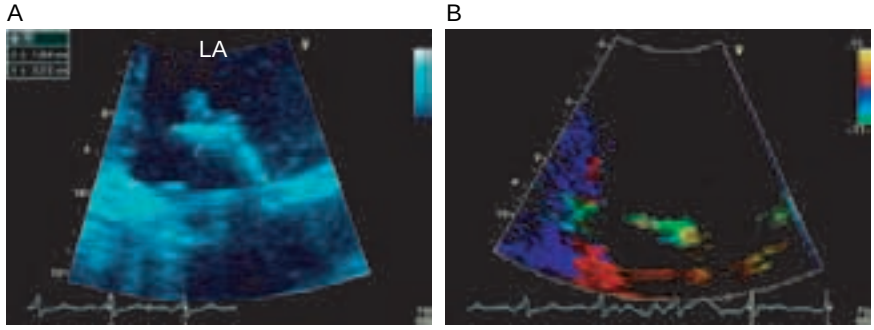

Figure 2.61 (A) Patient with endocarditis and a vegetation on a mitral prosthesis. (B) Tissue Doppler imaging shows incoherent motion of the vegetation (see Fig. 2.32).

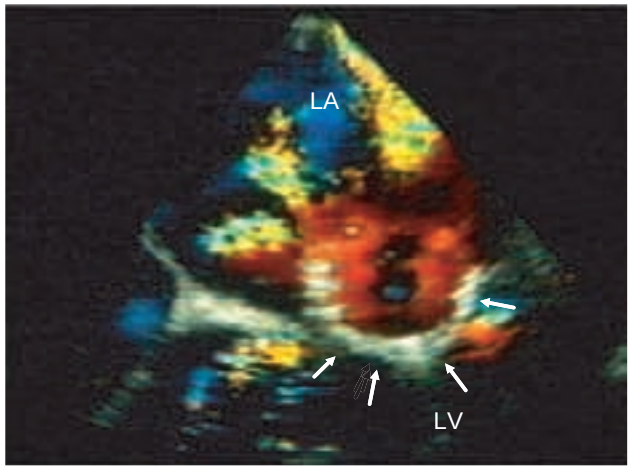

Figure 2.62 Transoesophageal echocardiography colour Doppler flow image of a patient with a mitral Björk–Shiley prosthesis (arrows) and infective endocarditis. Several paraprosthetic regurgitant turbulent jets are seen in the dilated atrium (LA). LV, left ventricle.

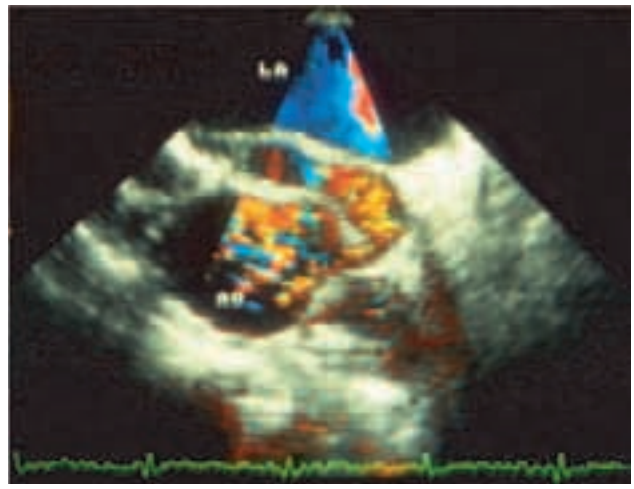

Figure 2.63 Transoesophageal echocardiography colour Doppler flow image of a patient with infective endocarditis and an abscess between the aorta (Ao) and left atrium (LA), which is septated by interconnected compartments. The turbulence in one of the compartments indicates a connection with the intravascular/intracardiac space and therefore represents a mycotic aneurysm.

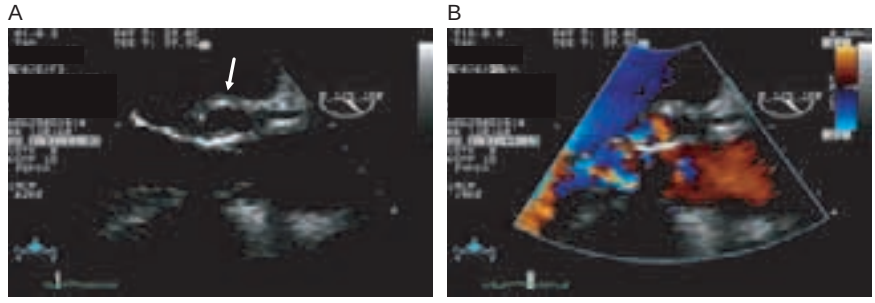

Figure 2.64 Infective endocarditis of the aortic valve. (A) There is a cavity at the base of the aorta (arrow). (B) Colour Doppler flow image shows turbulence in the cavity and diastolic regurgitation from the aorta into the left ventricle, indicating fistula formation between aorta and left ventricle.

involves bioprostheses, can be imaged and graded in order to guide reoperation in an appropriate time scale.

Infective endocarditis

In patients studied for suspected or proven infective endocarditis, transthoracic and transoesophageal echocardiography play an important role because, in addition to the history, clinical features and blood culture, they provide morphological information that was previously not available or only obtained at surgery or autopsy. Transthoracic echocardiography is less sensitive and specific than TOE. The diagnosis of endocarditis is based on clinical laboratory (bacteriological) and echocardiographic findings (Duke criteria) [83]. Echocardiography is the best diagnostic method for diagnosing the complications of infective endocarditis (Figs 2.61–2.65).

Echocardiography has changed the textbooks with regard to this severe disease, because the diagnosis can now be confirmed before valve destruction results in lesions that previously were only detected by auscultation. Infective endocarditis can now be diagnosed in the absence of heart murmurs. In addition, complications of the disease can be imaged (e.g. abscess formation). Follow-up studies are used in order to control medical or surgical therapy.

Pericardial disease (see Chapter 17)

The diagnosis of pericardial and pleural effusion was one of the major applications of M-mode echocardiography. Two-dimensional echocardiography has significantly improved the diagnosis and even allows quantification of pericardial effusion [84].

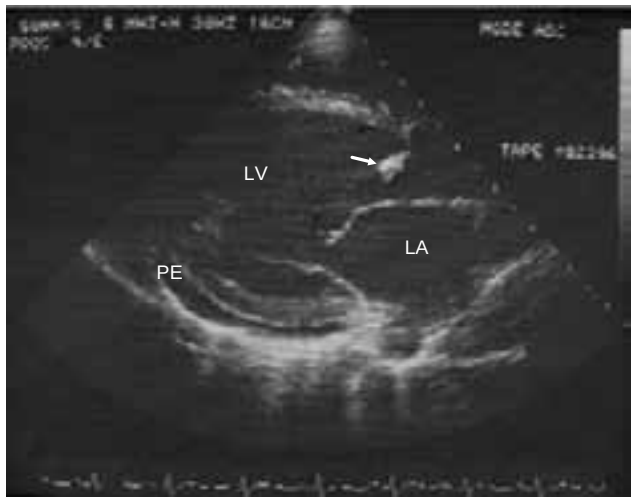

Figure 2.65 Parasternal long-axis view of a patient with infective endocarditis on the aortic valve (arrow) and vegetation. There is massive aortic regurgitation, the left ventricle (LV) is extremely dilated and the left atrium (LA) is enlarged. The patient had acute heart failure. There is also moderate pericardial effusion (PE). These findings are an indication for acute surgery.

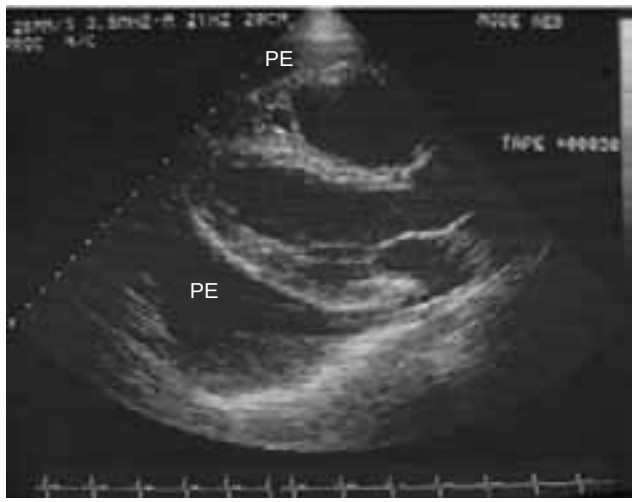

Figure 2.66 Large pericardial effusion (PE) seen as an echolucent area around the heart.

Pericarditis

This is a clinical diagnosis (pain, pericardial rub and ST changes) and pericardial effusion is not a necessary echocardiographic criterion as there is no correlation between its presence or absence and the diagnosis.

Pericardial effusion

Separation between epicardial and pericardial layers occurs when the pericardial fluid exceeds the normal level of 15–35 ml. Using M-mode echocardiography, different degrees of pericardial and epicardial separation have been distinguished (Figs 2.65 and 2.66). Also, pericardial thickening can be detected and is present when the signal exceeds 6 mm.

Two-dimensional echocardiography of pericardial effusion is best imaged using various scanning locations, including the subcostal, transthoracic, suprasternal and paravertebral. Whereas in acute pericardial effusion the pericardial space is free of masses, patients in the chronic stages of pericardial effusion or with acute inflammation can present with bands and masses that are free-floating or attached to the epicardium and pericardium, indicating fibrotic or thrombotic structures. Rarely, tumour masses are found within or adjacent to the pericardium.

Echolucent zones represent fluid between the epicardium and pericardium. The effusion appears first in the posterior part of the pericardial cavity, the posterior atrioventricular groove. An effusion appears behind the left atrium up to the oblique sinus only when there are very large collections. The differentiation between pericardial effusion and mediastinal fat may be misleading to pericardiocentesis because of similar appearance on the display. Accurate gain-setting, proper transducer location, and direction are the best ways to avoid potential pitfalls.

Localization of the pericardial effusion relative to the chest wall allows safe pericardiocentesis, especially for smaller and/or localized effusions. Some findings on M-mode and two-dimensional echocardiography are suggestive of cardiac tamponade. A greater than normal increase in RV dimension during inspiration and a reciprocal decrease in LV dimension is suggestive. Right atrial collapse on two-dimensional echocardiography may be seen in small effusions but is not specific. RV diastolic collapse is fairly specific and commonly observed during tamponade (Fig. 2.67).

After open heart surgery, even with the pericardium left open, localized effusion at the posterior wall can be found, with complete compression of the right atrium leading to cardiac tamponade. These images may be misinterepreted as cardiac tumours or atrial myxoma. A potential pitfall to be avoided is when bleeding into the pericardium occurs and complete or incompete thrombosis develops. This may be aggravated when thrombin is injected in order to stop acute iatrogenic-induced bleeding. The typical echolucent areas may disappear so that epicardial effusion and development of cardiac tamponade are overlooked if haemodynamics are not carefully monitored.

Quantification of pericardial effusion

Because cardiac tamponade is related to the amount of

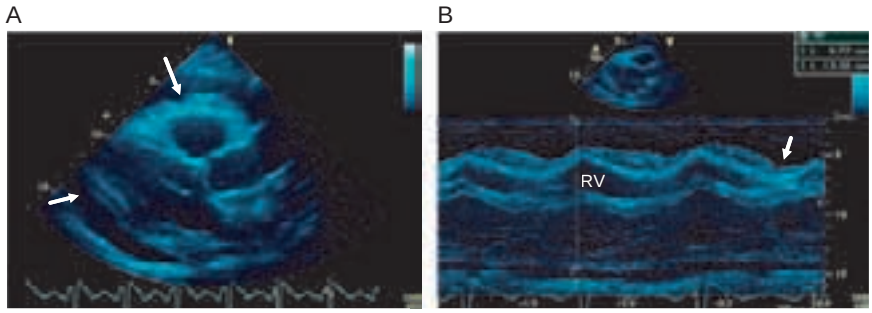

Figure 2.67 Patient with large pericardial effusion and cardiac tamponade. (A) Circumferential effusion (arrows). (B) M-mode recording showing right ventricular (RV) diastolic cavity collapse, which is accentuated during expiration (arrow).

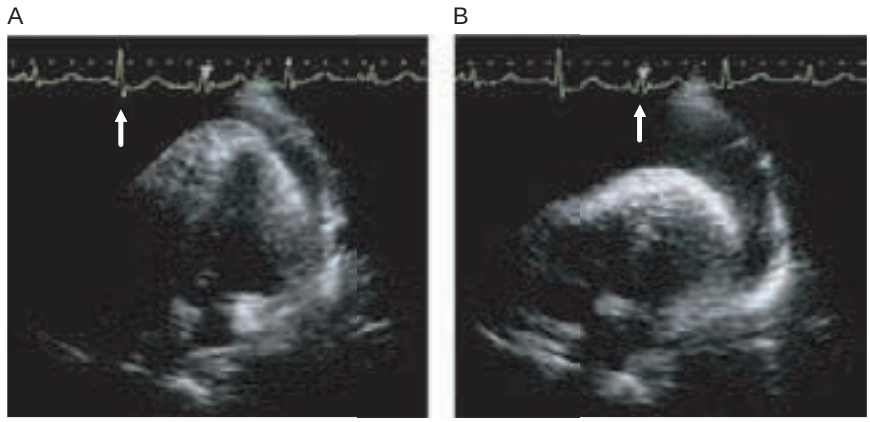

Figure 2.68 In the presence of a large pericardial effusion, the heart shows a 'swinging motion' in the pericardial sac. When the heart is close to the chest wall (A), the QRS voltage is increased; when the heart is away from the chest wall, the QRS voltage is decreased (B). This explains the electrical alternans on the ECG.

fluid, quantification of pericardial effusion has been attempted. Assuming that the pericardial sac approximates the shape of a barrel, the following formula has been developed:

$$V = {}^1\!/_6\pi(D_p^3 - D_v^3)$$

where V represents pericardial effusion volume, D_p the diameter of the parietal pericardium and D_v the diameter of the visceral pericardium at the centre of the heart just below the mitral valve. This method has been validated first with M-mode and subsequently with two-dimensional echocardiography. Stepwise reduction of pericardial effusion can be performed. A linear relationship has been demonstrated between 250 and 600 ml; for two-dimensional echocardiography the correlation coefficient is 0.97 and the regression equation is $y = 9.95x + 21.3$.

Pericardial tamponade is rarely found in patients with an effusion of less than 100 ml, although pericardial effusion of up to 400 ml has been found in 13% and > 400 ml in 39% of all patients. A semi-quantitative approach for effusion sizing has been proposed: small, < 10 mm in systole and diastole; moderate, 11–20 mm; large, > 20 mm. However, using these assumptions may lead to underestimation of the severity of the condition: a 10-mm effusion in a normal heart is less serious than a similar-sized effusion in an enlarged diseased heart. This underestimation also occurs when tangential subcostal scan planes are used.

In large pericardial effusions, the heart may move freely within the pericardial cavity, giving the typical phenomenon of the 'swinging heart'; this results in a voltage change on the ECG (electrical alternans) (Fig. 2.68).

Constrictive pericarditis

If pericardial thickening develops, typical echocardiographic images are obtained (Fig. 2.69). An increase in the size of left and right atrium is a typical consequence of constrictive pericarditis, which can be imaged by echocardiography. The visualization of pericardial thickening and the detection of calcification are better done with MRI or computed tomography (CT). If calcification is present, the thickening is accompanied by ultrasound shadowing, which is highly specific.

Indirect signs of constriction are enlargement of the left and right atrium with a normal left and right ventricle and normal systolic function. This is often a first clue to the diagnosis of constrictive pericarditis. Using M-mode echocardiography and careful observation of the two-dimensional images, an early pathological outward and inward movement of the interventricular septum can be observed, corresponding to the dip-plateau

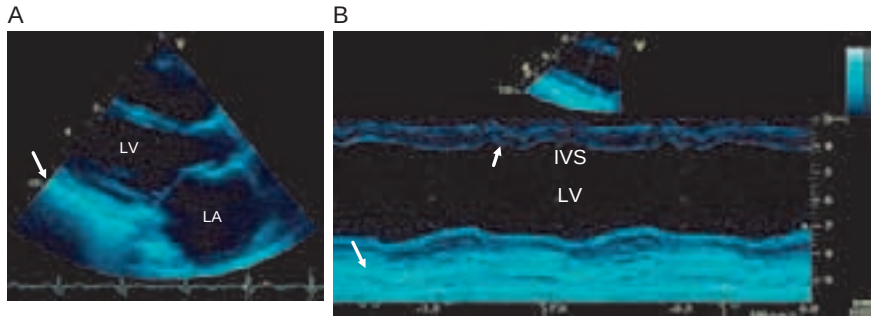

Figure 2.69 Patient with constrictive pericarditis. (A) Arrow indicates the thickened pericardium. Note the enlarged left atrium (LA). (B) M-mode recording of the left ventricle (LV). Note the flat diastolic posterior wall motion and the typical motion pattern of the interventricular septum (IVS) (see also Fig. 2.43). The recording shows an early diastolic notch with forward motion followed by a backward movement as a sign of the early diastolic filling abnormality and corresponds to the dip–plateau phenomenon seen on pressure recordings.

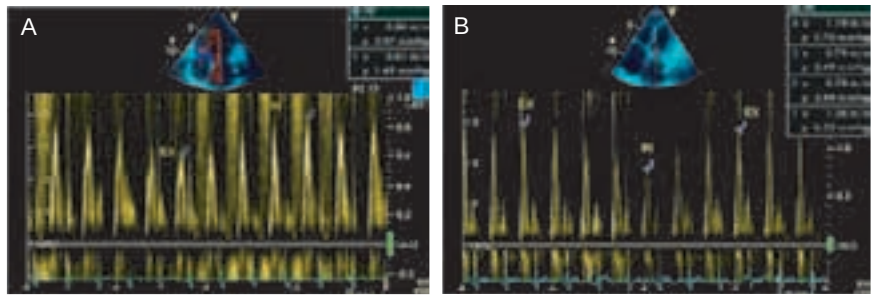

Figure 2.70 Same patient as in Fig. 2.69. (A) Transtricuspid and (B) transmitral Doppler flow patterns show opposite increase/decrease of flow velocities (note position of sample volume in the two-dimensional reference images). In the right heart the velocity increases during inspiration while it decreases in the left heart. This results from the fact that the total heart is constrained and reciprocal volume changes are influenced by the septal displacement during respiration.

phenomenon found by pressure recordings. This is reflected by M-mode echocardiography as an early diastolic notch within forward motion followed by a backward movement of the interventricular septum coinciding with the early diastolic abnormality (Figs 2.43 and 2.69). The diameter of the LV does not increase after the early rapid filling phase. Thus, M-mode shows a horizontal shape with no further increase in LV diameter during diastole and atrial contraction.

Two-dimensional echocardiography visualizes the bright and thickened pericardium (Fig. 2.69). The inferior vena cava is dilated as are the hepatic veins, with restricted respiratory fluctuations. Doppler echocardiography is necessary in order to differentiate constrictive from restrictive physiology [74].

Differential diagnosis has to include acute dilatation of the heart, pulmonary embolism, RV infarction, pleural effusion and chronic obstructive lung diseases. However, the most important differential diagnosis is chronic obstructive lung disease. In this situation, mitral inflow velocity usually decreases during inspiration and increases during expiration, with up to 100% change in velocity (Fig. 2.70). The highest mitral E-velocity occurs at the end of expiration, unlike in constrictive pericarditis where it occurs immediately after the start of expiration. The most reliable differentiation can be performed by measuring flow velocity in the superior vena cava. In chronic obstructive lung disease, superior vena cava flow increases with inspiration, whereas it does not change significantly with respiration in constrictive pericarditis. The difference is rarely more than 20 cm/s. In atrial fibrillation, the differentiation and diagnosis of constrictive pericarditis may be difficult. Diastolic flow reversal in the hepatic vein with expiration can be observed even when the pattern of flow velocity is not diagnostic.

After pericardectomy, the clinical status improves. The degree of reduction of respiratory variation in mitral inflow E wave and peak velocity of pulmonary vein D and S waves correlates with the improvement. After the procedure asymptomatic patients have less variation in both mitral and pulmonary venous flow than symptomatic patients. In addition, DT is prolonged. The persistence of postoperative respiratory variation is found in 9–25%. The percentage change of the peak mitral flow E wave decreases by up to 50%. As a result, ejection fraction determined by echocardiography increases because better LV but also RV filling is induced. Consistent changes in left and right atrial sizes are not reported.

Table 2.13 Thoracic aortic disease

Acute
Traumatic aortic injury
Intramural haematoma
Penetrating aortic ulcer
Aortic dissection
Chronic
Atherosclerotic aortic disease
Aortic aneurysm
Aortic pseudo-aneurysm
Congenital malformations (e.g. Marfan's syndrome)

Aortic diseases (see Chapter 34)

TOE has a prominent role in the detection of chronic aortic disease and in the emergency diagnosis of an acute aortic syndrome (Table 2.13) [23]. Nonetheless, the most important factor leading to a successful and rapid diagnosis remains a high index of suspicion by the clinician in the emergency room. CT and MRI have better spatial resolution and also better identify the extent and side-branch involvement. These techniques are important for detecting early progression and for follow-up studies. The TOE examination procedure for assessing aortic disease can be found in textbooks [33–35].

Atheromatous disease of the thoracic aorta is common and increases with age. It manifests as intimal thickening and protruding or mobile lesions. They can be complicated by erosion, superimposed mobile thrombi, penetrating ulcers and intramural haematoma, which may lead to an acute aortic syndrome. Mobile atheromas represent the greatest risk of an embolic event.

Aneurysm of the aorta is defined as an enlarged aortic diameter without evidence of an intimal flap, tear or intramural haematoma. The upper diameter limit of the ascending aorta is 2.1 cm/m^2 and of the descending aorta 1.6 cm/m^2. All diseases that weaken the aorta can lead to an aneurysm, classified as localized (saccular) or diffuse (fusiform) and true (intact aortic wall) or false (result from penetrating ulcer). An aortic diameter greater than 5 cm is a predictor of risk of rupture.

The increasing knowledge that intramural haematoma and penetrating ulcer are subtypes of aortic dissection has led to a new classification (Svensson classification) of aortic dissection, which may be localized in the ascending or descending aorta (or both) (Fig. 2.71). The echocardiographic criteria for diagnosing aortic dissection are well described [85]. The demonstration of an intimal flap and a false lumen with or without an entry are the hallmarks (Fig. 2.72). Additional findings are aortic regurgitation and pericardial effusion (Fig. 2.73).

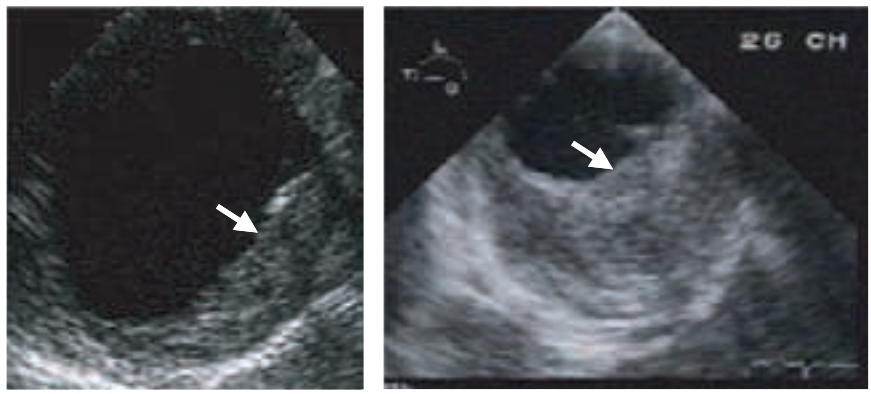

Figure 2.71 Intramural haematoma, a precursor of aortic dissection, is seen as an increased echodensity along the aortic wall as a result of thrombus formation between the intima (which has a smooth appearance, see arrows) and adventitia.

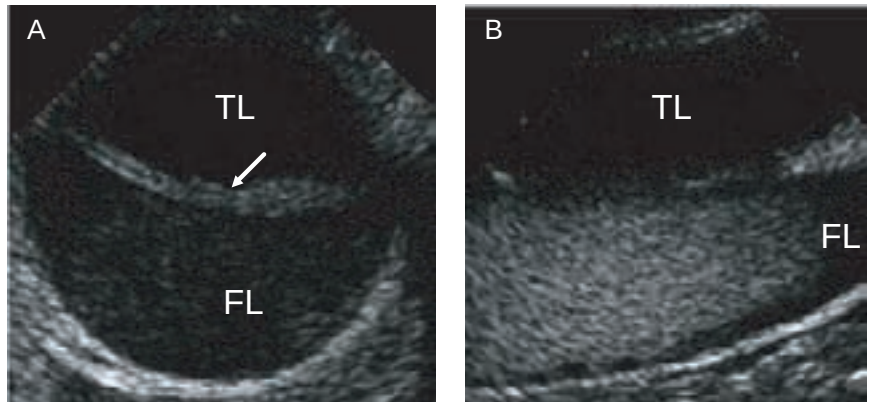

Figure 2.72 Transoesophageal echocardiography of aortic dissection. (A) Short-axis view of the aorta shows the intimal flap (arrow) separating the true lumen (TL) from the false lumen (FL). The slow/stagnant blood in the FL makes it echogenic. (B) Long-axis view shows the aortic dissection in the same area.

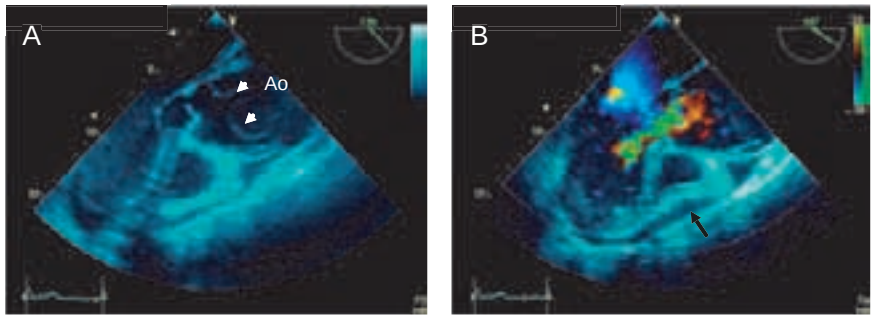

Figure 2.73 Transoesophageal echocardiography of a patient with type A, class 1 (Svensson classification) aortic dissection. (A) Note the dissected flap in the aorta (Ao) (arrows). (B) There is massive aortic regurgitation from the true lumen and a small pericardial effusion (arrow).

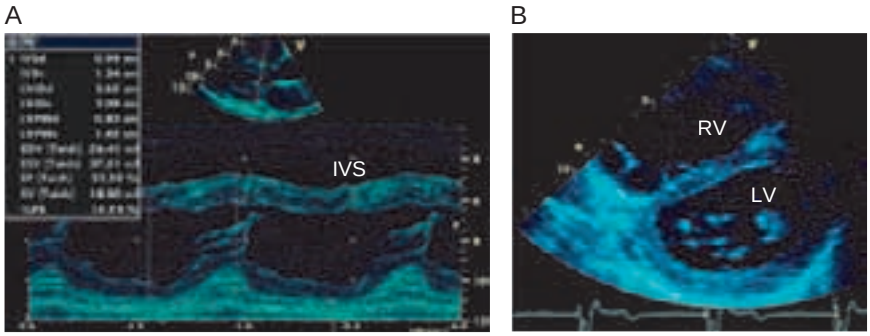

Figure 2.74 Chronic pulmonary hypertension. (A) The interventricular septum (IVS) has a typical paradoxical motion pattern (see Fig. 2.43). (B) Two-dimensional parasternal short-axis view shows the dilated right ventricle (RV) and flattened IVS resulting in the typical 'D-shaped' left ventricle (LV).

An acute aortic syndrome has to be included in the differential diagnosis of acute coronary syndrome in the emergency room. Rapid confirmation and patient management has to be organized in order to avoid deleterious events. Close cooperation between internal medicine, cardiology, radiology and cardiovascular surgeons is essential and the development of standard operating procedures (SOPs) is suggested. The most experienced physicians have to be included in decision-making.

Acute and chronic pulmonary disease

RV pressure overload may occur acutely or in a chronic fashion. Echocardiography is an ideal method for detecting right atrial and ventricular enlargement, which are usually accompanied by tricuspid insufficiency and distension of the inferior vena cava with reduced inspiratory collapse. Quantification of RV volumes remains a challenge. Three-dimensional echocardiography eliminates the need for standardized views and the use of geometric assumptions. It is therefore the optimal method for calculation of RV volume and function.

Pulmonary embolism results in pressure overload depending on the extent. In the case of small emboli no changes in haemodynamics occur. The first sign may be an increase in plasma levels of brain natriuretic peptide. In cases of moderate to severe pulmonary embolism, acute RV pressure overload occurs, characterized not only by ventricular enlargement but also by hypokinesia or akinesia of the RV free wall. In addition, the pulmonary diameter is distended (> 2 cm) as well as the inferior vena cava, with reduced inspiratory collapse. The pressure gradient rarely exceeds 45–50 mmHg, calculated with the Bernoulli equation from the tricuspidal regurgitant jet.

Thrombi within the right atrium and ventricle may be present but can be transient, disappearing in the pulmonary tree. Rarely with suprasternal scanning, but in up to 60% of patients scanned using TOE, emboli within the right, less often the left, pulmonary artery can be visualized when pressure overload is present. In type 1, the emboli are free-floating, whereas in type 2, which occur in acute recurrent events, emboli adherent to the vessel wall are found.

In chronic pulmonary hypertension, pressure overload results not only in right atrial and ventricular enlargement but also in hypertrophy (> 4 mm), which almost never exceeds 8 mm in the RV free wall. In addition, paradoxical interventricular septal motion is present and the size of the RV may exceed that of the LV in a very characteristic way (Figs 2.43 and 2.74). The Bernoulli equation allows estimation of pulmonary systolic as

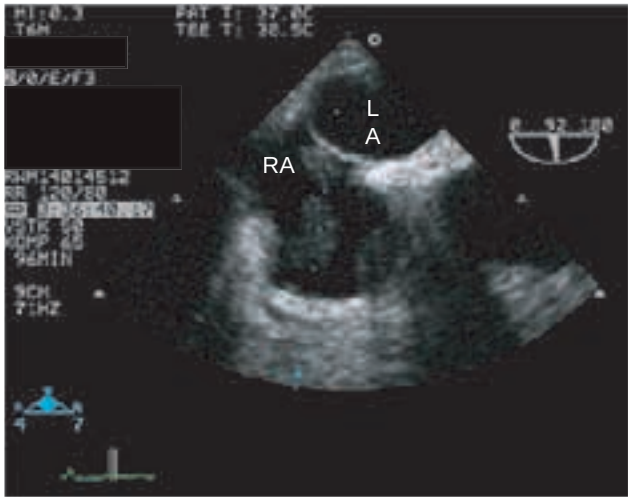

Figure 2.75 Transoesophageal echocardiography of patient with heparin-induced thrombocytosis (HIT). Multiple thrombi are seen in the right atrium (RA). LA, left atrium.

well as diastolic pressure (see Figs 2.40 and 2.41). This helps the clinician to follow the effects of medical treatment or surgery, when thrombectomy is performed. The prerequisite for surgery is the visualization of mural thrombus formation and wall thickening. Careful transoesophageal or intravascular ultrasound can be used for screening.

Intracardiac mass lesions (see Chapter 18)

Both transthoracic and transoesophageal echocardiography are highly accurate methods for detection and localization of mass lesions within the heart. These include primary and secondary tumours (metastatic tumours, hypernephroma, melanoma, sarcoma), thrombus and vegetations (Figs 2.58, 2.61, 2.65 and 2.75). Myxomas are the most common primary tumours in adults and are often located in the left atrium (Fig. 2.76). They are endocardial in origin while ventricular tumours are mostly myogenic and more often occur in children (rhabdomyosarcoma, fibroma, fibrosarcoma).

Echocardiography is the primary diagnostic tool in patients with clinical signs and/or symptoms suggesting an intracardiac mass or in patients with a cardiac disorder that predisposes to intracardiac mass formation. Not uncommonly, a mass lesion is detected during a routine echocardiographic examination. A histological diagnosis cannot be made by echocardiography however.

The differential diagnosis is with ultrasound artefacts and normal or variants of normal intracardiac structures (rete Chiari, Eustachian valve, hiatal hernia, lipomatous atrial septal hypertrophy, mitral annulus calcification, moderator band, Lambl's excrescences on valve cusps, false chordae in the LV).

Extracardiac masses may compress cardiac structures and mimic an intracardiac mass (mediastinal tumour).

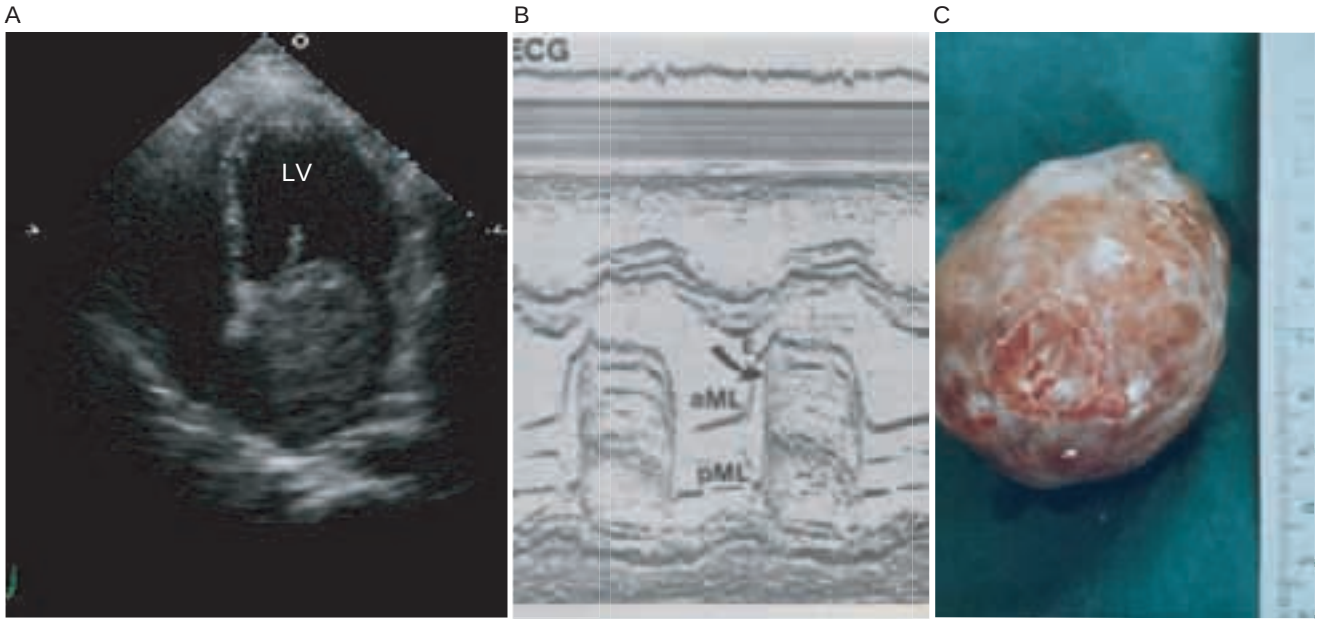

Figure 2.76 (A) Apical four-chamber view shows a large myxoma prolapsing into the mitral orifice in diastole. LV, left ventricle. (B) M-mode recording shows the tumour in the mitral orifice (arrow). Note that there is an interval between mitral valve (aML and pML) opening and diastolic prolapse of the tumour corresponding to the tumour plop heard on auscultation. Ventricular filling takes place during this short interval. (C) Anatomical specimen showing the excised attachment of the tumour to the interatrial septum.

Hydatid cysts are rare and are found in the heart or pericardium.

Embolic stroke

Source of embolism is one of the most common referral questions for TOE in patients with a transient ischaemic attack or stroke. Identification of an embolic source does not necessarily prove the causal relationship but is likely in patients who are < 45 years old and in whom vascular disease is likely to be absent. The detection of heart disease is also likely to be absent. The detection of heart disease makes the cardiac origin more likely: atrial fibrillation, mitral stenosis, endocarditis, prosthetic valve, thrombus and left atrial myxoma. Other potential sources of cardioembolic events are less clear because these are equally found in stroke victims and controls (mitral valve prolapse, annular calcification, septal aneurysm and patent foramen ovale). Contrast echocardiography demonstrating right-to-left shunting of blood flow increases the likelihood.

Emergency echocardiography

New technologies are continuously changing the way intensive-care physicians diagnose and treat their patients. Echocardiographic/Doppler examinations have numerous diagnostic applications in critically ill patients, especially when there is sudden haemodynamic deterioration. Acute circulatory failure and the haemodynamically unstable patient in both the intensive care unit and the emergency room are the most frequent indications. Obstructive shock (tamponade, pulmonary embolism) and hypovolaemic shock are readily diagnosed (or excluded). Expeditious diagnosis of acute cardiac problems requires rapid bedside imaging technology to assess patients with acute dyspnoea (atypical), chest pain and hypotension, syncope, shock and vascular (aortic) trauma. Many patients in the emergency room cannot be appropriately positioned for transthoracic echocardiography and patients in intensive care are often intubated for mechanical ventilation. Postoperative patients in intensive care have precordial dressings/tubes. All of these make TOE the first-line imaging approach [85] (see also p. 49—Substernal echocardiography).

Echocardiography/Doppler can detect acute or chronic mechanical problems, indeed all non-ventricular causes of low cardiac output (valve regurgitation or stenosis, pulmonary embolism, tamponade, constrictive pericarditis), hypovolaemia and low ventricular vascular resistance, as in anaphylactic shock, septic shock and acute failure.

Conclusion

This chapter has provided the physical and theoretical background of ultrasound applications in the heart. A few of its prominent clinical applications are also presented. It is obvious that the availability of smaller and faster microprocessors will further expand the potential and clinical applications of this non-invasive diagnostic method.

Personal perspective

In daily practice, echocardiographic/Doppler assessment is currently the first diagnostic test ordered whenever cardiac disease is suspected. In most instances a definitive diagnosis is made and further invasive procedures can be avoided. The application has recently extended into a variety of clinical scenarios including the emergency room, intensive care and both the operation and interventional suites where it is increasingly used as a routine method for guiding procedures and assessment of results.

As a result of advances in miniaturization and computer technology, newer modalities with increasing diagnostic functions and performance will continue to be developed. These will further increase the clinical questions that can be answered and the clinical scenarios in which echo/Doppler techniques are used.

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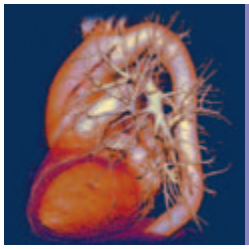

3 Cardiovascular Magnetic Resonance

Dudley J. Pennell, Frank E. Rademakers and Udo P. Sechtem

Summary

This chapter summarizes the contemporary clinical role of cardiovascular magnetic resonance (CMR) in clinical cardiology. A number of techniques are described which can be applied widely in the cardiovascular system, and these include assessment of morphology and dynamic function, blood flow, ventricular volumes and mass, myocardial interstitial abnormality, and the response to stress.

The best established indications for CMR are anatomical, with typical examples being assessment of the great vessels and congenital heart disease, pericardium and cardiac masses. More recently, assessment of morphology has started to include interstitial myocardial abnormalities, which include acute and chronic infarction, myocardial fibrosis and myocardial infiltration. This has opened up the fields of infarction and viability assessment in coronary artery disease, and phenotyping in cardiomyopathy where distinct distribution patterns of abnormality are associated with various pathologies. The prognostic value of myocardial fibrosis in these settings is now under investigation.

Basic principles

This technical introduction to cardiovascular magnetic resonance (CMR) aims to facilitate understanding but greater detail is available elsewhere [1]. MR depends on the interaction between some atomic nuclei and radio waves in the presence of a magnetic field. In clinical practice, imaging is almost exclusively performed using hydrogen-1, which is abundant in water and fat. A small excess number of hydrogen nuclei align to the magnetic field and can be excited by a radiowave at a resonant frequency (63 MHz with a 1.5 Tesla scanner). After the excitation pulse, the net magnetization decays (*relaxation*) and releases energy as a radio signal (used to form an *echo*). Sophisticated techniques convert these echoes into images that therefore represent a spatially resolved map of radio signals. Tissue contrast depends on the delay from excitation to signal read-out (*echo time*; *TE*) and the time between radiowave pulses (*repeat time*; *TR*). Two relaxation processes occur and are known as *T1* and *T2*, and these vary widely between different tissues. A CMR scanner has a magnet that is superconducting, *gradients* that are driven by pulses of electricity and which provide extra temporary magnetic fields, a *radiofrequency transmitter and receiver* connected to *radio coils* to transmit and receive the radio signals, and a *computer*. Images are formed using the electrocardiogram (ECG) as a trigger.

A scanner requires coordination of action of many individual processes to produce images and the controlling 'orchestral score' is known as a scanning *sequence*. Sequence components include *preparation pulses* (generates contrast between tissues), *excitation pulses* (localizes the excitation area), *gradient and magnetic field pulses* (formation of the imaging echo) and *signal read-out* (data collection). *Spin echo* sequences give anatomical images with black blood, and *gradient echo* sequences give cines. The *inversion recovery* pre-pulse is valuable for infarct imaging by yielding high T1 contrast. The signal read-out for CMR is usually fast to allow breath-hold imaging, and the faster schemes include fast low angle shot (FLASH), steady state with free precession (SSFP), spiral and echo-planar imaging (EPI). *Velocity mapping* displays

each pixel in the image as a velocity rather than a signal magnitude, and this is used to measure velocity and flow by integration over time of the product of mean velocity in a vessel and its cross-sectional area. For coronary CMR, *navigator echoes* are used to correct respiratory motion during long acquisitions by diaphragm monitoring. CMR *angiography* visualizes the vessel lumen after intravenous injection of a *gadolinium*-based MR contrast agent. A sequence called *tagging* measures myocardial contraction from the distortion of a magnetic grid laid across the image in diastole.

The safety of CMR is excellent and clearly advantageous compared with X-ray techniques. However, problems can occur with MR. Items that are ferromagnetic may be strongly attracted to the magnet, become projectile and have the potential to strike the patient. The more obvious problem items include scissors, injection pumps and oxygen cylinders, and strict safety protocols must be followed. A second issue is medical implants and electronic devices. Most metallic implants are MR compatible, including all prosthetic cardiac valves, coronary stents [2] and orthopaedic implants. Some cerebrovascular clips can be problematic, and specialist neurological advice is required in these patients. The high magnetic field may interfere with electronics devices such as pacemakers and cardioverter-defibrillators. In addition, the pacing wires can couple to the radiofrequency waves and heat significantly. These devices are a strong relative contraindication for CMR, although recent reports have shown MR to be safe under special circumstances [3].

Volumes and function

CMR is highly accurate and reproducible to determine the basic parameters used to characterize cardiac function such as ventricular volumes, ejection fraction and ventricular mass. CMR is independent of acoustic windows that may limit echocardiography. The high reproducibility of CMR is significantly better than that of echocardiography, which makes it the ideal tool for serial examination of patients over time [4,5]. Although it is possible to determine ventricular volumes with CMR, using the area length technique that is known from echocardiography, the more commonly used three-dimensional technique is preferred because geometric assumptions are not necessary. From the stack of short-axis images, the volumes and left-ventricular mass are determined using Simpson's rule. Semiautomatic techniques are available, which minimize the analysis time. As quantitative information on the functional capacity of both ventricles is necessary in most patients, the short-axis approach is routinely used in most CMR centres. As the right ventricle has a more irregular shape than the left ventricle, Simpson's rule calculations are the only reasonable approach for quantifying right ventricular volumes. In patients with diseases mainly related to the right ventricle therefore, CMR is often very useful.

Assessment of regional wall motion is greatly facilitated by the high-quality images acquired in most patients using SSFP cines. Wall-motion abnormalities are better seen and with greater confidence than with echocardiography [6]. Important parameters such as regional wall thickness and regional wall thickening can be derived. Nevertheless, image quality depends on the ability of the patient to breath hold, and the absence of poorly controlled cardiac rhythms. Using myocardial tagging techniques, the deformation of the tagging grid provides estimates of myocardial strain, torsion and shear. It has been suggested that a two-dimensional strain analysis may be better than measuring wall thickening to distinguish between dysfunctional and normal myocardium. Although myocardial tagging provides new ways of looking at cardiac physiology, it is rarely used at present in the clinical environment. CMR assessment of myocardial function should be used when the quality of echocardiography is reduced owing to patient-related factors [7]. Moreover, because of its superior image quality, CMR should be used when there is a discrepancy between echocardiographic findings and the overall clinical picture.

Myocardial infarction

Myocardial infarction can be detected with very high sensitivity using a CMR technique known as *late gadolinium enhancement* (Fig. 3.1). This is performed 10 minutes or more after the intravenous injection of a gadolinium MR contrast agent. These contrast agents enter the extracellular space and, owing to kinetic and partition effects, are concentrated in infarcted myocardium late after injection, where the extracellular space is expanded as a result of cell necrosis (acute infarction) or fibrotic replacement (chronic infarction) [8]. Using an inversion recovery sequence, the signal intensity of normal myocardium is driven to zero by adjusting the inversion time, and this leads to intense signal in infarcted areas that have a shorter T1 as a result of gadolinium accumulation. Thus CMR gives an almost histological depiction of myocardial

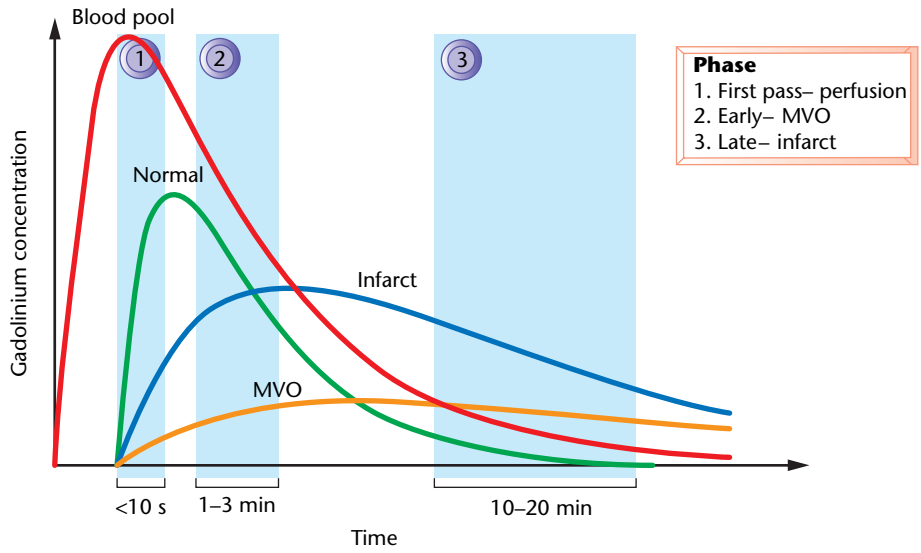

Figure 3.1 The use of intravenous gadolinium for CMR in detecting pathology depends on the time after injection that the images are taken. The bolus of gadolinium is given at time point 0, and the red line indicates gadolinium concentration in the blood (for clarity recirculation has been omitted). After a short delay, gadolinium enters the coronary arteries and the first pass through the myocardium is shown as the green line. At this time, ultrafast CMR can be used to measure myocardial perfusion (phase 1). After 1–3 min, early gadolinium enhancement imaging can be performed: at this time, the lowest gadolinium concentration is in avascular areas, such as in microvascular obstruction (MVO, orange line) in acute infarction; however, thrombus is also very well shown by this technique, and both appear very dark on the images (phase 2). When an MVO is present, it is surrounded by infarction, which is bright on the late gadolinium enhancement images taken after 10–20 min, when gadolinium is in highest concentration in infarcted areas (blue line, phase 3), or in cardiomyopathies in those areas of expanded extracellular space due to fibrosis or infiltration. The times given are for illustration of the principles and are dependent on the dose of gadolinium given and other factors.

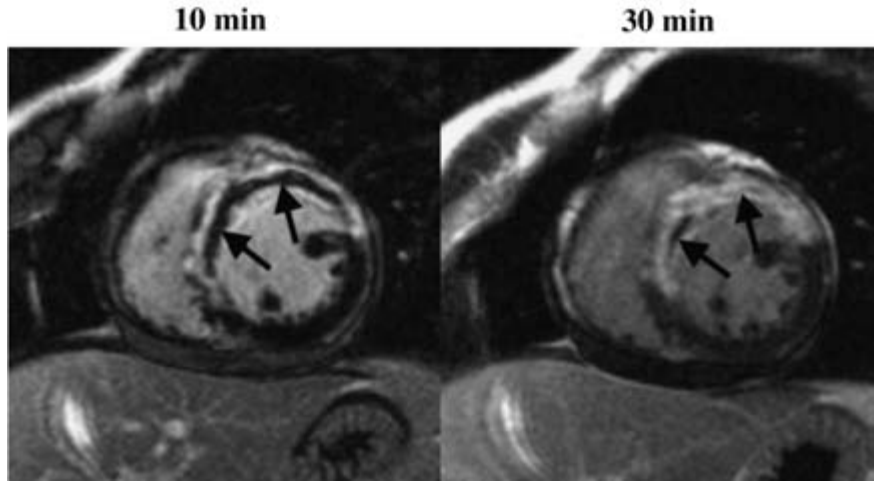

Figure 3.2 Large anterior myocardial infarction despite early reperfusion by percutaneous coronary intervention (PCI) and stenting. Left: At 10 min after the injection of contrast media (normal timing for assessment of enhancement) there is a central area of low signal intensity representing microvascular obstruction (arrows). This zone is surrounded by high signal intensity necrosis. Right: At 30 min after contrast injection the agent has also reached this central zone, leading to high signal intensity also in this portion of the infarct.

abnormality. Regions within the perfusion bed of an occluded coronary artery, which are underperfused but not necrotic, do not enhance. Some acute infarcts have a central dark zone in the area of late gadolinium enhancement, which represents microvascular obstruction, where it is difficult for gadolinium to penetrate (Fig. 3.2). These infarcts are associated with a poorer prognosis, as an independent predictor from the ejection fraction [9]. The area of microvascular obstruction slowly shrinks over weeks. In addition, the area of late gadolinium enhancement also shrinks substantially over time, both in volume and transmural extent, owing to scar formation with involution, and hypertrophy of adjacent and overlying myocardium. As CMR provides high spatial resolution,

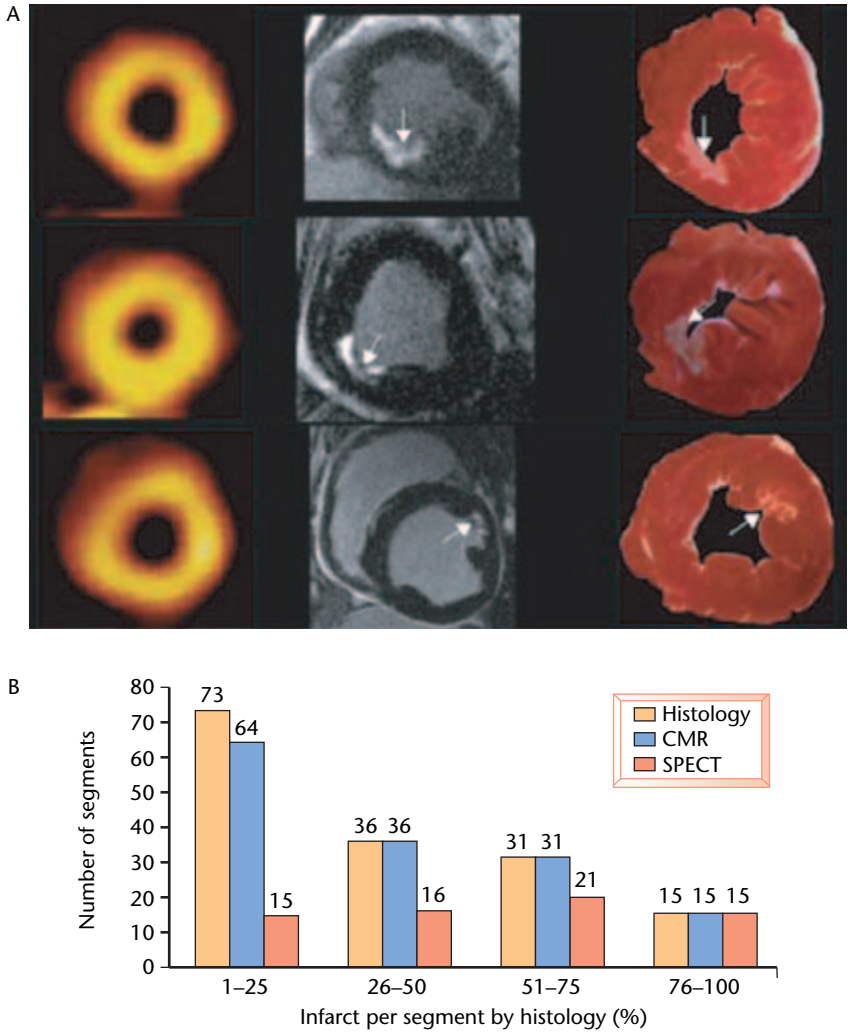

Figure 3.3 (A) Comparison of CMR and scintigraphy for detection of myocardial infarction in animals. The right column shows three experimentally induced infarcts with TTC staining as indicated by arrows. The *ex vivo* gadolinium images (middle column) show excellent correspondence, but the perfusion scintigraphy (left column) fails to resolve these small infarcts. (B) The graph relates the number of segments seen by each technique against the transmural extent of the infarction in quartiles. The light orange bar shows the results of histology, and comparison with the CMR (blue bar) is excellent. However, the proportion of missed infarct segments by scintigraphy (dark orange bar) increases as the infarcted segments become progressively more subendocardial. Reproduced with permission from Wagner *et al.*, *Lancet* 2003, **361**: 374–379.

has a high inter-study reproducibility and is completely non-invasive, it is the ideal tool to study acute infarction, healing and remodelling in man. In the chronic stage of myocardial infarction, the scar is still clearly visualized by late gadolinium enhancement. Late gadolinium enhancement CMR is significantly more sensitive for infarction detection than perfusion SPECT (Fig. 3.3) [10].

CMR can also depict the regional reduction in wall thickness and wall thickening associated with myocardial infarcts. However, the degree of abnormal systolic function is only a poor indicator of the degree of infarct transmurality. Myocardial stunning contributes to the observed loss of regional systolic function and it is not possible to distinguish this influence from the contractile dysfunction caused by infarct scar when using deformation imaging alone.

Viability

Accurate prediction of recovery of function following revascularization has been achieved with low-dose dobutamine CMR, with similar results to positron emission tomography (PET). However, late gadolinium enhancement CMR also allows the assessment of viable myocardium. Areas surrounding an infarct, which do not enhance, are composed of viable myocardium. The transmural extent of scarring is closely related to the likelihood of recovery of function after revascularization and also to recovery of ejection fraction [11]. However, low-dose dobutamine CMR may be more sensitive in predicting recovery of function [12]. This is not surprising as the

dobutamine-assisted test simulates the effects of revascularization. The main problem with late gadolinium-enhanced CMR is its reduced specificity in predicting the absence of recovery in non-transmural scars. The inability of non-transmural scar to recover function after adequate revascularization is poorly understood. One of the factors involved may be that recovery of function may require more time than the usual 3 months, which is the normal period after revascularization at which recovery function is studied. Moreover, coronary revascularization may be incomplete particularly in patients with extensive atherosclerosis and diffuse disease. Whatever CMR technique is used for assessing myocardial viability, it is appropriate to view viability as a continuum and not use a single threshold value for predicting functional improvement. Instead, one should base the clinical expectation of recovery on the extent of transmurality of the infarcts in a particular region. If more than 50% of the myocardium is infarcted, the probability of no recovery following revascularization is approximately 90% (negative predictive value) [11]. On the other hand, segments without scar have a 80% likelihood (positive predictive value) of recovery [12]. Late gadolinium enhancement CMR can also predict the effect of beta-receptor blocking agents in patients with severely reduced left-ventricular function. For larger scars, the improvement achieved by beta-blockade diminishes [13].

Stress ventriculography

Dobutamine stress CMR is now well established for diagnosing obstructive coronary artery disease (CAD) through induction of new wall motion abnormalities, and is superior overall to stress echocardiography because of better image quality [6]. Stress CMR is useful in patients who are unsuitable for dobutamine echocardiography. Normal stress CMR indicates a low event rate, and risk increases with ischaemia [14,15]. Ischaemia by stress CMR has been used for assessment of increased preoperative risk [14]. Ideally, stress CMR would allow quantification of wall motion assessment to reduce the high observer variability of dobutamine echocardiography. The most advanced, clinically, is tagging, which allows the measurement of myocardial strain, thus yielding increased sensitivity [15], but larger trials and faster post-processing are needed for clinical application. CMR stress ventriculography has been shown to be safe in large patient cohorts.

Myocardial perfusion

Myocardial perfusion CMR is the early phase of clinical adoption but it is attractive because when compared with scintigraphy, CMR has significantly enhanced in-plane spatial resolution with no ionizing radiation. A fast bolus of gadolinium contrast agent is given intravenously with a power injector and the first-pass signal changes in the myocardium are measured. At the current stage of development, perfusion CMR sequences typically image three or more slices per cardiac cycle, allowing a full segmental perfusion analysis. Areas of reduced perfusion are visualized as having persistent low signal, and in CAD appear to always involve the subendocardium with variable transmural extension. A rest study is not needed in principle, but it has been found useful for two reasons: first, to assist with the differentiation of endocardial artefacts from true ischaemic defects and second when the myocardial perfusion reserve is required for quantification. Late gadolinium enhancement is performed after 10 min and areas of infarction can be detected and compared with the stress perfusion images to determine whether peri-infarct ischaemia is present. The optimal imaging sequence for perfusion CMR is not yet determined. At least three fast sequences are being evaluated and these can be accelerated using parallel imaging and line-sharing techniques; however, it seems clear that faster and higher spatial resolution reduces artefacts. Perfusion CMR can also be analysed quantitatively using parameters such as the signal upslope. This allows the generation of parametric perfusion maps, indices of perfusion at rest and stress, and myocardial perfusion reserve [16]. More complex computer analysis may also be used with deconvolution of the myocardial signal curve with the input function taken from the left-ventricular blood pool, and this approach has been validated in animals. A CMR technique that does not require gadolinium contrast or ultra-fast imaging has also been described and this is called T2* blood oxygen level dependent (BOLD) [17]. However, the sensitivity of T2* to perfusion change may be quite low and its clinical role is not yet defined.

The results for the detection of CAD by myocardial perfusion CMR are very good in direct comparisons with coronary angiography, PET and single-photon emission computerized tomography (SPECT) [18]. Using perfusion CMR, the myocardial perfusion reserve has been shown to improve with coronary angioplasty, and the high resolution has allowed visualization of subendocardial perfusion abnormality in conditions such as cardiac syndrome X [16]. Perfusion CMR is likely to improve our

understanding of the pathophysiology of these types of conditions and have significant clinical application if the technique can be shown to have diagnostic and prognostic value.

Acute coronary syndromes

In an attempt to better and faster identify those patients with chest pain who present with true unstable coronary syndromes to the emergency room, CMR has been used to depict the abnormalities in wall motion, perfusion and infarct enhancement potentially associated with acute coronary chest pain. When performed at rest within 12 h of presentation, the sensitivity and specificity for detecting acute coronary syndromes was 84% and 85% by CMR, which was more sensitive than when ECG criteria for ischaemia, peak troponin I or the TIMI risk score were used [19]. CMR was also more specific than an abnormal ECG [19]. Whether CMR will be more useful than radionuclide imaging needs to be evaluated in a direct comparison trial.

CMR is helpful in detecting small acute myocardial infarctions such as those associated with coronary interventions. CMR shows areas of high signal intensity that are compatible with acute myocardial necrosis in the immediate vicinity of the intervention site or further downstream when embolization from the intervention site was the cause of the acute event [9]. After more extensive acute infarctions, CMR can depict large aneurysms and pseudo-aneurysms well, and ventricular thrombi are detected with higher accuracy than by echocardiography using an early gadolinium enhancement technique [20]. This has consequences in patients after myocardial infarction because thrombi mandate oral anticoagulation therapy for several months.

Coronary arteries

Although CMR angiography is an accepted technique for the visualization of arteries and veins throughout the body, its use in the coronary circulation is hampered by the inherent technical difficulties associated with imaging small, tortuous vessels on the curved surface of a continuously moving heart. The optimal spatial and temporal resolution for the visualization of coronary vessels cannot directly be achieved by conventional CMR sequences, so a number of special techniques are used (Fig. 3.4). To reduce blurring, coronary imaging is performed during cardiac diastasis in diastole when motion is limited; to image the tortuous vessels, a three-dimensional volume is acquired; to minimize cardiac displacement from respiratory movement, a breath-holding technique or diaphragmatic monitoring (called navigator echoes) is used; and to improve contrast, pre-pulses are used to suppress fat and non-coronary artery tissues (T2 preparation). At present, therefore, the most widely used technique is to combine a gradient echo or SSFP three-dimensional sequence with navigator diaphragm monitoring, T2 preparation and fat suppression. In the future, MR contrast agents may contribute to improved signal from the coronary lumen, and higher field magnets may also be useful.

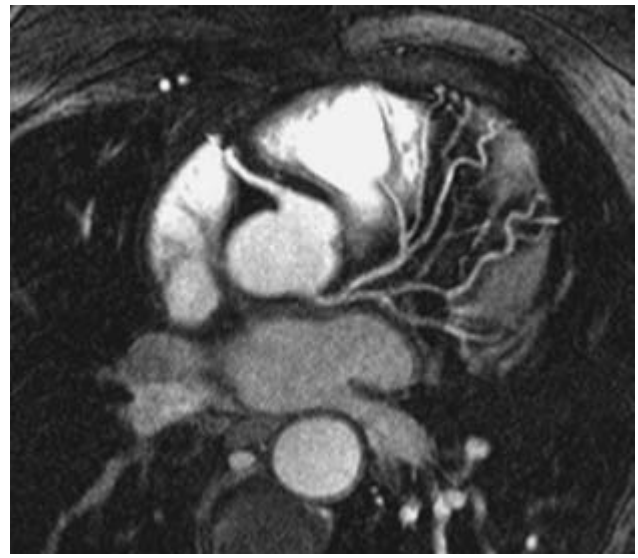

Figure 3.4 Coronary CMR showing a projection of a three-dimensional dataset into a single image. All three coronary arteries are visualized, as well as branch vessels.

With the current limitations, coronary CMR cannot replace conventional invasive coronary angiography. There are encouraging clinical results showing a high negative predictive value for left main stem or three-vessel disease [21], but the technique is not robust for routine use. Where coronary CMR has proven clinically valuable is in congenital abnormalities of the coronary tree with abnormal origin and course of the proximal artery. Here, the three-dimensional tomographic nature of coronary CMR gives superior results to projection conventional coronary angiography for the relation of the proximal coronary artery to the aortic root and pulmonary trunk (Fig. 3.5) [22]. The malign variants have an interarterial course. Bypass grafts can also be visualized confidently with CMR, allowing the exclusion of graft

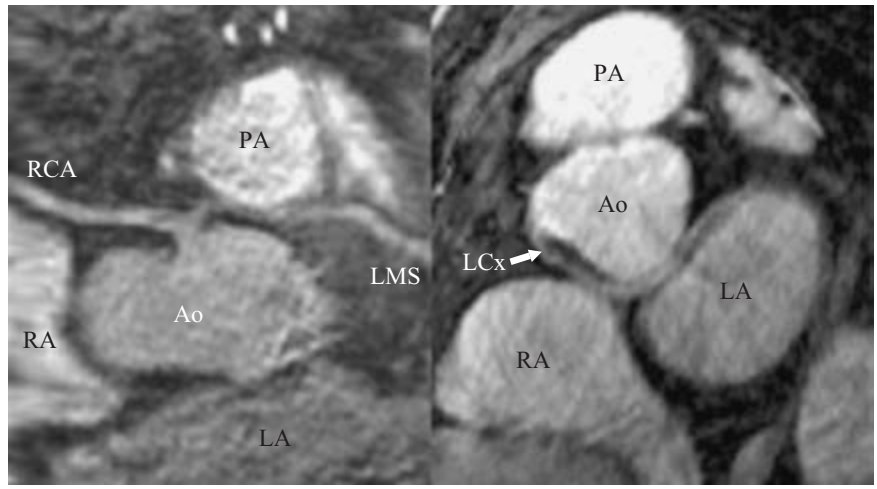

Figure 3.5 Coronary CMR of coronary anomalies. (A) The right coronary artery (RCA) and the left main stem (LMS) both arise from the anterior coronary sinus. The left main stem passes between the aorta (Ao) and the pulmonary artery (PA), and is considered a malignant course because of the risks of compression between the great vessels. (B) A benign anomaly with a left circumflex (LCx) arising from the anterior coronary sinus and passing posteriorly behind the aorta, in front of the right atrium (RA) and left atrium (LA), to reach the posterior atrioventricular groove. This variant is considered benign.

occlusion but the exact morphology of the connection with the native circulation (often the location of pathology) is frequently difficult to visualize accurately. Here the use of flow reserve measurements can be helpful [23]. Inflammatory diseases of the coronary arteries giving rise to aneurysm formation can be visualized and followed over time to judge evolution with treatment [24]. Currently, the performance of multislice CT is better than coronary CMR, but it too is not yet ready for routine clinical practice and carries a significant radiation burden, contrast hazards, and artefacts from calcium, which can obscure luminal interpretation.

Vessel wall

A new application of CMR is the direct assessment of atherosclerotic plaque. This is currently most easily accomplished in the carotid arteries, because the artery is superficial and surface coils allow high spatial resolution. Arterial wall CMR can be used to measure total plaque burden within an imaging volume by using T1-weighted images with blood signal suppression, and summing the difference in each image slice between the outer and inner vessel boundary to obtain the total vessel volume. This is highly reproducible and allows the demonstration of plaque regressions with statins [25]. The technique can also image coronary plaque. Plaque characterization is also possible with identification of features of plaque inflammation, cholesterol pools and the thickness of the fibrous cap using a combination of T1-, T2- and proton density-weighted images [26]. Thin or disrupted caps on CMR have been strongly linked with cerebrovascular events [27]. Arterial sclerosis can also be assessed using CMR including the measurement of compliance in the ascending aorta (change of aortic volume in a slice normalized to pulse pressure) and pulse wave velocity (rate of propagation of the flow wave around the aortic arch in metres per second). These age-dependent measures are abnormal in early atherosclerosis and predict cardiac events.

Endothelial function can also be measured reproducibly by CMR using stimuli that cause arterial vasodilatation, such as flow-mediated dilatation (endothelium dependent) and glyceryl trinitrate (endothelium independent). Flow-mediated dilatation of the brachial artery is assessed by forearm cuff occlusion for a standard time period, followed by release, which induces increased endothelial shear, the release of nitric oxide and arterial dilatation [28]. The use of CMR allows area measurement of the vessel, which has advantages over the diameter measurement made by ultrasound. Validation studies have been performed in humans using invasive techniques, and repeated measurements by CMR appear to have greater reproducibility than by ultrasound, suggesting smaller sample sizes for trials using CMR [28]. An additional advantage of CMR is that flow changes can also be measured directly in response to the standard stimuli.

Cardiomyopathy

Hypertrophic cardiomyopathy

The diagnosis of hypertrophic cardiomyopathy (HCM) is usually made by echocardiography, but CMR has

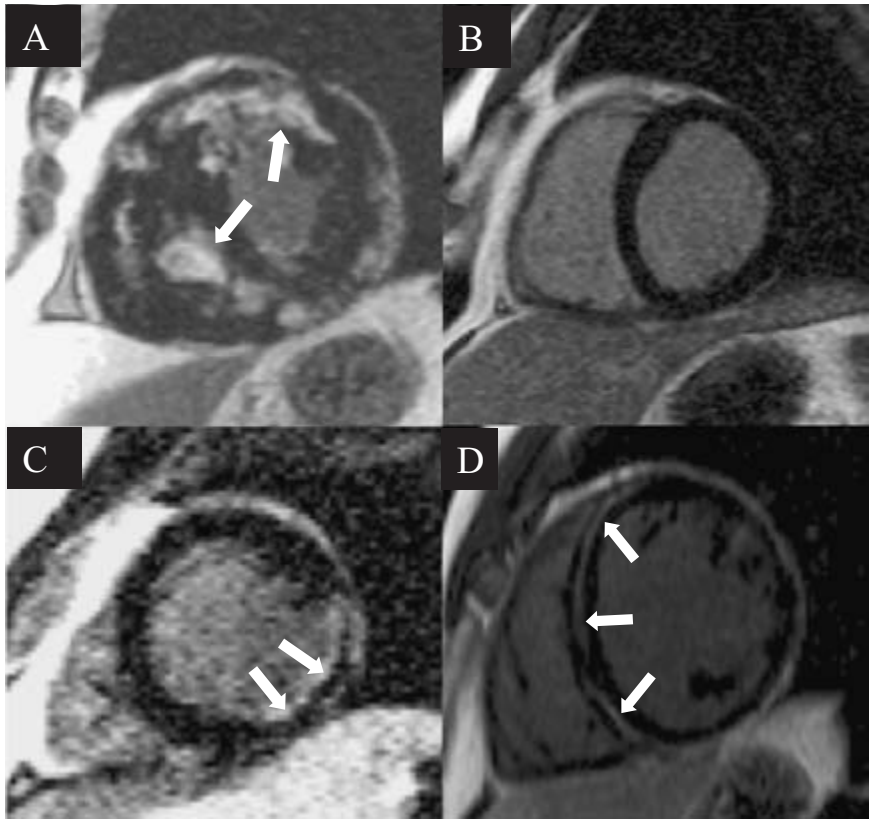

Figure 3.6 Late gadolinium enhancement CMR in cardiomyopathy. (A) A patient with hypertrophic cardiomyopathy (HCM) and the arrows depict areas of fibrosis that are discrete, of variable distribution across the thickness of the myocardial wall and not distributed in coronary territories. (B) A patient with dilated cardiomyopathy (DCM) and no late gadolinium enhancement is seen. (C) A patient who had been diagnosed as having DCM on the basis of normal coronary arteries; however, late gadolinium CMR clearly showed an inferolateral infarction (arrows), suggesting that the infarct-related artery had recanalized by the time of coronary angiography, and therefore that DCM was not the correct diagnosis. (D) Another patient with DCM is shown, in whom there is mid-wall enhancement (arrows), which is clearly different from HCM or infarction.

advantages in some clinical scenarios because of its excellent image quality with comprehensive ventricular coverage for identification of regional hypertrophy. Thus CMR is mainly used diagnostically when the results from echocardiography are inconclusive, such as in apical hypertrophy [29]. Other features of HCM can also be shown including obstruction in the outflow tract, and systolic anterior motion of the mitral valve. The accuracy of CMR for the phenotypic determination of HCM may also be helpful for screening of relatives of probands.

A number of other CMR techniques may also be helpful, although their place in clinical practice is not yet established. One feature of myopathic hypertrophy is impaired contraction and this can be quantified using CMR tagging. In HCM, tagging shows abnormal strain, shear and torsion in dysfunctional hypertrophic areas. This may prove to have value in differentiating HCM from hypertrophy as a result of exercise or hypertension. Another feature of myopathic heart is a bioenergetic defect in high-energy phosphate compounds such as ATP, which can be detected using complex CMR spectroscopic methods in patients with HCM who have varying genetic mutations. This suggests the hypothesis that inefficient energy utilization may be the underlying substrate for HCM [30]. Finally, late gadolinium enhancement CMR occurs in HCM, and this has been shown to represent myocardial fibrosis (Fig. 3.6) [31]. A common benign pattern of enhancement occurs at the insertion points of the right ventricle into the left ventricle. However, some patients have extensive late gadolinium enhancement. A link has been shown between the extent of late gadolinium enhancement and the risk of heart failure or sudden death (Fig. 3.7) [32]. This is thought to reflect the risk of re-entrant tachycardia and systolic failure from scar formation. It is not yet known whether late gadolinium enhancement in HCM is an independent risk factor in comparison with other established parameters. Late gadolinium enhancement also occurs in therapeutic septal myocardial infarction. This is useful for localizing and assessing the transmural extent of the infarction to assess procedural success.

CMR has also proved useful in other causes of hypertrophy, which form a differential diagnosis in HCM. About 4% of HCM patients have Fabry's disease, in which α-galactosidase is deficient which causes accumulation of glycosphingolipid GB3 in myocytes and endothelium. CMR typically shows lateral wall late gadolinium enhancement in these patients (Fig. 3.8) [33], which has been

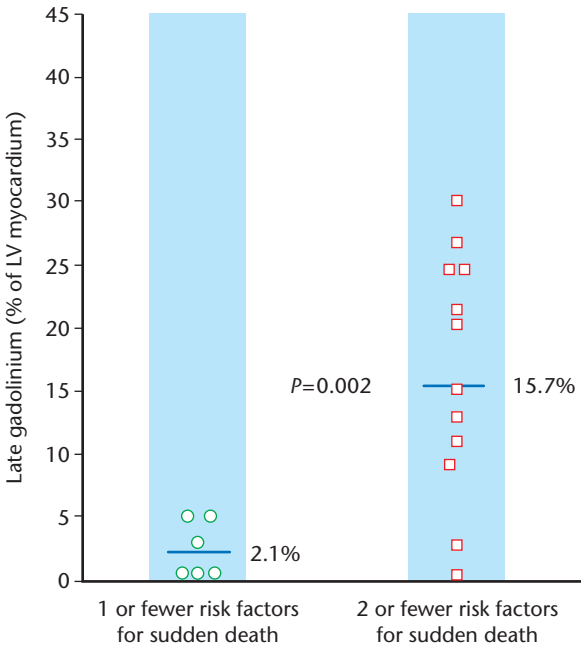

Figure 3.7 In hypertrophic cardiomyopathy, the extent of late gadolinium enhancement is related to the presence of risk factors for sudden death. These findings suggest that the extent of fibrosis may be a useful clinical marker of risk.

related to fibrosis, although the cause for this distribution is not known. It is, however, useful diagnostically. Another differential diagnosis is cardiac amyloidosis, which shows a different pattern again, with global subendocardial late gadolinium enhancement due to preferential endocardial amyloid deposition.

Dilated cardiomyopathy

CMR shows and quantifies the functional abnormalities in dilated cardiomyopathy (DCM) for both ventricles. Because CMR has excellent reproducibility, changes over time can be used for serial monitoring of function. However, the main clinical question in DCM is the differentiation from coronary artery disease (CAD). This may not be straightforward and many centres routinely perform coronary angiography as a gold standard. Late gadolinium enhancement CMR has been shown to be useful as a non-invasive alternative [34]. In a study of patients labelled with DCM following normal coronary angiography, 59% showed no late gadolinium enhancement and 28% presented with patchy or longitudinal striae of mid-wall enhancement sparing the subendocardium (Fig. 3.6). In all of these cases, CMR correctly identified

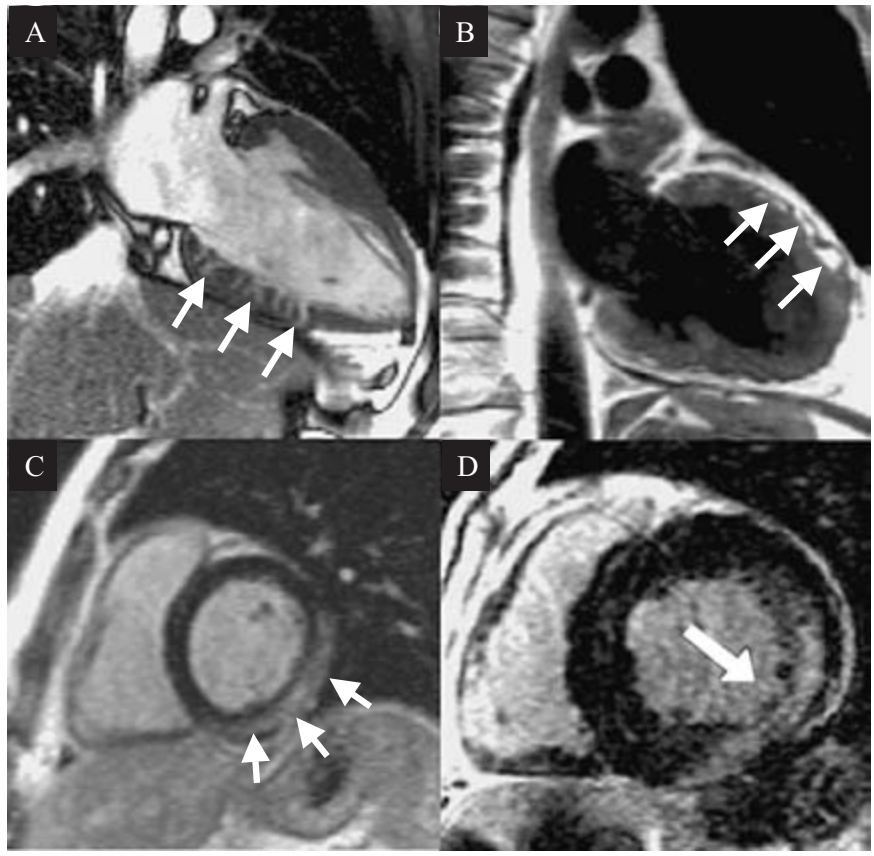

Figure 3.8 CMR in other myocardial conditions. The inferior wall in (A) shows deep recesses (arrows) diagnostic of non-compaction. The anterior wall in (B) shows high signal areas that were shown to be fat using fat-suppression sequences in a patient with left-ventricular involvement in ARVC. In (C), the inferolateral wall shows epicardial late gadolinium enhancement in a patient with myocarditis. In (D), there is mid-wall late gadolinium enhancement in the typical location for Fabry's disease.

that myocardial infarction was not the cause of ventricular dysfunction. Also of significant interest was the final group of 13% of patients in whom late gadolinium enhancement was present, which was indistinguishable from infarction. This suggests that these patients were incorrectly assigned the clinical label of DCM following 'normal' coronary angiography, probably as a result of coronary recanalization post infarction and untreated ventricular remodelling. When it is also considered that incidental coronary stenosis may occur in patients with true DCM that has not resulted in infarction, the use of coronary angiography as a gold standard for diagnosis of DCM appears flawed. If these results are confirmed in further studies, CMR may become established as an alternative to coronary angiography in the diagnostic work-up of DCM.

The mid-wall late gadolinium enhancement identified in patients with DCM is similar to the fibrosis found in these patients at post-mortem. This has not previously been identified *in vivo*, and studies are under way to determine whether the presence of such scars has prognostic importance as a source of re-entrant arrhythmias or accelerated ventricular dysfunction. The prognosis in DCM has also been assessed using CMR spectroscopy, with which a low phosphocreatine–ATP ratio predicts an adverse outcome [35].

Iron overload (siderotic) cardiomyopathy

Siderotic cardiomyopathy occurs in patients who require regular blood transfusions. The body has no mechanism for the excretion of iron, which therefore accumulates in the tissues, causing organ dysfunction and oxidative cellular damage. The most frequent condition associated with siderotic cardiomyopathy is β-thalassaemia major, in which heart failure occurs at a young age and is the cause of death in 71% of patients. Approximately 60 000 children are born annually with this condition, and all require lifelong treatment. In view of the high mortality rate from heart disease, protocols have been developed for clinical management, which are based on measurements of blood ferritin and liver iron levels. These are not ideal because they are surrogate measures for the target lethal organ, which is the heart. The measurement of cardiac iron clinically has been difficult, and myocardial biopsy has been rarely used because of the risk of complications and sampling error because of non-homogeneous myocardial iron distribution. Recently, however, it was shown that the myocardial relaxation parameter T2* measured by CMR can be used to assess iron in the heart [36]. Normal myocardial T2* is > 20 milliseconds (ms), and values lower than this indicate iron overload, which has been linked with left-ventricular dysfunction (Fig. 3.9),

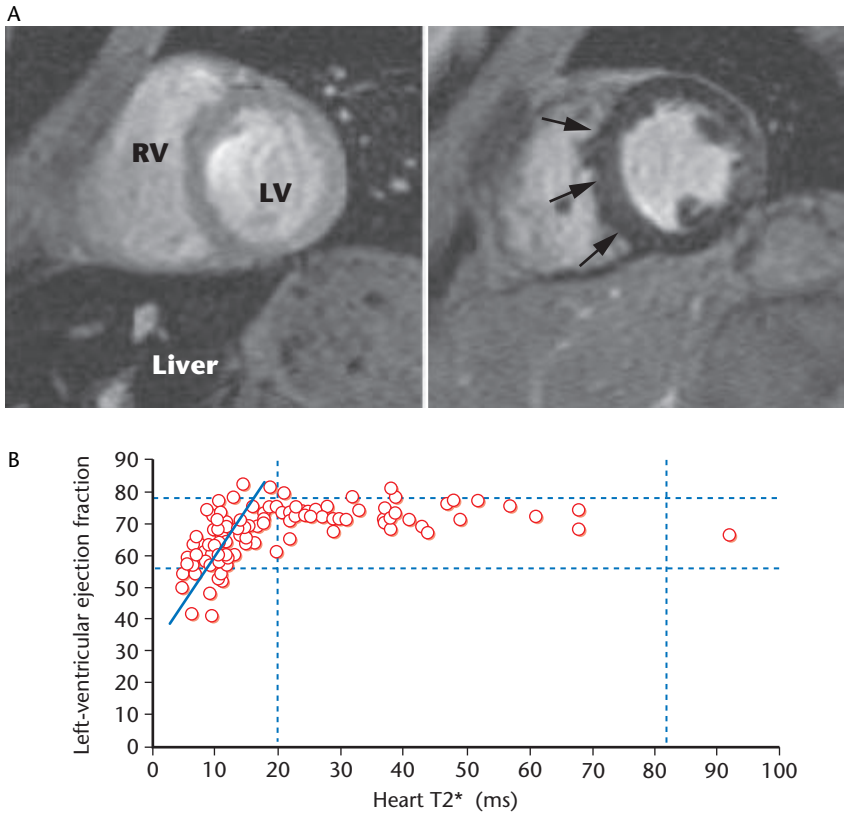

Figure 3.9 (A) T2* CMR in iron overload cardiomyopathy. The left panel shows an iron-loaded liver (dark) but normal myocardial signal. If a liver biopsy was performed, this would suggest iron loading, and chelation therapy might be increased with the risk of significant side-effects. The right panel shows a counter example, where the liver is normal but the heart is iron loaded (arrows). If a liver biopsy were performed on this patient, it would be falsely reassuring and the patient would be at risk of cardiac complications. The inter-organ disparity in iron loading explains why heart failure is the biggest cause of mortality in thalassaemia patients. (B) The relation between myocardial T2* and the ejection fraction. The normal myocardial T2* is > 20 ms, and this is associated with a normal ejection fraction but below this the ejection fraction falls with iron toxicity. Reproduced from Anderson *et al.*, *Eur Heart J* 2001, **22**: 2171–2179.

and increased volumes and mass typical of remodelling in heart failure [36]. Liver and heart iron can be at wide variance making clinical management using heart iron essential (Fig. 3.9). Myocardial T2* increases in thalassaemia patients undergoing intensive iron chelation treatment for heart failure as the heart function improves. The technique can now be completed in a single breathhold, making it cost-effective in countries with large patient numbers. In addition, early results suggest oral chelators may have preferential effects on myocardial iron compared with the established subcutaneous injected therapy.

Arrhythmogenic right ventricular cardiomyopathy

Structural and functional abnormalities of the right ventricle are well seen by CMR and therefore it is used in expert centres for the investigation of arrhythmogenic right ventricular cardiomyopathy (ARVC). CMR assists in locating diagnostic criteria for ARVC including the presence of regional wall motion abnormalities, increased volumes, morphological abnormalities, fatty infiltration and left-ventricular involvement (Fig. 3.8). Follow-up of right ventricular volumes over time can be helpful, as the condition is progressive and it can present in the early concealed phase. Scan interpretation is not straightforward, however, because the right ventricle has significant variation of normality, including hypokinesia at the moderator band insertion, variable trabeculation, and epicardial fat deposits that may mask the normal thin right ventricular myocardium, except in the best quality images. Fatty infiltration can also occur in circumstances other than ARVC. Recent work suggests that late gadolinium enhancement may be useful to demonstrate the fibrous replacement in the right ventricle that occurs in ARVC. Another protocol of interest is use of fat suppression imaging, which allows signal from fat to be reduced, which leaves the normal right ventricular myocardium better seen and fatty infiltration as dark areas. More work needs to be done in the use of CMR in ARVC. There is no doubt about its value, but no technique is ideal in investigating this difficult condition at present.

Myocardial sarcoidosis

Sarcoidosis of the heart is uncommon, but is a well-recognized cause of sudden death. The clinical diagnosis is difficult, although changes in the ECG can be indicative. Late gadolinium enhancement CMR has been used to show myocardial abnormalities in presumed areas of fibrosis in sarcoidosis [37], but more experience is needed. T2-weighted sequences may also be abnormal in active myocardial inflammation.

Myocardial amyloidosis

CMR can show the features of restrictive cardiomyopathy such as in amyloidosis, with diastolic dysfunction, ventricular hypertrophy and interatrial septum thickening. Recently, amyloid infiltration has been shown using late gadolinium enhancement, with a global subendocardial pattern that results from dominant interstitial expansion of the endocardial layer with amyloid protein.

Myocardial non-compaction

Non-compaction is a congenital disorder of endomyocardial embryogenesis in which the myocardium fails to compact properly and deep clefts occur in the left ventricle. It is associated with progressive dysfunction, arrhythmias and systemic embolism. The diagnosis can be made by echocardiography but CMR depicts the abnormality well, with comprehensive ventricular coverage if there is limited involvement (Fig. 3.8), and underlying fibrosis can be shown with late gadolinium enhancement.

Myocarditis

The clinical diagnosis of myocarditis is often difficult and may mimic infarction. A number of reports indicate that CMR may be useful in this diagnosis. Focal increase of myocardial signal is seen in acute myocarditis with gadolinium-enhanced T1-weighted spin-echo imaging at 1-2 min after injection, and myocardial enhancement relative to skeletal muscle may be increased [38]. The relative enhancement falls over time and is predictive of long-term ventricular function. T2-weighted spin-echo imaging may also show high signal. Late gadolinium enhancement CMR has also been shown to be abnormal in the acute phase, particularly in the epicardial portion of the lateral wall (Fig. 3.8) [39].

Valvular heart disease

Although echo Doppler is widely used for the diagnosis and follow-up of valvular disorders, it can be difficult in the individual patient to quantify the severity of the lesion, to judge the impact on ventricular morphology and function, and to evaluate prognosis with respect to timing of surgical vs. pharmacological treatment. CMR,

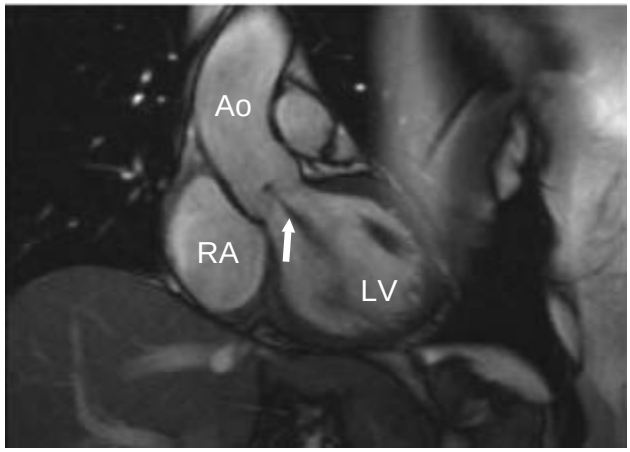

Figure 3.10 Coronal image in mid-diastole from an SSFP cine acquisition. There is a jet of aortic regurgitation (arrow). Ao, aorta; LV, left ventricle; RA, right atrium.

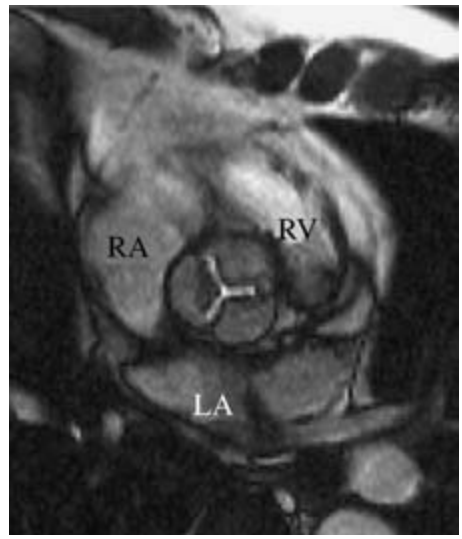

Figure 3.11 Planimetry of the aortic valve area in aortic stenosis. The tight tri-foil shape of the aortic valve can be seen, and the valve area can be planimetered directly. Good correlation of this technique with other investigations has been shown (RA, right atrium; RV, right ventricle; LA, left atrium). Reproduced with permission from Kupfahl *et al.*, *Heart* 2004, **90**: 893–901.

although presently underused for this indication, is useful in this area [40]. Breath-hold spin-echo sequences (for morphology) and the SSFP cine sequences (for dynamic visualization) can reliably study normal and abnormal valves. Turbulence of flow resulting from stenosis or regurgitation causes signal loss on cine sequences allowing ready identification of the abnormality (Fig. 3.10). The size and extension of the signal loss, however, is only a semi-quantitative measure for lesion severity because of the influence of haemodynamics, shape of the valve and parameters of the sequence, just as in colour flow mapping in echo Doppler. Imaging perpendicular to the stenotic valve with thin, adjacent slices enables the planimetry of the stenotic area (Fig. 3.11) [41]. Through plane motion, signal voids because of turbulence or calcification and distorted valve morphology may interfere with this measurement but good results have been reported. Velocity mapping permits the quantification of peak and mean flow velocities (m/s) (as with Doppler) as well as volume flow (ml/s) at multiple sites in the heart. Short TE sequences are needed to avoid loss of velocity information with turbulence. Integration over time of volume flow provides stroke volume, as well as antegrade and retrograde flow volumes. Combining such measurements with each other and with the stroke volumes from the left and right ventricles enables the calculation of gradients, resistance, valve area, regurgitant volumes and fraction. The impact of valvular dysfunction can be reliably and reproducibly followed over time by measuring myocardial mass, cavity volumes and shape. End systolic volume (among others) has been shown to be an important prognostic factor. Automated tracking of valve through plane motion may in the future improve the reliability of velocity-encoded measurements and make CMR the optimal technique to quantify valvular dysfunction.

Aortic regurgitation can be quantified by measuring retrograde diastolic flow immediately above the valve and below the coronary ostia. By dividing retrograde by antegrade flow volume, the regurgitant fraction is obtained. A similar approach is less obvious for mitral insufficiency because of the larger, less circular mitral ring area and the three-dimensional motion of the valve. Eccentric jets can also cause problems. The difference measurement between stroke volume obtained from cavity measurements and antegrade flow in the aorta is therefore a more reliable technique. For stenosis assessment, both in- and through-plane velocity measurements can be used, but in both instances multiple parallel planes are required to optimize alignment and to obtain true maximal velocities, which can be inserted in the modified Bernoulli's equation for calculation of gradients and valve area with the continuity equation [42].

It is safe to perform CMR in all prosthetic valves, although the metal in the prostheses causes focal artefacts that can obscure small jets. Quantification of valvular regurgitation remains possible, but even more care has to be taken to adjust the acquisition plane to the motion of the valve. Endocarditis lesions can be visualized if they do not show a rapid, erratic motion pattern that makes them 'invisible' on gated sequences but, typically, echocardiography is preferred. Real-time CMR may make

imaging of endocarditis lesions more reliable. Overall, in valve disease, CMR is a valid alternative when echocardiographic quality is suboptimal and is the technique of choice for individual patient follow-up with respect to volumes and mass.

Congenital heart disease

Congenital heart disease is a major indication for CMR. The three-dimensional character of CMR, together with the ability to quantify local flow and therefore shunts, the absence of radiation and the difficulties of using echocardiography post surgery, have all contributed to the successful use in this indication [43]. The full spectrum of CMR sequences is used in congenital heart disease: SSFP sequences for overall anatomy and function (left-ventricular, right ventricular and atrial volumes, stroke volumes and ejection fraction, myocardial mass); spin echo for morphological details, T2 imaging for tissue characterization; velocity mapping of local flow and for valvular function (aorta, pulmonary artery, caval veins, pulmonary veins, grafts and conduits, valve planes) and gadolinium angiography for three-dimensional representation of the great vessels and complex anatomy.

Viscero-atrial situs

The viscero-atrial situs (situs, solitus, inversus, ambiguous) and the malposition of the heart (dextrocardia) can be more easily obtained with CMR, as the technique offers a large field of view which includes the surrounding structures, including the abdomen, and identification of the different chambers from morphological and functional characteristics. A full set of images in the three orthogonal planes (transverse, sagittal, coronal) is the basis for this analysis. Depending on the anomalies observed, further images, taken in oblique planes, can be combined with functional imaging.

Atria and veins

Atrial septal defect can usually be visualized with echocardiography (especially transoesophageal echo), but the impact on the circulation (shunt quantification [44], right ventricular dilatation and function) is better evaluated with CMR. By measuring the flow in the ascending aorta and in the pulmonary artery the shunt flow and fraction can easily be determined. Right ventricular dimensions and function are notoriously difficult to evaluate with echo; CMR can quantify volumes, ejection fraction and pulmonary valve flow. Partial anomalous pulmonary venous return can be difficult to detect even with transoesophageal echocardiography. CMR visualizes well the (sometimes very variable) morphology of the pulmonary veins, but can also measure the flow in the aberrant vein, calculate the shunt fraction and show the abnormal connection [45]. Systemic venous abnormalities or variants can be visualized with contiguous two-dimensional scanning or three-dimensional volume acquisitions (left superior vena cava, interrupted inferior vena cava). After surgery, for example repair for transposition of the great arteries, the reconstructed venous conduits and baffles may become obstructed and stenotic, and the morphology and degree of stenosis can be measured from cine and flow imaging.

Atrioventricular connections

CMR can be used to identify atria and ventricles using characteristic morphological features, allowing the demonstration of discordant atrioventricular connections. Abnormal morphology or function of the valves (straddling, atresia, regurgitation, stenosis) can be visualized. A reliable quantification of ventricular volumes and function can be used for surgical decisions (repair vs. Fontan).

Ventricles

Complex ventricular anomalies (tetralogy of Fallot, univentricular hearts, valve atresia) can be depicted with CMR and the shunt fraction and morphological and haemodynamic consequences can be quantified. This can help in treatment decisions. Ventricular septal defects can be visualized (jet on cine images) and the shunt quantified, but it is mainly in complex lesions (double outlet) that CMR proves superior to echocardiography.

Valves

Although direct depiction of valves is less good with CMR than echocardiography, its main importance lies in the quantification of regurgitation and the impact on the receiving chamber, especially for the right ventricle. An example is pulmonary regurgitation after patch surgery for tetralogy of Fallot, where it is clinically difficult to decide on the appropriate timing for valve replacement.

Great arteries and conduits

Coarctation of the aorta is the most common anomaly of the thoracic aorta. CMR can visualize the lesion itself but also the collateral circulation. By comparing flow

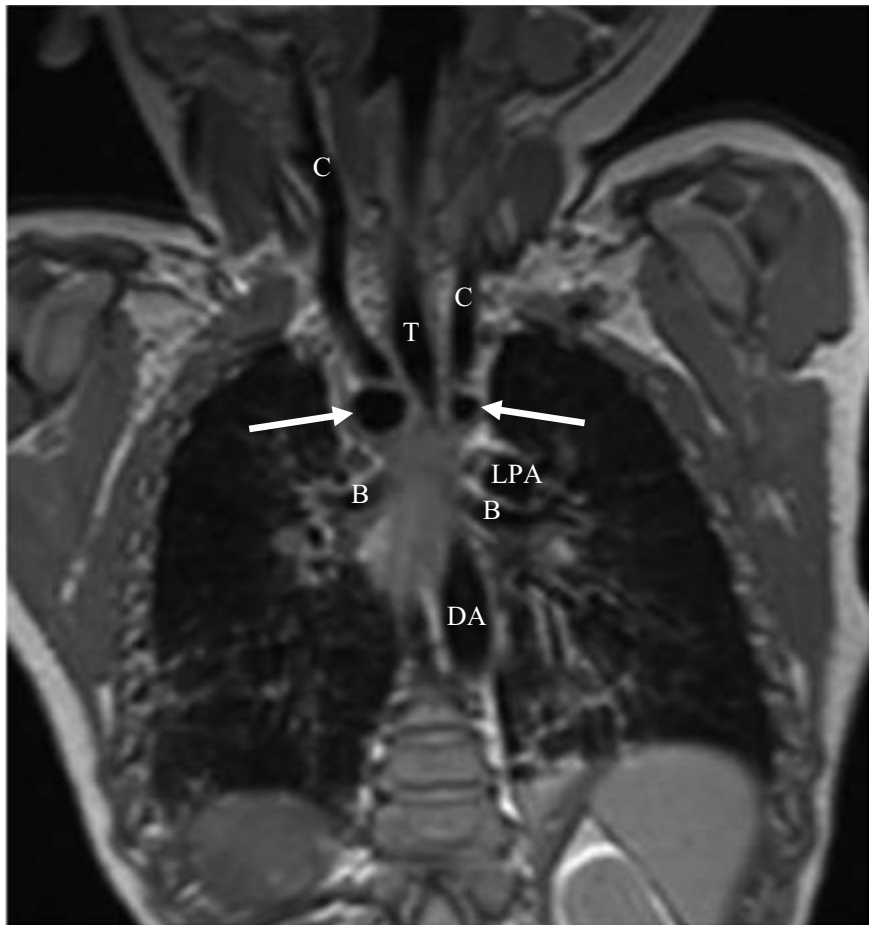

Figure 3.12 CMR in the posterior coronal plane (close to the spine) in a patient with double aortic arch seen in cross-section (arrows). B, bronchus; C, carotid artery; DA, descending aorta; LPA, left pulmonary artery; T, trachea.

before the coarctation and at the level of the diaphragm, the collateral circulation can be quantified and used to judge the success of invasive treatment. Other abnormalities of the aorta (double aortic arch, aneurysm of the sinus of Valsalva, dilatation in Marfan's and Ehlers–Danlos syndromes) can be followed over time (Fig. 3.12). Patent ductus arteriosus can be easily seen with echo in newborns, but in older patients CMR can be more reliable. Abnormalities of the pulmonary circulation in patients with reduced pulmonary artery flow or systemic to pulmonary collaterals, as well as pulmonary anomalies can be shown with CMR. Comparing flow in the right and left pulmonary artery, and comparing these to systemic return flow, can help in evaluating the severity of the lesions and the options for therapy. Also after intravascular or surgical treatment CMR can be useful to evaluate the effects and evolution (to stenosis) of the intervention.

Postoperative follow-up

CMR is very helpful after surgery for complex anomalies, as the echocardiographic quality is often degraded and a need exists for a quantitative technique that can reliably follow volumes, function and morphology over time. This is especially true for conduits and for the right ventricle, which is often overloaded as it functions as the systemic ventricle or due to pulmonary insufficiency.

Coronary arteries

CMR is the technique of choice for the diagnosis of congenital coronary abnormalities. It can show the abnormal origin of the artery but also the course with respect to aorta and pulmonary artery which is important for risk and surgical planning in congenital heart disease [22].

Comparison with other modalities

Echocardiography remains the technique of choice in newborns and young infants, as image quality is usually very good and CMR would require sedation or anaesthesia. On the other hand, in older infants, adolescents and adults, in complex pathology and after surgery, CMR is often useful. In the last two conditions, the full advant-

age of CMR becomes evident, offering unlimited image planes irrespective of scar or lung interposition and the capability of localized flow measurements for the evaluation of shunts, stenoses and valve lesions. The CMR information may allow cardiac catheterization to be avoided, significantly shortened or reserved for interventional procedures. For follow-up, CMR usually offers all the necessary information and cumulative radiation can be avoided.

Great vessels

CMR has become the primary imaging modality for assessment of great vessel disease. Gadolinium CMR angiography generates high-resolution three-dimensional angiograms, and velocity mapping provides reliable measurements of blood flow. The most common indications for performing CMR in aortic disease are to depict or follow aneurysms or dissections. Although CMR angiography shows the size, extent and shape of aneurysms, additional use of black-blood imaging is needed for depiction of the vascular wall and peri-aortic soft tissue. Image acquisition in at least two planes is helpful to identify inflammatory changes such as arteritis (Fig. 3.13), perivalvular abscesses and mycotic aneurysms or post-surgical infections. In dilated and especially dissected aortas, it is often necessary to identify the presence of thrombus and distinguish it from slow flow in a patent lumen.

CMR has a high accuracy in diagnosing and excluding aortic dissection [46], and the entire aorta can be imaged within 15 min. Therefore, even in cases with acute disease, CMR is competitive with more commonly used techniques such as CT and transoesophageal echocardiography. Patient monitoring in the magnet is straightforward, but full-time magnet availability with experienced operators may be problematic. The main feature of aortic dissection is the presence of an intraluminal intimal flap, which is easily demonstrated using transverse cine CMR. Gadolinium CMR angiography may provide additional information regarding branch vessel involvement. The presence of pericardial effusions and the function of the aortic valve can also be depicted and quantification of aortic regurgitation is possible using velocity mapping. In practice, CMR is often mostly used for follow-up or in patients with chronic disease. This is because CMR is free from ionizing radiation, MR contrast agents are not nephrotoxic and serial measurements at predefined landmarks are more reliably performed than from transoesophageal echocardiography.

Intramural haematoma is characterized by the presence of a false lumen without blood flow. The likely mechanism is intramural haemorrhage resulting from leaking vasa vasorum. Black-blood pulse sequences, such as spin-echo sequences with T1 weighting, are especially useful for depicting the bright crescentic thickening of the aortic wall. Another acute aortic syndrome is the penetrating aortic ulcer, which occurs predominantly in the

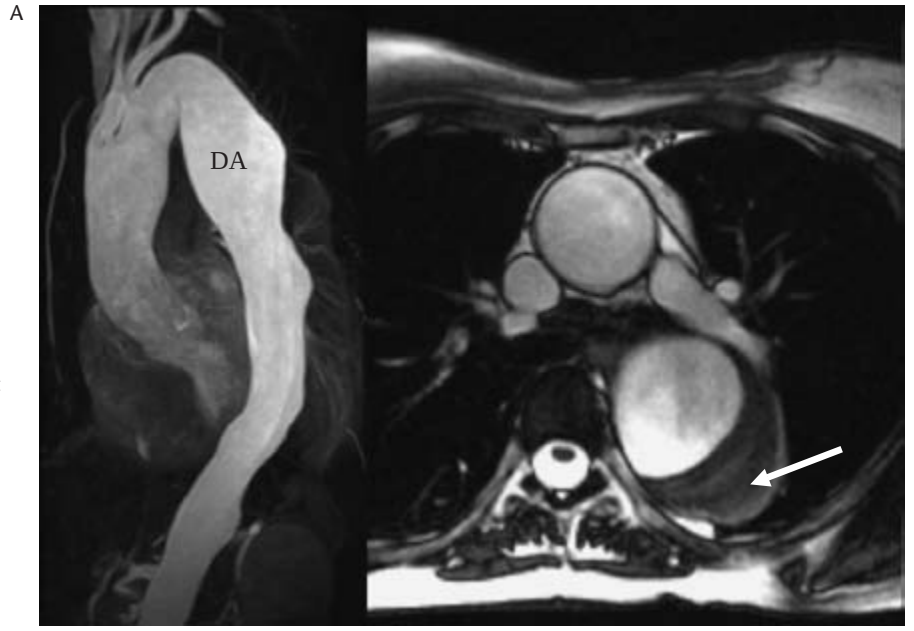

Figure 3.13 Aortic aneurysm in a patient with arteritis. (A) Three-dimensional MR angiogram shows grossly irregular contours of the descending aorta (DA) and vertical position of the aortic arch. (B) Transverse cine CMR image shows the large aneurysm of the descending aorta, which is filled to a large part by thrombus (arrow).

elderly with diffuse and severe forms of atherosclerosis. These ulcers can lead to large aneurysms, which may need placement of endovascular stent grafts. Such ulcers can be distinguished from small and benign ulcers by using both black-blood CMR and angiography.

CMR is also useful for depicting the pulmonary vasculature and may be a useful adjunct to functional CMR of right heart abnormalities. However, although the initial experience for pulmonary embolism is promising, pulmonary MR angiography requires long breath-holds, which may not be possible especially in this patient population. Consequently, CT remains the technique of choice for this clinical question.

Pericardium

CMR is able to depict the pericardium and the pericardial space with high spatial resolution. It is thus clinically helpful in patients with suspected pericardial disease in whom echocardiography may provide suboptimal image quality. Moreover, pericardial thickness can be accurately determined, which may be difficult with echocardiography. When compared with CT, CMR has the disadvantage of a longer examination time and inferior image quality in very sick patients who have poorly controlled atrial fibrillation or are unable to hold their breath for a longer period of time. CMR is also inferior in depicting pericardial calcification. However, CMR provides a functional assessment of the abnormalities associated with pericardial disease and this may make CMR the preferred technique in difficult cases.

As pericardial fluid is depicted as a high single intensity space between the epicardium and the fibrous pericardium, even small quantities of pericardial fluid can be reliably detected. This may be important in patients with infectious pericarditis and myocarditis with pericardial involvement (Fig. 3.14). Although systematic comparisons are lacking, the sensitivity and the confidence for detecting especially inferior localized diffusions may be better for CMR than for echocardiography. Acute pericardial inflammation is characterized by enhancement of the (thickened) pericardium following gadolinium MR contrast agent.

To distinguish between restrictive cardiomyopathy and constrictive pericarditis, reliable measurements of pericardial thickness are important. CMR is highly accurate in distinguishing between these two clinical entities, although it is limited in patients who develop constrictive pericarditis following cardiac surgery when the pericardium may have normal thickness [47]. Another helpful feature to distinguish restrictive cardiomyopathy from constrictive pericarditis is that CMR identifies amyloid heart disease, one of the most common causes of restrictive cardiomyopathy. CMR is also helpful to identify pericardial cysts and distinguish them from other tumours. It is also possible to identify a rare pericardial abnormality,

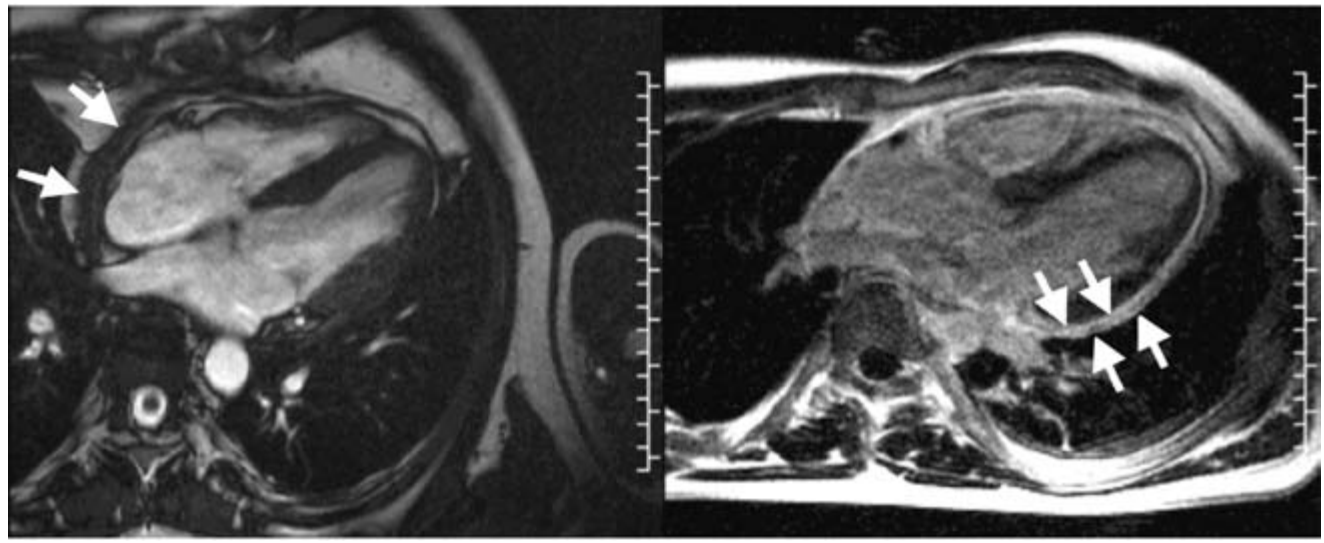

Figure 3.14 Patient with acute tuberculous pericarditis. (A) Cine image demonstrates pericardial thickening covering the right atrial surface (arrows). (B) Late gadolinium enhancement CMR shows that both layers of the pericardium are inflamed over the left ventricle with marked enhancement (arrows). The potential mechanism of tuberculous spread to the pericardium is suggested by the infiltration of the adjacent left lung.

absence of the pericardium or partial absence of the pericardium, by the unusual position of the heart.

Tumours and masses

Chest radiography and echocardiography are the first-line imaging techniques to visualize cardiac tumours and masses. CMR is useful to better obtain the relation with surrounding tissue and organs (extension, infiltration, vascular relation) and for tissue characterization, both of which can help to better plan treatment [48]. Simple visualization of a mass is usually carried out with the cine SSFP sequences, but tissue characterization requires T1- and T2-weighted spin-echo imaging, fat suppression and gadolinium studies including first pass, early enhancement and late enhancement for interpreting vascularity, necrosis or thrombus formation (Fig. 3.15) and fibrosis or expansion of the interstitial space. Together with the location of the tumour (right heart more malignant), its size, homogeneity and extension in surrounding tissues (malignancy), the presence of pleural and pericardial effusion (malignant, metastatic), this allows for a good but not perfect characterization of the mass. Furthermore the haemodynamic and functional effects of the tumour can be quantified. Cardiac tumours can be primary (benign or malignant) or metastatic. Malignant tumours of the heart often have a characteristic panoply of diagnostic features (Fig. 3.16).

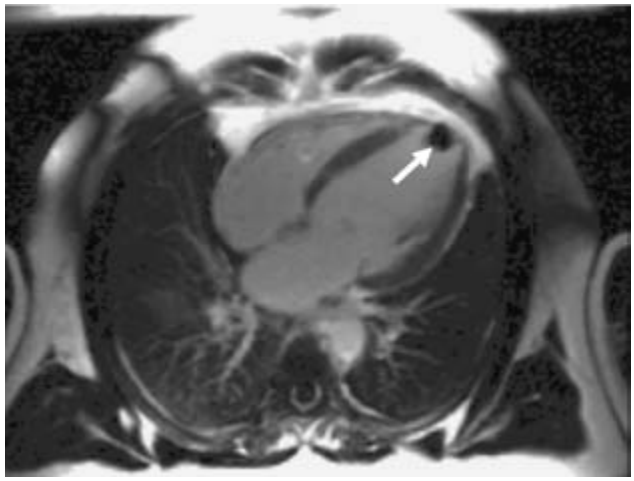

Figure 3.15 Ventricular thrombus. After gadolinium injection with early inversion recovery imaging at 2 min, the mass is well defined and the very low signal implies low penetration of gadolinium and low vascularity. This is compatible with thrombus in this patient with cardiomyopathy.

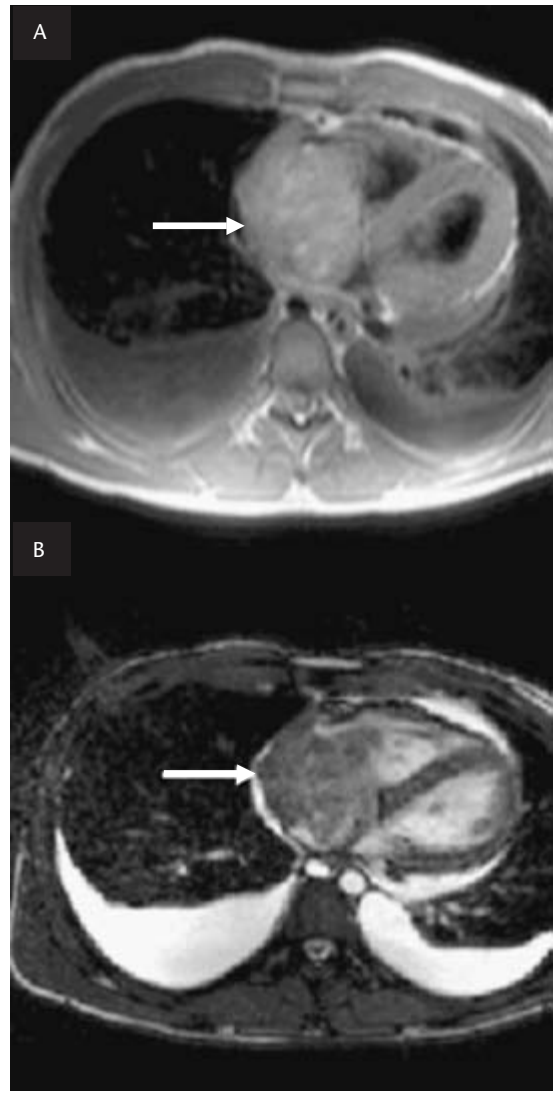

Figure 3.16 Sarcoma. The T1-weighted spin-echo image (A) in the transaxial plane shows a mass in the right atrium (arrow), which is irregular and of heterogeneous signal. The late gadolinium enhancement image (B) shows pericardial effusion with invasion and heterogeneity of signal suggesting patchy fibrosis. Many of these features suggest malignancy.

Interventional cardiovascular magnetic resonance

Interventional CMR is in its infancy, and clinical applications in the heart are only just starting to emerge. The technical innovations needed for interventional CMR are catheter tracking, real-time imaging, MR-compatible materials and devices and new imaging sequences. Two

main strategies exist for catheter tracking, passive and active, the former using regular sequences adapted to visualize the thin catheter, the latter using the catheter as an MR antenna allowing three-dimensional localization with superimposition of position on a morphological image. Clinical placement of devices has been greatly advanced by the development of robust real-time imaging, which is essential to allow interactive manipulation. Most catheters and devices contain metal that not only causes artefacts on the MR images, but also could induce electrical currents and heat at contact sites, which can be potentially harmful, and therefore MR-compatible devices such as catheters, stents and closure devices are now being developed.

The present areas of clinical use of interventional CMR are congenital heart disease, electrophysiology, peripheral vascular disease and stem cell work. In congenital disease, defects have been closed with interventional CMR [49], and implantation of stents and intravascular valves has been pursued. In some cases full CMR implantation and evaluation has been performed, and this area is expanding. In electrophysiology, CMR is used to guide the interventional cardiologist by supplying three-dimensional models of the chambers under investigation so that catheter manipulation is easier. Usually these CMR data are acquired separately at a previous occasion, but in an XMR suite (combined X-ray and CMR in joined rooms) the patient can be shifted between the modalities, allowing for a complete three-dimensional fusion of the CMR and catheterization data. It is also possible to directly visualize ablation lesions, showing their extent and continuity, which allows additional ablation in regions of discontinuity. In peripheral vascular atherosclerotic disease, interventional CMR has proved easier because of the larger vessel size and full diagnostic and therapeutic MR procedures are therefore feasible. Interventional CMR has also been used for direct injection of gene material or stem cells in the region of a previous infarct [50]. This requires a real-time sequence to visualize the infarction. By including iron particles in the cells, the location, extent and migration of the injected material can be followed *in vivo* over time.

Personal perspective

CMR has rapidly developed in recent years and now fulfils an indispensable role in major cardiac centres in the investigation and management of cardiovascular disease. Currently, the most frequent clinical referrals are in cardiomyopathy, arterial angiography (non-coronary), congenital heart disease and viability/infarction assessment. However, there are two other major sources of clinical referral, which can be given the generic titles of 'unusual or uncertain cardiovascular pathologies' and 'suboptimal results from other imaging techniques'.

However, the role of CMR in coronary artery disease is expanding relatively slowly for three main reasons: conventional techniques are well-entrenched clinically; there is limited availability of dedicated CMR scanners, CMR expertise and appropriate reimbursement; and publication of larger multicentre clinical trials with outcomes analysis is needed. The exception, as noted above, is the use of late gadolinium enhancement to identify infarction. This new high-resolution technique has made significant contributions to our understanding of infarction and viability because the circumferential and transmural extent of necrosis and scar can be imaged *in vivo* for the first time. Thus, not only is CMR now the most sensitive clinical method for detection of infarction other than cardiac enzymes in the acute phase, but also the presence of stunning and hibernation and therefore the likelihood of functional recovery can be directly determined. In CAD, the next likely area for significant clinical application by CMR will be perfusion imaging. The advantages include high resolution, lack of radiation burden, quantitative analysis of perfusion and a fast procedure time for the patient (approximately 30 min). The optimal imaging sequence and clinical protocol needs to be finalized but will come in the near future.

The future for CMR is bright. No other technology offers the combination of safety, image quality and versatility and the incorporation of CMR into cardiology training programmes recognizes the importance of this new technology for trainees and established cardiologists.

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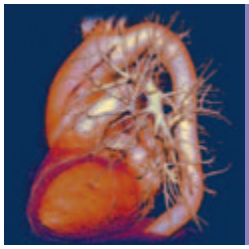

4 Cardiovascular Computerized Tomography

Pim J. de Feyter and Stephan Achenbach

Summary

The high prevalence of coronary artery disease with its associated high morbidity and mortality rates provides a strong stimulus for the development of a non-invasive diagnostic modality to image the coronary arteries. Contrast-enhanced computerized tomography (CT) coronary imaging has emerged as a reliable diagnostic modality to detect significant coronary stenoses in selected patients who have a slow (< 70 beats per minute) and stable heart rate. Severe calcifications and irregular heart rhythms significantly limit the clarity of CT coronary imaging, while the relatively high radiation exposure is of concern.

The cross-sectional nature of CT coronary imaging allows the non-invasive assessment of atherosclerotic changes in the coronary wall and has the potential for early detection of coronary atherosclerosis in asymptomatic individuals.

CT imaging for pulmonary embolism is highly accurate and may be considered the first-choice diagnostic option. CT imaging of the great thoracic vessels, for cardiac function, and of heart valves, cardiac tumours and thrombi or pericardial disease is feasible but the non-radiation diagnostic modalities echocardiography or magnetic resonance imaging should be considered the first diagnostic options.

Introduction

The development of X-ray computerized tomography (CT) in the 1970s is considered one of the greatest advances in diagnostic imaging because of its ability to image non-invasively the internal structures of the body with unprecedented accuracy. No other modality allows the scanning of large body regions with comparable spatial resolution and contrast within such a short time. The high spatial and tissue resolution of CT can be achieved because the collimated X-ray beam is transmitted selectively through a specific cross-section; this minimizes superimposition of structures above and below a specific cross-section (slice) while also reducing X-ray scatter and improving image contrast. Finally, CT makes use of refined detectors that can measure small differences in tissue contrast (to less than 0.1%).

The first commercially available CT system with an acquisition time fast enough to image dynamic cardiovascular structures was the electron-beam computerized tomography (EBCT) scanner. EBCT was initially developed in the late 1980s for functional analysis of the left ventricle (and was therefore originally called 'cine CT') [1] but soon thereafter became mainly used for the detection and quantification of coronary artery calcification. In 1995, contrast-enhanced EBCT coronary angiography was first described [2] and in subsequent evaluations was demonstrated to permit non-invasive detection of haemodynamically relevant coronary artery stenoses with moderate reliability.

'Spiral' or 'helical' CT—which combines continuous rotation of the X-ray tube with continuous movement of the patient table along the *Z*-axis—was introduced in the 1990s and, unlike EBCT, this technique has undergone such extremely rapid development in the past few years that it has now emerged as a very reliable, non-invasive

cardiovascular imaging technique that is able to create practically motion-free images of the heart and coronary arteries. Consequently, several studies have shown that spiral CT permits the detection of coronary stenoses and extraluminal coronary plaques.

Basics of computerized tomography

CT is an X-ray-based imaging technique. An X-ray source rotating around the patient emits a narrowly collimated fan-shaped beam of X-rays that passes through the body. Various tissue types (heart, lungs, etc.) have different absorption characteristics and the attenuation of the X-ray beam is recorded by detectors on the opposite side to the source. Based on the attenuation values measured at a multitude of projections, cross-sectional images are reconstructed (Fig. 4.1). To reconstruct one image, it is necessary to acquire data over an angle of at least 180° (one-half rotation).

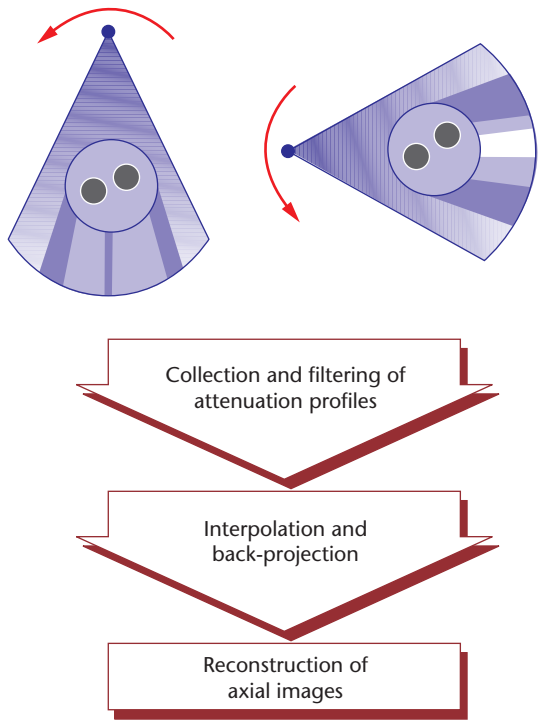

Figure 4.1 Principles of computerized tomography. Multiple attenuation profiles from different angles are acquired during a 180° rotation of the X-ray tube and detector system. After filtering of the data, the projection profiles are interpolated in the *Z*-axis (longitudinal axis), to create complete datasets (profiles) at each plane position. Using back-projection reconstruction algorithms, axial source images are created from the interpolated projection profiles.

After acquisition of the X-ray data, many parameters that can individually be chosen will influence the appearance of the reconstructed image. The size of the reconstructed image ('field of view') is usually adapted to encompass the target organ to be investigated. Images are reconstructed with a 1024×1024 or 512×512 matrix size so that the size of one image pixel will be:

$$\text{pixel size} = \text{field of view/matrix size}$$

The thickness of the reconstructed image can also be adjusted after the scan itself. It can be between 0.5 mm and several millimetres. Frequently, slice thickness will be set to a thickness somewhat larger than the collimation to reduce image noise. Usually, the reconstructed images have a distance ('reconstruction increment') that is lower than the slice thickness, so there is overlap between consecutive images (e.g. data are acquired with 0.6-mm collimation, and reconstructed with 0.75-mm thickness and 0.5-mm increment). Finally, appearance of the reconstructed image is influenced by the reconstruction kernel, a filter algorithm used in the reconstruction process which determines the relationship between resolution of the image ('sharpness') and image noise.

X-ray attenuation values measured by CT (also called ('CT number') are expressed in 'Hounsfield Units' (HU). The CT number of a given pixel is normalized to that of water:

$$\text{CT number (HU)} = [(\mu_{\text{tissue}} - \mu_{\text{water}})/\mu_{\text{water}}] \times 1000$$

where μ_{tissue} is the attenuation value of tissue and μ_{water} is the attenuation value of water. By definition, water has a CT number of 0 HU, air (no attenuation) has a CT number of –1000 HU. Bone (highly attenuating) usually has a CT number between + 1000 and + 3000 HU. Each pixel in the reconstructed CT image is assigned a brightness value in proportion to the determined CT attenuation, to create the digital reconstruction image. The digital reconstruction image is then converted into a grey-scale image (in which the shades of grey represent CT attenuation values) for display on a cathode ray tube, television monitor, or on film. However, the human eye can only distinguish a limited number of grey levels. Specific CT numbers within the image are therefore mapped to a smaller range of grey-scale levels. The 'window width' determines the range of grey levels to be displayed and allows the selective display of a restricted range of tissues. The centre of the range of CT numbers that are displayed is the window level. The tissue grey-scale ranges from white at one end of maximum attenuation (highest CT number in the range) to black at the other end where attenuation is minimal (lowest CT number in the range),

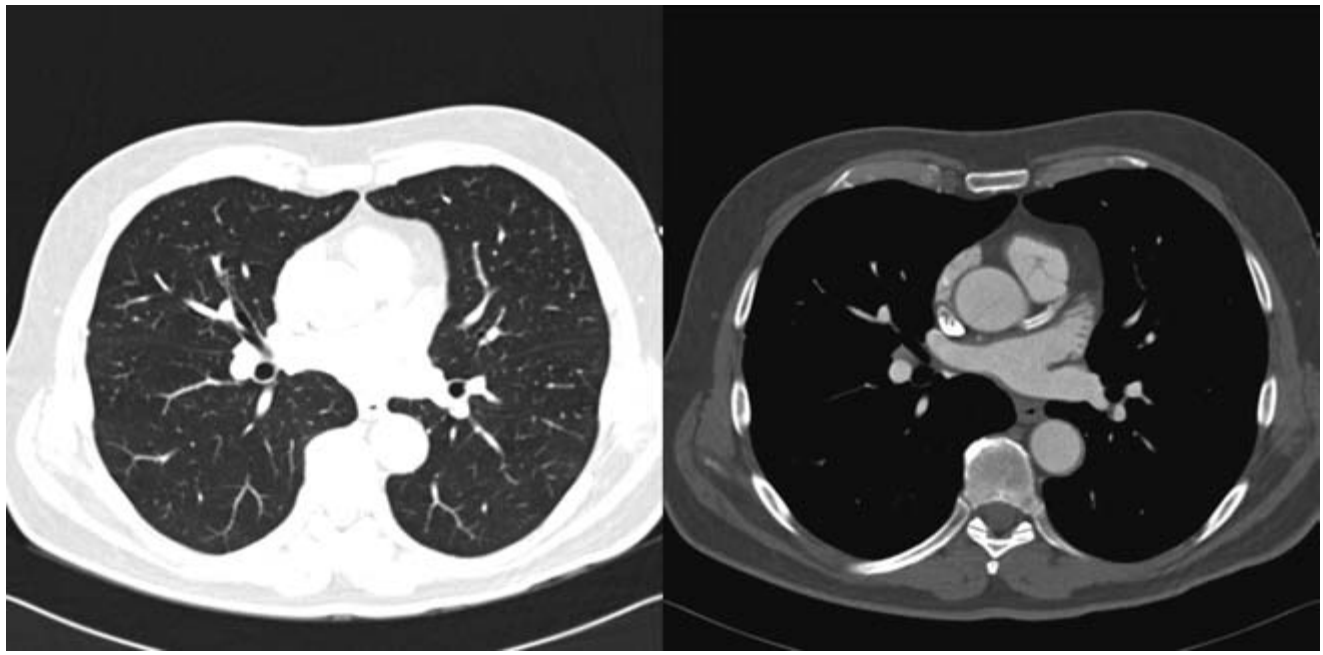

Figure 4.2 Axial CT image of the chest. Axial images of the thorax at the level of the origin of the left main coronary artery. The same image is displayed using (A) a 'lung' window (used for evaluation of lung parenchyma) and (B) a 'cardiac' window (used for evaluation of cardiac structures). The image is displayed as if looking from the patient's feet upwards.

with various shades of grey in between. The process of changing the CT imaging grey-scale is referred to as 'windowing'. Windowing is very useful because it is used to suit the needs of the observer reading the images. For instance, reading the heart and coronary arteries requires window settings in the CT range of soft tissue whereas reading pulmonary abnormalities or bone abnormalities would require window settings matched either to lung tissue or bone tissue (Fig. 4.2).

By convention, CT images are displayed as if looking upwards from the patient's feet.

Special considerations for computerized tomography imaging of the coronary arteries

Visualization of the coronary arteries and coronary stenoses, a major application of cardiac CT, is difficult because the coronary arteries are small, have low X-ray attenuation properties and are in constant, rapid motion during cardiac contraction and respiration. Thus, non-invasive CT coronary imaging requires high spatial and temporal resolution (i.e. time needed to acquire data for the reconstruction of one cross-section), superb low-contrast detectability and fast coverage of the entire heart within one breath-hold—which all have to be met at the same time.

Computerized tomography acquisition modes

Multidetector CT imaging is performed either in sequential mode or spiral mode. In the sequential mode ('slice by slice') the table, and thus the patient, is moved incrementally between successive rotations of the X-ray tube (Fig. 4.3). In the spiral mode, the patient is moved continuously during continuous rotation of the X-ray tube (Fig. 4.4). Because heart motion artefacts can be minimized by using image reconstruction data from the relatively motion-free diastolic phase of the heart cycle, the simultaneously recorded electrocardiogram (ECG) signal is

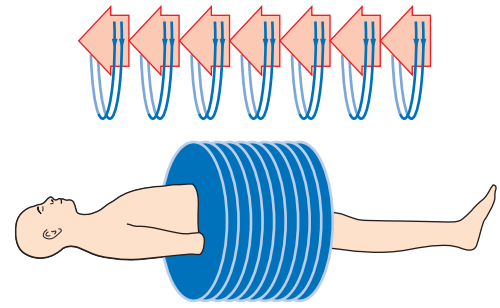

Figure 4.3 CT sequential acquisition mode. The table, and thus the patient, is moved incrementally between successive rotations of the X-ray tube.

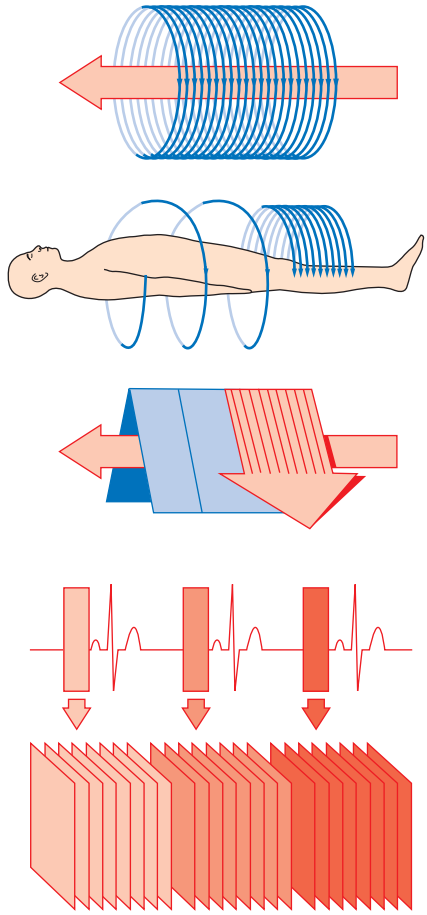

Figure 4.4 CT spiral acquisition mode. The X-ray tube and detectors in the spiral acquisition mode rotate constantly around the patient, while the table is advanced through the gantry. A collimated cone beam passes through the patient and data on X-ray attenuation are constantly collected by multiple rows of detectors. During table propagation, data are continuously acquired by 16–64 parallel detector rows, resulting in a spiral/helical data acquisition pattern from the patient's perspective. Overlapping sampling data, by applying a slow table feed per gantry rotation, are available during the entire cardiac cycle. Retrospectively, ECG-synchronized data from each cycle are extracted for reconstruction of the axial slices.

used to synchronize prospective data acquisition or retrospective data reconstruction in the diastolic phase.

Multidetector spiral computerized tomography

The geometry of the multidetector CT scanner is shown in Fig. 4.5. The most recent generations of multidetector spiral CT (MDCT) scanners are equipped with 16–64 detector rows and a rotation time between 330 ms and 500 ms, and allow high-resolution scanning of large sections in a short time.

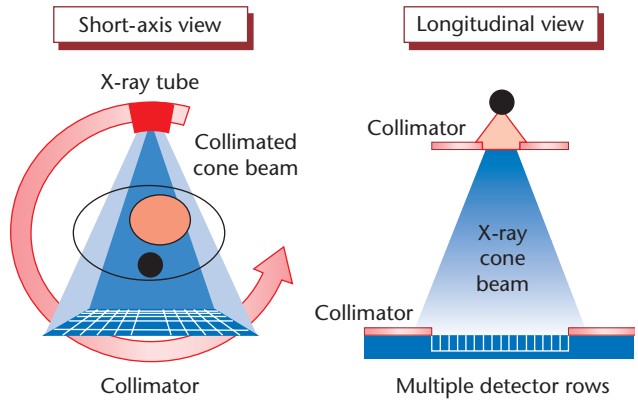

Figure 4.5 MDCT scanner geometry. The rotating X-ray tube produces a collimated cone beam which passes through the patient and the attenuated X-rays are collected on multiple detectors.

To acquire cardiac images during the same cardiac phase, images are reconstructed using retrospective ECG gating (Fig. 4.4). While X-ray data are acquired continuously throughout the cardiac cycle, the ECG is recorded simultaneously. Isophasic (raw) X-ray data are selected for image reconstruction based on the recorded ECG. Although images can be reconstructed at any cardiac time position within the R-to-R interval, reconstructions during the diastolic phase generally contain the fewest motion artefacts. To ensure availability of X-ray data from a sufficient number of projections at any cardiac phase, table feed is set to a speed low enough to assure that each plane position is sampled during an entire cardiac cycle (Fig. 4.6). The advantages of retrospective ECG-gating are the possibility to select the optimal (motion-sparse) reconstruction phase, the opportunity to deal with arrhythmias or faulty ECG signals after the scan, and the potential for functional studies. The disadvantage is the application of redundant radiation (X-ray data sampled during unsuitable cardiac phases and thus not actually used for image reconstruction) and therefore a considerable radiation dose.

Current CT scanners have X-ray tube rotation times of 330–500 ms. Because the first and second halves of the X-ray tube rotation provide comparable data, partial scan (180°) reconstruction algorithms are used that reduce the average temporal resolution down to 165–250 ms. Further improvement of the temporal resolution is possible by combining isophasic data from consecutive heart cycles (Fig. 4.7). If the same section is sampled during more than one cycle, data from several consecutive cardiac cycles can be combined to provide the necessary 180° of data. Thus, data acquisition windows of considerably less than one-half rotation can be used and the temporal resolution is improved. Despite the potential benefits, there are

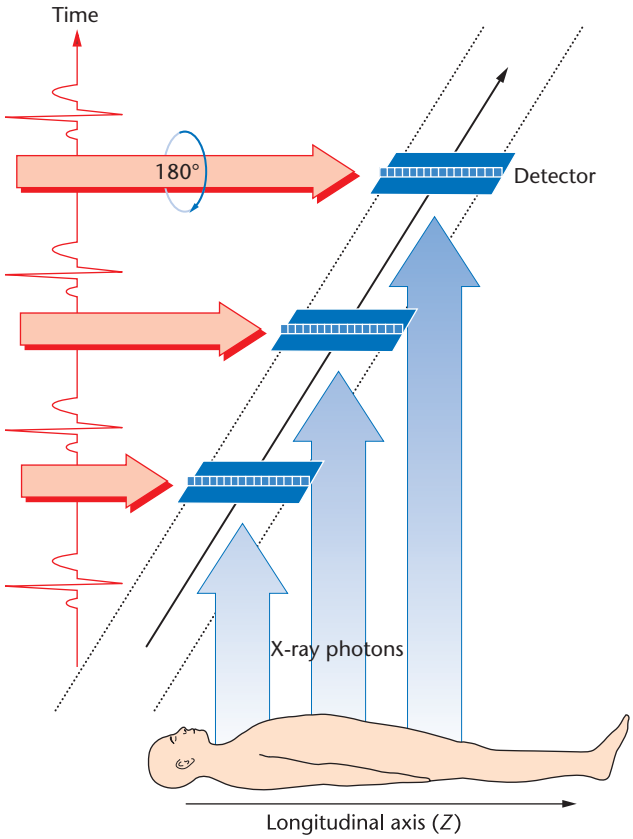

Figure 4.6 MDCT data acquisition. Graph depicting time (and ECG) on the vertical axis and the *Z*-position on the horizontal axis and detector position. Although data are acquired continuously, only data acquired during selectable intervals of approximately 200 ms (during which the gantry rotates 180°) are used for reconstruction. The *Z*-position of the detector rows during these instances needs to cover the entire heart to ensure gapless image reconstruction, which means that each plane position is sampled during at least one entire heart cycle by the consecutive detector rows. Because the position of each detector shifts in the *Z*-direction during these 200-ms periods, interpolation of the data is required to obtain a complete set of attenuation profiles at a given plane position.

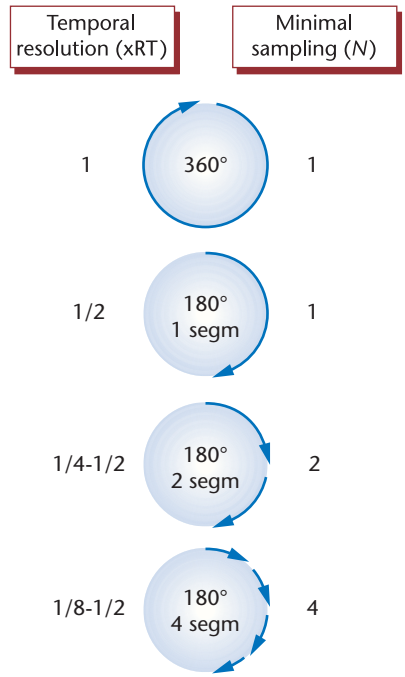

Figure 4.7 Temporal resolution and image reconstruction algorithms. Full scan (360°), monosegment (180°), bisegmental (180°) and quadrosegmental (180°) reconstruction algorithms and the temporal resolution for each as a ratio of the rotation time and required number of cycles during which the same position needs to be sampled.

disadvantages in terms of over-sampling and potentially excessive radiation, heart-rate-dependent effectiveness, and the fact that this approach assumes absolutely identical cardiac motion during each heart cycle.

The effective radiation dose of a four-slice MDCT is estimated to range from 1.0 to 4.1 mSv for calcium scanning and from 6.7 to 13.0 mSv for 'coronary angiography' [3,4], which is significantly higher than the dose of diagnostic coronary angiography reported to be between 2.1 and 5.6 mSv. The effective radiation doses of 16-slice or 64-slice CT scanners for coronary angiography are estimated to be between approximately 8 and 15 mSv. Reduction of radiation exposure can be achieved by using ECG-synchronized X-ray dose modulation which limits full tube current to a short time interval during diastole and reduced tube current during systole. This algorithm may reduce the total radiation dose by approximately 50% [5].

Image evaluation

The result of the reconstruction process is a large stack of overlapping slices, representing the contrast-enhanced heart and coronary arteries during a specific cardiac phase (Fig. 4.8). To optimize reconstructed images for visual analysis, 'windowing' is interactively performed by changing the grey-scale display of the CT values on the screen to improve delineation for the structures of interest.

Cross-sectional images in axial orientation are the source images and form the basis for all assessments. However, to facilitate analysis of the large number of cross-sectional images that is usually generated (200 or more), two-dimensional and three-dimensional image

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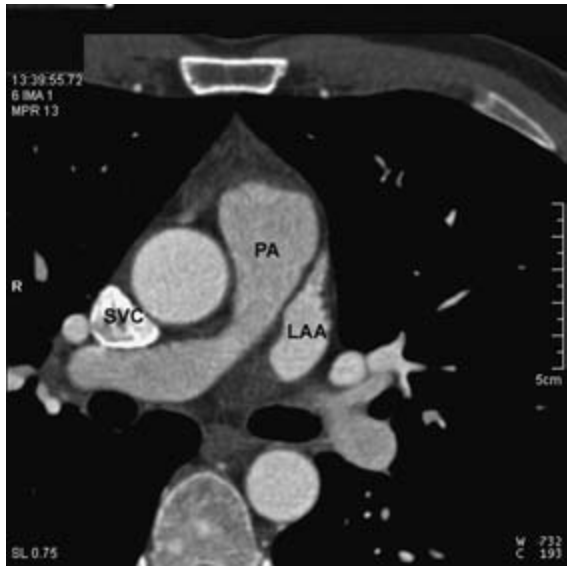

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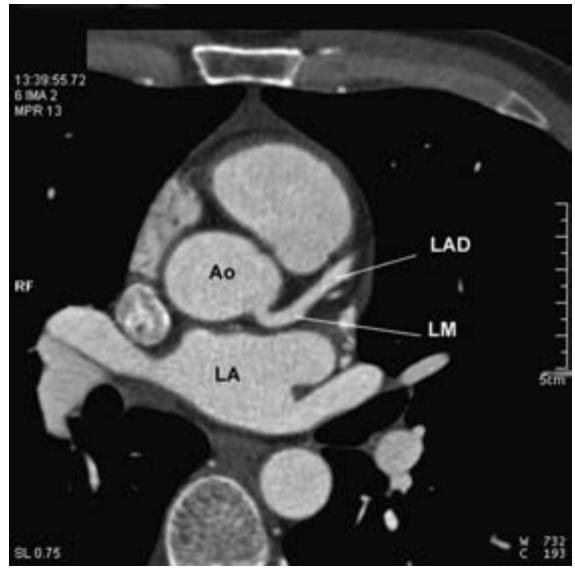

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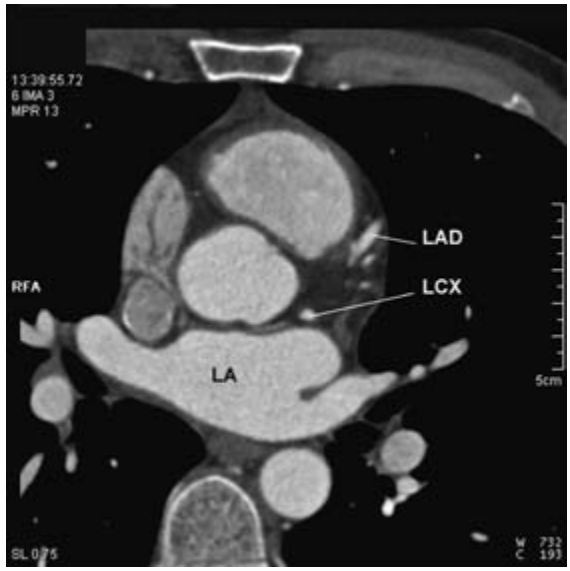

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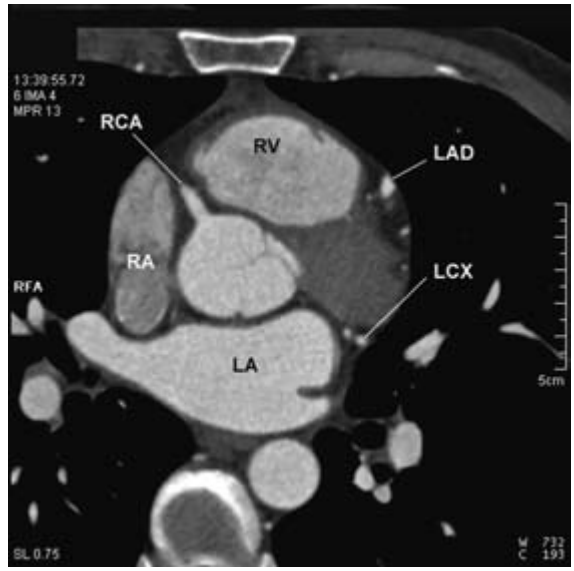

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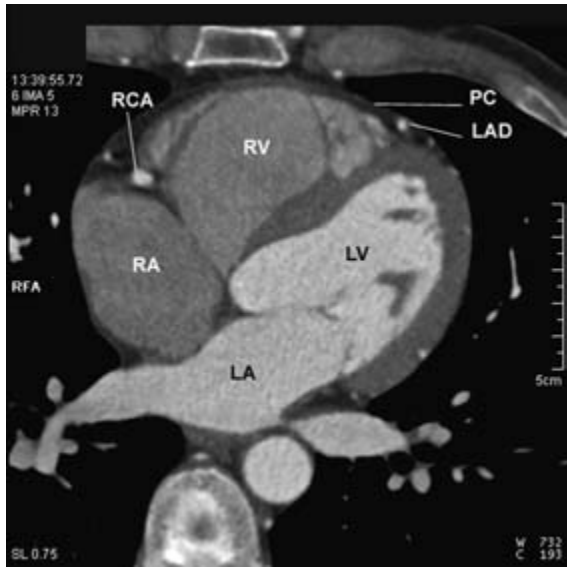

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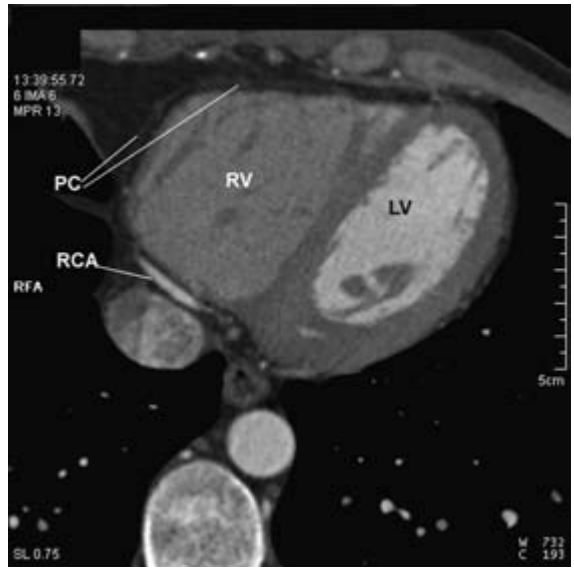

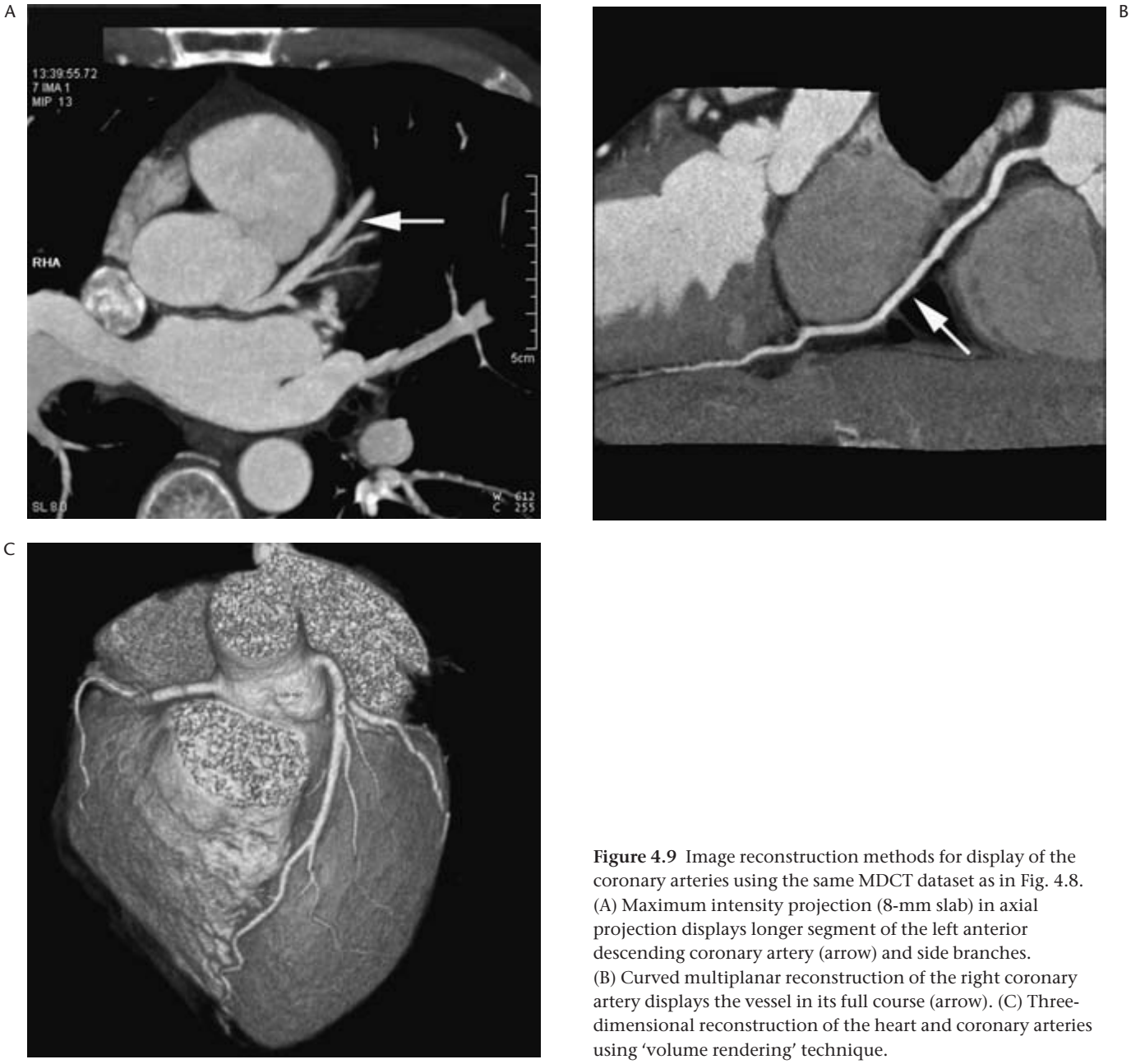

Figure 4.9 Image reconstruction methods for display of the coronary arteries using the same MDCT dataset as in Fig. 4.8. (A) Maximum intensity projection (8-mm slab) in axial projection displays longer segment of the left anterior descending coronary artery (arrow) and side branches. (B) Curved multiplanar reconstruction of the right coronary artery displays the vessel in its full course (arrow). (C) Three-dimensional reconstruction of the heart and coronary arteries using 'volume rendering' technique.

reconstruction methods, such as multiplanar reformation, (thin-slab) maximum intensity projection and volume rendering have been developed (Fig. 4.9). Thin-slab maximum intensity projections are selective two-dimensional displays of the highest densities (e.g. contrast medium, calcium or metal) within a given slab (typically with a thickness of 5–8 mm). In the analysis of 'CT coronary angiography' datasets, they allow for quick assessment

Figure 4.8 (*opposite*) Cross-sectional CT anatomy of the heart. Typical images of the heart acquired by 16-slice MDCT with 370-ms rotation time and retrospective ECG gating after intravenous injection of contrast agent. Reconstructed slice thickness 1.0 mm. Out of a dataset of approximately 250 axial images, six images at typical levels are selected to demonstrate typical cardiac anatomy in CT (A–F). Ao, ascending aorta; CS, coronary sinus; LA, left atrium; LAA, left atrial appendage; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LM, left main coronary artery; LV, left ventricle; PA, pulmonary artery; PC, pericardium; RA, right atrium; RCA, right coronary artery; RV, right ventricle; SVC, superior vena cava.

of luminal integrity, but are sensitive to overlap and less effective in the presence of severe coronary calcification or stents. In these situations, multiplanar reconstructions (two-dimensional cross-sections at freely selectable positions or angles) are more suitable. These cross-sections can be obtained in a two-dimensional plane, or curved along the course of a vessel of interest, to capture the vessel in a single image. Three-dimensional reconstruction of the coronary arteries allows an overview of coronary morphology and its relation to cardiac anatomy (Fig. 4.10). Three-dimensional volume rendering reconstructions are less suited for initial assessment of the coronary lumen, particularly in the presence of stents and calcified plaque tissue. However, a diagnostic advantage of these advanced image reconstruction techniques over evaluation of the axial source images has not been shown and, should a lesion be suspected based on two- or three-dimensional methods of image display, verification and confirmation on the original source images is always necessary.

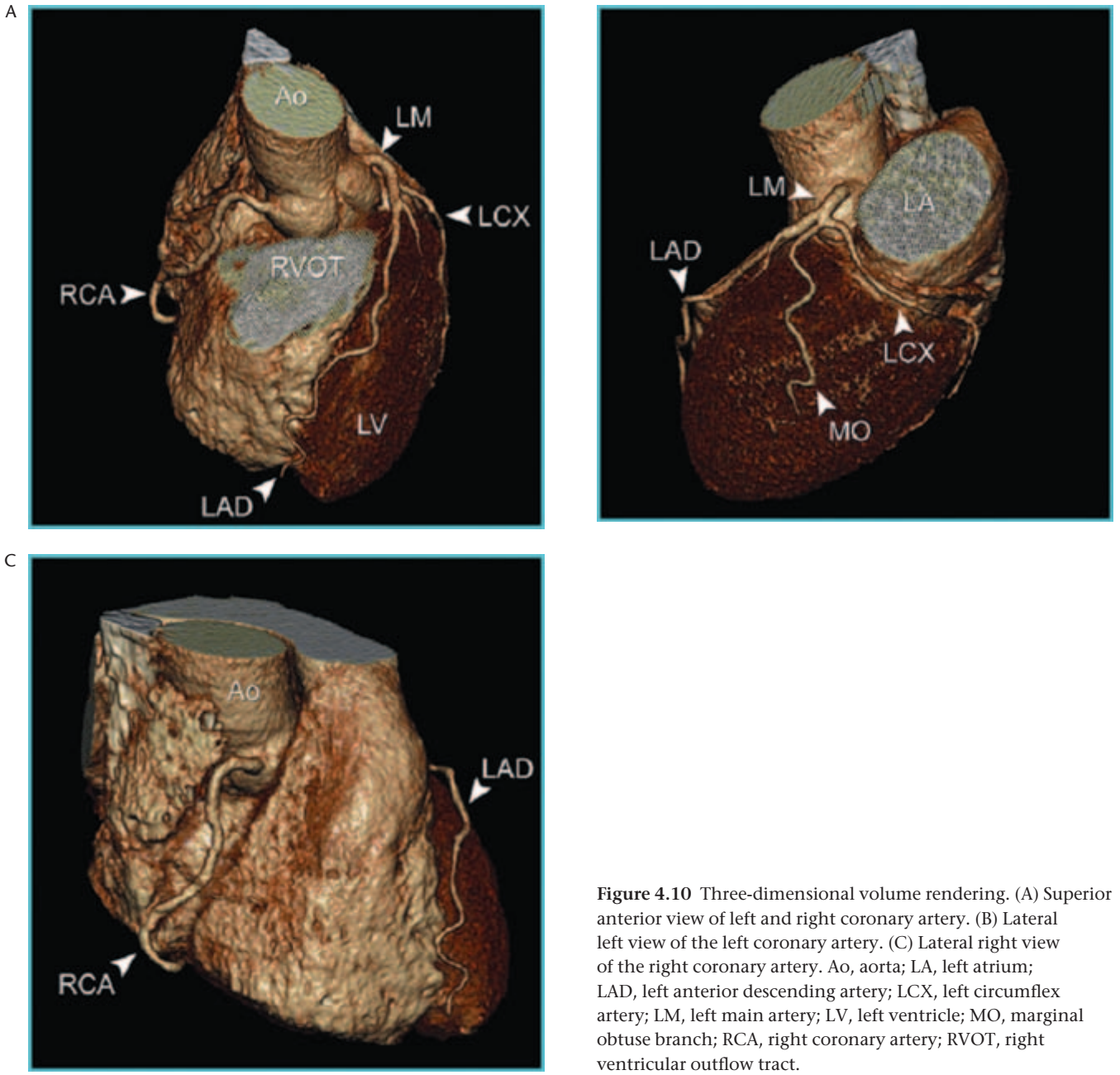

Figure 4.10 Three-dimensional volume rendering. (A) Superior anterior view of left and right coronary artery. (B) Lateral left view of the left coronary artery. (C) Lateral right view of the right coronary artery. Ao, aorta; LA, left atrium; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main artery; LV, left ventricle; MO, marginal obtuse branch; RCA, right coronary artery; RVOT, right ventricular outflow tract.

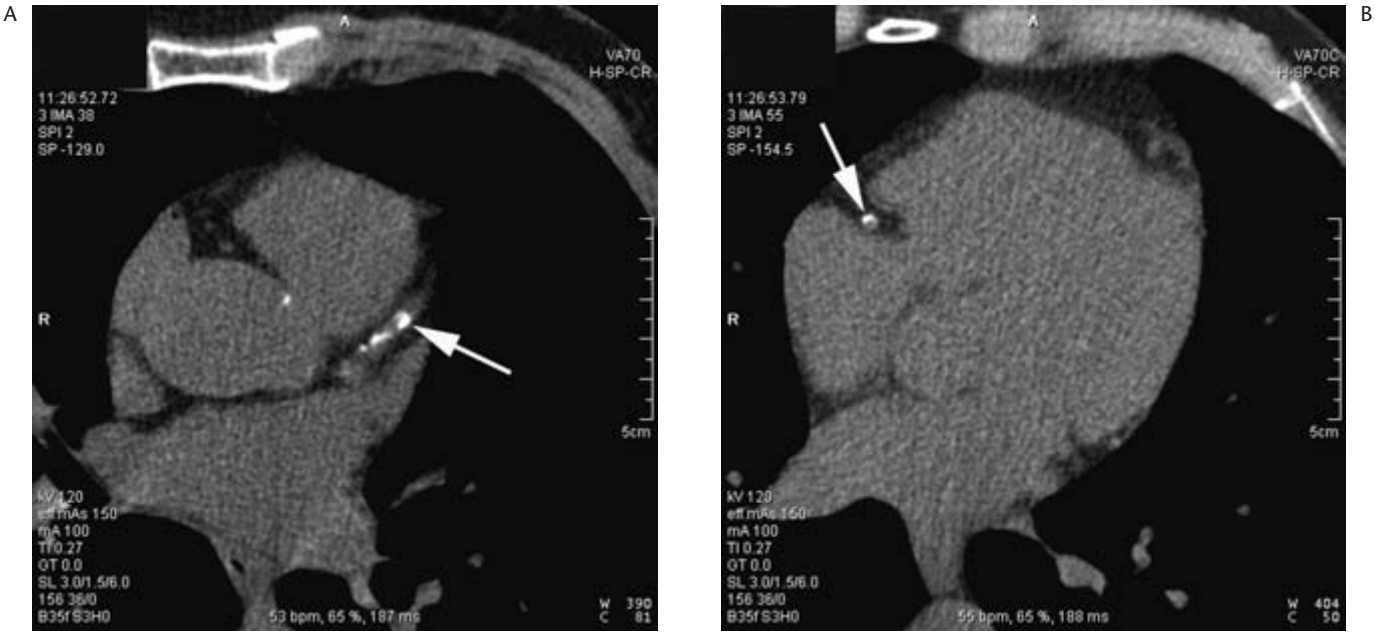

Figure 4.11 Visualization of coronary calcification by CT. Non-contrast enhanced MDCT scan (16 × 0.75 mm collimation, 370 ms rotation, retrospective ECG gating) to visualize coronary calcifications. (A) Calcification of the proximal left anterior descending artery (arrow). (B) Calcification of the mid right coronary artery (arrow).

Clinical applications of cardiac computerized tomography

Coronary artery calcification

CT provides a highly sensitive non-invasive diagnostic modality for the determination of the presence of coronary calcium because calcium has a high X-ray attenuation value (high CT number). Tissue within the vessel wall with a CT number of 130 HU or more is defined as calcified (Fig. 4.11).

Initially calcium detection has been performed with EBCT using a non-enhanced, ECG-triggered sequential CT technique [6]. Recently MDCT has emerged as an alternative modality by application of either the prospectively ECG-triggered sequential mode or the retrospectively ECG-gated spiral mode of the MDCT scanner.

The traditional method of quantifying coronary calcification is the 'Agatston score' [6]. This is derived from the area of a calcified lesion and the maximum CT attenuation within that lesion. Alternative quantification methods include assessment of the calcified volume (e.g. in mm^3) and of the mass of calcium (e.g. in mg) [7,8]. In spite of the potential advantages of these newer quantification methods, especially with regard to variability and independence from scanner type, no clinical studies of significant size have used these latter algorithms and all published studies demonstrating the predictive value of calcium are based on the 'Agatston score'.

With the possible exception of patients in chronic renal failure [9], the presence of coronary calcium is invariably associated with coronary atherosclerosis and the amount of coronary calcium correlates to the histological 'total coronary plaque burden' [10,11]. A high coronary calcium score, in particular when adjusted for age and gender, is predictive of coronary adverse events (Table 4.1) [12–18]. The absence of coronary calcium virtually rules out the presence of coronary atherosclerosis and is associated with a very low risk of adverse coronary events (Table 4.2).

The data on whether the predictive value of coronary calcium scoring is additional to the risk classification using traditional risk factors has been controversial [19] but several recent large studies have shown that coronary calcium quantification carries independent predictive value for adverse cardiac events and all-cause mortality [17,18,20]. This has resulted in the statements of the Third Joint Task Force of European and Other Societies on Cardiovascular Disease Protection in Clinical Practice that the 'calcium score is an important parameter to detect asymptomatic individuals at high risk for future

Table 4.1 Predictive value of electron-beam CT-determined coronary calcium score

Study	*n*	Mean age (years)	Gender (% male)	FUP	Events (death/MI)	Calcium score cut-off	Risk ratio
Wong *et al.* [12]	926	54	79	3.3	28	> 81–270	4.5*
Arad *et al.* [13]	1172	53	71	3.7	18	> 271	8.8*
Detrano *et al.* [14]	1196	66	89	3.4	44	> 44	2.3*
Raggi *et al.* [15]	676	52	51	2.7	30	> 100	> 4.1%†
Kondos *et al.* [16]	5635	51	74	3.1	222	≥ 0	Men 10.5 Women 2.6
Shaw *et al.* [17]	10 377	53	60	5.0	249 (death)	> 400–1000 > 1000	6.15* 12.3*
Greenland *et al.* [18]	1029	65.7	90	7.0	84 (death,MI)	> 300	3.9

*Risk ratio compared with patients with 0 score; †annualized event rate.
FUP, years of follow-up; MI, myocardial infarction.

Table 4.2 Significance of coronary calcium

Absent	Present
Presence of atherosclerosis unlikely	Presence of atherosclerosis
Low likelihood of severe luminal narrowing	Higher amount of calcium increases the likelihood of obstructions; however, this is not site-specific
Nearly always normal coronary angiogram	Total amount of calcium correlates with total plaque burden but still severely underestimates the amount of histological plaque burden
Low risk of cardiovascular event (2–5 years)	High calcium adjusted for age and gender is associated with higher likelihood of cardiac adverse event (in the next 2–5 years)

cardiac events, independent of the traditional risk factors' [21,22]. However, coronary calcium scanning cannot be recommended as a screening method for the unselected general population although it may play a role in selected individuals at intermediate risk of coronary events [18]. Absence or a low calcium score in these individuals may downgrade them to a low-risk group without an urgent need for preventive measures while a high calcium score may promote these individuals to a high-risk group in need of a more aggressive risk-factor modification [18].

Assessment of coronary stenoses

To visualize the coronary lumen and detect coronary stenoses by MDCT, data are acquired in spiral mode and retrospectively ECG-gated image reconstruction is applied to maximize temporal and spatial resolution. A large number of studies comparing 12-slice and 16-slice MDCT with conventional coronary angiography have been published [23–30]. It has been shown that in patients with a high heart rate, the occurrence of motion artefacts is frequent and the diagnostic performance of MDCT deteriorates [23]. Most recent studies performed with 12-slice and 16-slice systems incorporated the use of oral or intravenous beta-blockers prior to the scan to reduce heart rate and avoid motion artefacts. The detector collimation of 16-slice scanners varies between 16 × 0.75 mm, and 16 × 0.625 mm, the rotation time varies between 370 ms and 500 ms, and the total scan time is generally 20 s or less.

Contrast enhancement is achieved by intravenous injection of an iodine-containing contrast medium, preferably followed by a saline bolus ('bolus chaser') (Fig. 4.12). To synchronize data acquisition and the contrast enhancement, either a 'test bolus' can be injected to determine the contrast-transit time, or the entire bolus can be injected at once and then data acquisition is automatically initiated when the arrival of contrast medium is detected (by repeated acquisition of slices at the level of the aortic root). The radiation output, in terms of tube voltage (kV) and current (mA), can be adjusted according to the patient's weight to improve image quality.

The reported diagnostic accuracy of a 12-slice to 16-slice CT scanner to detect significant coronary stenoses (> 50% luminal diameter stenosis) has been found to be high (Figs 4.13, 4.14 and 4.15). Sensitivities between 63 and 95% and specificities between 86 and 98% have been reported, and, as compared to earlier scanner generations,

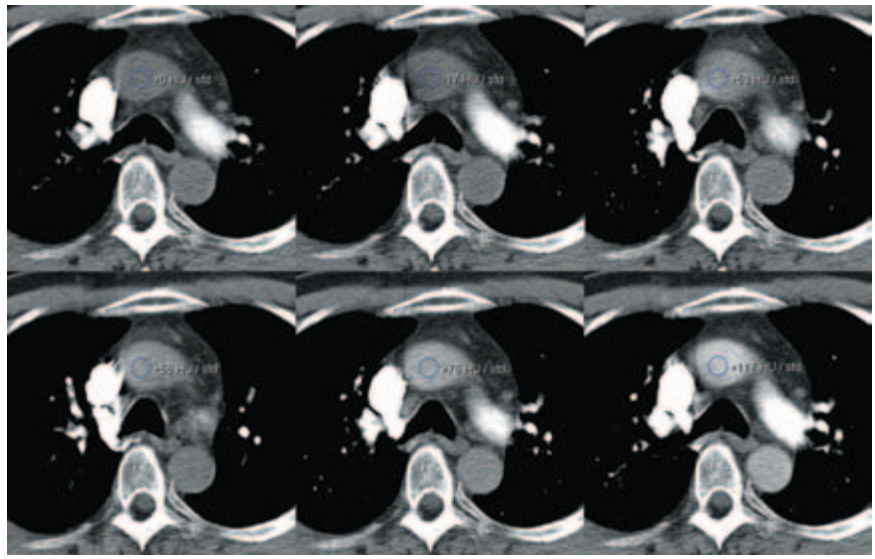

Figure 4.12 CT data acquisition technique. (A) Monitoring of the arrival of the contrast bolus in the aorta can be achieved after positioning a region of interest at the level of the ascending aorta and scanning the axial images at different time intervals (e.g. every second). (B) Hounsfield units within the region of interest are measured and the CT scan is automatically started when a predefined threshold has been reached (e.g. +100 HU).

fewer segments and vessels were excluded based on impaired image quality (Table 4.3) [23–30]. In a few studies, the average heart rate could be reduced to less than 60 beats per minute, and by limiting the evaluation to larger coronary vessels (≥ 2.0 mm diameter), a high sensitivity and specificity could be achieved without exclusion of any coronary segments because of impaired image quality (Table 4.3) [23,25,29]. Overestimation of stenosis severity, particularly in calcified vessels, resulted in a substantial number of false-positive diagnoses and a modest positive predictive value. Evaluation of smaller coronary segments and the presence of severe calcifications reduced the diagnostic accuracy of contrast-enhanced MDCT for detection of stenoses.

In particular, the high negative predictive value (97–98% in nearly all published studies) suggests that the

Table 4.3 Diagnostic performance of 16-slice multidetector CT to detect significant coronary artery stenosis, using conventional angiography as the standard of reference

Study	Collimation	Analysable segment %	NP	Sens. %	Spec. %	PPV %	NPV %
Nieman [23]	12 × 0.75	100	58	95	86	80	97
Ropers [24]	12 × 0.75	88	77	92	93	79	97
Kuettner [27]	16 × 0.75	—	60	72	97	72	97
Mollet [25]	16 × 0.75	100	128	92	95	79	98
Martuscelli [26]	16 × 0.625	84	64	89	98	90	98
Kuettner [28]	16 × 0.75	93.4	72	82	98	87	97
Mollet [29]	16 × 0.75	100	51	95	98	87	99
Hoffmann [30]	16 × 0.75	83	33	63	96	64	96

NP, study population size; sens., sensitivity; spec., specificity; PPV, positive predictive value; NPV, negative predictive value.

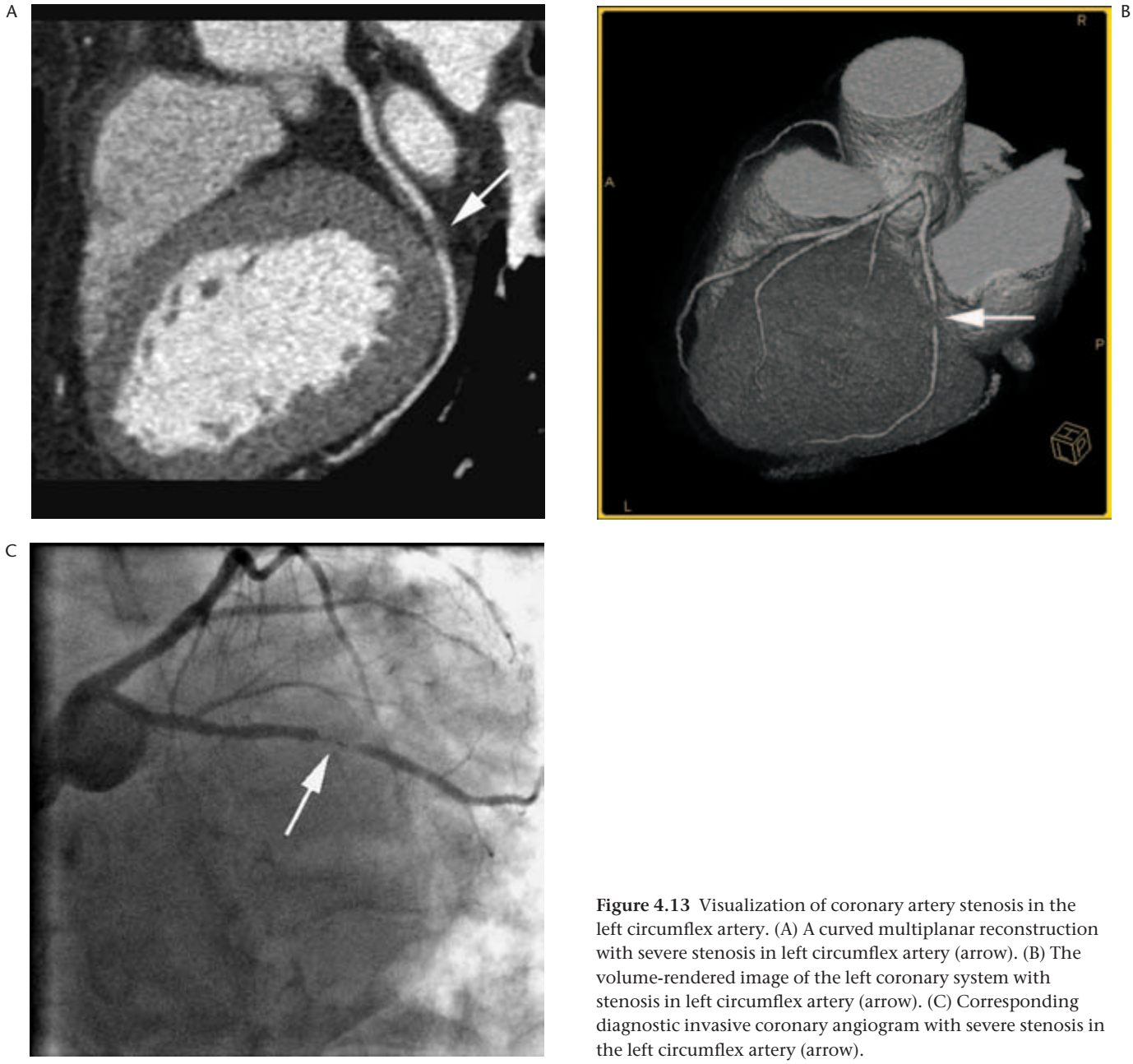

Figure 4.13 Visualization of coronary artery stenosis in the left circumflex artery. (A) A curved multiplanar reconstruction with severe stenosis in left circumflex artery (arrow). (B) The volume-rendered image of the left coronary system with stenosis in left circumflex artery (arrow). (C) Corresponding diagnostic invasive coronary angiogram with severe stenosis in the left circumflex artery (arrow).

current technique may be clinically useful to rule out significant coronary artery stenoses.

A severe limitation for CT coronary imaging is an irregular heart rhythm (for instance atrial fibrillation), which does not permit reliable visualization of the coronary arteries. Severe coronary calcification causes artefacts as a result of partial volume effects and beam hardening, which may lead to overestimation of plaque size and lumen narrowing while the high density of calcium obscures the underlying lumen which may prohibit reliable assessment of the integrity of the coronary lumen. The effects of coronary calcium are reduced by using thin-slice collimation, and are aggravated if motion artefact is additionally present. Of great concern is the rather high radiation exposure associated with MDCT imaging of the coronary arteries.

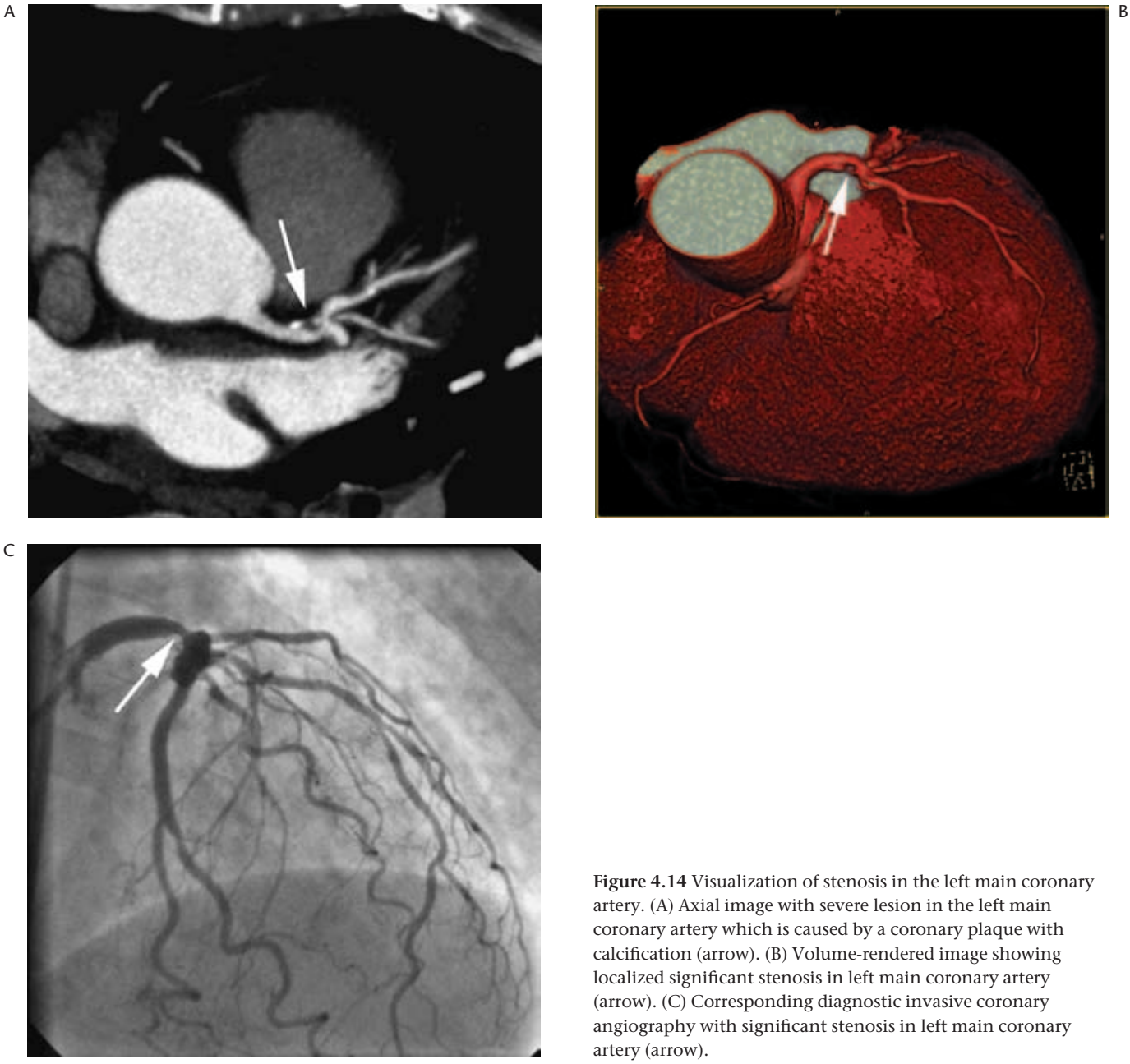

Figure 4.14 Visualization of stenosis in the left main coronary artery. (A) Axial image with severe lesion in the left main coronary artery which is caused by a coronary plaque with calcification (arrow). (B) Volume-rendered image showing localized significant stenosis in left main coronary artery (arrow). (C) Corresponding diagnostic invasive coronary angiography with significant stenosis in left main coronary artery (arrow).

Coronary anomalies

Cross-sectional MDCT imaging, especially in combination with two- and three-dimensional image reconstruction techniques, permits the accurate assessment of the aberrant origin and course of anomalous coronary arteries [31,32]. Because the origin and course of coronary anomalies can sometimes be difficult to assess with conventional coronary angiography, CT may be considered a first-choice diagnostic modality (Fig. 4.16). The course of an anomalous coronary artery running between the pulmonary outflow tract and aorta which may be the cause of sudden death can be readily assessed (Fig. 4.17).

Bypass grafts

Patency versus occlusion of venous and arterial coronary artery bypass grafts can accurately be assessed by CT [33].

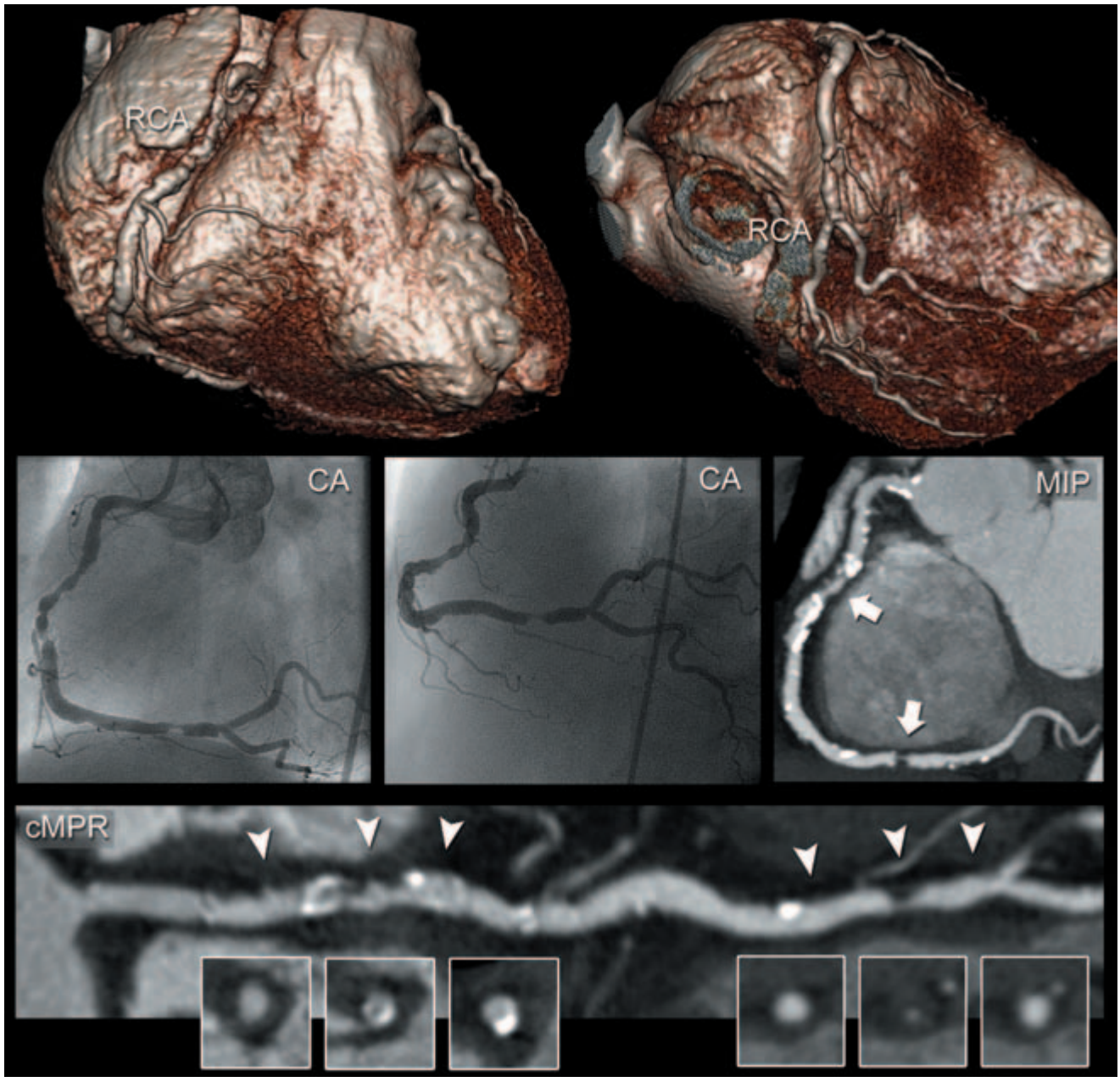

Figure 4.15 Visualization of stenoses in the right coronary artery. CT coronary angiogram and corresponding conventional angiogram (CA) of a right coronary artery (RCA). Volume-rendered CT images (coloured images) show the presence of a large, dominant RCA. Detailed maximum intensity projected and curved multiplanar reconstructed CT images reveal the presence of two significant lesions—one long significant lesion located at the mid RCA, another short significant lesion located at the distal RCA. Cross-sectional CT images (inlays) show the presence of both non-calcified and calcified plaque tissue within the proximal stenosis, whereas exclusively non-calcified plaque tissue is visualized within the more distal stenosis. The presence of two significant lesions was confirmed on the diagnostic conventional angiogram. CA, conventional angiogram; cMPR, curved multiplanar reconstructed image; MIP, maximum intensity projection; RCA, right coronary artery.

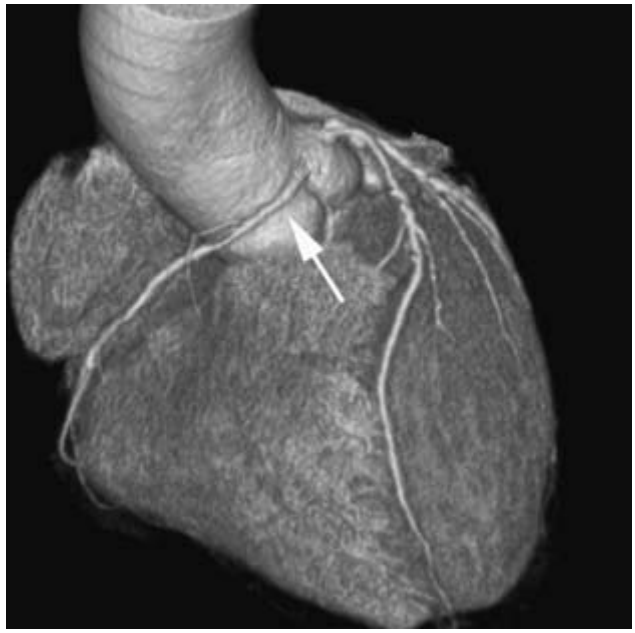

Figure 4.16 Visualization of anomalous coronary artery. The right coronary artery originates from the left coronary cusp (arrow).

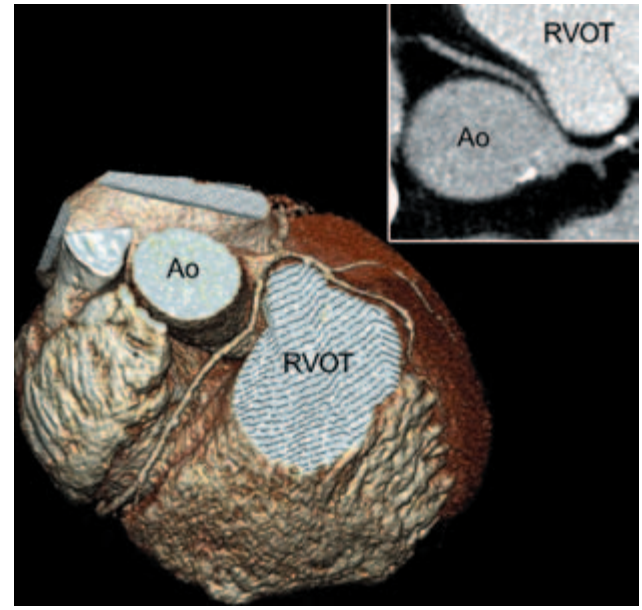

Figure 4.17 Visualization of anomalous coronary artery. Anomalous origin of the right coronary artery, which arises from the left main coronary artery. The proximal part of the right coronary artery runs between the aorta and the right ventricular outflow tract. Ao, aorta; RVOT, right ventricular outflow tract.

However, the accuracy for detection of graft stenosis, in particular at the distal anastomotic site, has so far been limited [26,34] (Fig. 4.18). Furthermore, clinical evaluation of patients after bypass surgery usually requires not only information about the status of the bypass grafts, but also about the native coronary arteries (and collaterals). As a result of both the severity and extent of disease and the usually severe calcification of native arteries in patients with bypass grafts, assessment of stenoses in the native coronary arteries in these patients is often difficult and the clinical role of comprehensive post-bypass evaluation using CT imaging in these patients is therefore limited.

Coronary stents

The occlusion or patency of a stent can be assessed by MDCT based on the presence of contrast-opacification within and distally from the stent. However, because of the significant artefacts caused by the dense stent material, accurate detection of obstructive lesions within the boundaries of small coronary stents is not reliable [35,36]. Current scanner generations permit, apart from patency assessment, also the detection of non-occlusive neo-intimal hyperplasia and in-stent restenosis (Fig. 4.19) in larger coronary stents (e.g. those > 4 mm in diameter) [37]. Clinical application of MDCT for the follow-up of patients after stent implantation cannot be recommended.

Coronary plaque imaging

MDCT delineates both extraluminal and intraluminal coronary atherosclerosis, and may thus provide information about the severity, extent and distribution of coronary disease, of plaque tissue composition and of vessel wall remodelling [38–40] (Fig. 4.20). Compared to intracoronary ultrasound as the standard of reference, the sensitivity of MDCT to detect the presence of non-stenotic coronary plaque was found to range between approximately 50–80% for non-calcified plaques and 95% for calcific plaques, with a specificity of approximately 90% [38,39]. However, MDCT significantly underestimated the plaque volume per coronary segment when compared with intracoronary ultrasound volume measurements [38].

Contrast-enhanced MDCT imaging has furthermore been shown to have the potential to differentiate calcified and non-calcified plaques in the coronary artery wall. Calcified plaques have a high tissue density and appear brighter than the contrast-enhanced coronary lumen on the CT images. Non-calcified plaques have a tissue density which is higher than the surrounding perivascular fat but lower than the contrast-enhanced lumen. Based on initial studies comparing MDCT with histology and intravascular ultrasound, it appeared that fibrous plaques

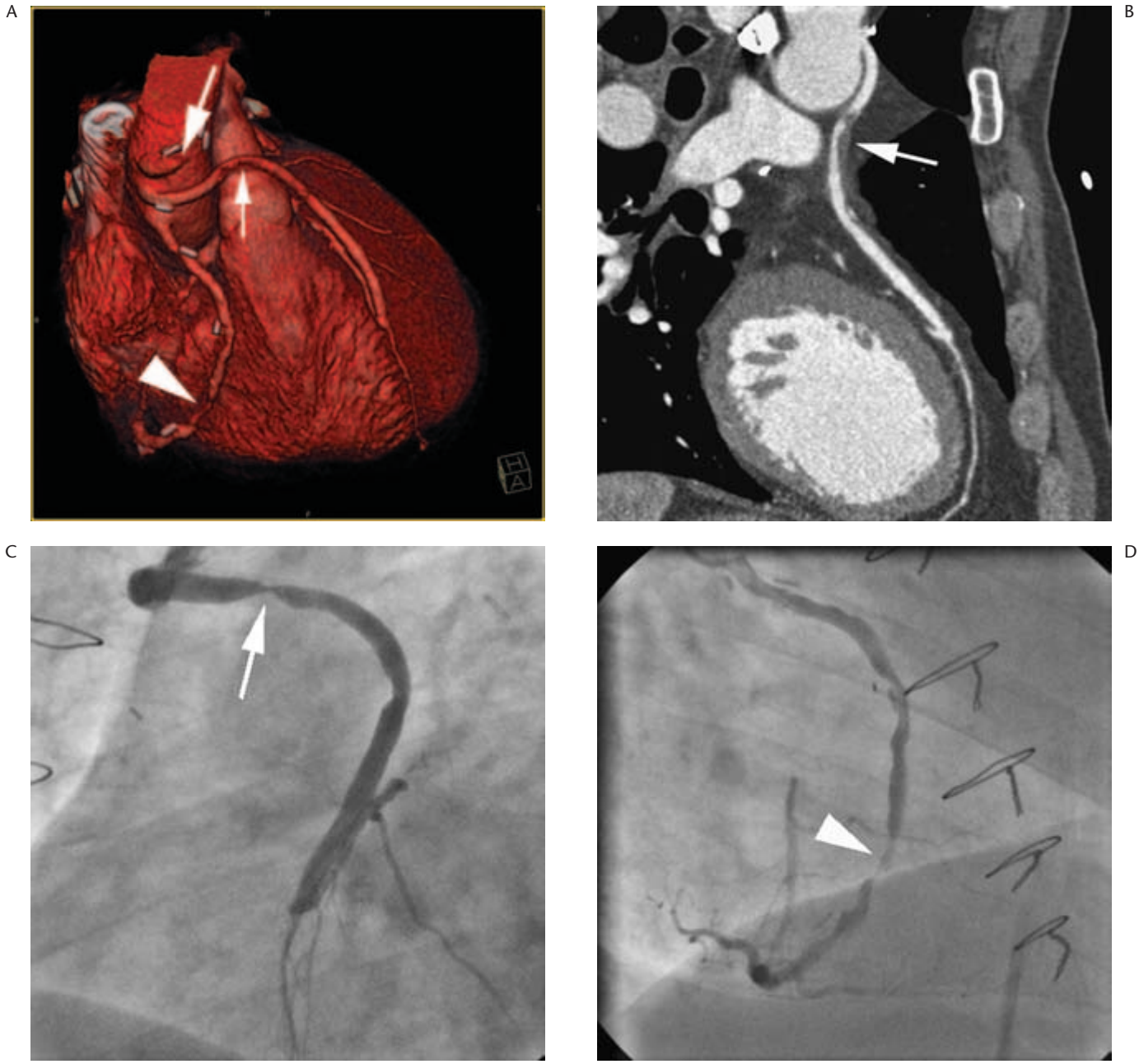

Figure 4.18 Visualization of coronary artery bypass grafts. Patient with three venous coronary bypass grafts. MDCT (16 × 0.75 mm collimation, 370 ms rotation time). (A) Three-dimensional reconstruction obtained by MDCT which shows occlusion of the graft to the left circumflex coronary artery (large arrow), stenosis of the graft to the left anterior descending coronary artery (small arrow), and stenosis of the graft to the right coronary artery (arrowhead). (B) Multiplanar reconstruction of the graft to the left anterior descending coronary artery showing the lumen reduction and the plaque material that causes the stenosis (arrow). (C) Invasive coronary angiogram of the graft to the left anterior descending coronary artery showing the stenosis (arrow). (D) Invasive coronary angiogram of the graft to the right coronary artery showing the stenosis (arrowhead).

and lipid-rich plaques may be differentiated based on their CT attenuation values. However, in clinical practice it was shown that the average density measured within lipid-rich plaques was lower than in fibrous plaques, but there was a considerable overlap in density values, making the assessment of plaque characteristics in a given lesion less reliable [39]. MDCT can also identify coronary plaques with positive (expansive) vessel wall remodelling

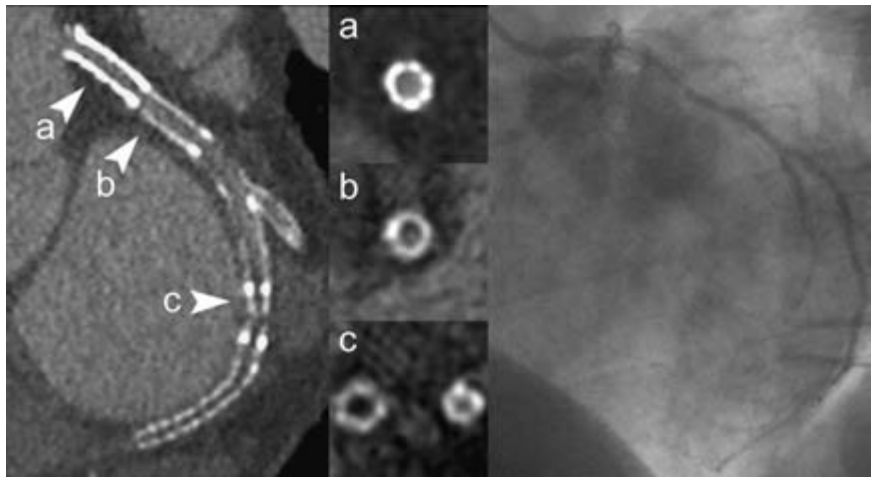

Figure 4.19 Visualization of coronary stent. Curved multiplanar reconstruction of the circumflex coronary artery (left). Cross-sectional images obtained at different levels reveal a patent left main stent (a), in-stent restenosis at the mid part of the circumflex (b), and an occluded stent more distal (c). These findings were confirmed on the conventional angiogram (right). A patent stent in a marginal branch is also displayed (c).

and negative (shrinkage) vessel wall remodelling [40]. MDCT allows the assessment of the total atherosclerotic plaque burden of the coronary tree [41].

The potential of MDCT for plaque detection and characterization, vessel remodelling and assessment of total CT plaque burden is promising but higher resolution imaging is needed before it can be embraced as a reliable diagnostic tool.

Cardiac and pericardial abnormalities

Cardiac CT, as a result of its capability for high-resolution imaging of the entire heart and high contrast between the contrast-enhanced blood pool and surrounding tissues, permits the assessment of cardiac morphology with high image quality. It can thus theoretically be applied in numerous clinical situations calling for accurate visualization of cardiac morphology. However, CT imaging is associated with radiation exposure and in most cases requires iodinated contrast agent. Therefore, the morphology of the heart and pericardium is usually assessed by echocardiography or magnetic resonance imaging. All the same, CT can serve as a second-choice technique and provide accurate information on cardiac morphology and pathology if echocardiography and magnetic resonance cannot be performed with satisfactory image quality.

Cardiac masses and thrombi

Cardiac tumours appear on CT as contrast-filling defects or deformities of the contrast-filled cardiac cavities or as thickening, often inhomogeneous, of the soft cardiac tissue (e.g. myocardium or pericardium). CT has limited capabilities for soft-tissue characterization and for exact delineation of tumours that infiltrate or are immediately adjacent to the myocardium can therefore be difficult [42]. However, the presence of calcium (e.g. in myxomas), can sometimes be diagnostically helpful and can easily be established or ruled out by CT.

Similar to tumours, intracardiac thrombi are depicted as contrast-filling defects within the opacified cardiac chambers. Thrombi may be solitary or multiple and may be sessile, pedunculated or laminar in shape. Atrial thrombi, mostly located within the left atrial appendage, are the most frequently occurring cardiac thrombi and will appear as a filling defect (Fig. 4.21). However, it has to be considered that poor atrial function, as in atrial fibrillation, may result in poor opacification of the atrial appendage after injection of contrast, even in the absence of thrombus.

Thrombi within the left ventricle are usually located adjacent to infarcted myocardium with associated wall motion abnormalities and are often seen after anterior wall myocardial infarction (Fig. 4.22). The differentiation of thrombus from myocardium and papillary muscle may be difficult. Older thrombi can be calcified.

Pericardial abnormalities

In CT images, the pericardium can usually be appreciated on the anterior face of the heart. It is delineated as a thin structure of soft-tissue density, adjacent to mediastinal fat ventrally and epicardial fat dorsally. The thickness of normal pericardium is 1–2 mm, but inferiorly, at the insertion of the pericardium to the diaphragm, it thickens to 3–4 mm [43].

Pericardial abnormalities include thickening and calcification of the pericardium, pericardial effusion and localized pericardial masses or intrapericardial tumours. Pericardial thickening may be localized or general. It may involve both parietal and visceral pericardium and

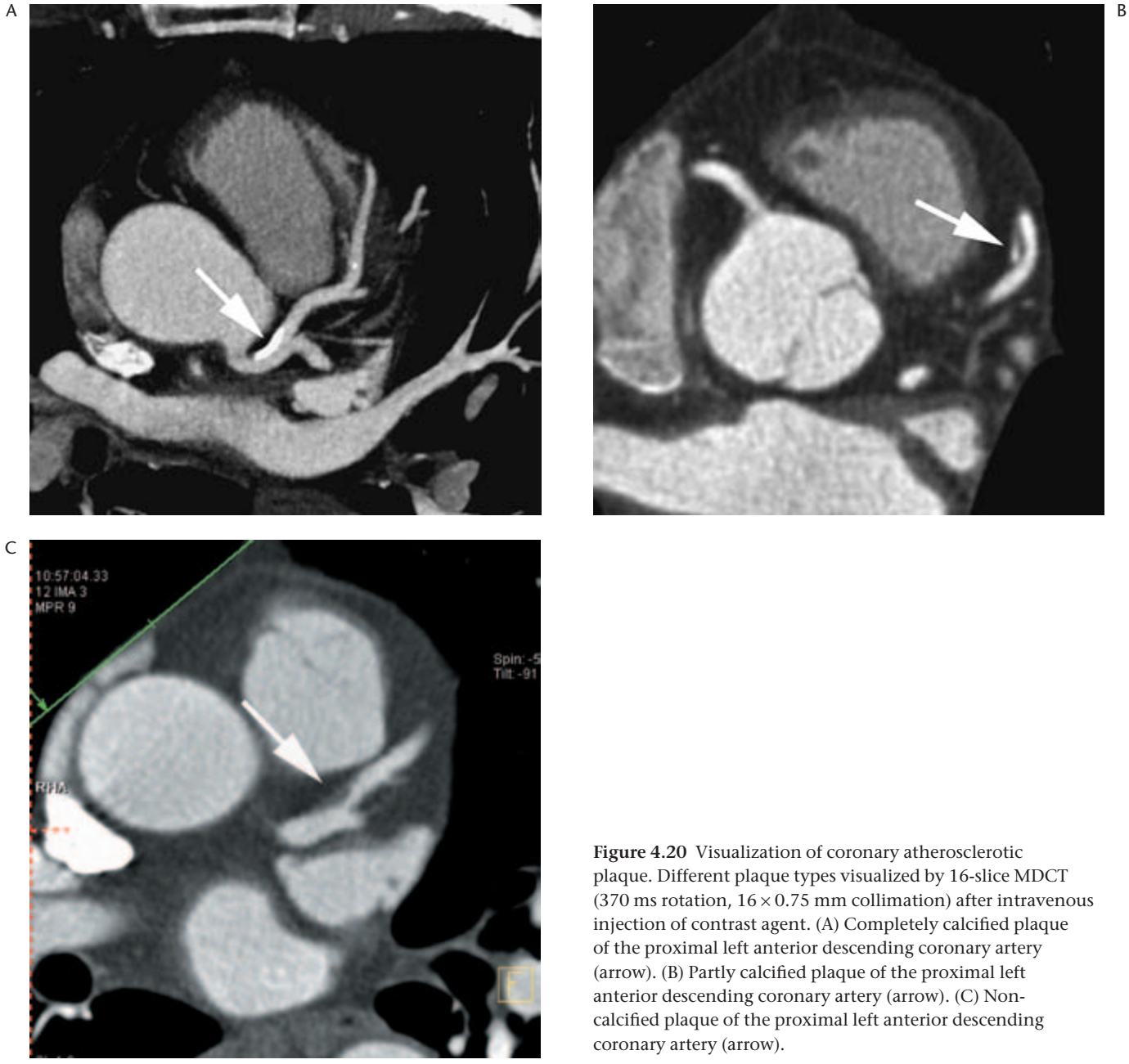

Figure 4.20 Visualization of coronary atherosclerotic plaque. Different plaque types visualized by 16-slice MDCT (370 ms rotation, 16 × 0.75 mm collimation) after intravenous injection of contrast agent. (A) Completely calcified plaque of the proximal left anterior descending coronary artery (arrow). (B) Partly calcified plaque of the proximal left anterior descending coronary artery (arrow). (C) Non-calcified plaque of the proximal left anterior descending coronary artery (arrow).

sometimes the myocardium. However, the presence of pericardial thickening by itself is no proof of haemodynamically relevant pericardial constriction. The detection of pericardial calcification can be helpful in this context (Fig. 4.23). Pericardial effusion usually accumulates in the caudal portion of the pericardium and appears as increased density dorsal to the left ventricular myocardium. As the effusion increases it will extend to the ventral surface of the right atrium and ventricle. Postoperative pericardial effusions can be localized, e.g. adjacent to the right atrium. Pericardial cysts appear as a round or oval mass usually in the right pericardiophrenic angle (Fig. 4.24). The cysts are filled with fluid that has a CT density similar to water. Breast and lung carcinoma can metastasize to the pericardium.

Great vessels

Since the great vessels are subjected to motion caused by cardiac contraction, the high imaging speed of the modern CT scanner, its high spatial resolution and high contrast between vessel lumen and surrounding tissue

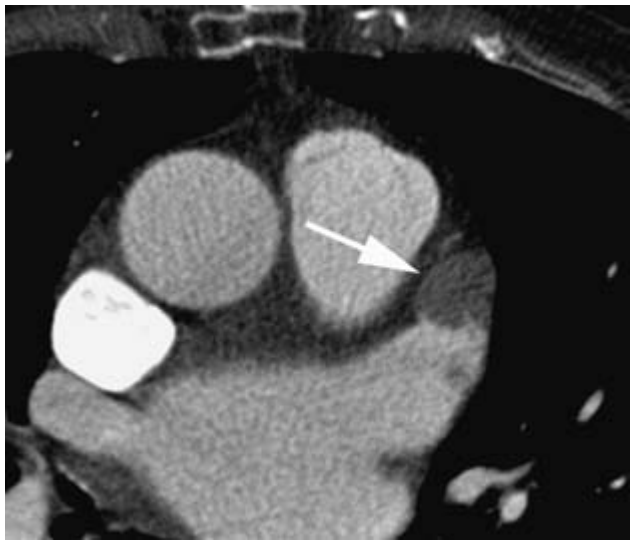

Figure 4.21 Visualization of atrial thrombus. A filling defect is shown in the left atrial appendage (arrow).

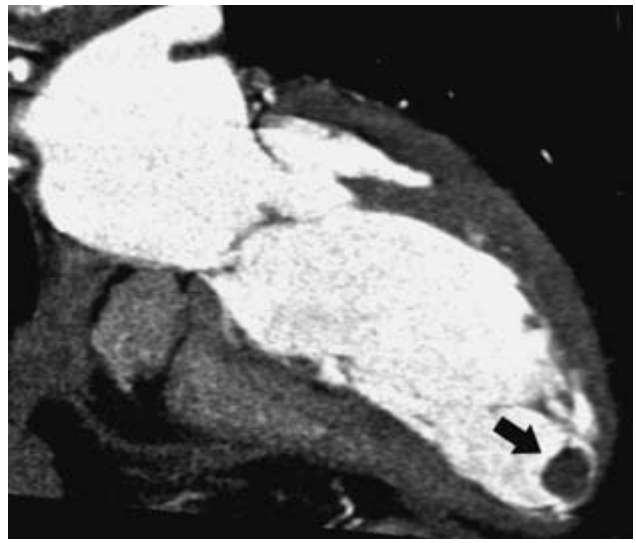

Figure 4.22 Visualization of a ventricular thrombus. The thrombus is at the apex of the left ventricle (arrow).

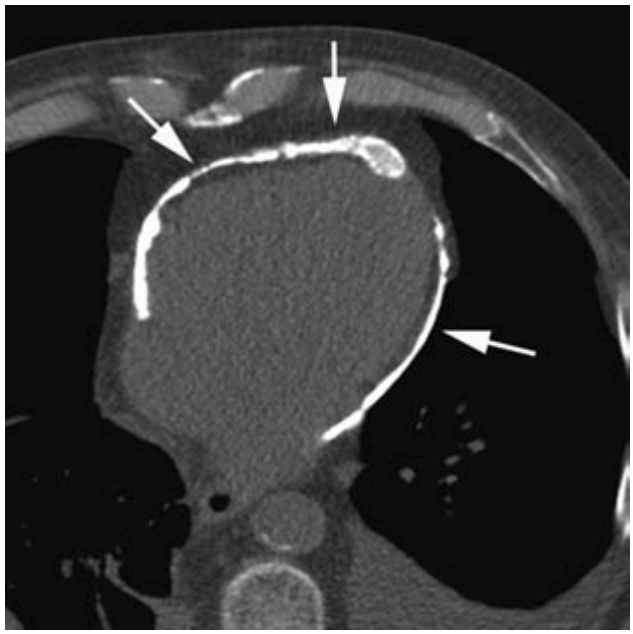

Figure 4.23 Visualization of pericardial calcification. Thickened pericardium with severe calcifications (arrows).

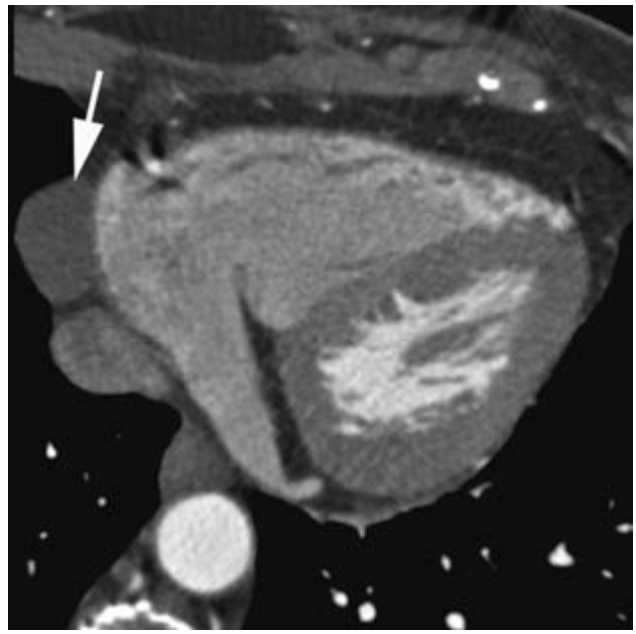

Figure 4.24 Visualization of pericardial cyst. Pericardial cyst in the right costophrenic angle (arrow).

have made MDCT scanning an important, reliable clinical diagnostic modality in evaluating the great vessels of the thorax. To visualize the great vessels by CT, the blood pool has to be enhanced by intravenous contrast agent and data acquisition has to be timed correctly to ensure peak enhancement of the vessel lumen during image acquisition. ECG-gated image acquisition is not necessary in all cases and untriggered data acquisition may lead to significant reduction in radiation dose.

Thoracic aortic aneurysm

Aneurysms of the aorta are caused by degeneration of the media. This is most frequently seen in atherosclerotic disease but is also seen as a consequence of Marfan syndrome, cystic medial necrosis, trauma, post-stenotic dilatation or infectious mycotic diseases.

Aneurysms can be divided into true aneurysms and false aneurysms. A true aneurysm involves all wall layers,

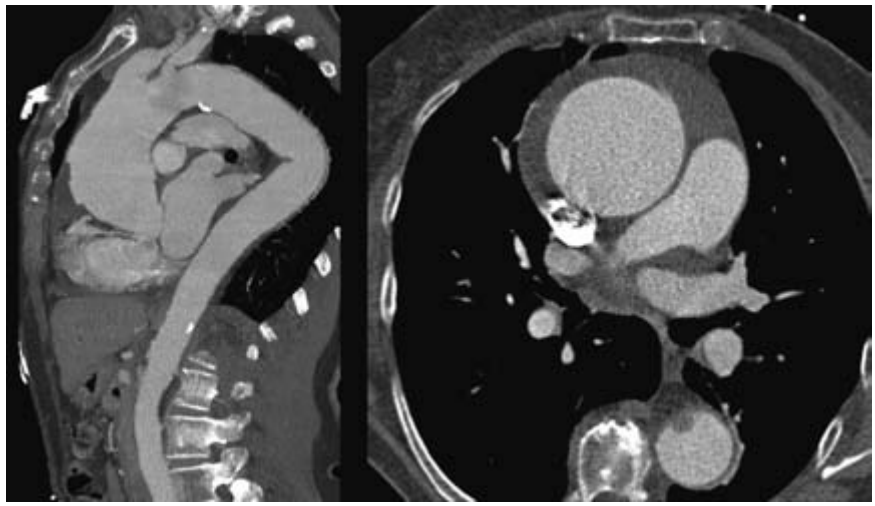

Figure 4.25 Visualization of aneurysm of the aorta. Aneurysmatic dilatation of the ascending aorta (A). An axial image at the level of the aortic arch (B) reveals a significant difference in lumen diameter between the ascending and descending aorta. A significant amount of fluid in the pericardial space is surrounding the ascending aorta.

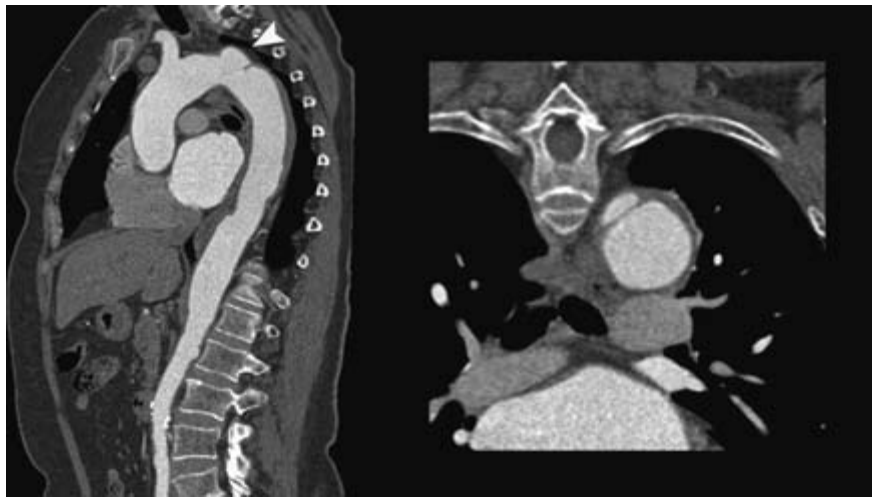

Figure 4.26 Visualization of aneurysm of the aorta. Small saccular aneurysm at the level of the aortic arch (arrowhead, A). The small neck and the location are easily appreciated on the para-coronal plane. The cross-section of the aortic arch shows the eccentric configuration of the aneurysm (B).

is often associated with atherosclerosis and is usually fusiform in shape (Fig. 4.25). False aneurysms consist of a perforation or penetration of the intima and media of the vessel wall, and are contained by adventitia and perivascular tissue (Fig. 4.26). They are often saccular in shape, have a narrow neck and are associated with trauma or infection.

Thoracic aneurysms are often filled with mural thrombi and long-standing aneurysms may be calcified. On CT, aneurysms are seen as (localized) increases of the aortic diameter.

Aortic dissection

A dissection is caused by a tear within the intimal layer of the artery with subsequent development and antegrade propagation of a false lumen tracking along the media. There can also be retrograde extension of a dissection with involvement of the aortic valve. The false lumen is often large in diameter and may end blindly or re-enter the true lumen. The false lumen may become occluded by thrombus or may remain patent. Dissections are usually associated with hypertension or Marfan syndrome. They can be classified according to the De Bakey or Stanford classifications, which both differentiate involvement of the ascending aorta (DeBakey I and II, Stanford A), which constitutes a surgical emergency and serious prognosis, from dissections limited to the descending aorta (DeBakey III, Stanford B) which in the absence of complications are best treated medically and have a relatively good prognosis.

On CT, a dissection can be recognized by the presence of an intimal flap separating the true and false lumens

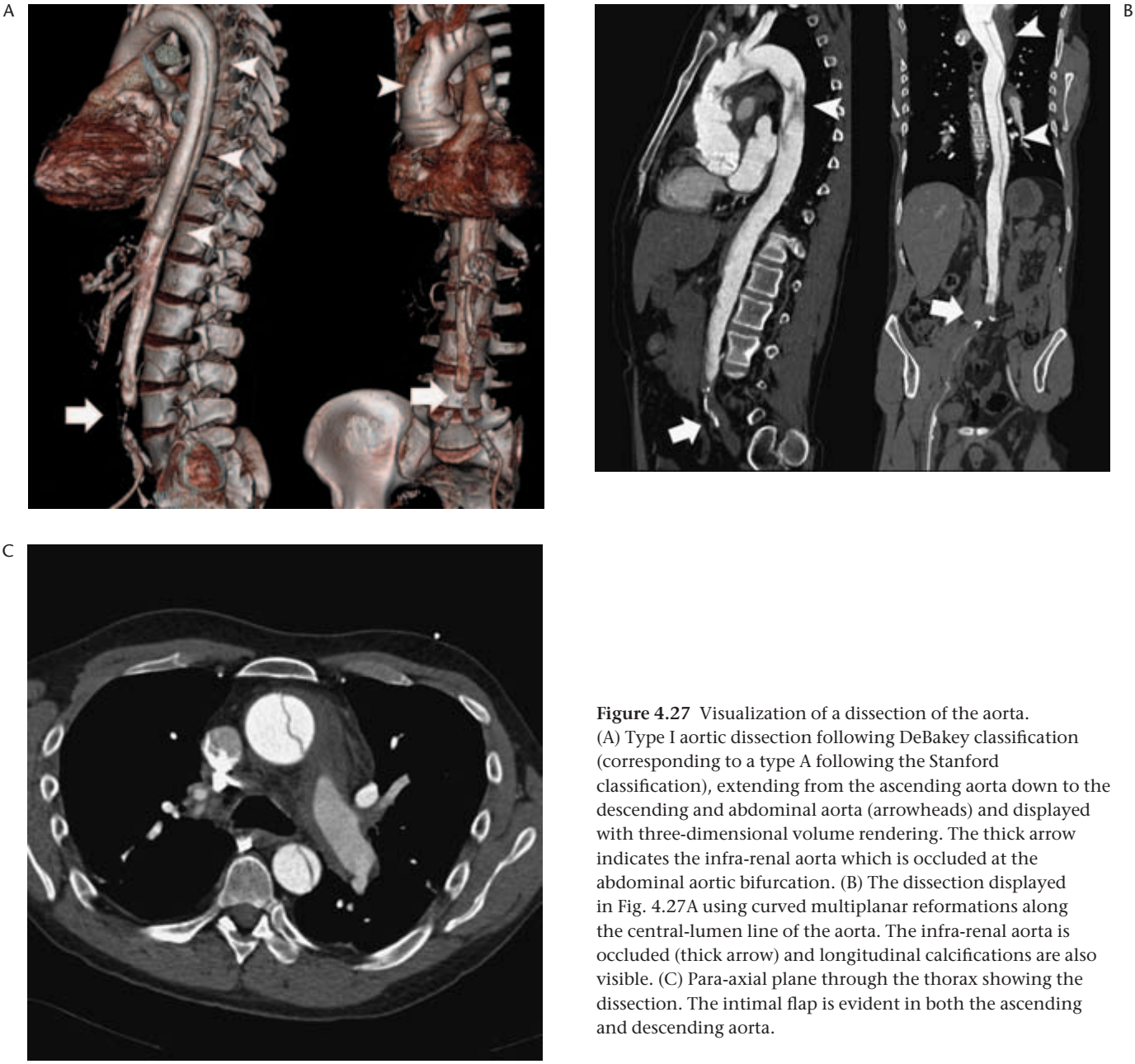

Figure 4.27 Visualization of a dissection of the aorta. (A) Type I aortic dissection following DeBakey classification (corresponding to a type A following the Stanford classification), extending from the ascending aorta down to the descending and abdominal aorta (arrowheads) and displayed with three-dimensional volume rendering. The thick arrow indicates the infra-renal aorta which is occluded at the abdominal aortic bifurcation. (B) The dissection displayed in Fig. 4.27A using curved multiplanar reformations along the central-lumen line of the aorta. The infra-renal aorta is occluded (thick arrow) and longitudinal calcifications are also visible. (C) Para-axial plane through the thorax showing the dissection. The intimal flap is evident in both the ascending and descending aorta.

(Fig. 4.27). More indirect CT signs of dissection include inward displacement of intimal calcification by the false lumen, differential contrast opacification between the true and false lumens, presence of (unenhanced) thrombus in the false lumen, thickening of the aortic wall, and, potentially, pericardial effusion.

Pulmonary emboli

CT scanning has been demonstrated to provide high diagnostic accuracy for the detection of pulmonary embolism. Pulmonary emboli on CT are shown as obstruction or filling defects of the contrast-enhanced common pulmonary artery, right or left pulmonary arteries or their side branches (Fig. 4.28). Pulmonary emboli are usually bilateral [44].

Pulmonary veins

CT imaging can accurately depict the anatomy of pulmonary venous return to the left atrium (Fig. 4.29). This can be important in the context of electrophysiological interventions, such as pulmonary vein isolation as a treatment for atrial fibrillation. In addition, the

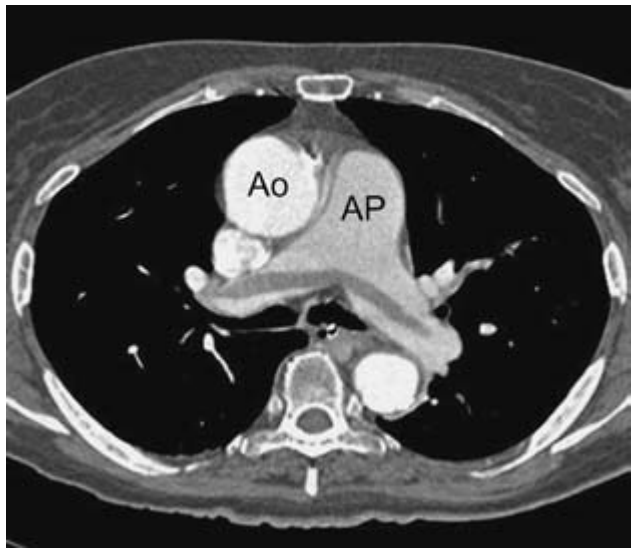

Figure 4.28 Visualization of pulmonary embolism. Large pulmonary embolism at the level of the bifurcation of the pulmonary artery. Ao, aorta; AP, arteria pulmonalis.

occurrence of pulmonary vein stenosis after ablation can be assessed by CT [45].

Functional imaging with computerized tomography

Because data are acquired throughout the complete cardiac cycle, MDCT allows reconstruction of multiple phases and assessment of global and regional cardiac function. Short-axis images at different levels (e.g. apical, mid and basal) of the ventricle and at different cardiac phases in the cardiac cycle can be reconstructed using dedicated software. Tracing of the left ventricular cavity (semi-automatic) at end-systole and end-diastole provides exact information about end-systolic and end-diastolic volumes and permits the calculation of stroke volume and ejection fraction. Additional tracing of the left ventricular epicardial contour provides quantitative information about left ventricular wall motion, wall thickness and thickening (Fig. 4.30). Regional myocardial wall thinning after myocardial infarction can be seen on the CT datasets. Several studies have shown that there is a good correlation of the various parameters of left ventricular function derived from MDCT in comparison to magnetic resonance imaging, biplane ventriculography and echocardiography [46,47].

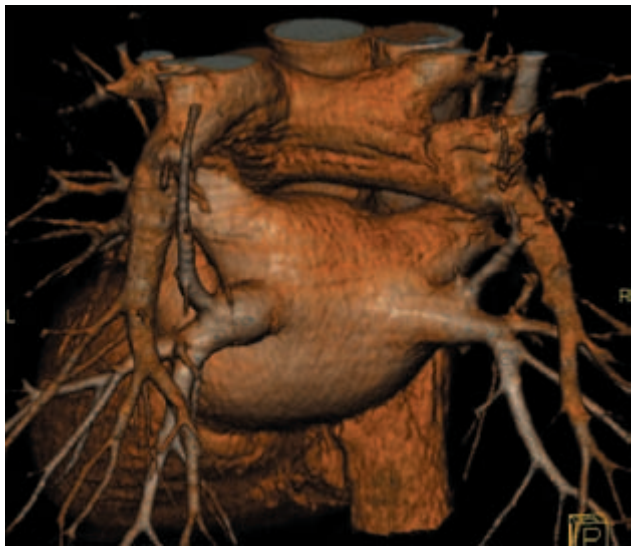

Figure 4.29 Visualization of pulmonary veins. Volume-rendered CT images can be used to evaluate the anatomy of the pulmonary veins (posterior view).

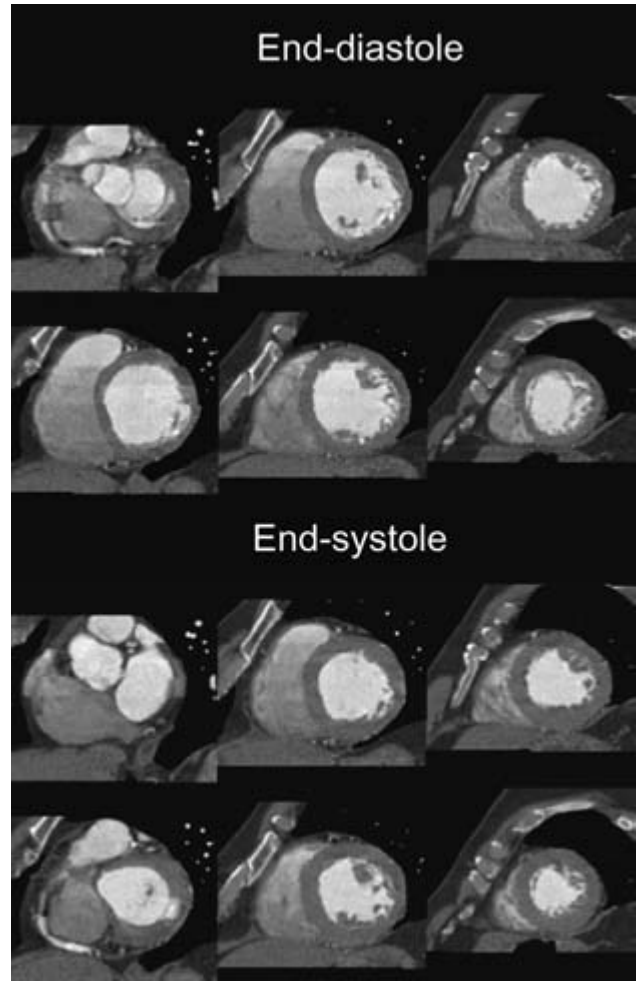

Figure 4.30 Visualization of left ventricle during systole and diastole. Reconstruction of short-axis images of the left ventricle during different time intervals of the cardiac cycle can be used to evaluate the left ventricular performance.

Personal perspective

Selective conventional coronary angiography still remains vital to planning catheter-based or surgical treatment of coronary artery stenoses and serves as a road map for catheter-based coronary diagnostic modalities such as intravascular ultrasound, optical coherence tomography, thermography. The high spatial and temporal resolution of invasive coronary angiography will not be matched by MDCT, but it is to be expected that the imaging performance of this technique will become sufficient to allow clinically reliable assessment of the coronary anatomy either to exclude the presence of any significant coronary obstruction and avoid catheterization, or to detect the presence of one or more significant coronary stenoses and avoid diagnostic angiography prior to coronary revascularization. The technical advances of CT scanners in recent years have been rapid and will continue to take place. The clinical role of CT coronary artery imaging may thus be expected to evolve further in the years ahead. Established and evolving indications in relation to coronary calcium and the coronary (bypass graft) lumen are presented in Table 4.4. The prospect that CT will allow early detection of coronary atherosclerosis in asymptomatic individuals is exciting; however, this would require a significant reduction of the radiation exposure of current CT scanners.

Table 4.4 Clinical role of cardiac CT

Established indications	Evolving indications
Coronary calcium for risk stratification	Coronary stenosis detection
Anomalous coronary arteries	Evaluation of bypass grafts
Pulmonary embolism	Evaluation of coronary stents
Cardiac masses and thrombi	Left ventricular function
Aortic aneurysms and dissection	Assessment of total coronary plaque burden
Cardiac calcification (valvular, pericardial)	Assessment of vulnerable plaque

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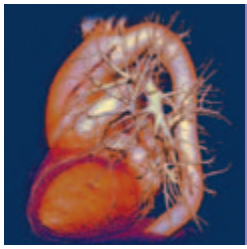

5 Nuclear Cardiology

Philipp A. Kaufmann, Paolo G. Camici and S. Richard Underwood

Summary

Non-invasive images of the myocardium that reflect myocardial perfusion can be obtained either by using conventional nuclear medicine radiopharmaceuticals and cameras or by positron emission tomography (PET). Myocardial perfusion scintigraphy (MPS) with thallium-201- and/or technetium-^{m}99-labelled sestamibi and tetrofosmin, in combination with single photon emission computerized tomography (SPECT), is a robust and well validated technique for the identification of myocardial ischaemia and infarction with high sensitivity and specificity. In selected subsets, e.g. patients with left bundle branch block and those unable to exercise, MPS can be the technique of choice for the demonstration of myocardial ischaemia. ^{99m}Technetium-labelled myocardial perfusion agents have a high-count density which enables acquisition of electrocardiogram-gated images. Spatial and temporal changes in activity during the cardiac cycle reflect regional myocardial motion and thickening and this technique allows left ventricular volume, ejection fraction, myocardial motion and thickening to be measured in addition to the information on perfusion. Since the main feature of an acute coronary syndrome is reduced myocardial perfusion, MPS can provide important diagnostic and prognostic information in the emergency department and allows patient stratification in the postinfarction phase. PET provides absolute measurement of myocardial blood flow and metabolism and, although potentially usable as a clinical tool, so far has been mainly employed as a powerful research instrument. PET has enabled the demonstration of coronary microvascular dysfunction and has highlighted the potential contribution of the microcirculation to myocardial ischaemia in patients with angiographically normal coronary arteries. Finally, both SPECT and PET are invaluable tools for the identification of viable and hibernating myocardium in patients with coronary artery disease and congestive heart failure.

Diagnosis of coronary artery disease

Chronic chest pain

Sensitivity and specificity

A range of investigations is normally used in patients with suspected coronary artery disease (CAD), the simplest 'investigation' being the history. Typical angina is a good indicator of myocardial ischaemia and abolition of symptoms is the primary aim of treatment. Symptoms, however, can be indeterminate and they do not indicate the site or extent of underlying ischaemia. It is therefore often helpful to proceed to further investigations to aid the diagnosis and to guide future management. Myocardial perfusion scintigraphy (MPS) is a robust, non-invasive and widely available method of assessing regional myocardial perfusion, and has an obvious role in the clinical setting. Many studies have assessed the sensitivity and specificity of this technique for the detection of CAD, coronary arteriography usually being used as the standard by which the accuracy of scintigraphy is judged. The wisdom of this approach can be debated but at least the arteriogram provides a universal standard for coronary anatomy even if it is less suited to the assessment of coronary arterial function. Published figures for

sensitivity and specificity of MPS vary widely and depend upon the characteristics of the population studied (its gender, presenting symptoms, medication, previous infarction, etc.), the imaging technique used [planar or single photon computed emission tomography (SPECT), qualitative or semi-quantitative analysis], and the experience of the centre. Good accuracy can be achieved using the modern techniques with tomographic imaging; sensitivity and specificity as high as 91% and 89%, respectively, can be obtained [1]. This is significantly better than exercise electrocardiography (ECG) for which a large meta-analysis has shown sensitivity of 68% and specificity 77%.

It is reasonable to ask therefore whether MPS should not replace exercise ECG in patients with suspected CAD. Several factors militate against this. The most important is the relative availability of the two techniques, but radiation burden and cost are also relevant. Although the cost of myocardial perfusion imaging (370 euros) is higher than that of the exercise ECG (120 euros) [2], this is more than outweighed by its greater effectiveness. Studies of cost-effectiveness have shown significant advantages for strategies of investigation using MPS, with savings in total diagnostic and management costs over 2 years in the region of 20% in centres routinely using scintigraphy.

Many centres use a staged approach with the exercise ECG being the initial stress test, followed by MPS if the likelihood of disease is indeterminate after the exercise ECG, or if further information on myocardial perfusion is required to assist management decisions. MPS should be the initial investigation in patients who are unlikely to exercise adequately, in women (because of the very high number of false-positive ECGs), and if the exercise ECG will be uninterpretable because of resting abnormalities such as left bundle branch block, pre-excitation, left ventricular hypertrophy, or drug effects.

The three commercially available perfusion tracers have equal accuracy for the detection of CAD [3]. Thallium-201 (^{201}Tl) has better uptake characteristics and, in theory, provides defects with greater contrast, but technetium-^{m}99 (Tc)-labelled sestamibi and tetrofosmin images are superior in terms of resolution and susceptibility to attenuation artefacts. The net effect of these technical differences in clinical practice is negligible, but the technetium tracers are preferred in obese patients or when ECG-gating is required. In fact, ECG-gating can aid the distinction between artefact and perfusion defect (Fig. 5.1) and can increase confidence in reporting [4]. Attenuation correction is another technique that can reduce artefacts, although it is controversial whether this can be achieved without loss of sensitivity and attenuation correction is not used routinely in most centres.

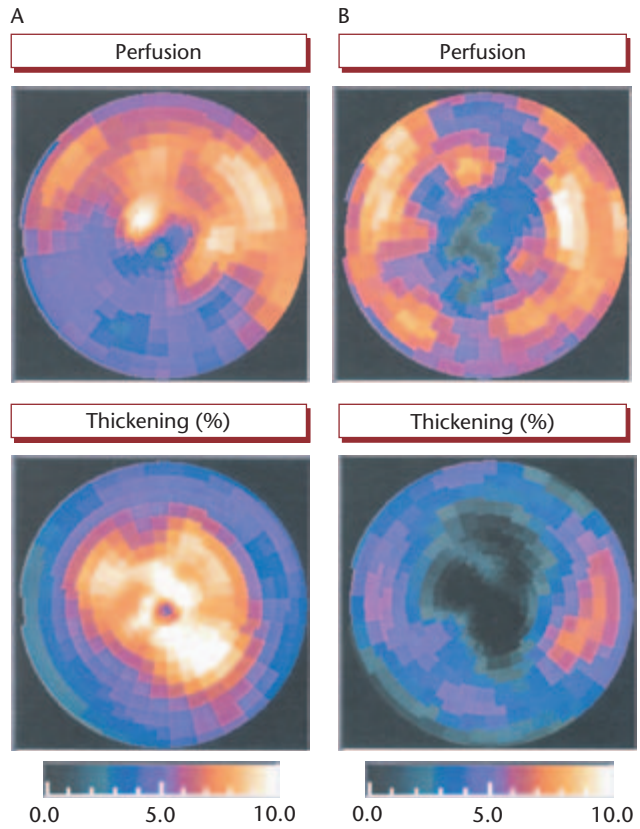

Figure 5.1 Polar map of a normalized rest perfusion scan (top) with the corresponding map representing the thickening assessed by gated SPECT (bottom). (A) Example of a patient with a fixed inferoseptal perfusion defect but normal thickening, identifying the perfusion defect as an attenuation artefact. (B) Example of a patient with a fixed apical perfusion defect with congruent decreased wall thickening, confirming that the perfusion defect is a scar.

Attenuation correction

Soft-tissue attenuation in the chest produces regional inhomogeneities in the normal pattern of tracer uptake and is one of the most frequent causes of artefact in MPS. Attenuation refers to the combined effects of photoelectric absorption and Compton scattering. The former occurs when a photon interacts with an orbital electron in the tissue and the total energy of the photon is lost. The latter indicates the interaction of a photon in the patient prior to detection, which makes the photon change direction. If patient positioning for rest and stress acquisition is kept constant, soft-tissue attenuation appears as a fixed defect. The resulting uncertainty in differentiating between a fixed defect due to an attenuation artefact and myocardial infarction can reduce the specificity of the test for detecting CAD. Several methods of non-uniform

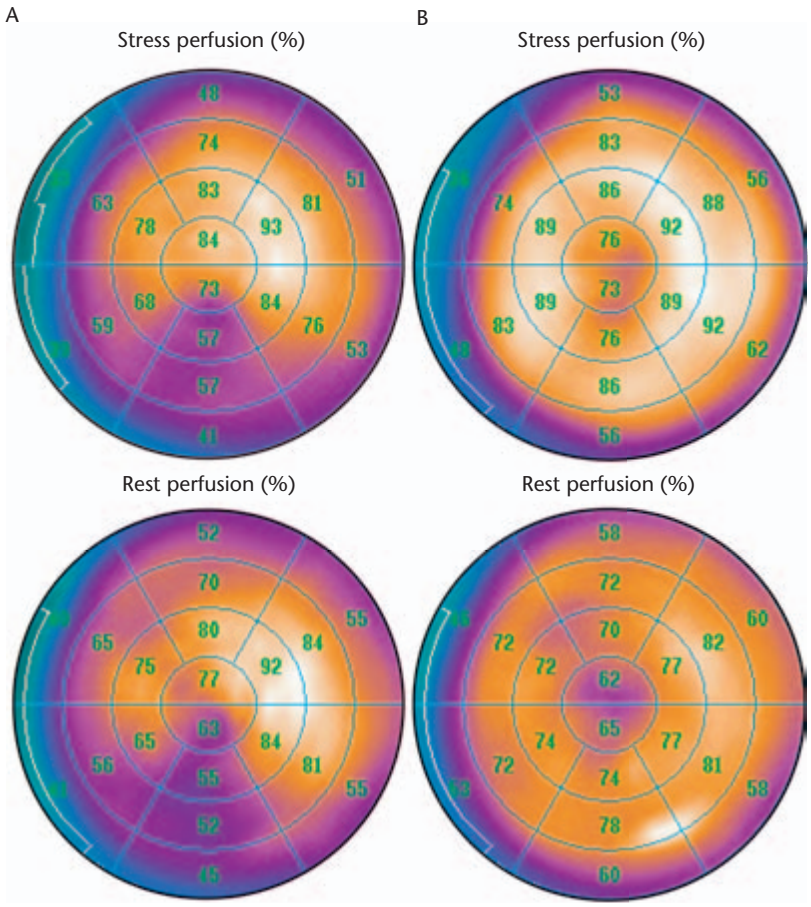

Figure 5.2 Polar map of a normalized stress (top) and corresponding rest perfusion scan (bottom) of an obese male patient with normal coronary arteries. (A) There appears to be a fixed inferior defect in the images without attenuation correction. (B) After attenuation correction with a CT (using a hybrid SPECT-CT scanner) perfusion appears normal, indicating that the inferior defect was the result of attenuation.

attenuation correction are now available commercially, albeit with variable clinical success (Fig. 5.2). Although several studies of attenuation-corrected SPECT have demonstrated improved specificity with no change in overall sensitivity, attenuation correction is not yet widely used. The relative capabilities of gated SPECT and attenuation correction to improve diagnostic specificity are still uncertain.

ECG-gated SPECT

^{99m}Tc-labelled myocardial perfusion agents are valid alternatives to ^{201}Tl for the assessment of CAD. Their high-count density has enabled the acquisition of ECG-gated SPECT studies. ECG-gating allows simultaneous assessment of resting ventricular function and either stress or rest perfusion. Spatial and temporal changes in activity during the cardiac cycle reflect regional myocardial motion and thickening respectively and automated detection of endocardial and epicardial contours allows left ventricular volume, ejection fraction, myocardial motion and thickening to be measured accurately and normally without user intervention. Assessment of motion aids the distinction between attenuation artefact and true perfusion abnormality because infarcted myocardium is unlikely to move or thicken normally and hence reporting confidence is increased and additional prognostic information is obtained [5].

Several fully automatic methods of measuring left ventricular function (Fig. 5.3) have been developed [6] and validated against a variety of techniques, such as equilibrium and first-pass radionuclide ventriculography, X-ray contrast ventriculography, magnetic resonance imaging and two-dimensional echocardiography.

Positron emission tomography

The most commonly used radiopharmaceuticals for positron emission tomographic (PET) imaging of myocardial perfusion are [^{15}O]water, [^{13}N]ammonia and rubidium-82 (^{82}Rb). For the last two tracers sensitivities between 83% and 100% have been reported for the detection of CAD with specificities between 73% and 100%. The main advantages of ^{82}Rb are its short half-life of 78 s and the

A

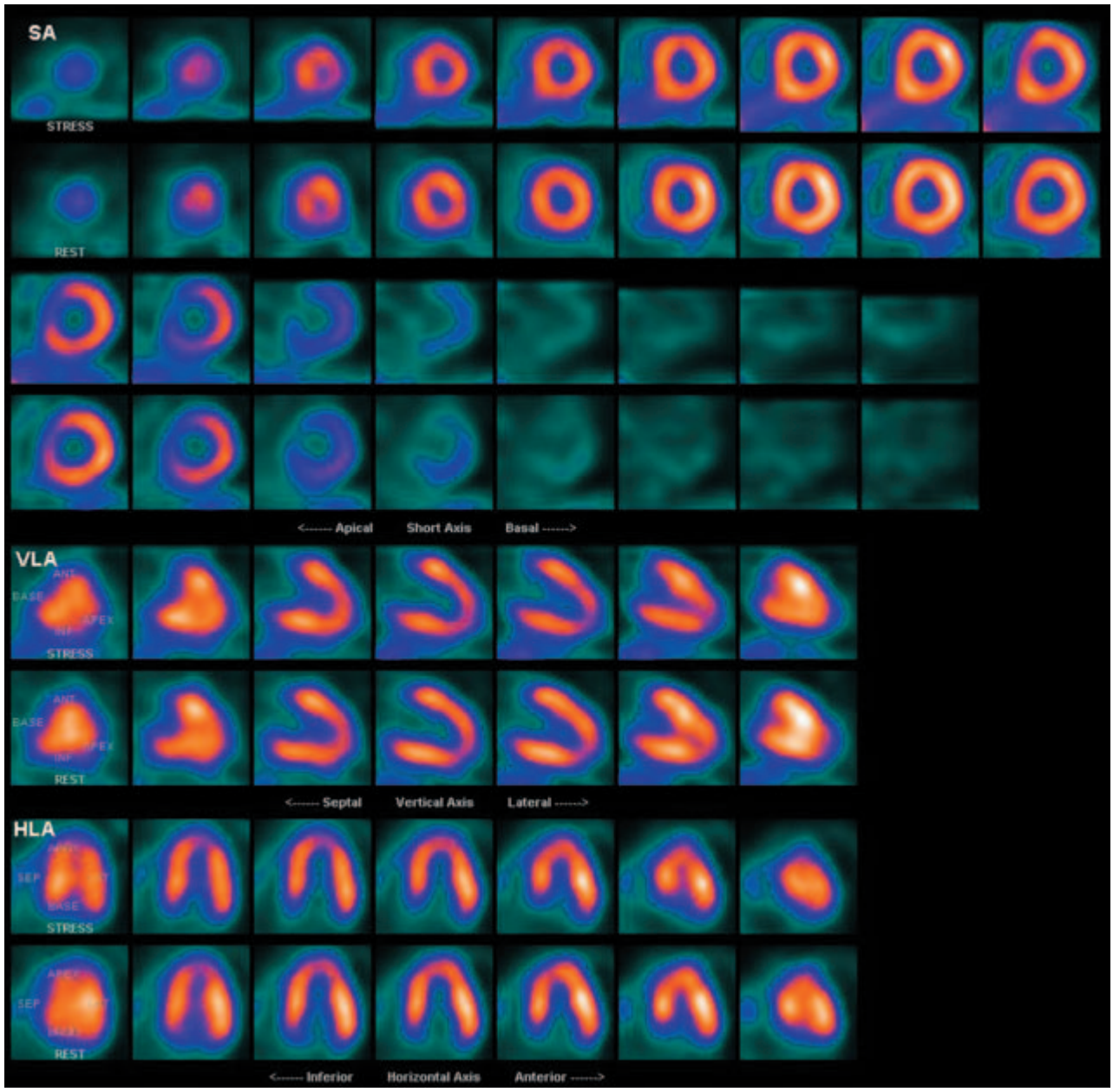

Figure 5.3 (A–C) Example from a female patient with normal coronary arteries and normal myocardial perfusion at rest and at stress assessed with ^{99m}Tc-labelled tetrofosmin. (A) The top four rows contain short-axis (SA) slices (stress and rest), the lower four rows represent the vertical (VLA) and horizontal (HLA) long-axis slices. All slices show normal perfusion without defect.

fact that it is readily produced at the point of use by an ^{82}Rb generator without the need for a cyclotron. Although several methods of quantifying regional myocardial perfusion using ^{82}Rb have been described, their accuracy is limited by the dependence of myocardial extraction of this tracer on perfusion and on the metabolic state of the myocardium. The high energy of the positron emitted (3.15 MeV) also reduces resolution of the images because of the long track of the positron before annihilation with an electron.

Both [^{13}N]ammonia and [^{15}O]water are the most commonly used PET tracers for the quantification of regional

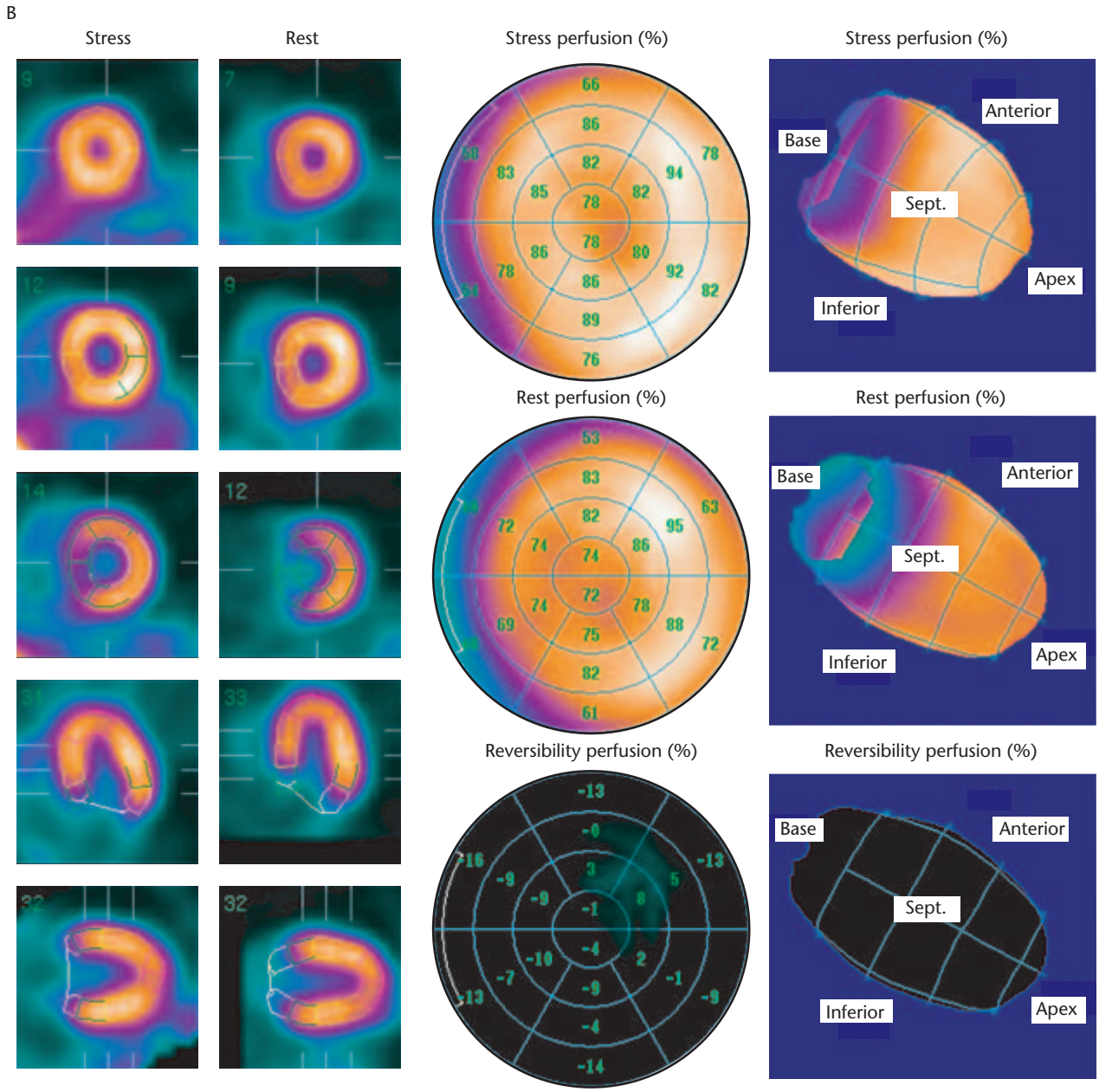

Figure 5.3 (*cont'd*) (B) Right: Polar plots and three-dimensional view of the perfusion scan indicating normal perfusion at rest and at stress. Left: The apical, mid-ventricular and basal short-axis slices illustrate the location of the radial-search boundaries. The mid-ventricular vertical and horizontal long-axis slice images illustrate the placement of the apical and basal slice selections.

myocardial perfusion. They have similar half-lives of 10 and 2 minutes respectively and so they both require an on-site cyclotron, which limits their widespread use. [^{15}O]water is superior to [^{13}N]ammonia as a perfusion tracer because it is metabolically inert and it diffuses freely across capillary and sarcolemmal membranes. It equilibrates rapidly between the vascular and extravascular spaces and its myocardial uptake varies linearly with perfusion over a wide range. However, [^{15}O]water has an important shortcoming compared with [^{13}N]ammonia: it does not accumulate in myocardial cells and it does not therefore provide images for clinical use. In contrast, [^{13}N]ammonia accumulates in myocardial cells and provides high-quality images of perfusion (Fig. 5.4). Therefore, it is the preferred tracer for clinical use provided that a cyclotron is available. The problem of attenuation

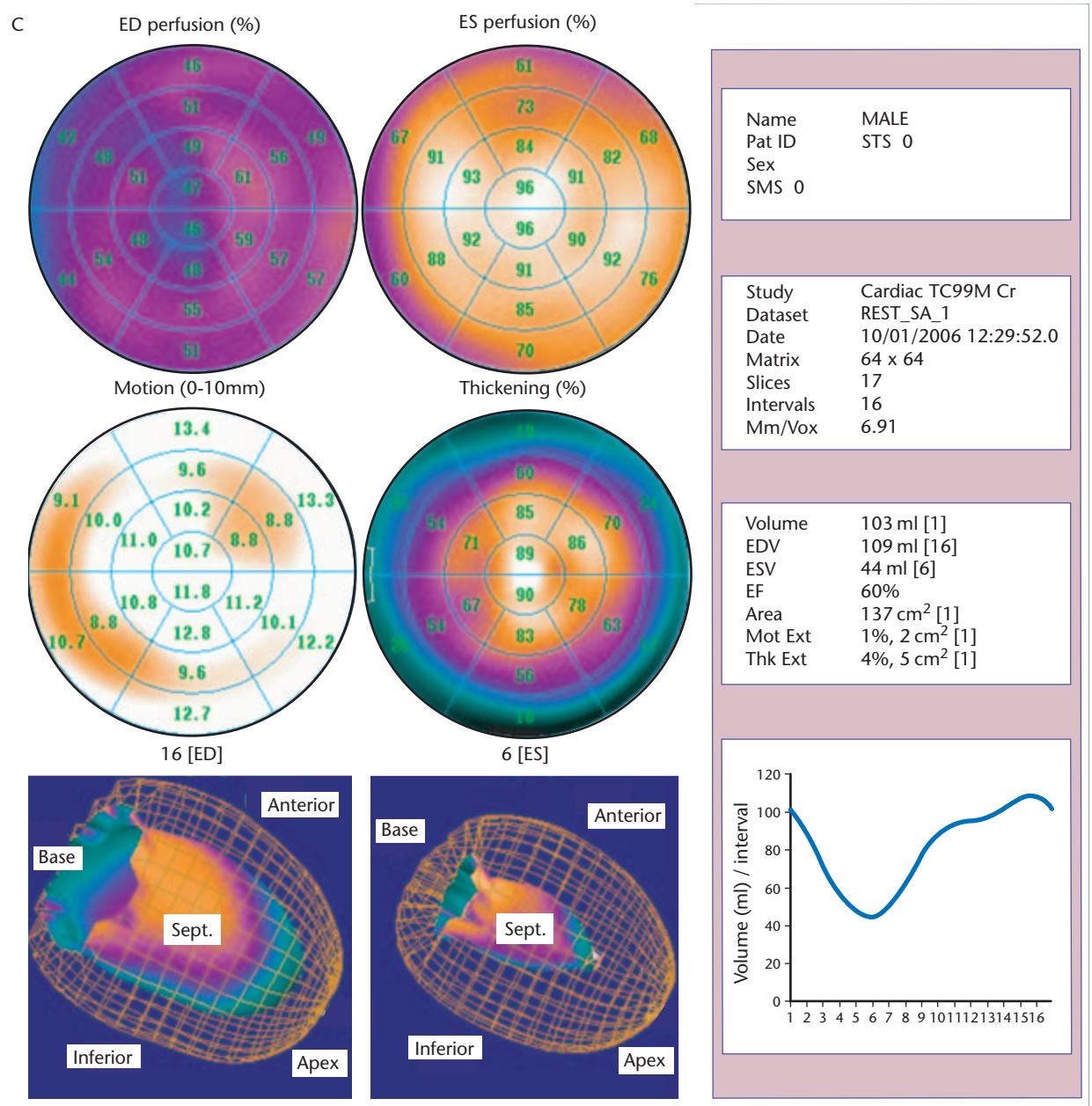

Figure 5.3 (*cont'd*) (C) Quantitative gated SPECT analysis (normal female patient). Left ventricular ejection fraction (LVEF) is 84%: in patients with end-systolic LV volume less than 15 ml EF is often overestimated. Nevertheless there is quantitative proof of normal LV wall motion and thickening, with a summed wall motion (SMS) and summed wall thickening score (STS) of 0. The LV time–volume curve shows excellent diastolic function (rapid filling as a result of rapid relaxation in the early diastolic time and second peak filling as a result of atrial contraction in the late diastolic phase).

correction has been solved for PET by using external ^{68}Ge or X-ray sources as recently established in the hybrid PET/CT scanners [7].

Because of the higher resolution of PET and its integrated attenuation correction, its accuracy for the detection of CAD is thought to be superior to that of SPECT, although only a small number of studies has directly compared the techniques [3] and it is not known if its higher cost outweighs its greater accuracy. In complex coronary disease, particularly multivessel disease where there may be no normal reference segment, PET is preferred (Fig. 5.5). Quantification may allow the demon-

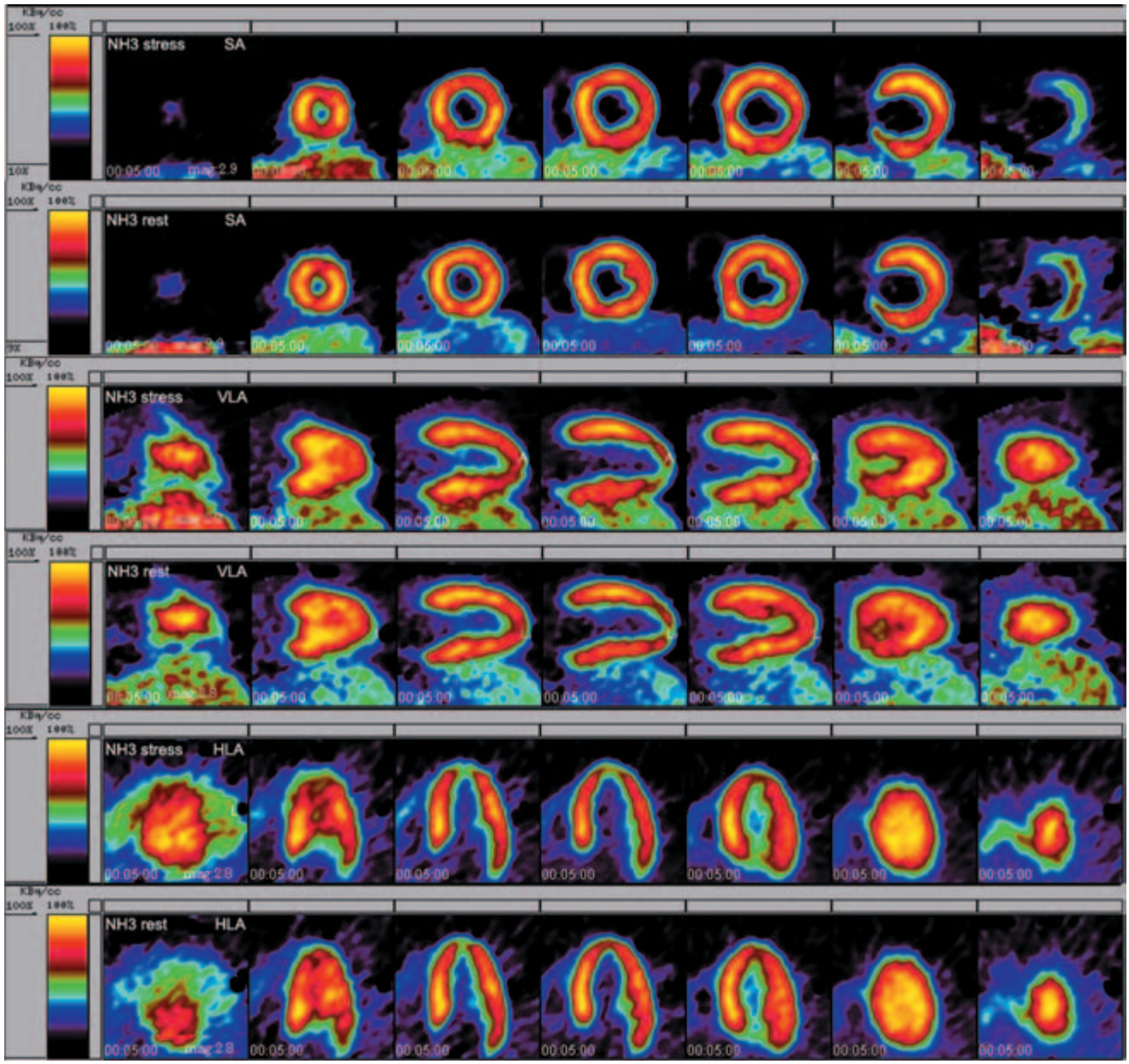

Figure 5.4 PET perfusion scan using [^{13}N]ammonia as perfusion tracer. Short axis (SA), vertical (VLA) and horizontal long axis (HLA) indicate normal perfusion during adenosine stress as well as at rest.

stration of endothelial dysfunction before an anatomical stenosis is apparent and it has had a great impact on our understanding of the pathophysiology of coronary disease [8].

Multislice X-ray computerized tomography (MSCT) is a rapidly developing technology that may facilitate the broader application of cardiac and coronary CT in the near future. The combination of non-invasive coronary angiography with the assessment of myocardial perfusion by radionuclide techniques provides a new non-invasive strategy for assessing known or suspected coronary disease with simultaneous assessment of coronary anatomy and function. Preliminary studies are promising (Fig. 5.6).

Acute coronary syndromes

Chest pain unit

The majority of patients presenting to emergency departments with chest pain are admitted because the initial

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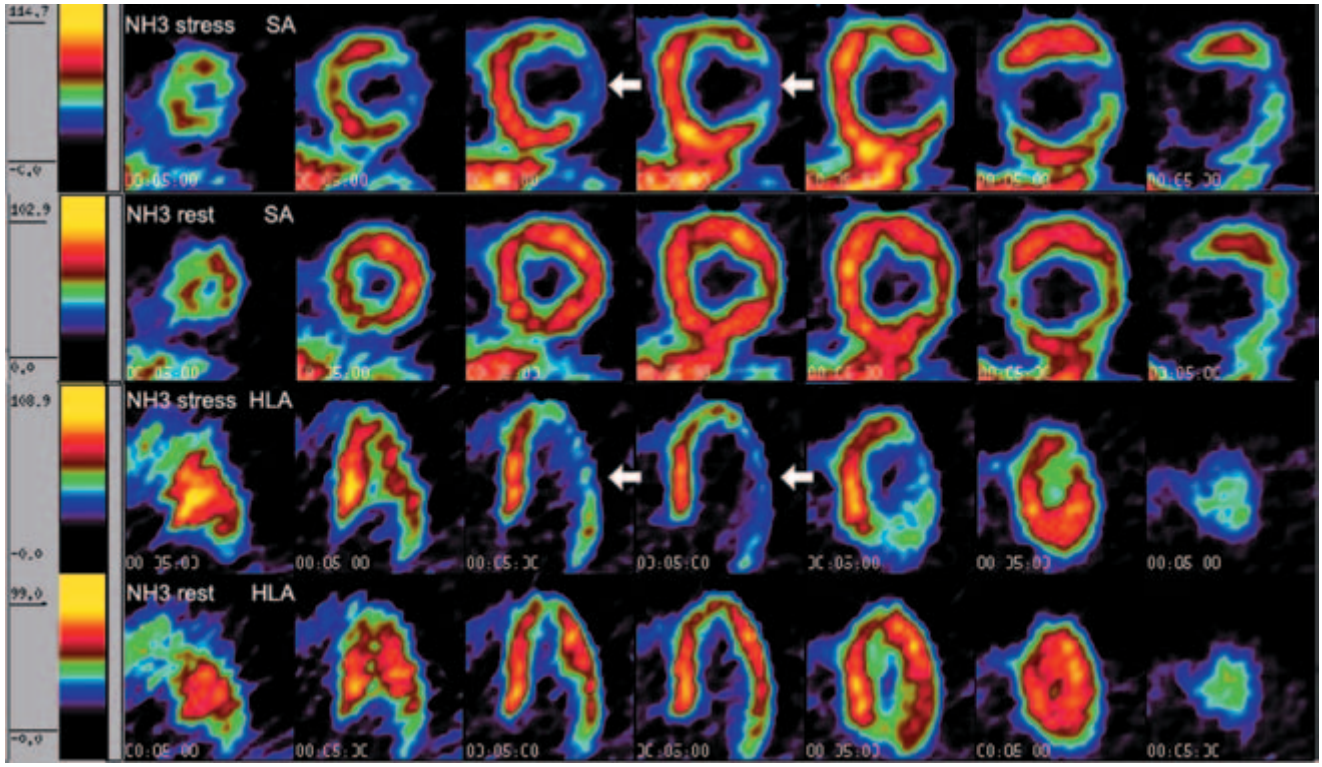

B

Segment	Flow (rest) (ml/min/ml)	Flow (adenosine) (ml/min/ml)	CFR (Norm >2.0)	Flow difference
Septum	0.662	1.891	2.86	1.23
Apex sep	0.657	1.888	2.87	1.23
Mid sep-i	0.746	2.265	3.04	1.52
Mid sep-a	0.618	2.001	3.24	1.38
Basal sep-i	0.706	1.563	2.21	0.86
Basal sep-a	0.592	1.857	3.14	1.27
Anterior	0.515	1.322	2.57	0.81
Apex ant	0.477	1.046	2.19	0.57
Mid ant	0.539	1.232	2.29	0.69
Basal ant	0.515	1.504	2.29	0.99
Lateral	0.557	0.634	1.14	0.08
Apex lat	0.503	0.543	1.08	0.04
Mid lateral	0.632	0.413	0.65	–0.22
Basal lat	0.527	0.831	1.58	0.30
Inferior	0.544	1.861	3.42	1.32
Apex inf	0.562	1.468	2.61	0.91
Mid inf-p	0.512	1.119	2.19	0.61
mid inf-i	0.626	2.562	4.09	1.94
Basal inf-p	0.508	1.851	3.64	1.34
Basal inf-i	0.506	1.996	3.94	1.49
Global	0.561	1.407	2.51	0.85

Figure 5.5 (A) Short-axis (SA, upper rows) and horizontal long-axis (HLA) cuts of PET perfusion scan with [^{13}N]ammonia from a patient with suspected coronary artery disease. The images show a defect in the left ventricular lateral wall that becomes evident during adenosine stress. Blunted hyperaemic response cannot be distinguished from a decrease in absolute flow (potentially induced by a steal phenomenon). (B) Quantification of myocardial blood flow reveals an absolute decrease in blood flow during adenosine stress, indicating that steal phenomena may be involved. Coronary angiography confirmed subtotal occlusion of the left circumflex coronary artery. Sep, septum; ant, anterior; lat, lateral; inf, inferior; CFR, coronary flow reserve; sep-i, septal inferior; sep-a, septal anterior.

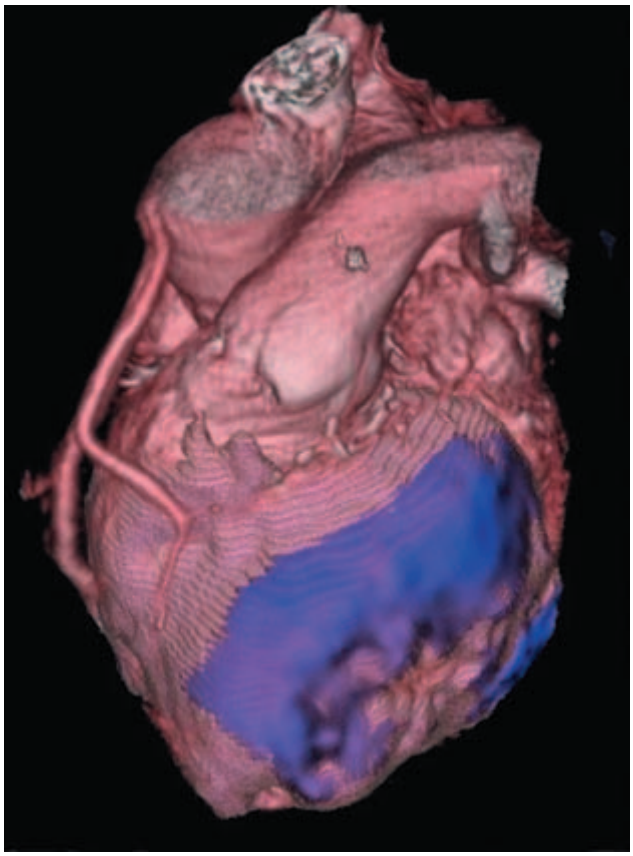

Figure 5.6 Anterior three-dimensional image of the heart obtained by CT in a patient with multivessel coronary disease and previous bypass grafting. Stress perfusion information from PET is superimposed with blue indicating an area of reduced perfusion. Bypass grafts to the left anterior descending and right coronary arteries are patent but a graft to the left circumflex artery is occluded and is therefore not visualized. The ischaemic area is in the territory of this graft.

clinical examination, ECG results and cardiac enzyme levels are insufficient to exclude an acute coronary syndrome, although most patients without obvious ECG changes do not have an acute syndrome. Conversely, a substantial minority of patients who are discharged from the emergency department have undetected acute ischaemia and an adverse outcome. Because the main feature of an acute coronary syndrome is reduced myocardial perfusion, MPS in the emergency department can provide important diagnostic and prognostic information. It has not been used widely because of the logistical problems of providing an acute radionuclide-imaging service, but several studies have now shown the effectiveness and cost-effectiveness of MPS in the acute setting, especially when the resting ECG is not diagnostic of myocardial ischaemia. A resting perfusion defect has a high positive predictive value for acute infarction in patients without history of previous myocardial infarction, particularly if it is associated with a wall motion abnormality on gated imaging, and these patients should be admitted to the coronary care unit. Conversely, a normal perfusion scan excludes acute infarction and exercise ECG or stress MPS can be the next diagnostic step. If the perfusion tracer can be injected during chest pain, a normal perfusion scan excludes a cardiac cause and allows the patient to be discharged. In patients with symptoms suggestive of an acute coronary syndrome, acute MPS reduces unnecessary hospital admission without reducing the appropriate admission of patients with a genuine acute coronary syndrome [9]. The sensitivity of acute rest MPS for the diagnosis of myocardial infarction is high very early after the onset of ischaemia, in contrast to serum enzyme markers, which require several hours to become clearly abnormal. Patients discharged with normal MPS have a very low likelihood of future cardiac events whereas patients with abnormal scans are at higher risk [10].

An intriguing option in patients with acute chest pain that has settled is to perform SPECT with free fatty acids [e.g. ^{123}I-labelled (*p*-iodophenyl)-3-(R,S)methyl-pentadecanoic acid (BMIPP)] because fatty acid metabolism is reduced for some time after acute ischaemia has resolved. This 'metabolic memory' might allow diagnosis for up to 24 hours after ischaemic chest pain and the theory is proven in principle although it has not been widely applied.

Risk assessment after myocardial infarction

Because the prognosis of ST segment elevation myocardial infarction (STEMI) is determined by left ventricular ejection fraction (LVEF), infarct size and residual viable myocardium, radionuclide techniques provide important information that aids patient management. MPS provides additional prognostic information over clinical factors and LVEF and coronary angiography may not provide prognostic information beyond this. MPS with vasodilator stress allows the risk to be assessed safely 2–5 days after infarction and is superior to early submaximal exercise testing.

Patients with small, fixed perfusion defects have a good prognosis, and are unlikely to benefit from invasive investigation and revascularization. Conversely, patients with MPS markers of high risk can be referred for coronary angiography and possible revascularization, although the superiority of revascularization over medical therapy has not been established in this setting [11]. Although primary percutaneous coronary intervention is the treatment of choice in STEMI, it is not currently available in all centres and some patients present too late for

alternative thrombolysis. When this is the case, MPS is very helpful for risk stratification and a large prospective randomized trial (INSPIRE—Adenos*IN*e *S*estamibi SPECT *P*ost *I*nfa*R*ction *E*valuation) will determine the value of early MPS in assessing risk and subsequent changes after medical therapy and revascularization [12].

In unstable angina and non-STEMI an early invasive strategy is recommended for patients with indicators of high risk and no serious comorbidities and this can be assessed by exercise ECG and by MPS [13]. MPS is particularly useful for assessing the risk of unstable angina once it has been stabilized.

Specific patient populations

The exercise ECG has moderate specificity for the detection of CAD in the absence of resting repolarization abnormalities, left ventricular hypertrophy and if patients are not treated with digoxin. Thus, when the resting ECG is normal and the likelihood of CAD from clinical assessment is low (for instance less than 25%) a stepwise strategy is appropriate with an exercise ECG as the initial diagnostic test. When the likelihood of CAD is very low (for instance less than 10%) then the best strategy will be reassurance without any provocative testing. If the resting ECG is abnormal or the likelihood of CAD is greater than 25% then MPS may be the better initial test on grounds of cost-effectiveness [2].

Women

The exercise ECG has lower specificity for the detection of CAD in women than in men and so MPS is a better diagnostic test even at lower likelihoods of disease. Pharmacological stress MPS is particularly valuable in women who are unable to exercise maximally. Although perfusion images are susceptible to breast attenuation artefacts, specificity can be maintained with awareness of the potential for artefacts, by using ^{99m}Tc perfusion tracers rather than ^{201}Tl, and employing ECG-gating and attenuation correction. The sensitivity of MPS is similar in men and women. PET perfusion imaging, when available, may be an additional way of avoiding attenuation artefacts.

Normal ECG, unable to exercise

Patients unable to exercise because of physical limitations, such as arthritis, amputations, peripheral vascular disease or pulmonary disease, should undergo MPS with pharmacological stress as the initial diagnostic test. Inability to exercise is itself an adverse prognostic indicator, presumably because of the increased incidence of CAD, and this should be borne in mind when interpreting MPS in these subjects.

Conduction abnormality

Patients with conduction abnormalities, such as left bundle branch block, bifascicular block and paced rhythms, may have inducible and fixed perfusion abnormalities on MPS even in the absence of underlying CAD, particularly when imaged during exercise or dobutamine stress (Fig. 5.7). Similar defects are much less common in patients with right bundle branch block although they can occur. These defects most commonly are confined to the septum although they can be more extensive. The causes of these defects in patients with conduction abnormalities

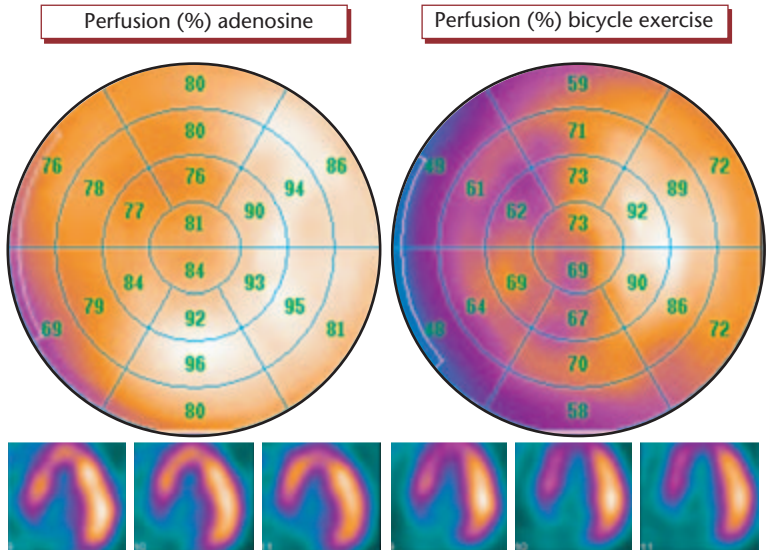

Figure 5.7 Polar maps of two perfusion scans, obtained using different stressors, in the same patient with left bundle branch block. During adenosine stress (left) perfusion is homogeneous while during bicycle exercise stress (right) there is reduced septal perfusion despite normal coronary arteries.

are still uncertain and are likely to be multifactorial, but they generally reflect true perfusion heterogeneities related to delayed septal relaxation and shorter diastolic perfusion time, or possibly to reduced regional afterload and hence reduced myocardial oxygen demand. Fixed defects may be the result of reduced myocardial thickening or they may result from an underlying myocardial abnormality such as cardiomyopathy.

The specificity of MPS for the detection of CAD is therefore reduced in these patients when dynamic exercise is used, but specificity is maintained using vasodilator stress if the heart rate does not increase significantly. In practice, when there is a diagnostic problem in a patient with left bundle branch block or paced rhythm MPS should be performed with adenosine or dipyridamole without additional exercise. A normal study excludes underlying coronary obstruction but an abnormal study may be less helpful diagnostically.

Prognosis of CAD

Beyond diagnosis, the most valuable contribution that MPS can make to the management of known or suspected CAD is to assess the likelihood of a future coronary event such as myocardial infarction or coronary death. Prognosis is strongly influenced by the extent and severity of inducible perfusion defects and this can guide the need for further invasive investigation and revascularization. MPS is a more powerful prognostic indicator than clinical assessment, the exercise ECG and coronary angiography, and provides incremental prognostic value even once the other tests have been performed [14].

The most important variables that predict the likelihood of future events are the extent and depth of the inducible perfusion abnormality. The relative value of the fixed component of a stress defect is unclear, but it is likely that left ventricular function is the best indicator of prognosis in patients with predominantly fixed defects. Thus, the patient with extensive ischaemia is at high risk of a coronary event and sudden death irrespective of the presence of infarction, and the patient without ischaemia but with a fixed defect is only at risk if the defect leads to significantly impaired function. Additional markers of risk are increased lung uptake on stress thallium images, because this indicates raised pulmonary capillary pressure either at rest or in response to stress, and ventricular dilation that is greater in stress thallium images than at rest. Transient ischaemic dilation can also be seen with ^{99m}Tc imaging and it may be the result of extensive subendocardial ischaemia giving the impression of cavity dilation.

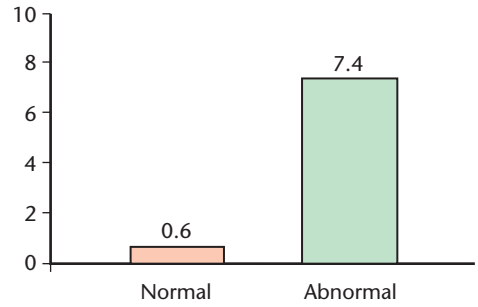

Figure 5.8 Rate of death or non-fatal myocardial infarction in patients with normal and abnormal stress MPS from 14 published reports comprising more than 12 000 patients. Reprinted with permission [15].

In patients with known or suspected CAD, a normal perfusion scan is very valuable because it indicates a likelihood of coronary events of less than 1% per year [15], a rate that is lower than that in an asymptomatic population (Fig. 5.8). Thus, whether non-obstructive CAD is present or not, further investigation can be avoided. This negative predictive value is independent of the imaging agent and technique, the method of stress, the population studied and the clinical setting. Exercise radionuclide ventriculography has also been used to assess prognosis because abnormal regional contraction is an early manifestation of inducible ischaemia [16]. Stress LVEF provides more information than resting LVEF because it reflects the extent of both infarction and transient ischaemia. However, the comparative prognostic value of perfusion imaging and exercise ventriculography has not been fully assessed, although it has been suggested that knowledge of rest and stress LVEF from resting gated MPS and stress first-pass ventriculography provides additional prognostic information compared with the perfusion information alone.

Preoperative risk assessment

A common clinical problem is that of assessing cardiac risk in patients who require non-cardiac surgery. In this, as in other clinical settings, MPS provides useful information although these patients are generally at low cardiac risk and the predictive value of a normal perfusion study is greater than that of an abnormal study. Whether investigation beyond simple clinical assessment is required should be based upon the urgency of the surgery and its own cardiac risk, the risk factors of the individual, and the individual's exercise tolerance. Patients with only minor clinical predictors (age > 70 years, abnormal resting ECG,

history of stroke or hypertension) who require low-risk (endoscopic or superficial procedures, cataract surgery and breast surgery) to moderate-risk surgery (carotid endarterectomy, head and neck surgery, intraperitoneal and intrathoracic surgery, orthopaedic surgery and prostate surgery) are not at high risk and do not require further investigation. Patients with intermediate clinical predictors (stable angina, prior infarction, treated heart failure, or diabetes) or with minor predictors and impaired exercise tolerance need further assessment if they are to undergo moderate-risk or high-risk surgery. Patients at high clinical risk (recent infarction or unstable angina, decompensated heart failure, or significant arrhythmias) require investigation even for low-risk surgery.

For patients who are able to exercise, further investigation normally means exercise ECG, but if the resting ECG is abnormal or in patients who are unable to exercise, MPS should be used instead. If further testing suggests a low risk, then surgery can proceed as planned. If it suggests a high risk then the need for coronary angiography and revascularization is determined by the clinical setting. In general terms, revascularization should not be performed if it would not have been performed in the absence of surgery because the risk of revascularization may still exceed the risk of non-cardiac surgery. In patients at intermediate risk after further testing, the best strategy is uncertain but aggressive medical management at the time of surgery rather than revascularization is preferred. This medical management involves rigorous control of pain, fluid balance and coagulation state after surgery, as well as preoperative beta-blockade and possibly perioperative nitrate infusion.

Management of myocardial revascularization

MPS can be valuable both before and after myocardial revascularization, either by angioplasty or bypass surgery. Neither procedure should be undertaken without objective evidence of ischaemia and perfusion imaging is often the most reliable way of obtaining this information and of ensuring that angioplasty is targeted at the culprit lesion [17]. It has an excellent negative predictive value for predicting restenosis and clinical events after angioplasty, and this can be particularly helpful in patients with recurrent but atypical symptoms. Routine MPS after angioplasty in the absence of symptoms is not common, although it can sometimes be useful as a new baseline in case symptoms recur. It can, however, be justified routinely in patients with impaired left ventricular function, proximal disease of the left anterior descending coronary artery and multivessel disease, suboptimal results of angioplasty, diabetes, and in those with occupations requiring low coronary risk. If MPS is performed after angioplasty then it should ideally be performed at least 6 weeks after the procedure because perfusion abnormalities can persist for some time even with a good anatomical result. Possible exceptions to this are patients with high-risk anatomy who can benefit from earlier imaging.

As with angioplasty, patients who are asymptomatic after bypass surgery do not routinely undergo perfusion imaging, although it can be helpful as a baseline for future management because revascularization is not infrequently incomplete. More commonly it is used for follow-up and it can be used roughly 5 years after surgery to guard against silent progression of prognostically important disease. Patients with symptoms after surgery may certainly benefit from MPS and the algorithms to be used are very similar to those in the diagnostic setting.

Myocardial infarction

Infarct detection

The diagnosis of acute myocardial infarction is normally made from the clinical history, the ECG, and from cardiac enzymes. In most cases these provide a conclusive answer but the diagnosis can be unclear in those seen late after the onset of chest pain, those with a conduction abnormality or pacemaker, those with perioperative infarction, and those in whom right ventricular infarction is a possibility. Nuclear techniques may then be helpful.

A number of radiopharmaceuticals have an affinity for acutely necrotic myocardium. Imaging of ^{99m}Tc-pyrophosphate has a sensitivity of at least 85% for the detection of acute infarction when performed 1–3 days after the event. Specificity is lower because uptake may occur in areas of old infarction or aneurysm, and also in areas of subclinical myocardial damage after unstable angina. Persistent blood pool activity or activity in bone and skeletal muscles can also cause difficulties, although these may be overcome by tomographic acquisition. In clinical practice, the technique is not used commonly, but it can be helpful in cases of doubt.

Imaging with anti-myosin antibodies labelled with indium has also been used and it has both high sensitivity and specificity. A multicentre trial of 492 patients showed sensitivities of 94% in Q-wave infarction and 84% in non-Q-wave infarction. Specificity was 93% in patients with chest pain but no infarction and there was focal uptake in 48% of patients with unstable angina suggesting subclinical infarction [18]. Despite this, the long time that is required after injection to obtain images limits its use for the early detection of infarction. This is also a drawback when using this compound for the detection of myocarditis and transplant rejection.

Myocardial salvage

Because ^{99m}Tc-labelled perfusion agents (MIBI and tetrofosmin) do not redistribute, they can be used in acute infarction to demonstrate the territory at risk before thrombolysis or acute angioplasty, and to assess the amount of myocardial salvage. The tracer is injected immediately before intervention and imaging can be performed several hours later once the intervention is complete and the clinical situation is stable. The defect will then correspond to the territory at risk and repeat injection and imaging several days later will show the actual extent of infarction. This is not a technique that can guide the need for intervention but it has been used in a number of clinical trials to assess the effect of acute intervention and to compare different regimes of thrombolysis on infarct size.

Management after infarction

An important aspect of clinical management after infarction is to identify patients at high risk of further events such as re-infarction or death, and hopefully to intervene to prevent these events. Clinical indicators of high risk in the acute phase include hypotension, left ventricular failure and malignant arrhythmias and these patients are candidates for early coronary angiography. After the acute phase however, prognosis is related to the degree of left ventricular dysfunction and the extent and severity of residual ischaemia; radionuclide imaging can assess both of these objectively. LVEF at the time of discharge or 10–14 days after infarction is a strong predictor of mortality, and patients with impaired function in particular can benefit from MPS to assess whether viable but jeopardized myocardium remains in the infarct zone and whether remote territories may also be jeopardized by ischaemia.

Heart failure: myocardial viability and hibernation

The term 'viable' is an umbrella term that includes several different subtypes of myocardium. One of these is hibernating myocardium, which is chronically dysfunctional but still viable myocardium that recovers function after coronary revascularization. For many years the functional sequelae of chronic CAD were considered to be irreversible and amenable only to palliative therapy. For example akinesis on the left ventriculogram implied infarcted myocardium or scar. We now know that chronic left ventricular dysfunction in patients with CAD is not necessarily irreversible and areas of akinetic myocardium have frequently been observed to improve in function after revascularization.

In 1978 Diamond *et al*. [19] suggested the possibility that 'ischaemic non-infarcted myocardium can exist in a state of function hibernation'. Several years later Rahimtoola [20] popularized the concept of hibernating myocardium and noted 'there is a prolonged subacute or chronic stage of myocardial ischaemia that is frequently not accompanied by pain and in which myocardial contractility and metabolism and ventricular function are reduced to match the reduced blood supply'. It is now known that perfusion is not always significantly reduced at rest in myocardial hibernation, but the debate on whether resting myocardial blood flow to hibernating myocardium is reduced or not has attracted a lot of interest and, undoubtedly, has contributed significantly to stimulate new research on heart failure patients with coronary artery disease. Although the debate is not over yet, some of the initial paradigms have been shown to be incorrect while new pathophysiological concepts have emerged. Clinically, the concept of hibernation has made a significant contribution to our understanding and management of patients with advanced ischaemic left ventricular dysfunction. Failure to identify and rescue hibernating myocardium may lead to loss of viable myocytes, progressive deterioration of heart failure and death. A number of imaging techniques have been used to detect viable myocardium and to characterize it as hibernating.

PET

Initial studies indicated that myocardial hibernation and infarction could be distinguished by a combination of PET perfusion imaging using [^{13}N]ammonia and metabolic imaging using the glucose analogue [^{18}F]fluorodeoxyglucose (FDG) after an oral glucose load. Regions with a concordant reduction in both [^{13}N]ammonia and FDG uptake ('perfusion–metabolism match', Fig. 5.9) were predominantly infarcted, whereas regions with reduced [^{13}N]ammonia uptake but preserved or increased FDG uptake ('perfusion–metabolism mismatch', Fig. 5.9) were hibernating [21]. Myocardial FDG uptake, however, depends on many factors such as dietary state, cardiac workload, insulin sensitivity, sympathetic drive and the presence and severity of ischaemia. These factors lead to variable FDG uptake in the fasted or glucose-loaded state and complicate image interpretation.

Semi-quantitative and quantitative analyses of FDG uptake improve the detection of viable myocardium but require standardization of imaging conditions particularly with regard to myocardial glucose uptake. Many

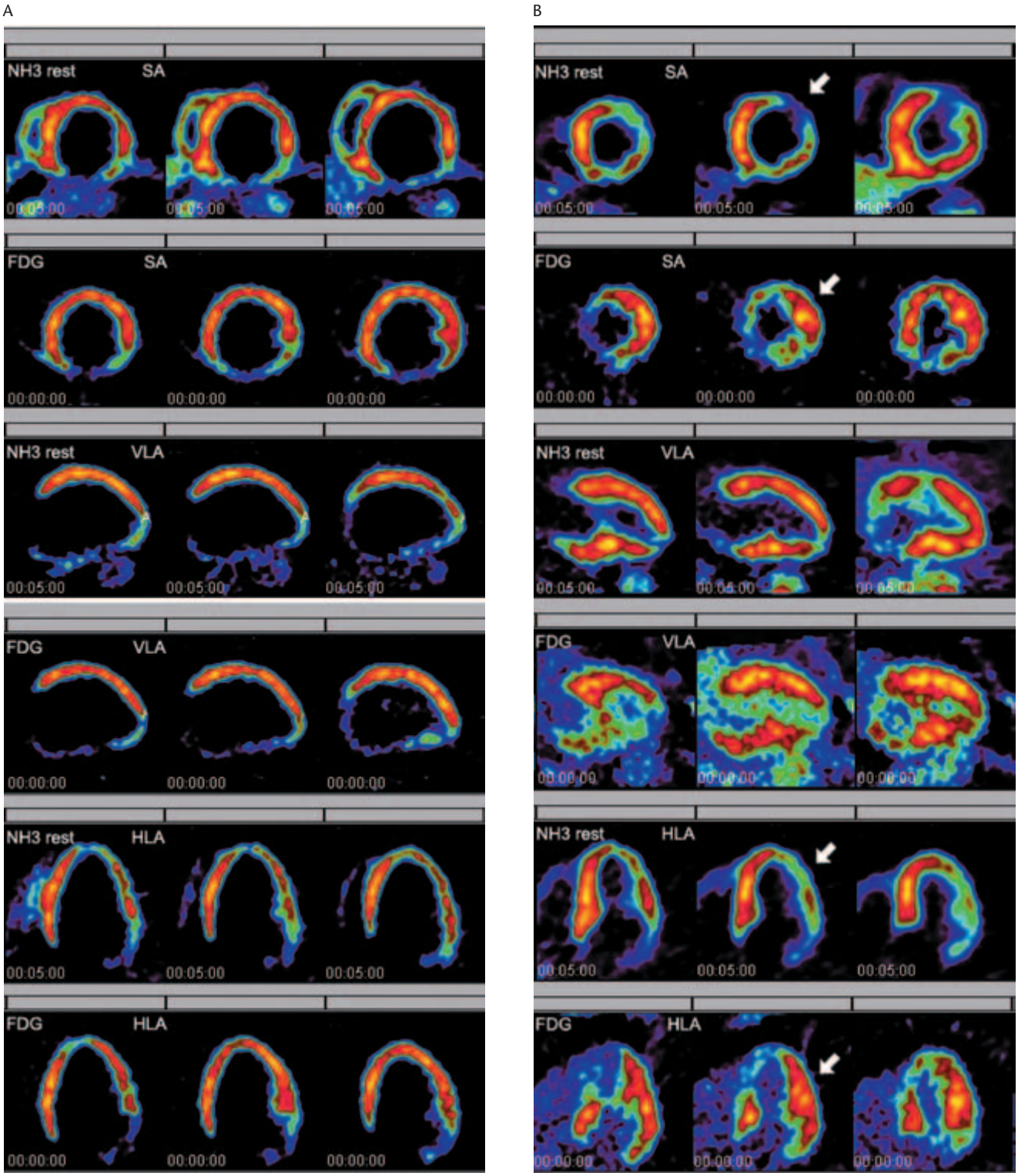

Figure 5.9 Short-axis (SA), vertical long-axis (VLA) and horizontal long-axis (HLA) tomograms of [^{13}N]ammonia (NH_3) perfusion at rest and [^{18}F]fluorodeoxy-glucose (FDG) metabolism. (A) Matched inferior defect of perfusion and metabolism indicating infarction without viable myocardium. (B) Anterolateral defect of perfusion with preserved FDG uptake indicating viable tissue. The mismatch of perfusion and metabolism indicates hibernating myocardium (white arrow).

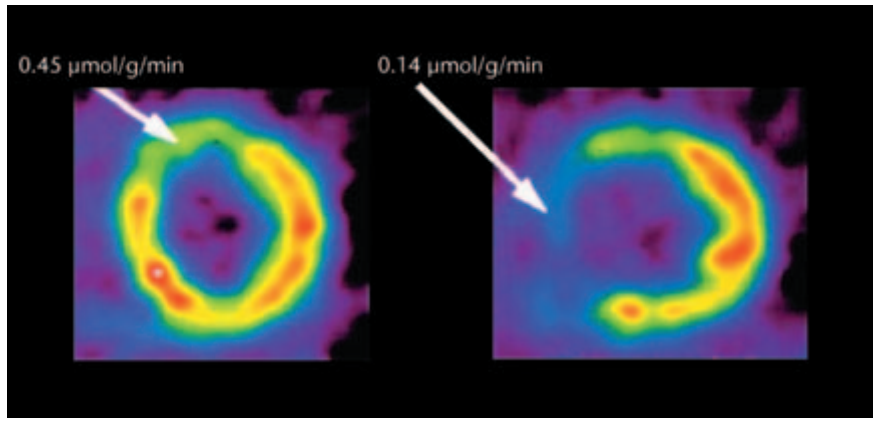

Figure 5.10 Quantitative images of myocardial [^{18}F]fluorodeoxy-glucose (FDG) uptake. Left, the anterior wall is viable with FDG uptake above the threshold of 0.25 µmol/g/min. Right, the septum does not contain clinically significant viable myocardium.

patients with CAD are insulin resistant and have poor FDG image quality after an oral glucose load. Myocardial glucose metabolism can therefore be standardized using the hyperinsulinaemic–euglycaemic clamp, essentially the simultaneous infusion of insulin and glucose acting on the tissue as a metabolic challenge and stimulating maximal FDG uptake [22]. This allows absolute values of glucose metabolism to be measured (µmol/g/min) and aids comparisons between different subjects and centres (Fig. 5.10). To determine the threshold value above which the best prediction of improvement in functional class of at least one grade could be obtained, in a prospective study in 24 patients undergoing coronary revascularization, a receiver–operator characteristic curve (ROC) was constructed. According to this analysis the optimal operating point on the curve (point of best compromise between sensitivity and specificity) was at the absolute threshold of FDG uptake of 0.25 µmol/g/min (where the gold standard was the evidence of functional recovery at follow-up) [23]. By comparing FDG images obtained under these conditions with regional wall motion from another imaging technique, the need for a simultaneous perfusion tracer is avoided.

In summary, clinically there is now wide consensus on the importance of identifying and treating hibernating myocardium in patients with coronary artery disease and heart failure. Although randomized studies are needed before a definitive influence on clinical practice is achieved, the contribution of the existing experimental studies is compelling.

Single photon tracers

The disadvantage of PET is that it is not widely available. Thallium provides information on both myocardial perfusion and viability and has been widely used for identifying myocardial hibernation. Because redistribution can be slow or incomplete in regions of reduced perfusion, the usual stress/redistribution protocol can underestimate myocardial viability and additional steps to ensure complete assessment of viability are required. These include late redistribution imaging at 8–72 hours after stress injection, re-injection of tracer at rest after redistribution imaging, and a resting injection on a separate day with both early and delayed imaging.

In any of these viability images, the amount of viable myocardium is proportional to the amount of tracer uptake relative to a normal area. A common threshold for defining clinically significant viability is 50% of maximal uptake although the best threshold may be higher. In addition to detecting viable myocardium in an area of akinesis it is important to demonstrate inducible ischaemia before diagnosing hibernation because hibernation is an ischaemic syndrome.

MIBI and tetrofosmin have also been used for the detection of viable and hibernating myocardium. In theory these tracers may underestimate viability in areas with reduced resting perfusion because they are combined tracers of viability and perfusion without the property of redistribution that allows viability to be assessed independently. Some studies have therefore found thallium to be better for the assessment of viability but others have found them to provide comparable information. It does appear though that if the tracers are given under the cover of intravenous or sublingual nitrates, then resting perfusion is improved and the technetium tracers are good markers of viability.

ECG-gated SPECT

An important problem in studies of hibernation is that viability and function are often assessed from different techniques, and it can be difficult to be sure that the same myocardial segments are being compared. Thus, the ideal technique should combine information on viability, perfusion and function in a single image, and ECG-gated

technetium MPS is very helpful. In regions of previous infarction with reduced tracer uptake, the assessment is more difficult, but this is not a major limitation because these areas contain little viable myocardium and may not benefit from revascularization.

Microvascular disease

Until recently, ischaemic heart disease was primarily thought be caused by disease of large vessels, particularly the conduit coronary arteries. However, it is now clear that abnormalities of the coronary microcirculation may contribute to the generation of ischaemia even in the absence of demonstrable disease of the large epicardial arteries. Microvascular disease often precedes epicardial coronary disease and its extent may have independent prognostic value.

Myocardial perfusion reserve is the ratio of myocardial perfusion during maximal coronary vasodilation and at baseline. It is an integrated measure of flow through the epicardial coronary arteries and perfusion through the microcirculation and it can be used to assess the function of the coronary circulation as a whole. An abnormal perfusion reserve can be the result of narrowing of the epicardial coronary arteries or, in the absence of angiographically demonstrable atherosclerotic disease, may reflect dysfunction of the coronary microcirculation. The latter can be caused by structural (e.g. vascular remodelling with reduced lumen to wall ratio) or functional (e.g. vasoconstriction) changes, which may involve neurohumoral factors and/or endothelial dysfunction. Furthermore, an abnormal perfusion reserve may also reflect changes in coronary and/or systemic haemodynamics as well as changes in extravascular coronary resistance (e.g. increased intramyocardial pressure).

The coronary microcirculation cannot be imaged directly in man *in vivo*. The resistance vessels in the coronary circulation are not generally visible on angiography and are too small to be catheterized selectively. Instead, indirect parameters such as myocardial perfusion and perfusion reserve can be used because, in the absence of coronary stenoses, they provide an index of microvascular function.

PET can be used to measure both absolute myocardial perfusion and perfusion reserve and microvascular dysfunction has been demonstrated in patients with hypercholesterolaemia, hypertension and diabetes and in those who smoke. The measurements can also be used as surrogate end-points to assess the effectiveness of therapeutic interventions such as α- and β-adrenoreceptor blockade [24], lipid-lowering, antioxidants [25], cardiovascular conditioning and coronary angioplasty. They also provide prognostic information [26,27] and microvascular dysfunction assessed by PET is an independent predictor of long-term outcome and cardiovascular death in patients with hypertrophic and dilated cardiomyopathies (Fig. 5.11).

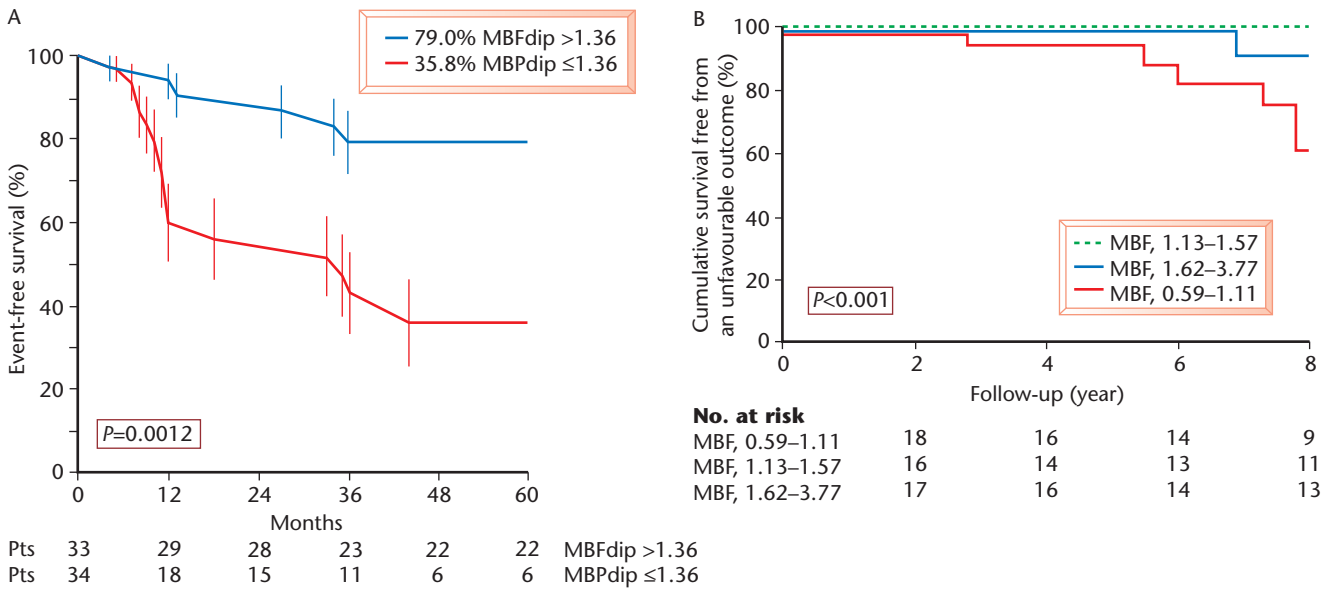

Figure 5.11 Kaplan–Meier event-free survival curves over 5 years in patients with dilated (A) and hypertrophic cardiomyopathy (B). Event-free survival is lowest in those patients with a severely blunted blood flow response to dipyridamole. Reprinted with permission [26,27].

Personal perspective

The first nuclear cardiology examinations were performed as early as 1927, when Blumgart and Weiss measured circulation times by intravenously injected radon gas. The next milestone followed in 1965 when Anger and colleagues first demonstrated the ability to define cardiac transit with a single-crystal scintillation camera. Although the 1970s and the early 1980s witnessed the onset of quantification of planar and tomographic imaging with SPECT and later with PET, it was only two decades ago that the prognostic applications of stress radionuclide imaging modalities were defined and pharmacologic stress imaging protocols were validated. In the 1990s, the role of nuclear imaging in the assessment of myocardial viability was established. Since then, nuclear cardiology has become an important cornerstone of cardiovascular evaluation in daily clinical routine. Myocardial perfusion study is a well-established, non-invasive technique with a large body of evidence to support its effectiveness in the diagnosis and management of angina and myocardial infarction. Nuclear cardiology procedures are an integral part of many clinical guidelines for the investigation and management of angina and myocardial infarction.

Despite its well-defined role with a broad-based set of clinical applications, the main strength of nuclear cardiology appears to lie in its enormous potential for innovation and progress. The combination of new biologically derived radiopharmaceuticals and advances in imaging technologies such as the integration of CT into PET and SPECT will undoubtedly continue to stimulate much scientific activity and provide new clinical applications for diagnosis, functional characterization and prognosis as well as evaluation of therapeutic strategies.

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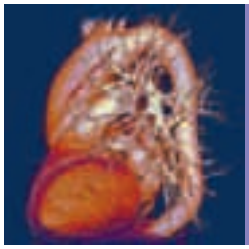

6 Invasive Imaging and Haemodynamics

Christian Seiler and Carlo Di Mario

Summary

Right- and left-sided cardiac pressure, oxygen and ventricular volume measurements together with coronary angiography are the basis for the functional and structural characterization of the majority of heart diseases.

Cardiac output is calculated as: oxygen consumption ÷ arteriovenous oxygen difference.

Detection and localization of intracardiac shunts can be performed using blood oxygen saturation as the indicator.

Vascular resistance is determined on the basis of Ohm's law (= pressure gradient ÷ flow).

The calculation of valve orifice area is based on its direct relationship to cardiac output, and on its inverse association to the square root of the pressure drop across the valve.

The coronary artery tree structure is intimately linked to its functional obligation of myocardial oxygen supply.

Varying oxygen demands by the myocardium are satisfied by altering coronary flow rates.

The main cause of a mismatch between myocardial oxygen demand and supply is coronary artery disease with its atherosclerotic narrowings.

In the event of an acute coronary occlusion, myocardial infarct size is determined by the following factors: time of occlusion, the size of myocardial area at risk, and the inverse of collateral supply to the occluded vascular territory.

Coronary pressure-derived fractional flow reserve is a useful way to describe the functional severity of coronary artery stenoses.

Introduction

Therapeutic decisions in cardiology are crucially determined by invasive circulatory imaging and haemodynamics, which are essential for understanding the pathophysiological and diagnostic aspects of cardiovascular disease. This is related to the fact that the cardiovascular system can be elegantly conceptualized using mechanical laws and the basic dimensions of mass (M), length (L), time (t) and temperature. Invasive examination allows the most direct determination of parameters derived from these dimensions, such as volume (L^3), force ($F = M \times$ acceleration), pressure (F/L^2) and flow (L^3/t), i.e. variables that permit the exact description of the forces generated by the different cardiac chambers. Thus, assessment of the haemodynamics of the circulation enables one to grasp the system's function, whereas invasive imaging depicts its structure in terms of lumen size, arterial branch lengths, branching patterns, etc. Accordingly, the goal of this chapter is to provide practical suggestions on how to become familiar with invasive techniques, how haemodynamic variables are obtained invasively and how the structure of the coronary artery tree is visualized. Finally, the epidemiologically important issue of coronary artery haemodynamics, including the relevance of coronary atherosclerotic lesions, is also discussed.

Percutaneous techniques of cardiac catheterization

Right side of the heart

Following local anaesthesia, the femoral vein is punctured before the common femoral artery is catheterized, and the sheath introduced by the Seldinger technique [1]. Using a 6F Swan–Ganz catheter allows a mostly easy passage to the pulmonary artery with low risk of injury to the right-heart chambers. To advance the catheter from the femoral vein to the pulmonary artery, the tip of the catheter is advanced from the lower right atrium by clockwise rotation over the tricuspid orifice, and then advanced into the right ventricle. To reach the pulmonary artery, the catheter must be slightly withdrawn so that its tip lies horizontally and just to the left of the spine. Clockwise rotation then causes the tip of the catheter to point upwards towards the right ventricular outflow tract. The catheter should only be advanced when it is in this position in order to minimize the risk of arrhythmia and injury to the right ventricular wall. If these manoeuvres fail to gain access to the pulmonary artery due to enlarged right-heart chambers, the catheter may be withdrawn to the right atrium and formed into a large 'reverse loop' by catching the tip in a hepatic vein and advancing the catheter quickly into the right atrium. This allows the tip of the catheter to advance through the tricuspid valve in an upward position. The catheter should then cross the pulmonic valve and advance to a pulmonary wedge position without difficulty. If the pulmonic valve cannot be passed, a 0.53-mm (0.021-inch) guidewire can be employed to facilitate positioning in the pulmonary artery. Once in the pulmonary wedge position, measurements of pressure and blood oxygen saturation are started. Following measurement of the wedge pressure, the catheter is withdrawn into the proximal pulmonary artery, into the right ventricle and then into the right atrium, with corresponding recordings of pressure and oxygen saturation. Unsuspected anatomical abnormalities encountered during right-heart catheterization include passage across a patent foramen ovale into the left atrium (Fig. 6.1), a persistent left superior vena cava, a patent ductus arteriosus or an anomalous pulmonary vein (Fig. 6.2).

Left side of the heart

The common femoral artery is punctured as follows: the three middle fingers of the left hand palpate the pulse and the skin is pierced with the needle three finger-breadths below the inguinal ligament [2]. After puncture of the artery, a 0.89-mm (0.035-inch) J-guidewire should be advanced carefully into the needle. It should move freely up the aorta and be placed at the level of the diaphragm. When it is difficult to advance the guidewire close to the tip of the needle, the wire should be withdrawn to ascertain that forceful arterial flow is still pre-

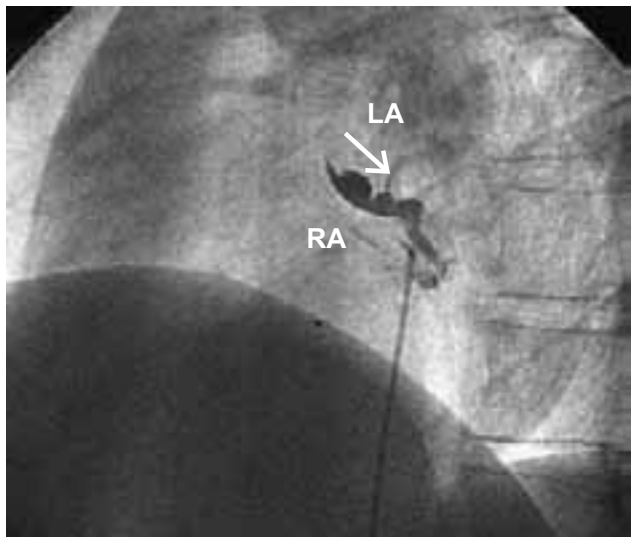

Figure 6.1 Patent foramen ovale. Imaging (lateral view) using radiographic contrast medium of the interatrial septum ('tunnel' between septum primum and septum secundum) with a small jet (arrow) between the right atrium (RA) and left atrium (LA).

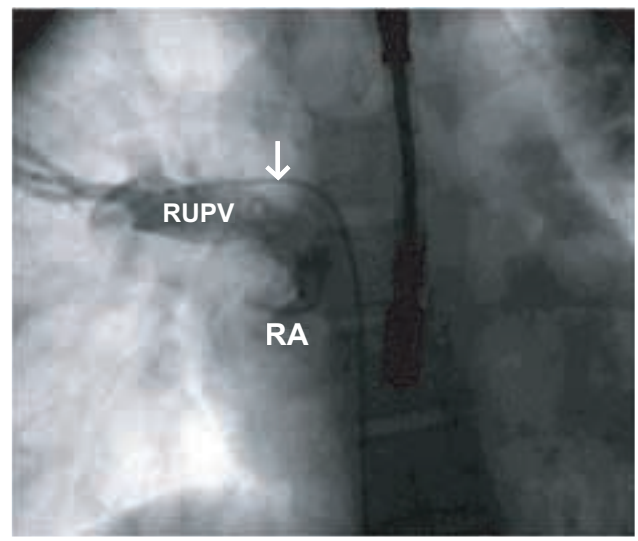

Figure 6.2 Anomalous right upper pulmonary venous return. Injection of contrast material via a multipurpose catheter (arrow) inserted in the right upper pulmonary vein (RUPV). The catheter is introduced in the right femoral vein. The contrast is filling the right atrium (RA).

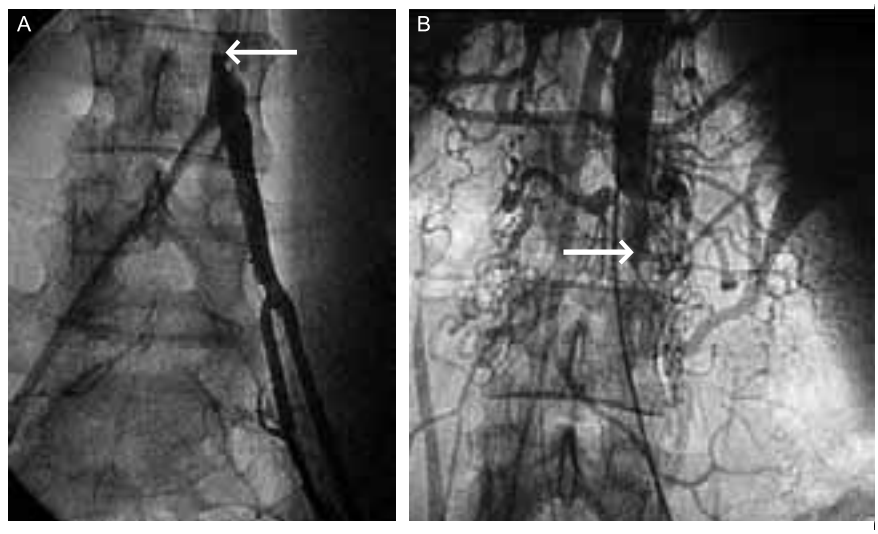

Figure 6.3 Chronic occlusion of the abdominal aorta immediately proximal to the iliac artery bifurcation (arrows). (A) Contrast injection from the left superficial femoral artey. (B) Contrast injection from the thoracic aorta descendens: imaging of multiple corkscrew-like collateral arteries bypassing the occlusion.

sent; if not, the needle should be removed and the groin compressed for 5 min. Problems that can be encountered in advancing the guidewire include severe arterial tortuosity, stenosis, occlusion (Fig. 6.3) or dissection. Left heart catheterization via the femoral approach is performed using an appropriately sized vascular sheath (we use 4–5F for diagnostic coronary angiography, 5–6F for percutaneous coronary interventions). The sheath is introduced via the guidewire and flushed with heparinized saline. In our institution, intravenous anticoagulation using heparin 5000 units is established in all cases except those undergoing diagnostic coronary angiography only. All left-heart catheters are exchanged via the guidewire, which is positioned with its tip at the level of the diaphragm. The pigtail catheter for left ventricular pressure measurements and angiography can be easily advanced across the aortic valve in the absence of aortic stenosis. If the latter is present, a 0.89-mm (0.035-inch) straight guidewire is employed to cross the valve, with its soft tip leading and pointing towards the stenotic valve and with the pigtail catheter pulled back into the ascending aorta by about 4–5 cm. In this position, the wire tip usually quivers in the systolic jet. The pigtail catheter remains fixed and the guidewire is moved towards the valve in attempts to cross it. If this is not possible, the process can be repeated using a Judkins right coronary catheter or a left Amplatz catheter, both of which allow better targeting of the valve opening than the pigtail catheter. When the guidewire has crossed the valve, it should be placed in the left ventricle, with a loop to minimize the risk of injury to the left ventricle. Relative contraindications for left heart catheterization via the femoral artery include occlusive peripheral vascular disease (Fig. 6.3), extreme iliac tortuosity, aortic abdominal aneurysm, femoral graft surgery and gross obesity.

Haemodynamic measurements during cardiac catheterization

Pressure measurements

An important goal of cardiac catheterization is precise assessment of pressure waves generated by the different cardiac chambers. Pressure is equal to force per unit area (in dynes/cm^2), force being transmitted through fluid as a wave. Considered as a complex periodic waveform, the pressure wave can be subdivided into a series of sine waves of variable amplitude and cycle frequency, whereby the sine wave frequency is expressed as harmonics or multiples of the fundamental frequency of the composite wave. This is important practically because an ideal pressure recording system must respond with identical amplitude for a given input throughout the range of frequencies contained within the pressure wave. The sensitivity of such an instrument can be defined as the amplitude ratio of the recorded (output) to the input signal. Its frequency response is the ratio between output and input amplitude over a range of frequencies of the input signal. A stiff as opposed to a flabby pressure-sensing membrane renders the recording instrument less sensitive but more frequency responsive. The useful frequency response of commonly used pressure measurement systems is less than 20 cycles/s (1 cycle/s corresponds to a heart rate of 60 b.p.m.). For example, the dicrotic notch of the aortic pressure curve contains frequencies above 10 cycles/s. The natural frequency of a sensing membrane and how it determines the degree of damping (by friction) is another important feature of the instrument, because its dynamic response is largely

determined by them. The amplitude of an output signal tends to be augmented as the frequency of the input signal approaches the natural frequency of the membrane. In this situation, the sensing membrane begins to vibrate with increasing energy, i.e. it resonates. Damping dissipates the energy of the oscillating membrane, and optimal damping dissipates the energy gradually such that there is a constant output/input amplitude ratio. Optimally, the system must be set up to have the highest possible natural frequency and optimal damping: the former is directly proportional to the size of the catheter system, and inversely related to the length of the catheter plus tubing and to the square root of the catheter and tubing compliance and the fluid density filling the system. Damping is introduced into the system by filling the tubing with a viscous medium.

Blood oxygen measurement and flow and shunt calculations

According to the Fick principle [3], the total uptake or consumption of a substance by an organ is the product of the blood flow to that organ and the arteriovenous concentration difference of the substance. Since measurements of flow, particularly cardiac output, is of central importance in invasive cardiology, the determination of blood oxygen is similarly pivotal, since cardiac output is most often calculated on the basis of the Fick oxygen method:

$$\text{Cardiac output} = \frac{\text{oxygen consumption}}{\text{arteriovenous oxygen difference}}$$

Oxygen consumption is measured directly by a polarographic method or the Douglas bag method. Alternatively, oxygen consumption can be predicted on the basis of the patient's body surface area corrected for age and gender. Thus it is assumed that resting oxygen consumption is 125 ml/m^2, or 110 ml/m^2 for older patients. Assumed versus directly obtained values for oxygen consumption are likely to introduce errors of > 10% [4].

The arteriovenous oxygen difference is determined on the basis of blood sampling from appropriately positioned catheters in the left ventricle and the pulmonary artery. The oxygen content of the arterial and venous blood samples is the product of the measured oxygen saturation (percent) and the oxygen-carrying capacity (in millilitres of oxygen per litre of blood). The former can be determined by reflectance oximetry of heparinized blood, which measures the percentage of haemoglobin present as oxyhaemoglobin. Oxygen-carrying capacity is approximated by multiplying the patient's haemoglobin (in grams per litre) by 1.36 (i.e. millilitres of oxygen per gram of haemoglobin).

Detection and localization of an intracardiac shunt can be easily performed using blood oxygen saturation as the indicator, which is obtained at many different sites within and close to the heart (i.e. 'oximetry run'; Figs 6.4 and 6.5) [5]. Quantification of the shunt is based on

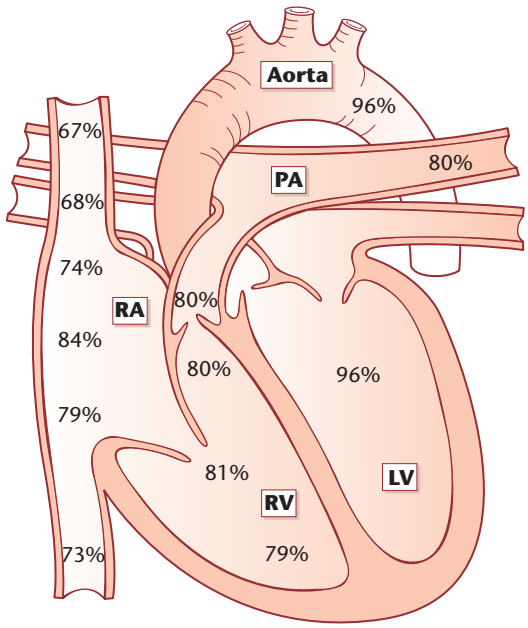

Figure 6.4 'Oximetry run' with multiple intracardiac oxygen saturation values in a patient with atrial septal defect. The 'step-up' detected in the right atrium (RA) identifies a left-to-right shunt at this location. LV, left ventricle; PA, pulmonary artery; RV, right ventricle.

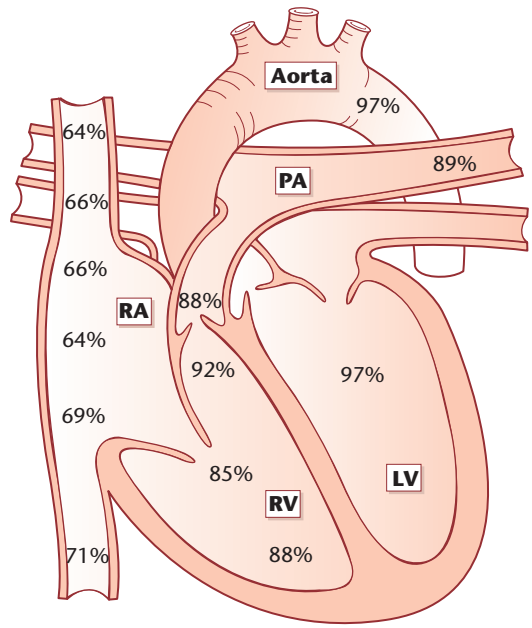

Figure 6.5 'Oximetry run' with multiple intracardiac oxygen saturation values in a patient with ventricular septal defect. The 'step-up' detected in the right ventricle (RV) identifies a left-to-right shunt at this location. LV, left ventricle; PA, pulmonary artery; RA, right atrium.

measurements of pulmonary (Q_p, l/min) and systemic (Q_s) cardiac output as outlined above. Specifically

Q_p = Oxygen consumption/(pulmonary venous oxygen content – pulmonary arterial oxygen content)

Q_s = Oxygen consumption/(systemic arterial oxygen content – mixed venous oxygen content)

The key to measuring Q_s in the presence of an intracardiac shunt is that the mixed venous oxygen content must be obtained in the chamber immediately proximal to the shunt.

Ventricular volume

Quantitative information on ventricular dimension, area and wall thickness derived from left ventricular cineangiography allows assessment of ventricular volume, ejection fraction, mass and wall stress (together with pressure measurement). Ventriculograms are usually recorded on cine film at 30–60 frames/s, and radiographic contrast agent is injected at rates of 7–15 ml/s for a total volume of 30–50 ml. For the calculation of left ventricular volume, the outermost margin of visible radiographic contrast is traced. Volume (V) is computed using long-axis (L) and short-axis (S) measurements ($V = {}^1/_6\pi LS^2$) or area–length measurements ($V = 8A^2/3\pi L$) using an ellipsoid approximation for ventricular shape. Alternatively, techniques based on Simpson's rule, which is independent of assumptions regarding ventricular shape, may be used. Correction has to be made for magnification of the ventricular image onto the image intensifier.

Vascular resistance

Calculations of vascular resistance are usually applied to the pulmonary circulation (normal value 67 ± 30 dynes/s/cm^{-5}) and systemic circulation (normal value 1170 ± 270 dynes/s/cm^{-5}). Vascular resistance (R) is determined on the basis of Ohm's law ($R = \Delta P/Q$), where Q is the cardiac output and ΔP is the pressure gradient across the pulmonary circulation (mean pulmonary artery pressure – mean left atrial pressure) or across the systemic circulation (mean aortic pressure – mean central venous pressure). The mentioned equations yield arbitrary resistance units (also called hybrid resistance units or Wood units in mmHg/l/min), and for conversion to metric units expressed in dynes/s/cm^{-5} a factor of 80 has to be used.

Valve area calculations

As valvular stenosis develops, the valve orifice poses progressively greater resistance to flow across the opening, resulting in a pressure drop across the valve. Greater flow across the valve yields greater pressure gradient. These qualitative relationships, Torricelli's law describing flow across a round orifice ($A = Q/VC_C$) and the relation between flow velocity and pressure drop ($V = C_v(2g\Delta P)^{1/2}$), form the basis of the calculation of valvular orifice area (A) using cardiac pressure (ΔP; Figs 6.6 and 6.7) and flow (Q) measurements [6]:

$$A = Q/C_vC_C(2g\Delta P)^{1/2}$$

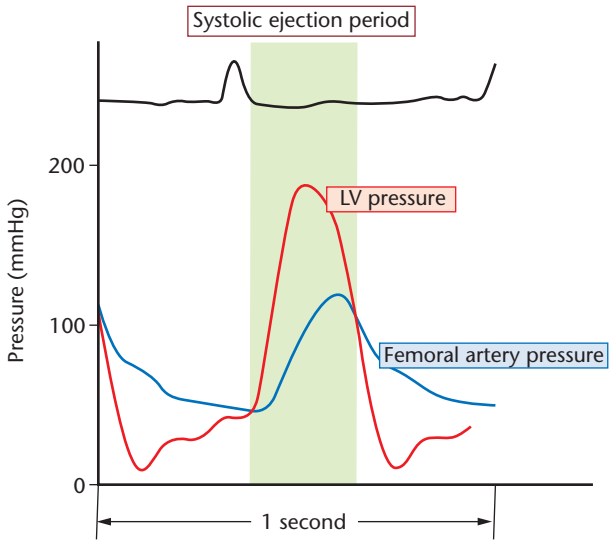

Figure 6.6 Simultaneous ECG, left ventricular (LV) and femoral artery pressure recordings in a patient with aortic stenosis and insufficiency. During the systolic ejection period, there is a marked pressure gradient. At end-diastole, aortic regurgitation leads to pressure equilibration of systemic arterial and left ventricular pressure.

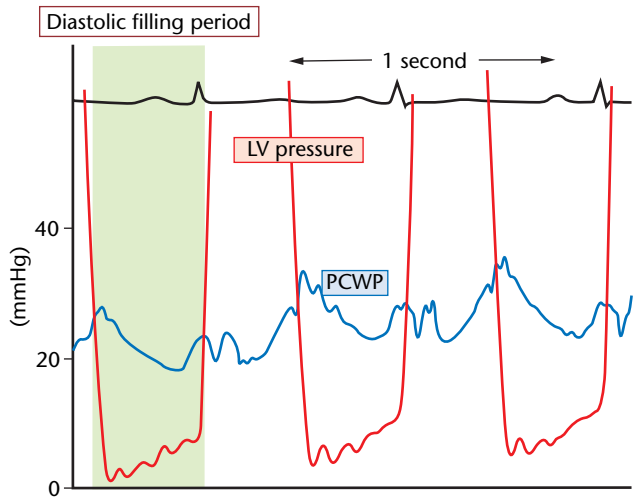

Figure 6.7 Simultaneous ECG, left ventricular (LV) and pulmonary capillary wedge pressure (PCWP) recordings in a patient with mitral stenosis indicated by the severe pressure gradient during the diastolic filling period.

where C_C and C_v are a coefficient of orifice contraction and a coefficient of velocity correcting for energy loss as pressure energy is converted to kinetic energy, respectively; and g is acceleration due to gravity (980 cm/s^2). In the case of aortic valve area (AVA) and mitral valve area (MVA), the following specific formulae can be used:

$$\text{AVA} = (\text{cardiac output/systolic ejection period} \times \text{heart rate})/44.3\Delta P^{1/2}$$

$$\text{MVA} = (\text{cardiac output/diastolic filling period} \times \text{heart rate})/37.7\Delta P^{1/2}$$

Invasive imaging techniques and coronary morphology

Coronary angiography

Consent for the procedure, risks and benefits of angiography

Although the techniques of angiography and angioplasty should only be performed by qualified and dedicated operators, every cardiologist treating adult patients must be aware of the indications, risks and potential benefits of this procedure. Table 6.1 indicates the complications in a general population but the data are too old to reflect practices such as the radial approach or the use of new contrast agents [7]. These figures are a good indication for average patients but they must be individualized for morbid obesity, diabetes, peripheral vascular disease and poor left ventricular function. The most frequent complications of angiography occur at the catheter entry site. The 2–5% incidence currently quoted is based on series using a femoral approach before the use of 4F and 5F catheters. Closure devices have reduced the time to ambulation, increased patient comfort and shortened the hospital stay but do not appear to have modified the bleeding risk and have added some rare specific new complications (infection, embolization or arterial stenoses due to components of the closure device or procoagulant factors injected into the bloodstream). Large haematomas requiring drainage, blood transfusions and prolonged bed rest, severe obesity and hospitalization are rare and often consequent to inability to comply with bed rest or clinical need for prolonged anticoagulation. Other more serious vascular complications include pseudo-aneurysm, fortunately often closed with ultrasound-guided compression and/or selective thrombin injection, arteriovenous fistulae, arterial thrombosis and distal embolization. The most dreadful but fortunately rare vascular complication is retroperitoneal bleeding, mostly managed conservatively, while iliac or aortic dissections tend to seal spontaneously if antegrade flow is preserved. For radial procedures a negative Allen test is sufficient to exclude critical hand ischaemia even in cases of total radial occlusion (1–4% of patients), and large haematomas are rare. The possibly serious complications of the brachial approach, percutaneous or surgical, can be prevented by not using this route, which can almost always be substituted by radial puncture. The frequency of serious complications, such as death, myocardial infarction or cerebrovascular accident with permanent damage, is very low (0.1–0.2%). Myocardial infarction is often due to catheter-induced ostial damage due to pre-existing severe pathology or the presence of unstable plaques at risk of embolization and can potentially be treated with angioplasty and stenting. Stroke is the consequence of thromboembolism due to thrombi in the access sheath or the catheter, dislodgement of plaques from the iliac vessels or aorta, calcium from the aortic valve or thrombi in the left ventricle. Meticulous attention to catheter flushing and atraumatic wire-lead insertion can reduce but not eliminate the risk, whilst there is no evidence that systemic heparinization is required for diagnostic catheterization. Death can be the direct consequence of infarction, stroke or cardiac and vascular perforation but

Table 6.1 Complications of diagnostic angiography

	Incidence (‰)	
Death	1.0–1.5	
Myocardial infarction	1.0–2.0	
Neurological events		Cumulative incidence 1.5–2.5‰
Permanent	1.0–2.0	
Transient deficit	3.0–5.0	
Ventricular fibrillation/tachycardia requiring defibrillation	1.0–2.0	
Vascular/bleeding complications		
Requiring surgery or late US-guided compression or thrombin injection	10–20	
Managed conservatively	10–50	

US, ultrasound.

can also be induced by late complications of prolonged hospitalizations triggered by relatively minor complications such as bleeding events and renal dysfunction. A clear explanation of other more frequent albeit minor and promptly controlled adverse effects helps the patient to accept them without unnecessary stress. Reactions to the contrast medium (nausea, vomiting, rash) are very rare and the amount of contrast used for a diagnostic angiogram cannot induce permanent renal damage unless a severe previous dysfunction was present. Bradycardia and hypotension develop because of periprocedural vasovagal reactions, prevented by generous sedation, liberal local anaesthesia, reassurance and appropriate filling with intravenous fluids. Other major arrhythmias (ventricular fibrillation and tachycardias, supraventricular arrhythmias) can be induced by catheter dumping, excessively prolonged injection or mechanical stimulation.

Catheter selection and manipulation

Improvements in catheter technology have allowed the flow rate obtained with old 8F (1F = 0.33 mm) diagnostic catheters to be achieved with 6F thin-walled catheters and satisfactory coronary opacification with 4F and 5F diagnostic catheters. Newly developed automatic injectors with adjustable increases in injection pressure have the potential to allow more consistent homogeneous opacification of large left coronary arteries through 4–5F catheters. Pre-shaped catheters (e.g. Judkins, Amplatz) can be used for injection of both coronary vessels, not only via the femoral and left radial or brachial approach but also the right radial/brachial approach. A reduction in pressure with ventricularization (low diastolic values) of the pressure waveform indicates that the catheter is obstructing flow. This may be caused by the presence of a true ostial stenosis, by the small size of the coronary ostium or by deep engagement of the catheter beyond the left main or first curve of the right coronary artery, often causing ostial spasm. Injection of intracoronary nitrates and gentle test injections with careful withdrawal of the catheter can identify and solve these various problems. It is very important not to start the injection before the angiographic acquisition in order to identify calcifications or late staining of contrast. Contrast injection should be sufficiently rapid and large to fully replace the epicardial vascular volume and avoid the phenomenon of streaming or incomplete visualization. When the proximal coronary segments are fully opacified, the prolongation of injection offers no diagnostic advantage, increases the contrast volume used and carries potential risks in vessels with a large epicardial volume and slow flow. On the other hand, angiographic acquisition should be prolonged to allow visualization of the distal vessels, identification of TIMI flow and characterization of type of dissection (with/without persistence of contrast at the end of the injection). An important determinant of injection duration is the need to visualize collaterals for occluded vessels, which also means adjustment of the view to include the recipient vessel in the image.

Left coronary artery

CANNULATION

In the majority of cases a standard 4.0 Judkins catheter can be used. Occasionally, in small females a 3.5-mm or even 3.0-mm left Judkins catheter can be used as first choice; if it is known by previous invasive or non-invasive examination that there is an enlarged ascending aorta, a 4.5 or 5.0 left Judkins catheter can be preferred. The optimal view for engaging both the right and left coronary arteries is the left anterior oblique view where the ostium is not covered by the aorta (Fig. 6.8). The left coronary artery requires only minimal catheter manipulation; the J-tipped 0.89-mm (0.035-inch) wire is

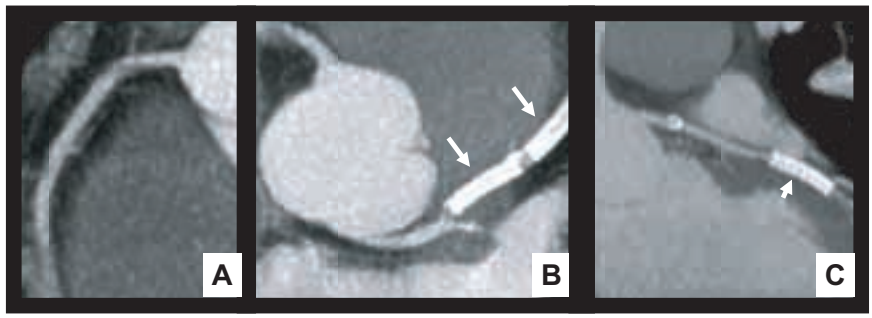

Figure 6.8 Multislice computerized tomography (B) shows the origin of both coronary ostia in an axial view simulating an angiographic spider view (note the two stents in the proximal left anterior descending artery, arrows). The two multiplanar reconstructions on the right and left delineate the ostium of the right coronary artery (A) and left coronary artery (C) with a stent easily visible in the left circumflex artery (arrow). If cannulation of the arteries is performed using an anteroposterior view, a common mistake repeatedly performed, injections in the aortic root will never catch the position and level of the coronary ostia. It is also intuitive that the left catheter will often directly cannulate the left coronary ostium while anterior rotation is required to engage the right coronary ostium.

atraumatically advanced to the level of the aortic valve and the tip of the previously flushed Judkins catheter is opened as low as possible pointing to the left coronary ostium. When retrograde bleeding ensures the catheter has been purged of air, a pressure line is connected and a test injection performed, often showing that the catheter is already engaged or is located immediately below or in front of the ostium. In the latter case, gentle withdrawal of the catheter tip (helped by asking the patient to take a deep breath) will allow engagement of the catheter tip in most cases. If the tip of the catheter immediately closes in the ascending aorta, prolonged attempts with the same catheter should be avoided and rapid switching to a larger catheter is probably advantageous in terms of time lost and contrast used. When it is known that the coronary ostia are of an unusual size or position (aortic valve disease, Marfan's syndrome, congenital heart disease), it is probably worthwhile performing an aortic angiogram in the left anterior oblique view in order to guide catheter selection, since this may require unusual shapes (e.g. left Judkins 6.0 or left Amplatz 2.0 and 3.0).

OPTIMAL VIEWS (Fig. 6.9)

The main advantage of the so-called spider view (left 40–55°, caudal 25–40°) is to delineate the branching of the left main coronary artery from the aorta and its bifurcation into the left anterior descending (LAD) and left circumflex (LCX) arteries (or trifurcation if an intermediate artery is present). For this reason it is better to acquire this view first in order to exclude this most fearsome lesion location, at risk of plaque disruption during catheter injection and which may require an urgent surgical approach. The LAD artery is greatly foreshortened in the mid and distal segments in this view but stenosis of the proximal segment or of the ostium of the first diagonal branch is often optimally shown. The LCX artery, on the other hand, is optimally opened in its proximal and mid segments. The classical 30–40° right view is limited by the frequent superimposition of the proximal LAD and LCX and should be replaced by shallow right caudal views, which also offer less movement during respiration for angioplasty and which minimize irradiation. A smaller angulation to the right (10–20°) avoids superimposition of the catheter and the spine and, combined with relatively skewed caudal angulations (30–40°), opens the angle between LAD and LCX (and intermediate branch, if present) sufficiently to obtain optimal images of the proximal and mid segment of the LCX and bifurcation of its marginal branches. The image is of more limited interest for the proximal and mid LAD because of the frequent superimposition of diagonal and septal branches but remains the most important view for the distal LAD. Skewed cranial views (40° or more), with 5–10° angulation to the right to avoid superimposition of the catheter and the vertebral spine, elongate the proximal and mid LAD and open the bifurcation of the proximal diagonal branches which run to the right, clearly distinguished from the septal branches which run to the left of the screen. The segments that are foreshortened in this view are the distal LAD and the proximal LCX but this view is also ideal for visualizing the distal posterolateral branches of the LCX and, in the 15–20% of cases with left dominance or codominance, the left posterior descending artery (PDA). In the left cranial view (30–45° left, 25–40° cranial) the LAD is further elongated by asking the patient to take a deep breath and maintain breath-holding during injection. The cranial view also offers optimal views of the mid and distal segments of the LCX, and is especially useful in the presence of a dominant LCX. The lateral view is far from standard in modern coronary angiography because the additional value of this view is quite limited, only providing excellent visualization of the mid/distal LAD around the apex, information which is at most complementary to right caudal views. Occasionally, however, eccentric short lesions of the proximal and mid segment of the LAD might be covered by septal or diagonal branches in all the conventional previously reported views and can be better visualized in the lateral projection, sometimes using variable cranial or caudal angulations to ensure no superimposition from the diagnostic catheter and side branches.

Right coronary artery

CANNULATION

For visualizing the right coronary artery (RCA) the standard strategy uses a 4.0 right Judkins diagnostic catheter in the left anterior oblique view. In this view, the catheter must be rotated to point to the left of the screen and this is better achieved when the rotation is performed during a slow pull-back motion of the catheter from the right coronary sinus. Breath-holding after a deep inspiration may facilitate this manoeuvre. In 10–15% of cases a high origin of the RCA complicates the search for the right coronary ostium. Even in the presence of a hypoplastic non-dominant RCA, selective injection is still required because small proximal branches can be an important source of collaterals for occluded vessels. It is often possible to obtain a semi-selective injection with the Judkins catheter that will further guide catheter selection. A multipurpose catheter should be used for downward-looking RCAs, and Amplatz right 2 or Amplatz left 1 or 2 are required in patients with high take-off and/or with dilatation of the coronary sinus and ascending aorta. Careful review of the images should be performed before finishing the examination in order to avoid missing a

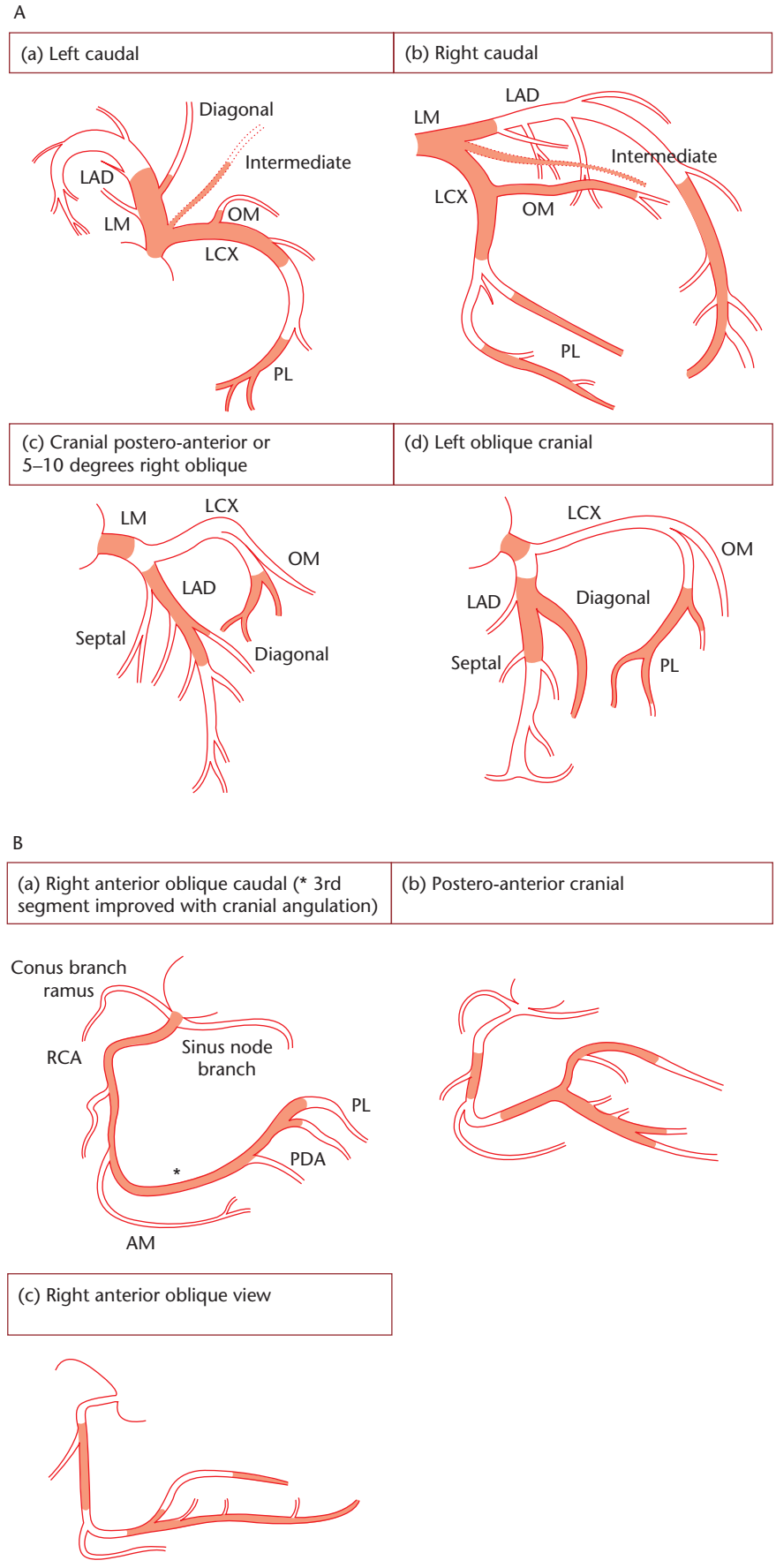

Figure 6.9 The most frequent angiographic projections: their relative merits in the visualization of different coronary segments are indicated.

separate origin from the aorta or an abnormal origin from the proximal RCA of the LCX, the most frequent coronary anomaly, or the separate origin of a conus branch that provides important collaterals to occluded arteries.

OPTIMAL VIEWS

The RCA has few branches in the first, second and third segments (from the ostium to the crux cordis) and often two views (left anterior and right anterior oblique views) are sufficient to identify all stenoses, including eccentric stenoses. The lateral view might be ideal for assessment of the mid segment of the artery and may occasionally be used as a working projection for occlusions in this segment or stent positioning. The problems with these standard views lie in the difficulties of interpretation in the presence of stenoses at the crux cordis or at the ostia of the PDA and posterolateral branches. Cranial angulation (30°) of the left anterior view is often sufficient to solve diagnostic questions but many operators prefer to use as a routine view a cranial (30°) postero-anterior view of the RCA, which clearly delineates the region of the crux cordis and possible lesions of the PDA or posterolateral branches.

Venous bypass grafts and left internal mammary artery

Aortic anastomoses of radial arteries or venous grafts are rarely indicated by radio-opaque markers positioned at the time of operation (a neglected practice in cardiac surgery), but can often be visualized in the left anterior oblique view a few centimetres above the ostium of the RCA by dragging the right Judkins catheter along the right profile of the ascending aorta. Although the position and direction of aortic anastomoses is influenced by the surgical technique, in general the anastomosis for the RCA tends to be the lowest and to have a more vertical origin from the aorta, so that selective cannulation may require the use of a multipurpose catheter. Grafts for the marginal or diagonal branches often require catheter rotation and occasionally catheters with a longer tip (right or left Amplatz 1 and 2, left coronary bypass catheters) are required. Instead of wasting a large amount of contrast in locating the ostium, it can be cost-effective to perform an aortogram with the pigtail catheter slightly above the usual supravalvular position, immediately above the level of the RCA, in order to ascertain at least the number of open grafts. A limitation is obviously the inability to detect grafts with extremely slow flow; however, these are often identified because of the presence of contrast staining in cases of recent occlusion.

For the left mammary artery, the origin of the subclavian arteries can be more easily engaged in a left anterior oblique view (40–60°). Complete visualization of the internal mammary is of paramount importance because it is crucial not only to know whether the left internal mammary artery is patent but also to exclude the presence of distal stenoses (anastomotic or in the distal native vessels) and to visualize collaterals for other occluded vessels. The selective visualization of the mammary artery is more easily achieved with a specially designed catheter, which has a longer tip than the classical right Judkins catheter. In case of failure, other types of modified left internal mammary catheter with a hook-like shape can be tested. Selective engagement is often made difficult by the presence of severe tortuosity of the proximal subclavian artery, which makes manipulation of the left internal mammary catheter very difficult. The problems are greater for the right internal mammary artery because of the more tortuous track from the ascending aorta. A power injection through 6F large-lumen diagnostic or guide catheters can occasionally avoid the troubles and risks of a true superselective injection of the internal mammary arteries in very tortuous and frail subclavian vessels, reducing brachial flow with a pressure cuff inflated around the arm. Alternatively, a radial approach (more often left as the left mammary is most frequently used) can be the safest solution if multiple attempts from the groin remain unsuccessful. The distal anastomosis of the mammary artery is often optimally opened in the lateral view, which is also ideal for excluding adhesion of the left internal mammary to the sternum, a condition that may increase the risk of surgical reintervention with median sternotomy.

Angiographic report

Coronary angiography requires a report indicating the vascular access site, type and size of catheters used, type and total amount of contrast, allergic reactions or other procedural complications, closure devices, aortic pressure and heart rate and rhythm before and after the procedure. After having described the type of dominance and possible anomalies of origin and location, each individual coronary segment (from the left main to three segments for the LAD and RCA, two for the LCX plus the main diagonal, intermediate, marginal and posterolateral branches) and the presence of a lesion must be indicated, with description of the characteristics as indicated in Table 6.2. While the terms 'irregular' and 'mild' can be used to describe stenoses of < 30% and 30–50%, stenoses of 50% or greater require attempts at visual estimation of severity based on comparison with the closest normal-looking reference segment. The presence of thrombus and irregularities of stenosis contour are often more subjective, although the presence of multiple unfavourable characteristics (graded ABC in the ACC/AHA Task Force definitions [8]) is still predictive of immediate success and complications.

Besides the pressure measurements, in the angiographic report the operator must indicate the semi-

Table 6.2 Qualitative definitions of angiographic lesions

Eccentric: luminal edge in outer one-quarter of the normal lumen
Irregular: ulceration, aneurysm or saw-tooth pattern
Discrete: estimated lesion length < 10 mm
Tubular: estimated lesion length 10–20 mm
Diffuse: estimated lesion length ≥ 20 mm
Ostial: within 3 mm from origin
Angulated: ≥ 45° angle between centre-line of proximal and distal segments
Bifurcational: branch ≥ 1.5 mm involving the lesion
Calcified: readily apparent densities within the vessel wall at the site of the lesion
Functionally occluded (99% diameter stenosis): antegrade flow TIMI 1
Totally occluded (100% diameter stenosis): antegrade flow TIMI 0 with/without opacification from collaterals
Thrombotic: intraluminal filling defect separated from the vessel wall in two views (with or without contrast staining)

Type A (ACC/AHA): discrete, concentric, non-angulated, readily accessible, regular, non-calcified or minimally calcified, non-occlusive, non-ostial, non-bifurcational, non-thrombotic lesion
Type B: tubular, eccentric, with two ≥ 75% bends proximal to the stenosis, angulated (but less than 90°), irregular, calcific, occluded (functional or > 3 months), ostial, bifurcational (side branch accessible for wire protection), thrombotic lesion
Type C: diffuse, three ≥ 75° bends in the proximal segment, angulated (≥ 90°), occluded > 3 months old or unknown duration), bifurcational (side branch non-accessible), degenerated vein graft

quantitative estimate of left ventricular cavity size and the presence and type of wall motion abnormality (from normal to hypokinetic, akinetic or dyskinetic). Five regions should be reported for the right anterior oblique view and two for the left anterior oblique view (Fig. 6.10). The presence of thrombi or other filling defects and abnormalities in shape must also be reported.

Mitral insufficiency is graded 1–4 according to the presence and amount of regurgitant flow (Table 6.3) and, for the most severe levels, also allows delineation of the contours of the left atrial cavity. Obviously, the size of the left ventricular and, especially, left atrial cavity, the acuteness of the process, the position of the catheter and rate and volume injected may modify this semi-quantitative assessment, which remains subjective, although the distinction between non-surgical (grade 1 and 2) and possible surgical (grade 3 and 4) severity is established in most patients. Whilst angiography is not the easiest technique for defining absolute volumes, relative changes such as left ventricular ejection fraction must be regularly measured using the quantitative packages all digital systems offer.

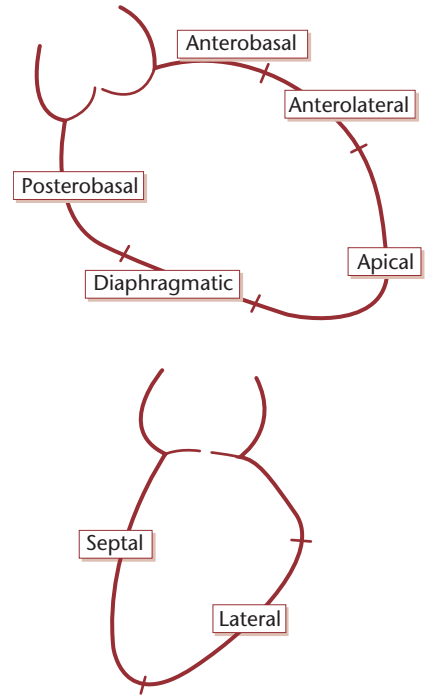

Figure 6.10 Regional wall motion during left ventriculography as assessed in the right and left oblique views.

Table 6.3 Semi-quantitative classification of mitral regurgitation

Trivial (grade 1 or 1+/4+): contrast material enters the left atrium during systole without filling the entire atrial cavity and is cleared in the subsequent beat
Mild (grade 2 or 2+/4+): contrast opacification of the left atrium is less dense than the opacification of the left ventricle but contrast is not cleared with each beat
Moderate/severe (grade 3 or 3+/4+): opacification of the left atrium is as dense as the opacification of the left venticle
Severe (grade 4 or 4+/4+): opacification of the left atrium greater than that of the left ventricle and/or complete atrial filling in one systole and/or contrast opacifies the pulmonary veins

Angiography in heart valve diseases and cardiomyopathies

The progress of echocardiography has made angiography redundant for the evaluation of many valvular disorders and cardiomyopathies. When the severity of valve disease requires surgical replacement or repair, coronary angiography is required in all candidates above 40 years of age (or younger if multiple risk factors or anginal symptoms are present). While no other acquisitions or injections in heart cavities are strictly necessary, in the absence of severe haemodynamic compromise or renal impairment, left ventriculography is recommended for all

patients with mitral valve disease and aortic insufficiency. Besides confirming the presence and severity of mitral regurgitation or indirect signs of mitral stenosis, the examination will define the presence and pattern of left ventricular dysfunction. For aortic stenosis, crossing the valve when the need for valve replacement is already unequivocally confirmed by symptoms and non-invasive tests is not recommended. If, however, there is any doubt concerning the accuracy and reproducibility of the Doppler flow velocity measurement, the additional minimal risk of embolization and perforation while crossing a stenotic and calcific aortic valve becomes clinically acceptable. Pre-shaped catheters (right or left Judkins or Amplatz) are more likely to obtain good orientation of the straight floppy end of a conventional or hydrophilic wire. Once the gradient is measured, for left ventriculography it is recommended that a pigtail catheter for injection is advanced over a 0.89-mm (0.035-inch) J-tipped 260-cm wire. Occasionally, when pressure measurements in the right heart are required to better define the severity of mitral valve stenosis and pulmonary hypertension, injection of the right ventricle can offer additional data to confirm presence and severity of right ventricular dilatation and tricuspid regurgitation. In the laevophase, after having delineated the size of the arterial and venous pulmonary tree and circulation time, the dilatation of the left atrium and abnormal movement of the mitral cusps can be observed. In patients with aortic valve disease, the presence and severity of calcifications of the aortic cusps and ascending aorta, number of cusps and deformity of cusp opening, and presence of a pre-shaped aortic jet can be judged from both left ventriculography and aortography. The semi-quantitative assessment of the degree of aortic dilatation, the severity of aortic insufficiency (Table 6.4) and the description of irregularities and calcifications of the aortic wall are other key features to describe in a patient with aortic valve disease, hypertension or Marfan's syndrome.

Table 6.4 Semi-quantitative classification of aortic regurgitation

Trivial (grade 1 or 1+/4+): contrast visible in the left ventricle, without reaching the apex, clears during each heart beat
Mild (grade 2 or 2+/4+): contrast opacification less dense than that of the ascending which does not clear during a single heart beat
Moderate/severe (grade 3 or 3+/4+): opacification of the left ventricle as intense as that of the ascending aorta
Severe (grade 4 or 4+/4+): opacification of the left ventricle more intense than that of the ascending aorta and/or full left ventricular cavity opacified in one beat

Intracoronary ultrasound imaging

When intravascular ultrasound (IVUS) was introduced 15 years ago, the pioneers of this technique believed it could replace angiography in the same way that endoscopic techniques have replaced conventional radiological assessment in gastroenterology. There are a number of reasons why this has not happened.

1. Unlike endoscopy, the technique does not stand alone, since it requires fluoroscopy and contrast injection to advance the IVUS probe.
2. Complete IVUS examination of all the major coronary vessels and their branches including the distal segments is impossible.
3. Despite the fact that the fundamental insights derived from IVUS have dramatically improved our techniques of percutaneous revascularization and our approach to atherosclerosis, no studies have shown clinical benefit over angiographic guidance alone.

Image acquisition

Miniaturized flexible intracoronary ultrasound probes of 2.8F (Atlantis Boston-Scientific) and 2.9F (Eagle-Eye, Volcano Endosonics), compatible with conventional 6F guiding catheters, generate high-resolution cross-sectional images by spinning a single piezoelectric crystal at 360° or by activating in sequence multiple (64) transducer elements. Larger probes with lower frequencies to improve penetration (10–15 MHz) are used for intracardiac or intravascular examination of peripheral arteries but their use is illustrated with the specific technique of application. To add a third dimension (length) to the tomographic representation of the vessel wall, the catheter (in multi-element array systems) or the inner driving cable of the ultrasound crystal (in mechanical probes) is connected to a precise pull-back system. Some investigators prefer the greater resolution and dynamic range that a mechanical system with a single large crystal (centre frequency 40 MHz) can offer and consider favourably the unusual modality of imaging through a steady distal sheath that remains in position during the IVUS examination, with accurate pull-back allowed by the absence of friction against the vessel wall (Table 6.5).

The safety of the technique was investigated in the early days [9], when stiffer and larger probes were available, although these studies showed that the main complication was spasm with dissection and thrombosis limited to before and after angioplasty. More interestingly, no difference was observed in the mean diameter of arteries of heart transplant recipients repeatedly instrumented or non-instrumented with ultrasound probes [10].

Table 6.5 Protocol of intravascular ultrasound image acquisition

Before imaging
Connection of the ultrasound catheter with the imaging console
Patient demographics and vessel examined entered
For mechanical transducer, accurate flushing with a small syringe
Connect the catheter/handle to the motorized pull-back system set to 5 mm/s
Activate and test that an image is generated before insertion
Inject 0.1–0.3 mg nitroglycerine or 1–3 mg isosorbide dinitrate according to pressure and risk of spasm

During imaging
For electronic catheters, before intracoronary insertion withdraw the guiding catheter, obtain an image immediately outside the coronary ostium and and subtract the ring down artefact
Advance the catheter distal to the segments of interest
Optimize the ultrasound setting (depth and gain), start tape recording and/or digital archiving and activate mechanical pull-back
Check ECG and pressure during pull-back to exclude prolonged ischaemia, especially during pre-dilatation imaging
Complete the pull-back, in general waiting until the catheter reaches the coronary ostium or is withdrawn inside the guiding catheter
Avoid stopping mechanical pull-back at all cross-sections of interest, which should be recalled from the tape or digital archive
Re-insert the catheter for acquisition of images in a segment of interest only if there are doubts about image interpretation, for example if there is a need to use saline flushing in a specific segment to confirm the presence of ulcerated plaques, dissections, lumen/intima border in the presence of slow flow or if there is a need to use contrast injection to identify the location of a given cross-section along the vessel

After imaging
Flush the ultrasound catheter (particularly mechanical probes) and clean it
Reposition the catheter ready for a new pull-back
Identify and perform measurements (diameter and areas) of the most important cross-sections (usually reference segment, proximal and/or distal or both, minimal cross-sectional area within the lesion or minimal cross-sectional stent area or other segments of interest)
Allow longitudinal display of the image after longitudinal reconstruction (long view) and measure the length of the segment of interest (e.g. length of segment to be stented)
Store the images in a DICOM digital format ideally with the same CD or in a server with the same identification of the DICOM angiographic images
Prepare a report including measurements and qualitative image interpretation

Image interpretation

MEASUREMENTS

A truly normal intima is beyond the axial resolution of IVUS which, even at 40 MHz, is greater than 70 μm *in vivo*. However, in most patients treated for coronary artery disease, almost all the sites explored in the coronaries will exhibit much intimal thickening, due to ageing as well as to early atherosclerotic changes, and which is separate from the underlying adventitia. The acoustic interface between the echo-poor muscular media and the intensely bright collagen and elastic fibres of the adventitia induces an appearance often described as 'threelayered' or 'target-like'.

Table 6.6 indicates the main measurements available with ultrasound. Both the European Society of Cardiology [11] and the American College of Cardiology [12] provide guidelines regarding common nomenclature and methods of qualitative and quantitative analysis of IVUS images. The most obvious measurement available with a technique that provides a circumferential image of the vessel is area, with the external contour drawn at the leading edge of the surrounding structures (Fig. 6.11). The area of the lumen and the area within the external elastic membrane (EEM), also called total vessel area, are the two most important dimensions and their difference provides the area of the intima–media complex. After treatment, stent area can also be measured but this is equivalent to the lumen area immediately after deployment unless a strut is not apposed to the vessel wall or there is plaque prolapse narrowing the lumen. In the era before the advent of drug-eluting stents (DES), weeks and months after stent deployment a rim of tissue of variable thickness constantly covered the stent struts, allowing easy definition of the neointimal area, calculated as the difference between stent area and lumen area at follow-up. The antiproliferative effect of DES often reduces intimal coverage to a thickness beyond the resolution capabilities of ultrasound.

Linear measurements are also possible with ultrasound and are required when IVUS is used to size devices

Table 6.6 Intracoronary ultrasound measurements in common use

Measurement	Units	Definition	Comments
Lumen area	mm^2	Area inside the intimal leading edge	If separation between intima and lumen is unclear because of lumen irregularities (ulcus within plaques of dissections) or because of slow flow, injection of saline may facilitate contour detection. Ideally do not perform measurement during saline infusion (increased lumen because of higher pressure, and different speed of ultrasound in saline than in blood)
EEM area (total vessel area)	mm^2	Area inside the leading edge of the adventitia	Do not trace if > 90° of vessel circumference not visible because of shadowing or attentuation
Stent area	mm^2	Area inside the stent struts	Stented area corresponds to lumen area unless a strut is not apposed to the vessel wall (under-expansion or localized aneurysm) or there is plaque prolapse
Plaque plus media area	mm^2	Difference between EEM area and lumen area in a corresponding cross-section	Not detectable if obscured by the presence of superficial calcium or stent struts
In-stent neointimal area	mm^2	Difference between stent area and lumen area images in images acquired late after stent deployment	Can be missed because of very poor echogenicity of the intimal areas, difficult to distinguish from the lumen, especially in cases of subocclusive restenosis or because (drug-eluting) stent is reduced to a micrometric rim of thickening below the threshold of measurement with ultrasound
Percentage plaque area	%	Percentage of EEM area occupied by plaque and calculated as: (EEM area – lumen area)/EEM area × 100	
Percentage neointimal area	%	(Stent area – lumen area)/stent area × 100	
Plaque eccentricity index		Measurement of plaque eccentricity calculated as the ratio between minimal and maximal plaque plus media thickness	1 indicates concentric plaque, < 1 indicates increasing plaque eccentricity. **NB** American authors tend to use the reverse index, with larger numbers indicating progressively greater eccentricity
In-stent lumen volume	mm^3	Lumen volume inside the stent segment calculated with multiple equispaced area measurements and Simpson's rule or with automatic contour detection of multiple cross-sectional and longitudinal contours	Immediately after stent deployment, area should be equal to stent volume
Stent volume	mm^3	Volume inside the stent	Easily calculated because of the bright stent landmarks
Neointimal stent volume	mm^3	Difference between stent volume and lumen volume inside the stent	More difficult to assess with drug-eluting stents because of the extremely thin rim of intimal hyperplasia
Percentage intimal volume in-stent	%	(Stent area – lumen area)/stent area × 100	Ideal biological indicator of intimal proliferation inside a stent

EEM, external elastic membrane.

for vessel dilatation, such as balloons and stents. Unfortunately, the vessel lumen and, especially, the area inside the EEM are rarely truly circular because plaques mostly grow eccentrically or because the probe is not perfectly aligned with the long axis of the vessel, generating an oblique cut of the vessel. Two linear measurements are normally required for each cross-sectional image: minimal and maximal diameter. Minimal and maximal plaque thickness are also used to provide an index of plaque eccentricity (Fig. 6.11). In clinical practice, area and linear measurements are rarely taken in more than two or three locations, corresponding to the minimal lumen or stent area and to a reference site outside the stenotic segment or the stent. This last site is more subjective, although a cross-section with the largest area and/or the smallest plaque burden within 5–10 mm of the margins of the

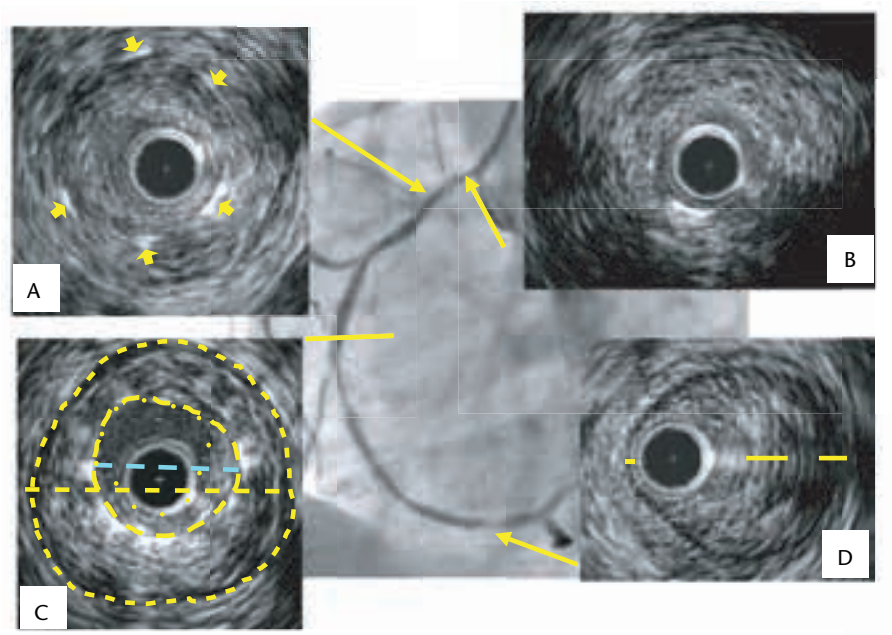

Figure 6.11 Four intravascular ultrasound cross-sectional images corresponding to the positions indicated in the left anterior oblique angiographic image of a right coronary artery in a patient with diffuse restenosis 3 months after multiple stents were implanted from the ostium to the mid segment. (A) Gross under-expansion and diffuse hyperplasia within the stent indicated by the bright dots/strips (arrowheads). (B) In this cross-section at the level of the vessel ostium the absence of stents is obvious, with restenosis probably due to recoil of the large concentric lesion not covered during the initial procedure. (C) Lumen (inner dotted line), stent (dashed lines around circumference and across maximal diameter) and vessel (external elastic membrane, EEM) area (outer dotted line around circumference and across maximal diameter). Using the 1-mm divisions of the calibration grid, it is apparent that the stent diameter is 2.3 mm compared with an EEM diameter of 4.5 mm. (D) Distal stenosis: the extreme eccentricity (0.2 mm minimal plaque thickness, 1.9 mm maximal plaque thickness) cannot be understood with ultrasound.

stenotic segment or stent edge is often used. If there is obvious vessel tapering, a proximal and distal reference should always be measured. The comparison between vessel area in the stenosis and at a reference site allows calculation of the remodelling index. This is able to confirm the main mechanism of plaque accommodation *in vitro* (described by Glagov in pathology studies) and verifies the presence of total vessel enlargement and positive remodelling; also, but more rarely, it allows determination of the presence of negative remodelling, both as a spontaneous process or as a consequence of shrinkage promoted by angioplasty (Fig. 6.12). In research applications, especially assessment of plaque changes over time, IVUS must overcome its limitations in order to provide precise identification of the same site in serial examinations and to obtain a more reliable assessment of biological processes involving multiple vessel segments (restenosis or progression of atherosclerosis), accomplished by averaging the lumen, stent and/or vessel measurements over a certain length, with longitudinal measurements determined by steady pull-back at known speed during examination. This allows either estimation of volumes by measurement of multiple equidistant cross-sections (Simpson's rule) or precise measurement by interpolating longitudinal and cross-sectional contours [13]. Unfortunately, the lack of sharp contours between lumen and intima and, especially, between intima–media and adventitia rarely allows measurements so perfect as not to require tedious manual corrections of the automated contour detection methods now incorporated in all modern IVUS equipment.

QUALITATIVE ASSESSMENT

The echo-intensity of the different plaque components in the image varies according to the system settings and requires a standard intensity for comparison. The adventitia, relatively spared by the disease process, offers a natural site for comparison of the different components of the atherosclerotic plaque, which are rarely homogeneous and often contain various components of different echo-reflectivity (Fig. 6.13). The presence of acoustic shadowing and reverberations are specific landmarks of the presence of calcifications, which can be detected with greater sensitivity than with angiography, and can be measured as their circumferential extension (in degrees or quadrants), length and location within the plaque (from superficial subendothelial calcium speckles to deep deposits at the base of the plaque). Plaques with low

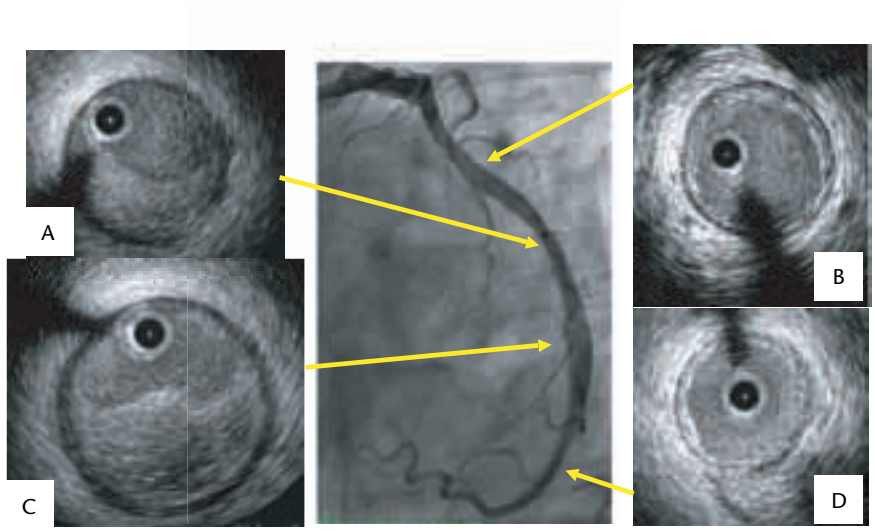

Figure 6.12 Four intravascular ultrasound cross-sectional images corresponding to the positions indicated in the left anterior oblique angiographic image of a left circumflex artery in a patient with recent ST-elevation lateral myocardial infarction 3 days after thrombolysis. The absence of severe residual stenosis is confirmed by ultrasound, which shows extreme positive remodelling when the cross-sections at the level of the culprit lesion (A and C) are compared with the proximal (B) and distal (D) reference cross-sections, where only a concentric rim of fibrous plaque is observed. Note that the eccentric plaque in (A) has a much lower echogenicity than the surrounding adventitia and that the inhomogeneous texture of the plaque in (C) is due to plaque rupture with channels communicating with the lumen inside the plaque. The absence of regular concavity of the intimal edge suggests recent thrombosis.

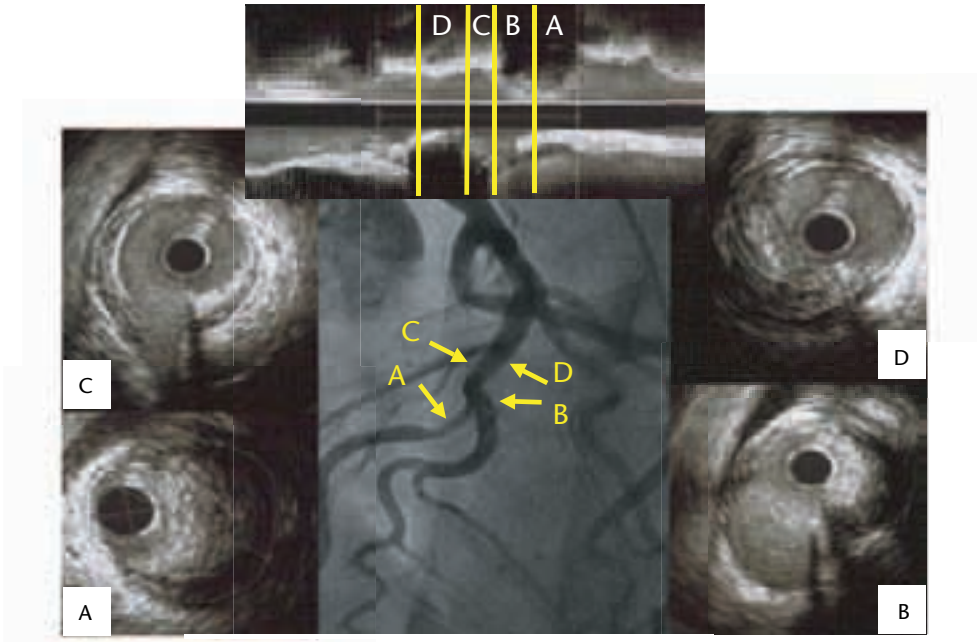

Figure 6.13 Four intravascular ultrasound cross-sectional images corresponding to the positions indicated in the cranial left anterior oblique angiographic image of a left anterior descending coronary artery in a patient with a lesion immediately distal to the bifurcation of a large diagonal branch. The heterogeneous plaque composition and involvement of the main vessel proximal to the bifurcation are clearly displayed in the longitudinal reconstruction of the multiple images acquired during pull-back. (A) Main subocclusive eccentric fibrotic lesion with no lumen around the ultrasound catheter. (B) Cross-section at the origin of the diagonal branch (below) shows normal intima in the branch but a large eccentric plaque opposite the bifurcation. More proximally (C) a fibrous concentric plaque is observed, with a large inhomogeneous eccentric plaque in (D) at a level which appears angiographically normal.

echo-reflectivity are often described as 'soft', a very unfortunate term since most of these plaques are far from mechanically pliable and include histological components as dyshomogeneous as fibrofatty tissue, thrombus, and neointima inside stents.

Other qualitative characteristics include the presence of plaque disruption, both before treatment (niches, ulcus, spontaneous dissections with thrombi, with positive pathological remodelling and frequently multifocal, are the pathognomonic changes expected in unstable syndromes) (Fig. 6.12) [14] and after angioplasty (rupture, dissection, mural haematoma). In the stent era other qualitative characteristics are important, such as strut malapposition with blood speckles visible between stent and wall. These changes are rather frequent immediately after stent deployment unless a consistent attempt is made to use IVUS to size the balloons for final stent expansion. At follow-up, only IVUS examination immediately after deployment can distinguish between persistent malapposition, present from the time of deployment, and acquired malapposition, possibly a more worrisome phenomenon related to wall remodelling, lysis of thrombus or toxic vascular effects of the antiproliferative drug.

Prestenotic atherosclerosis

Patients with angina or silent myocardial ischaemia dismissed as 'false positive' or 'possible vasospastic angina' [15] or 'cryptogenic' myocardial infarction because of the presence of a normal or near-normal coronary angiogram show atherosclerotic changes on IVUS in the majority of cases, suggesting more aggressive treatment of the risk factors in order to tackle both disease progression and impaired coronary vasomotion. The new challenge for treatment of coronary artery disease is the detection of plaques not yet impairing flow but at risk of rapid progression and destabilization. 'Vulnerable' plaques, characterized by a thin fibrous cap and a large superficial lipid pool, can be detected with increasing frequency and greater reliability using high-frequency IVUS probes [16]. Still, not all episodes of unstable angina and infarction are caused by 'vulnerable' plaques (erosion, protruding calcium, ischaemia secondary to increased demand), and the resolution and qualitative interpretation of IVUS is insufficient to precisely measure the fibrous cap and fully ascertain the presence of areas of lipid infiltration. IVUS can be a very reliable tool for validating other accurate non-invasive imaging modalities, such as cardiac magnetic resonance imaging and high-resolution 64-slice electron beam computed tomography. The other important application is the serial study of atherosclerotic segments before and after aggressive treatment of plaque progression. Three-dimensional reconstruction of IVUS cross-sections generates a volume of plaque in a given segment, identified by reliable anatomical markers (side branches, aortic anastomosis) and has become the technique of choice for the assessment of progression/regression of coronary atherosclerosis and comparison of the effects of different drug regimens. Allograft vasculopathy is another field now of limited application because of the decreasing number of transplants performed and the shortness of donors. In donor-related coronary athero-sclerosis, IVUS often shows spectacular regression after heart transplantation. Both the early development of atherosclerotic changes (> 0.5 mm thickness in the first year post transplant) and its progression in serial studies carry a negative prognostic value. IVUS can also be used to monitor the effect of drugs to prevent or delay coronary vasculopathy.

Lesions of intermediate severity

The superiority of IVUS over angiography for detecting coronary stenoses that are difficult to assess in multiple views allows its use in the study of lesions of questionable severity. The threshold of absolute cross-sectional area that determines whether intervention must be carried out is 4.0 mm^2 in a native coronary artery [17]. The threshold for the left main coronary artery is more controversial, but an absolute area > 5.9 mm^2 (or 2.8 mm diameter) has recently been shown to be associated with a normal fractional flow reserve and a good 3-year prognosis, even if left untreated [18]. The diameter of the lumen and size and characteristics of the plaque, the relationship of the lesion with other branches, especially for ostial and bifurcational lesions, and the type of remodelling are important factors that guide the angioplasty procedure; IVUS can also be used after the procedure to confirm the effectiveness of treatment.

Guidance of coronary interventions

The wealth of data accumulated in the attempt to demonstrate the usefulness of IVUS for guiding balloon angioplasty and atherectomy is now obsolete because of the universal use of coronary stenting. Nevertheless, it is obvious from trials such as PICTURE [19] and CLOUT [20] that IVUS is the most sensitive technique for detecting dissection after balloon dilatation and for determining the most appropriate balloon size to safely achieve a large lumen gain. Other trials showing the equivalence of IVUS-guided coronary angioplasty and stenting are only of historical interest. Stenting was the main promoter of the use of ultrasound in the interventional community [21]. The detection of incomplete stent deployment and apposition as causes of subacute stent

thrombosis and the consequent development of the technique of high-pressure stent implantation made IVUS almost routine during stenting procedures. The use of IVUS has progressively decreased since this technique was first developed as multiple randomized trials have shown the efficacy of adequate double antiplatelet treatment without ultrasound guidance in reducing subacute stent thrombosis to 1–1.5% in discrete lesions suitable for stenting. Registry data and meta-analysis on the ability of IVUS to reduce restenosis after stenting have given conflicting results, with the most important published randomized trial being completely negative [22].

The use of antiproliferative stent coatings to reduce intimal hyperplasia has revolutionized modern interventional cardiology and profoundly modified the technique of stent implantation. Serial IVUS examinations in large multicentre randomized trials have confirmed a consistent reduction of in-stent hyperplasia in comparison with conventional stents and have excluded the development of acquired stent malapposition and late aneurysms, thus contributing to the rapid success of DES [23].

With in-stent restenosis dramatically reduced to single figures in most lesion subsets, edge restenosis has become a more frequent cause of treatment failure. Ultrasound can be used to optimize the selection of stent length and for precise placement of the stent, and also to avoid leaving segments of severe plaque accumulation or dissection uncovered. Meticulous attempts to over-expand DES in order to reduce the risk of restenosis ('the bigger the better') has become a technique of the past. However, in most restenoses within DES, gross under-expansion has been observed [24]. A threshold of absolute minimal lumen cross-sectional area within the stent of 5.0 mm^2 has been advocated based on IVUS analysis of the SIRIUS trial [25]. For long lesions or calcified vessels or in segments of difficult angiographic assessment (ostia or bifurcations), ultrasound is the only way to properly control expansion.

Complete apposition of equispaced stent struts is not only important for reducing thrombogenicity but also allows the stent to work as a reservoir, delivering the antiproliferative drugs where needed [26]. Incomplete apposition cannot be assessed with angiography, and in large vessels and long lesions in tapering vessels is a frequent phenomenon, possibly explaining some of the failures of DES. Full lesion coverage is very difficult to confirm with angiography in ostial stenoses or bifurcational lesions (Fig. 6.13), no matter which technique is used for stent implantation. In bifurcational lesions, even modern ultrasound probes cannot easily cross in the direction of the side branch, especially if T-stenting or crush techniques are used, but IVUS might be the only way to understand how often treatment failure is due to incomplete stent expansion and lesion coverage or to excessive deformation of the stent struts with these techniques. Even with optimal IVUS guidance to select the irradiating dose, brachytherapy has too narrow a therapeutic window, with stimulatory effects at the edges and persistent late stent thrombosis. With both conventional bare metal stents and DES, retreatment is currently performed with the use of DES, although knowledge of the initial mechanism of restenosis (under-expansion, hyperplasia, incomplete lesion coverage) (Fig. 6.11) is important for selecting the proper length and diameter of stent to be deployed and for guiding its expansion.

Functional assessment of the coronary circulation

Basic structure–function relation of the coronary circulation

In the normal heart, there is a match between myocardial oxygen requirements and coronary supply, the reason for which lies in the unique structural design but also functional adaptability of the coronary artery circulation and the interrelation between the two [27]. Myocardial oxygen demand is mostly determined by ventricular wall stress, heart rate and myocardial contractility. Oxygen supply meets the respective demand by the capacity of the blood to carry oxygen and by the rate of coronary blood flow (in ml/min). Since oxygen-carrying capacity remains quite constant, varying oxygen demands by the myocardium are predominantly satisfied by altering coronary flow rates (Q). According to Ohm's law, $Q = \Delta P/R_m$, where ΔP is the coronary perfusion pressure drop between the aorta and the coronary sinus, and R_m is coronary microcirculatory resistance (Fig. 6.14). Oxygen supply under physiological conditions is not adjusted by coronary perfusion pressure but rather by the vascular resistance R_m, a composite of serial resistances and the result of the following factors: basic architecture of the coronary arterial tree, external compression exerted on the coronary vessels during the cardiac cycle, and intrinsic control of coronary tone. Epicardial coronary artery atherosclerotic narrowings are serial resistance elements further contributing to R_m by their static presence but also by their functional sequelae.

The basic anatomical structure of the human coronary artery tree represents an integral determinant of R_m and can be described in terms of lumen cross-sectional areas, arterial branch lengths and branching patterns. The relation among these variables and the blood flow

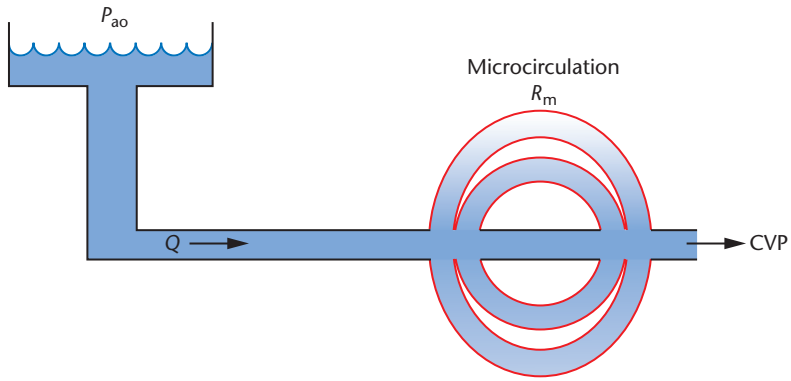

Figure 6.14 Schematic model of the coronary circulation with the parameters essential for the description of coronary flow rate (Q) according to Ohm's law: pressure drop between aortic pressure (P_{ao}) and central venous pressure (CVP) across the coronary circulation is the product of Q and microcirculatory resistance (R_m).

rate (Q) supplied to the downstream myocardial mass (M) has been theoretically derived on the basis of physical principles [27]. One of these principles assumes that the pressure drop (ΔP) along the streamline of the coronary circulation results solely from viscous friction of the blood. Thus, ΔP or the viscous energy loss can be described by the Hagen–Poiseuille equation, $\Delta P = Q \times 8\eta L/\pi r^4$, where ΔP is mean aortic minus mean central venous pressure, Q is coronary blood flow rate, η is the viscosity of blood, L is the vessel segment length and r is vessel radius. The principle of minimum viscous energy loss for the transport of blood in the coronary circulation defines the smallest possible energy balance between viscous energy loss and the energy content of blood plus vasculature (potential energy) (Fig. 6.15). For any given value of Q or M (assuming a constant normal absolute myocardial perfusion at rest of ~1 ml/min/g myocardium), the

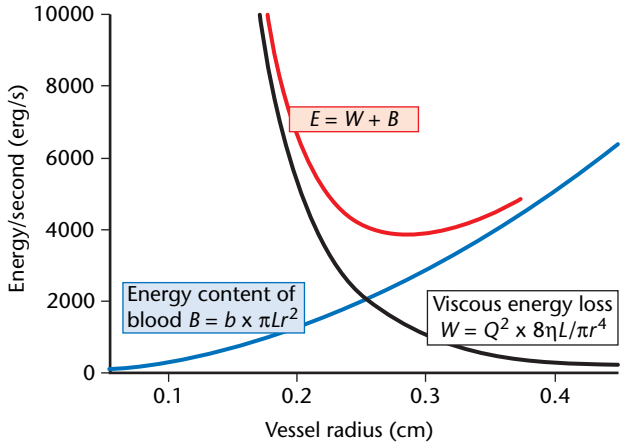

Figure 6.15 Principle of minimum viscous energy loss for the transport of blood governing the design of the coronary artery tree. Ideally, the vessel radius at a site within the tree where flow is 200 ml/min is such that the balance between the energy required to overcome viscous friction of blood flow (W) and the energy cost for the maintenance of the vasculature and blood (B) is minimal: $d(W + B)/dr = 0$ (nadir of the red curve).

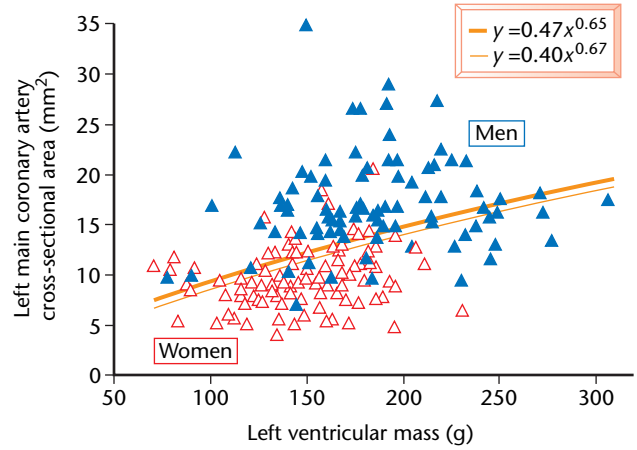

Figure 6.16 Association between left main coronary artery cross-sectional area (vertical axis) and left ventricular mass (horizontal axis) in men (closed symbols) and women (open symbols) without cardiovascular disease. The thin regression curve indicates the theoretically expected relation according to the law of minimum viscous energy loss for the transport of blood.

cross-sectional area A (in mm^2) at any corresponding site within the coronary artery tree can be given as $A = 0.4M^{2/3}$ [27].

The correctness of this equation in describing the basic structure–function relation of the coronary arterial tree has been confirmed empirically in humans using coronary angiographic and echocardiographic data (Fig. 6.16) [27,28]. Total left ventricular mass (M_{tot}) can be determined by echocardiography, whereas regional myocardial mass M at any point in the coronary artery tree has been documented to be tightly related to the product of M_{tot} and the ratio between regional and total summed coronary artery branch lengths (Fig. 6.17) [29]. Regional myocardial mass M represents the prognostically important variable 'area at risk for myocardial infarction' [30].

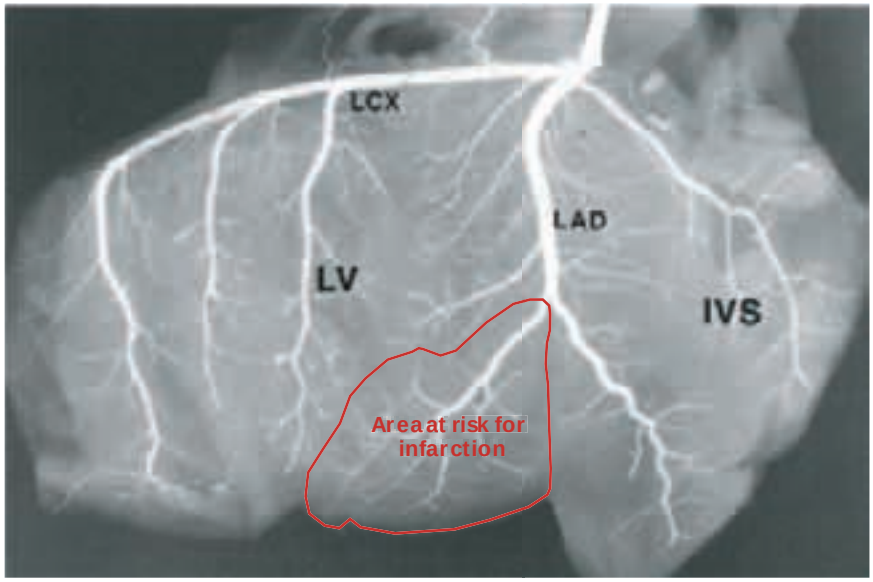

Figure 6.17 Post-mortem preparation of canine left coronary artery tree filled with barium gelatine. The red perimeter encircles the area at risk for left ventricular (LV) myocardial infarction in the case of a hypothetical distal left anterior descending coronary artery (LAD) occlusion. IVS, interventricular septum; LCX, left circumflex coronary artery.

Measurement of flow and Doppler flow velocity measurements

Absolute perfusion (ml/min/g) is the gold standard for assessing myocardial blood supply. Hence, its measurement in humans using positron emission tomography [31] or, very recently, myocardial contrast echocardiography [32] under resting and hyperaemic conditions provides the principal variable for judging whether there is a mismatch between myocardial supply and demand. Invasively, absolute myocardial perfusion cannot be directly obtained. However, it can be calculated on the basis of flow rate (Q) and regional myocardial mass (M) measurements as described above (perfusion = Q/M). Based on the continuity equation, Q is the product of coronary artery cross-sectional area (A) and spatial mean velocity (v_{mean}, cm/s). Invasively, these parameters or estimates of it (in the case of v_{mean}) can be obtained by quantitative coronary angiography and by intravascular Doppler measurements using sensor-tipped angioplasty guidewires. Currently available 0.36-mm (0.014-inch) Doppler guidewires determine temporarily averaged

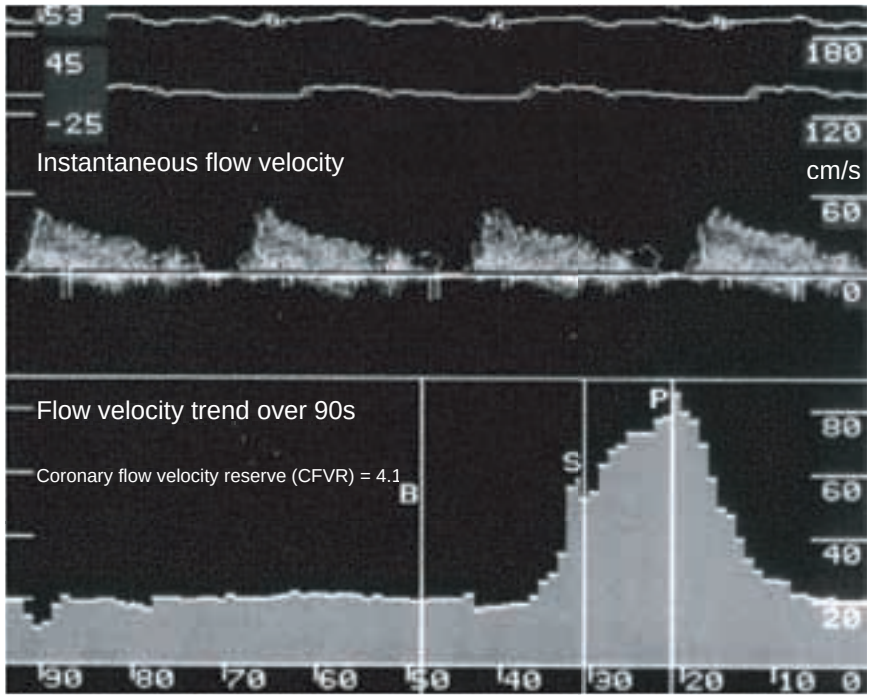

Figure 6.18 Intracoronary Doppler flow velocity recordings. The upper panel shows instantaneous flow velocity obtained during resting conditions; horizontal axis shows time in seconds. The lower panel depicts the flow velocity trend at rest (B, baseline) and during hyperaemia (P, peak velocity).

coronary peak flow velocities. Average peak flow velocity roughly corresponds to $^1/_2 v_{mean}$ [33]. Figure 6.18 depicts a coronary Doppler flow velocity profile obtained in a normal coronary artery with an average peak flow velocity of 21 cm/s. Given that the epicardial coronary artery calibre is maintained constant at maximal vasodilation by nitroglycerine, the vascular capacity to increase flow in response to a hyperaemic stimulus can be estimated invasively by assessing flow velocity during hyperaemia and at rest. The ratio between the two mentioned parameters is called coronary flow velocity reserve. Since a Doppler flow velocity guidewire can be employed as a regular angioplasty guidewire, it may be placed distal to an inflated angioplasty balloon located in an atherosclerotic stenotic lesion undergoing percutaneous coronary intervention (Fig. 6.19). In this particular setting, coronary occlusive flow velocity is obtained, which is directly indicative of (but not equal to) the flow via collateral arteries to the vascular area of interest (Fig. 6.20). A coronary occlusive flow velocity relative to the flow velocity during vessel patency under resting conditions ≥ 25% (i.e. collateral flow index, CFI; Fig. 6.20) has been shown to be sufficiently high to prevent electrocardiographic signs of myocardial ischaemia during a 1-min coronary balloon occlusion [34].

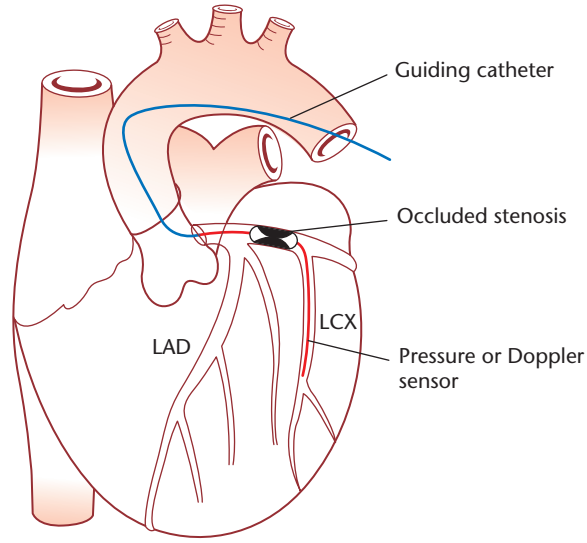

Figure 6.19 Schematic drawing of the heart and great vessels with the invasive set-up used for sensor-tipped angioplasty guidewire measurements of distal coronary occlusive pressure or velocity values. LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery.

Coronary collateral circulation

In the event of acute coronary occlusion, the prognostically crucial variable of myocardial infarct size is determined by the following factors: time of occlusion, size of the above-mentioned area at risk (see Fig. 6.17), whether the myocardium has been preconditioned before complete occlusion by repetitive bouts of ischaemia, and the inverse of collateral supply to the occluded vascular territory [30]. In fact, the area at risk for infarction can be entirely replaced by a sufficiently developed collateral

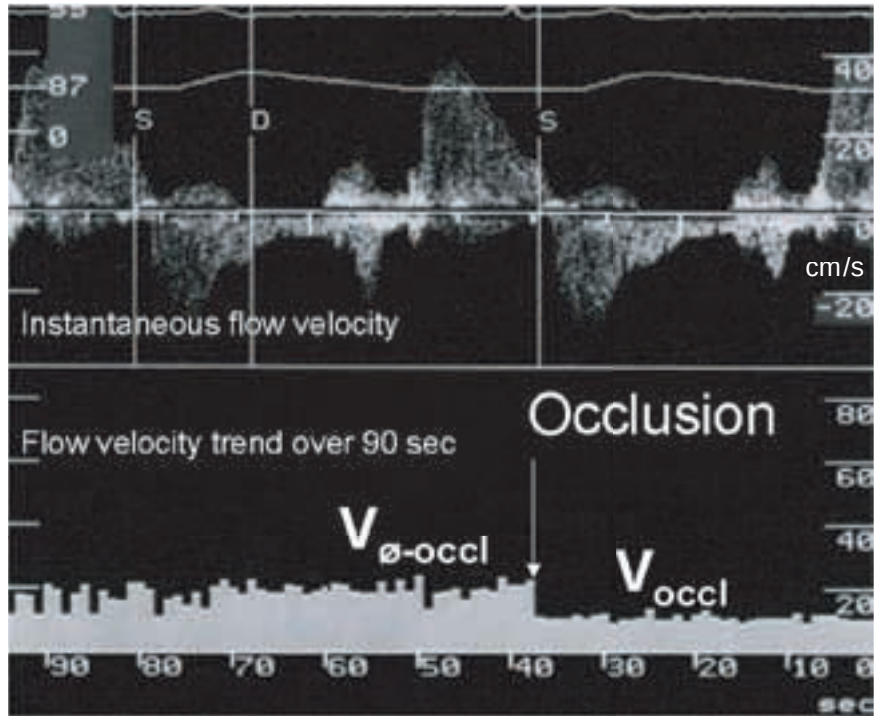

Figure 6.20 Upper panel: instantaneous bidirectional occlusive coronary flow velocity signal (V_{occl}). Lower panel: coronary flow velocity trend obtained during occlusion (right side) and during vessel patency ($V_{ø\text{-}occl}$; left side). The ratio between V_{occl} and $V_{ø\text{-}occl}$ is an index for coronary collateral relative to normal flow (collateral flow index, CFI).

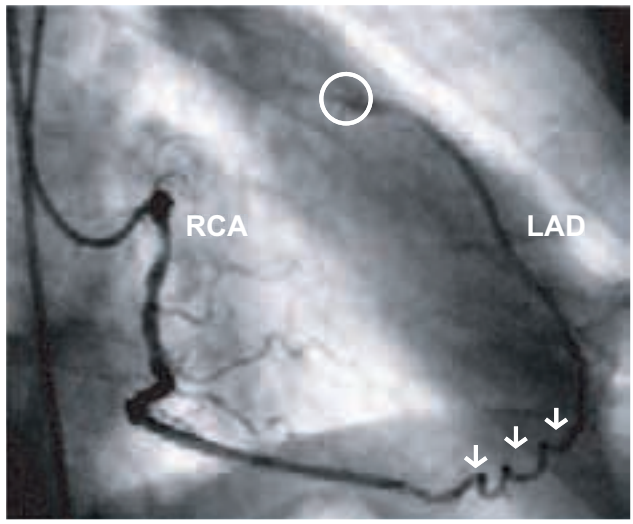

Figure 6.21 Right coronary artery (RCA) angiogram with entire retrograde filling of the occluded (circle) left anterior descending coronary artery (LAD) via a single large collateral artery (arrows).

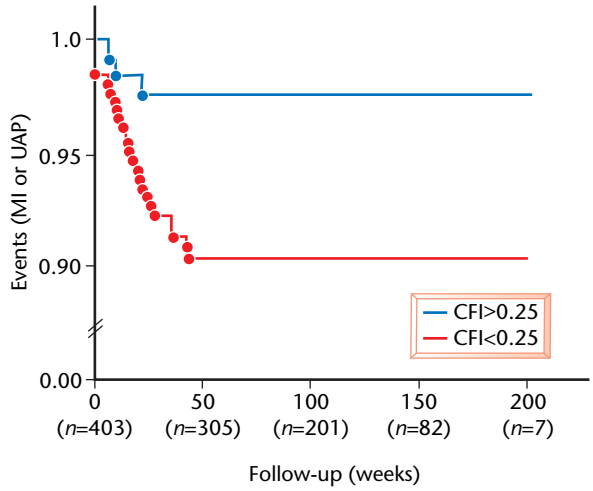

Figure 6.22 Cumulative 4-year event rate (vertical axis) of myocardial infarction (MI) or unstable angina pectoris (UAP) in patients with stable coronary artery disease and an invasively obtained collateral flow index (CFI) of < 0.25 or ≥ 0.25 ($P = 0.01$). CFI < 0.25 indicates collateral flow insufficient to prevent myocardial ischaemia during a 1-min coronary occlusion.

circulation, thus 'shrinking' it to zero and, accordingly, reducing infarct size to zero irrespective of coronary occlusion time (Fig. 6.21). Numerous earlier investigations have shown a protective role of well versus poorly grown collateral arteries, with smaller infarcts, less ventricular aneurysm formation, improved ventricular function, fewer future cardiovascular events (Fig. 6.22) [35] and improved survival [36]. However, the functional relevance of coronary collateral vessels in humans was also a matter of debate for many years [37]. Much of this controversy was likely due to inadequate means for gauging human coronary collaterals and the investigation of populations too small to be representative of all patients with coronary artery disease. The latter is well illustrated by the fact that among patients with haemodynamically significant atherosclerotic lesions, only about one-third have functionally sufficient coronary collaterals able to prevent signs of myocardial ischaemia during brief vascular occlusions (Fig. 6.23) [38]. In the absence of stenoses, it has been traditionally assumed that coronary arteries are functional end-arteries. Using direct and quantitative intracoronary collateral measurements, however, it has been documented very recently that the notion of the human coronary circulation being built without preformed functioning anastomoses between vascular territories is a myth rather than reality; in the

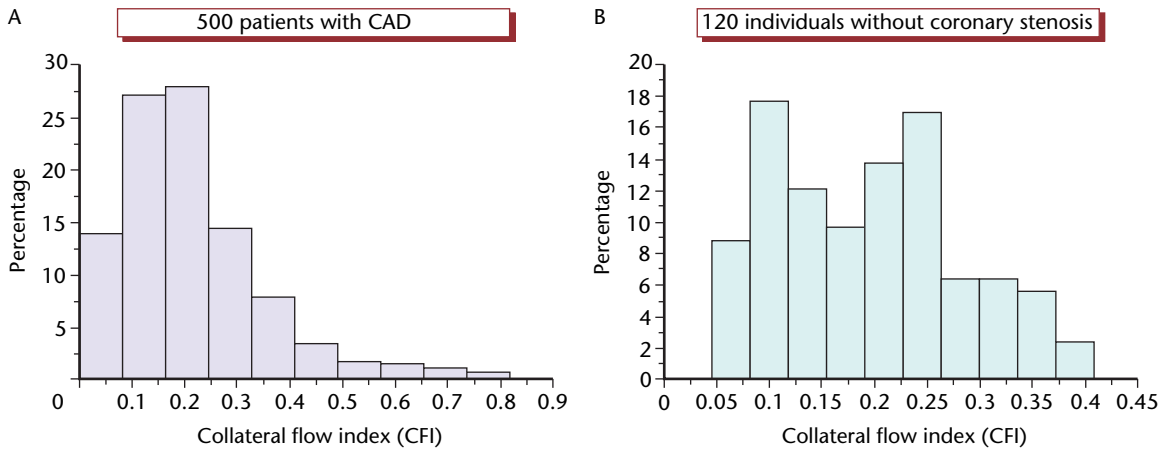

Figure 6.23 Percentage distribution of collateral flow index (CFI; horizontal axis) among (A) 500 patients with coronary artery disease (CAD; two-thirds with CFI < 0.25) and (B) among 120 individuals without coronary artery stenoses (three-quarters with CFI < 0.25).

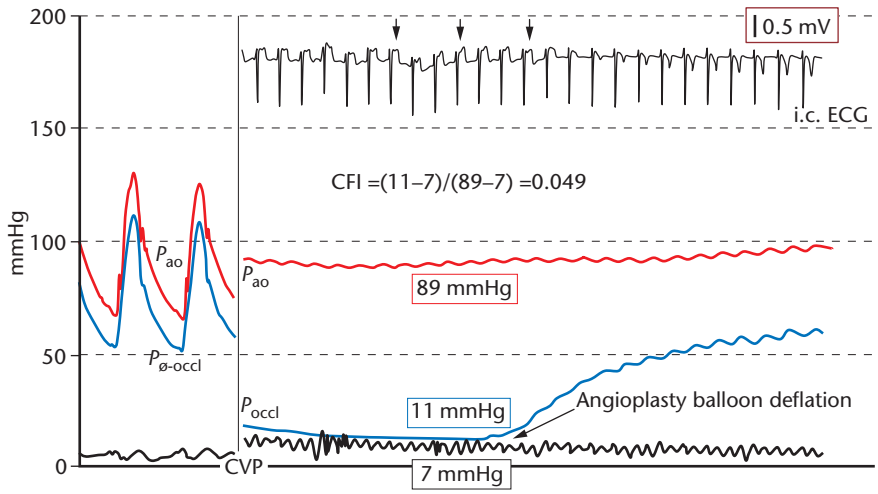

Figure 6.24 Determination of pressure-derived collateral flow index (CFI). Left side: non-occlusive phasic aortic pressure (P_{ao}), distal coronary pressure ($P_{ø\text{-}occl}$) and central venous pressure (CVP). During coronary balloon occlusion, mean coronary occlusive pressure (P_{occl}, blue curve) is 11 mmHg, while mean aortic pressure (red curve) is 89 mmHg. Coronary collateral flow is not sufficient to prevent ECG signs of myocardial ischaemia (arrows).

absence of obstructive coronary artery disease or even in entirely normal hearts, there is collateral flow to a briefly occluded coronary artery sufficient to prevent ECG signs of myocardial ischaemia in one-fifth to one-fourth of the population studied (Fig. 6.23) [39].

Coronary collateral flow can be precisely determined only during vascular occlusion of the collateral-receiving artery (see Fig. 6.19). Presently, the gold standard for quantitative clinical coronary collateral assessment is measurement of intracoronary occlusive flow velocity- or pressure-derived CFI, which expresses collateral flow as a fraction of flow during vessel patency. Pressure-derived CFI is determined by simultaneous measurement of mean aortic pressure (P_{ao}), mean distal coronary occlusive pressure (P_{occl}) and central venous pressure (CVP) (Figs 6.24 and 6.25) [34].

$$CFI = (P_{occl} - CVP)/(P_{ao} - CVP)$$

The coronary angiographic method for collateral qualification most widely used is similar but not identical to the one first described by Rentrop *et al.* [40]. The latter provides a score from 0 to 3 for recruitable collateral vessels upon occlusion of the ipsilateral artery, the former an identical score for spontaneously visible collaterals without artificial vascular occlusion.

A variety of physiological molecules have been identified that appear to promote angiogenesis (formation of capillary-like vessels) and arteriogenesis (formation of collateral arteries). Most act by stimulating migration and proliferation of endothelial cells and/or smooth muscle cells, like the family of fibroblast growth factors (FGF) and vascular endothelial growth factors (VEGF). Other growth factor candidates include placental growth factor, angiopoietin 1, transforming growth factor β, platelet-derived growth factor, and about half a dozen other cytokines, proteases and proteins [41]. Arteriogenesis has

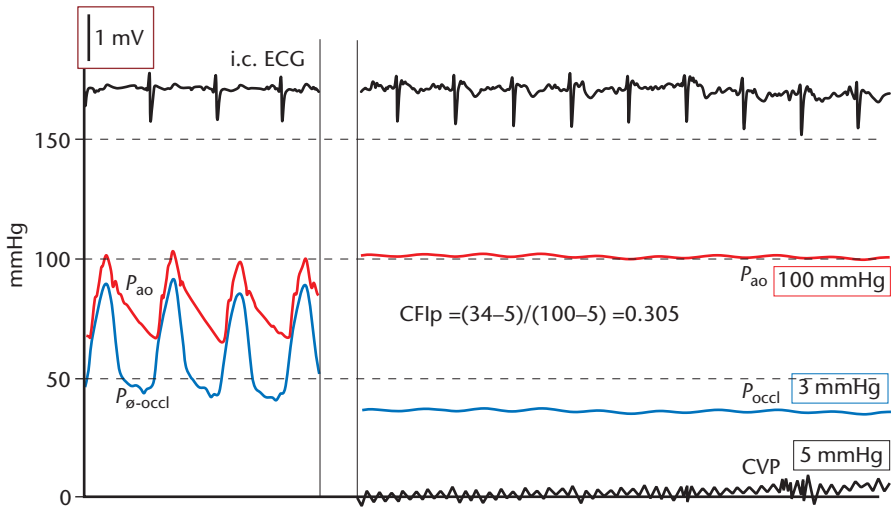

Figure 6.25 Determination of pressure-derived collateral flow index (CFI) in a patient with sufficient coronary collateral flow (see also Fig. 6.18). See Fig. 6.24 for explanation of abbreviations.

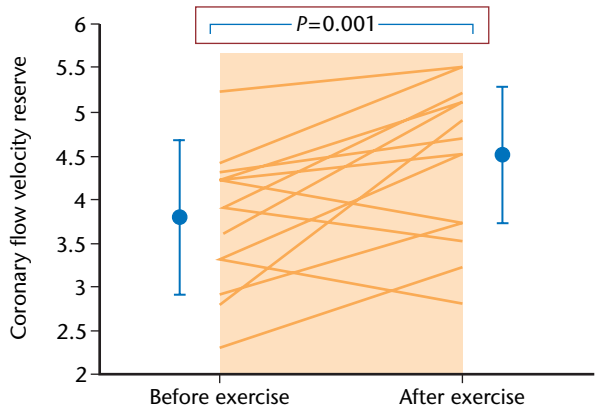

Figure 6.26 Intracoronary Doppler-derived coronary flow velocity reserve (vertical axis) before and after a long-term physical endurance exercise programme in eight healthy volunteers.

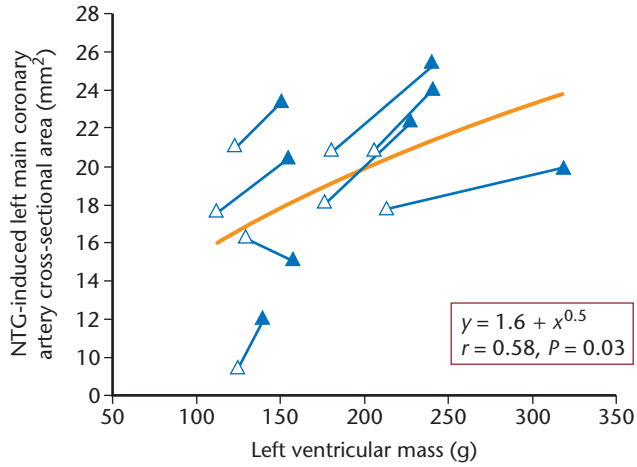

Figure 6.27 Left main coronary artery size (vertical axis) in relation to left ventricular mass in eight healthy volunteers before (open symbols) and after (closed symbols) a long-term physical endurance exercise programme.

been shown to be induced by activated macrophages, lipopolysaccharide, monocyte chemotactic protein 1, tumour necrosis factor α, FGF, and also via granulocyte–macrophage colony-stimulating factor (recombinant human GM-CSF; Molgramostim) [42]. In the first randomized placebo-controlled clinical trial, GM-CSF has been shown to be effective with regard to sequentially and invasively obtained collateral flow among 21 patients with coronary artery disease [43]. Arteriogenesis is related to enhanced shear forces at the vessel wall in response to increased flow through pre-existing collateral connections [44].

Regulation of myocardial blood flow

Likely induced by a similar mechanism of flow-induced vascular functional adaptation and structural remodelling, chronic endurance exercise in healthy individuals leads to enhanced coronary hyperaemic flow capacity (Fig. 6.26) as well as to more sizeable coronary arteries (Fig. 6.27) [45]. Such a chronic response to enhanced myocardial blood flow demand is based on its acute adaptability, which is pivotal since the heart cannot increase oxygen extraction on demand. Thus, any additional oxygen requirement must be met by an increase in coronary flow, and regulation including autoregulation of coronary vascular resistance (R_m) is the most important mediator of this process. Autoregulation refers to the intrinsic mechanisms that maintain blood flow constant at aortic perfusion pressures between 60 and 130 mmHg [46]. Acute regulation of myocardial blood flow is mediated by extrinsic factors, but mainly by the following intrinsic factors: accumulation of local metabolites, neural innervation and endothelium-derived substances.

1 *Local metabolites*. Adenosine, a product of adenosine diphosphate and monophosphate metabolized during states of hypoxaemia, is thought to be the prime metabolic mediator of vascular tone resulting in vasodilation. By binding to receptors on vascular smooth muscle cells, adenosine decreases calcium entry into cells, which leads to relaxation, vasodilatation and decreased vascular resistance. Other mediators include lactate, acetate, hydrogen ions and carbon dioxide.
2 *Neural innervation*. The neural control of vascular resistance has both sympathetic and parasympathetic components. Under normal conditions, the contribution of the parasympathetic system seems to be minor, but sympathetic receptors play an important role. Coronary vessels contain both α and β adrenergic receptors. Stimulation of α-adrenergic receptors results in vasoconstriction, while β_2-receptor stimulation promotes vasodilatation. Stimulation of β_1 receptors, by causing enhanced metabolic demand through augmented myocardial contractility, increases heart rate and conduction and secondarily results in increased myocardial blood flow.
3 *Endothelial factors*. Endothelial cells of the arterial wall produce a number of vasoactive substances that contribute to the regulation of vascular tone. Endothelial vasodilators include nitric oxide, prostacyclin and endothelium-derived hyperpolarizing factor. A very powerful endothelial-derived vasoconstrictor is endothelin 1. Nitric oxide regulates vascular tone by diffusing into and relaxing adjacent arterial smooth muscle via a cyclic

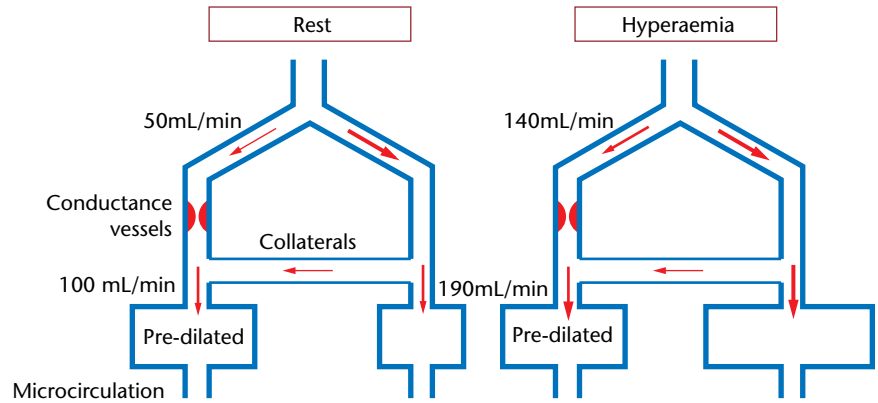

Figure 6.28 Schematic drawing of the concept of coronary flow reserve. At rest (left side), the microcirculatory vascular resistance downstream of a coronary stenosis is reduced in order to maintain myocardial perfusion. During hyperaemia (right side), the capacity for further dilatation of the pre-dilated microcirculation in the stenotic vascular region is reduced, resulting in only a limited increase in coronary flow (coronary flow reserve = 190/100 ml/min, normal value > 2–2.5).

guanosine monophosphate-dependent mechanism. Under normal basal conditions, nitric oxide is constantly released and is additionally stimulated by factors such as low oxygen tension, thrombin, platelet products, acetylcholine and increased wall shear stress (e.g. during exercise). A blunted response to these stimuli may occur in different diseases (e.g. hypertension, diabetes, hypercholesterolaemia) even in the absence of a flow-limiting coronary artery stenosis.

Coronary atherosclerotic stenotic lesions on their own also influence the regulation of myocardial blood flow by inducing microvascular dilatation, which is directly dependent on the degree of pressure drop across the lesion (Fig. 6.28). This adaptive mechanism is a specific facet of coronary autoregulation aimed at maintaining constant coronary flow. Under resting conditions, flow distal to a stenotic lesion remains normal until a tight obstruction of 80–85% in diameter is reached (Fig. 6.29). However, coronary flow achieved during hyperaemia begins to decline when the diameter of the stenosis is already < 50% (Fig. 6.29). This is related to the fact that the vasodilatory capacity of the microcirculation downstream of a stenosis is partly or entirely expended under resting conditions. The extent to which microvascular resistance can be lowered or to which coronary or myocardial flow can increase is generally referred to as absolute coronary or myocardial flow reserve (CFR). Specifically, CFR is defined as coronary flow during hyperaemia divided by flow obtained at rest [47]. A four- to five-fold increase after a maximum vasodilatory stimulus identifies a normal CFR. Apart from a stenotic lesion, CFR is influenced by several other factors, such as heart rate, blood pressure, left ventricular hypertrophy and microvascular disease. Relative flow reserve, i.e. the maximum blood flow in a stenotic artery divided by maximum flow in an adjacent normal artery [48], is less dependent on some of the mentioned cofactors of CFR because it does not account for baseline flow. Fractional flow reserve (FFR) is defined as the ratio of hyperaemic coronary flow in the stenotic region to hyperaemic flow in the same area if no lesion were present [49].

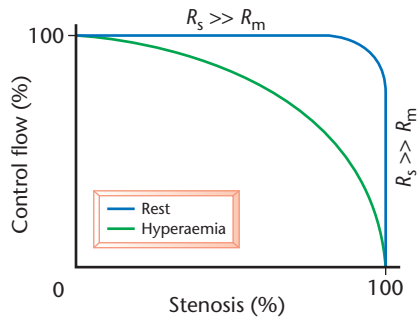

Figure 6.29 At rest, microcirculatory vascular resistance (R_m) downstream of a coronary stenosis dominates the resistance of the stenotic lesion (R_s), which explains why only a very severe stenosis (horizontal axis) leads to a reduction in coronary flow. During hyperaemia, the presence of only mild stenosis leads to the situation where R_s is predominant, and coronary flow is thus reduced.

Hyperaemic stimuli

In the absence of sufficient coronary collateral flow, a brief coronary occlusion of 1 min in a normal coronary artery typically induces a four to five times increase in coronary blood flow above resting level immediately after release of the occlusion. Initially, it was thought that short-lasting myocardial ischaemia is the most potent stimulus for achieving maximum flow or minimal myocardial resistance. However, in animals it appears that even during low-flow ischaemia the resistance vessels retain some degree of vasomotor tone [50]. Similarly, some residual flow reserve has been described in humans even in the presence of ischaemia [51]. Conversely, it has been found in patients after successful angioplasty that intracoronary flow velocity increased similarly in response to vascular occlusion as after administration of

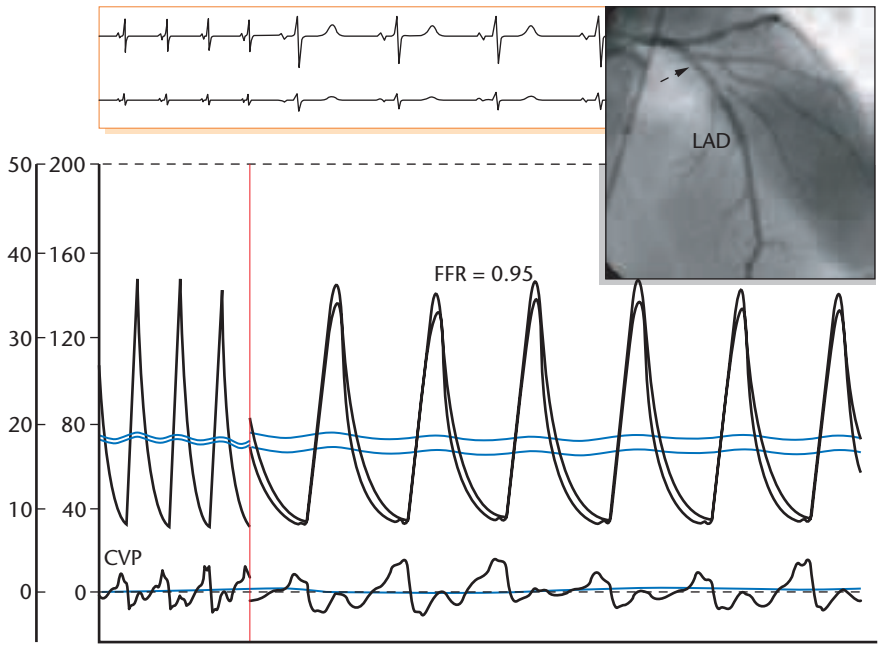

Figure 6.30 Recording of phasic and mean aortic pressure (P_{ao}), distal coronary artery pressure (P_d) and central venous pressure (CVP) at rest (left side) and during hyperaemia in a patient with mild narrowing (arrow) of the left anterior descending coronary artery (LAD; right panel). Fractional flow reserve (FFR) is 0.95 and thus the LAD stenosis is not haemodynamically relevant.

papaverine [52]. Such controversies on the maximally achievable hyperaemic response may be related to different degrees of ischaemia induced by coronary occlusion, i.e. the lack of accounting for collateral supply to the blocked vascular area. The most physiological stress that induces hyperaemia is physical exercise. Cardiac pacing increases coronary flow only modestly by a factor of 2–2.5. Among the pharmacological agents to induce hyperaemia, acetylcholine is the only direct endothelium-dependent vasodilator: in the presence of an injured endothelial cell layer, an inappropriate coronary constriction likely occurs, which can be relieved using nitroglycerine. Adenosine is a very safe coronary vasodilator due to its short half-life of only a few seconds; it acts via reduction of microcirculatory resistance, leading to coronary flow enhancement [53]. Intracoronary papaverine causes relatively brief (15–30 s) maximal hyperaemia, but the total dose that can be given is limited by its slow systemic excretion (half-life 3–6 h). Intracoronary papaverine prolongs the QT interval and can cause polymorphous ventricular tachycardia. Intravenous dipyridamole also elicits maximal hyperaemia, but its duration of action is too long (> 30 min) to allow repeated measurements during the same study.

Fractional flow reserve

As indicated above, there are several non-invasive and invasive methods for gaining information on the physiological relevance of epicardial coronary stenoses and also on microvascular coronary disease. The recent development of sensor-tipped angioplasty guidewires as well as the inclusion of hyperaemia into the routine test protocol has revived interest in the invasive functional assessment of coronary artery disease. Measurements of CFR and of hyperaemic flow versus pressure slope index have been documented to be critically influenced by altering heart rate, blood pressure, etc., whereas pressure-derived FFR appears to be less dependent on haemodynamic changes [54]. Pijls *et al*. [49] have provided the theoretical coronary haemodynamic background relevant when using simultaneous aortic and distal coronary *pressure* measurements during hyperaemia as the basis for calculation of a coronary *flow* index. Aside from the practical ease of obtaining measurements with sensor-tipped pressure wire as opposed to Doppler wire (problem of wall artefacts and position dependency within the coronary tree), there is a clear threshold of < 75% coronary hyperaemic flow across a stenotic lesion relative to normal flow in the absence of lesions (myocardial FFR < 0.75) (Figs 6.30 and 6.31) that reliably detects myocardial ischaemia as found by nuclear myocardial perfusion imaging or stress echocardiography [55]. However, distal pressure (P_d, the numerator in the calculation of FFR) depends on flow across the stenotic lesion, which is determined not only by stenotic resistance but also by microvascular resistance. A change in the latter affects distal pressure and flow inversely. Accordingly, a recent investigation has found that categorized cut-off values for simultaneously obtained FFR and CFR of 0.75 and 2.0 respectively have agreed in only 73% [56]. In the group with normal FFR but pathological CFR, the microvascular resistance index was higher than in the group with pathological FFR but normal CFR.

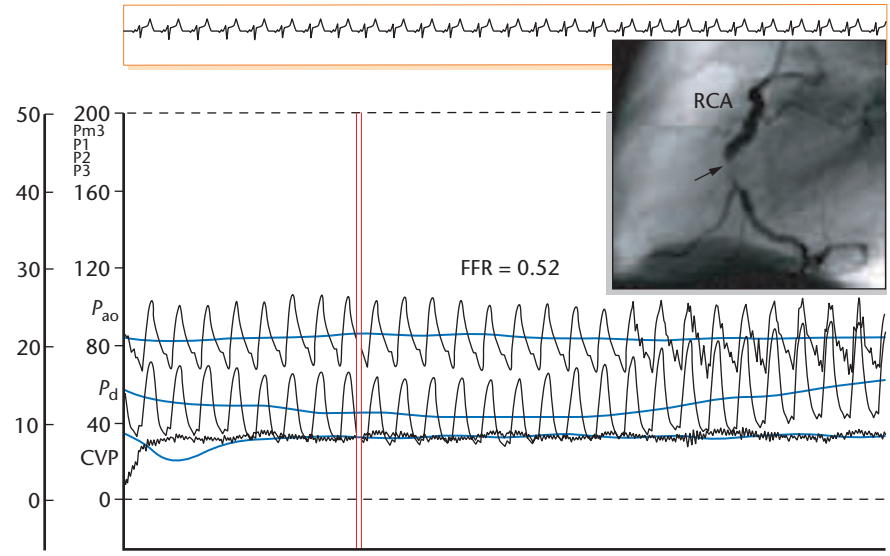

Figure 6.31 Recording of phasic and mean aortic pressure (P_{ao}), distal coronary artery pressure (P_d) and central venous pressure (CVP) during hyperaemia in a patient with severe narrowing (arrow) of the right coronary artery (RCA; right panel). Fractional flow reserve (FFR) is 0.52 and thus the RCA stenosis is haemodynamically highly relevant.

Personal perspective

Therapeutic decisions in cardiology are crucially determined by invasive circulatory imaging and haemodynamics, both of which are essential for understanding pathophysiological and diagnostic aspects of cardiovascular disease. The latter has been and will continue to be indispensable for the thorough choice of treatment plans for cardiovascular diseases. Since *invasive* examination is the only tool providing directly all the *basic* physical dimensions for the comprehensive description of the circulatory system, and since it also allows impromptu therapeutic action for treating cardiovascular disease, it is and will continue to be conceptually advantageous over several other non-invasive haemodynamic and imaging techniques. Presently, the most important entity for invasive imaging and treatment in the Western world is atherosclerotic coronary artery disease (CAD). Percutaneous coronary artery intervention (PCI) has become much more important than bypass surgery as treatment pillar for CAD during the past 25 years. The introduction of coronary stenting and drug-eluting stents for preventing arterial restenosis has decisively contributed to the success of PCI. In patients with no option for the traditional forms of coronary revascularization (about one-third of individuals with CAD), the therapeutic promotion of natural coronary bypasses, i.e. collateral growth or coronary arteriogenesis, has emerged as a promising treatment option which will steadily gain momentum.

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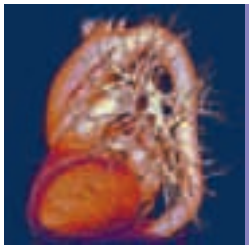

7 Genetics of Cardiovascular Diseases

Silvia G. Priori, Carlo Napolitano, Stephen Humphries, Maria Cristina Digilio, Paul Kotwinski and Bruno Marino

Summary

Molecular genetics is progressively entering clinical practice and it is affecting patients' management. Most of our current knowledge derives from the application to molecular diagnosis of the findings of the pivotal studies that have unveiled the genes that cause the so-called monogenic diseases. Thanks to these studies we have learnt that disorders such as hypertrophic cardiomyopathy, dilated cardiomyopathy or long QT syndrome arise from a large spectrum of genetic defects and that the type of DNA abnormality is not only a molecular curiosity but also bears prognostic and therapeutic implications. Furthermore, thanks to the genetic studies on monogenic diseases, our knowledge of basic mechanisms leading to structural and electrical derangements of the myocardium has grown remarkably. The next challenge for molecular geneticists involved in cardiovascular disease is to investigate the role of DNA variants or single nucleotide polymorphisms in determining the predisposition to develop more complex phenotypes such as ischaemic heart disease, hypertension and heart failure.

This chapter will review the current understanding of genetic determinants of cardiovascular diseases with a focus on the practical role of genetic testing for risk stratification and management.

Inheritance of human diseases: monogenic versus polygenic diseases

Inherited diseases can be divided into monogenic and polygenic forms. Monogenic diseases are inherited as Mendelian traits while polygenic disease encompasses a large group of human diseases in which the evidence of 'familial clustering' suggests a role for genetic factors but the phenotype is not the consequence of mutations in a single gene (e.g. hypertension, coronary artery disease). In the last decade, the distinction between monogenic and polygenic diseases has become less obvious [1,2]. Phenomena such as incomplete penetrance, repeatedly reported in monogenic diseases, strongly suggest that even those diseases inherited as Mendelian traits are not simply the consequence of a single genetic defect. Accordingly, even in monogenic diseases the presence of additional genetic modifiers may concur to determining the severity of clinical manifestations.

Monogenic diseases

Monogenic diseases are inherited as dominant or recessive traits with five major inheritance patterns.

- *Autosomal dominant* (autosomes are all human chromosomes with the exception of the sex-related X and Y chromosomes). The chance of transmission to the offspring is 50%; both males and females can be affected. Only one mutated allele is sufficient to cause the phenotype.
- *Autosomal recessive*. Only the homozygote is clinically affected (two mutated alleles must be present) while the heterozygote is defined as a 'healthy carrier' or shows very mild signs of the disease. The chance of receiving two defective alleles/genes (one from the mother and one from the father) is 25%. Fifty per cent of the offspring will receive only one defective allele (heterozygotes) and 25% will receive two normal alleles (homozygotes).

Table 7.1 Clinical applicability of genetic testing in monogenic cardiac diseases*

	Success rate	Identification of silent carriers/diagnosis	Reproductive risk assessment	Prognosis	Therapy
HCM	60–65%	+	+	+/–	–
DCM	na	+	+	–	–
ARVC	< 10%	+	+	–	–
MFS	80–90%	+	+	–	–
LQTS	60–65%	+	+	+	+
BrS	20%	+	+	–	–
CPVT	50%	+	+	+	–
NS	40%	+	+	–	–

*Only conditions in which consistent epidemiological data are available have been listed. HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; MFS, Marfan syndrome; LQTS, long QT syndrome; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; NS, Noonan syndrome; na, not applicable.

- *X-linked dominant*. Both males and females can be affected but no male-to-male transmission is possible and an affected male has a 100% chance of transmitting the disease to daughters. For female-to-female transmission of the defective allele there is a chance of 50%.
- *X-linked recessive*. Heterozygous females are healthy carriers and 50% of their sons are clinically affected. No female-to-female transmission of the disease is possible but 50% of daughters are silent carriers. Affected males will generate unaffected males and heterozygous unaffected females (healthy carriers). [The Y chromosome is usually involved in gross chromosomal anomalies (translocation, deletions) but very rare cases of monogenic disorders have been reported.]
- *Matrilineal transmission*. This refers to diseases caused by mitochondrial DNA. Since mitochondria are only present in oocytes and not in sperm, only females may transmit the disease to the offspring.

In clinical practice, it is often arduous to identify the patterns of inheritance based on the analysis of the phenotype because low penetrance and variable expressivity may obscure the picture. Time-dependent penetrance is a frequent phenomenon in genetics. The clinical manifestations become progressively worse during a lifetime because the organ damage induced by the defective gene accumulates. This is the case in hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and dilated cardiomyopathy where disease penetrance may reach 100% when patients live long enough to manifest the symptoms.

The practical value of genetic analysis in monogenic diseases ranges from moderate to very high. In all diseases the principal role of identifying a mutation in the proband of a family is that of allowing an accurate diagnosis among family members including the silent carriers (i.e. presymptomatic diagnosis). In selected diseases, the identification of a mutation is of major importance for risk stratification and treatment of the patients. Table 7.1 summarizes the clinical value of genetic testing in different monogenic diseases.

Polygenic diseases

Many of the most prevalent cardiovascular disorders, such as coronary artery disease, hypertension and heart failure, are clearly not inherited as Mendelian traits but they 'cluster in families' whose members appear to be particularly susceptible to developing a specific phenotype. It is suggested that common DNA variations or single nucleotide polymorphisms (SNPs) account for this 'predisposition' to become affected by these acquired conditions. The human genome sequence is now published and much research involves identifying and cataloguing the extent of human genetic diversity, leading to the development of the SNPs 'Map' (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Snp). By definition, a SNP is a nucleotide sequence variation within organisms of the same species. SNPs are most frequently silent (silent polymorphisms) but there are functionally active variants. These latter result in altered biological function by affecting differential gene expression or protein function and they are usually located either in regulatory or in coding regions of the genes. Functional SNPs may have neutral, beneficial or detrimental consequences as determined by interaction with environmental stressors.

Inherited (monogenic) diseases with myocardial involvement

Hypertrophic cardiomyopathy

Clinical presentation

Hypertrophic cardiomyopathy (HCM) is diagnosed when left ventricular hypertrophy (typically asymmetric in distribution) is present in the absence of cardiac or systemic conditions (e.g. hypertension or aortic stenosis), that could potentially induce a hypertrophy of the magnitude observed in a given patient. At histology the disease is characterized by myocyte disarray and hypertrophy, interstitial fibrosis and thickening of the media of the intramural coronary arteries [3]. The severity of the phenotype is largely heterogeneous and hypertrophy preferentially involves the interventricular septum. Most patients have remarkable regional variations in the extent of hypertrophy.

The guidelines for diagnosis and management of HCM were recently outlined in a joint consensus document of the American College of Cardiology and European Society of Cardiology [3].

Genetic bases

Most cases of HCM are transmitted as an autosomal dominant trait while other uncommon variants are inherited as autosomal recessive, X-linked or 'mitochondrial' disorders. A positive family history is noticeable in only two-thirds of cases but this may be an underestimate because of the incomplete penetrance. The prevalence of HCM is estimated to be 1 per 500, making HCM one of the most prevalent genetic diseases. The list of genes implicated in HCM has grown impressively over the last 10 years and, to date, 19 genes and two loci have been identified. Recent data suggest that mutations in the HCM genes also cause some of the milder forms of ventricular hypertrophy in the elderly, which are usually considered as acquired conditions [4].

An altered function of proteins of the cardiac sarcomere is the most frequent cause of HCM (Fig. 7.1). In such instances, myocardial hypertrophy is the only phenotype ('pure' HCM). Non-sarcomeric proteins have also been associated with HCM in a minority of cases. These variants usually show additional phenotypes such as abnormal conduction pathways (Wolff–Parkinson–White), sensorineural deafness, neurological and neurogenic muscular atrophy, trunk hypotonia and encephalopathy.

Although HCM is primarily an autosomal dominant trait, rare instances of sarcomeric protein mutations are inherited as a recessive trait (homozygous or compound heterozygous). In these cases the phenotype is usually severe since patients are carriers of two abnormal alleles.

Pathophysiology

The general scheme for HCM pathophysiology is that of a primary disorder of contractile function (Fig. 7.1). In this context, hypertrophy represents an adaptation to the inability to generate sufficient contractile strength to maintain adequate cardiac output. Fibroblast proliferation (fibrosis) and tissue disarray are the result of such adaptive modifications.

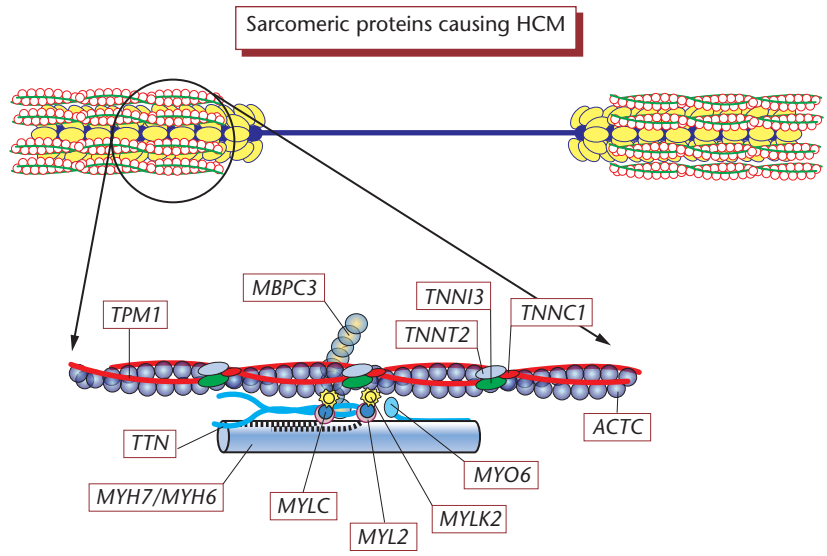

Figure 7.1 Schematic representation of a cardiac muscle sarcomere. The circled section represents the area in which myosin–actin interaction take place. Most of the key proteins involved in the hypertrophic cardiomyopathy pathogenesis take part in this macromolecular complex.

Functional expression studies of mutant sarcomeric proteins show a variety of abnormalities, spanning defects in myofibril formation, altered ATPase activity, Ca^{2+} sensitivity and impaired actin–myosin interaction.

In vitro studies have shown that mutant sarcomeres are usually incorporated in the myofibril, but assembly abnormalities (reduced incorporation efficiency and accelerated disruption/catabolism) may occur. Whether the myocardial disarray observed at a clinical level may be a direct consequence of mutant protein mis-incorporation and/or mis-folding has not yet been definitely established.

The globular (head) domain of β-myosin heavy chain is the site of actin binding and the region of ATP utilization (hydrolysis). *MYH7* mutations may alter the actin-dependent ATPase activity by disrupting the actin–myosin interaction. Several experimental studies also suggest that at least some HCM mutations increase the calcium sensitivity of the contractile apparatus. Additionally, functional studies from muscle biopsies in humans and in mouse models of HCM demonstrate a depressed shortening velocity and power, and increased Ca^{2+} mobilization. These phenomena may represent the initial signal for myocardial compensatory hypertrophy. For a review see ref. [5].

Genotype–phenotype correlation

HCM is characterized by a wide spectrum of clinical phenotypes. Therefore, the attempt to derive prognostic information based on the specific defect is an attractive perspective. However, limitation to this approach still exists. Most HCM patients carry mutations that are unique to their family, so genotype–phenotype correlations may only apply to a small subset of patients. Furthermore, the spectrum of clinical presentation is so wide that one single genetic factor is probably not enough to account for it, and environmental modifiers may play a significant role.

MYH7

The β-myosin heavy-chain gene is mutated in approximately 35–50% of the genotyped families [6]. A single mutation R403Q appears to have higher prevalence and together with other mutations (R719W, R453C) it has been associated with an adverse prognosis [7]. Near normal life expectancy was reported for other allelic variants such as Vl606M, L908V and G256Q, P513C [7,8].

TNNT2

TNNT2 defects are often associated with milder cardiac hypertrophy than other genetic variants of the disease, yet may manifest with a high proportion of arrhythmic events and sudden cardiac death. Incomplete penetrance has also been reported [9]. The relative prevalence of the *TNNT2* mutation is between 6.5 and 15% [9].

MYBPC3

Recent data suggested that the *MYBPC3* gene is probably the most prevalent variant [6]. *MYBPC3*-HCM is characterized by late onset and severe prognosis related to a high incidence of sudden arrhythmic death [4]. Epidemiological data collected in patients with *MYBPC3* mutations emphasize the need to continue tight monitoring of individuals belonging to families affected by HCM because delayed onset may unexpectedly pose a risk of sudden death in adults and middle-aged individuals who were considered unaffected at an early age.

TPM1

Mutations of the α-tropomyosin gene are a relatively infrequent cause of HCM, representing approximately 3–5% of the genotyped individuals [7]. The phenotype is of intermediate severity with heterogeneous cardiac hypertrophy. However, in the individual patient the possibility of developing severe hypertrophy and clinical manifestations cannot be ruled out. Variable levels of cardiac hypertrophy and also of cardiac dilatation with heart failure have been reported among carriers of α-tropomyosin mutations [10].

Too few families and too little information are available to attempt genotype–phenotype correlations in the remaining genetic variants of HCM. In these patients genetic testing is useful for diagnostic purposes and reproductive risk assessment but not for clinical management.

PRKAG2 (HCM and pre-excitation syndrome)

A short PR interval, prolonged QRS, with a slurred upstroke of the R wave ('delta' wave) and a predisposition to paroxysmal supraventricular tachycardia in the context of an otherwise normal heart are the characterizing features of the Wolff–Parkinson–White (WPW) syndrome. In rare instances, this WPW pattern is observed with a familial distribution.

More recently two independent groups [11,12] reported familial cases in which HCM and WPW phenotypes cosegregated with a mutation in the *PRKAG2* gene. This gene encodes for the gamma2 regulatory subunit of the AMP-activated protein kinase and it is directly implicated in the synthesis of cardiac energy substrates. The mutations in this gene induce a compensatory hypertrophy as a result of the reduced energy supply to the contractile elements. From a clinical standpoint it must be pointed out that the association of HCM and WPW is more frequent than the known prevalence of *PRKAG2* mutation. Thus, this phenotype is likely often to be an aspecific finding [13].

Table 7.2 Modifier genes in hypertrophic cardiomyopathy

Gene/variant	Gene product	Clinical variable	Result	Number of patients	Ref
ACE-D allele	Angiotensin converting enzyme	Cardiac hypertrophy SCD	Allelic frequency 0.69 HCM vs. 0.57 not affected Allelic frequency 0.74 (high SCD incidence) Allelic frequency 0.55 (low SCD incidence)	100	[14]
AGT	Angotensinogen	LVMI	Not significant	108	[15]
AT1a	Angiotensin II Receptor 1a	LVMI	Not significant		
END1–AA and *–AG* alleles	Endothelin 1	LVMI	Accounts for 7.3% of the variability of the LVMI		
TNF-α—*G308A* allele	Tumour necrosis factor	LVMI	Accounts for 6.0% of variability	142	[16]
IL-6—*G174C* allele	Interleukin-6	LVMI	Not significant		
IGF-2—*G829A* allele	Insulin-like growth factor-2	LVMI	Not significant		
TGF-β1—*C509T*	Transforming growth factor β-1	LVMI	Not significant		
CTP11B2—*T344C*	Aldosterone synthase	LVMI	Not significant		

LVMI, left ventricular mass index; SCD, sudden cardiac death.

Genetic modifiers in HCM

The identification of 'modifier genes' is an attractive possibility for the improvement of genotype-based risk stratification. Hints for the existence and clinical relevance of genetic modifiers in HCM have been brought to light [14–16] (Table 7.2). Despite their early stage, these studies suggest that the clinical course of HCM may be influenced by additional genetic factors. In the future this approach may allow individualized risk profiling by elucidation of a series of genetic variables. However, it is still too early to implement these observations in clinical practice.

Clinical applicability of genetic testing in HCM

The molecular epidemiology of HCM has been systematically addressed [6] by screening the entire open reading frame of nine HCM genes in 197 probands (*MYH7*, *MYBPC3*, *TNNI3*, *TNNT2*, *MYL2*, *MYL3*, *TPM1*, *ACTC* and *TNNC1*). Approximately 63% of these patients have been successfully genotyped (Table 7.1). Interestingly two genes, *MYH7* and *MYBPC3*, made up 82% of genotyped patients, while troponin T and troponin I were present in 6.5% of probands. Therefore, a genetic screening limited to the four major genes leads to the identification of the genetic defect in more than 60% of patients with clinically confirmed HCM. Two additional findings are worth mentioning: (1) nearly all genotyped families have a different mutation, thus indicating that the screening for known mutations is not useful; and (2) approximately 5% of patients present with more than one genetic defect (on the same or on two different genes), therefore genetic testing of all genes has to be completed in all patients even if a first genetic defect has been found.

Dilated cardiomyopathy

Clinical presentation

Ventricular dilatation can have different causes ranging from myocarditis as a result of viral infections to coronary artery disease and systemic diseases. The most frequent forms of dilated cardiomyopathy (DCM) are those secondary to ischaemic and valvular heart disease. In some instances, no aetiological factor can be identified and the disease is defined as 'idiopathic'. Idiopathic DCM may occur in sporadic as well in familial forms. The familial form of DCM frequently presents with associated cardiac phenotypes (e.g. conduction delays, bradycardia, atrioventricular and intraventricular conduction delay) or extracardiac phenotypes (e.g. skeletal muscle dystrophy, myopathy, deafness, mental retardation, endocrine system abnormalities, granulocytopenia).

In the absence of a familial distribution of the phenotype and of extracardiac manifestations pointing to specific syndromes no clear-cut differences of clinical

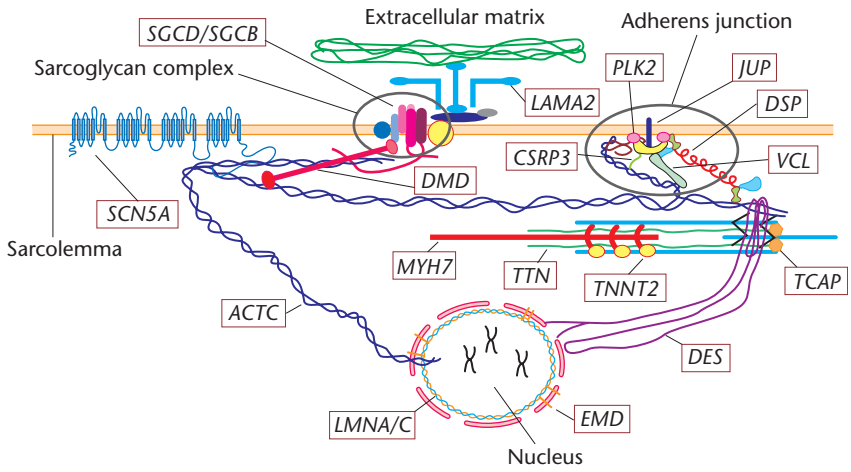

Figure 7.2 Structural proteins associated with inherited dilated cardiomyopathy. Four groups of proteins are identified: cytoskeletal proteins, sarcoglycan complex proteins, nuclear envelope proteins and adherens junction proteins.

manifestations exist between familial and non-familial cases. Therefore, the diagnosis of idiopathic DCM (which may have a genetic origin) is often made by excluding all clinically detectable causes.

Genetic bases and pathophysiology

The list of DCM genes is still expanding. Some additional genetic loci (a chromosomal region where the affected gene is likely to be located) have been identified by linkage analysis but no genes or mutations have been so far identified.

The most frequent pattern of inheritance is autosomal dominant, but autosomal recessive, matrilineal and X-linked transmissions have also been reported.

No studies have systematically assessed the relative prevalence of the various DCM subtypes. The genetic screening of single genes in a relatively large series of patients with idiopathic DCM yielded few genotyped probands [5]. Therefore, either several genes account for a few patients each, or a major DCM-related gene is yet to be identified.

An important consequence of this blurred picture is the limited clinical applicability of genetic testing (Table 7.1). The only exception is probably the *LMNA* gene, which appears to account for a relatively large number of patients and is associated with a specific phenotype that facilitates the selection of patients who are likely to benefit from the genetic analysis (see below).

The genetic heterogeneity of DCM is impressive and five major groups of molecules are involved:

- cytoskeletal proteins;
- adherens junction proteins;
- nuclear envelope and nuclear lamina proteins;
- sarcomeric proteins;
- mitochondrial DNA.

CYTOSKELETAL PROTEINS

The cytoskeletal-protein-encoding genes known to cause DCM are: desmin (*DES*), δ- and β-sarcoglycan (*SGCD, SGCB*), dystrophin (*DMD*) and cardiac actin (also considered a sarcomeric protein by some authors) (Fig. 7.2).

Desmin belongs to the intermediate filaments protein family and is thought to take part in force transmission. The *DES* gene may cause both DCM associated with skeletal myopathy, and pure DCM. Desmin-related disease is a familial disorder characterized by skeletal muscle weakness, cardiac conduction blocks, arrhythmias, restrictive heart failure, and by intracytoplasmic accumulation of desmin-reactive deposits in cardiac and skeletal muscle cells.

δ-Sarcoglycan is a transmembrane protein that heterotetramerizes with the other sarcoglycan isoforms (α, β and γ) to form a protein aggregate defined as 'dystrophin-associated transmembrane complex' (Fig. 7.2). This structure plays an important role in maintaining the correct assembly of the cytoskeleton and in allowing efficient force transmission in contractile cells. Mutational analysis has demonstrated that the *SGCD* gene may also cause a pure DCM phenotype in the absence of any sign of skeletal muscle involvement [17]. An additional sarcoglycan complex protein involved in a few DCM cases [18] is the β-sarcoglycan (*SGCB*) that primarily causes a severe autosomal recessive variant of limb-girdle muscular dystrophy.

The first hint for the involvement of dystrophin in a gene of X-linked DCM came from the observation of low levels of cardiac dystrophin but normal skeletal muscle dystrophin in some patients, and by linkage data mapping the X-linked DCM locus to the short arm of chromosome X. These data have subsequently been confirmed by other authors who identified DCM mutations in the *DMD* gene [19].

ADHERENS JUNCTION PROTEINS

Inherited DCM may also develop as a result of mutations of the genes encoding for adherens junction proteins (Fig. 7.2), a macromolecular complex connecting the cytoskeleton to the adjacent cells. Metavinculin results from a cardiac-specific splice variant of the vinculin gene (*VCL*). It interacts with α-actinin to anchor the cytoskeleton with the sarcolemma at the adherens junction level, thus participating in the cell-to-cell adhesion process. Altered interactions between metavinculin and actin have been reported in patients with *VCL* mutations [20]. There are anecdotal reports of additional genes (*DSP* and *CSRP3*) but their epidemiological relevance is not known at the present time.

NUCLEAR ENVELOPE AND NUCLEAR LAMINA PROTEINS

Two proteins of the nuclear structure have been associated with DCM: emerin, which causes the X-linked Emery–Dreifuss muscular dystrophy and lamin, which causes the more frequent autosomal dominant variant (Fig. 7.2).

Dilatation and conduction defects are the typical cardiac features of Emery–Dreifuss muscular dystrophy that may present with or without skeletal muscle abnormalities. In heart, the specific localization of emerin to desmosomes and adherens fascia could account for the characteristic conduction defects described in patients with Emery–Dreifuss muscular dystrophy. Since emerin is a ubiquitous protein the existence of alterations limited to skeletal and cardiac muscle remains difficult to explain.

There is another autosomal dominant muscular dystrophy with cardiac involvement that closely resembles Emery–Dreifuss muscular dystrophy but with normal emerin distribution. The locus for this autosomal dominant variant was mapped in 1999 [21] to chromosome 1 (1q11-q23) and mutations were reported in the *LMNA* gene, encoding two proteins of the nuclear lamina: lamins A and C. Lamins form dimers through their rod domain and interact with chromatin and with other key proteins of the inner nuclear membrane. When mutated, *LMNA* causes not only autosomal dominant Emery–Dreifuss muscular dystrophy but also autosomal dominant DCM with conduction defects with no muscular involvement. More than 60 known *LMNA/C* mutations may not only cause DCM and Emery–Dreifuss muscular dystrophy but also other allelic phenotypes: partial lipodystrophy, Charcot–Marie–Tooth disease, limb-girdle muscular dystrophy, partial lipodystrophy, mandibulosacral dysplasia and increased plasma leptin levels. The association of DCM with conduction defects is a typical feature of the *LMNA* mutation and it represents an indication for genetic testing in all patients with this phenotype.

SARCOMERIC PROTEINS

Actin has been traditionally considered a sarcomeric protein but its functional role is not only related to force generation but also to force transmission to the cytoskeleton. Although cardiac actin was known to be a cause of inherited HCM, its physiological role indicates that the *ACTC* gene is also a potential candidate for DCM. Olson *et al*. [22] were able to identify a single amino acid substitution in two families with DCM. Both mutations affected conserved amino acids in domains of actin that attached to Z bands and intercalated discs. Other studies have attempted to define the prevalence of actin defects in DCM families but have failed to find other relatives with actin-related disease [5].

While the 'double function' of the cardiac actin gene made it rational to suggest this protein as a potential candidate gene for both DCM and HCM, the identification of mutations of force-generating (sarcomeric) proteins in DCM patients has introduced a novel concept in the interpretation of DCM pathophysiology. Two of the major determinants of HCM, *MYH7* (cardiac myosin heavy chain) and *TNNT2* (cardiac troponin T) genes, may cause DCM [23] (Figs 7.1 and 7.2). Thus, DCM and HCM are allelic disorders in many instances and may have a similar pathogenesis. The thin border between HCM and DCM is well depicted by genotyped HCM patients who progress to DCM. Some cases of DCM may represent a final stage of HCM.

An additional sarcomeric protein causing DCM but not HCM is telethonin (*TCAP* gene) which is probably a very rare cause of cardiac dilatation and heart failure [24]. Telethonin is a sarcomeric protein that localizes to the Z discs of skeletal and cardiac muscle where it acts as a molecular 'ruler' for the assembly of the sarcomere by providing spatially defined binding sites for other sarcomeric proteins.

MITOCHONDRIAL DNA

Evidence of a mitochondrial form of DCM initially came from two cases of early-onset fatal DCM associated with the presence of large deletions of mitochondrial DNA [25]. Other reports followed and mutations in mitochondrial DNA encoding for histidine tRNA [26] and isoleucine tRNA [27] were identified. Interestingly, both mitochondrial DNA genes have also been implicated in HCM. Mitochondrial DNA defects cause very complex phenotypes with multiorgan involvement including deafness, focal glomerulosclerosis and epilepsy. The pathophysiological mechanisms leading from these mutations

to the clinical phenotype are largely unknown but are likely to involve energetic substrate production.

OTHER VARIANTS

A mutation in the *G4.5* gene in a family with malignant form of DCM co-segregating with an X-linked pattern has been reported [28]. This finding indicates that Barth syndrome and this DCM variant are allelic diseases. *G4.5* is expressed at high levels in cardiac and skeletal muscle and encodes for an alternatively spliced protein called tafazzin, which has no known similarities to other proteins and of which the function is unknown. Another *G4.5* allelic disease is left ventricular non-compaction (see below).

Additional genes that may cause rare instances of DCM have been reported. These genetic variants not only involve structures devoted to force transmission control (*DSP*) and chaperone-like proteins (*CRYAB*), but also transmembrane ion channel subunits (*ABCC9*). This latter finding has been very recently confirmed in two independent studies in which cardiac sodium channel (*SCN5A*) mutations have been identified in six families with DCM, heart failure and atrial fibrillation (the *SCN5A* gene is discussed in more detail below).

In summary, genetically determined abnormalities of several proteins have been associated with DCM. Most of the DCM genes have an important physiological role in maintaining cell shape, mechanical resistance and morphological integrity. The cytoskeleton contributes substantially to cell stability by anchoring subcellular structures and it is also linked with desmosomes, thus participating in cell-to-cell adhesion. Sarcomeric proteins, and possibly mitochondrial DNA, may cause DCM by an impairment of the force generation capabilities. Given the important physiological role of DCM-related genes, it is not surprising that mutations cause often severe phenotypes with multiorgan involvement.

Left ventricular non-compaction

Left ventricular non-compaction is the result of an arrest of myocardial morphogenesis. The disorder is characterized by a hypertrophic left ventricle with deep trabeculations and poor systolic function, with or without associated left ventricular dilatation. In some cases, the right ventricle is also affected. Left ventricular non-compaction may be an isolated disorder or it may be associated with congenital heart anomalies such as ventricular septal defects, pulmonary valve stenosis, and atrial septal defects. It becomes clinically overt at any time from infancy through adolescence and the clinical course of the disease is often severe with a progressive worsening of contractile function. Three genes causing left ventricular non-compaction are known:

- Alpha-dystrobrevin (*DTNA*), a protein participating in the dystrophin-associated complex [29].
- Cypher/*ZASP*, a gene encoding for a component of the Z-line in both skeletal and cardiac muscle, participating in assembly and targeting of cytoskeletal proteins [30] .
- *G4.5*, a gene with unknown function also causing X-linked DCM [29].

This evidence shows that the pathophysiology of left ventricular non-compaction is similar to that of DCM associated with cytoskeletal protein mutations.

Arrhythmogenic right ventricular cardiomyopathy

Clinical presentation and management

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC) is a predominantly autosomal dominant disease characterized by myocardial degeneration and fibro-fatty infiltration of the right ventricular free wall, the subtricuspid region and the outflow tract. A rare autosomal recessive variant (Naxos disease) characterized by the typical myocardial involvement, palmar keratosis and woolly hair has been also described.

Syncope and sudden death as a result of ventricular arrhythmias, often precipitated by intense physical activity, are the typical manifestations of ARVC. Conversely, the cases progressing to heart failure are rare. Diagnosis is based on the identification of right ventricular dilatation, adipose tissue infiltration and kinetic abnormalities. Electrocardiographic (ECG) abnormalities are also important diagnostic criteria (T-wave inversion in leads V1–V3 and late potentials on the signal-averaged ECG. Major and minor diagnostic criteria have been defined by a task force of the European Society of Cardiology) [31].

Genetic bases and pathophysiology

The estimated prevalence of ARVC ranges from 6 per 10 000 in the general population to 4.4 per 1000 in some areas with higher prevalence. However, it is unclear whether such regional clustering of the disease is related to real differences in the distribution of disease alleles in certain areas or to referral bias occurring in some specialized centres. Nine genetic loci are known. For three of them, the autosomal dominant *ARVD2* [32], *ARVD8* [33] and *ARVD9* [34], and for the autosomal recessive *NAXOS1* [35] the corresponding gene has been identified.

Based on the published data the *ARVD9* (plakophilin gene, *PLK2*) appears to be the most prevalent variant. Desmoplakin (*DSP*), identified in few *ARVD8* families, and plakoglobin (*JUP*), causing *NAXOS1*, are major constituents of the desmosomes and the intermediate junc-

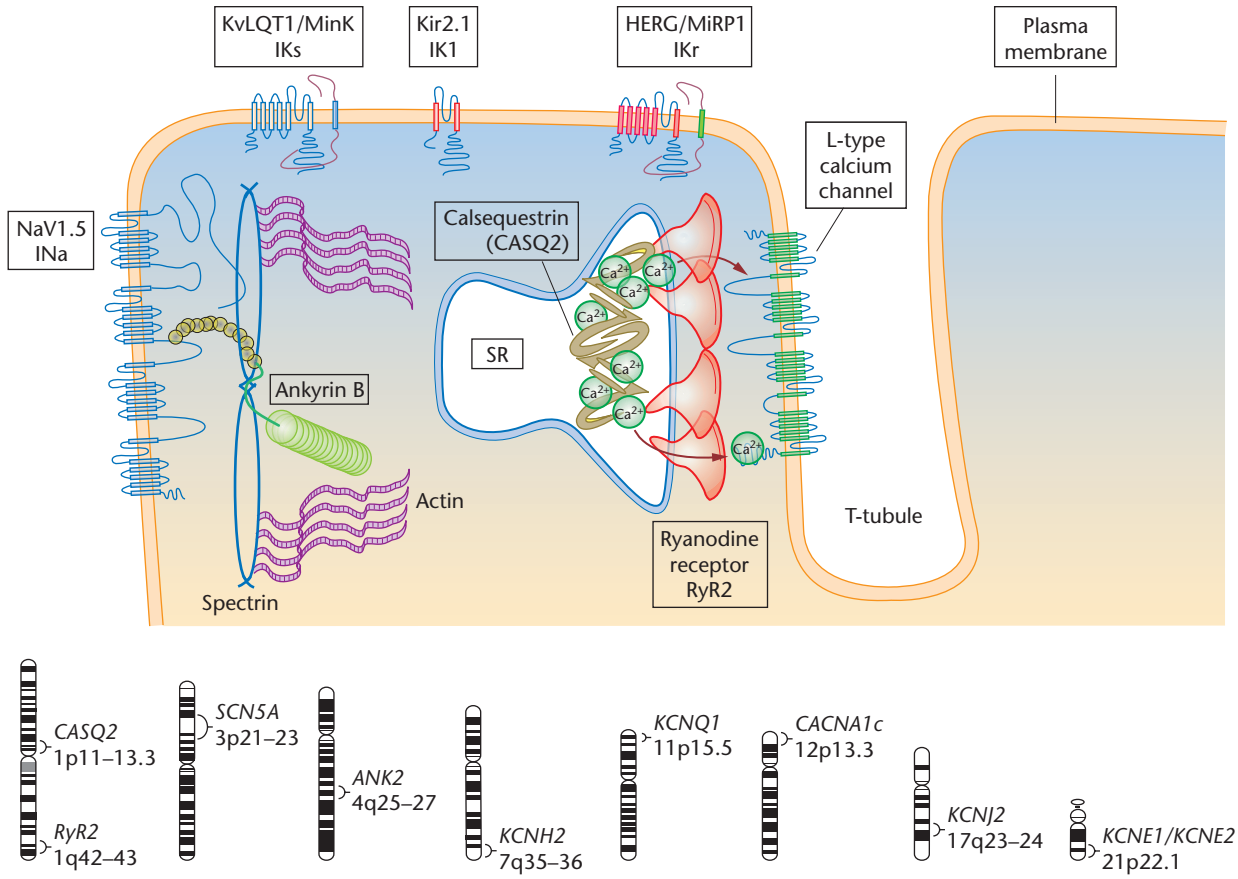

Figure 7.3 Diagram showing the proteins involved in the pathogenesis of monogenic diseases causing arrhythmias and sudden death in the structurally normal heart. The relevant proteins are highlighted with boxes. The inset at the bottom shows the chromosomal localization of the corresponding genes (see text for details).

tions (Fig. 7.2). They link the cytoskeleton, by binding the intermediate filaments, to the plasmalemma and adjacent cells. Mutations in genes encoding for desmoplakin and plakoglobin suggest that altered integrity at cardiac myocyte cell–cell junctions may promote myocyte degeneration and death. Interestingly the pathogenetic mechanisms of right ventricle dilatation likely to be involved in these variants appear similar to those of dilated cardiomyopathy as a result of abnormalities in cytoskeletal proteins.

The fourth ARVC gene (locus: *ARVD2*) is the cardiac ryanodine receptor, RyR2 (see section on catecholaminergic polymorphic ventricular tachycardia for details) (Fig. 7.3). *ARVD2* constitutes a rare and clinically atypical or 'concealed' form of arrhythmogenic right ventricular dysplasia and presents with exercise-induced bidirectional ventricular tachycardia very similar to those of catecholaminergic polymorphic ventricular tachycardia. It is still a matter of debate whether such patients fulfil the diagnostic criteria for ARVC.

Few patients with ARVC have been successfully genotyped so far, and the genes mentioned above account for a minority of the clinically affected patients. If we consider that apoptosis [36] and inflammation [37] may also play a role in ARVC pathogenesis, it is rational to hypothesize that only a fraction of ARVC cases could be determined by a single gene mutation. Some cases might be the result of environmental factors (e.g. viral myocarditis) acting on a vulnerable substrate that in turn may be determined by several genetic factors (SNPs), thus setting the picture of a polygenic disease.

Marfan syndrome

Clinical presentation and diagnosis

Marfan syndrome (MFS) affects mainly the skeletal apparatus, the eyes and the cardiovascular system. Skeletal abnormalities include: increased height, disproportionately

long limbs and digits, anterior chest deformity, mild to moderate joint laxity and vertebral column deformity (scoliosis and thoracic lordosis) [38]. Myopia, increased axial orbital length, corneal flatness and subluxation of the lenses (ectopia lentis) are ocular findings. At the cardiovascular level, mitral valve prolapse, mitral regurgitation, dilatation of the aortic root and aortic regurgitation have been reported [38]. The major life-threatening cardiovascular complication is aneurysm of the aorta and aortic dissection, which represent the major cause of mortality and morbidity [38].

The mean age of death for overt MFS is 45 years, but the survival is modulated by gender, with males having a worse prognosis. Usually, sporadic MFS cases present with more severe phenotypes compared with the familial ones. In these latter instances, diagnosis during infancy may be difficult. Diagnostic criteria for MFS have been published pointing to the need for the application of strict rules, especially for relatives, to avoid over-diagnosis [39]. MFS is usually treated with beta-blockers and surgery, when indicated, to correct aortic dilatation.

Genetic bases and pathophysiology

MFS presents with highly variable expression, but complete non-penetrance (silent gene carriers) has not been definitively documented. In the pregenetic era, a number of abnormalities of connective tissue proteins were reported and the pathophysiology of the disease was attributed to abnormalities of collagen primary structure and cross-linking and to abnormal hyaluronic acid synthesis. A consistent deficiency of elastin-associated microfibrillar fibres was also shown, and directed attention toward fibrillin, a glycoprotein of the microfibrillar component of the elastic fibre system.

When MFS was mapped to chromosome 15, the fibrillin gene (*FBN1*) was immediately identified as a strong candidate. In 1991 [40] the first *FBN1* mutation in a patient with MFS was reported. This finding was subsequently confirmed by several groups and it is now evident that *FBN1* accounts for the vast majority of MFS with more than 300 mutations published in the last decade. A second locus on 3p25–p24.2 was mapped in 1994 but the corresponding gene has not yet been identified [41].

Interestingly, *FBN1* mutations have been found not only in MFS but also in a range of connective tissue disorders, collectively termed 'fibrillinopathies', ranging from mild phenotypes, such as isolated ectopia lentis, to severe disorders including neonatal MFS, which generally leads to death within the first 2 years of life.

The pathophysiology of fibrillin-linked MFS is characterized by an abnormal metabolism of this protein. Mutated fibrillin subunits appear to exert a dominant-negative effect on the wild-type subunits, thus inhibiting the correct polymerization of collagen fibres. Other *in vitro* assays have suggested that, while synthesis and secretion of the polypeptides is unaffected, mutated polypeptides were significantly more susceptible to proteolytic degradation as compared with their wild-type counterparts.

Genetic screening of *FBN1* leads to the identification of a pathogenetic mutation in the majority of cases (Table 7.1).

Inherited (monogenic) disorders in the structurally normal heart

This group of diseases typically occurs in the absence of morpholoigical abnormalities of the heart. They are also called 'primary electrical disorders' or 'inherited arrhythmogenic diseases' because their primary manifestation is a cardiac arrhythmia (Fig. 7.3). A peculiar electrocardiographic phenotype, marker of electrical instability, is often recognized. Common symptoms are syncope and sudden death as a result of ventricular fibrillation. The common denominator is the abnormality of proteins controlling the excitability of myocardial cells. In recent years, mounting evidence has highlighted the concept that allelic variants (i.e. two or more phenotypes caused by mutations in the same gene) are the rule rather than the exception in these conditions [42]. The *KCNQ1* gene causes the type 1 variant of long QT syndrome, and the type 2 variant of short QT syndrome and familial atrial fibrillation. Likewise, *KCNH2* causes both long QT syndrome type 2 and short QT syndrome type 1, and the cardiac sodium channel gene (*SCN5A*) causes long QT syndrome, Brugada syndrome, progressive cardiac conduction defect and sick sinus syndrome (Fig. 7.4). Finally *KCNJ2* (the inward rectifier gene) causes Andersen syndrome and short QT syndrome [42,43].

Long QT syndrome

Clinical presentation

The long QT syndrome (LQTS) is an inherited arrhythmogenic disease occurring in the structurally normal heart that may cause sudden death. The mean age of onset of symptoms (syncope or sudden death) is 12 years and earlier onset is usually associated with a more severe form of the disease. The estimated prevalence of this disorder is between 1 per 10 000 and 1 per 5000. Two major

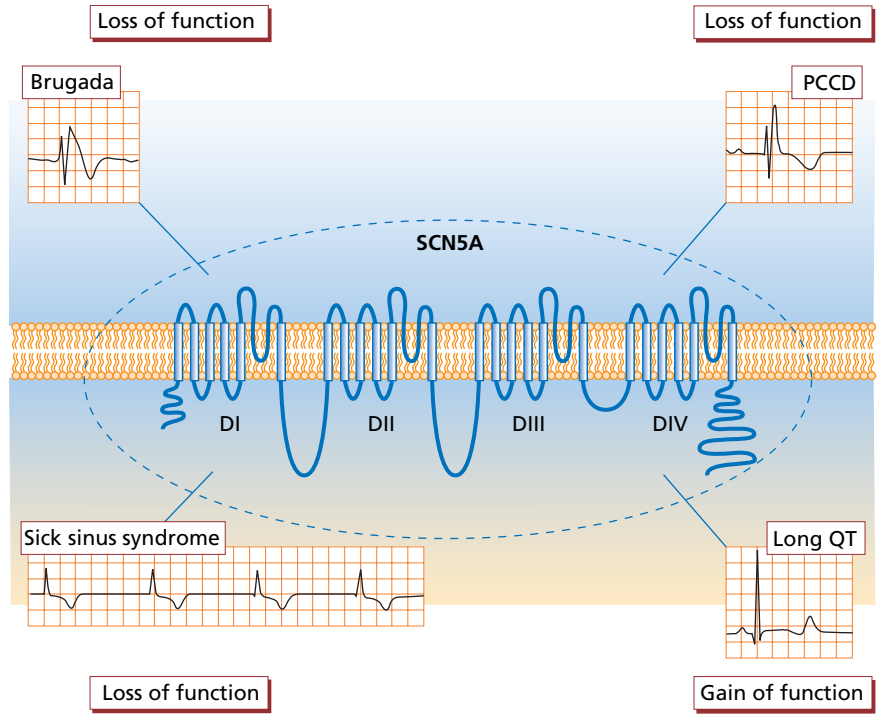

Figure 7.4 Schematic representation of the Nav1.5 protein and ECG phenotypes caused by cardiac sodium channel (*SCN5A*) mutations. The net effects of the genetic defects demonstrated in the *in vitro* studies are also reported.

phenotypic variants were originally described in the early 1960s: one autosomal dominant (Romano–Ward syndrome) and one rare autosomal recessive (Jervell and Lange-Nielsen syndrome, JLN) also presenting with sensorineural deafness. Another rare LQTS variant presenting with syndactyly and congenital heart defects has recently been linked to a cardiac calcium channel mutation.

Affected patients have abnormally prolonged repolarization (QT interval on the surface electrocardiogram), abnormal T-wave morphology and life-threatening cardiac arrhythmias [44]. Cardiac events are often precipitated by physical or emotional stress but in a small subset cardiac events occur at rest [44]. This observation constitutes the basis for the effectiveness of beta-blockers, which are the cornerstone of therapy in LQTS. For patients unresponsive to this approach, an implantable cardioverter-defibrillator and/or cardiac sympathetic denervation have been proposed. As discussed in the 'genotype–phenotype' section LQTS is the inherited cardiac disease in which genetic data have proved to be most helpful for patient management. Accordingly, locus-specific risk stratification for therapeutic management has been proposed.

Genetic bases and pathophysiology

There are currently eight identified LQTS genes. The typical LQTS phenotype with or without deafness may be the result of mutations in five different genes while three variants display QT interval prolongation in the context of a multiorgan disease (Andersen syndrome and Timothy syndrome) or with additional electrocardiographic features (LQT4—see below). The discovery of the genetic basis of LQTS started in the early 1990s with the mapping of four LQTS loci on chromosomes 11, 3, 7 and 4 [42]. The genes for these loci have been subsequently identified as *KCNQ1* (LQT1), *KCNH2* (LQT2) and *SCN5A* (LQT3) [42]. More recently, mutations in two additional genes on chromosome 21, *KCNE1* (LQT5) and *KCNE2* (LQT6), were reported. All the LQT1–3 and LQT5–8 genes encode for cardiac ion channel subunits (Figs 7.3 and 7.5). The exception is LQT4 which is caused by mutations in the *ANK2* gene: an intracellular protein called ankyrin B that is involved in ion channel anchoring and proper localization to the plasmalemma [45] (Fig. 7.3).

Sporadic LQTS patients have been described clinically and molecular genetics has allowed the distinction between patients who have *de novo* mutations and those that are the only clinically affected subject in a family with low penetrance [46] or, probably in rare instances, they may originate from parental mosaicism [47].

Defective I_{Ks} (LQT1, LQT5, JLN1 and JLN2)

KCNQ1 (causing LQT1 and JLN1) and *KCNE1* (causing LQT5 and JLN2) encode respectively for the alpha-subunit (*KvLQT1*) and the beta-subunit (*MinK*) of the potassium

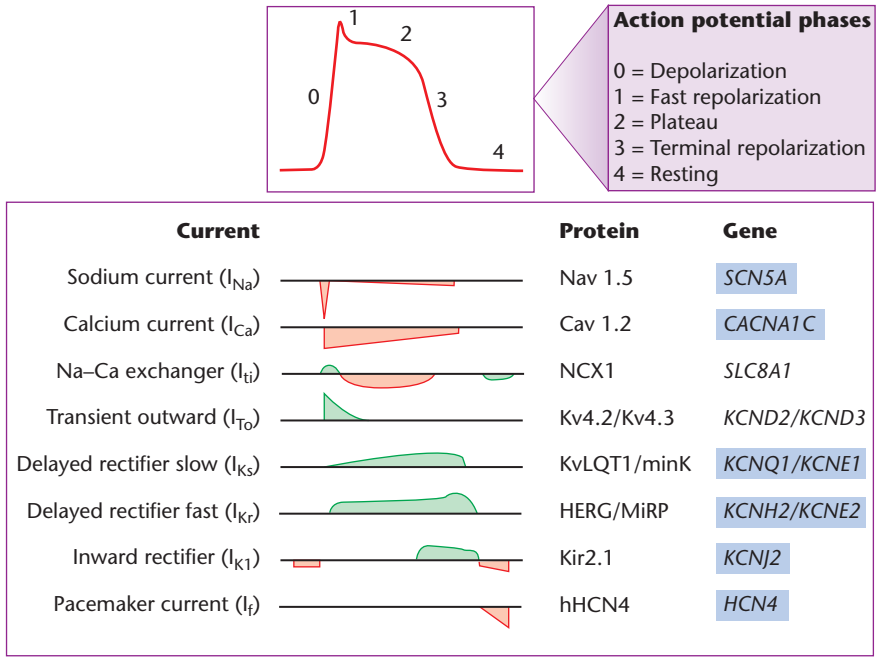

Figure 7.5 Ionic currents underlying the cardiac action potential. A ventricular action potential is represented with its four distinct phases, which are defined in the inset. The bottom panel from left to right shows the ionic current names with the abbreviated standard definition in brackets, a schematic representation of their time course during the action potential phases (red colour indicates an inward—going into the cell—current while outward currents are depicted in green). Some channels may conduct in inward or outward direction according to the membrane voltage at any given time point of the electrical cycle. The standard names of the protein and their respective genes are reported on the left. Blue-boxed gene symbols are those causing one or more clinical entities.

channel conducting the I_{Ks} current, the slow component of the delayed rectifier current (I_K), the major repolarizing current during phase 3 of the cardiac action potential (Fig. 7.5). To form a functional channel, KvLQT1 proteins form homotetramers and co-assemble with MinK subunits (Fig. 7.3).

LQT1 is the most prevalent genetic form of LQTS accounting for approximately 50% of genotyped patients. Hundreds of different mutations have been reported and *in vitro* expression of mutated proteins suggests multiple biophysical consequences but all of them ultimately causing a loss of function [48]. Homozygous or compound heterozygous mutations of *KCNQ1* also cause a Jervell and Lange-Nielsen form of LQTS (JLN1).

KCNE1 (LQT5) mutations are rather infrequent, accounting for approximately 2–3% of genotyped LQTS patients and they may cause both Romano–Ward (LQT5) and, if homozygous, Jervell and Lange-Nielsen (JLN2) syndromes.

From a clinical standpoint LQT1 patients present with a more straightforward adrenergic trigger for cardiac events [49]. LQT1 is also characterized by a lower penetrance and more benign prognosis compared with LQT2 and LQT3 [50].

Defective I_{Kr} (LQT2 and LQT6)

The *KCNH2* (LQT2) and *KCNE2* (LQT6) genes encode for the alpha-subunit (HERG) and the beta-subunit (MiRP) of the potassium channel conducting the I_{Kr} current, the rapid component of the cardiac delayed rectifier (Figs 7.3 and 7.5). The *KCNH2*-encoded protein, HERG, is a transmembrane protein that forms homotetramers in the plasmalemma to make up functional channels. LQT2 is the second most common variant of LQTS accounting for 35–40% of mutations. Functional expression studies have demonstrated that *KCNH2* mutations cause a reduction of the I_{Kr} current, but, similarly to LQT1 mutations, this effect is realized through different biophysical mechanisms [42] and also through intracellular processing abnormalities (trafficking defect) of the mutant proteins. LQT2 is characterized by higher penetrance and severity than LQT1, especially for females [50]. Mutations in the *KCNE2* gene (MiRP protein) cause the LQT6 variant of LQTS, which has a very low relative prevalence (< 1%) and the associated phenotypes are characterized by incomplete penetrance and very mild manifestations.

Defective I_{Na} (LQT3)

SCN5A encodes for the cardiac sodium channel conducting inward current (I_{Na}) (Fig. 7.5). At variance with the KvLQT1 and HERG proteins (which form homotetramers), a single *SCN5A* transcript forms a fully functional channel protein (called Nav1.5) (Fig. 7.3). The first reported *SCN5A* mutations in LQT3 patients were clustered in regions controlling channel inactivation, i.e. the linker between the third (DIII) and fourth (DIV) transmembrane domain (Fig. 7.4). Subsequently several allelic variants have been reported and functional expression studies have shown that, at variance with LQT1- and LQT2-associated mutations, LQT3 defects cause a gain of func-

tion (Fig. 7.4) with an increased I_{Na} [42]. The prevalence of LQT3 among LQTS patient is estimated to be 10–15%.

Defective ankyrin B (LQT4)

The phenotype of the LQT4 patients differs from typical LQTS. Most of the affected individuals, besides having QT interval prolongation, also present with severe sinus bradycardia, paroxysmal atrial fibrillation (detected in > 50% of the patients) and with polyphasic T waves. Recently, a missense mutation in the *ANK2* gene was identified in one family [45]. *ANK2* encodes for an intracellular protein (ankyrin B) that regulates the proper intracellular localization of plasmalemmal ion channels (calcium channel, sodium channel, sodium/calcium exchanger) and sarcoplasmic reticulum channels (ryanodine receptor, inositol triphosphate receptor). The low number of LQT4 patients genotyped so far prevents the definition of prevalence (which appears low) and phenotypic features of this variant of LQTS.

Defective I_{Ca} (LQT8—Timothy syndrome)

LQT8, also called Timothy syndrome, is a complex disorder in which severe QT interval prolongation is invariably associated with cutaneous syndactyly (hands and feet) and a number of additional abnormal phenotypes occurring with variable incidence among affected subjects. The markedly prolonged ventricular repolarization (the QT interval duration often exceeds 600 ms) frequently causes the appearance of 2 : 1 functional atrioventricular block. This severe cardiac phenotype is the major cause of the high mortality of this variant. A high proportion of LQT8 patients have congenital heart defects, mild mental retardation, autism and metabolic disturbances (severe hypoglycaemia, recurrent infections).

The therapeutic approach to LQT8 is unavoidably empiric because of the limited clinical experience. No indication of the effectiveness of beta-blockers or other drugs is available and, because of the high risk of severe arrhythmias, primary prevention with implantable cardioverter-defibrillator therapy may be considered.

A missense mutation (*G408R*) in the *CACNA1c* gene encoding for the cardiac voltage-gated calcium channel (CaV1.2) is the cause of all LQT8 cases so far reported [51]. The functional characterization *in vitro* showed a net increase of calcium inward current and a prolongation of action potential duration [51].

Genotype–phenotype correlation

In the last few years several studies have outlined the distinguishing features of the three most common genetic variants of LQTS (LQT1, LQT2, LQT3), which account for approximately 97% of all genotyped patients.

Locus-specific repolarization morphology (Fig. 7.6) and locus-specific triggers for cardiac events have been described [52]. LQT1 patients usually develop symptoms during physical activity, conversely LQT3 patients have events while at rest. Auditory stimuli and arousal are relatively specific triggers for LQT2 patients while swimming is a predisposing setting for cardiac events in LQT1 patients [52].

Locus-specific differences of the natural history of LQTS have also been demonstrated and allow genotype-based risk stratification [52] (Fig. 7.7). A QTc interval > 500 ms, and an LQT2 or LQT3 genotype determines the worst prognosis. Gender differentially modulates the outcome according to the underlying genetic defect: the LQT3 males and LQT2 females are the highest risk subgroups.

Finally, a recent study has demonstrated that the response to beta-blocker therapy is significantly modulated by the genotype and, specifically, the protection afforded by this therapy is only partial for LQT2 and LQT3 patients [53].

Brugada syndrome

Clinical presentation

Brugada syndrome is clinically characterized by ST segment elevation in the right precordial leads (V1 to V3), right bundle branch block and susceptibility to ventricular tachyarrhythmia (Fig. 7.6). The age of onset of clinical manifestations (syncope or cardiac arrest) is the third to fourth decade of life, although malignant forms with earlier or neonatal onset have been reported. Cardiac events typically occur during sleep or at rest [54]. The disease is inherited as an autosomal dominant trait but there is a striking male to female ratio of 8 : 1 of clinical manifestations. Since no effective pharmacological treatment has so far proved effective for Brugada syndrome patients, the implant of an automatic defibrillator (implantable cardioverter-defibrillator) is currently the only available option for high-risk patients. Therefore, risk stratification is a primary issue for Brugada syndrome management. Available evidence attributes the highest risk to patients with a spontaneously abnormal ECG and a history of syncope (Fig. 7.7). The usefulness of programmed electrical stimulation in the identification of high-risk patients is less certain. Implantable cardioverter-defibrillator therapy is also indicated in all cases for secondary prevention of ventricular fibrillation.

Genetic basis and pathophysiology

The initial report of *SCN5A* mutations in Brugada syndrome was published in 1998 and, as of today, tens of

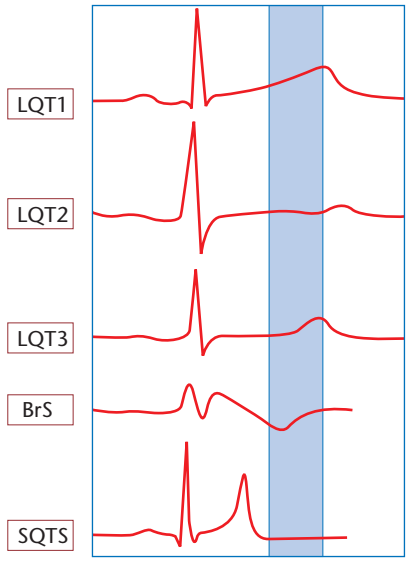

Figure 7.6 Examples of repolarization patterns caused by transmembrane cardiac ion channel mutations. The highlighted area depicts the range of a normal QT interval. LQT1, broad-based smooth T wave; LQT2, low amplitude and notched T wave; LQT3, straight ST segment with small, relatively rapid T wave; BrS, ST segment elevation and right bundle branch block. SQTS, short QT interval (< 320 ms), peaked and very fast T wave (resembling hyperkalaemia). LQT1/2/3, long QT syndromes type 1, type 2 and type 3; BrS, Brugada syndrome; SQTS, short QT syndrome.

different mutations have been reported (Fig. 7.8). Unfortunately, *SCN5A* accounts for no more than 20% of cases [55]. Therefore, genetic testing is not conclusive in 80% of Brugada syndrome patients. Another Brugada syndrome locus was mapped on the short arm of chromosome 3 (3p22-25) but so far the gene responsible for Brugada syndrome at this locus remains unknown. Given such limited knowledge the management and the risk stratification must be done on a clinical ground (Fig. 7.7). Nonetheless, genetic testing, when successful, allows confirmation of the diagnosis in borderline cases, identification of silent carriers and assessment of the reproductive risk (Table 7.1).

Several electrophysiological abnormalities have been identified by *in vitro* expression or Brugada syndrome mutation but the overall effect is that of a loss of sodium current [42] (Fig. 7.4). Very recently a novel mechanism was described for a *SCN5A* mutation that does not directly impair sodium current but causes a loss of binding of Nav1.5 with its intracellular targeting chaperone ankyrin G [56]. Consequently, mutated Nav1.5 is not properly localized at the level of intercalated discs.

Progressive cardiac conduction defect

Clinical presentation

Progressive cardiac conduction defect (PCCD) is a common disorder especially in the older population. It is characterized by progressive slowing of cardiac conduction through the His–Purkinje system with right or left bundle branch block and widening of the QRS complexes. In many cases the conduction block generates long pauses and severe bradycardia that may cause dizziness and syncope. PCCD is a major cause of pacemaker implantation in the world. In the majority of cases, it develops as a sporadic trait and is a degenerative disease that occurs with aging. However, in other instances familial cases have been reported, thus suggesting a genetic predisposition.

Genetic defects and pathophysiology

The first identified PCCD, also defined as progressive familial heart block (or PFHB), locus maps to 19q13.3 with an autosomal dominant inheritance. The linkage with this region was subsequently confirmed by other authors but the corresponding gene is yet to be identified. Conversely, by candidate gene screening, after the exclusion of the 19q linkage, another group [57] described two families with conduction defects and identified in both a mutation in the *SCN5A* gene (Fig. 7.8). *In vitro* assays suggest a loss of function effect [42] (Figs 7.4 and 7.8).

Sick sinus syndrome

Clinical presentation

Sick sinus syndrome (SSS) is a disorder phenotypically associated with PCCD that manifests with bradycardia, syncope, dizziness and fatigue. In some cases sinus node dysfunction and cardiac conduction defects may co-exist. As for PCCD, the majority of cases of SSS occur among older subjects and are thought to represent a manifestation of aging of myocardial specialized tissues controlling rhythm generation and conduction. Familial recurrence of SSS has been anecdotally reported and an autosomal dominant inheritance has been suggested but it is considered an 'exceptional finding'.

Genetic defects and pathophysiology

In 2003, Benson *et al*. [58] described five affected children from three kindreds with congenital SSS, and identified compound heterozygosity for six distinct mutations in the *SCN5A* gene. Two of these mutations had previously

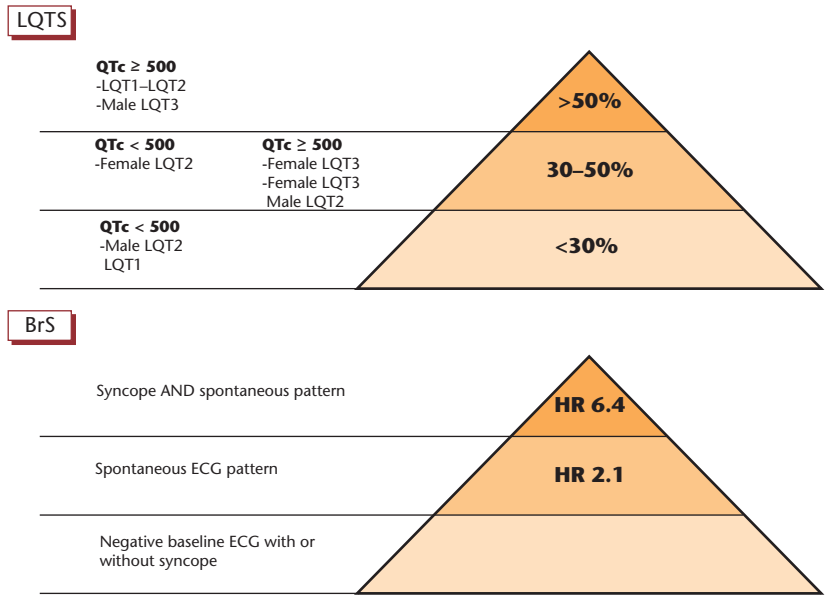

Figure 7.7 Upper panel: risk stratification according to clinical presentation and genotype in the long QT syndrome (LQTS). Three risk groups are identified for both diseases (low risk—pale orange, intermediate risk—light orange, and high risk—orange) according to the probability of experiencing a first cardiac event (syncope or cardiac arrest) in the absence of therapy from birth up to age 40 years. QTc, genotype and gender participate in the subgroup's definition among LQTS patients. Lower panel: risk stratification in Brugada syndrome (BrS) patients according to clinical presentation. The three risk groups (low risk—pale orange, intermediate risk—light orange, and high risk—orange) represent the variable risk of cardiac arrest or sudden death. The highest risk group comprises patients with a history of syncope and a spontaneously abnormal ECG (see text). These subjects have a more than six-fold risk increase (HR, hazard ratio 6.4) compared with reference category (negative baseline ECG, i.e. diagnostic only after administration of sodium-channel blockers—without syncope).

been associated with Brugada syndrome. Heterozygous carriers were asymptomatic, but showed subclinical cardiac conduction disease, particularly first-degree heart block suggesting a close relationship between PCCD and SSS. These data support an autosomal recessive pattern. As for PCCD, *in vitro* expression of the SSS mutation is consistent with a loss of function (Figs 7.4 and 7.8).

Familial atrial fibrillation

Clinical presentation

Atrial fibrillation is the most common sustained arrhythmia encountered in clinical practice. It is the most frequent cause of embolic stroke, accounting for

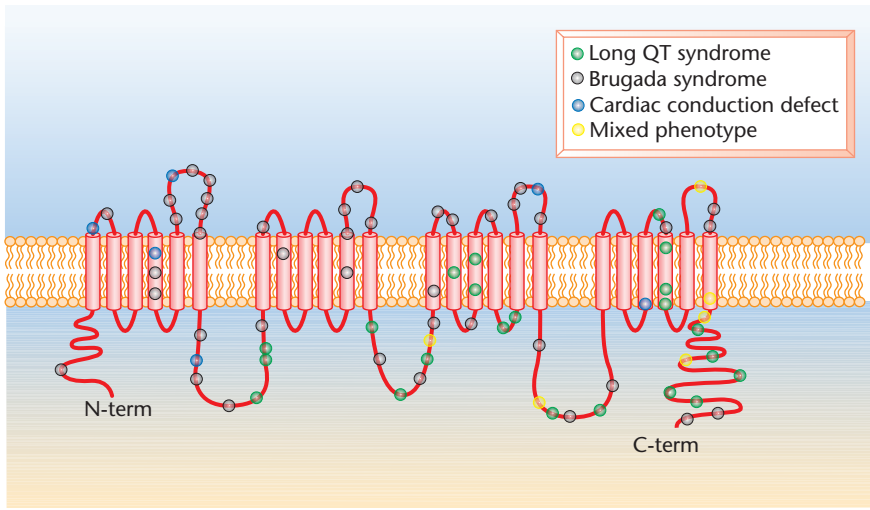

Figure 7.8 Schematic representation of a cardiac sodium-channel protein localizing across the lipid bilayer (as for the other ion channels of the plasmalemma, both amino- and carboxy-terminal extremities are in the intracellular compartment). Each reported mutation (as of January 2004) is represented by a circle with the number indicating the mutated codon with colour coding for the identified phenotypes. From http://pc4.fsm.it:81/cardmoc, with permission.

approximately 75 000 strokes per year in the USA and leading to more hospital admissions than any other arrhythmia. In the majority of cases atrial fibrillation is an acquired disorder but in 3–31% of cases no underlying cardiovascular disease can be detected and in some of them a familial inheritance is evident [59].

Genetic bases and pathophysiology

The first hint for a genetic predisposition to familial atrial fibrillation was published in 1997 [60]. In this report an autosomal dominant inheritance was demonstrated and linkage analysis mapped the familial atrial fibrillation locus to the long arm of chromosome 10 (10q22-q24) in three families. The gene located in this region has not been discovered yet. More recently, an additional locus has been mapped to the short arm of chromosome 11 (11p15.5) [61] and a missense mutation of *KCNQ1* has been reported. This genetic defect causes a gain-of-function effect on the KvLQT1/minK channel (see LQT1). The authors speculated that the *KCNQ1* familial atrial fibrillation mutation is likely to initiate and maintain the arrhythmia by reducing action potential duration and the effective refractory period in atrial myocytes.

Very recently, another familial atrial fibrillation mutation has been reported in the *KCNE2* gene (R27C) [62]. Functional studies revealed also in this case a gain-of-function of I_{Ks} (it should be recalled here that some authors suggest that KvLQT1 coassembles not only with minK but also with MirP protein).

Despite such important developments, it is important to emphasize the fact that the genetic determinants of the majority of familial atrial fibrillation cases remain poorly characterized. Therefore, the clinical applicability of genetic testing for familial atrial fibrillation is now limited to research activity.

Short QT syndrome

Clinical presentation

The first anecdotal report of a clinical condition characterized by abnormally short repolarization and ventricular arrhythmias was published in the year 2000 [63]. A persistently short QT interval (260–275 ms) has been reported with narrow and peaked T wave (absence of ST segment). Short QT syndrome (SQTS) is also characterized by the absence of structural heart defects, a quite remarkable familial history of sudden cardiac death and a typical, hyperkalaemic-like T-wave pattern at the resting ECG (Fig. 7.6).

Genetic bases and pathophysiology

Two different *KCNH2* missense mutations resulting in the same amino acid substitution were identified in two SQTS families [64]. By means of *in vitro* expression the authors observed a gain of function effect that explains the abbreviation of the action potential, which manifests as QT interval shortening on the surface ECG. Mutations in *KCNH2* are therefore the substrate for type 1 short QT syndrome (SQT1).

Genetic heterogeneity in SQTS was recently demonstrated by two groups of scientists who reported gain of function mutations in *KCNQ1* (SQT2 is therefore allelic to familial atrial fibrillation) [65] and in *KCNJ2* (SQT3 is therefore allelic to LQT7) [43].

The recent findings on the genetic defects underlying the SQTS phenotype, together with the data on LQT3 and BrS, demonstrate that at least five genes involved in the inherited arrhythmogenic diseases (*KCNQ1*, *KCNH2*, *SCN5A*, *KCNE2* and *KCNJ2*) may harbour both gain and loss of function mutations and that according to these primary biophysical consequences they give rise to different phenotypes. While the electrocardiographic manifestations diverge, the common denominator of these different clinical entities is the electrically unstable substrate that leads to cardiac arrhythmias and sudden death.

Catecholaminergic polymorphic ventricular tachycardia

Clinical presentation

Catecholaminergic polymorphic ventricular tachycardia (CPVT) [66] is characterized by exercise-induced or acute emotion-induced polymorphic ventricular arrhythmias, often causing syncope, a normal resting electrocardiogram and the absence of structural cardiac abnormalities. Symptoms usually develop during childhood or adolescence although there are anecdotal reports of first symptoms during adulthood. In approximately 13% of cases a cardiac arrest is the first manifestation of the disease and familial history of one or multiple sudden deaths is present in 30% of cases [67].

The resting electrocardiogram is unremarkable with the exception of sinus bradycardia and prominent 'U' waves reported in some patients [67]. Therefore, the diagnosis of CPVT at resting ECG is not feasible. Conversely ventricular arrhythmia is reproducibly induced during graded exercise (Fig. 7.9) with an alternating 180° QRS axis on a beat-to-beat basis (the so-called bidirectional VT), in some patients, and irregular polymorphic VT without a 'stable' QRS vector alternans in others. Stress-induced

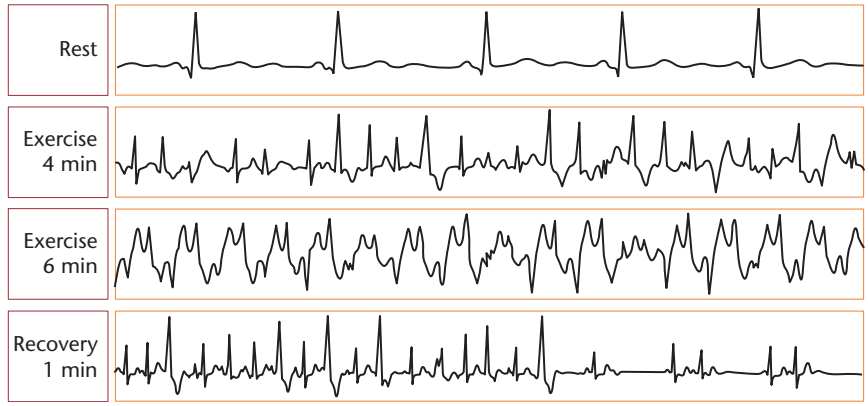

Figure 7.9 Electrocardiographic manifestations of catecholaminergic polymorphic ventricular tachycardia. The unremarkable ECG at rest is depicted in the top panel. During exercise ventricular tachyarrhythmia develops and progressively worsens while rapid relapse is evident during the recovery phase. Supraventricular arrhythmias are also evident in this patient.

supraventricular arrhythmias are also present in some patients [67].

Genetic bases and pathophysiology

CPVT1—AUTOSOMAL DOMINANT

Based on previous linkage analysis studies [68], the first CPVT gene was identified at the end of the year 2000 [69] as being the cardiac ryanodine receptor (*RyR2*). The role of RyR2 in the pathogenesis of CPVT was subsequently confirmed by other authors [70].

The ryanodine receptor is a large protein that tetramerizes across the membrane of the sarcoplasmic reticulum and forms the major sarcoplasmic reticulum Ca^{2+}-releasing channel in heart muscle. It plays a major role in the regulation of the intracellular calcium fluxes and excitation–contraction coupling. The identification of *RyR2* mutations in CPVT pointed attention for the first time to sarcoplasmic reticulum channels and to the pivotal role of intracellular Ca^{2+} handling in arrhythmogenesis and sudden death pathogenesis.

RyR2 mutant proteins have been expressed in different *in vitro* models (lipid bilayer, HEK293 cells, HL1-cardiomyocytes) and the results consistently showed that *RYR2* defects cause a Ca^{2+} 'leakage' from the sarcoplasmic reticulum during sympathetic (catecholamine) activation [71,72] while the basal channel activity appears normal.

CPVT2—AUTOSOMAL RECESSIVE

An autosomal recessive variant of CPVT has been described and linked to the short arm of chromosome one (1p23-21) [73]. Subsequently the same authors identified *CASQ2* as the gene for this locus [74]. *CASQ2* encodes the cardiac isoform of calsequestrin, a highly expressed transcript in the heart. It serves as a major Ca^{2+}-binding/buffering protein localized in the terminal cisternae of the sarcoplasmic reticulum. Calsequestrin is bound physically and functionally to the ryanodine receptor and cooperates in the control of the excitation–contraction coupling. The *CASQ2* defects so far identified cause the CPVT phenotype only in individuals carrying two abnormal alleles (homozygous or compound heterozygous) [67].

One experimental study [75] has shown that *CASQ2*-D307H mutation impairs the sarcoplasmic reticulum Ca^{2+}-storing and Ca^{2+}-release functions and destabilizes the Ca^{2+}-induced Ca^{2+}-release mechanism via reduced Ca^{2+} buffering inside the sarcoplasmic reticulum and/or altered responsiveness of the Ca^{2+}-release channel complex to luminal Ca^{2+}.

Taken together the experimental data demonstrated that both genes involved in CPVT pathogenesis affect the amount of Ca^{2+} released from the sarcoplasmic reticulum during adrenergic stimulation. Such an effect may create an electrically unstable substrate probably through triggered activity-mediated arrhythmogenesis.

Congenital heart defects

General aspects

Congenital heart defects (CHDs) are the most common form of birth defect, affecting about 8 in 1000 newborns. The classification of CHDs introduced by Clark in 1986 [76] groups cardiac malformations according to morphopathogenetic criteria instead of clinical or anatomical criteria to aid the identification of links among causes, mechanisms and defects. Epidemiological studies, particularly the Baltimore–Washington Infant Study, have shown that one-third of all CHDs are associated with

genetic syndromes or extracardiac anomalies [77]. The study of chromosomal disorders and autosomal dominant syndromes associated with specific anomalies of heart development is an essential step in identifying the genes involved in the pathogenesis of CHD. Furthermore, the accurate analysis of cardiac anatomy in patients with syndromic and non-syndromic CHDs has revealed that peculiar morphological subtypes of CHDs are related to specific genetic conditions.

Syndromic congenital heart defects

Down syndrome

Down syndrome, affecting 1 in 700 live births, is one of the most common genetic syndromes. It is related to trisomy 21, and clinical features include mental retardation, CHD, gastrointestinal malformations and characteristic facial dysmorphisms.

The prevalence of CHD in patients with Down syndrome ranges from 40 to 50%. Atrioventricular canal defect and ventricular septal defect are the CHDs more frequently found in Down syndrome (Table 7.3). The anatomical abnormalities in Down syndrome are quite specific: atrioventricular canal defect is usually complete, and is associated with left-sided obstructions, and ventricular septal defect is usually perimembranous. In some cases patients with Down syndrome may present with tetralogy of Fallot and atrial septal defect. Conversely, muscular and subarterial ventricular septal defects are rare.

Interestingly, 'mosaic' trisomy 21 is associated with a lower prevalence of CHD (30%) and less severe CHD. A Down syndrome 'critical region' on chromosome 21 has been identified following phenotypic, cytogenetic and molecular characterization of patients with partial trisomy 21. These studies showed that the 21q22.2-22.3 locus is crucially involved in Down syndrome-related CHDs [78]. This region contains about 60 genes, which are still poorly characterized.

Deletion 22 syndrome

Microdeletion of chromosome 22q11.2 is detectable in the majority of patients with DiGeorge, velocardiofacial and conotruncal anomaly syndrome. Clinical features include conotruncal CHD, palatal anomalies, neonatal

Table 7.3 Syndromic congenital heart defects

Genetic defect	OMIM ID	Cardiac defect
Trisomy 21 (DS)	190685 http://www.genetests.org/query?mim=190685	Atrioventricular canal defect Ventricular septal defect Atrial septal defect Tetralogy of Fallot
Microdeletion 22q11.2 (DiGeorge)	188400 http://www.genetests.org/query?mim=188400	Tetralogy of Fallot Pulmonary atresia with ventricular septal defect Interrupted aortic arch Truncus arteriosus Ventricular septal defect
PTPN11 gene mutations (Noonan)	163950 http://www.genetests.org/query?mim=163950	Pulmonary valve stenosis Hypertrophic cardiomyopathy Atrial septal defect Atrioventricular canal defect
PTPN11 gene mutations (LEOPARD)	151100 http://www.genetests.org/query?mim=151100	Hypertrophic cardiomyopathy Pulmonary valve stenosis
Microdeletion 7q11.2 (Williams)	194050 http://www.genetests.org/query?mim=194050http://www.ncbi.nlm.nih.gov/ - Menu605678	Supravalvular aortic stenosis Peripheral pulmonary stenosis
EVC gene mutations (Ellis–van Creveld)	225500 http://www.genetests.org/query?mim=225500	Atrioventricular canal defect Common atrium
TBX5 gene mutations (Holt–Oram)	142900 http://www.genetests.org/query?mim=142900	Atrial septal defect Ventricular septal defect Atrioventricular canal defect Conduction defect

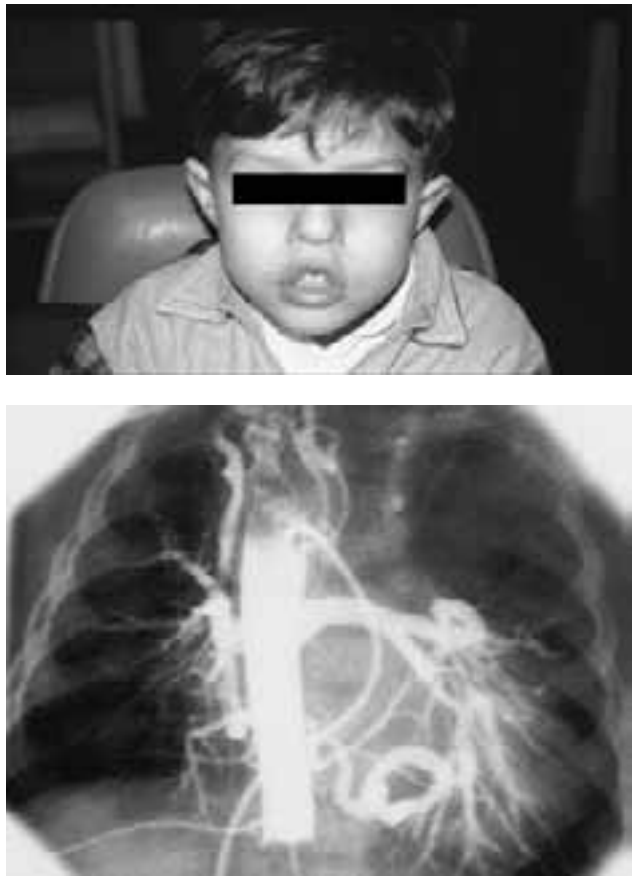

Figure 7.10 (A) Facial appearance of a patient with deletion 22 syndrome, and (B) aortography injection showing pulmonary atresia with ventricular septal defect and major aorto-pulmonary collateral arteries in deletion 22.

hypocalcaemia, thymic hypoplasia and immunological deficiency, characteristic facial dysmorphisms (Fig. 7.10A), speech and learning disabilities. There is wide variability in the clinical spectrum, ranging from death in the neonatal period to presentation with mild facial features and hypernasal speech.

Patients with deletion 22 syndrome often have abnormalities in four areas of the cardiovascular system: the aortic arch, the pulmonary arteries, the infundibular septum and the semilunar valves. In particular, the aortic arch can be right-sided, cervical, double, and the subclavian artery can be aberrant [79] (Fig. 7.10B; Table 7.3). The most frequently diagnosed abnormalities are tetralogy of Fallot (20–45%), pulmonary atresia with ventricular septal defect (15–30%), interrupted aortic arch (5–20%) and truncus arteriosus (5–10%) [79–81]. Interrupted aortic arch, truncus arteriosus and pulmonary atresia with ventricular septal defect demonstrate a specific association with deletion 22. In fact, deletion 22 is diagnosed in 45–50% of patients with interrupted aortic arch (particularly the 60–80% of those with interrupted aortic arch type B), in 45% of patients with pulmonary atresia and ventricular septal defect, and in 30–35% of patients with truncus arteriosus [79,82].

Deletion 22 is exceptionally rare among children with non-syndromic conotruncal defects, and patients with CHD and deletion 22 always present one or more extracardiac anomalies. Therefore, testing for deletion 22 is only indicated for patients in whom the heart defects are associated with the phenotypic spectrum of DiGeorge/velocardiofacial syndrome, and in those presenting with distinct anatomic conotruncal defect subtypes.

The majority of patients carry a common 3-Mb deletion, and at least 30 genes have been mapped in the deleted region. Although *TBX1* mutations have been detected recently in some patients with clinical features of DiGeorge/velocardiofacial syndrome without a detectable deletion 22 [83], it remains unclear whether several genes must be haplo-insufficient to cause a clinical phenotype or whether a single locus predominates.

Noonan syndrome and LEOPARD syndrome

Noonan syndrome is a genetic disorder characterized by CHD, facial dysmorphisms, short stature, webbed neck, chest deformities, undescended testes and cardiac malformations (50% of the cases), and hypertrophic cardiomyopathy. Pulmonary stenosis, atrioventricular canal defect, left-sided obstructive lesions, atrial septal defect and tetralogy of Fallot have been described [84]. The atrioventricular canal defect of patients with Noonan syndrome is generally 'partial', and is frequently associated with subaortic stenosis. Left-sided anatomic obstruction in Noonan syndrome can also occur (left mitral abnormalities or coarctation of the aorta).

Approximately 40% of patients with Noonan syndrome have missense mutations in the *PTPN11* gene, which encodes for the protein tyrosine phosphatase SHP2 [85].

LEOPARD syndrome is an autosomal dominant condition characterized by lentigines and 'café-au-lait' spots, CHD or arrhythmia, facial anomalies, short stature, retarded growth and sensorineural deafness. This syndrome shares several clinical features with Noonan syndrome. Specific *PTPN11* mutations have been found in almost all analysed patients with LEOPARD syndrome, proving that LEOPARD and Noonan syndromes are allelic conditions [86].

A genotype–phenotype correlation analysis shows that the distribution of CHDs is different among the two syndromes: pulmonary valve stenosis is most common in Noonan syndrome patients (mutation in exon 8), while

hypertrophic cardiomyopathy is predominant in patients with LEOPARD syndrome, associated with mutations in exons 7 and 12 [86,87]. Atrial septal defect is related to exon 3 mutations, while atrioventricular canal defect and mitral valve anomalies are related to different exon mutations [86,87].

Williams syndrome

Williams syndrome is a congenital disorder characterized by typical facial appearance, CHD, renal anomalies, growth delay, and mental retardation with a specific psychocognitive profile. The syndrome arises from a hemizygous deletion in chromosome band 7q11.23, including the gene for elastin (*ELN*) and approximately 20 surrounding genes [88]. The cardiovascular effect of the *ELN* deletion is a generalized elastin arteriopathy. The most commonly detected cardiovascular abnormality is supravalvular aortic stenosis, with a prevalence of 75% in most reported series. Histologically, there are hypertrophy and focal necrosis of the intima, and disorganization of the media of the aortic wall.

Supravalvular aortic stenosis may be isolated or, more frequently, associated with peripheral pulmonary arterial stenosis. This figure represents a rather typical phenotype, which is almost exclusive to patients with Williams syndrome. Other phenotypes include peripheral pulmonary stenosis (particularly in infants) (50%), aortic insufficiency (20%) and mitral valve prolapse (15%), and hypertension (50%).

Ellis–van Creveld syndrome

Ellis–van Creveld syndrome is an autosomal recessive disorder characterized by osteochondrodysplasia with narrow thoracic cage and short-limb dwarfism, distinct CHD, postaxial polydactyly of hands (Fig. 7.11A) and feet, and ectodermal anomalies. Cardiac involvement occurs in 60% of the patients. Partial atrioventricular canal defect with common atrium and persistent left superior vena cava is the prevalent CHD in this syndrome. Linkage analyses have mapped Ellis–van Creveld syndrome to locus 4p16.1, and a mutation in *EVC*, a gene located inside this 'critical region', has been detected [89].

Holt–Oram syndrome

The Holt–Oram syndrome is a developmental disorder characterized by malformations of the radial ray of the forelimb and CHD (Fig. 7.11B). The syndrome is transmitted as an autosomal dominant trait that is highly penetrant, although the clinical manifestations vary in differently affected subjects. Cardiac abnormalities include atrial septal defect, muscular ventricular septal defect, atrioventricular canal defect and conduction defects (Table 7.3).

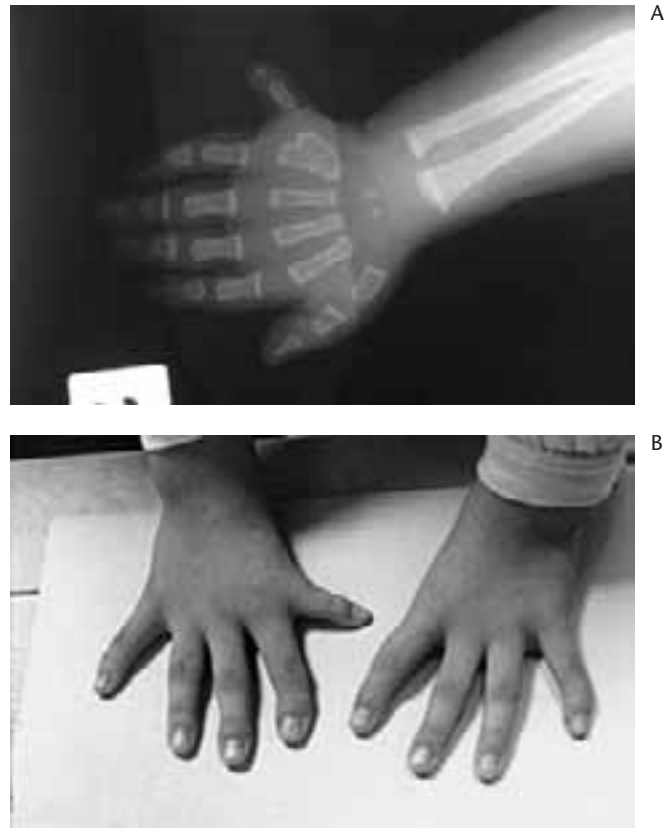

Figure 7.11 Hand X-ray examination of a patient with Ellis–van Creveld syndrome (A), showing postaxial polydactyly, and hands of a patient with Holt–Oram syndrome (B), showing radial aplasia and hypoplasia.

Mutations in *TBX5*, a member of the Brachyury(T) gene family, have been reported in Holt–Oram syndrome [90,91]. Animal models show that *TBX5* is particularly expressed at the atrial level and in the left-sided endocardium of the ventricular septum. This observation may explain the presence of atrial septal defect and muscular ventricular septal defect in this syndrome. Interestingly *TBX5* also causes a non-syndromic variant of CHD (see below).

Heterotaxia

Heterotaxia is a very complex condition including various forms of lateralization defects such as polysplenia syndrome, also known as left isomerism, and asplenia syndrome, also known as right isomerism. Left- or central-sided liver and intestinal heterotaxia can be detected as additional lateralization defects in these patients.

Table 7.4 Chromosomal loci and genes implicated in heterotaxia

Locus	Locus name	Gene symbol	Definition/gene function	OMIM ID
Xq26.2	HTX1	*ZIC3**	Zinc finger protein of cerebellum	306955 http://www.genetests.org/query?mim=306955
2q21.2	HTX2	*CFC1**	Cryptic protein	605376
6p21	HTX3	Unknown	Heterotaxy, visceral	606325 and 601086
3p25.3	—	*CRELD1**	Cysteine-rich protein	607170
3p22–p21.3	—	*ACVR2B*	Activin A receptor, type IIB	602730
1q42.1	—	*LEFTYB*	Left–right determination factor	601877
18p	—	Unknown	Deletion 18p syndrome	607500

*Also implicated in non-syndromic CHD.

The cardiac defect in heterotaxia consists of anomalies of the systemic and pulmonary veins, anomalies of the atrial septation and ventricular loop, and anomalies of the conotruncal region. Patients with the asplenia phenotype have right pulmonary isomerism and more severe cardiac defects, including total anomalous pulmonary venous drainage, transposition of the great arteries, complete atrioventricular canal defect and pulmonary atresia [92]. In contrast, patients with the polysplenia phenotype have left pulmonary isomerism and, usually, less severe cardiac defects, including interruption of the vena cava, partial atrioventricular canal defect and systemic outflow tract obstructions [92,93].

Several genes and chromosomal loci are implicated in heterotaxia (Table 7.4), and the available evidence suggests that an apparently single genetic defect can result in multiple phenotypes.

In addition, deletions of *LEFTYA* and *LEFTYB* in humans are found in association with left pulmonary isomerism, complete atrioventricular canal and left ventricular hypoplasia [94]. Among chromosomal anomalies, deletion 18p syndrome is specifically associated with laterality defects and heterotaxia, suggesting that this could be a 'critical region' [95].

Non-syndromic congenital heart defects

Familial recurrence risk

A 'multifactorial' model has been proposed for non-syndromic CHDs, suggesting an interplay between several genetic loci and between these loci with environmental factors [96]. Notwithstanding this general concept, co-segregation analysis suggests monogenic or oligogenic inheritance in some specific cases. The risk of recurrence for CHD in sibs of patients with non-syndromic CHD is estimated to be around 3% [96]. The risk of recurrence for non-syndromic patients with atrioventricular canal defect, tetralogy of Fallot and transposition of the great arteries is between 1 and 4%. However, if two first-degree relatives are affected, the recurrence risk for the next child is two- to three-fold greater. The evaluation of risk figures in large series of patients has practical implications in genetic counselling. The evaluation of the anatomic features of CHD segregating in single families can be an important aid in the analysis of pathogenetic links between CHDs.

Monogenic congenital defects

The relevance of the polygenic model is challenged by the increasing number of cardiac defects found to be related to a monogenic or oligogenic inheritance:

- *CFC1* is one of the four members of the EGF-CFC gene family. *CFC1* mutations have been identified in humans with CHDs in heterotaxia syndrome and in patients with non-syndromic CHD.
- *CRELD1* is a cell adhesion molecule which is developmentally expressed in the heart. Mutations in this gene have been identified in 6% of a population including patients with non-Down syndrome atrioventricular canal defect.
- *FOG2* is a co-regulator of the transcription factor GATA4, which is expressed during early heart development. Gene mutations in mice can cause tricuspid atresia and tetralogy of Fallot. *FOG2* mutations have been recently identified in humans with tetralogy of Fallot.
- *GATA4* is a transcription factor essential for heart formation. Missense *GATA4* mutations have been found in two families segregating cardiac septal defects.

- *NKX2-5* gene is a transcription factor important in early cardiac development that plays a central role in the determination of myocardial cell fate. Mutations in the *NKX2-5* gene have been identified in individuals with CHD, prevalently atrial septal defect and tetralogy of Fallot, with and without atrioventricular conduction block.
- Mutations in *Prosit240*, a gene with high expression within the heart (aorta) and brain during development, were recently identified in three patients with transposition of the great arteries.
- *TBX5*, a gene belonging to the family of transcription factors T-box, is important for cardiac septation. Mutations in the human *TBX5* gene cause CHD in the setting of Holt–Oram syndrome. Recently, somatic mutation of *TBX5* in the cardiac tissue cells of nine patients with CHD without Holt–Oram syndrome, including atrial septal defect and atrioventricular canal defect, have been detected.
- *ZIC3* is a zinc finger transcription factor causing X-linked heterotaxia. Nevertheless, mutations in *ZIC3* have also been identified in patients with non-syndromic CHDs, including transposition of the great arteries.

Incomplete penetrance is very common among inherited non-syndromic CHD (the identification of a mutation in the normal parent of an affected child), suggesting the presence of strong genetic and/or epigenetic (environmental) modifiers. Furthermore the available data suggest a high degree of genetic heterogeneity in non-syndromic CHD. Therefore the polygenic/oligogenic and the monogenic hypotheses are not mutually exclusive.

Genetic predisposition to coronary artery disease

Polygenic coronary artery disease—principles

The vast majority of common coronary artery disease (CAD) occurs on the background of polygenic susceptibility. Whilst single gene disorders, such as familial hypercholesterolaemia, can cause CAD they represent only a small minority of cases. It is the nature of polygenic disease that any single genetic variant will only provide a small or modest contribution to risk. Atherosclerosis is a time-dependent, multistep process involving the interaction of many different key biochemical pathways, lipoprotein metabolism, coagulation and inflammation. Gene variants in any of these metabolic pathways may lead to altered function of key proteins and upset the delicate balance of homeostasis. Intermediate phenotypes such as hypertension, diabetes and obesity, themselves all polygenic traits, will interact to modulate risk.

Environmental risks such as smoking, sedentary lifestyle and high-calorie diets are not simply additive with genetic risk. Gene–environment interactions are critically important, and are believed to determine which genes are recruited to determine disease susceptibility—so-called 'context dependency' (Fig. 7.12). Thus, a polymorphism may have a modest or a negligible effect on CAD risk in different individuals according to their particular environment. This is discussed further below in relation to specific variants. Gene–gene interactions are also likely to

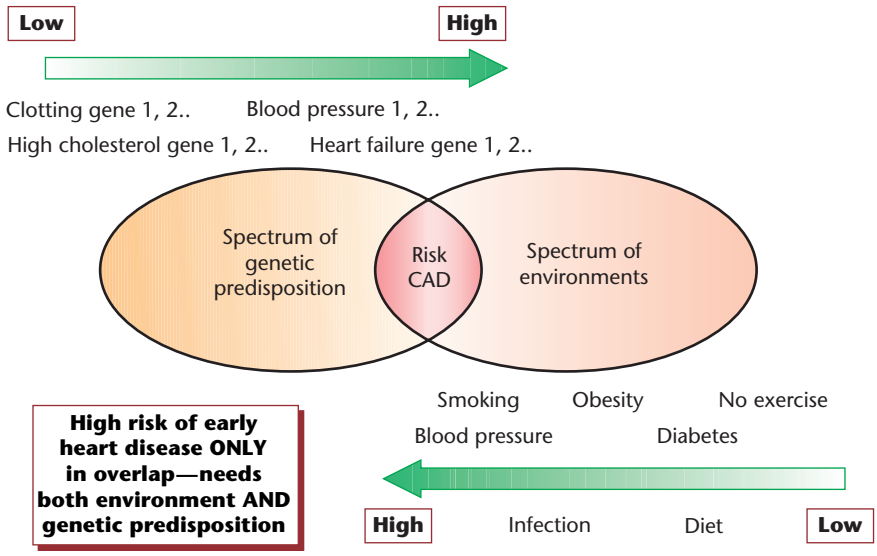

Figure 7.12 Model for gene–environment interaction (see text for details).

be important, although relatively little is understood about these in the context of CAD. Hundreds of genes may play a role in determining susceptibility to CAD [97]. Furthermore, different genes are likely to be important in different populations because of both genetic and environmental heterogeneity.

Two extreme models of allelic structure exist to explain the genetic basis of common polygenic diseases. It is likely that CAD will prove to be a mixture of the two but which model predominates will be highly significant. The common disease—common variant hypothesis predicts that common alleles at a restricted number of loci interact to cause disease [98]. The second model is that many rare alleles at a large number of loci cause disease, either single-handedly or in concert (multilocus–multiallele hypothesis) [98]. If the majority of CAD in the population is caused by common variants, considerably less time and effort will be required to determine the polygenic basis of CAD. Genetic testing would be more complicated and could be prohibitively expensive in the latter case. Thus far, most of the variations identified consist of a small number of common alleles (Table 7.5). Although too few loci have been identified for firm conclusions to be reached, this is consistent with theoretic calculations that predict that rare diseases result largely from recent mutations (thousands of years old or less), whereas common diseases result from old alleles present in ancestral populations [98].

The persistence of these alleles in the gene pool despite their propensity to cause fatal disease requires explanation. The first and most plausible reason is that most victims of CAD are past their reproductive years and therefore these genes are ignored by natural selection. The second is that alleles for cardiovascular disease are, for the most part, only lethal in the novel environment of modern humans, for example with cigarettes, abundant food and little exercise. The relative youth of modern society on an evolutionary time-scale means that these variants have not been subjected to natural selection. Finally, there may be some CAD-promoting alleles that are under positive selective pressure for unknown reasons.

Monogenic causes of CAD

Familial hypercholesterolaemia

Familial hypercholesterolaemia (FH) is an autosomal dominant inherited disorder. It has an estimated prevalence of 1 per 500, but is much more common in some populations which have recently increased in size (e.g. French-Canadians, Afrikaners and Lebanese) as a consequence of the 'founder' effect [99]. It is characterized by hypercholesterolaemia as a result of elevated plasma low-density lipoprotein (LDL) levels, cutaneous and tendon xanthomas, and premature CAD; there is usually a family history of one or more of these. Clinical coronary disease typically manifests in heterozygous FH men between the ages of 30 and 50 years, and in heterozygous FH women between 50 and 70 years [100]. FH is present in 5–10% of individuals who develop CAD under the

Table 7.5 Gene variants with published meta-analysis on coronary artery disease risk and > 2000 cases

Gene/polymorphism(s)	Risk genotype	No. of studies (No. of cases)	Size of effect (95% CI)
Cholesteryl ester transfer protein (*CETP*) TaqIB	B2B2	7 (7681)	0.78 (0.66–0.93)
Apolipoprotein B (*APOB*)			
Signal peptide Ins/Del	DD	22 (6007)	1.19 (1.05–1.35)
Gln4154Lys (Q4154L)	LL	14 (1796)	1.73 (1.19–2.50)
Lipoprotein lipase (*LPL*) Ser/Ter (S447X)	X+	4 (2252)	0.80 (0.7–1.0)
Apolipoprotein E (*APOE*) ε2, ε3, ε4	E3	10 (2152)	0.98 (0.85–1.14)
	E4		1.26 (1.13–1.41)
Paraoxonase-1 Q192R	Per R192	44 (10 106)	1.12 (1.07–1.16)*
Factor V-Leiden R506Q	Q+	6 (2390)	1.26 (0.94–1.67)‡
Plasminogen activator inhibitor-1 (PAI1) 5G/4G	4G4G	7 (2813)	1.20 (1.04–1.39)
Prothrombin G20210A	A+	19 (4944)	1.21 (0.99–1.59)†
GPIIb-IIIa P1(A2)	A2+	34 (6173)	1.13 (1.02–1.26)
Methylenetetrahydrofolate reductase (*MTHFR*) C677T	TT	40 (11 162)	1.14 (1.01–1.28)
Endothelial nitric oxide synthase (*eNOS*) Glu298Asp (E298D)	DD	14 (6036)	1.31 (1.1–1.51)
Angiotensin-converting enzyme (*ACE*) I/D	DD	51 (15 680)	1.22 (1.11–1.35)
Angiotensinogen Met235Thr (*M235T*)	TT	21 (4001)	1.19 (1.10–1.30)

*Risk fell to 1.05 (0.98–1.13) in five largest studies; †Odds ratio was 1.71 (1.16–3.42) in the 1359 subjects < 45 years; ‡Odds ratio 1.29 (1.03–1.61) upon inclusion of subjects < 55 years.

age of 55 years. Early identification of these high-risk individuals and implementation of primary prevention strategies will not only lead to longer healthier lives for those with FH but also to a decrease in the burden of coronary disease on a population basis [101]. Cost–benefit modelling based on data in the UK has demonstrated the effectiveness of cascade testing based on lipid measures in the relatives of FH patients [100], and an active programme in Holland based on molecular diagnosis has been particularly successful in identifying FH relatives [102]. Individuals with two FH-causing mutations (homozygotes and compound heterozygotes) are rare (less than 1 per million of the population in most countries); they have very severe hypercholesterolaemia and develop clinically significant CAD in the first or second decade of life.

FH is caused by a mutation in the low-density lipoprotein receptor gene (*LDLR*). To date over 700 different mutations have been identified world-wide (see http://www.ucl.ac.uk/fh) although the spectrum within a single country is much smaller. Another gene for FH is the apolipoprotein B-100 gene (*APOB*), a ligand for the LDL-receptor in which mutations have been identified in approximately 3% of FH patients in the UK, North Europe and the USA. This disorder has been designated familial defective apolipoprotein B-100 (FDB) [103]. FDB is somewhat milder in its expression but hypercholesterolaemia occurs in childhood, and early CAD is frequent. Additionally, a third locus has been identified on chromosome 1, with mutations in the gene encoding a secreted proteinase PCSK9 [104]. Finally, a recessive form of hypercholesterolaemia has been reported, caused by defects in a chaperone protein [105].

Genetic testing demonstrates a mutation in the LDLR or APOB gene for many of these patients, but this type of test is usually only available in a research setting. The usefulness of identifying the precise molecular cause of FH in a patient is primarily for the unambiguous identification of relatives, because cholesterol measures alone do not allow a clear-cut diagnosis in 10–15% of subjects.

Familial combined hyperlipidaemia

Familial combined hyperlipidaemia (FCH) is the most common of the severe hyperlipidaemias, with a prevalence of perhaps 1 per 100. The genetic inheritance pattern is complex and is likely to be polygenic/multifactorial, but the identification of the gene(s) involved is clinically relevant in identifying at-risk relatives. Recently a major gene (*USF1*) determining this phenotype has been identified in families from Finland [106]. It is a member of the basic helix–loop–helix leucine zipper (bHLH-zip) family of transcription factors. USFs are ubiquitously expressed and control the expression of genes involved in glucose and lipid metabolism. In the liver *USF1* regulates the expression of fatty acid synthase, a key enzyme in lipogenesis, in response to glucose, and is also active in adipose tissue and the pancreas. Currently no specific mutation in the *USF1* gene has been identified in patients, but a common haplotype defined by several SNPs is associated with risk of developing FCHL [106]. Whether any of these SNPs are truly functional, or whether the haplotypes are markers of an as yet undetermined functional variant, is unclear.

Coagulation disorders

Mutations in the genes for clotting factor V (factor V Leiden) and for prothrombin have been identified, each with a carrier frequency of 2–3%, but these mutations primarily increase the risk of venous thrombosis and have little effect on arterial thrombosis and risk of CAD.

The 'polygenic approach' to coronary artery disease

Phenotypes

For many measurable traits (phenotypes) there is good evidence for a relatively strongly genetic contribution to the determination of levels, which is usually estimated by 'heritability' (Fig. 7.13). For apoproteins and lipid traits, heritability varies between 40 and 60% [107], meaning that genetic factors are determining around half of the variability. For CRP and for fibrinogen, heritability is rather lower [108], reflecting the fact that they are acute-phase proteins and levels are greatly influenced by factors such as infection, malignancy or autoimmune disease. The consequence of this is that DNA-based tests do not add significantly to diagnostic utility or patient management, over-and-above the use of measures of established CAD risk factors.

Plasma lipoprotein a [Lp(a)] is a factor where levels are remarkably stable within an individual over time, and heritability is reported to be > 90% [109]. Variability at the locus coding for the apo(a) gene itself accounts for almost all of the variance of plasma Lp(a) in normal populations. The relevance of this is that a recent meta-analysis reported that levels of Lp(a) in the top tertile was associated with a 1.6-fold greater risk of CAD [110], an effect which is of similar magnitude as smoking, and

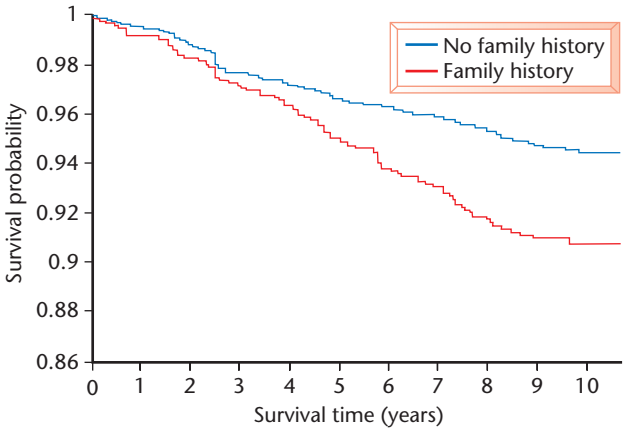

Figure 7.13 Kaplan–Meier plot for coronary artery disease (CAD) events in NPHSII, split by those with and without a family history of CAD. The NPHSII study enrolled healthy European middle-aged men. Of these 2827 answered unequivocally either yes or no to the question 'Has any person in your family ever had a heart attack?'. CAD events were defined as fatal and non-fatal myocardial infarction, plus coronary artery surgery and evidence of silent myocardial infarction on the follow-up ECG. The frequency of coronary events in men with a family history was 9.0% in comparison to 5.3% for those without. A positive family history was associated with a hazard ratio for CAD of 1.73 (95% CI 1.30, 2.31), which was 1.86 (1.37, 2.52) after adjustment for baseline age, body mass index, smoking, alcohol, cholesterol, triglyceride, fibrinogen and Lp(a).

thus the *APO*(*A*) gene would appear to be a major genetic factor for CAD.

Candidate genes for polygenic CAD

A large number of 'candidate' genes have already been investigated and a comprehensive list is beyond the scope of this report. One of the best studied genes codes for a plasma apolipoprotein called ApoE. The common *APOE* allele is called ε3, and there are two variants, ε4 and ε2 (the allele frequencies in Europeans are roughly 0.15 and 0.07 respectively). The sequence changes in the gene affect plasma clearance of the protein and the cholesterol-rich lipoproteins carrying them. The consequence of this is that there is a strong and consistent impact on plasma lipid levels (ε2 lowering and ε4 raising), which translates into an ε4 higher impact on CAD risk such that this genotype may explain 5–8% of the attributable risk of CAD in the population [111].

As shown in Table 7.5, several variants, including those in ApoE, appear to be associated with statistically robust although with rather modest effects on risk. Although these data seem encouraging, based as they are on the combined results from many studies, they need to be interpreted with some caution. Several analyses have suggested the presence of a publication bias: small statistically significant studies have been published, while those where the result was not significant have not appeared in the literature. Therefore, the meta-analysis estimates in Table 7.5 may actually be inflated, with the true value being smaller if data were available from all studies.

Although the meta-analysis risk estimates for each gene variant are modest they may still have some clinical value if they can be combined in developing a genetic risk profile. Thus, to develop useful genetic tests will require the simultaneous study of many genes and to understand how their effects add up and interact. Such understanding is still several years away.

Exemplars of environmental modification of genotype effects

The angiotensin-converting enzyme (ACE) polymorphism has probably been the most extensively studied polymorphism so far. One important feature of this polymorphism is that it appears to be a response modulator to a wide range of inducing factors. For example, it has been reported to modify the hypertrophic response of the heart to physical training, the restenotic process after stent angioplasty, the evolution of cardiac function after myocardial infarction and the survival of patients with congestive heart failure. Interestingly, other candidate gene polymorphisms may also have the characteristic of being response modifiers to a number of stimuli. A fibrinogen promoter polymorphism may affect the plasma fibrinogen response to cigarette smoking, physical training, or acute-phase reactions [112–114].

Cholesterol ester transfer protein and alcohol dehydrogenase genotypes modify the relationship between alcohol consumption and plasma high-density lipoprotein cholesterol [115,116], an amino acid variant that causes enzyme instability in the methylenetetrahydrofolate reductase protein affects the relationship between folate intake and plasma homocysteine [117] and the α-adducin polymorphism between that of salt intake and blood pressure and risk of myocardial infarction [118]. These interactions also need to be more widely replicated in larger studies but if confirmed they offer potential prospects for CAD prevention through the identification of responders to deleterious factors or beneficial ones.

Gene–environment interaction and risk prediction

Since it is now well-accepted that atherosclerosis and cardiovascular disease develop as a result of the interplay between the environment adopted by an individual and their genetic predisposition, any genetic test to predict

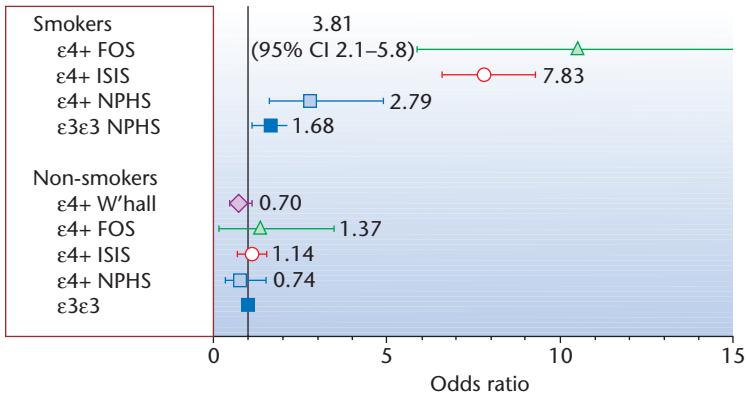

Figure 7.14 Risk of development of coronary artery disease and myocardial infarction according to *APOE* genotype and smoking habit. For each study the non-smokers with the genotype ε3–ε3 are set as the referent group. From references 119, 120 and 121.

cardiovascular disease must include such interactions in the algorithm. This interaction has also been termed the 'context dependency' to define the concept that, at the molecular level, the effect or by-product of the environmental insult modifies the molecular function of the product of the gene under observation. Genetic predisposition will also be confounded by gene–gene interactions, gender, ethnicity and pre-existing conditions such as obesity, diabetes and hypertension, as well as by factors such as medication, diet, alcohol consumption, exercise and stress. Taking into account such genotypic modifications of environmental factors for cardiovascular disease risk represents the second hurdle to successfully devising and implementing any genetic test.

Smoking is one of the major environmental risk factors influencing cardiovascular disease and there are several examples where the risk associated with smoking is modified by an individual's genotype. Several studies have reported that subjects carrying the *APOE-4* allele who were smokers had a particularly high cardiovascular disease risk compared to *APOE-4*-positive never-smokers, while risk was also low in *APOE-4*-positive ex-smokers, supporting the benefit of smoking cessation (Fig. 7.14). A re-analysis [119] of a recent large case–control study showed that compared with '*APOEε2,ε3* never-smokers', '*APOEε4* smokers' had significantly higher risk of CAD, with a greater than additive interaction on risk between genotype and smoking (relative excess risk of interaction of 1.62; 95%CI 0.4, 2.97). These data suggest that carrying the *APOEε4* allele does not significantly increase risk of cardiovascular disease unless the subject is a smoker. Clearly, any *APOE* genetic test result estimating risk in the absence of information about smoking will be misleading.

Personal perspective

In the last decade, we have learnt a lot about the genetic basis of cardiovascular diseases. Most of the knowledge gathered relates to the gene abnormalities causing monogenic diseases. This information, besides allowing the discovery of the causes of specific clinical entities, has allowed a deeper understanding of cardiovascular pathophysiology. It has now clearly shown that even in 'acquired' conditions (such as coronary artery disease) genetic factors are primary players for disease development and progression. The genotype information already has a clinical role for risk stratification and management for some specific disease, while in other instances there are still knowledge gaps to fill before this step may be achieved. Another limiting factor is the lack of availability of large-scale genotyping to assess the prevalence of inherited disorders in the population and to allow epidemiological studies to better quantify the role of SNPs in polygenic diseases.

In the future, genetics will become an important tool for defining patient-specific risk profiles in many diseases and it is likely to provide novel therapeutic strategies for patients that will eventually encompass gene therapy.

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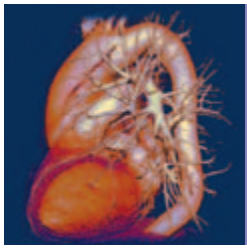


8 Clinical Pharmacology of Cardiovascular Drugs

Aroon Hingorani, Patrick Vallance and Raymond MacAllister

Summary

Rational use of drugs to treat cardiovascular disease requires an appreciation of the key principles of clinical pharmacology and specific knowledge about individual therapies. Amongst the medical disciplines, cardiovascular medicine has been in the vanguard of the development of an expanding evidence base upon which to base therapeutic decisions. Critical appraisal of this evidence has extended the remit of traditional clinical pharmacology. Therefore it is essential for those training in cardiology and cardiovascular medicine to be able to assess evidence from cardiovascular trials so that appropriate weighting can be given to trial data to inform therapeutic choice. This chapter summarizes the principles of clinical pharmacology that are relevant to cardiovascular drug therapy and provides a summary of the drugs commonly used to treat cardiovascular disease. In addition, it introduces fundamental concepts in the critical appraisal of trial data.

Introduction

Atherosclerosis and thrombosis underlie the occurrence of most clinical cardiovascular events such as stroke, angina, acute coronary syndromes, heart failure and dysrhythmias. The most widely used cardiovascular therapies modify these processes in the primary prevention, acute treatment and secondary prevention of these disorders (Fig. 8.1). Given the high incidence and prevalence of cardiovascular disease, its management represents a substantial cost for health-care providers. Moreover, in individual patients, several clinical syndromes may coexist, and be complicated by the presence of diabetes or renal impairment. As a result, many patients receive multiple drugs, often for many years. For these reasons, the therapeutic choice must be based on evidence detailing the efficacy, safety and cost of available therapies in a comparative manner. Special considerations may also apply in the elderly, in young women with childbearing potential or during pregnancy. The principles of rational prescribing, taking into account these factors, form the basis of clinical pharmacology, so that the right drug is administered to the right patient at the right time and for the right cost.

In the first section, basic concepts in clinical pharmacology are reviewed. The second section will cover relevant aspects of drug development and licensing while the third section discusses clinical trials, their design and interpretation. In each section, key principles will be highlighted using examples from cardiovascular therapeutics, with an emphasis on how to use the information contained in each section to make a rational choice of therapy. Specific details of commonly prescribed cardiovascular drug classes are covered in Tables 8.1 to 8.5. It is hoped that the principles outlined in this chapter will allow the rational prescriber to make informed and unbiased assessments of the efficacy and safety of new treatments as they arise.

Basic concepts in clinical pharmacology

Pharmacodynamics and dose–response relationships

The majority of cardiovascular drugs act on specific sites

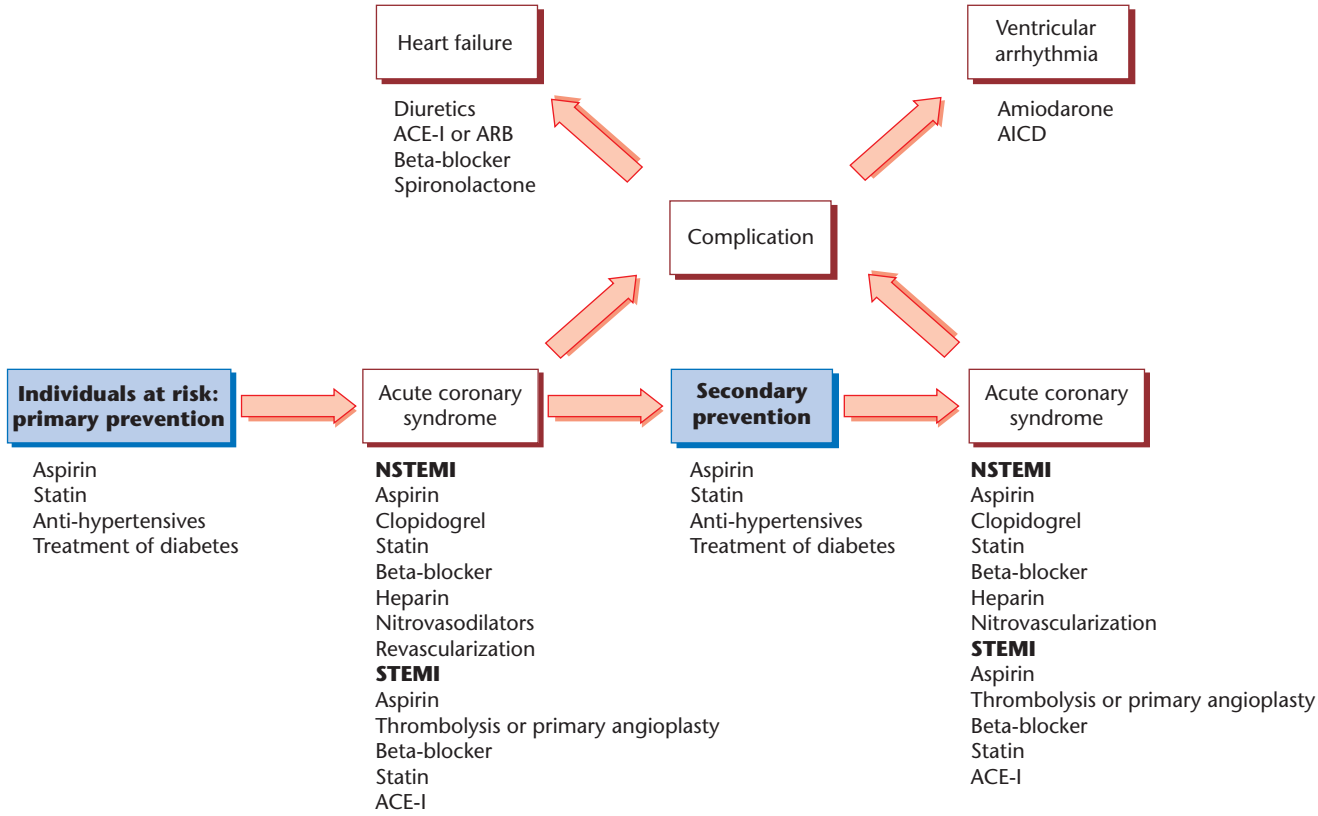


Figure 8.1 Place of drug therapies in treatment as defined by the natural history of atherothrombotic cardiovascular disease. ACE-1, angiotensin-converting enzyme inhibitor; AICD, automatic implantable cardioverter defibrillator.

on proteins, either inhibiting or stimulating enzymes, blocking or activating receptors or ion channels (an exception is cholestyramine, a cholesterol-binding agent that acts independently of a biological receptor). For certain older drugs the mechanism of action remains unclear (e.g. the vasodilator effects of hydralazine or the thiazide diuretics).

Classical molecular pharmacology deals with the interaction of a drug with its receptor. At a molecular level, the relationship between drug concentration (on a log scale) and response is typically sigmoidal. A similar relationship can be seen in patients between the dose administered and the physiological response (Fig. 8.2), although the dose–response relationship *in vivo* will also depend on pharmacokinetic parameters that determine the concentration of a drug that actually reaches its receptor. When a drug is introduced into clinical practice, the licensed dose-range ought to fall on the steep part of the dose–response curve, to facilitate dose-titration (Fig. 8.2). Occasionally, therapies are introduced into practice at a dose close to that producing a maximal response; e.g. captopril was first introduced at starting doses that were close to the plateau of the dose–response curve, resulting in significant first-dose hypotension [1]. Similarly,

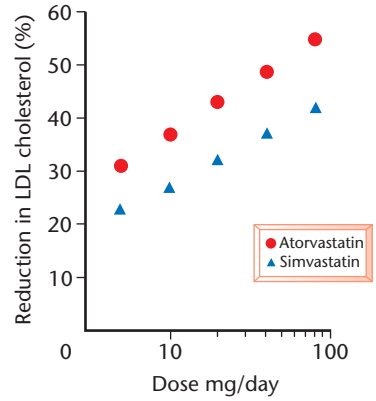


Figure 8.2 Dose–response curve of the effect of statins on low-density lipoprotein (LDL) cholesterol.

thiazide diuretics were used at supramaximal hypotensive doses for many years before it was realized that five-fold to 10-fold lower doses produced similar reductions in blood pressure but minimized adverse effects [2].

Potency and efficacy of drugs

Potency refers to the concentration (or dose) of a drug

Table 8.1 Antiplatelet agents

Drugs	Indications	Mechanism	Pharmacokinetics	Adverse effects
Aspirin	**Acute intervention** Acute coronary syndrome: STEMI, non-STEMI, unstable angina Transient ischaemic attack Acute stroke **Primary and secondary prevention of vascular events (see text)** **Coronary stent implantation** Combination with clopidogrel for 4–6 weeks. Aspirin alone continued thereafter	Irreversible inhibition of platelet COX-1 (acetylation of serine 529) resulting in inhibition of platelet thromboxane synthesis	Oral Once daily Antiplatelet dose: 75–160 mg Initial dose for acute presentations is 300 mg Plasma half-life 20 minutes Biological effect is longer lasting as a consequence of irreversible platelet COX inhibition Platelet function normalizes ~7 days after withdrawal (new platelet turnover to recover platelet COX activity)	Major gastrointestinal bleeding rate 0.1–0.2% per annum at a dose of 75 mg daily. No additional benefits of enteric coated preparations Higher doses associated with increased bleeding risks with no evidence for greater efficacy Allergic reactions Exacerbation of asthma
Clopidogrel	**Acute intervention** In addition to aspirin in patients with NSTEMI ACS at high risk **Secondary prevention of vascular events** Patients intolerant of aspirin	Inhibition of ADP-induced platelet activation by modification of the platelet $P2Y_{12}$ ADP receptor	Oral Once daily Maintenance dose is 75 mg daily Initial dose for in-patients with NSTEMI ACS 300 mg	Rash (0.26%) Major gastrointestinal bleeding (0.5%)*
Platelet IIB/IIIa receptor blockers (abciximab, eptifibatide, tirofiban)	Patients with ACS undergoing intervention Elective high-risk PCI	Inhibit the bridging of activated platelets by blocking the interaction of the IIb/IIIa receptor with fibrinogen	Intravenous weight adjusted bolus followed by an infusion	Bleeding Thrombocytopenia

*Data from the CAPRIE trial in which the equivalent rate for aspirin over a median follow-up of 18 months was 0.7%.
ACS, acute coronary syndrome; ADP, adenosine diphosphate; COX, cyclo-oxygenase; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction.

required to achieve a given effect. Figure 8.3(A) shows the relative potencies of two drugs that inhibit the same hypothetical enzyme. Drug A is more potent than drug B, and its dose–response curve is placed leftward on the *x*-axis. Note however that both drugs achieve the same maximal effect, so they are of equivalent maximal efficacies. It should also be evident that coadministration of A and B at their maximal doses will not produce a

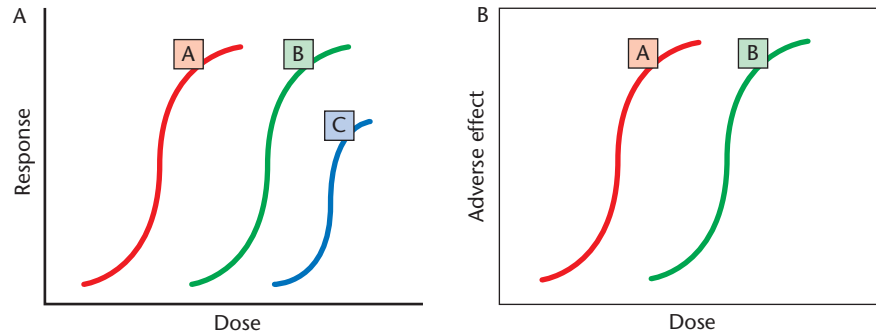


Figure 8.3 (A) Dose–response curves for drugs A, B and C that target the same receptor. A is more potent than B, but there are no differences in efficacy. C is less potent and less efficacious than A or B. (B) The increased potency of A over B is associated with increased chance of dose-dependent adverse effects; the smaller dose of A required to produce an effect will not necessarily be associated with fewer adverse effects.

Table 8.2 Anticoagulants and fibrinolytics

Drugs	Indications	Mechanism	Pharmacokinetics	Adverse effects
Heparins Unfractionated heparins (UFH) Low-molecular-weight heparins (LMWH)	**Venous thromboembolism** Prophylaxis and treatment of DVT and PE **Coronary artery disease** NSTEMI as adjunct to aspirin (and clopidogrel) STEMI only following treatment with tPA **Valvular heart disease** Anticoagulation in patients with mechanical valves undergoing surgery or other interventions	LMWH and UFH Indirect inhibition of thrombin (factor IIa) and factor Xa mediated through binding and activation of antithrombin III. UFH Additional direct binding and inhibition of IIa Ratio of Xa : IIa inhibition UFH 1:1 LMWH: 2:1 to 4:1	UFH Variable absorption by subcutaneous route. Therefore intravenous infusion adjusted to activated partial thromboplastin time LMWH Single or twice daily weight-adjusted subcutaneous injection Monitoring (by factor Xa assay) usually unnecessary	Bleeding Heparin-induced thrombocytopenia Osteoporosis LMWH preferred to UFH for most indications Exception is bridging anticoagulation around the time of surgery where intravenous UFH is preferred because of the rapid offset of action when the infusion is stopped
Warfarin	Treatment of venous thromboembolic disease Anticoagulation for a few weeks before and after cardioversion for atrial fibrillation Prevention of thromboembolic events in patients with mechanical valves	Inhibits vitamin K-dependent carboxylation and activation of factors II, VII, IX and X	Oral loading dose at initiation, with subsequent adjustment of single daily oral dose according to the international normalized ratio (INR)* Hepatic metabolism via CYP2C9 Potential for drug interactions is high	Narrow therapeutic window Bleeding risk substantially increased when INR > 4 Thromboembolic risk increased with INR < 1.7
Streptokinase (SK) **Alteplase (tPA)**	AMI in patients presenting with regional ST segment elevation or new LBBB	Promote conversion of plasminogen to plasmin either directly (tPA) or by forming a complex with plasminogen (SK)	SK: intravenous infusion over 30–60 minutes SK has up to 24-hour duration of action tPA: Intravenous bolus followed by a weight-adjusted infused dose over 90 minutes tPA infusion is followed by adjunctive intravenous heparin for 24–48 hours Action of tPA largely complete after 1 hour	Net excess of approximately two haemorrhagic strokes per 1000 patients treated more than offset by approximately 50 deaths prevented per 1000 patients treated if given within 12 hours of STEMI Major non-cerebral bleeding (4–13%) Hypotension (SK) Allergic reactions (SK) Absolute contraindications: haemorrhagic stroke at any time, ischaemic stroke within 6 months, major trauma or surgery within 3 weeks

*Target INR for treatment of venous thromboembolic disease and prevention of stroke in atrial fibrillation is 2.5. Target INR in patients with mechanical heart valves is 3.75.
DVT, deep vein thrombosis; LBBB, left bundle branch block; INR, international normalized ratio; NSTEMI, non-ST segment elevation myocardial infarction; PE, pulmonary embolism; STEMI, ST segment elevation myocardial infarction.

larger effect than administration of either A or B alone. For this reason, drugs with different mechanisms of action and different molecular targets tend to be used in combination therapy for cardiovascular disease, rather than combining drugs with the same mechanism. Drug C is both less potent and less efficacious than A or B.

Modest differences in potency between drugs with the same mechanism of action are rarely of clinical

Table 8.3 Vasodilators

Selected examples	Indications	Mechanism	Adverse effects
α-Adrenoceptor blockers Prazosin Doxazosin Phenoxybenzamine	Hypertension Heart failure Phaeochromocytoma (phenoxybenzamine)	Block α-adrenoreceptors on vascular smooth muscle Arteriolar and venodilatation	Headache, flushing, syncope, oedema
Angiotensin-converting enzyme inhibitors (ACEI) Captopril Enalapril Lisinopril	Hypertension Heart failure Secondary prevention following myocardial infarction	Inhibition of ACE leading to reduced formation of angiotensin II and impaired breakdown of bradykinin Blood pressure reduction Arterial and venous dilatation Promotion of sodium and water excretion	Hypotension Cough (5–10%) Hyperkalaemia Renal impairment (especially in presence of bilateral renal artery stenosis) Angioedema
Angiotensin receptor blockers (ARBs) Losartan Candesartan Irbesartan	As for ACEI inhibitors	Block angiotensin II receptor	As for ACE inhibitors (minus cough)
Calcium-channel blockers Dihydropyridine Nifedipine Amlodipine Benzothiazepine Diltiazem Phenylalkylamine Verapamil	Angina Hypertension Rate control of atrial flutter/fibrillation (diltiazem and verapamil only) Nifedipine used safely as antihypertensive in pregnancy	Blockade of L-type calcium channels Dihydropyridines exhibit *in vitro* selectivity for vascular L-type calcium channels Arteriolar vasodilatation, reflex tachycardia Non-dihydropyridines exhibit equivalent binding to vascular and cardiac channels Reduction in heart rate, atrioventricular nodal conduction Negative inosotropic effects and reduction in blood pressure	Flushing Headache Ankle oedema Reflex tachycardia (dihydropyridines) Bradycardia (other types)
Nitrovasodilators Glyceryl trinitrate Isosorbide mononitrate Isosorbide dinitrate Sodium nitroprusside	Angina Unstable angina Heart failure Pain relief post myocardial infarction Treatment of hypertensive encephalopathy (sodium nitroprusside)	Metabolized in vascular smooth muscle to release nitric oxide Relax arteries and veins, effect on veins predominates Reduce myocardial oxygen requirements (by reducing preload and afterload)	Headache, flushing, syncope Co-administration with phosphodiesterase V inhibitors (e.g. sildenafil) can lead to profound hypotension Cyanide toxicity (sodium nitroprusside)

importance. First, most prescribers are unaware of the molecular weights of the drugs they are prescribing, without which it is not possible accurately to compare the potency of drugs; e.g. weight for weight, amlodipine is approximately six times more potent than nifedipine (60 mg of nifedipine is needed to produce the same blood pressure lowering effect as 10 mg of amlodipine), but mole for mole, amlodipine is closer to 10 times more potent because of its greater molecular weight. Second, these differences in potency seldom make a material difference to prescriber or patient, as long as the drugs have the same vasodilator effect (efficacy). Similarly, atorvastatin is approximately four-fold more potent than simvastatin (weight for weight), but for most of the dose-range, the effect of atorvastatin can be reproduced by administering a larger dose of simvastatin [3]. Occasionally the issue of potency may become a problem if other effects of the drug molecule produce unwanted effects and the concentration–response relationship for these differ substantially from the concentration–response relationship for the wanted (therapeutic) effect. However, given that 90% of all adverse reactions to drugs are a consequence of their primary mechanism of action [4], the dose–response curve and the dose–adverse effect curve will usually both be shifted leftward for a more potent drug (Fig. 8.3B). There is evidence that this is the case for statins; the most potent statin, cerivastatin, had its marketing licence withdrawn because of toxicity [5], and

Table 8.4 HMG-CoA reductase inhibitors (statins)

Drugs	Indications	Mechanism	Pharmacokinetics	Interactions	Adverse effects
Simvastatin Pravastatin Lovastatin Fluvastatin Atorvastatin Rosuvastatin	Primary and secondary prevention of coronary heart disease	Inhibition of hepatocyte HMG-CoA reductase leading to increased expression of the hepatocyte LDL-receptor Statins lower total and LDL-cholesterol, as well as triglycerides, and raise HDL-cholesterol	Single daily dose usually administered in the evening Hepatic metabolism most via cytochrome P450 enzymes **Metabolized by CYP3A4** Atorvastatin Simvastatin Lovastatin **Metabolized by CYP2C9** Fluvastatin Rosuvastatin **Metabolized independently of CYP enzymes** Pravastatin	Toxicity may be enhanced by drugs which inhibit metabolism **Drugs which inhibit CYP3A4** Erythromycin Clarithromycin Fluoxetin Verapamil Cyclosporin **Drugs which inhibit CYP2C9** Amiodarone Fluoxetine Metronidazole	Muscle pain ± elevation of creatine kinase to 3–10 times normal (1–5%) Myositis with creatine kinase to > 10 times normal (0.1%) Rhabdomyolysis (0.15 deaths per 10 million prescriptions) Elevation of liver enzymes to less than three times normal (0.5–2.5%) Hepatitis

CK, creatinine kinase; CYP, cytochrome P450; HDL, high density lipoprotein; LDL, low density lipoprotein.

Table 8.5 Miscellaneous

Drugs	Indications	Mechanism	Adverse effects
Beta-blockers *lipid-soluble* Bisoprolol Carvedilol Metoprolol Propranolol *water-soluble* Atenolol Labetalol Sotalol	Hypertension Angina Secondary prevention post myocardial infarction Heart failure Adjunct to digoxin for rate control in atrial fibrillation Prophylaxis of paroxysmal atrial fibrillation (sotalol)	Blockade of β-adrenoreceptors with varying β1 and β2 selectivity Bradycardia Inhibition of renin production contributes to hypotensive response Improve left ventricular function in heart failure	Bronchospasm Bradycardia Cold peripheries Fatigue Impotence Sleep disturbance
Loop diuretics Furosemide	Heart failure	Natriuresis by blocking sodium/chloride co-transporter in ascending limb of the loop of Henle Intravascular volume depletion Intravenous administration may cause pulmonary vasodilatation in acute heart failure	Largely the same as thiazides
Potassium-sparing diuretics Amiloride Spironolactone	Weak antihypertensive effect Heart failure (particularly spironolactone) Diuretic-induced hypokalaemia	Amiloride blocks the sodium/potassium exchanger in the distal tubule; spironolactone blocks the aldosterone site of this transporter	Hyperkalaemia Gynaecomastia (spironolactone)
Thiazide diuretics Bendroflumethiazide	Hypertension Heart failure	Open potassium channels, natriuresis by blocking sodium/chloride co-transporter in proximal tubule Transient fall in cardiac output which returns to normal after 2–3 months; hypotensive effect by vasodilatation	At low doses metabolic adverse effects are minimal and of uncertain significance, postural hypotension, hypokalaemia Polyuria, gout, postural hypotension, hypokalaemia

dose-for-dose, the toxicity of atorvastatin is greater than for simvastatin [6].

Specificity of cardiovascular drug action

Specificity is determined by action on a single receptor or enzyme or subtypes of receptors. Depending on the location of the therapeutic target, it is also possible to achieve a degree of specificity of drug action within the cardiovascular system. For example, voltage-gated calcium channels make only a small contribution to the control of venous smooth muscle tone, and for this reason calcium-channel blockers are selective arterial dilators [7]. Vasoconstricting drugs with a degree of tissue specificity are used in the treatment of migraine; serotonin type 1 (5HT1) agonists targeting a receptor population on the cerebral vasculature. Similarly, vasopressin agonists produce a degree of preferential splanchnic vasoconstriction, and are used in the treatment of portal hypertension [8]. The selective dilator effects of sildenafil (type V phosphodiesterase inhibitor) on the penile and pulmonary vasculature may reflect the expression of this enzyme in these vascular beds [9]. However, many of these receptors are expressed in other cells and tissues, and when activated at these sites result in many of the recognized adverse effects of 5HT1 and vasopressin agonists (coronary spasm), and phosphodiesterase V (PDE V) inhibitors (systemic hypotension). Moreover, loss of specificity is commonly seen as the dose increases; Fig. 8.4 shows the dose–response curves for a drug acting at two receptors but with different potencies; at low doses receptor A is specifically activated but at higher doses where the dose–response curves converge, there is equivalent activation of receptors A and B. Selectivity of drugs is relative, not absolute.

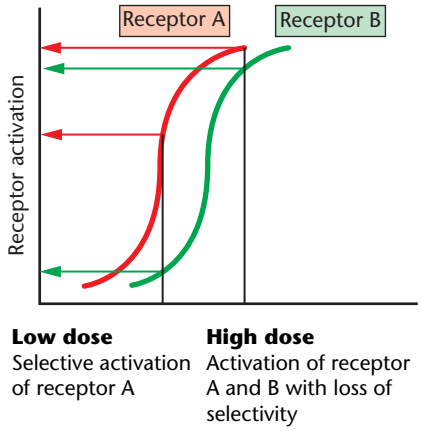


Figure 8.4 The effect of a drug with differing selectivity for two receptor subtypes. At low doses, and therefore low tissue concentrations, there is selective activation of receptor A; with increasing doses selectivity is lost as receptor B is activated. Gradual recruitment of additional molecular targets (receptors on enzymes) with increasing dose accounts for many common dose-dependent adverse effects.

Variation in the response to drug therapy

There appears to be substantial interindividual variation in the dose–response to drug therapy, which can arise because of differences in drug metabolism or elimination (pharmacokinetic), or because of physiological differences in the receptor or systems targeted (pharmcodynamic). At one extreme, a patient may be resistant to the effects of a drug, a good example being low-renin hypertension. This is common in patients of African-Caribbean origin and is responsible for the poor hypotensive response to therapies that block the renin–angiotensin system [beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers] when used as monotherapy [10]. Similarly, the response to unfractionated heparin is variable because of unpredictable absorption and protein binding following subcutaneous administration, and for this reason therapy needs to be monitored by measuring the activated partial thromboplastin time. Low-molecular-weight heparin has much more reliable absorption and has a predictable interaction with proteins, so it can be administered at a dose based solely on body weight rather than on clotting times. In the majority of cases, variation in response to a drug does not have such potentially catastrophic effects as can occur with poorly controlled anticoagulation, but nevertheless a threshold dose in one patient might be near maximal in another. In the case of warfarin, variation in response may reflect differential antagonism by endogenous vitamin K between individuals. Alternatively, variation may be a consequence of differences in drug metabolism, arising from common genetic variations; cytochrome CYP2C9 activity is a determinant of warfarin metabolism, and variation in the gene for this enzyme might account for a proportion of the variability in warfarin effect and susceptibility to bleeding [11].

The mean dose–response of a drug is in effect the aggregate of individual curves from individual patients. To avoid over-treatment, it is commonplace to perform some degree of dose-titration when initiating therapy; e.g. in elderly patients who are often more sensitive to the effects of vasodilators, it is usually appropriate to start treatment with low doses. Lastly, variation in response may be factitious; a patient might not be adhering to medication, an occurrence that is not uncommon when (as is the case in cardiovascular disease) preventative therapies are being used in combination without any symptomatic benefit apparent to patients.

Genetics as a cause of variation in response to drug therapy

The influence of genetic variation on drug response has been recognized for many years. For example, even before the precise genetic alteration was identified it was clear that the population could be divided into 'fast' or 'slow' acetylators and that this had implications for the metabolism and effects of certain drugs. In cardiovascular medicine, certain adverse responses to hydralazine were more common amongst slow acetylators. Similarly, it is known that a single gene defect can dramatically affect responses to drugs; individuals with deficient glucose-6-phosphatase dehydrogenase are prone to developing haemolytic anaemia in response to oxidizing drugs such as antimalarials [12].

However, in the past few years, interest in pharmacogenetics has increased as the human genetic sequence and its common variations have been identified and the concept of 'personalized medicines' has taken hold. Single gene defects tend to be rare and to be disease-causing mutations. Currently, there are a few examples of important changes that alter responses to cardiovascular drugs. Patients with the monogenic hypertensive syndromes exhibit exquisite hypotensive responsiveness to certain drugs. One example is Liddle's syndrome in which, as a result of activating mutations in the beta- or alpha-subunits of the epithelial sodium channel, amiloride, which targets this channel, reduces blood pressure and normalizes the electrolyte disturbance. Another example is that of glucocorticoid-remediable hyperaldosteronism, which is characterized by abnormal corticotropin-dependent aldosterone production because of the presence of a chimaeric gene; in these patients dexamethasone produces a reduction in blood pressure by suppressing corticotropin synthesis [13].

A more complex issue, and one that may impact significantly on prescribing, relates to common genetic variation. Most (probably all) genes show polymorphic variation with alterations in the base sequence between individuals. These base changes often occur in non-coding regions, when they may cause minor alterations in protein expression or gene transcription. When they occur in a coding region, they may alter the amino acid sequence of the mature protein in a conservative manner that causes subtle alterations in protein function.

These variants are insufficient to cause disease on their own but may alter disease susceptibility to a small degree. They may also alter the metabolizing enzymes, or protein targets of a drug to modify its effect. To date no polymorphic variant has been identified that exerts such a profound effect that it should alter prescribing patterns for cardiovascular drugs. A number of common variants in candidate genes that might influence statin responsiveness have been evaluated. Of these, small effects of polymorphisms in the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and apolipoprotein E genes have been reported but, given the inconsistency of genetic association studies of common variants, these findings require validation in very large studies. Even if confirmed, these effects are likely to be small in size, and unlikely to alter prescribing decisions for this group of drugs.

In the field of metabolism, genetic variation in the cytochrome P450 (CYP) enzymes is discussed later in this chapter. In neurology it has been shown that resistance to anti-epileptic medication is predicted in part by common genetic variation in *p*-glycoprotein, and it is conceivable that such changes would also influence responses to antiarrhythmics. As technologies for rapid genotyping emerge, and it becomes possible to identify patterns of relevant polymorphic variations, it may be possible to identify individuals who are at more or less risk of specific unwanted effects, who are resistant to the desired therapeutic effect, or for whom dose adjustment would be beneficial. However, it remains to be determined how important genetic variation will be in determining overall drug effects, compared to the effects of diet, comorbidity, polypharmacy, or even psychosocial factors affecting adherence to therapy [12].

Comparing drugs with identical mechanisms of action

Whilst major advances in therapy follow from the discovery of new molecular targets and new molecules to modulate their function, it is much more common for a new chemical entity to mimic the action of an established drug. In the UK a prescriber can choose from 11 ACE inhibitors, 11 calcium-channel blockers, 7 angiotensin-receptor blockers and 5 statins. The main reason for the proliferation of such similar drugs is the commercial imperative; pharmaceutical companies need market share, especially of large markets (as is the case in cardiovascular disease). An important premise behind the development of a new agent from within the same class is that efficacy is the result of a 'class effect'. The corollary of this is that it is not rational to expect drugs that target the same mechanism to have substantially different pharmacodynamic effects in clinical practice, other than clinically insignificant differences in potency.

Pleiotropic effects of drugs

Additional mechanisms of action may be proposed for a particular class of cardiovascular drugs, often after

licensing. Such multiplicity of effects/action is known as pleiotropic, and pleiotropic effects have been ascribed to ACE inhibitors (not only vasodilators, but antiproliferative, antioxidant, etc.) and statins (not only reduction in low-density lipoprotein cholesterol, but also anti-inflammatory effects). Often these adventitious effects are based solely on the results of *in vitro* or animal studies, so it is often difficult to be certain of their clinical relevance. The cardiovascular effects of ACE inhibitors are just as easily explained by their vasodilator and blood pressure lowering effects [14], and the protective effects of statins by their reduction in blood cholesterol [15].

Pharmacokinetics

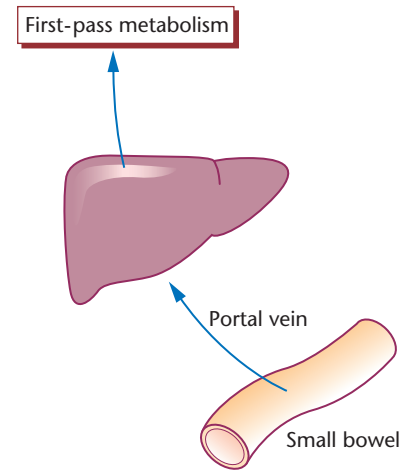
Absorption of drugs

The majority of cardiovascular drugs are administered orally, which is best suited for patients being treated for the conditions outlined in Fig. 8.1. The intravenous route is restricted to drugs that are not readily absorbed through the gastrointestinal tract (heparin) or digested (e.g. proteins such as thrombolytics), when faster onset of action is required (antiarrhythmic drugs in haemodynamically unstable patients), when it is important to rapidly titrate drug dose against effect (intravenous heparin in patients at high risk of bleeding) and when the gut is unavailable (patient is unconscious) or non-functioning (diuretics in severe heart failure to avoid the uncertainties of absorption consequent upon gut oedema). The sublingual route is used for drugs that undergo extensive rapid hepatic metabolism; sublingual absorption of glyceryltrinitrate avoids first-pass metabolism by the liver (which is why it is ineffective when swallowed whole). Dosing interval, although determined by metabolism and excretion (see below), is also influenced by speed of absorption. Dosing interval is important because patients are more likely to adhere to drug therapy if it is administered once or twice daily (these regimens have similar compliance) than drugs with more frequent dosing intervals [16].

Drug distribution

Most cardiovascular drugs distribute freely throughout the cardiovascular system, and will have generalized effects in all vascular beds that contain target receptors and enzymes. Widespread distribution of drugs outside the cardiovascular system is to be expected though there will be differences between water- and lipid-soluble drugs. Amiodarone is sequestered in body fat on account of its very high lipid solubility, which results in the requirement for high loading doses when initiating therapy, and the long time required to elute the drug from the body on cessation of treatment. Penetration of the blood–brain barrier by lipid-soluble beta-blockers may be responsible for some adverse effects (notably sleep disturbance and nightmares), and switching to a water-soluble drug alleviates this problem.

Higher concentrations of aspirin in the portal circulation than the systemic circulation (because of first-pass metabolism; Fig. 8.5) may be important in the effect of aspirin on platelet function. In the time taken to absorb aspirin from the gut, most of the circulating platelets will have traversed the portal circulation and been exposed to concentrations of aspirin sufficient to maximally block cyclo-oxygenase, whilst systemic concentrations, being much lower, may have a lesser effect on endothelial cyclo-oxygenase [17].



Drug	Oral (mg)	i.v. (mg)
Metoprolol	50–100	5–15
Atenolol	50–100	2.5–10

Figure 8.5 Metabolism by the liver reduces the oral bioavailability of beta-blockers and aspirin; consequently, when the first-pass metabolism is bypassed by intravenous administration of beta-blockers, the dose required is substantially smaller than for the oral dose.

Drug metabolism and excretion

Many cardiovascular drugs require metabolism to become active (pro-drugs), with examples including nitrate vasodilators (an as yet unknown process yields the active moiety, nitric oxide), many ACE inhibitors (e.g. enalapril is metabolized to enalaprilat). Otherwise, most drug metabolism increases the water solubility to allow excretion

in the urine. Phase 1 reactions result in oxidation or reduction of drug molecules, inactivating the drug. Subsequent phase 2 reactions (conjugation with glucuronide, sulphate, or acetate) lead to water solubility and excretion in the urine. Phase 1 reactions are of most interest, as many of these are carried out by CYP enzymes. This family of enzymes is responsible for the metabolism of a large number of antiarrhythmic drugs, and genetic variation affecting 10% of Europeans can lead to poor metabolism of these drugs, accumulation and toxicity [18]. One CYP is inhibited by a constituent of grapefruit juice, and is associated with an increased effect of calcium-channel blockers [19]. CYP enzymes exhibit common and potentially important polymorphisms. Several variants influence the metabolism of cardiovascular drugs. Among the most important of these is variation in the CYP2C9 enzyme that metabolizes warfarin. Two common variants (*CYP2C9*2* and *CYP2C9*3*) exist with about 20% of individuals carrying at least one copy. Carriage of these variants is associated with reduced warfarin requirement, and a 1.5-fold to two-fold increase in risk of haemorrhage. However, whether information on *CYP2C9* genotyping will impact on bleeding rates in clinical practice will require prospective evaluation in clinical trials [11].

First-pass metabolism is a determinant of the antiplatelet effect of aspirin, and explains the poor bioavailability of oral nitrates. Beta-blockers also undergo extensive first-pass metabolism, which explains why the intravenous dose of atenolol is 10-fold lower than the oral dose (Fig. 8.5).

Drug interactions

Patients with cardiovascular disease will generally be taking several medications and such polypharmacy predisposes to drug interactions. Whole books have been written about drug interactions, so it is impractical to remember them all (especially when many interactions are clinically unimportant). A few basic concepts will suffice, together with an awareness of the possibility that an interaction may occur in any patient.

Pharmacodynamic interactions

These are amongst the commonest; between vasodilator drugs they result in augmented hypotensive responses, a desirable interaction when treating hypertension, undesirable when patients are taking organic nitrates and phosphodiesterase V inhibitors (e.g. sildenafil). Conversely drugs that cause sodium and water retention (non-steroidal anti-inflammatories, corticosteroids) commonly block the effects of diuretics. Antiplatelet drugs and anticoagulants mutually increase the risk of bleeding in patients taking both types of medication. All classes of antiarrhythmic drugs become more pro-arrhythmic when used together either as causes of ventricular arrhythmias (e.g. amiodarone and flecainide) or bradycardia (concomitant use of beta-blockers, calcium-channel blockers and digoxin). Co-administration of ACE inhibitors, angiotensin-receptor blockers and potassium sparing diuretics predisposes to hyperkalaemia.

Pharmacokinetic interactions

These occur when the metabolism or excretion of drugs is altered. Important examples include the induction (anti-epileptic drugs) or inhibition (certain antibiotics, amiodarone) of CYP enzymes to reduce or enhance respectively the anticoagulant effect of warfarin. Other clinically important interactions include the reduction of renal excretion of digoxin by amiodarone and calcium-channel blockers, or the range of drugs (fibrates, antifungal and antiviral drugs) that impair the metabolism of statins and increase the risk of myositis and rhabdomyolysis. Prescribers should be aware of such common and important problems.

Drugs with a narrow therapeutic index merit special consideration; for such a drug the effective therapeutic plasma concentration is close to the concentration range where adverse effects occur. Therefore even minor changes in plasma concentration can have adverse effects. Good examples are warfarin, digoxin, anti-epileptic drugs and cyclosporin; drug interactions should be anticipated when these therapies are co-prescribed with cardiovascular drugs.

Adverse effects of cardiovascular drugs

The high incidence and prevalence of cardiovascular disease means that the drugs to treat it are widely prescribed often for many years, with the attendant risk of adverse effects. In 2004, it was estimated that between 6000 and 10 000 deaths in general hospitals in the UK per annum might be attributed to an adverse reaction to drugs, and seven of the top 10 culprits were those used for the prevention or treatment of cardiovascular disease [20]. The major reason for the high absolute number of adverse events attributable to the use of cardiovascular medications is not that they are inherently unsafe, but rather that they include some of the most commonly prescribed medications in current use. In the last 10 years xamoterol (beta-agonist for heart failure), and mibefradil (calcium-channel blocker) have had their licences revoked as a result of drug toxicity. Most recently, the cardiovascular toxicity of rofecoxib led to its temporary withdrawal, and raised concerns about all other cyclo-oxygenase-2 inhibitors [21].

The commonest types of adverse event are of type 1 (i.e. they are a consequence of the mechanism of action of the drug, e.g. asthma precipitated by beta-blockers). Type 2 adverse events are unrelated to the mechanism of action of the drug and are unpredictable, often serious but rare. By the time any new agent comes to market, it has usually only been administered to 5000 or so individuals. If serious adverse events occur at a rate of 1 in 5000 or less, it is unlikely that they will come to light until the drug comes to market. Type 2 adverse events are unpredictable in nature, and can only be detected by post-marketing surveillance, which is an integral component of assessment of the performance of any new drug. In the UK, the 'Yellow Card Scheme' has been used since 1964 to detect adverse effects of drugs in clinical use. National Drug Regulatory Authorities in other European countries have their own arrangements for reporting adverse drug reactions, with global co-ordination of reports through the WHO Collaborating Centre for International Drug Monitoring (www.who-umc.org). Within the cardiovascular field, examples of utility of spontaneous reporting include the withdrawal of encainide and flosequinan (excess mortality), mibefradil (multiple drug interactions) and terfenadine (fatal cardiac arrhythmias).

Note that serious but unpredictable adverse effects can occur in just one member of a particular class of drug that targets the same mechanism of action. A good example is practolol, a beta-blocker withdrawn because it increased the risk of retroperitoneal fibrosis, a complication that was not evident with other beta-blockers. More recently, cerivastatin was withdrawn because it had an unacceptably high risk of rhabdomyolysis compared to other statins. The limited safety information that is usually available when a drug is licensed remains a persuasive reason for avoiding prescribing of newer members of a class of drug, until there becomes a compelling reason to take this risk.

Rosuvastatin is the latest statin, with as yet no data on efficacy with respect to hard clinical outcomes, yet uptake into clinical practice has been rapid [22]; since its launch in Holland in 2003, rosuvastatin has acquired 5% of the market share and, in 35% of cases where a statin was newly initiated or changed, rosuvastatin was the statin prescribed. This, despite a concern about a greater risk of adverse events with this agent in comparison to other statins [23].

Prescribing for special groups

Elderly patients make up the largest group of patients in whom special considerations apply. They have a particularly high burden of concurrent cardiovascular and non-cardiovascular disease and are usually taking many different medications. Age-related decline in renal function and a reduction in the rate of drug metabolism can lead to drug accumulation in the elderly. These pharmacokinetic changes with old age underpin the widely held view that drugs should be used at low doses when initiating therapy [24]. However, the pharmacodynamic response to cardiovascular drugs may be diminished in the elderly; e.g. the cardiac effects of calcium-channel blockers and beta-blockers are reduced with age. Therefore it is possible that the resultant drug effect may be similar to that seen in younger subjects. There is a greater incidence of adverse effects of drugs in the elderly, but whether this is caused by polypharmacy, comorbidity or a specific effect of aging is unclear in many cases. Aging seems to increase the risk of non-steroidal anti-inflammatory-induced bleeding and renal impairment, and bleeding on warfarin or following thrombolysis [24].

Prescribing in young women of childbearing potential poses problems related to the real risk of unplanned pregnancy whilst on a teratogenic drug. Organogenesis takes place during the first 8 weeks of pregnancy, the time of maximum risk to a fetus from a drug when a woman might not realize that she is in fact pregnant. To guard against this it is good advice to restrict the choice of medication in such women to those that are not known to be teratogenic. These are typically older drugs, which have been safely used to treat hypertension in early pregnancy (e.g. thiazides and beta-blockers). If a drug has recently been licensed, its teratogenic potential will be unknown (because no studies will have been performed in pregnant women) so using it in young women poses an unknown risk that can be avoided by choosing a safe alternative. If a potentially teratogenic drug is being used such as ACE inhibitors and angiotensin-receptor blockers (responsible for ear and kidney malformation) or statins, then the prescriber must warn the patient of these risks and advise that effective contraception be used. If pregnancy is being planned, then all drugs need to be reviewed for their teratogenic potential and safe alternatives must be substituted. A particular problem is warfarin, which is teratogenic in early pregnancy (facial abnormalities) and poses a high risk of fetal bleeding and peripartum haemorrhage in the third trimester. In these cases, heparin would be the drug of choice because it does not cross the placenta.

In children, particular problems arise because many drugs are unlicensed for use in children, and extrapolation must be made from data in adults. The most obvious problem in this case is that the dose range will not have been established during drug development, and dose adjustments are necessary (either on a body weight or a body surface area basis).

In patients with liver disease, accumulation of calcium-channel blockers, and angiotensin-receptor blockers requires dose reduction because of impaired metabolism.

Special care is needed with anticoagulants, as many patients will have prolonged clotting times because of liver disease. In liver disease, there may be reduced activation of pro-drugs (e.g. many ACE inhibitors including enalapril and ramipril); lisinopril is not a pro-drug and may be preferred. Statins are a recognized cause of transaminitis and it is usual to monitor liver function tests more frequently when being used in patients with established liver disease.

In renal disease, dose modification is indicated if the drug is primarily excreted by the kidney, and dose-related adverse effects are common. As a general principle it is advisable to check for the requirement to reduce the dose of any cardiovascular drug used in renal failure. Specific examples include digoxin, which is not metabolized but is eliminated from the body by renal excretion, and requires dose reduction in the presence of even mild renal impairment (glomerular filtration rate 20–50 ml/min), titrated against plasma concentration. ACE inhibitors and angiotensin-receptor blockers also require dose reduction in mild and moderate renal impairment (glomerular filtration rate 10–20 ml/min), as a result of an increased risk of adverse effects including hyperkalaemia. Similar arguments apply to potassium-sparing diuretics. Many beta-blockers also need dose reduction in moderate renal impairment because of accumulation. It is worth remembering that patients with significant renal impairment are under-represented in many of the large cardiovascular trials. This raises uncertainty when extrapolating the results of these studies to patients with kidney disease, who have a very high risk of cardiovascular disease.

Cardiovascular drugs that impair renal function include diuretics (through volume depletion leading to pre-renal failure if administered at excessive dose), ACE inhibitors and angiotensin-receptor blockers, which can reduce filtration fraction through efferent arteriolar dilatation, a particular problem in the presence of bilateral renal artery stenosis but which can also complicate the use of these drugs in patients with chronic renal failure. Up-to-date guidance on the prescribing of cardiovascular drugs in patients with kidney or liver disease is obtained from http://www.bnf.org/bnf/.

Drug development

Role of the pharmaceutical industry

The cost of developing new medicines is large and, as a society, we have devolved this responsibility to the pharmaceutical industry. In return, the industry is obliged to recoup the costs of development, marketing and distribution, and return a profit for shareholders during the patentable life of the product. An expressed concern with this model is that the profit motive may distort the priorities of drug development at the expense of clinical need. For example, there has been a disproportionate focus on the development of drugs for the management of common, chronic diseases of the Western world, as these treatments are likely to have the largest markets and be the most profitable, though there are signs that this may be changing. Moreover, as the principal funder of most cardiovascular trials world-wide, and given its primary responsibilities to its shareholders, it would be naive in the extreme to gloss over the influence of the pharmaceutical industry in setting the agenda for clinical trial activity, design of studies and dissemination of results.

It was reported in the early 1990s that the pharmaceutical industry spent more on medical research than the National Institutes of Health in the United States [25]. An even larger budget is spent on the dissemination of information about drugs to doctors and, in the United States, to patients themselves. It has been estimated that the 13 largest research-based pharmaceutical companies allocated 13% of their revenues to research and development but nearly 35% to marketing and administration [26]. Although it is difficult to obtain exact figures, in the industry as a whole, there are twice as many employees in marketing as in research and development. Ten years ago these numbers were roughly equivalent. In addition, the sums spent on advertising are huge. In 2000, Merck spent $161 million on direct-to-consumer advertising of rofecoxib in the USA, more than was spent by Pepsi advertising cola ($125 million) or Budweiser advertising beer ($146 million) (http://www.nihcm.org/DTCbrief2001.pdf; accessed 2004). With the shift in focus toward marketing, sometimes at the expense of research and development, true innovation may now be suffering [27]. In 2002, the National Institute of Healthcare Management reported on the licensing of new drugs by the US Food and Drug Administration between 1988 and 2000, and concluded that 76% of all new drugs were no advance over existing products. Between 1995 and 2000 such products accounted for nearly 50% of the increase in the drug budget for the USA (http://www.nihcm.org/innovations.pdf; accessed 2004). These developments are often driven by the need to extend the patent life (evergreening) of an existing product through modest, though patentable, changes in formulation such as extended release, combinations or even chiral forms of existing drugs.

Role of the licensing agencies

The decline in innovation is also in part a consequence of licensing arrangements. In the vast majority of cases, the European Medicines Evaluation Agency and the US Food and Drug Administration grant a licence to new therapies that appear to be as safe as established therapies (though it is clear from earlier in this chapter that safety is only really established once a drug is licensed and used widely), and which demonstrate efficacy when compared to placebo. In addition, it is not generally a requirement that the new therapy has been shown to be an advance over existing treatment, merely that it has efficacy (above placebo) in modifying a surrogate end-point believed to be important in disease pathogenesis. Therefore, where there is an existing effective therapy, subsequent comparator trials are required to establish whether a new product has advantages over existing therapies. Indeed, the evidence required to obtain a licence may be less comprehensive for later than earlier members of a class, with the emphasis on establishing safety rather than obtaining information on drug efficacy. For example, of the ACE inhibitors licensed in the USA, four (captopril, enalapril, ramipril and trandalopril) have licences based on a reduction in cardiovascular events in clinical trials, whereas three others (fosinopril, lisinopril and quinapril) were granted licences on the basis of improvements in haemodynamic indices of potential relevance to heart failure [28].

Many industry-funded studies will therefore be designed to satisfy the minimum requirements for licensing, will be placebo-controlled, and a licence will be awarded if a new therapy has a treatment benefit compared to placebo. Until recently a pharmaceutical company could be confident of a licence for its own HMG-CoA reductase inhibitor without having to demonstrate that the new therapy was a substantial advance over existing statins.

When an established medication seeks approval for an additional licensed indication, again the comparison can be made with placebo. For example, the placebo-controlled HOPE and EUROPA trials examined the effect of fixed doses of ACE inhibitors (ramipril in HOPE; perindopril in EUROPA) on cardiovascular events in patients at high risk (older patients with risk factors or prior stroke or peripheral vascular disease in HOPE; stable coronary disease in EUROPA) [29,30]. In both studies there was a reduction in cardiovascular events in the subjects allocated to ACE inhibitors but, unsurprisingly, treatment was also associated with a reduction in blood pressure (3/2 mmHg in HOPE; 5/2 mmHg in EUROPA). Though both trials have been interpreted by some as providing evidence for a specific atheroprotective effect of ACE inhibition, it is clear that the observed reduction in cardiovascular events could be accounted for, in whole or in large part, by the reduction in blood pressure. If so, a similar reduction in events might have been observed whatever the antihypertensive agent used. It was the absence of a comparator agent in these trials that has engendered uncertainty surrounding this issue. Thus prescribers need to consider carefully the underlying reasons for apparent advantages of one drug over another.

When, for ethical or other reasons, comparison is made with an existing treatment, the choice of comparator drug, its dose, or preparation may favour the new therapy. In the COMET trial, the effect of the beta-blocker carvedilol on mortality in patients with heart failure was compared to that of metoprolol, a beta-blocker whose efficacy when added to standard heart-failure treatment had been demonstrated in previous trials [31]. Mortality was lower among the patients allocated to carvedilol, and this finding has been interpreted as providing evidence for a specific action of carvedilol (perhaps, the argument goes, the result of non-selective beta-blockade, or an additional antioxidant action). However, it has also been suggested that the choice of the comparator dose of metoprolol (lower than in the previous trials with this agent), and the preparation (short-acting compared to long-acting in the previous trials) might have led to the observed difference in outcomes [32,33].

Clinical trials and assessment of evidence

Evidence for drug efficacy: the pre-eminence of randomized controlled trials

Evidence for the efficacy of commonly used cardiovascular drug therapies comes from clinical trials. Indeed, it can be argued that the best clinical trials in cardiovascular disease have informed the development of the basic methodology, and provided an impetus for the conduct of such trials in other areas of medicine. Many have been of the highest quality and have led to important changes in practice that impact on the outcome of thousands of patients. The two critical components of the major clinical trials in cardiovascular disease have been their large size and the use of randomized allocation of patients to the experimental treatment or its comparator.

The value of very large trials is that, by reducing the play of chance, they allow the detection of small to moderate treatment effects with a high degree of reliability.

Table 8.6 Commonly used antiarrhythmic drugs

Drugs	Indications	Mechanism	Pharmacokinetics	Adverse effects
Digoxin	Rate control in atrial fibrillation	Increased vagal tone (central nervous system effect) and direct effect on atrioventricular node	Requires loading dose to achieve steady-state plasma concentrations for rapid control of atrial fibrillation	Pro-arrhythmic (especially if hypokalaemia) Nausea, vomiting and constipation when plasma concentrations in toxic range
Adenosine	Treatment of atrioventricular nodal re-entrant tachycardia Diagnostic evaluation of narrow- and broad-complex tachycardia	Activates adenosine receptors to cause atrioventricular nodal blockade	Half-life is short (seconds) so given intravenously by rapid bolus	Wheezing so contraindicated in asthma
Amiodarone	Supraventricular and ventricular tachyarrhythmias	Prolongs refractory period by blocking potassium rectifier channel	Very long half-life so loading dose required; sequestered in adipose tissue so large apparent volume of distribution	Lung and hepatic fibrosis, hyper/hypothyroidism, photosensitivity, corneal deposits
Flecainide	Supraventricular and ventricular tachyarrhythmias	Blocks sodium channels and increases depolarization threshold	Administered intravenously to rapidly cardiovert atrial fibrillation or orally for long-term prophylaxis	Pro-arrhythmic especially in patients with ischaemic heart disease with poor left ventricular function

Apparently small treatment effects can have considerable impact on the public health when the clinical event prevented is important, and the population at risk is large. In 1988, the ISIS-2 trial of about 17 000 patients with suspected myocardial infarction showed that aspirin (300 mg) reduced mortality at 30 days by about 3% in absolute terms [34]. In other words, for every 100 patients treated with aspirin rather than placebo, three fewer died. A treatment effect of this size might be considered small, and it is clear that a study of several thousand patients was required for it to be demonstrated unequivocally. Nevertheless it was important to ascertain this apparently small treatment effect reliably, because myocardial infarction is such a common clinical event with a high fatality rate. Thus, even though only three more patients survive for every 100 patients treated with aspirin, this translates to many thousands of lives saved annually, at very low cost. It transpires that many other therapies in cardiovascular disease produce treatment effects of similar size (Table 8.8), and their detection relies on very large studies (e.g. MRC/BHF Heart Protection Study, ALLHAT) [35,36].

The counterpoint is that many such therapies (with the exception perhaps of thiazides or beta-blockers for hypertension) are still under patent and cannot match aspirin for cost. The high cost of newer medications with small to moderate treatment benefits minimizes their public-health implications because funding such developments will usually mean that revenue will need to be redirected from other health-care interventions that may have greater treatment benefits. Thus, the 'cost–quality' trade-off is becoming increasingly important in many areas of cardiovascular therapeutics. In the UK, the National Health Service's National Institute for Health and Clinical Excellence (NICE) is charged with making 'recommendations on treatments and care using the best available evidence'. Its evaluations of new treatments commonly include some form of pharmacoeconomic analysis.

The second important element of a clinical trial is the allocation of patients at random to the experimental treatment or its comparator. This process ensures that the patients in the two arms of the trial are, on average, equally healthy (or unhealthy) at the outset and are also automatically matched for other factors (confounders), both measured and unmeasured, which might influence the eventual outcome. Any difference in outcome that is then observed between the two arms of the trial must be the result of the treatment allocation. This design contrasts with studies where the treatment allocation is non-randomized, where any association between treatment and outcome could be subject to bias, such as the preferential uptake of therapies by subjects who are healthier, or by confounding. For example, observational (non-randomized) studies suggested that the use of hormone

replacement therapy (HRT) protected women from cardiovascular disease [37]. In contrast, recent randomized trials have indicated no effect or even a slightly adverse effect of HRT on cardiovascular outcomes [38]. The reasons for this discordance between observational and randomized studies of HRT have been debated, but bias and confounding in the observational data seem the most likely explanations. Women who used HRT in the observational studies were on average less likely to smoke, more likely to come from higher socioeconomic groups, to have a healthy diet and to exercise. While it is possible to perform statistical adjustment to control for these factors, some potential confounders, such as socioeconomic position, are measured with a considerable degree of uncertainty, usually at a single time in the lifecourse, making adequate adjustment difficult and residual confounding a real concern [39]. In contrast, in the randomized controlled trials (RCTs), known confounders (and even unknown or unmeasured ones) were automatically distributed in similar proportions among women allocated to HRT or placebo, by virtue of the randomization process; (readers have only to scrutinize what is usually the first table in any publication reporting the results of a large RCT to be reassured of this). The results of such trials are therefore essentially unbiased and, provided they are of sufficient size, provide a much more reliable assessment of efficacy than observational studies. It is noteworthy that a similar discordance has been noted between the results of observational and randomized studies of antioxidant vitamins in the prevention of cardiovascular disease [40] and similar considerations are likely to apply.

It is for this reason that RCTs are regarded as the highest grade of evidence on the efficacy of a treatment. The Oxford Centre for Evidence-Based Medicine categorizes the hierarchy of medical evidence on a treatment and details can be found at http://www.cebm.net/. The grades of recommendation for use of a treatment that follow from this are also shown and these are now widely used in full or modified form to underpin clinical practice guidelines. See http://www.escardio.org/knowledge/guidelines/ for a full set of guidelines and scientific statements from the European Society of Cardiology.

Statistical aspects of clinical trials

> If your experiment needs statistics, you ought to have done a better experiment

When making this statement, the physicist Ernest Rutherford was probably referring to interventions with large treatment effects. To illustrate, the efficacy of a parachute in preventing fatality following a jump from an aircraft has never been tested in a randomized trial. Nonetheless, observational experience indicates that almost (but not quite) 100% of individuals who have jumped from an aircraft with a parachute survive, whereas almost (but not quite) 100% of individuals who leave a flying aircraft without a parachute die. An RCT of this intervention, as well as being unethical, is probably unnecessary because the effect of the parachute is manifestly large. As we have seen, cardiovascular interventions, such as aspirin, with major impact on the public health exert relatively small treatment effects at an individual level, making very large randomized intervention studies with the appropriate statistical analysis necessary to ascertain their effects reliably.

Rutherford was correct, however, in implying that a clinical trial should be regarded as an experiment designed to test a hypothesis. The usual approach in a trial testing the potentially superior efficacy of a new treatment over placebo (or the existing best therapy) is to develop the null hypothesis that the experimental treatment offers no therapeutic advantage. When complete, the trial provides an estimate of the effect of the treatment with the new agent but, because the participants in a trial form only a sample of the population of all potential participants, and the trial itself is only one of a potentially infinite number of trials that could have been conducted, the estimate of the treatment effect obtained (sometimes called the point estimate) is surrounded by a degree of uncertainty. The usual approach to quantifying the degree of uncertainty is to define a 95% confidence limit for the point estimate, i.e. a boundary within which the point estimates would lie in 95 of every 100 such trials. The size of this confidence limit will depend on the number of subjects studied, the rate of adverse events or outcome measures used to define efficacy (e.g. death, myocardial infarction or stroke), and the size of the treatment effect. If the trial assesses a dichotomous outcome, such as the occurrence or not of acute myocardial infarction, the point estimate of the risk ratio in the treatment arm is less than one (i.e. there is a lower rate of new infarction in the treatment arm), and the upper bound of the confidence limit fails to cross unity, the trial is considered positive and the new agent is considered to offer a therapeutic advantage.

From an alternative perspective of trial design, it is possible to use statistical theory to estimate the minimum number of subjects that would be required for a new trial to detect a treatment effect of a given size with narrow confidence limits. In making this estimate, two constraints are set. The first is the maximum acceptable rate of false-negative results, also referred to as the power or β value. The second is the maximum acceptable rate of false-positive results, also referred to as the level of significance or α value. In a trial that provides 90% power

Table 8.7 Calculation of treatment benefits in three hypothetical clinical trials (see text for explanation)

Profile of trial participants	No. of events in placebo group ($n = 1000$)	No. of events in treatment group ($n = 1000$)	Percentage absolute risk reduction (ARR) (95% CI)	Percentage relative risk reduction (RRR) (95% CI)	χ^2-statistic, *P*-value	Number-needed-to-treat (95% CI)
Trial A High risk	200	100	10 (6.9, 13.1)	50 (37.5, 60)	$\chi^2 = 38.5$, $P < 0.0001$	10 (8, 14)
Trial B Intermediate-risk	100	50	5 (2.7, 7.3)	50 (30.6, 64)	$\chi^2 = 17.3$ $P < 0.0001$	20 (14, 37)
Trial C Low- risk	20	10	1 (−0.1, 2.1)	50 (−6.3, 76.5)	$\chi^2 = 2.74$ $P = 0.098$	100 (48, 1000)

ARR, event rate in control group minus event rate in treatment group; RRR = ARR/control group event rate; NNT = 100/ARR.

to ascertain a given treatment effect, the trial designers accept that 100 – 90 (or 10%) of all such trials would fail to detect a treatment effect of given size when one really existed (a false-negative result). Conversely, in choosing a significance level of 5%, those running the trial accept that 5% of all such studies would provide evidence for a treatment effect of given size when none existed (a false-positive result). Given the intimate link between sample size and the confidence limit, it is unsurprising that the sample size in any clinical trial will vary according to the desirable power and level of significance, the size of the treatment effect deemed clinically important and worth detecting, and the rate of adverse events being examined as the outcome in the group of patients being studied. If a trial is interpreted as positive, it is important to assess if this result is likely to be real or whether it could have arisen by chance. For negative studies, it is important to consider whether the negative result might have arisen because the trial was too small to detect a clinically important treatment effect before ruling out the new therapy. Indeed, when clinical trials are considered in this way, four potential outcomes are possible. The first two are desirable: either the trial detects a real treatment effect or it fails to detect an effect when none exists. The second two are undesirable: they occur when either the trial detects a treatment effect where none exists (false-positive, type I error), or fails to detect a real treatment effect (false-negative, type II error). In a later section, we will discuss how systematic reviews of clinical trial data can help to minimize the possibility of type I and type II errors.

Measuring the size of treatment effects; absolute risk reduction and relative risk reduction

If the trial is considered positive, i.e. the therapy under evaluation offers a therapeutic advantage, the next important question is 'how large is the treatment benefit?' The degree of statistical significance (the '*P*-value') provides no information about the size of the treatment effect. A very small treatment benefit could be detected very precisely by a very large trial and, conversely, a substantial treatment effect might be detected with only marginal levels of significance in a small trial. What then is the best measure of the effect of treatment—an important issue in assessing if the new treatment warrants a change in clinical practice?

Consider a hypothetical clinical trial of an antiplatelet treatment being evaluated among 2000 men and women at high risk of coronary heart disease (CHD). Let us assume that 1000 subjects were allocated to the treatment and 1000 to placebo, and that follow-up was complete at 5 years when the trial closed. The results are presented as Trial A in Table 8.7. Among the group allocated placebo, 200/1000 suffered a CHD event, but among those allocated the treatment only 100/1000 suffered an event. This difference is statistically significant ($P < 0.0001$), but is this an important treatment benefit?

If we first consider the participants allocated to placebo, 200/1000 suffered a CHD event. In other words, the 5-year event rate, or 5-year absolute risk, of CHD was 20%, confirming the high risk of the participants. In the intervention arm of the trial, the treatment lowered the absolute risk to 10% over 5 years. Two measures of the treatment effect can now be derived, the absolute risk reduction (ARR) and the relative risk reduction (RRR). The formulae for deriving these values are simple and are shown in the footnote to Table 8.7. The ARR is simply the difference in risks (or event rates) between the two groups, while the RRR is this difference expressed as a proportion of the control group event rate. It is clear that in our hypothetical trial the ARR is 10% (20 – 10%), and the RRR is 50% [ARR/control group event rate (i.e. 10/20) × 100%]. For completeness, the 95% confidence limits around these values are also shown. By analogy with the previous aspirin example, a 10% ARR equates to 10 fewer events

for every 100 patients treated in this trial for 5 years. The RRR tells us that this treatment halves the event rate. Which of these, the ARR or RRR, provides the best single indication of the treatment benefit? To answer this, consider a second clinical trial of the same drug in a different group of 2000 individuals at lower risk of CHD (Table 8.7, Trial B). In this study, the event rate among the control group over 5 years is lower (10%), but this is still halved by the treatment to 5%. Thus the RRR remains the same (50%) but the ARR is smaller (5%). In a third trial (Trial C, Table 8.7), an even lower risk population has been studied. The corresponding event rates in the placebo and treatment groups are 2% and 1% respectively, the RRR is again unchanged at 50% but the ARR is smaller still at 1%. Some important points emerge from these examples.

First, because the same RRR can be observed in trials with very different ARRs, the RRR does not distinguish trivial from substantial treatment effects. This helps us answer which is the best single measure of the treatment effect—it is the ARR. Second, for a given proportionate reduction in risk, the ARR is highly dependent on the event rate among the participants being studied. Indeed the ARR can be described by the equation ARR = RRR × control group event rate. The higher the event rate, the higher the ARR. Two things follow from this. First, it may make sense to target treatment to those with the highest likely event rate (or risk). This is the strategy currently used to guide statin or antiplatelet therapy in the primary prevention of CHD events. Second, it illustrates why the control group event rate is such an important determinant of sample size and of the confidence limits surrounding the treatment effect. Scrutiny of the χ^2-statistics and *P*-values in Table 8.7 shows that as the control group event rate falls (from Trial A to Trial C), a study of 2000 participants becomes progressively underpowered to detect a 50% RRR.

Numbers needed to treat

Although it is a good indicator of treatment benefit, the ARR can be difficult to conceptualize. In Trial A the ARR of 10% indicates that 10 CHD events are prevented for every 100 subjects treated for 5 years. By extrapolation, one event would be prevented for every 10 subjects treated. The number of subjects that need to receive treatment to prevent one adverse event is defined as the number-needed-to-treat (NNT). In this trial, the NNT is therefore 10. The NNT is related to the ARR by the formula NNT = 100/ARR (when this is expressed as a percentage, as in this case) or 1/ARR if the ARR is expressed as a decimal.

Despite the value of the ARR and NNT, scrutiny of the abstract or promotional material of many clinical trials will reveal a recurring pattern. Treatment benefit will usually be expressed as the RRR (a larger number, with greater immediate impact than the ARR), whereas rates of adverse events will usually be expressed as absolute rather than relative risks, perhaps so as to minimize the impact of information on drug toxicity.

The ideal NNT would be one, i.e. every patient who receives treatment, benefits. NNTs of one are rare. Insulin treatment to prevent ketoacidosis in type I diabetes mellitus, and thyroxine treatment to prevent symptoms in patients with hypothyroidism, might be two examples. NNTs of less than 10 are seen with antimicrobial treatments for certain infections. In cardiovascular disease, however, NNTs to prevent major clinical end-points are substantially higher (Fig. 8.6). Though estimates of treatment benefits are rarely presented to patients in this way in clinical practice (though many argue they should be), studies have shown that when such information is provided patients are reluctant to take medications with NNTs greater than 30 [41].

A related concept is the number needed to harm (NNH), which is a measure of the risks of drug treatment. The Cardiac Arrhythmia Suppression (CAST) trial provides a good example; in patients post myocardial infarction, class I antiarrhythmic drugs increased the relative risk of death by 60%, and the absolute risk by 4.8% [42]. The NNH was therefore 100/4.8 = 21. For every 21 patients treated an additional one patient died who would not otherwise have done so. All drugs carry risks and benefits and a comparison of NNT and NNH is a useful quantitative way of expressing this. A good recent example is the use of cyclo-oxygenase-2 inhibitors to reduce the incidence of peptic ulceration and its complications (NNT = 100) at the cost of increased cardiovascular events (NNH = 100).

The relative risk reduction observed across a wide range of baseline event rates or risks is relatively constant for a number of preventive treatments in cardiovascular disease (Table 8.8). Thus the proportional reduction in risk is fairly similar for antihypertensive agents in the primary prevention of stroke or coronary events, for warfarin in the primary prevention of stroke in atrial fibrillation, and for statins or aspirin in the primary and secondary prevention of coronary events [43], whichever patient group is studied, though, as we have seen the absolute benefits depend on the risk profile of the group being treated.

Survival curve analysis; assessing the time-scale of treatment effects

Effective cardiovascular drugs reduce event rates but do not abolish all events. Whether on placebo or active

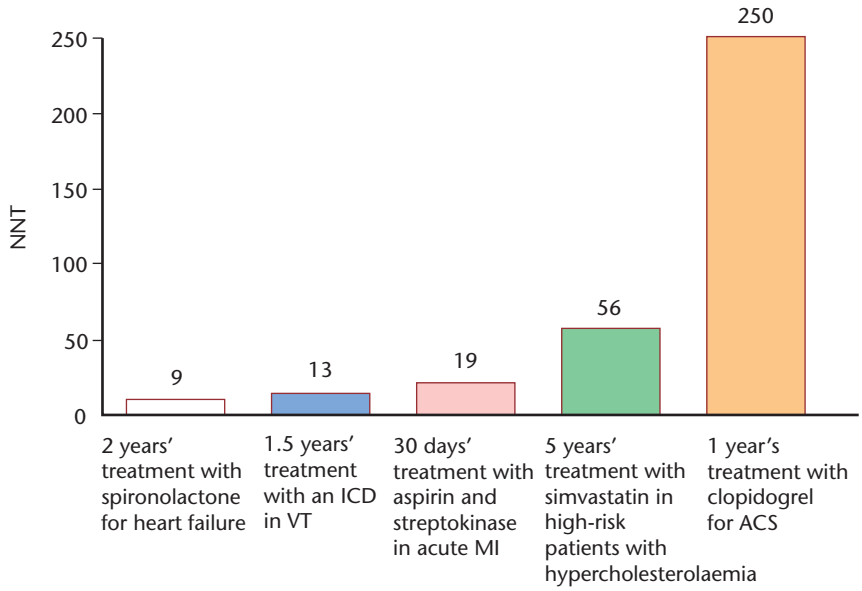


Figure 8.6 Number needed to treat (NNT) of common cardiovascular interventions for mortality reduction. The lower the NNT the more effective the therapy is in preventing death. Note that some interventions are effective in relatively short periods of time [thrombolysis and aspirin in acute myocardial infarction (MI)], some require lengthy treatment (statins) and some are relatively ineffective (clopidogrel; for mortality the absolute risk reduction is not significant (NS) and the confidence intervals for the NNT span infinity). VT, ventricular tachycardia; ACS, acute coronary syndrome.

Table 8.8 Relative risk reductions from some common cardiovascular interventions

Intervention	Outcome	Relative risk reduction	Reference
Thiazide diuretics for primary prevention in hypertension	Myocardial infarction Stroke	22% 31%	61
Statins in secondary prevention	Coronary heart disease mortality or non-fatal myocardial infarction	25%	62
Aspirin in long-term secondary prevention	Any serious vascular event	25%	63
ACE inhibitors in heart failure	Death	20%	48
Beta-blockers in heart failure	Death	37%	64

drug, survival curves inexorably slope downward (Fig. 8.7), and if the trial is long enough (or the death rate is high enough as it is in cancer trials) survival curves will converge when all participants have died. The vertical difference between the curves is a measure of the absolute risk reduction at any given time point (Fig. 8.7A). Note that the absolute risk reduction (and hence the NNT) will vary depending on the time point chosen. The absolute risk reduction reported at the end of the trial will therefore be specific to that particular time point. If the study has a low event rate (as is the case for many cardiovascular trials), the survival curves will be shallow and the trial will only provide data about the early part of the survival curve. Extrapolating beyond the available data will require one of three assumptions to be made. The survival curves will continue to diverge (treatment benefit will increase with time, e.g. the Heart Protection Study [35], the RALES study of spironolactone in heart failure [44]), will separate early and then run parallel (treatment benefit will remain constant; this pattern is expected when a treatment has been administered on a single occasion, e.g. streptokinase in the ISIS-2 cohort [45]), or will converge after the trial has finished (treatment benefit will wane with time; the PROWESS study of activated protein C in bacterial sepsis [46].

The second point to make about survival curves is that the horizontal separation is a measure of the event-free time gained (Fig. 8.7B). In ISIS-2, the combination of aspirin and streptokinase separated the curves (i.e. prolonged life) by approximately 1 year; a similar estimate describes the treatment effect of ACE inhibitors in heart failure [47]. As for estimates of risk reduction, event-free

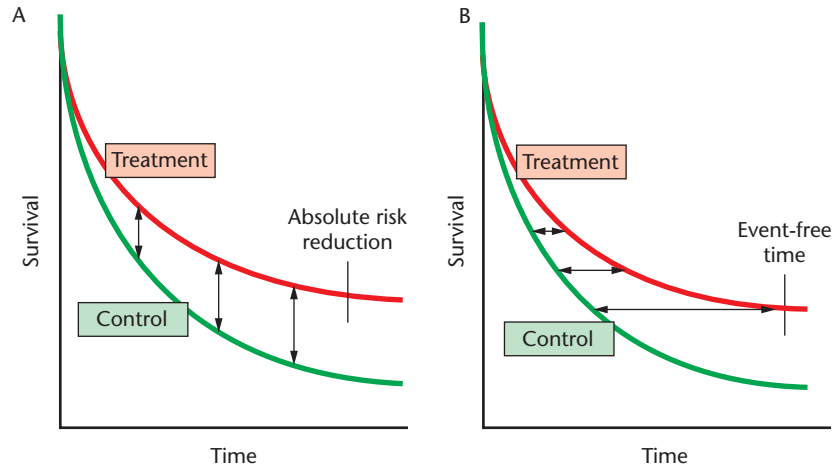


Figure 8.7 Survival curves showing the treatment effect of a cardiovascular drug compared to the placebo group. At the start of the trial survival is 100% in both groups but with time more patients in the placebo group reach the end-point (e.g. death) and the curves diverge. (A) shows that the absolute reduction in death (vertical difference between the two curves) depends on the time point chosen. Similarly, (B) shows how the event-free time (horizontal difference between the two curves) also depends on the time point evaluated.

time will depend on the time point chosen and cannot be extrapolated beyond the trial closure with certainty.

End-points in clinical trials

In the examples considered so far, most of the end-points have been the so-called 'real' end-points of death or major cardiovascular events. However, not all trials consider such end-points. A surrogate outcome measure is an end-point that is easy to measure that is believed to predict an outcome of direct clinical relevance. Examples would be blood pressure, serum cholesterol, carotid artery intima-media thickness, or the number of ectopic beats or periods of ST-segment depression on a 24-hour ECG recording. Because the relationship between the surrogate measure and the real end-point is often uncertain, trials that evaluate surrogate end-points alone must be interpreted with a high degree of caution. In the CAST trial [42], the effects of class 1 antiarrhythmic drugs (including flecainide and encainide) on cardiovascular mortality were examined in patients with myocardial infarction. Although previous studies had shown that these drugs reduced ventricular ectopy following MI, and other studies had shown an association between ventricular ectopy and adverse outcome, there were no firm data prior to the CAST trial on the effect of these agents on mortality. The CAST study showed that arrhythmia suppression notwithstanding, mortality rates over 10 months were higher at 8.3% among the patients receiving antiarrhythmic drugs compared to 3.5% among those receiving placebo, in direct contrast to the expectation from earlier trials that had used surrogate outcome measures.

An increasing trend in more recent clinical trials of cardiovascular drugs has been the use of so-called 'composite' end-points. A composite end-point is constructed by combining several real and/or surrogate end-points to produce a single composite outcome measure. An example might be the composite of death or myocardial infarction or re-hospitalization in an intervention trial of patients with acute coronary syndromes. In reaching any one of these end-points the patient is considered to have achieved the primary end-point, but patients and doctors might attach very different values to the individual components (e.g. death versus hospitalization). This combination of some hard and some soft end-points within the composite one contrasts sharply with the early large trials in cardiovascular disease where hard end-points were the usual primary outcome measures. The reason for this is that event rates in clinical trials of acute coronary syndromes, for example, have fallen because of the widespread application of proven therapies established as effective in prior trials. In the ISIS-2 trial in 1988, the control group 30-day mortality of patients presenting with suspected acute myocardial infarction was 12%. In the GUSTO V trial in 2001, which examined the effect of abciximab or placebo in addition to standard antiplatelet treatment and fibrinolysis in patients with acute myocardial infarction, the 30-day mortality in the control group was only 6% [48].

This reduction in event rate makes the detection of the incremental benefit of any new agent even more challenging. Trials would require truly huge sample sizes if mortality was to be the sole outcome measure. If the event rate is halved, then to detect the same reduction in relative risk, the sample size required may be up to four-fold greater. In an attempt to 'increase' the rate of adverse events, those running the trials have adopted a strategy of a moderate increase in sample size coupled with the use of composite end-points that combine relatively infrequent outcomes. A good example is the CURE study of clopidogrel in acute coronary syndromes, where the primary end-point was non-fatal myocardial infarction

(detected solely by a rise in troponin T in many cases), stroke or cardiovascular death [49]. Accordingly, the CURE study demonstrated that clopidogrel caused an 18% RRR in the rate of non-fatal myocardial infarction, stroke or death. It turns out that in the CURE study, clopidogrel reduced the incidence of non-fatal myocardial infarction alone (ARR 1.5; NNT 67 per year), with no significant effect on death or stroke. Combining these end-points contributes to the common misconception that clopidogrel reduces the risk of myocardial infarction, cardiovascular death *and* stroke rather than myocardial infarction, cardiovascular death *or* stroke [50]. Clopidogrel might reduce these other end-points but we do not have the data to show that it does.

Assessing the risk to benefit ratio of drug therapy

Anticoagulant and antithrombotic drugs are used widely for the treatment and prevention of cardiovascular disease. The therapeutic efficacy of these agents, derived from their effects on platelets or the clotting cascade, is inexorably linked to their potential to cause harm by increasing the risk of gastrointestinal and intracerebral haemorrhage. Net benefits depend on the balance between the reduction in the rate of cardiovascular events and the increase in the rate of bleeding complications. By considering both the NNT and the NNH, it becomes possible to begin to quantify the absolute benefits and risks of a particular intervention. The benefits of treatment are best quantified using data from RCTs (or better still, systematic reviews of several RCTs) as we will discuss. In attempting to balance benefits and risks in an individual patient, however, two additional pieces of data are helpful: the absolute rate of adverse events arising from the treatment (sometimes available from RCTs in which adverse events are recorded), and the absolute risk of the cardiovascular event for which the treatment is being considered (usually obtained from prospective observational studies).

Consider a 70-year-old man with atrial fibrillation, hypertension and type II diabetes. His annual risk of stroke based on prospective observational data incorporated into the CHADS 2 risk score is 5% [51]. We know from a systematic review [52] that warfarin, adjusted to achieve an international normalized ratio (INR) of 2.0–3.0, reduces the risk of stroke by 59%. In other words, we would expect warfarin to reduce our patient's absolute annual risk from 5% to 59/100 × 5% = 2.95%. This equates to an annual absolute risk reduction of 2.05%, equivalent to an annual NNT of about 50. From clinical trials of stroke prevention, the absolute increase in the rate of major extracranial bleeding with adjusted dose warfarin is about 0.3% per annum, and that of intracranial haemorrhage is about 0.2% per annum [53]. Thus the respective NNH values are 333 and 500. We can attempt to quantify the balance of benefits and harm in our patient by considering what would happen to 1000 similar patients treated with warfarin rather than placebo. At the end of 1 year of treatment we would expect that, among the 1000 patients, there would be 20 fewer thromboembolic strokes, but three extra major extracranial bleeds, and two additional intracranial haemorrhages. Absolute benefits of warfarin in the prevention of thromboembolic stroke are much lower in young patients with atrial fibrillation (because the risk of stroke is lower), while the rates of harm may not be substantially different from that in older subjects. For this reason, in many young patients with atrial fibrillation, aspirin may be the preferred intervention to prevent stroke. While its efficacy in stroke prevention is less than that of warfarin (RRR of 30%), the rates of major bleeding are correspondingly lower too. Another illustration of the sometimes fine balance between benefit and harm is the use of aspirin in the primary prevention of coronary disease. In contrast to the clear benefits of aspirin in the prevention of recurrent events in high-risk patients with established vascular disease, the use of aspirin in the primary prevention (in patients who are at much lower risk of events) is more uncertain; in patients at very low risk of vascular events the increased risk of bleeding with aspirin may outweigh any benefit. A threshold coronary heart disease risk of 15% over 10 years (1.5% per annum) has been suggested as an appropriate threshold above which aspirin might provide a net benefit in the primary prevention of coronary events. Quantifying the balance between benefit and harm is thrown into sharpest relief when considering the use of intravenous thrombolysis in acute ischaemic stroke [54].

Systematic review, meta-analysis: RCTs in context

Before the era of the mega-trial that followed the publication of the ISIS-2 and GISSI studies in the late 1980s, which unequivocally established the benefits of aspirin and thrombolysis following myocardial infarction, considerable uncertainty existed about the efficacy of these treatments. A number of RCTs had been conducted up to that point but the findings had been inconsistent. All the trials had been too small to reliably detect the RRR of about 30% produced by each of these treatments alone (40% in combination). Motivated in part by the recognition that RCTs in many fields of medicine were underpowered, the discipline of systematic reviewing has evolved with the aim of obtaining and collating all

available evidence on a treatment. Meta-analysis has been developed in parallel, as a formal statistical method for pooling data from individual RCTs to derive a single summary measure of treatment effect. In 1992, a retrospective meta-analysis of the small RCTs of thrombolysis that predated the ISIS-2 and GISSI studies showed that the summary estimate for the treatment effect obtained by pooling the results of 15 smaller randomized trials published up to 1997 was almost precisely that detected in the subsequent mega-trials [55]. This observation highlighted the potential for meta-analysis of individually underpowered studies to provide reliable risk estimates. Systematic review and meta-analysis are now established as important analytical tools that help inform treatment decisions in clinical practice. The Cochrane Database of Systematic Reviews provides an important function of continually updating systematic reviews of treatments as more evidence accrues. The simplest approach to meta-analysis is to utilize the summary data from several clinical trials. Estimates of the treatment effects are weighted according to the size of the trial (larger trials carrying greater weight than smaller ones) and are then pooled by standard procedures to derive a single summary estimate of the treatment effect.

Sometimes it is important to consider whether there are important differences in the size of the treatment effect in subjects with differing clinical characteristics, or in relation to some aspect of the intervention itself, e.g. the time at which it is administered after the diagnosis is made. To answer these sorts of questions some sort of subgroup analysis becomes necessary. Subgroup analysis within a single clinical trial is fraught with difficulty because any form of data splitting poses two problems. The first is that by reducing the size of the study groups statistical power is lost, rendering subgroup analysis insensitive to the detection of real differences. The converse is perhaps more of a concern, i.e. the detection of a difference in treatment effect in a certain subgroup that arises through the play of chance. A well-publicized example comes from the ISIS-2 trial [34]. A subgroup analysis of the data from the aspirin arm of the trial, conducted to illustrate the dangers of a subgroup analysis even in a very large RCT, indicated an apparent difference in the effect of aspirin on mortality after myocardial infarction by astrological birth sign, aspirin being apparently ineffective for those born under Libra or Gemini [34]. In this situation, meta-analysis may help since pooling data from many trials reduces the play of chance, but an alternative meta-analytical technique is then preferred. Rather than using the aggregate data, the raw data from individual participants in all trials are used. Though more time- and labour-intensive, and requiring many collaborators, this type of analysis allows more reliable inferences to be made about variation in treatment effects in different types of patient. Good examples of this approach are the individual participant data meta-analysis of trials of thrombolysis in acute myocardial infarction [56], ACE inhibitors in heart failure [47] and carotid endarterectomy in patients with transient ischaemic attacks or minor stroke and a carotid stenosis [57]. As a result of these analyses, it is accepted that the benefits of thrombolysis were greatest in patients presenting with ST-segment elevation on the ECG, or new left bundle branch block, that ACE inhibitors are effective in heart failure at all clinical grades of disease, and that endarterectomy should be confined to patients with a greater than 70% stenosis of the carotid artery.

Despite its potential benefits, meta-analysis also has the potential to mislead if the source data are not considered carefully. There are several examples where the results of meta-analyses of smaller trials have subsequently been refuted or modified by the publication of a very large RCT. The most notable example is that of intravenous magnesium in the treatment of acute myocardial infarction, where the results of a meta-analysis published in 1993 [58] were subsequently overturned by the publication of the very large ISIS-4 trial in 1995 [59]. Other examples include the studies of aspirin in the prevention of pre-eclampsia [60]. The most likely explanation in each case is that the meta-analyses of smaller RCTs that predated the very large and definitive mega-trial were biased by the preferential publication of positive results. Publication bias remains one of the greatest obstacles to reliable meta-analysis, but such bias can be minimized by using strategies to actively seek out unpublished data.

Conclusion

To prescribe a drug for a patient with cardiovascular disease, it will be necessary to take into account the efficacy and safety of the therapy in comparison with alternative treatments, and this will rely upon an assessment of aggregate data from clinical trials. However, therapy will have to be individualized to take into account the presence of comorbidity, the potential for drug interactions and perhaps, in the future, genetic variation. The costs of treatment will be a factor, regardless of whether this is borne individually by the patient, or collectively by society.

Personal perspective

Major advances in the treatment of cardiovascular disease have been made in the last 20 years. Notable examples include ACE inhibitors and beta-blockers in the treatment of heart failure, thrombolysis for acute myocardial infarction, and use of aspirin and statins and blood pressure lowering in the prevention of cardiovascular events. Absolute benefits in each case have been small but, because cardiovascular disease is so common, the public-health implications of these interventions have been substantial. Whilst future advances will bring incremental benefits to those already achieved, new treatments are likely to be expensive, and balancing clinical benefits and costs will present a challenge to all health-care systems. Moreover, not all new developments represent a substantial therapeutic advance. In the future, it will become more important than ever to quantify both the treatment effect and the cost, as choices will have to be made that will have an impact on public health as much as on the individual patient.

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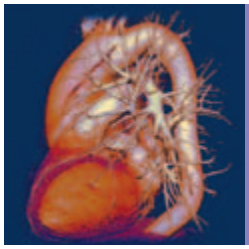

9 Prevention of Cardiovascular Disease: Risk Factor Detection and Modification

Joep Perk, Annika Rosengren and Jean Dallongeville

Summary

The prevention of cardiovascular disease (CVD) is of major importance because CVD is expected to remain the leading cause of premature death in Europe in the coming decades. The prevalence of symptomatic disease is still increasing. Can this be prevented in clinical practice? What is the role of the physician in preventive cardiology?

A large part of the population at risk can be identified by assessing known risk factors. Risk behaviour can be modified successfully through life-style management. Single risk factors such as hyperlipidaemia and hypertension can be adequately controlled by adding pharmacotherapy. Thus, there are effective tools both for the detection and for the modification of CVD risk.

In this chapter the concept of total-risk calculation based upon the SCORE project is proposed to replace previously used single-risk assessment tools. SCORE risk charts for high- and low-risk regions in Europe are shown and its computer-based application 'HeartScore' is introduced. Prevention strategies and priorities are presented in agreement with the recent guidelines of the Third Joint European Societies Task Force on CVD prevention in clinical practice.

The detection and modification of risk factors is described in the sections on smoking, physical activity and blood pressure and on nutrition, obesity and lipids. It includes specific methods for life-style counselling; drug therapy has been recommended, whenever deemed necessary. Finally, new evidence on the importance of psychosocial risk factors and the influence of gender will be discussed in this chapter.

Introduction

Cardiovascular disease (CVD), including coronary heart disease and stroke, is the major cause of premature death in adults. In Europe it accounts for 49% of all deaths [1]. Almost one in three deaths occurring before the age of 65 is the result of CVD. The disease results in substantial disability and loss of productivity and contributes in large part to the escalating costs of health care. In 2000 CVD accounted for 22% of all disability-adjusted life years (DALYs) lost in Europe [2].

Even though the age-standardized mortality rates have declined over the past decades in most European countries, the prevalence of CVD is increasing because of improved treatment and higher survival rates and because of the increasing elderly population. The prevalence of patients who are at risk of recurrent disease (re-infarction, recurrent stroke, heart failure, sudden death) is likewise on the increase. Furthermore, with the current pandemic of obesity in childhood and adolescence CVD may extend into younger age groups in the future. Thus, CVD is expected to remain the largest burden on health care in Europe in the coming decades.

There are marked gradients in CVD morbidity and mortality within European countries [3,4]. This is partly explained by differences in conventional risk factors such as smoking, blood pressure and blood cholesterol but differences in psychosocial factors related to the work place and to the social environment and in coronary care and secondary prevention may also contribute.

In seeking to prevent CVD in European populations the objectives are to reduce mortality and morbidity and thus improve the chances of a longer life expectancy with preserved quality of life. CVD is strongly related to

Table 9.1 Population-attributable risk associated with life-style-related risk factors in men and women by geographic regions in Europe [8]

	Region	Smoking (%)	Fruits and vegetables (%)	Exercise (%)	Alcohol (%)	All life-styles (%)
Men	Western Europe	39.0	13.3	37.7	14.1	69.6
	Central and Eastern Europe	40.4	7.6	–0.4	10.4	48.9
Women	Western Europe	11.1	8.4	38.3	34.2	65.2
	Central and Eastern Europe	13.1	12.8	42.7	29.9	65.4

life-style characteristics and associated risk factors. There is clear scientific evidence that life-style modification and risk factor reduction can retard the development of the disease both before and after the occurrence of a clinical event.

Traditionally, preventive cardiology has been concerned with unifactorial risk assessment, as in the management of hypertension, hyperlipidaemia or diabetes. This has resulted in emphasis being placed on single high-risk factors rather than on the overall level of risk based on a combination of factors. The total-risk concept, on the other hand, acknowledges that CVD has a multifactorial aetiology and that risk factors can have a multiplicative effect, enhancing the effect of one another.

A genetic predisposition does play a role in the development of CVD and a detailed family history of coronary heart disease (CHD) or other atherosclerotic disease should be part of the assessment of all patients with CVD and in the identification of high-risk individuals. However, except in rare cases, as for example in familial hypercholesterolaemia, the influence of a positive family history is not among the strongest risk factors. Moreover, it is not amenable to intervention and serves alongside other risk factors to identify individuals who are at increased risk. Even with a positive family history CVD only rarely occurs in the absence of other risk factors.

The importance of comprehensive risk factor intervention in patients with established CVD and in high-risk subjects has been emphasized by several expert groups. Previous recommendations were based on reports from the Framingham Study [5]. Because this risk score was based on a limited North American sample its applicability to European populations has been questioned. Accordingly, the development of a risk estimation system based on a large pool of representative European data was instigated: the SCORE (Systematic COronary Risk Evaluation) for total CVD risk [6]. The design of this project allows the development of methods for creating national or regional risk charts based on published mortality data. Thus, there is unanimity on the clinical priorities for coronary prevention and the need to target those at highest risk on the basis of a comprehensive multifactorial risk assessment. Yet, surveys have revealed that there is considerable potential to improve risk factor management [7].

There is a wealth of evidence that tobacco smoking, lack of physical activity, nutritional habits and psychosocial factors play important roles both as causes of the mass occurrence of CVD in populations and as contributing factors to the risk of CVD in individuals within populations. In the INTERHEART study almost 70% of all cases with a first myocardial infarction could be related to life-style factors (Table 9.1), and up to 90% could be related to nine easily identifiable risk factors, thus showing the importance of continuing efforts to prevent CVD [8] (Table 9.2). The cumulative effect of these risk factors on the odds ratio for myocardial infarction is shown in Fig. 9.1.

Table 9.2 Population-attributable risk associated with other risk factors in men and women by geographic regions in Europe [8]

	Region	Hypertension (%)	Diabetes (%)	Abdominal obesity (%)	All psychosocial (%)	Lipids (%)	All nine risk factors (%)
Men	Western Europe	20.5	12.8	68.6	23.7	36.7	92.0
	Central and Eastern Europe	15.9	5.8	31.7	–0.9	38.7	71.9
Women	Western Europe	25.9	21.0	50.6	67.1	47.9	97.1
	Central and Eastern Europe	42.7	15.7	20.0	15.0	26.8	86.1

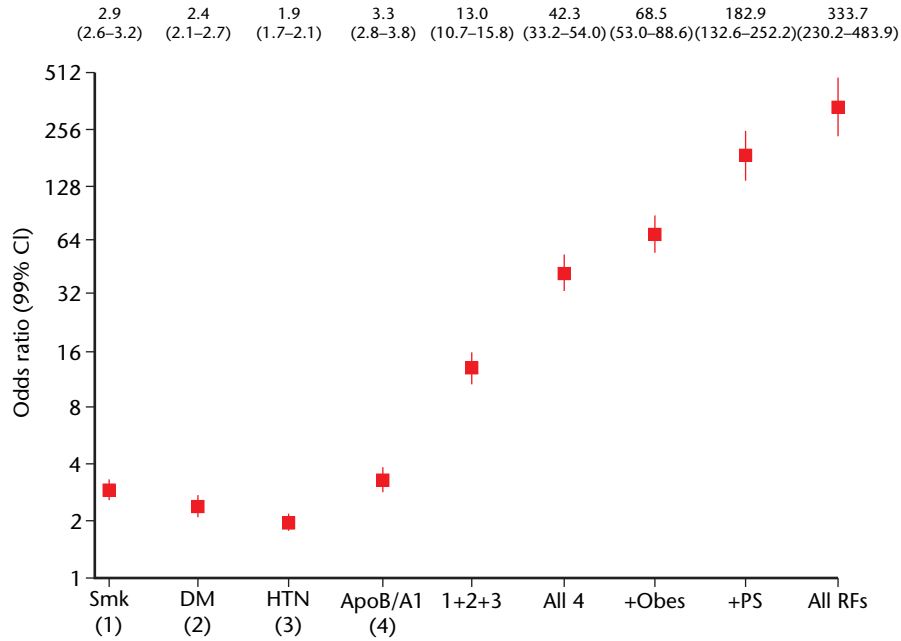

Figure 9.1 Risk of acute myocardial infarction associated with exposure to multiple risk factors [8]. Smk, smoking; Fr/vg, fruits and vegetables; Exer, exercise; Alc, alcohol. Note the doubling scale on the *y*-axis.

For a proper assessment of the total cardiovascular risk each individual risk factor has to be considered and the impact of modifying risk has to be assessed against the background set by the non-modifiable risk characteristics. Therefore the concept of total CVD risk estimation has been proposed as an important principle in the development of preventive strategies aimed at a good match between the intensity of intervention versus magnitude of CVD risk.

Prevention strategies

The 1982 report of the World Health Organization (WHO) Expert Committee on Prevention of Coronary Heart Disease considered that a comprehensive action for prevention has to include three components:

- **Population strategy**—for altering at the population level life-style and environmental factors and their socioeconomic determinants, which are the underlying causes of CHD.
- **High-risk strategy**—identification of high-risk individuals, and action to reduce their risk factor levels.
- **Secondary prevention**—prevention of recurrent events and progression of the disease in patients with clinically established CHD.

The last two correspond to prevention activities targeted at individuals and should be an integral part of clinical practice. They are the focus of this chapter. The population strategy, targeted at entire communities, should be an integral part of food and nutrition, transport, employment, education, health and other policies at European, national, regional and local levels. Table 9.3 summarizes the most important distinctions between the population and the clinical prevention strategies.

Population strategy

The population and clinical approaches are complementary, but the population strategy is fundamental to reducing the burden of CVD in Europe by targeting the social and economic determinants of the disease through political action. The population strategy must lead eventually to changes in life-style: a reduction in the number of people who smoke, enhancement of physical activity and the promotion of adequate and balanced food habits. These goals can be reached in different ways, but political will and development of *ad hoc* policies and investments at all levels are a condition without which they cannot be achieved.

Social inequalities affect cardiovascular health. A population strategy should ensure actions against the determinants of these inequalities. The strategy has to ensure equity of access to preventive advice and to diagnostic and therapeutic interventions, to reduce the social differences in health. A preventive population strategy can be

Table 9.3 Main differences between population and clinical prevention strategies

Prevention in clinical practice	Population strategy: health promotion
The aim is the prevention of onset and progression of disease in an individual	The aim is the reduction of incidence of disease in the population
The targets are individuals	The target is the community
Use quantitative methods	Use quantitative and qualitative methods
Instruments are medical interventions	Instruments are development and implementation of *ad hoc* policies
Standards are randomized controlled trials	Standards are outcome and process evaluation
Easier to treat an individual	Difficult to scale up health promotion programmes that reach the whole population
Outcomes of interventions are individual change	Outcomes are to change the social norms, environments and behaviour of entire populations
Interventions can focus on most factors relevant to the outcome	Interventions take on social determinants external to the community

Modified from the OSAKA declaration [10].

successful, as demonstrated in Finland [9], but is critically dependent on the participating parties such as government, insurance companies, the food industry, etc. Cardiologists, however, should not underestimate the impact that they as professionals can have in the public domain.

High-risk strategy

Prevention targeted at individuals who are at high risk but otherwise healthy should be an integral part of clinical practice. These persons may be identified by their life-style, e.g. smoking cigarettes or obesity, or through the detection of hypertension, hyperlipidaemia, diabetes, or by a combination of risk factors, as in the metabolic syndrome. A substantial number can be identified in daily practice without having to resort to cardiovascular screening of the entire population.

High-risk individuals are defined as those with:

- markedly raised levels of single risk factors, i.e.
  - total cholesterol ≥ 8 mmol/l (320 mg/dl)
  - low-density lipoprotein (LDL)-cholesterol ≥ 6 mmol/l (≥ 240 mg/dl)
  - blood pressure ≥ 180/100 mmHg;
- multiple risk factors
  - resulting in a 10-year fatal CVD risk of ≥ 5% at present according to SCORE
  - or ≥ 5% if extrapolated to age 60;
- diabetes mellitus
  - diabetes mellitus
  - diabetes type 1 with microalbuminuria.

Secondary prevention

Patients who present with CVD have already declared themselves to be at high risk of recurrent ischaemic events and therefore their modifiable risk factors need to be reduced. These include the basic elements of life-style counselling (stopping smoking, modifying food and physical activity habits, taking action against psychosocial stress and depression) and the use of prophylactic medication and are an integral part of post-event cardiological or stroke care.

The treatment goals of prevention in patients with established CVD are:

- stopping smoking;
- daily physical activity;
- adequate nutritional habits aiming at
  - total cholesterol < 5 mmol/l (190 mg/dl)
  - LDL-cholesterol < 3 mmol/l (115 mg/dl);
- blood pressure < 140/90 mmHg.

Patients with established CVD or diabetes, whose untreated values of total and LDL-cholesterol are already close to 5 and 3 mmol/l, respectively, probably benefit from further reduction of total cholesterol to < 4.5 mmol/l (175 mg/dl) and from further reducing LDL-cholesterol to < 2.5 mmol/l (100 mg/dl), with moderate doses of lipid-lowering drugs. In patients with diabetes target levels for blood pressure are < 130/80 mmHg.

Preventive action should lead to contacting close relatives for risk assessment and providing them with preventive advice and intervention if necessary.

Priorities in clinical practice

The number of patients with established CVD and of otherwise healthy individuals who are at high risk is large. This presents a considerable challenge to the medical community for which the tasks of CVD prevention are difficult to accomplish in the context of the daily workload. Therefore, it is useful to define priorities for CVD prevention. The Third Joint European Societies Task Force on CVD prevention in clinical practice [10] has developed guidelines proposing the order in which preventive action should be taken, because with limited resources full-scale action directed to all groups potentially needing preventive advice may not be feasible in the national health-care structure. As soon as progress has been made in the top priority groups, action may be directed to groups with a lower rank order in the list. The highest priority is given to patients with established CVD, the lowest to the general population met in clinical practice.

Furthermore, cardiologists and other physicians should act as opinion leaders and influence public health decisions, aiming at facilitating healthy life-styles at a broad population level.

Proposed list of priorities:

1 Patients with established CHD, peripheral artery disease and cerebrovascular atherosclerotic disease.
2 Asymptomatic individuals who are at high risk of developing atherosclerotic CVD.
3 First-degree relatives of patients with early-onset CVD (defined as males < 55 years, females < 65 years).
4 First-degree relatives of asymptomatic individuals at high risk.
5 Other individuals met in connection with ordinary clinical practice.

Total-risk estimation

Total risk means the likelihood of a person developing a fatal cardiovascular event over a defined period of time. It is well established that risk factor management decisions should not be based on consideration of a single risk factor. Table 9.4 illustrates how a 60-year-old woman with a cholesterol level of 8 mmol/l can have a nine times lower CVD mortality risk than a man with a cholesterol level of 5 mmol/l if the man smokes and is hypertensive. Estimating the combined effect on CVD mortality of several major risk factors is more complex than assessing single risk factors. It is essential for the clinician to be able to assess risk rapidly and with sufficient accuracy to allow evidence-based management decisions. To this end, several risk charts have been published [3,11]. These charts use age, sex, smoking status, total cholesterol and systolic blood pressure to estimate the risk of coronary or cardiovascular events over the next 10 years. In the widely used Framingham risk charts a 10-year risk ≥ 20% was used arbitrarily as a threshold for risk factor intervention. However, the charts had several weaknesses: they were derived from North American data and the applicability of the risk chart to European populations was uncertain. In addition, the dataset used for the chart was small and the definition of non-fatal end-points differed from that used in other studies.

The risk chart presented in the Third Joint Task Force recommendations was developed as part of an EU Concerted Action Project: the SCORE (**S**ystematic **CO**ronary **R**isk **E**valuation) chart. The SCORE risk prediction system is derived from 12 European cohort studies and comprises over 200 000 persons, 3 million person-years of observation and over 7000 fatal cardiovascular events. The main differences from the Framingham charts are:

- CVD mortality, rather than total events, is used as a primary end-point because this allows risk to be calculated for countries or regions where only mortality data are available.
- All atherosclerotic deaths (not only CHD) are included in the risk model by using a calculation method that allows stroke deaths to be considered separately from CHD deaths if required. Stroke deaths may be proportionately more important in low-risk populations.
- The risk chart has been modified to provide more detail for middle-aged subjects in whom risk changes more rapidly with age.

Table 9.4 Examples of how other risk factors may negate the advantages of having a desirable cholesterol level. Risk figures refer to the 10-year risk of CVD death.

Sex	Age (years)	Cholesterol (mmol/l)	Blood pressure (mmHg)	Smoking	Risk (%)
Female	60	8	120	0	2
Female	60	7	140	+	5
Male	60	6	160	0	8
Male	60	5	180	+	19

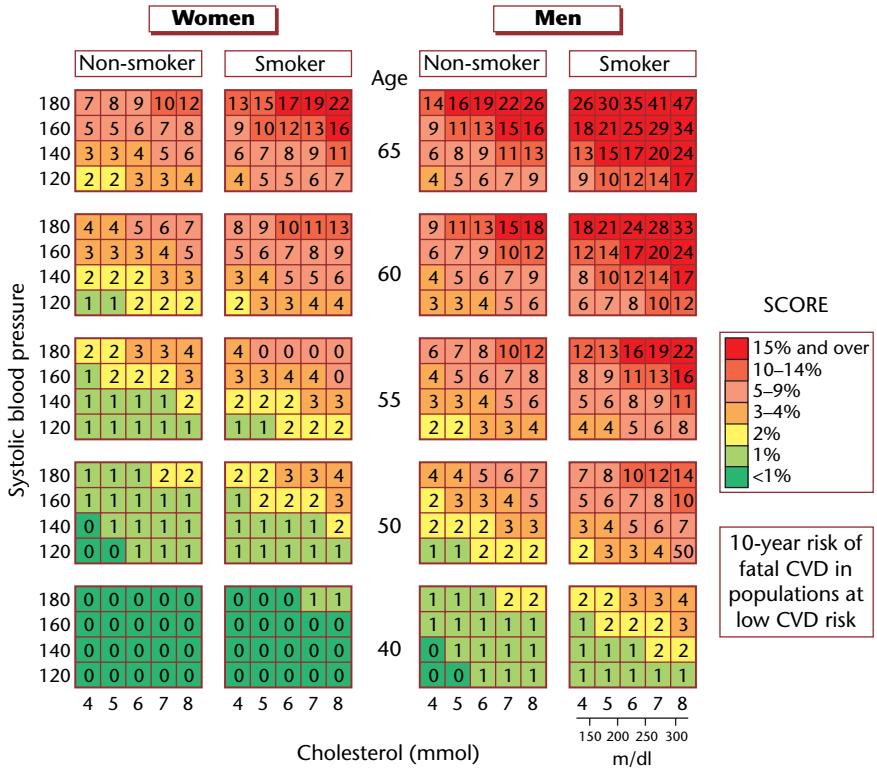

Figure 9.2 Ten-year risk of fatal CVD in high-risk regions of Europe by gender, age, systolic blood pressure, smoking status, total cholesterol or HDL/total cholesterol ratio.

- Separate charts have been prepared for higher and lower risk areas of Europe (see Figs 9.2, 9.3). In the future it will be possible to produce individualized risk charts for individual countries, provided reliable mortality information is available.

It should be stressed that the SCORE charts are only for use in subjects without known vascular disease. Subjects with manifest atherosclerotic vascular disease are already at high risk of vascular events and should be treated accordingly.

The SCORE chart has several functions:

- An individual's total risk of CVD death over the next 10 years can be read from the chart without any calculations.
- Relative risk can readily be estimated by comparing the risk in one cell with any other cell in the same age group.
- The chart can be used to give some indication of the effect of change from one risk category to another, i.e. when the subject stops smoking or reduces other risk factors.
- Although young people are generally at low risk, this will rise as age increases. The chart can be used by following the tables upward to illustrate the effects of lifetime risk by observing the increased risk with an increase in age.

Low-risk individuals should be offered life-style advice to maintain their low-risk status. In the previous chart, based on the Framingham study results, high risk for CHD mortality and morbidity was defined as a level of 20% or more. This equates to a risk of approximately 5% CVD mortality in the SCORE chart. Anybody at or above this level would merit intensive risk factor advice. Because the chart has several practical limitations the European Society of Cardiology has launched an interactive computer-based tool for total risk estimation: HEARTSCORE®.

HEARTSCORE®

HEARTSCORE® is a combination of the PRECARD® program operating with SCORE data, and has been adopted as the standard in European CVD risk management by the Third Joint European Societies Task Force on CVD Prevention. The PRECARD® program is a health educational risk management program which has been developed in Denmark [12]. It is the electronic counterpart to the risk chart and is aimed at supporting both the clinician and the patient in optimizing individual cardiovascular risk management.

The program operates with the same risk factors, endpoints, colours, etc. as the risk chart, but shows total risk

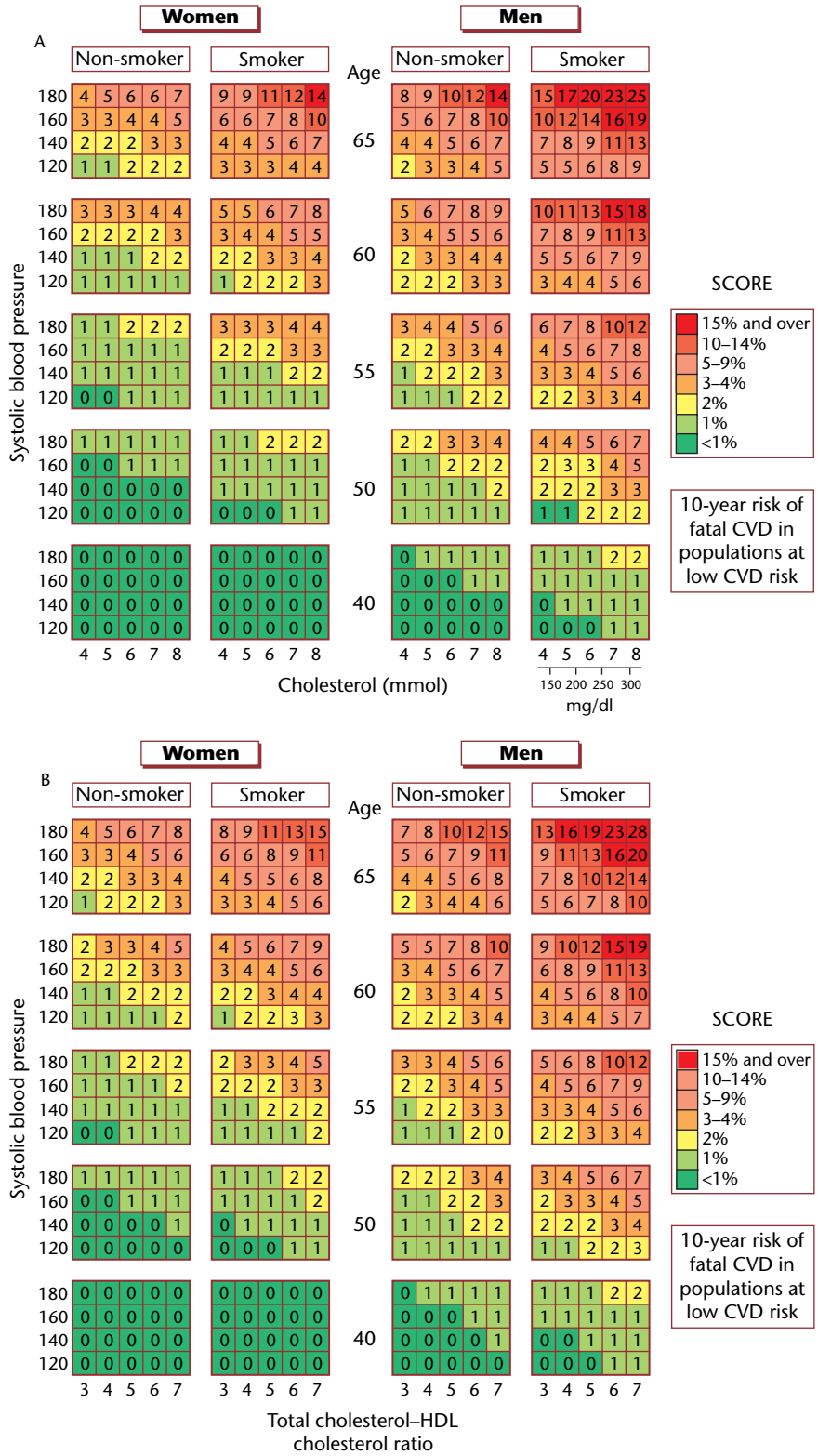

Figure 9.3 Ten-year risk of fatal CVD in low-risk regions of Europe by gender, age, systolic blood pressure, smoking status, total cholesterol or HDL/total cholesterol ratio.

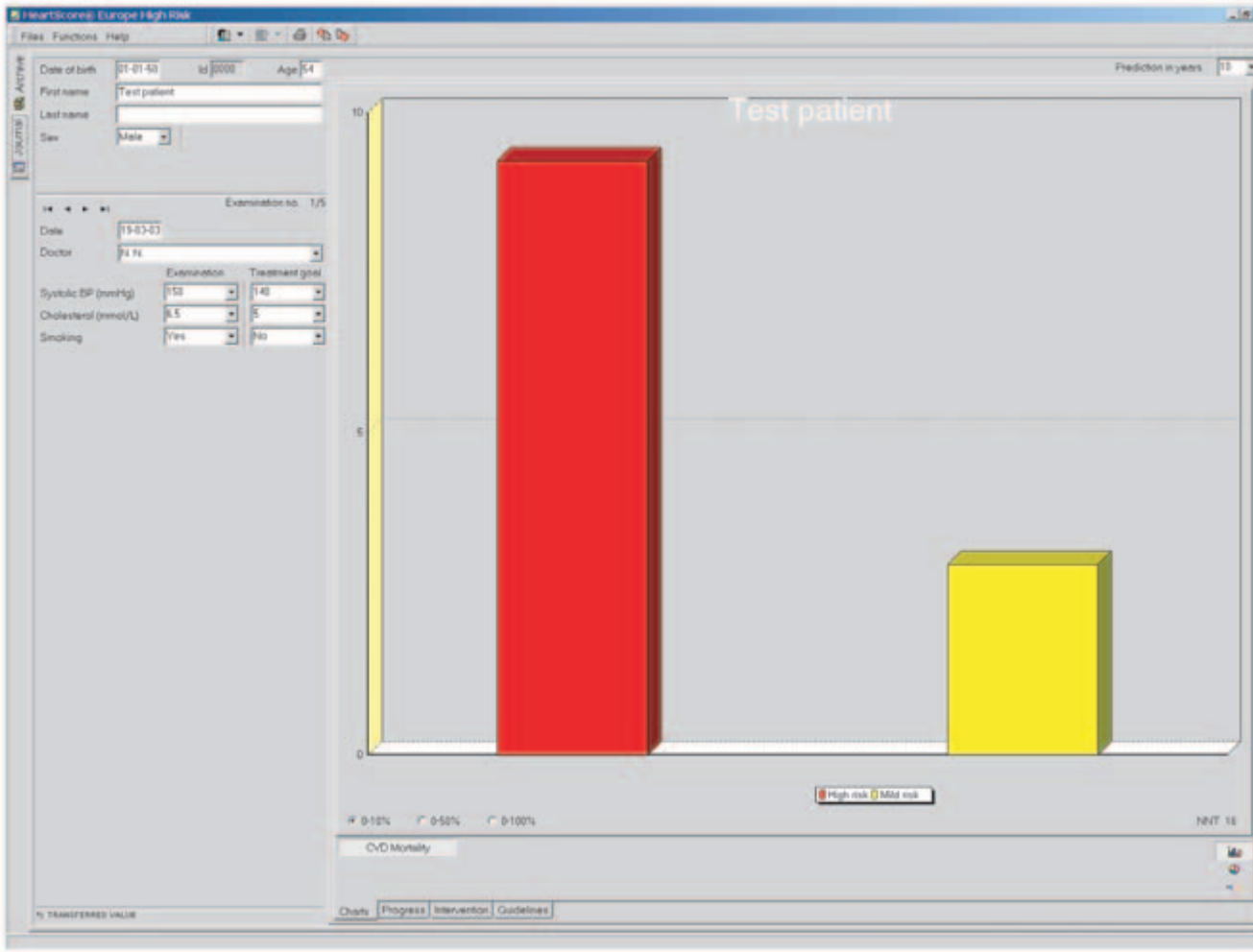

Figure 9.4 Main screen for HEARTSCORE®.

in a bar-chart (left bar in Fig. 9.4) and the distribution of modifiable risk factors in a pie chart (Fig. 9.5). The expected effect of intervention is calculated from large randomized clinical trials in hypertension and hypercholesterolaemia and is also shown in a bar chart (right bar in Fig. 9.4). At the end of the consultation an individual sheet of health advice based on the actual risk profile can be printed. The health promotion texts to the patient are compiled from endorsed sources in each country.

The program is flexible and interactive. It can be updated as new cohort studies become available, and can incorporate new languages, new risk factors and new end-points as knowledge evolves. It can be easily adapted to different countries and settings allowing clinicians to have immediate and interactive access to appropriate local preventive advice.

HEARTSCORE® is available for downloading in a version for low-risk and high-risk regions via the ESC website: www.heartscore.org. National versions will be gradually made available from this website.

Instructions on how to use the chart

- To estimate a person's total 10-year risk of CVD death, find the table for their gender, smoking status and age. Within the table find the cell nearest to the person's systolic blood pressure (mmHg) and total cholesterol (mmol/l or mg/dl).
- The effect of lifetime exposure to risk factors can be seen by following the table upwards. This can be used when advising younger people.
- Low-risk individuals should be offered advice to maintain their low-risk status. Those who are at 5% risk or higher, or who will reach this level in middle age, should be given maximal attention.

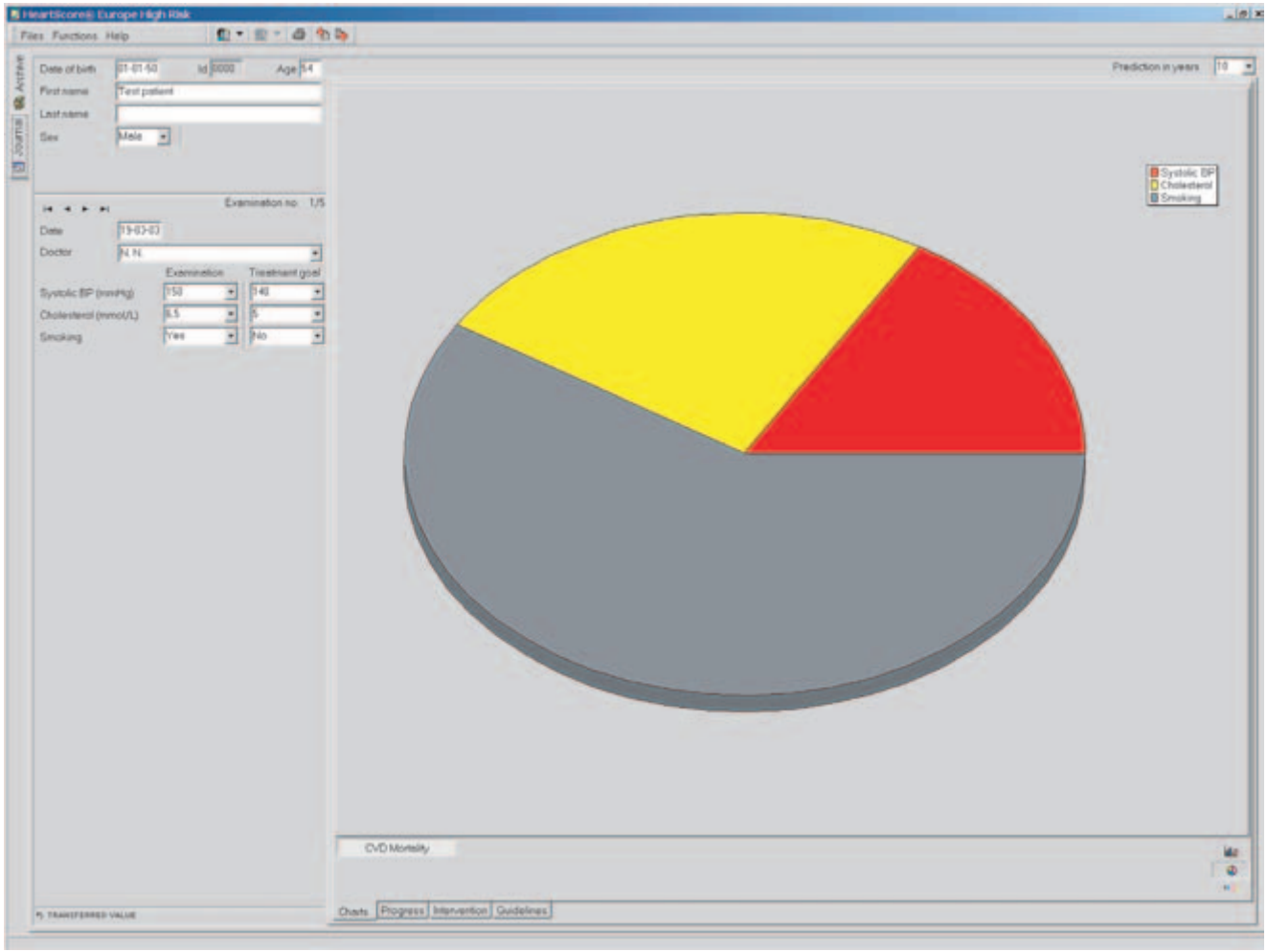

Figure 9.5 Pie chart for HeartScore®.

- To define a person's relative risk, compare their risk category with that of other people of the same age and gender.
- The effect of changing cholesterol, smoking status or systolic blood pressure can be estimated from the chart.

Qualifiers

Total CVD risk may be higher than indicated in the chart:

- as the person approaches the next age category;
- in asymptomatic people with paraclinical evidence of atherosclerosis (e.g. CT scan, ultrasonography);
- in people with a strong family history of premature CVD;
- in people with low high-density lipoprotein (HDL) cholesterol levels, with raised triglyceride levels, with impaired glucose tolerance, with raised C-reactive protein, fibrinogen, homocysteine, apolipoprotein B or lipoprotein(a) levels;
- in obese and sedentary people.

Modifying CVD risk

Smoking

Smoking as a risk factor for cardiovascular disease

Cigarette smoking continues to be a dominant risk factor for both CVD and non-CVD mortality and morbidity. The total number of smokers is expected to reach about 1.6 billion by 2025, with a predicted annual tobacco-related mortality rate of 10 million by 2030. The major part of these deaths will be in the middle- and low-income countries. Thus, smoking remains the single most important preventable cause of disease and early death [13].

The main cardiovascular effects of smoking are shown in Table 9.5, all of which contribute to inflammatory processes in the vascular wall and to thrombotic events.

Table 9.5 Main cardiovascular effects of smoking

Heart rate	↑
Blood pressure	↑
Platelets	Activation → thromboembolism
Endothelium	Dysfunction
Coronary arteries	Provokes arterial spasm
Vascular plaque	Increase in numbers and size
LDL-cholesterol	↑
HDL-cholesterol	↓

These effects are related to the amount of tobacco smoked daily and to the duration of smoking [11]. Genetic disposition is probably important and starting smoking at a young age (< 15 years) significantly increases the risk of premature CVD mortality [14]. In the presence of other risk factors (diabetes, hypertension, dyslipidaemia, overweight) smoking-related risk increases even further. Even passive smoking influences CVD risk.

Quitting smoking is the most effective of all preventive measures for cardiac patients. It leads to a marked reduction in CVD risk: asymptomatic smokers who quit reach the risk level of non-smokers after up to 10 years [11,15]. The effect is more pronounced in patients with CHD: a recent review has shown that quitting smoking is associated with a substantial reduction in risk of all-cause mortality: pooled crude relative risk (RR) 0.64 (95% CI 0.58–0.71). There was also a reduction in non-fatal myocardial infarctions—RR 0.68 (95% CI 0.57–0.82) [15].

Assessment of smoking

A full assessment of the smoking status of the patient is mandatory. This includes: motivation to quit smoking, amount and type smoked, social and family environment, knowledge of nicotine's role in health, signs of nicotine dependence, earlier cessation experience, existing relevant comorbidity, especially chronic obstructive lung disease. A simple lung function test may be valuable. In addition, the degree of addiction and the state of changing smoking habits are highly relevant. Here, the Fagerström test for nicotine dependence can be used (Table 9.6) [16,17]. Motivation and dependency are key elements in the assessment.

Management of smoking, quitting smoking programmes

The doctor's clear and strict advice that a cardiac patient should quit smoking is of decisive importance at the start of the smoking cessation process. At the time of an acute cardiac event or coronary intervention patients may be highly motivated to change life-style, and this is an opportunity to initiate or reinforce anti-smoking advice that should not be missed. Continued reinforcement and encouragement by the physician are also important.

There is a broad variety of options in smoking cessation therapy varying from simple self-help interventions to drug therapy (Table 9.7):

Table 9.6 The Fagerström test for nicotine dependence [19]

Question	Answer	Points
1 How soon after you wake up do you smoke your first cigarette?	Within 5 min	3
	6–30 min	2
	31–60 min	1
	After 60 min	0
2 Do you find it difficult to refrain from smoking in places where it is forbidden?	Yes	1
	No	0
3 Which cigarette would you hate most to give up?	The first in the morning	1
	Any other	0
4 How many cigarettes per day do you smoke?	≤ 10	0
	11–20	1
	21–30	2
	≥ 31	3
5 Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes	1
	No	0
6 Do you smoke if you are so ill that you are in bed most of the day?	Yes	1
	No	0

Average score in representative samples of smokers: 3–4 points.
Questions 1 and 4 have the highest informative value.

Table 9.7 Success rate of different interventions to stop smoking [20–24]

Type of intervention	Odds ratio	95% Confidence interval	Reference
Self-help interventions	1.24	1.07–1.45	9
Individual behavioural counselling	1.62	1.35–1.94	10
Group therapy programmes	1.95	1.57–2.48	11
Nicotine replacement therapy	1.74	1.64–1.86	12
nicotine gum	1.66		
nicotine patches	1.74		
nasal spray	2.27		
inhaled nicotine	2.08		
sublingual nicotine	2.08		
Antidepressants			13
bupropion	1.97	1.67–2.34	
nortriptyline	2.80	1.81–4.32	
Anxiolytics	–	No consistent evidence	
Community interventions	–	No significant effect	

- **Self-help interventions**—Smokers may give up smoking on their own but leaflets with advice and information may help. Standard self-help materials may increase quitting rates compared to no intervention but the effect is limited. Materials that are tailored for individual smokers may be more effective [18].
- **Individual behavioural counselling**—When compared to control or minimal intervention, individual counselling is more effective and may lead to a quitting smoking rate of up to 40% 6 months after starting the programme [19].
- **Group therapy programmes**—These provide smokers with an opportunity to learn behavioural techniques combined with mutual support within the group, although not all smokers accept this option. Groups are better than self-help and other less intensive interventions. However, there is not enough evidence on their effectiveness, or cost-effectiveness, compared to individual counselling with similar intensity. Addition of group therapy to treatment, such as advice from a health professional or nicotine replacement, has limited additional benefit [20].
- **Nicotine replacement therapy**—The aim is to replace nicotine from cigarettes, thus reducing withdrawal symptoms associated with smoking. Different forms of nicotine replacement are available: chewing gum, transdermal patches, nasal spray, inhalers and tablets. The use of nicotine patches is well tolerated by CVD patients. According to a recent review of 110 trials all of the commercially available forms of nicotine replacement therapy are effective in promoting smoking cessation [21]. They increase quitting rates approximately 1.5- to 2-fold regardless of the setting and largely independent of the intensity of additional support. Provision of more intense levels of support is not essential to the success of nicotine replacement therapy.
- **Antidepressants**—Smoking cessation and nicotine withdrawal may precipitate depression. Nicotine may have an antidepressant action; antidepressants may substitute for this effect. The antidepressants bupropion and nortriptyline can aid smoking cessation. Trials of extended therapy with bupropion to prevent relapse after initial cessation have failed to show a long-term benefit. There is no consistent evidence that anxiolytics aid smoking cessation [22].

Despite these options, many patients who succeed in quitting manage to do this without any special programmes or treatment. Support by the spouse and family is important in smoking cessation.

A community approach will remain an important part of health promotion activities but the largest and best conducted community-based programmes against smoking have thus far failed to diminish the prevalence of smoking. Yet, in several European countries 'smoke-free' environments have been created, including restrictions of smoking at work sites, in public places, restaurants, etc. These changes are important public-health developments that may in the future provide good support to the individual's smoking cessation efforts.

Physical activity

Physical inactivity as a risk factor for CVD

Physical inactivity is a major and growing component in the burden of chronic disease. At least 60% of the global population fails to achieve the minimum recommendation

Table 9.8 Benefits of regular physical activity

- Reduces the risk of premature death
- Reduces the risk of death from CVD
- Reduces the risk of developing diabetes mellitus
- Reduces the risk of developing hypertension
- Reduces the risk of developing colon cancer
- Helps control weight
- Helps build and maintain healthy bones, muscles and joints
- Helps elderly become stronger and better able to move about without falling
- Reduces feelings of depression and anxiety
- Promotes psychological well-being

Table 9.9 Cardiovascular effects of regular physical activity

Antiatherogenic effect		
1	Body fat mass	↓
2	LDL-cholesterol	↓
3	HDL-cholesterol	↑
4	Triglycerides	↓
5	Insulin sensitivity	↑
6	Blood pressure	↓
Antithrombotic effect		
7	Platelet adhesiveness	↓
8	Fibrinolysis	↑
9	Fibrinogen	↓
10	Blood viscosity	↓
Anti-ischaemic effect		
11	Coronary flow	↑
12	Endothelial dysfunction	↓
Antiarrhythmic effect		
13	Vagal tone	↑
14	Adrenergic activity	↓
15	Heart rate variability	↑

of 30 minutes' moderate intensity physical activity daily. The risk of CVD increases by 1.5 times in people who do not follow these recommendations. Physical inactivity is estimated to cause 2 million deaths world-wide annually and 22% of all ischaemic heart disease [23,24]. It will have a major impact as physical activity in the younger generation tends to decrease. In the younger age groups activity patterns decline consistently from ages 12 through 21. In young adulthood (18–29 years) erosion continues whereas in middle age (30–64 years) the activity pattern stabilizes, with a tendency to improve in older age [25]. The combination of excessive caloric intake and insufficient exercise are life-style factors contributing to the development of the metabolic syndrome, which has reached an almost epidemic level in Europe and elsewhere.

Regular physical activity is protective through a wide variety of beneficial effects (Table 9.8). It has a direct effect on vascular lesions and an indirect effect through influencing other risk factors (Table 9.9). Thus, the promotion of regular physical activity and maintenance of fitness at school, at work and during commuting, at home, during leisure time and after old-age retirement is an important task for preventive cardiology.

CHILDREN AND ADOLESCENTS

The risk of a premature onset of atherosclerosis is increasing as children are becoming less active. Today children expend 600 kcal/day less than their counterparts 50 years ago [26]. School children rarely exercise the recommended daily 30–45 minutes. More than half of adolescents become physically inactive after leaving school.

Atherosclerosis begins in childhood: the first stage, a reversible fatty streak, is seen in most children. The harmful later stage, the atheromatous plaque, does not appear until after puberty in boys and much later in girls [27]. Traditional risk factors, such as hypertension, dyslipidaemia and smoking, act in the early stages of this process. At present, blood pressure levels in children are rising, the prevalence and the degree of obesity increases, insulin resistance and type 2 diabetes mellitus (non-insulin dependent diabetes mellitus) are more often found in young individuals [28].

HEALTHY ADULTS

Changes in society and the individual adaptations to these contribute to a mainly sedentary life-style. The exertional demands at the work place have decreased; only a minority of labourers will experience breathlessness in their daily work. Commuting has become less physically demanding. There is lower energy expenditure at home and during leisure time.

Since the landmark studies by the groups of Morris [29] and Pfaffenberger [30] the relation between physical activity and CVD has become well established. Maintaining physical fitness has a direct protective effect independent of other risk factors and exercise capacity, as well as physical activity, are powerful predictors of mortality [31–33]. Regular exercise diminishes the risk of a myocardial infarction under strenuous exertion [34].

ADULTS WITH CVD

CVD patients tend to restrict physical activity for fear of deterioration in the disease or because of symptoms. Overprotection by the family may contribute. Restoration and maintenance of physical fitness are both needed and beneficial.

Many of the beneficial effects of an active life-style observed in the healthy population (Table 9.9) apply to

the CVD patient. Physical activity reduces the progression of atherosclerosis by alleviating endothelial dysfunction. It affects the production of free radicals, protecting patients from oxidative stress; it improves insulin sensitivity and reduces plasma homocysteine levels. Protection against malignant arrhythmias and less myocardial wall stress is obtained through modifying the sympathovagal balance [35–37]. In a recent meta-analysis including 8440 patients a 27% reduction of total mortality as a result of exercise training was estimated, and cardiac mortality was reduced by 31% [38]. In spite of these benefits only a minority of patients are referred to exercise training programmes. Physical inactivity is common in patients with congestive heart failure. The benefit of improving physical fitness in these patients has been demonstrated [39].

THE ELDERLY

Age-related physiological changes may result in physical inactivity: a decrease in maximum heart rate, stroke volume, cardiac output and down-grading of β-adrenergic receptors. Peripheral changes contribute with decreases in muscular strength and coordination, peripheral O_2^- uptake, bone mineral content and lung function. With increasing age the activities of daily life put a greater demand on the person's work capacity. Regular physical activity will counteract or effectively slow down the age-related changes, thereby improving quality of life and extending disease-free survival. As the elderly account for the main part of all myocardial infarctions and coronary interventions, cardiologists should use the therapeutic potential of physical activity.

Assessment of physical activity

In youth, assessment of physical activity remains a challenge for research: differing stages of growth, discrepancies between physical strength and fitness and difficulties with the validity of questionnaires confound assessment. Formal exercise testing including measuring oxygen consumption or direct observation are resource-consuming methods. Yet, assessment is needed to evaluate physical activity programmes. Heart rate monitors, pedometers and accelerometers are used, although they do not register all forms of physical activity in children. Accelerometers may be the preferred choice [40]. In high-risk children, as in hereditary dyslipidaemia, a heavy family CVD burden or diabetes mellitus, standard exercise testing can provide a ground for life-style advice and follow-up.

In healthy adults a brief interview concerning physical activity at work and in leisure time if needed, together with a recall questionnaire, diary or pedometer may act as a base for the physician's advice. This may be completed with an exercise test using a bicycle ergometer or treadmill to obtain an objective assessment of exercise capacity.

In adults with CVD the patient's history usually needs objective assessment by exercise testing to detect myocardial ischaemia, to stratify for risk of a new event, to select for coronary intervention, or to assess the effect of revascularization or the response to medication. We refer to guidelines issued by the European Society of Cardiology (ESC) and the American Heart Association (AHA) [41,42].

In the elderly the patient interview remains the cornerstone in assessing physical activity. The specific problems of deteriorating physical capacity should be addressed, especially regarding the activities of daily living and the need for support. Exercise testing on a bicycle ergometer or treadmill may be indicated in persons with symptoms of CVD. However, less demanding methods, such as the Six-minute Walk Test or the Shuttle Walk Test, may also provide valuable information on the physical capacity of the elderly.

Management of physical activity

CHILDREN AND ADOLESCENTS

Every child should be encouraged to spend a minimum of 30–45 minutes every day in physical activities that increase heart rate to a significant degree, be it in school or during leisure time. Special efforts should be made to maintain activity levels during and after adolescence.

HEALTHY ADULTS

In high-risk individuals the family doctor should specifically promote regular physical exercise. For all healthy adults, regardless of risk, an active life-style should include work, commuting, domestic life and leisure time. Healthy adults are recommended to be active for 30–45 minutes most days of the week in enjoyable activities which fit into their daily routine (Table 9.10). Recommended intensity may be defined as heart rate during exercise at 60–75% of the maximum. As a simple method for estimating maximum heart frequency the formula of '220—age = max. heart rate' can be used. Alternatively the Borg scale of perceived exertion may be applied, using the level of 'moderate exertion' as the target [43]. This level is easily achieved by exercises involving large muscle groups, e.g. brisk walking or jogging, cycling, swimming, aerobic dancing, tennis, golf, or cross-country skiing. The duration of physical activity should preferably be 30–45 minutes, including a 5- to 10-minute warm-up phase, an aerobic phase of 20–30 minutes and a 5- to 10-minute cool-down phase at its end. A frequency of at

Aim	In all age groups: 30–45 minutes of physical activity at least five days a week
Rationale	• To prevent or delay the onset of cardiovascular disease • To limit the progress of existing cardiovascular disease
Method	• Promote daily physical exercise at school • Provide options for regular physical activity at the work site, encourage an active leisure time, e.g. brisk walking, cycling, swimming, gardening or other in/outdoor sports and hobbies • For coronary patients: participation in supervised or home-based programmes of physical training • For elderly: stimulate the maintenance of a physically active life-style, even in higher age groups
Some examples	Moderate activity: • Gardening for 30–45 minutes • Walking 3 km in 30 minutes (10 min/km) • Bicycling 8 km in 30 minutes • Dancing fast (social) for 30 minutes • Water aerobics for 30 minutes • Swimming laps for 20 minutes • Rowing for 20 minutes More strenuous activity: • Running 2.5–3 km in 15 minutes (5–7 min/km) • Stairwalking for 15 minutes • Shovelling snow for 15 minutes

Table 9.10 Recommendations for physical activity

least four or five times weekly is recommended. There is no scientific evidence of further preventive gains of a higher intensity or frequency of exercise.

ADULTS WITH CVD

Recommendations for CVD patients should be based on a clinical examination including exercise testing. Patients with stable angina pectoris or recovering from a myocardial infarction or coronary intervention should be referred to a rehabilitation programme provided by a multidisciplinary team on an ambulatory basis or for selected cases to a specialized in-patient institute. Individual home training programmes and other aids (books, CD-Rom, etc.) are available and effective although regular follow-up and encouragement are needed. Heart-rate monitors or pedometers may be helpful in home-based programmes. We refer to Chapter 26 (Cardiac Rehabilitation) for detailed information. The prescription of physical training programmes in congenital heart disease should remain in the hands of paediatric cardiologists and specially trained physiotherapists.

THE ELDERLY

In healthy elderly persons daily physical activity should be maintained on a moderate level. Brisk walking at a pace at which a conversation still can be held ('walk-and-talk model') is a good example. Senior CVD patients of both genders will benefit equally from rehabilitation programmes: training is safe, improves strength, aerobic fitness, endurance and physical function. It will affect risk factors, mental state and quality of life [44]. Resistance training may be an attractive alternative as it can be used in home-training (thera-band, weight lifting, etc.). The goal should be the prevention of physical inactivity so that the efforts of an active life-style are rewarded by its cardiovascular and other health benefits.

Blood pressure

Hypertension as a risk factor for CVD

Hypertension, defined as a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg, is one of the most important preventable causes of premature death world-wide, contributing to approximately half of all global CVD. In many countries, up to 30% of adults have hypertension; a further 50–60% would be in better health if they reduced their blood pressure by increasing physical activity, maintaining an ideal body weight and eating more fruits and vegetables. CVD doubles for every 10 mmHg increase in diastolic blood

pressure or every 20 mmHg increase in systolic blood pressure [45].

Blood pressure usually rises with age, except where salt intake is low, physical activity high, and obesity largely absent. Most natural foods contain salt; processed food may be high in salt; and individuals may add salt for taste. Dietary salt increases blood pressure in most people with hypertension, and in about a quarter of normotensives, especially with increasing age. In addition to effective life-style changes medication may be needed for control of hypertension.

Life-style management

Blood pressure can be reduced either by life-style interventions or by pharmacotherapy. Life-style interventions have been evaluated in mild blood pressure elevation [46]. Blood pressure was moderately reduced in individuals exposed to dietary sodium reduction, increased potassium intake, decreased alcohol consumption, body weight reduction, dietary regimens based on fish oils, increased physical activity and cessation of smoking [47,48]. In compliant individuals life-style changes reduce the total CVD risk, prevent a restart of medication after drug treatment has been stopped and may decrease the number and doses of drugs needed. Treatment based on these interventions alone may be sufficient for patients with mild hypertension and should always be advised even for patients on antihypertensive drugs. Frequent reinforcement is needed because long-term compliance in life-style changes may be lacking.

Life-style recommendations include:

- weight reduction in overweight individuals;
- reduction of salt intake to < 6 g daily;
- restriction of alcohol consumption to < 10–30 g/day (men) and < 10–20 g/day (women);
- regular physical activity in sedentary individuals;
- quitting smoking;
- dietary changes in cases of hyperlipidaemia.

Drug treatment (see Chapter 10)

The decision to start treatment depends both on the level of blood pressure and on the assessment of total CVD risk. Because risk factors may interact, the total cardiovascular risk of hypertensive patients may be high even if blood pressure is only mildly elevated [49].

In patients with established CVD or if target organ damage is present the choice of drugs depends on the underlying disease.

Drug therapy is necessary in case of a sustained systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg despite life-style interventions. Individuals with systolic blood pressure ≤ 140 mmHg and/or diastolic blood pressure ≤ 90 mmHg and no other risk factors do not require drug therapy as a rule.

Nutrition

Nutritional treatment for the prevention of cardiovascular diseases

The relation between nutritional habits and cardiovascular risk is well established. The initial observations of the 'Seven Countries Study' relating food consumption to ischaemic heart disease rates in countries with contrasting nutritional habits and CHD rates showed clear associations between the intake of saturated fats and the incidence of ischaemic heart disease. Since then, the relationship between dietary factors and dyslipidaemia or hypertension has been demonstrated in prospective investigations, confirming the findings from the ecological studies. In continuing research, many epidemiological or clinical studies have demonstrated the close relationships between food or nutriments and cardiovascular risk factors or events. Furthermore, multifactorial or targeted nutritional interventions have clearly demonstrated the beneficial effects of preventive or therapeutic nutritional approaches. In view of this strong evidence nutrition therapy is a full component of cardiovascular risk prevention.

Diet and cardiovascular diseases

The principal properties of foods and nutrients are summarized in Table 9.11.

TOTAL FAT, SATURATED, MONOUNSATURATED AND TRANS FATTY ACIDS

Dietary lipids play a major role in the formation of the atheromatous plaque and thrombotic complications. In Western countries, dietary intake of fat is often over 100 g/day. Dietary fatty acids affect cholesterol and lipoprotein levels [50], arterial blood pressure and haemostasis. In cohort studies, the positive relationship between fat intake and CVDs was linked to their saturated fatty acid content [51,52]. Animal products, industrially manufactured meals and certain cooking fats are the principal sources of saturated fats. These fatty acids increase LDL-cholesterol concentrations. Epidemiological data for monounsaturated fatty acids are scarcer. However, monounsaturated fatty acids have been associated with a reduced coronary risk compared to saturated fatty acids [51].

Trans fatty acids are isomers of monounsaturated or polyunsaturated fatty acids produced by hydrogenation.

Table 9.11 General recommendations for high cardiovascular risk subjects, to be adapted according to local and cultural particularities

Nutrient and food	Goal	Affect cardiovascular risk factors	Affect cardiovascular events
Energy	Keep BMI < 25 kg/m^2 and waist girth < 102 cm in men and < 88 cm in women	Triglycerides, HDL-cholesterol, insulin, glycaemia, blood pressure	Effect of BMI reduction Unknown
Total fat	30% of total energy	LDL-cholesterol and body fat	Little evidence
Saturated fat	10% of total energy	LDL-cholesterol, HDL-cholesterol, body fat, glycaemia	Yes
Trans fatty acids	< 2% of total energy		Yes
Polyunsaturated	≥ 10% of total energy		Yes
Monounsaturated	≥ 10% of total energy		Yes
n-3 fatty acid	1 g/day	Triglyceride, blood pressure, haemostasis, heart rate	Decrease fatal cardiovascular events
Dietary cholesterol	< 300 mg/day	LDL-cholesterol	Little evidence
Fruit and vegetable	≥ five portions a day	LDL-cholesterol and blood pressure	Yes
Salt	< 6 g/day	blood pressure	Little evidence

BMI, body mass index.

They are mainly derived from meat, dairy products, hard margarines and products from the food-processing industry. Compared with oleic acid, trans fatty acids increase blood LDL-cholesterol [53]. Epidemiological studies have shown positive associations between trans fatty acids and cardiovascular morbidity and mortality.

n-6 and n-3 polyunsaturated fatty acids

Linoleic acid is the main representative of the n-6 group. These fatty acids are mainly derived from vegetal oils. Clinical studies have shown that the consumption of n-6 polyunsaturated fatty acids decreases LDL-cholesterol. In cohort studies, the intake of polyunsaturated fatty acids is associated with a reduced coronary risk compared to saturated fatty acids or trans fatty acids. Intervention studies combining a reduction in risk factors and an increase in polyunsaturated fatty acid intake have shown reduced CVD incidence and mortality.

α-Linolenic acid is the precursor of the n-3 fatty acid group. Primary food sources are soya bean, rapeseed, safflower and linseed oils. In cohort studies, the intake of α-linolenic acid is inversely correlated to cardiovascular events and in secondary prevention trials coronary deaths are less frequent in patients randomly assigned to a Mediterranean diet with a high α-linolenic acid content [54].

Eicosapentaenoic acids (EPA) and docosahexaenoic acids (DHA) are two important members of the n-3 group that are mainly derived from oily fish. The intake of EPA and DHA reduces plasma triglycerides, arterial blood pressure, the occurrence of arrhythmias and improves haemostasis. Prospective studies show a reduced risk of fatal cardiovascular events in people who regularly eat fish [55]. In patients with CVD, the intake of fish and of EPA and DHA supplements reduces coronary mortality [54].

Fruits, vegetables, vitamins and vitamin supplements

Fruits and vegetables are important sources of vitamins and fibre. Intervention trials have demonstrated that regular intake of a diet with a high fruit and vegetable content and reduced dairy product content lowers systolic and diastolic blood pressure [56]. Observational studies have shown a lower incidence of cerebral or coronary vascular attacks in regular fruit and vegetable consumers.

Antioxidant vitamins have beneficial effects on cardiovascular risk factors in laboratory experiments. Most epidemiological observation studies have shown negative associations between the intake of vitamin E or carotenoids [57] and CVD. Similarly, leaf vegetable vitamins have a clear impact on homocysteine levels, another vascular risk factor. However, when intervention therapeutic trials were conducted, results were disappointing, showing at best no protective effect of vitamin supplements.

ALCOHOL

In the population, the connection between alcohol use and mortality follows a U- or J-shaped curve. Optimum consumption ranges between 10 and 30 g of alcohol per day for men, and is lower for women [58]. Reduced coronary mortality is the major cause for the reduction in mortality, with no evidence of higher benefit with any specific type of drink [59]. Conversely, 'binge drinking' is associated with a higher risk of sudden death and cerebrovascular stroke. No randomized study proved the benefit of alcohol in the prevention of CVD.

SALT

Sodium intake affects arterial pressure levels. Community-based intervention studies and meta-analyses of randomized trials have shown that a reduction in salt intake resulted in reduced arterial blood pressure in normo- and hypertensive subjects.

ASSESSMENT OF FOOD INTAKE

Quantitative dietary assessment methods consist of recalls or food records designed to measure the quantity of individual foods consumed over a given period. Nutrient intake can be calculated from food consumption data collected by quantitative or semi-quantitative methods using computer programs adapted to each country.

Qualitative dietary assessment methods include food frequency questionnaires and dietary history. Both collect retrospective information of the patterns of food use during a longer, less precise time period. They are most frequently used to assess habitual intake of foods in clinical settings.

Practical aspects of nutritional prevention of cardiovascular diseases

The principal objective of dietary intervention is to control risk factors to prevent the formation and rupture of the atheromatous plaque. Dietary recommendations should be individually adapted taking into account the patient's risk profile and eating habits as well as the cultural characteristics. The general nutritional recommendations for high cardiovascular risk patients are presented in Table 9.12.

Table 9.12 General recommendation on nutrients and foods for high cardiovascular risk subjects

Keep a varied and well-balanced diet
Control body weight by adapting energy intake to needs and perform exercise regularly
Consume fish regularly
Consume fruits and vegetables, cereals and grain products
Choose skimmed milk and low-fat cheeses
Choose lean meat and poultry instead of fat meat and processed meat
Choose vegetal oils and margarines rich in mono- and polyunsaturated fatty acids instead of hard margarines and butter
Reduce salt-rich processed food, salty ready-cooked foods

General issues

- A varied and balanced diet and regular exercise are critical to the preservation of good cardiovascular health.
- It is appropriate to eat fish because the n-3 fatty acids which they contain protect against fatal cardiovascular events.
- It is recommended to eat fruits and vegetables, cereals and grain products, skimmed dairy products and low-fat meat.
- To maintain the ideal weight the intake of calories should be adjusted to energy expenditure by restricting fatty products and products with a high caloric density.
- The total lipid intake should not exceed 30% of calorie intake. The saturated fatty acid intake should not exceed 30% of total lipids and should be replaced by monounsaturated or polyunsaturated fats of vegetal origin.
- The cholesterol intake should be less than 300 mg/day.

Nutritional treatment of dyslipidaemias

- Reduction of blood LDL-cholesterol is the main objective of dietary treatment of subjects at high cardiovascular risk, aiming at less saturated and trans fatty acid intake, and, to a smaller degree, food cholesterol intake. The primary sources of trans and saturated fatty acids are hard margarines and products of animal origin, such as meat and dairy products.
- Increasing intake of omega-3 fatty acids from fish oils and certain vegetal oils to decrease plasma concentrations of triglycerides and prevention of sudden death.
- Increasing intake of polyunsaturated fatty acids, soluble fibres and phytosterols to reduce plasma concentrations of LDL-cholesterol.
- Exercise, body weight reduction in the obese and normalization of glycaemia in diabetic patients to increase blood HDL-cholesterol levels. However, the prescription of exercise should be adapted to the physical condition of the patient.

- Moderate use of alcohol is not contraindicated in cases of hypoalphalipoproteinaemia (low HDL-cholesterol).
- Reduction in the intake of refined sugars, which is associated with reduced concentrations of HDL-cholesterol and increased triglycerides in certain sensitive subjects. They may be replaced by complex sugars from fruits, vegetables and grain products.

Arterial pressure

Diet plays a significant part in the control of arterial pressure.

- The main nutritional targets are the control of the salt and alcohol intake, loss of weight in obese subjects and increase in potassium intake.
- The salt intake should not exceed 6 g/day and the alcohol intake should not exceed 20 g/day (two glasses). Special attention should be paid to insidious salt sources such as industrially prepared food, bread and cheese.
- A varied diet with a high fruit and vegetable content, which is an important source of potassium, and low dairy product content is also associated with lower diastolic and systolic blood pressure.

Excess weight control

A reduction in the weight of obese subjects is associated with improvement of the main risk factors.

- Weight loss is obtained by reducing calorie intake and increasing exercise.
- The calorie intake is obtained by decreasing high energy density food such as dietary lipids (9 kcal/g) and alcohol (7 kcal/g). The reduction of saturated fats of animal origin is the favoured target because of their effects on the lipoprotein profile.
- The lipid intake should be less than 30% of the energy intake.
- Aim at a weight loss from 0.5 to 1 kg/week until target weight has been achieved. Upon weight loss completion, the objective becomes to maintain a stable weight and block weight recovery. Exercise should be adjusted to the physiological condition of the patient.

In conclusion, nutritional strategies have proven to be an efficient means of reducing events in subjects at high cardiovascular risk. Therefore, all patients with manifest CVD and subjects with high cardiovascular risk should receive professional advice on food and dietary choices to lower their risk.

Obesity and problems related to obesity

Obesity and conditions related to obesity are major determinants of cardiovascular morbidity in Europe and world-wide. With technological advances, jobs have become more sedentary and production of large quantities of cheap food has increased. Smoking rates are declining in many countries whereas obesity is a growing problem world-wide; for this reason an increasing number of future cardiovascular events will be attributable to obesity. Figures from the mid-1990s indicate that obesity [defined as body mass index (BMI) at or above 30 kg/m^2] affects more than one in five in several European middle-aged populations, and less than half have normal BMI (< 25 kg/m^2). Even more alarming are reports that show increasing obesity rates in children and young people, indicating that the current favourable trends with respect to smoking and serum cholesterol may be offset by increasing effects of obesity when those who are now young approach middle age.

Despite the fact that overweight and obesity are linked to hypertension, dyslipidaemia, diabetes and thrombotic and fibrinolytic processes, as well as inflammatory reactions, findings with respect to CHD and stroke have not been consistent. Whereas serum cholesterol, smoking and high blood pressure have established roles as predictors of CVD, studies with respect to obesity are more heterogeneous, with many of the early studies showing no, or only a weak, relation with cardiovascular outcomes [60]. In later years, however, several sufficiently large studies have, in fact, demonstrated significant associations between body mass index, the most widely used measure of fatness, and CVD [61,62], although usually at a relatively high body mass index, and thus identifying limited subsets of the population at increased risk.

The inconsistent findings with respect to body mass index are, to some extent, the result of methodological problems, because body mass index does not discriminate between muscle and fat, which may be why moderately elevated levels have generally not been significantly associated with CVD. In addition, BMI does not take the distribution of excess fat into account. Several studies indicate that abdominal fat, as measured by the waist to hip ratio, is a more important predictor than BMI [8]. Another methodological problem is that many studies have used multivariate techniques to investigate whether the effect of obesity is independent of hypertension and dyslipidaemia, conditions that are a result of excess body fat. Even though obesity alone may not be sufficient to produce cardiovascular complications, this is an approach that will lead to an underestimation of the effects of obesity.

In later years there is more than sufficient documentation to support the role of obesity in the pathogenesis of CVD, either directly or via intervening factors. Several studies show increasing risk of myocardial infarction, coronary deaths and stroke with increasing BMI, or abdominal obesity. Recent autopsy studies in young men and women have demonstrated that obesity is associated with more extensive and severe early atherosclerotic lesions [63,64]. Some studies have indicated that the optimal BMI with respect to coronary disease and stroke is probably in the lower reference range [65,66]. Even so, measures of obesity are still not included in cardiovascular risk prediction, probably mostly as a result of the methodological problems and inconsistencies in prior research.

Overweight and abdominal obesity are associated with several adverse factors, such as low HDL-cholesterol, high serum triglycerides, small and dense atherogenic LDL, hypertension, glucose intolerance, insulin resistance and diabetes. The clustering of these factors has been termed the metabolic syndrome [67]. According to a recent definition [68], a diagnosis of metabolic syndrome can be made if a person has three or more of the following five features:

- increased waist circumference (> 102 cm in men and > 88 cm in women);
- elevated triglycerides (> 1.7 mmol/l);
- reduced HDL-cholesterol (< 1 mmol/l in men and < 1.3 mmol/l in women);
- elevated blood pressure (> 130/85 mmHg or on treatment for hypertension);
- elevated glucose (> 6.1 mmol/l).

There is a strong association between multiple metabolic risk factors and insulin resistance, and the metabolic syndrome has alternatively been termed the insulin resistance syndrome. The interactions between the various components of the metabolic syndrome and insulin resistance are complex and partly determined by genetic factors. However, the increasing prevalence of the metabolic syndrome world-wide is predominantly the result of increasing rates of overweight and obesity. In the US population, who have high obesity rates, the prevalence of the metabolic syndrome, using the definition above, was stated to be over 40% back in the early 1990s in people aged 60 years or more [69].

The current rapid increase in the prevalence of obesity is determined by environmental factors but it is equally clear that genetic factors predispose some individuals to develop overweight and obesity in the presence of abundant food. Twin, adoption and family studies have shown that genetic factors play a significant role in the pathogenesis of obesity. However, in the absence of environmental factors, obesity will not develop.

Treatment of obesity, once established, is notoriously difficult. Although there is evidence for short-term effects with medical treatment (orlistat, sibutramine) the relapse rate remains high. New potential anti-obesity drugs currently undergoing phase III trials, such as rimonabant, may produce greater and more prolonged weight loss [70]. Surgical intervention has been demonstrated to be associated with sustained weight loss in patients with a BMI between 35 and 40 kg/m^2 but is an option only in a small proportion of all overweight and obese people. Curbing the effect of the current high prevalence of overweight or obesity will accordingly have to rest with prevention, particularly in children and young people but there is, as yet, little sign of abatement in the current epidemic.

Lipids

Lipid metabolism is complex and regulated by several processes [71]. Most of the cholesterol in blood plasma is normally carried as LDL, and, over a wide range of cholesterol concentrations, there is a strong and graded positive association in men and women between total as well as LDL-cholesterol and the risk of CVD [72]. A 25-year follow-up of the populations of the Seven Countries Study [73] showed that the relative risk associated with high as opposed to low serum cholesterol was virtually identical in men from Finland, Italy, Greece, the Netherlands, and the former Yugoslavia, with Japan, which had only very few cases, as the only exception. However, the absolute risk associated with any particular level of serum cholesterol varied markedly between different countries. Coronary artery disease is rare in populations with total cholesterol less than 3–4 mmol/l, even in the presence of other risk factors, but even in a very-low-risk population with low cholesterol levels, such as the Chinese, an association has been found between serum cholesterol and coronary mortality [74].

By itself, hypercholesterolaemia produces no symptoms; it is only an indicator of elevated risk. Except in those rare cases with inherited lipid disorders, such as familial hypercholesterolaemia, an elevated serum cholesterol can be associated with almost any risk of developing coronary disease. In an otherwise healthy non-smoking woman the risk may be next to negligible, but the risk increases with the number of other risk factors and can be up to 10 times higher in a man of the same age who is also a smoker [75]. The highest absolute risk associated with high serum cholesterol is run by people who already have manifest coronary disease or who have diabetes.

In contrast to LDL-cholesterol, increased concentrations of HDL-cholesterol protect against atherosclerotic

disease in populations at high risk. The cardioprotective effects of HDL-cholesterol have been attributed to reverse cholesterol transport, positive effects on endothelial cells, and to antioxidant activity [76]. Elevated serum triglycerides are associated with increased risk of CVD but the association is not as strong, nor as consistent, as it is for serum cholesterol. Low HDL levels and increased triglycerides are both components of the metabolic syndrome, and are also associated with a number of other adverse factors, for example type 2 diabetes, hypertension, low physical activity, obesity and low consumption of fruits and vegetables. Statistically, lipid fractions in the blood are highly intercorrelated; in particular, there is an inverse correlation between serum triglycerides and HDL-cholesterol. Accordingly, an independent role for serum triglycerides has been difficult to establish. However, given the complex pathophysiology concerning lipids and atherosclerotic disease, the concept of statistical independence does little to enhance our understanding of the role of triglycerides in risk. Even so, a meta-analysis of 17 population-based studies, comprising more than 46 000 men and more than 10 000 women, showed that risk of CVD in fact does increase with increasing degrees of hypertriglyceridaemia, independently of serum cholesterol [77]. The effect of serum triglycerides seems to be stronger for women than for men [72].

Drug treatment of dyslipidaemia

Pharmacological agents that reduce serum cholesterol have long been available. However, the WHO clofibrate trial published in the early 1980s [78], which showed that patients on active treatment, although they had significantly fewer coronary events, had higher all-cause mortality, led to therapeutic nihilism that lasted for more than a decade. In 1994, the 4S study was published [79]. This was the first large study that unequivocally demonstrated a survival advantage in coronary patients on active treatment with a statin. This study, and several more large placebo-controlled trials, have clearly demonstrated that patients with coronary disease benefit from cholesterol-lowering treatment, with an estimated 20–40% reduction in coronary events, almost regardless of initial serum cholesterol level [80]. Likewise, recent primary prevention trials have demonstrated significant reductions in coronary events [81] (Fig. 9.6).

Data derived from several sources show a log-linear relation between LDL-cholesterol and risk of coronary disease. As the absolute reduction in LDL-cholesterol induced by cholesterol-lowering drugs will be larger with higher initial levels and, as the relation between LDL-cholesterol is curvilinear, this larger reduction will result in a proportionately greater net reduction in coronary events. In terms of reduction in absolute risk in a particular individual, the reduction will be determined as much by his or her overall coronary risk, as by the initial cholesterol level. The presence of coronary disease, diabetes, or an accumulation of other risk factors means a higher absolute risk and the same net benefit in terms of reduced coronary events can therefore be expected at lower lipid levels in patients with any of these conditions. In contrast to findings for CHD, plasma cholesterol is not associated with overall rates of stroke [83].

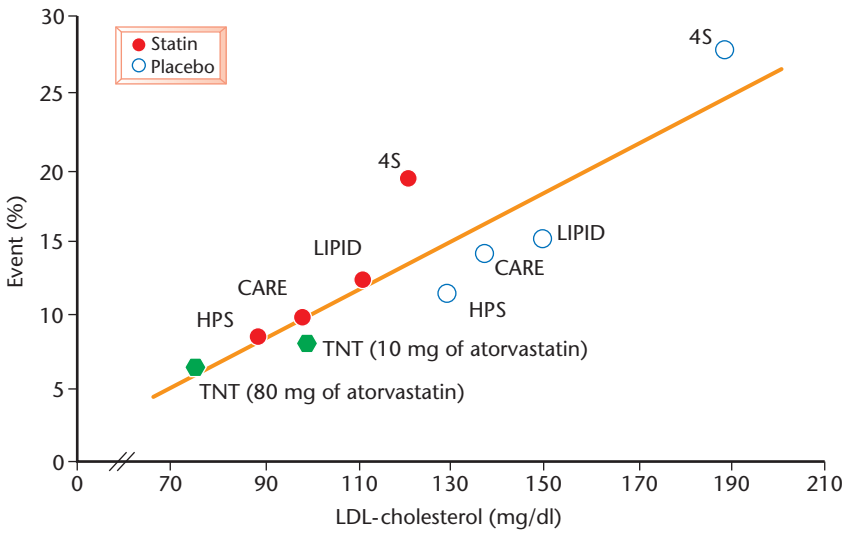

Figure 9.6 Event rates plotted against LDL-cholesterol levels during statin therapy in secondary-prevention studies. HPS denotes the Heart Protection Study, CARE denotes the Cholesterol and Recurrent Events Trial, LIPID denotes the Long-term Intervention with Pravastatin in Ischaemic Disease study and 4S denotes the Scandinavian Simvastatin Survival Study. Event rates for HPS, CARE and LIPID are for death from CHD and non-fatal myocardial infarction. Event rates for 4S and the TNT Study (82) also include resuscitation after cardiac arrest. To convert values for LDL-cholesterol to mmol/l, multiply by 0.02586. Reproduced with permission from LaRosa JC *et al*. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005; **352**: 1425–1435.

From a population perspective, pharmacological treatment of a subset of the population with high cholesterol levels will achieve comparatively little. Several Western countries have, in fact, experienced important decreases in mortality from CHD during the last decades, resulting from life-style changes. One example is Finland, which has experienced a very large decrease in CHD mortality since 1970. During the same period serum cholesterol levels in middle-aged men decreased from approximately 7 mmol/l to below 6.5 mmol/l and intake per day of saturated fat from liquid dairy products and spreadable fat decreased from 45 to 16 g in men [84].

In terms of life-years saved or coronary events avoided a population strategy makes more sense as the reduction in risk factors and attack rate will also involve those with moderately increased levels and the intervention will be targeted at more than one risk factor. Optimal serum cholesterol, as defined by the European guidelines as being a serum cholesterol < 5 mmol/l, is found in a minority of European middle-aged populations. If normotension, normal weight and non-smoking are added, only a tiny fraction have truly optimal risk factor status [85]. Most cases of coronary disease occur in the large group in the population with combinations of moderately elevated levels of risk factors. From a population perspective, intervention only in persons with high cholesterol will achieve comparatively little with respect to reduction in coronary disease incidence and mortality.

When faced with an individual patient with high serum cholesterol, however, the aim must be to attempt to minimize risk in that individual patient. Evidence from the trials shows unequivocally that treatment prevents coronary disease in patients at high risk. In accordance with the recommendations on prevention of coronary disease from the Joint European Societies and other national recommendations this will mean not only treatment with a statin in an important number of patients, but also aiming for reducing overall risk. This will involve anti-smoking advice, treatment of hypertension, weight-reducing regimens and advice on physical activity, whenever appropriate. Although the reduction in risk achieved by treatment is more or less the same regardless of initial risk the gain in terms of absolute risk is greater the higher the risk in the individual.

Current European recommendations hold that, in general, total plasma cholesterol should be < 5 mmol/l (< 190 mg/dl), and LDL-cholesterol should be < 3 mmol/l (< 115 mg/dl). Concentrations of HDL-cholesterol and triglycerides are not used as goals of therapy, but as markers of increased risk [HDL-cholesterol < 1.0 mmol/l (< 40 mg/dl) in men and < 1.2 mmol/l (> 46 mg/dl) in women; fasting triglycerides > 1.7 mmol/l (> 150 mg/dl)]. A recent small study found that a combination regimen (gemfibrozil, niacin and cholestyramine) aimed at increasing HDL-cholesterol levels prevented angiographic progression of coronary stenosis, and may have helped towards preventing cardiovascular events, when added to regular exercise and a low-fat diet [86].

Patients with established CVD, and patients at high risk of developing CVD, whose untreated values of total and LDL-cholesterol are already close to 5 and 3 mmol/l, respectively, benefit from further reduction of total cholesterol and LDL-cholesterol with moderate doses of lipid-lowering drugs. Use of higher doses of lipid-lowering agents has not yet been sufficiently well documented in unselected patients who are close to treatment targets.

In asymptomatic subjects (see Fig. 9.7), the first step is to assess total cardiovascular risk. If the 10-year risk of cardiovascular death is < 5%, even if projected to age 60, advice concerning diet, physical activity and smoking should be given to keep the cardiovascular risk low. If the 10-year risk of cardiovascular death is ≥ 5%, or will

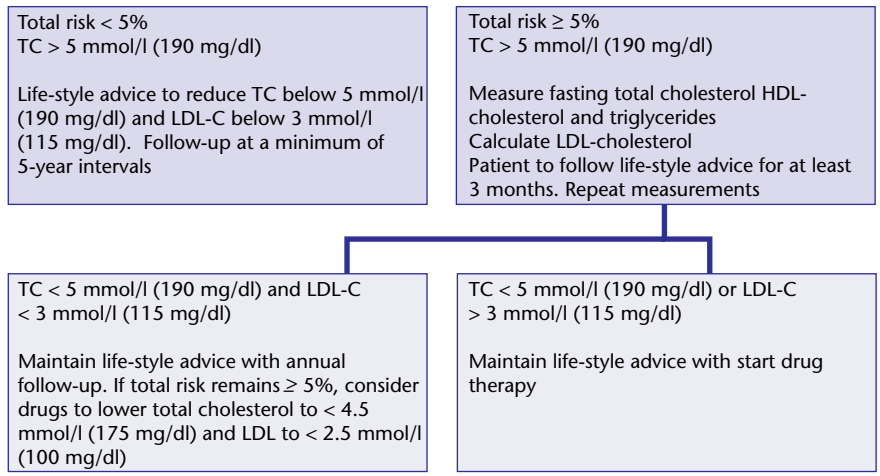

Figure 9.7 Guide to lipid management in asymptomatic subjects.

become ≥ 5% if the subjects' risk factor combination is projected to age 60, serum LDL-cholesterol, HDL-cholesterol and triglyceride should be analysed and intensive life-style advice should be given. If total and LDL-cholesterol levels < 5 mmol/l and < 3 mmol/l, respectively, are achieved, and the total CVD death risk estimate has become < 5%, yearly follow-up is warranted to ensure that cardiovascular risk remains low. If total CVD risk remains elevated or progresses to ≥ 5%, lipid-lowering drug therapy should be considered to lower total and LDL-cholesterol. Current European recommendations in high-risk individuals are to lower total cholesterol to < 4.5 mmol/l and to lower LDL-cholesterol to < 2.5 mmol/l. However, these values are not therapy targets for patients with lower untreated values. To achieve target values combination therapy will have to be used in some patients. Even with maximal therapy, targets will not be achieved in some patients, but they will still benefit from treatment.

Psychosocial factors

During the last two decades, considerable evidence has accumulated with respect to the association of markers of stress and other psychosocial factors with coronary disease [87,88]. However, compared to other major risk factors, psychosocial variables are more difficult to define objectively because several different dimensions are involved. Despite this, several separate constructs within the broad conceptual framework of psychosocial factors are increasingly considered as being causally related to CHD. Stress at work and in family life, life events, low perceived control, lack of social support, socioeconomic status, and depression are some of the dimensions that have been shown to either influence the risk of CHD or affect prognosis in CHD patients [3,88–99].

There are several methodological problems in the study of psychosocial factors and health outcomes. First, compared to other biological and life-style risk factors, psychosocial factors represent a more problematic construct in that there is little uniformity with respect to either definition or measurement of these factors. Second, most of the dimensions involved are subjective, and hence potentially open to biases and confounding. Third, even though some persons may be more vulnerable than others with respect to adverse circumstances, exposure probably varies considerably over a lifetime, and hence, prospective follow-up studies with extended follow-up may not adequately capture short-term influences.

According to popular opinion, stress is one of the most important risk factors for CHD but this view has not so far been altogether accepted by the medical profession. However, accumulating evidence does, in fact, demonstrate that it is likely that stress is causally related to CHD, and possibly even to stroke. To date, most studies have dealt with stress at work, with stress outside the workplace receiving less attention. Both cross-sectional and prospective studies have demonstrated a positive association between level of work stress and disease [92,94,100–102]. Even so, not all studies have found an association between indices of job stress [103]. It has also been held that associations between stress and coronary disease are mainly the result of confounding by low socioeconomic status [103] or may be spurious, because people with stress tend to report more symptoms [104].

Shift work has been described as increasing future risk of CHD, both in women and men. Decreased heart-rate variability, a marker of autonomic imbalance, has been related to exposure to shift work [105]. In the Helsinki Heart Study shift workers, who had a 50% excess risk of CHD over day workers, exhibited large increases in perceived job stress, suggesting a direct stress-related mechanism explaining part of the CHD risk [106].

In addition to perceived stress at work, stressful conditions in family life have been shown to increase CHD risk. In women in Stockholm, marital discord was found to worsen prognosis in acute coronary syndrome and reduce event-free survival over and above the effects of standard clinical prognostic factors [97]. Although all women were employed outside the home, the hazards of marital stress were stronger than those of stress at work in these women. Other measures of stress have also been used. In a prospective survey of middle-aged Swedish men, self-reported permanent stress was associated with an increased risk of incident CHD (OR 1.5; 95% CI 1.2–1.9) after adjustment for conventional coronary risk factors during a 12-year follow-up [95]. Similar results were observed in a large prospective study involving 281 cases in 73 424 Japanese men and women, which reported an association between perceived mental stress and CHD mortality [93].

Clinical depression, depressive symptoms and other negative emotions have been associated with an increased risk of CHD incidence in both men and women [89,107]. In established CHD, clinical depression is associated with a three-fold risk for recurrent major cardiac events [108], particularly if there was also a lack of social support [109].

Some studies have investigated the effect of external influences such as financial stress or life events on risk of coronary disease. In a previous case–control study, having experienced one life event or more during the year preceding an acute myocardial infarction study and dissatisfaction with one's financial situation was twice as common among cases than controls in men, but no significant relation was found in women [100]. An extreme external stressor such as the death of a child was

demonstrated to be associated with increased risk of future acute myocardial infarction in a Danish registry-based study [91].

Men and women with low socioeconomic status have an increased risk of coronary disease. Several population-based studies have examined this question [96,110,111]. Controlling for standard risk factors reduced the size of the gradient, but a relevant proportion of the variance according to socioeconomic status was explained by distinct psychosocial factors which either mediate or modify the effect of socioeconomic status on CHD [112,113].

People with poor social networks have been demonstrated to have higher mortality from several causes [114]. However, data are less consistent with respect to the effect of social ties and activities on CVD, but some studies have reported an association with coronary disease [89]. Similarly, lack of social support leads to decreased survival and poorer prognosis among people with clinical manifestations of CVD [115].

The mechanism by which psychosocial factors increase the risk of CVD is complex. In experimental studies worsened coronary atherosclerosis [116] and endothelial dysfunction [117] occur in response to social disruption. Several studies have demonstrated links between psychosocial variables and vascular function, inflammation, increased blood clotting and decreased fibrinolysis. The exact pathophysiological nature of the influence of psychosocial factors remains to be determined, as does the temporal sequence of events.

Gender aspects in cardiovascular disease, risk factors and prevention

In both men and women, acute myocardial infarction arises as a complication of coronary atherosclerosis. Although the incidence of acute myocardial infarction increases sharply with age, women are less prone to develop it than men at any given age, with an approximate 9- to 10-year difference between the sexes. Below the age of 65, approximately four times as many men as women develop acute myocardial infarction, with corresponding differences in coronary death rates. The difference in mortality and morbidity diminishes with age, but even at ages between 75 and 85, the incidence is almost two-fold in men compared to women. Eventually, however, almost as many women as men die from coronary disease and in large parts of the world, CHD is the most important single cause of death in both men and women. After acute myocardial infarction, the prognosis is by and large similar, however, women stand to lose more because of their longer life expectancy. The sex difference with respect to stroke is less marked, but at least in the age span below 65, stroke is twice as common in men as in women.

Smoking may be a stronger risk factor for acute myocardial infarction in middle-aged women than in men, but relative risks associated with serum total cholesterol and blood pressure are similar [75]. However, serum triglycerides, which are strongly related to obesity, have been demonstrated to be a better predictor of future coronary events in women, compared to men [72]. Risk factors for stroke are similar in women and men [118]. The INTERHEART case–control study demonstrated similar odds ratios for acute myocardial infarction in women and men for most risk factors, including smoking, but the increased risk associated with hypertension and diabetes seemed to be greater in women than in men [8]. Because smoking is more prevalent among men than in women in most nations of the world, more cases of acute myocardial infarction are attributable to this factor among men, compared to women, whereas hypertension and diabetes cause proportionately more acute myocardial infarctions among women than among men.

In primary prevention, the higher absolute risk among men in a 5- or 10-year perspective should be taken into account, for example when pharmacological treatment of hypertension or hypercholesterolaemia is being considered. In a lifetime perspective, however, the absolute risk among women is not much different from that among men. Hence, life-style modifications with respect to anti-smoking advice, diet, physical activity and avoidance of obesity should be the same, irrespective of gender. Among people who already have manifest CVD, or diabetes, preventive efforts should be the same for men and women.

Personal perspective

Genetic disposition and behavioural and environmental factors are the main contributors to the onset or to the recurrence of cardiovascular disease. Ameliorating the last two is a rewarding challenge for the physician as effective and evidence-based methods are available.

Prevention commences with detecting and assessing risk: marked raised levels of single risk factors (total cholesterol, LDL-cholesterol, blood pressure) or of total risk as a result of multiple risk factors (using the SCORE algorithm or HeartScore), the presence of CVD, type 2 diabetes mellitus, or type 1 diabetes mellitus with microalbuminuria.

Modification of risk should be tailored to the needs of the individual patient. It includes life-style management and the use of pharmacotherapy, if considered appropriate. This may demand the efforts of a multidisciplinary team, which should act under the guidance of a cardiologist. The main targets of risk modification are a cessation of smoking, an active life-style with daily 30–60 minutes of physical activity on at least a moderate level, making healthy food choices and reducing excess weight, preserving normal levels of blood pressure and lipids. Psychosocial support and stress-coping techniques may be needed and gender differences should be considered.

The cardiologist has a decisive initial role in motivating the patient to commit to a healthy life-style once significantly raised risk and/or the presence of cardiovascular disease has been confirmed. Yet, special attention should be paid to a lasting maintenance of risk reduction, for which long-term follow-up in cooperation with the family doctor is mandatory.

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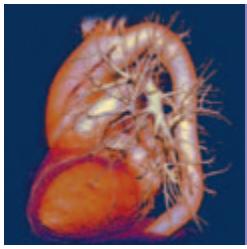

10 Hypertension

Sverre E. Kjeldsen, Henrik M. Reims, Robert Fagard and Giuseppe Mancia

Summary

Hypertension, usually defined as persistent blood pressure at 140/90 mmHg or higher, affects about a quarter of the adult population in many countries and particularly in Western societies. Hypertension is a risk factor for most, if not all, cardiovascular diseases and renal failure. While blood pressure should be measured repeatedly for the diagnosis, new techniques such as 24-hour ambulatory blood pressure and self-measured home blood pressure taking are increasingly being used for diagnosis and assessment during treatment. Modern work-up of hypertensive patients focuses on the detection of target organ damage, i.e. left ventricular hypertrophy and renal effects including microalbuminuria.

While diagnosis of secondary causes of hypertension should be kept in mind, the detection of concomitant diseases or risk factors should be clearly identified for the purposes of assessing total cardiovascular risk and choosing the optimal treatments. While life-style changes may be appropriate, i.e. increase physical exercise, reduce body weight if needed, and eat healthily, these kinds of interventions should not unnecessarily delay initiation of drug treatment for hypertension when clearly indicated. Drug treatment has repeatedly proven effective in outcome studies in preventing stroke, heart failure, deteriorated renal function, new onset diabetes and, to some extent, coronary heart disease and other complications. Modern drug treatment of hypertension usually contains a combination of well-tolerated doses of two or more drugs aiming at blood pressure below 140/90 mmHg and below 130/80 mmHg in patients with diabetes and already established cardiovascular disease. Acetylsalicylic acid and statins are recommended as add-on treatment if total 10-year cardiovascular risk is above 20%.

Introduction

This chapter is based on the 2003 ESH-ESC *Guidelines for Detection, Prevention and Treatment of Arterial Hypertension* jointly issued by the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) [1]. A concise summary of these guidelines has also been published [2]. For in-depth reading of the pathophysiology and aetiology of *essential hypertension*, the most common form of hypertension, there are extensive reviews recently published [3,4].

Definition and classification of hypertension

Systolic, diastolic and pulse pressures as predictors

Both systolic and diastolic blood pressures show a continuous graded independent relationship with risk of stroke and coronary events [5]. The relationship between systolic blood pressure and relative risk of stroke is steeper than that for coronary events, reflecting a closer aetiological relationship with stroke, but the attributable risk—

Category	Systolic	Diastolic
Optimal	< 120	< 80
Normal	120–129	80–84
High–normal	130–139	85–89
Grade 1 hypertension (mild)	140–159	90–99
Grade 2 hypertension (moderate)	160–179	100–109
Grade 3 hypertension (severe)	≥ 180	≥ 110
Isolated systolic hypertension	≥ 140	< 90

When a patient's systolic and diastolic blood pressures fall into different categories, the higher category should apply. Isolated systolic hypertension can also be graded (grades 1, 2, 3), according to systolic blood pressure values in the ranges indicated, provided that diastolic values are < 90.

Table 10.1 Definitions and classification of blood pressure levels (mmHg)

excess deaths due to raised blood pressure—is greater for coronary events than stroke. However, with population ageing the relative incidence of stroke is increasing, as shown in recent randomized controlled trials [6].

The apparently simple direct relationship between increasing systolic and diastolic blood pressure levels and increasing cardiovascular risk is complicated by the relationship that normally prevails between blood pressure and age, namely systolic blood pressure rises throughout the adult age range, whereas diastolic blood pressure peaks at about age 60 years in men and 70 years in women, and falls gradually thereafter [7]. Although both the continuous rise in systolic blood pressure and the rise and fall in diastolic blood pressure with age are usual, they represent the results of some of the pathological processes that underlie 'hypertension' and cardiovascular diseases [8].

These observations help to explain why, at least in elderly populations, a wide pulse pressure (systolic blood pressure minus diastolic blood pressure) has been shown in some observational studies to be a better predictor of adverse cardiovascular outcomes than either systolic or diastolic pressures individually [9,10]. However, in the largest compilation of observational data in almost 1 million patients from 61 studies [11], both systolic and diastolic blood pressures were independently predictive of stroke and coronary mortality, and more so than pulse pressure.

In practice, given that we have randomized controlled trial data supporting the treatment of isolated systolic hypertension [12,13] and treatment based purely on diastolic entry criteria [14], we should continue to use both systolic blood and diastolic blood pressures as part of guidance for treatment thresholds.

Classification of hypertension

The continuous relationship between the level of blood pressure and cardiovascular risk makes any numerical definition and classification of hypertension arbitrary.

The real threshold of hypertension should therefore be considered a mobile one, being higher or lower on the basis of the global cardiovascular risk profile of each individual (Table 10.1). Accordingly, the definition of high normal blood pressure in Table 10.1 includes blood pressure values that may be considered as 'high' (i.e. hypertension) in high-risk subjects or fully normal in low-risk individuals.

Total cardiovascular risk

Because of the clustering of risk factors in individuals and the graded nature of the association between each risk factor and cardiovascular risk [15], a contemporary approach has been to determine threshold, at least for cholesterol and blood pressure lowering, on the basis of estimated global coronary or cardiovascular (coronary plus stroke) [16] risk over a defined relatively short-term (e.g. 5- or 10-year) period. It should be noted that although several methods may be used, most risk estimation systems are based on the Framingham study [17]. Although this database has been shown to be reasonably applicable to some European populations [18], estimates require recalibration in other populations [19] owing to important differences in the prevailing incidence of coronary and stroke events. The main disadvantage associated with intervention threshold based on relatively short-term absolute risk is that younger adults (particularly women), despite having more than one major risk factor, are unlikely to reach treatment thresholds despite being at high risk relative to their peers. By contrast, most elderly men (e.g. > 70 years) will often reach treatment thresholds although being at very little increased risk relative to their peers. This situation results in most resources being concentrated on the oldest subjects, whose potential lifespan, despite intervention, is relatively limited, and young subjects at high relative risk remain untreated despite, in the absence of intervention, a predicted significant shortening of their otherwise much longer potential lifespan [20,21].

On the basis of these considerations, total cardiovascular risk classification may be stratified as suggested in Table 10.2. The terms *low*, *moderate*, *high* and *very high*

Table 10.2 Stratification of risk to quantify prognosis

	Blood pressure (mmHg)				
Other risk factors and disease history	**Normal SBP 120–129 or DBP 80–84**	**High normal SBP 130–139 or DBP 85–89**	**Grade 1 SBP 140–159 or DBP 90–99**	**Grade 2 SBP 160–179 or DBP 100–109**	**Grade 3 SBP ≥ 180 or DBP ≥ 110**
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
One or two risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
Three or more risk factors or TOD or diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
ACC	High added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

ACC, associated clinical conditions; DBP, diastolic blood pressure; SBP, systolic blood pressure; TOD, target organ damage.

Table 10.3 Factors influencing prognosis

Risk factors for cardiovascular disease used for stratification
Levels of systolic and diastolic BP
Men > 55 years
Women > 65 years
Smoking
Dyslipidaemia (total cholesterol > 6.5 mmol/l, > 250 mg/dl*; or LDL-cholesterol > 4.0 mmol/l, > 155 mg/dl*; or HDL-cholesterol M < 1.0, W < 1.2 mmol/L, M < 40, W < 48 mg/dl)
Family history of premature cardiovascular disease (at age < 55 years M, < 65 years W)
Abdominal obesity (abdominal circumference M ≥ 102 cm, W ≥ 88 cm)
C-reactive protein ≥ 1 mg/dl

Target organ damage
Left-ventricular hypertrophy (electrocardiogram: Sokolow–Lyon > 38 mm; Cornell > 2440 mm × ms; echocardiogram: LVMI M ≥ 125, W ≥ 110 g/m^2)
Ultrasound evidence of arterial wall thickening (carotid IMT ≥ 0.9 mm) or atherosclerotic plaque
Slight increase in serum creatinine (M 115–133, W 107–124 µmol/L; M 1.3–1.5, W 1.2–1.4 mg/dl)
Microalbuminuria (30–300 mg/24 h; albumin–creatinine ratio M ≥ 22, W ≥ 31 mg/g; M ≥ 2.5, W ≥ 3.5 mg/mmol)

Diabetes mellitus
Fasting plasma glucose 7.0 mmol/l (126 mg/dl)
Postprandial plasma glucose > 11.0 mmol/l (198 mg/dl)

Associated clinical conditions
Cerebrovascular disease: ischaemic stroke; cerebral haemorrhage; transient ischaemic attack
Heart disease: myocardial infarction; angina; coronary revascularization; congestive heart failure
Renal disease: diabetic nephropathy; renal impairment (serum creatinine M > 133, W > 124 µmol/L; M > 1.5, W > 1.4 mg/dl); proteinuria (> 300 mg/24 h)
Peripheral vascular disease
Advanced retinopathy: haemorrhages or exudates; papilloedema

HDL, high-density lipoprotein; IMT, intima media thickness; LDL, low-density lipoprotein; LVMI, left-ventricular mass index; M, men; W, women.
*Lower levels of total and LDL-cholesterol are known to delineate increased risk, but they were not used in the stratification.

added risk are calibrated to indicate, approximately, an absolute 10-year risk of cardiovascular disease of < 15%, 15–20%, 20–30% and > 30%, respectively, according to Framingham criteria [17] or an approximate absolute risk of fatal cardiovascular disease < 4%, 4–5%, 5–8%, and > 8% according to the SCORE chart [22].

Table 10.3 indicates the most common risk factors, target organ damage (TOD), diabetes and associated clinical conditions (ACCs) to be used to stratify risk.

1 Obesity is indicated as 'abdominal obesity' in order to give specific attention to an important sign of the metabolic syndrome [23].
2 Diabetes is listed as a separate criterion in order to underline its importance as risk, at least twice as large as in absence of diabetes [24].
3 Microalbuminuria is indicated as a sign of TOD, but proteinuria as a sign of renal disease (ACC).
4 Slight elevation of serum creatinine as sign of TOD

is indicated as a serum creatinine concentration of 115–133 μmol/l (1.3–1.5 mg/dl) in men and 107–124 μmol/l (1.2–1.4 mg/dl) in women, and concentrations > 133 μmol/L (> 1.5 mg/dl) in men and > 124 μmol/l (> 1.4 mg/dl) in women as ACC [25,26].

5 Generalized or focal narrowing of the retinal arteries is omitted among signs of TOD, as too frequently seen in subjects aged 50 years or older [27], but retinal haemorrhages and exudates as well as papilloedema are retained as ACCs.

Diagnostic evaluation

In hypertension, diagnostic procedures are aimed at (1) establishing the blood pressure levels, (2) excluding or identifying secondary causes of hypertension and (3) evaluating the overall cardiovascular risk of the subject by searching for other risk factors, TOD and concomitant diseases or accompanying clinical conditions.

The diagnostic procedures consist of:

- repeated blood pressure measurements;
- medical history;
- physical examination;
- laboratory and instrumental investigations, some of which should be considered essential in all subjects with high blood pressure, some are recommended and may be used extensively, some are useful only when suggested by some of the more widely recommended examinations or the clinical course of the patient.

Blood pressure measurement

Blood pressure is characterized by large spontaneous variations both within the 24 h and between days. The diagnosis of hypertension should thus be based on multiple blood pressure measurements, taken on separate occasions. If blood pressure is only slightly elevated, repeated measurements should be obtained over a period of several months to define as accurately as possible the patient's 'usual' blood pressure. If, on the other hand, the patient has a more marked blood pressure elevation, evidence of hypertension-related organ damage or a high or very high cardiovascular risk profile, repeated measurements should be obtained over shorter periods of time, i.e. weeks or days. Blood pressures can be measured by the doctor or the nurse in the office or in the clinic (office or clinic blood pressure), by the patient at home or automatically over the 24 h. These procedures can be summarized as follows [28].

Office or clinic blood pressure measurement

Blood pressure can be measured by a mercury sphygmomanometer, whose various parts (rubber tubes, valves, quantity of mercury, etc.) should be kept in proper condition. Other non-invasive devices (aneroid and auscultatory or oscillometric semi-automatic devices) can also be used and will indeed become increasingly important because of the progressive banning of medical use of mercury. These devices, however, should be validated according to standardized protocols [29] and their accuracy should be periodically checked by comparison with mercury sphygmomanometric values.

Ambulatory blood pressure measurement

Several devices (mostly oscillometric) are available for automatic blood pressure measurements in patients who are allowed to conduct a near-normal life. This allows information to be obtained on 24-h average blood pressure, as well as on average blood pressure values on more restricted portions of the 24 h, such as the day, the night and the morning [28]. This information should not be regarded as a substitute for information derived from conventional blood pressure measurements. It may be considered, however, of additional clinical value because cross-sectional and longitudinal studies have shown that office blood pressure has a limited relationship with 24-h, and thus daily life, blood pressure [30]. These studies have also shown that ambulatory blood pressure: (1) correlates with the TOD of hypertension more closely than office blood pressure [31–34], (2) predicts, both in populations and in hypertensive patients, the cardiovascular risk more and above the prediction provided by office blood pressure values [35–38] and (3) measures more accurately than office blood pressure the extent of blood pressure reduction induced by treatment, because of the absence of a 'white coat' [39], a placebo [40] effect and a higher reproducibility over time [41]. Although some of the above advantages can be obtained by increasing the number of office blood pressure measurements [42], 24-h ambulatory blood pressure monitoring before and during treatment can be recommended at the time of diagnosis and, occasionally, during treatment, whenever the facilities make it possible.

When measuring 24-h blood pressure [28] care should be taken to:

- Use only devices validated by international standardized protocols.
- Use cuffs of appropriate size and compare the initial values with those from a sphygmomanometer to check that the differences are not greater than ± 5 mmHg.
- Set the automatic readings at no more than 30-min intervals to obtain an adequate number of values and

have most hours represented if some readings are rejected because of artefacts.
- Instruct the patients to engage in normal activities but to refrain from strenuous exercise, and to keep the arm extended and still at the time of cuff inflations.
- Ask the patient to provide information in a diary on unusual events, and on duration and quality of night sleep; although in the population and the hypertensive patients at large day and night blood pressures normally show a close correlation, there is evidence that subjects in whom nocturnal hypotension is blunted and thus exhibit a relatively high night blood pressure may have an unfavourable prognosis [43].
- Obtain another ambulatory blood pressure monitoring if the first examination has less than 70% of the expected values because of a high number of artefacts.
- Remember that ambulatory blood pressure is usually several mmHg lower than office blood pressure [44–46]. As shown in Table 10.4, in the population office values of 140/90 mmHg correspond to about 125/80 mmHg 24-hour systolic and diastolic blood pressure average values, and to about 135/85 mmHg daytime average values. These values may be approximately taken as the threshold values for diagnosing hypertension by ambulatory blood pressure.
- Base clinical judgement on average 24-h, day or night values only; other information derivable from ambulatory blood pressure (e.g. blood pressure standard deviations, trough–peak ratio, smoothness index) is clinically promising but is still in the research phase.

Table 10.4 Blood pressure thresholds (mmHg) for definition of hypertension with different types of measurement

	Systolic	Diastolic
Office or clinic	140	90
24-hour ambulatory	125	80
Daytime ambulatory	135	85
Night-time ambulatory	120	70
Home (self)	135	85

Home blood pressure

Self-measurements of blood pressure at home cannot provide the extensive information on 24-h blood pressure values provided by ambulatory blood pressure monitoring. It can provide, however, values on different days in a setting close to daily life conditions. When averaged over a period of a few days these values have been shown to share some of the advantages of ambulatory blood pressure, i.e. to have no white coat effect and to be more reproducible and predictive of the presence and progression of organ damage than office values [31,47]. Home blood pressure measurements for suitable periods (e.g. a few weeks) before and during treatment can therefore be recommended also because this relatively cheap procedure may improve the patient's adherence to treatment regimens [48].

When advising self-measurement of blood pressure at home, care [28] should be taken to:
- Advise only use of validated devices; not one of the present available wrist devices for measurement of blood pressure is satisfactorily validated—should any of these wrist devices become validated, the subject should receive recommendation to keep the arm at heart level during measurement.
- Use semi-automatic devices rather than mercury sphygmomanometer to avoid the difficulty posed by patient's instruction and the error originated from hearing problems in elderly individuals.
- Instruct the patient to perform measurement in the sitting position after several minutes' rest—inform him or her that values may differ between measurements because of spontaneous blood pressure variability.
- Avoid asking for an excessive number of values to be measured and ensure that measurements include the period prior to drug intake to have information on duration of the treatment effect.
- Remember that, as for ambulatory blood pressure, normality values are lower for home than office blood pressure—take 135/85 mmHg as the values of home blood pressure corresponding to 140/90 mmHg measured in the office or clinic (Table 10.4).
- Give the patient clear instructions on the need to provide the doctor with proper documentation of the measured values and to avoid self-alterations of the treatment regimens.

Isolated office or white coat hypertension

In some patients, office blood pressure is persistently elevated, whereas daytime or 24-h blood pressure falls within their normality range. This condition is widely known as '*white coat hypertension*' [49], although the more descriptive and less mechanistic term '*isolated office (or clinic) hypertension*' is preferable because the office ambulatory blood pressure difference does not correlate with the office blood pressure elevation induced by the alerting response to the doctor or the nurse, i.e. the true '*white coat effect*' [50]. Regardless of the terminology, evidence is now available that isolated office hypertension is not infrequent (about 10% in the general population) [51] and that it accounts for a noticeable fraction of individuals in whom hypertension is diagnosed. There is also

evidence that in individuals with isolated office hypertension cardiovascular risk is less than in individuals with both office and ambulatory blood pressure elevations [51]. Several, although not all, studies, however, have reported this condition to be associated with a prevalence of organ damage and metabolic abnormalities greater than those of normal subjects, which suggests that it may not be an entirely innocent phenomenon [52].

Physicians should diagnose isolated office hypertension whenever office blood pressure is >140/90 mmHg at several visits, whereas 24-h and daytime ambulatory blood pressure are <125/80 and <135/85 mmHg respectively. Diagnosis can also be based on home blood pressure values (average of several day readings <135/85 mmHg). Identification should be followed by search for metabolic risk factors and TOD. Drug treatment should be instituted when there is evidence of organ damage or a high cardiovascular risk profile. However, lifestyle changes and a close follow-up should be implemented in all patients with isolated office hypertension in whom the doctor elects not to start pharmacological treatment.

Although less frequently, the reverse phenomenon of 'white coat hypertension' may occur, namely individuals with normal office blood pressure (< 140/90 mmHg) may have elevated ambulatory blood pressure values ('isolated ambulatory or masked hypertension') [52–55]. These individuals have been shown to display a greater than normal prevalence of TOD [56] and may have a greater cardiovascular risk than truly normotensive individuals [54,55].

Family and clinical history

A comprehensive family history should be obtained, with particular attention to hypertension, diabetes, dyslipidaemia, premature coronary heart disease, stroke or renal disease.

Clinical history should include: (1) duration and previous levels of high blood pressure, (2) symptoms suggestive of secondary causes of hypertension and intake of drugs or substances that can raise blood pressure, such as liquorice, cocaine, amphetamines; oral contraceptives, steroids, non-steroidal anti-inflammatory drugs, erythropoietin and cyclosporins, (3) lifestyle factors, such as dietary intake of fat (animal fat in particular), salt and alcohol, quantification of smoking and physical activity, weight gain since early adult life, (4) past history or current symptoms of coronary disease, heart failure, cerebrovascular or peripheral vascular disease, renal disease, diabetes mellitus, gout, dyslipidaemia, bronchospasm or any other significant illnesses, and drugs used to treat those conditions, (5) previous antihypertensive therapy, its results and adverse effects; and (6) personal, family and environmental factors that may influence blood pressure and cardiovascular risk, as well as the course and outcome of therapy.

Physical examination

In addition to blood pressure measurement, physical examination should search for evidence of additional risk factors (in particular abdominal obesity), for signs suggesting secondary hypertension, and for evidence of organ damage.

Laboratory investigations

Laboratory investigations are also aimed at providing evidence of additional risk factors, at searching for hints of secondary hypertension and at assessing absence or presence of TOD. The younger the patient, the higher the blood pressure and the faster the development of hypertension, the more detailed the diagnostic work-up will be.

Essential laboratory investigations should include: blood chemistry for fasting glucose, total cholesterol, HDL-cholesterol, triglycerides, urate, creatinine, sodium, potassium, haemoglobin and haematocrit; urinalysis (dipstick test complemented by urine sediment examination); and an electrocardiogram. Whenever fasting glucose is above 6.1 mmol/l (110 mg/dl), post-prandial blood glucose should also be measured or a glucose tolerance test performed [57]. A fasting glucose of 7.0 mmol/l (126 mg/dl) or a 2-h post-prandial glucose of 11 mmol/l (198 mg/dl) is now considered threshold value for diabetes mellitus [57].

Searching for target organ damage

Owing to the importance of TOD in determining the overall cardiovascular risk of the hypertensive patient, evidence of organ involvement should be sought carefully. Recent studies have shown that without ultrasound cardiovascular investigations for left-ventricular hypertrophy and vascular (carotid) wall thickening or plaque, up to 50% of hypertensive subjects may be mistakenly classified as at low or moderate added risk, whereas presence of cardiac or vascular damage stratifies them within a higher risk group. Likewise, searching for microalbuminuria can be strongly recommended because of the mounting evidence that it may be a sensitive marker of organ damage, not only in diabetes, but also in hypertension.

Heart

Electrocardiography should be part of all routine assessment of subjects with high blood pressure. Its sensitivity

to detect left-ventricular hypertrophy is low but, nonetheless, hypertrophy detected by the Sokolow–Lyon index or of the Cornell voltage QRS duration product is an independent predictor of cardiovascular events [58]. Electrocardiography can also be used to detect patterns of ventricular overload ('strain'), known to indicate more severe risk [58], ischaemia, conduction defects and arrhythmias. Echocardiography is undoubtedly much more sensitive than electrocardiography in diagnosing left-ventricular hypertrophy [59] and predicting cardiovascular risk [60]. An echocardiographic examination may help in more precisely classifying the overall risk of the hypertensive patient and in directing therapy. The best evaluation includes measurements of interventricular septum and posterior wall thickness and of end-diastolic left-ventricular diameter, with calculation of left-ventricular mass according to available formulae [61]. Classifications in concentric or eccentric hypertrophy, and concentric remodelling by also using the wall–radius ratio have been shown to have risk predicting value [62]. Echocardiography also provides means of assessing left-ventricular diastolic distensibility (diastolic function) by Doppler measurement of the ratio between the E and A waves of transmitral blood flow (and, more precisely, by adding measurement of early diastolic relaxation time and evaluating patterns of pulmonary vein outflow into the left atrium) [63].

There is current interest to investigate whether patterns of 'diastolic dysfunction' can predict onset of dyspnoea and impaired effort tolerance without evidence of systolic dysfunction, frequently occurring in hypertension and in the elderly ('diastolic heart failure') [64]. Finally, echocardiography can provide evidence of left-ventricular wall contraction defects due to ischaemia or previous infarction and, more broadly, of systolic dysfunction. Other diagnostic cardiac procedures, such as nuclear magnetic resonance, cardiac scintigraphy, exercise test and coronary angiography, are obviously reserved for specific indications (diagnosis of coronary artery disease, cardiomyopathy, etc.). On the other hand, a radiograph of the thorax may often represent a useful additional diagnostic procedure, when information on large intrathoracic arteries or the pulmonary circulation is sought.

Blood vessels

Ultrasound examination of the carotid arteries with measurement of the intima media complex thickness and detection of plaques [65] has repeatedly been shown to predict occurrence of both stroke and myocardial infarction. A recent survey indicates that it can usefully complement echocardiography in making risk stratification of hypertensive patients more precise.

The increasing interest in systolic blood pressure and pulse pressure as predictors of cardiovascular events [66] has stimulated the development of techniques for measuring large artery distensibility or compliance [67,68]. This has been further supported by the observation that a reduction of arterial distensibility per se may have a prognostic significance [69]. One of these techniques, the pulse wave velocity measurement [69], may be suitable because of its simplicity for diagnostic use. Another technique, the augmentation index measurement device [70], has also raised wide interest as a possible tool to obtain an assessment of aortic blood pressure from peripheral artery measurement in view of the claim that aortic blood pressure (and therefore the pressure exerted on the heart and brain) may be different from that which is usually measured at the arm, and may be differently affected by different antihypertensive drugs.

Finally, there has been widespread interest in investigating endothelial dysfunction or damage as an early marker of cardiovascular damage [71,72]. The techniques used so far for investigating endothelial responsiveness to various stimuli are either invasive or too laborious and time consuming to envisage their use in the clinical evaluation of the hypertensive patient. However, current studies on circulating markers of endothelial activity, dysfunction or damage may soon provide simpler tests of endothelial dysfunction and damage to be investigated prospectively.

Kidney

The diagnosis of hypertension-induced renal damage is based on the finding of an elevated value of serum creatinine, of a decreased (measured or estimated) creatinine clearance or the detection of an elevated urinary excretion of albumin below (microalbuminuria) or above (macroalbuminuria) the usual laboratory methods to detect proteinuria. The presence of mild renal insufficiency has recently been defined as serum creatinine values equal or above 133 μmol/l (1.5 mg/dl) in men and 124 μmol/l (1.4 mg/dl) in women [73,74] or by the finding of estimated creatinine clearance values below 60–70 ml/min [26]. An estimate of creatinine clearance in the absence of 24-h urine collection can be obtained based on prediction equations corrected for age, gender and body size [74]. A slight increase in serum creatinine and urate may sometimes occur when antihypertensive therapy is instituted or potentiated, but this should not be taken as a sign of progressive renal deterioration. Hyperuricaemia, defined as a serum urate level in excess of 416 μmol/l (7 mg/dl), is frequently seen in untreated hypertensives and has also been shown to correlate with the existence of nephrosclerosis [75].

Although an elevated serum creatinine concentration points to a reduced rate of glomerular filtration, an increased rate of albumin or protein excretion points to a derangement in the glomerular filtration barrier [76]. Microalbuminuria has been shown to predict the development of overt diabetic nephropathy in both type 1 and type 2 diabetics [77], whereas the presence of proteinuria generally indicates the existence of established renal parenchymatous damage [76]. In non-diabetic hypertensive patients, microalbuminuria, even below the threshold values currently considered [78], has been shown to predict cardiovascular events, and a continuous relation between urinary albumin excretion and cardiovascular, as well as non-cardiovascular, mortality has recently been found in a general population study [79].

The finding of deranged renal function in a hypertensive patient, expressed as any of the above-mentioned alterations, is frequent and constitutes a very potent predictor of future cardiovascular events and death [25,26]. It is therefore recommended that serum creatinine (possibly with estimated creatinine clearance calculated on the basis of age, gender and body size) [74] and serum urate levels are measured, and urinary protein (by dipstick) searched in all hypertensive patients. Whenever possible, microalbuminuria may also be measured (in dipstick-negative patients) by using one of the validated commercial methods on urine samples collected during the night, and possibly related to creatinine excretion.

Fundoscopy

In contrast with the 1930s, when the Keith Wagener and Barker classification of hypertensive eye ground changes in four grades [80] was formulated, nowadays most hypertensive patients present early in the process of their illness, and haemorrhages and exudates (grade 3), or even papilloedema (grade 4), are very rarely observed. A recent evaluation of 800 hypertensive patients attending a hypertension outpatient clinic [27] showed that the prevalence of grades 1 and 2 retinal changes was as high as 78% (in contrast with 43% for carotid plaques, 22% for left-ventricular hypertrophy and 14% for microalbuminuria). It is therefore doubtful whether grades 1 and 2 retinal changes can be used as a sign of TOD to stratify global cardiovascular risk, whereas grades 3 and 4 are certainly markers of severe hypertensive complications.

Brain

In patients who have suffered a stroke, imaging techniques allow improved diagnosis of the existence, nature and location of a lesion [81,82]. Cranial computerized tomography (CT) is the standard procedure for diagnosis of a stroke but, with the exception of prompt recognition of an intracranial haemorrhage, CT is progressively being replaced by magnetic resonance imaging (MRI) techniques. Diffusion-weighted MRI can identify ischaemic injury within minutes after arterial occlusion. Furthermore, MRI, particularly in fluid attenuated inversion recovery (FLAIR) sequences, is much superior to CT in discovering silent brain infarctions, the large majority of which are small and deep (lacunar infarction). As cognition disturbances in the elderly are, at least in part, hypertension related [83,84], suitable cognition evaluation tests, such as the Mini Mental State Evaluation, should be used more often in the clinical assessment of the elderly hypertensive.

Screening for secondary forms of hypertension

A specific cause of blood pressure elevation can be identified in a minority (from < 5% to 10%) of adult patients with hypertension. Therefore, screening for secondary forms of hypertension is indicated, if possible before initiation of antihypertensive therapy. Findings suggesting a secondary form of blood pressure elevation are severe hypertension, sudden onset of hypertension and blood pressure responding poorly to drug therapy.

Renal parenchymal hypertension

Renal parenchymal disease is the most common cause of secondary hypertension, detected in about 5% of all cases of hypertension. The finding of bilateral upper abdominal masses at physical examination is consistent with polycystic kidney disease and should lead to an abdominal ultrasound examination. Renal ultrasound has now almost completely replaced intravenous urography in the anatomical exploration of the kidney. Although the latter requires the injection of nephrotoxic contrast media, ultrasound is non-invasive and provides all necessary anatomic data about kidney size and shape, cortical thickness, urinary tract obstruction and renal masses, in addition to evidence of polycystic kidneys. Assessment of the presence of protein, erythrocytes and leucocytes in the urine and measurement of serum creatinine concentration are the proper functional screening tests for renal parenchymal disease [85,86], and should be performed in all patients with hypertension. Renal parenchymal disease may be excluded if urinalysis and serum creatinine concentration are normal at repeated determinations. The presence of erythrocytes and leucocytes should be confirmed by microscopic examination of the urine. If the screening tests for renal parenchymal hypertension are positive, a detailed work-up for kidney disease should ensue.

Renovascular hypertension

Renovascular hypertension is caused by one or several stenoses of the extrarenal arteries and is found in about 2% of adult patients with blood pressure elevation. In about 75% of the patients, the renal artery stenosis is caused by atherosclerosis (particularly in the elderly population). Fibromuscular dysplasia accounts for up to 25% of total cases (and is the most common variety in young adults). Signs of renal artery stenosis are an abdominal bruit with lateralization, hypokalaemia and progressive decline in renal function. However, these signs are not present in many patients with renovascular hypertension. Determination of the longitudinal diameter of the kidney using ultrasound can be used as a screening procedure. However, a difference of more than 1.5 cm in length between the two kidneys—which is usually considered as being diagnostic for renal stenosis—is only found in about 60–70% of the patients with renovascular hypertension. Colour Doppler sonography is able to detect stenosis of the renal artery, particularly stenosis that is localized close to the origin of the vessel [87], but the procedure is highly observer dependent. There is evidence that investigations of the renal vasculature by breath-hold three-dimensional, gadolinium-enhanced magnetic resonance angiography may become the diagnostic procedure of choice for renovascular hypertension in the future [88]. Another imaging procedure with similar sensitivity is spiral computerized tomography, which requires the application of contrast media and relatively high X-ray doses. Once there is a strong suspicion of renal artery stenosis, intra-arterial digital subtraction angiography should be performed for confirmation. This invasive procedure is still the gold standard for the detection of renal artery stenosis.

Phaeochromocytoma

Phaeochromocytoma accounts for less than 0.1% of all cases of elevated blood pressure. The determination of catecholamines (noradrenaline and adrenaline) as well as of metanephrines in several 24-h urine samples is a reliable method for detection of the disease. In most patients with phaeochromocytoma, no further confirmation is required [89]. If the urinary excretion of catecholamines and their metabolites is only marginally increased or normal despite a strong clinical suspicion of phaeochromocytoma, the glucagon stimulation test can be applied. This test requires the measurement of catecholamines in plasma and should be performed after the patient has been effectively treated with an alpha-blocker. This pretreatment prevents marked blood pressure rises after injection of glucagon. The clonidine suppression test is used to identify patients with essential hypertension, who have slight elevations of the excretion of catecholamines and their metabolites in urine [90]. Once the diagnosis of phaeochromocytoma has been established, localization of the tumour is necessary. As phaeochromocytomas are often big tumours localized in, or in the close vicinity of, the adrenal glands, they often are detected by ultrasound. A more sensitive imaging procedure is CT. The meta-iodobenzylguanidine scan is useful in localizing extra-adrenal phaeochromocytomas and metastases of the 10% of phaeochromocytomas that are malignant.

Primary aldosteronism

Primary aldosteronism accounts for about 1% of all patients with hypertension. The determination of serum potassium levels is considered to be a screening test for the disease. However, only about 80% of the patients have hypokalaemia in an early phase [91], and some authorities maintain that hypokalaemia may even be absent in severe cases. Particularly in patients with bilateral adrenal hyperplasia, serum potassium levels may be normal or only slightly decreased [92]. The diagnosis is confirmed by a low plasma renin activity (< 1 ng/ml/h) and elevated plasma aldosterone levels (after withdrawal of drugs influencing renin, such as beta-blockers, ACE inhibitors, angiotensin receptor antagonists and diuretics). A plasma aldosterone (pg/ml)–plasma renin activity (ng/ml/h) ratio of > 50 is highly suggestive of primary aldosteronism [92]. The diagnosis of primary aldosteronism is confirmed by the fludrocortisone suppression test [93]. Imaging procedures such as CT and MRI are used to localize an aldosterone-producing tumour, but adrenal morphology correlates poorly with function, and adrenal venous sampling, although invasive and difficult to perform, is considered by some investigators to be a more reliable procedure [94].

Cushing's syndrome

Cushing's syndrome affects less than 0.1% of the total population. On the other hand, hypertension is a very common finding in Cushing's syndrome, affecting about 80% of such patients. The syndrome is suggested by the typical habitus of the patient. The determination of 24-h urinary cortisol excretion is the most practical and reliable index of cortisol secretion and a value exceeding 110 nmol (40 µg) is highly suggestive of Cushing's syndrome. The diagnosis is confirmed by the 2-day, low-dose dexamethasone suppression test or the overnight dexamethasone suppression test. A normal result of either of the two suppression tests excludes the possibility of

Cushing's syndrome [95]. Further tests and imaging procedures have to be used to differentiate the various forms of the syndrome [96].

Coarctation of the aorta

Coarctation of the aorta is a rare form of hypertension in children and young adults. The diagnosis is usually evident from physical examination. A mid-systolic murmur, which may become continuous with time, is heard over the anterior part of the chest and also over the back. Hypertension is found in the upper extremities concomitantly with low or not measurable blood pressure in the legs.

Genetic analysis

There is often a family history of high blood pressure in hypertensive patients, suggesting that inheritance contributes to the pathogenesis of this disorder. Essential hypertension has a highly heterogeneous character, which points to a multifactorial aetiology and polygenic abnormalities [97,98]. Variants in some genes might render an individual sensitive to a given factor in the environment. A number of mutations in the genes encoding for major blood pressure controlling systems has been recognized in humans, but their exact role in the pathogenesis of essential hypertension is still unclear. The search for candidate gene mutations in the individual hypertensive is therefore not useful at present. However, the patient's genetic disposition might influence drug-metabolizing enzymes, which might translate into differences in drug effects or tolerability, and several extremely rare monogenic forms of inherited hypertension have been described.

Therapeutic approach

When to initiate antihypertensive treatment

Guidelines for initiating antihypertensive treatment are based on two criteria: (1) the level of total cardiovascular risk, as indicated in Table 10.2 and (2) the level of systolic and diastolic blood pressure, as classified in Table 10.1. Consideration of subjects with systolic blood pressure of 120–139 mmHg and diastolic blood pressure of 80–89 mmHg for possible initiation of antihypertensive treatment is so far limited to subjects with stroke [99], coronary artery disease [100] and diabetes [101]. Antihypertensive treatment is recommended within this blood pressure range only for patients at least at high total risk. Close monitoring of blood pressure and no blood pressure intervention is only recommended for patients at moderate or low total risk, who are considered to mostly benefit from lifestyle measures and correction of other risk factors (e.g. smoking).

In patients with grade 1 and 2 hypertension, antihypertensive drug treatment should be initiated promptly in subjects who are classified as at high or very high risk, whereas in subjects at moderate or low added risk blood pressure, as well as other cardiovascular risk factors, should be monitored for extended periods (from 3 to 12 months) under non-pharmacological treatment only. If after extended observation systolic values ≥ 140 mmHg or diastolic values ≥ 90 mmHg persist, antihypertensive drug treatment should be initiated in patients at moderate risk, and considered in patients at lower risk. In the latter group, decision as to whether to adopt drug treatment should be influenced by the patient's preference and/or resources rather than a higher blood pressure threshold (systolic ≥ 150 or diastolic ≥ 95 mmHg).

Table 10.5 also includes recommendations about initiation of treatment in patients with grade 3 hypertension. In these subjects confirmation of elevated blood pressure values should be obtained within a few days, and treatment instituted immediately, without the preliminary need of establishing the absolute risk (high even in absence of other risk factors). Complete assessment of other risk factors, TOD or associated disease can be carried out after institution of treatment, and lifestyle measures can be recommended at the same time as initiation of drug therapy.

Several studies have shown that in high or very high risk patients, treatment of hypertension is very cost-effective, i.e. the reduction in the incidence of cardiovascular disease and death largely offsets the cost of treatment despite its lifetime duration. Some pharmacoeconomical studies suggest that treatment may be less cost-effective in grade 1 or 2 hypertensives who are at low or moderate added risk. This may be more apparent than real, however, because in these patients the purpose of treatment is not to prevent an unlikely morbid or fatal event in the subsequent few years but rather to oppose appearance and/or progression of organ damage that will make the patient a high risk in the long term. Several trials of antihypertensive therapy, foremost the HDPP [102] and HOT [103] studies, have shown that under these circumstances and despite intensive blood pressure lowering, residual cardiovascular risk remains higher than in patients with initial moderate risk. This suggests that some of the major cardiovascular risk changes may be difficult to reverse and that restricting antihypertensive

Table 10.5 Initiation of antihypertensive treatment

	Blood pressure (mmHg)				
Other risk factors and disease history	**Normal SBP 120–129 or DBP 80–84**	**High normal SBP 130–139 or DBP 85–89**	**Grade 1 SBP 140–159 or DBP 90–99**	**Grade 2 SBP 160–179 or DBP 100–109**	**Grade 3 SBP ≥ 180 or DBP ≥ 110**
No other risk factors	No BP intervention	No BP intervention	Lifestyle changes for several months then drug treatment if preferred by the patient and resources available	Lifestyle changes for several months then drug treatment	Immediate drug treatment and lifestyle changes
One or two risk factors	Lifestyle changes	Lifestyle changes	Lifestyle changes for several months, then drug treatment	Lifestyle changes for several months then drug treatment	Immediate drug treatment and lifestyle changes
Three or more risk factors or TOD or diabetes	Lifestyle changes	Drug treatment and lifestyle changes	Drug treatment and lifestyle changes	Drug treatment and lifestyle changes	Immediate drug treatment and lifestyle changes
ACC	Drug treatment and lifestyle changes	Immediate drug treatment and lifestyle changes	Immediate drug treatment and lifestyle changes	Immediate drug treatment and lifestyle changes	Immediate drug treatment and lifestyle changes

therapy to patients at high or very high risk may be far from an optimal strategy.

Goals of treatment

The primary goal of treatment of the patient with high blood pressure is to achieve the maximum reduction in the long-term total risk of cardiovascular morbidity and mortality. This requires treatment of all the reversible risk factors identified, including smoking, dyslipidaemia or diabetes and the appropriate management of associated clinical conditions, as well as treatment of the raised blood pressure per se.

As to the blood pressure goal to be achieved, randomized trials comparing less with more intensive treatment [101,104–106] have shown that in diabetic patients more intensive blood pressure lowering is more protective [101,103,105,107]. This is not yet conclusively established in non-diabetic subjects. This is because the only trial not exclusively involving diabetics is the HOT study [103,104], which, because of the small diastolic blood pressure differences achieved (2 mmHg) among the groups randomized to = 90, 85 or 80 mmHg, was unable to detect significant differences in the risk of cardiovascular events (except for myocardial infarction) between adjacent target groups. However, the results of the HOT study have confirmed that there is no increase in cardiovascular risk in the patients randomized to the lowest target group, which is relevant to clinical practice because setting lower blood pressure goals allows a greater number of subjects to at least meet the traditional ones. Furthermore, a recent subgroup analysis of the HOT study [108] suggests that except for smokers a reduction of diastolic blood pressure to an average of 82 mmHg rather than 85 mmHg significantly reduces major cardiovascular events in non-diabetic patients at high or very high risk (50% of HOT study patients), as well as in patients with previous ischaemic heart disease, in patients older than 65 years and in women. Finally, in patients with a history of stroke or transient ischaemic attack, the PROGRESS trial [99] showed less cardiovascular mortality and morbidity by reducing diastolic blood pressure to 79 mmHg (active treatment group) rather than 83 mmHg (placebo group). Similar observations has been made in patients with coronary disease, although the role of blood pressure reduction in these trials has been debated [109]. As far as systolic blood pressure is concerned, evidence of a greater benefit by a more aggressive reduction is limited to the UKPDS study, which has shown, through retrospective analysis of the data, fewer cardiovascular morbid events at values below 130–120 compared with 140 mmHg. Most trials, however, have been unable to reduce systolic blood pressure below 140 mmHg, and in no trials on diabetic and non-diabetic patients have values below 130 mmHg been achieved [109].

As for patients with non-diabetic renal disease, data about the effects of more or less intensive blood pressure lowering on cardiovascular events are scanty: the HOT study was unable to find any significant reduction in cardiovascular events in the subset of patients with plasma creatinine > 115 μmol/l (> 1.3 mg/dl) [108] or > 133 μmol/l (> 1.5 mg/dl) [26] when subjected to more vs. less intensive blood pressure lowering (139/82 vs. 143/85 mmHg). However, not one of these trials suggests an increased cardiovascular risk at the lowest blood pressure achieved.

In conclusion, on the basis of current evidence from trials, it can be recommended that blood pressure, both systolic and diastolic, can be intensively lowered at least below 140/90 mmHg and to definitely lower values if tolerated, in all hypertensive patients, and below 130/80 mmHg in diabetics. The achievable goal may depend on the pre-existing blood pressure level, and systolic values below 140 mmHg may be difficult to achieve, particularly in the elderly.

When home or ambulatory blood pressure measurement are used to evaluate the efficacy of treatment, it must be remembered that daytime values provided by these methods (compared with office measurement) are on average at least 10 mmHg lower for systolic and 5 mmHg lower for diastolic blood pressure, although these differences tend to become smaller at lower office blood pressure values, such as those recommended as treatment goals [45].

Lifestyle changes

Lifestyle measures should be instituted whenever appropriate in all patients, including subjects with high/normal blood pressure and patients who require drug treatment. The purpose is to lower blood pressure and to control other risk factors and clinical conditions present. However, lifestyle measures are undocumented in preventing cardiovascular complications in hypertensive patients and should never delay the initiation of drug treatment unnecessarily, especially in patients at higher levels of risk, or detract from compliance to drug treatment.

Smoking cessation

Smoking cessation is probably the single most powerful lifestyle measure for the prevention of a large number of non-cardiovascular and cardiovascular diseases, including stroke and coronary heart disease [110]. Those who quit before middle age typically have a life expectancy that is not different to that of lifelong non-smokers. Although smoking cessation does not lower blood pressure [111], smoking may predict a future rise in systolic blood pressure [112], and global cardiovascular risk is greatly increased by smoking [110]. For several reasons, therefore, hypertensive smokers should be counselled on smoking cessation. In addition, some other data suggest that smoking may interfere with the beneficial effects of some antihypertensive agents, such as beta-blockers, or may prevent the benefits of more intensive blood pressure lowering [108]. Where necessary, nicotine replacement or buspirone therapy should be considered, as they appear to facilitate other interventions for smoking cessation [113].

Moderation of alcohol consumption

There is a linear relationship between alcohol consumption, blood pressure levels and the prevalence of hypertension in populations [114]. Beyond that, high levels of alcohol consumption are associated with high risk of stroke [115]; this is particularly so for binge-drinking. Alcohol attenuates the effects of anti-hypertensive drug therapy, but this effect is at least partially reversible within 1–2 weeks by moderation of drinking by around 80% [116]. Heavier drinkers (five or more standard drinks per day) may experience a rise in blood pressure after acute alcohol withdrawal and are more likely to be diagnosed as hypertensive at the beginning of the week if they have a weekend drinking pattern. Accordingly, hypertensive patients who drink alcohol should be advised to limit their consumption to no more than 20–30 g of ethanol per day for men, and no more than 10–20 g per day for women. They should be warned against the heightened risks of stroke that are associated with binge-drinking.

Weight reduction and physical exercise

Excess body fat predisposes to raised blood pressure and hypertension [117]. Weight reduction reduces blood pressure in overweight patients and has beneficial effects on associated risk factors, such as insulin resistance, diabetes, hyperlipidaemia and left-ventricular hypertrophy. The blood pressure lowering effect of weight reduction may be enhanced by simultaneous increase in physical exercise [118], by alcohol moderation in overweight drinkers [119] and by reduction in sodium intake [120]. Physical fitness is a rather strong predictor of cardiovascular mortality, independent of blood pressure and other risk factors [121]. Thus, sedentary patients should be advised to take up modest levels of aerobic exercise on a regular basis, such as walking, jogging or swimming for 30–45 min, three to four times per week [122]. The extent of the pre-training evaluation will depend on the extent of the envisaged exercise and on the patient's symptoms, signs, overall cardiovascular risk and associated clinical

conditions. Even mild exercise may lower systolic blood pressure by about 4–8 mmHg [123]. However, isometric exercise such as heavy weightlifting can have a pressor effect and should be avoided. If hypertension is poorly controlled, and always in severe hypertension, heavy physical exercise should be discouraged or postponed until appropriate drug treatment has been instituted and found to work.

Reduction of high salt intake and other dietary changes

Epidemiological studies suggest that dietary salt intake is a contributor to blood pressure elevation and to the prevalence of hypertension [124]. The effect appears to be enhanced by a low dietary intake of potassium-containing foods. Randomized controlled trials in hypertensive patients indicate that reducing sodium intake by 80–100 mmol (4.7–5.8 g) per day from an initial intake of around 180 mmol (10.5 g) per day will reduce blood pressure by an average of 4–6 mmHg [125] or even more if combined with other dietary counselling [126]. Patients should be advised to avoid added salt, to avoid obviously salted food, particularly processed foods, and to eat more meals cooked directly from natural ingredients containing more potassium. Counselling by trained dietitians may be useful. Hypertensive patients should also be advised to eat more fruit and vegetables [127], to eat more fish [128] and to reduce their intake of saturated fat and cholesterol.

Pharmacological therapy

Introduction

Recommendations about pharmacological therapy are here preceded by analysis of the available evidence (as provided by large randomized trials based on fatal and non-fatal events) of the benefits obtained by antihypertensive therapy and of the comparative benefits obtained by the various classes of agents. This is the strongest type of evidence available. It is commonly recognized, however, that event-based randomized therapeutic trials have some limitations; among these, the special selection criteria of the subjects included: the frequent selection of high-risk patients in order to increase the power of the trial, so that the vast majority of uncomplicated and lower risk hypertensives are rarely represented; the therapeutic programmes that often diverge from usual therapeutic practice; and the stringent follow-up procedures enforcing patients' compliance well beyond that obtained in common medical practice. The most important limitation is perhaps the necessarily short duration of a controlled trial, in most cases 4–5 years, whereas additional life expectancy and hence expectancy of therapeutic duration for a middle-aged hypertensive is of 20–30 years [20,129].

Long-term therapeutic benefits and long-term differences between benefits of various drug classes may also be evaluated by using intermediate end-points (i.e. subclinical organ damage changes), as some of these changes have predictive value of subsequent fatal and non-fatal events. Several of the recent event-based trials have also used 'softer' end-points, such as congestive heart failure (certainly clinically relevant, but often based on subjective diagnosis), hospitalization, angina pectoris and coronary revascularization (highly subjected to local clinical habits and facilities), etc. Treatment-induced alterations in metabolic parameters, such as serum LDL- or HDL-cholesterol, serum potassium, glucose tolerance, induction or worsening of the metabolic syndrome or diabetes, although they can hardly be expected to increment cardiovascular event incidence during the short term of a trial, may have some impact during the longer course of the patient's life.

Trials based on mortality and morbidity end-points comparing active treatment with placebo

The results of trials performed in mostly systolic–diastolic hypertension and in elderly with isolated systolic hypertension have been included in meta-analyses [5,129–132]. Antihypertensive treatment resulted in significant and similar reductions of cardiovascular and all-cause mortality in both types of hypertension. With regard to cause-specific mortality, Collins and colleagues [14] observed a significant reduction in fatal stroke (–45%, $P < 0.001$), but not in fatal coronary heart disease (–11%, NS). This could be related to age because coronary mortality was significantly reduced by 26% ($P < 0.01$) in a meta-analysis on elderly with systolic–diastolic hypertension [133]. Fatal and non-fatal strokes combined and all coronary events were significantly reduced in the two types of hypertension. The Blood Pressure Lowering Treatment Trialists Collaboration (BPLTTC) [107] performed separate meta-analyses of placebo-controlled trials in which active treatment was initiated by a calcium antagonist or by an ACE inhibitor and showed the reductions in cardiovascular end-points were similar to those found in the trials in which active treatment was based on diuretics or beta-blockers. The proportional reduction of the cardiovascular risk appears to be similar in women and in men [134].

Additional information has more recently been provided by other trials, not yet included in the previously mentioned meta-analysis. Placebo-controlled trials addressed the effect of the angiotensin receptor antagonists

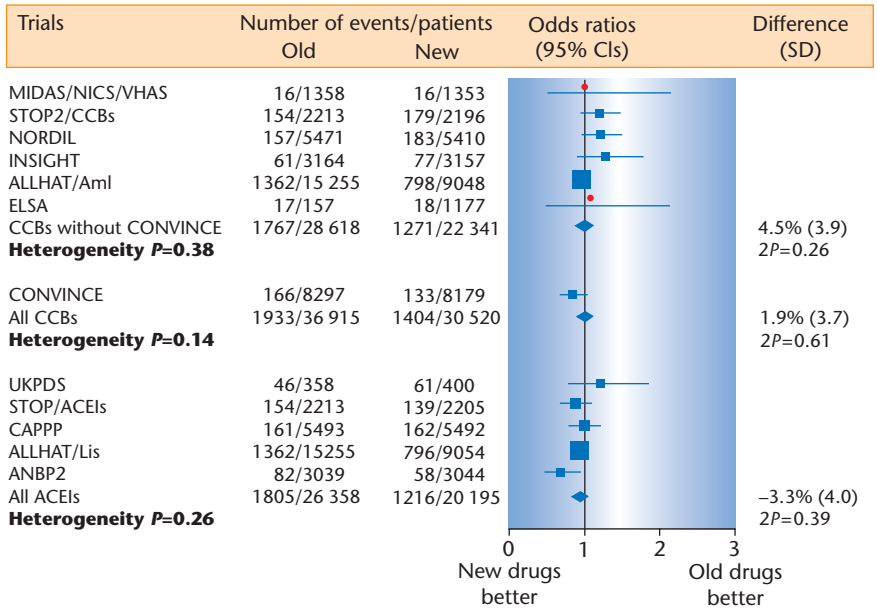

Figure 10.1 Fatal and non-fatal myocardial infarction in randomized clinical trials comparing 'newer' with 'old' antihypertensive drugs.

losartan [135] and irbesartan [136,137] in patients with type 2 diabetes and nephropathy. All studies concluded that the drug treatment was renoprotective but that there was no evidence of benefit in secondary cardiovascular end-points (for the evaluation of which, however, these trials had insufficient power). It can be concluded from these recent placebo-controlled trials that blood pressure lowering by angiotensin II antagonists can also be beneficial, particularly in stroke prevention, and, in patients with diabetic nephropathy, in slowing down progression of renal disease.

Trials based on mortality and morbidity end-points comparing treatments initiated by different drug classes

During the last 5 years, a large number of controlled randomized trials has compared antihypertensive regimens initiated with different classes of antihypertensive agents, most often comparing older (diuretics and beta-blockers) with newer ones (calcium antagonists, ACE inhibitors, angiotensin receptor antagonists, alpha-blockers), and occasionally comparing newer drug classes. Several trials [138–146] with > 67 000 randomized patients, comparing calcium antagonists with older drugs, have recently been reviewed [147]. For none of the outcomes considered in this analysis, including all-cause and cardiovascular mortality, all cardiovascular events, stroke, myocardial infarction and heart failure, did the *P*-values for heterogeneity reach statistical significance ($0.11 \leq P \leq 0.95$). The pooled odds ratios expressing the possible benefit of calcium antagonists over old drugs were close to unity and non-significant for total mortality, cardiovascular mortality, all cardiovascular events and myocardial infarction (Fig. 10.1). Calcium antagonists provided slightly better protection against fatal and non-fatal stroke than old drugs (Fig. 10.2). For the trials combined, the odds ratio for stroke reached formal significance (0.90, 95% confidence interval 0.82–0.98, $P = 0.02$) after CONVINCE [146], the only large trial based on verapamil, was excluded. For heart failure, calcium antagonists appeared to provide less protection than conventional therapy, regardless of whether or not the CONVINCE trial was incorporated in the pooled estimates.

Six trials with about 47 000 randomized patients compared ACE inhibitors with old drugs [139,142,148,149]. The pooled odds ratios expressing the possible benefit of ACE inhibitors over conventional therapy were close to unity, and non-significant for total mortality, cardiovascular mortality and myocardial infarction (Fig. 10.1). Compared with old drugs, ACE inhibitors provided slightly less protection against stroke (Fig. 10.2), heart failure and all cardiovascular events. For all-cause and cardiovascular mortality, stroke and myocardial infarction, *P*-values for heterogeneity among the trials of ACE inhibitors were non-significant ($0.16 \leq P \leq 0.88$). In contrast, for all cardiovascular events and heart failure, heterogeneity was significant owing to the ALLHAT [139] findings. Compared with chlorthalidone, ALLHAT patients allocated to lisinopril had a greater risk of stroke, heart failure and hence combined cardiovascular disease [139]. Similar findings were previously reported for the comparison of the alpha-blocker doxazosin with chlorthalidone, an ALLHAT arm that was interrupted prematurely

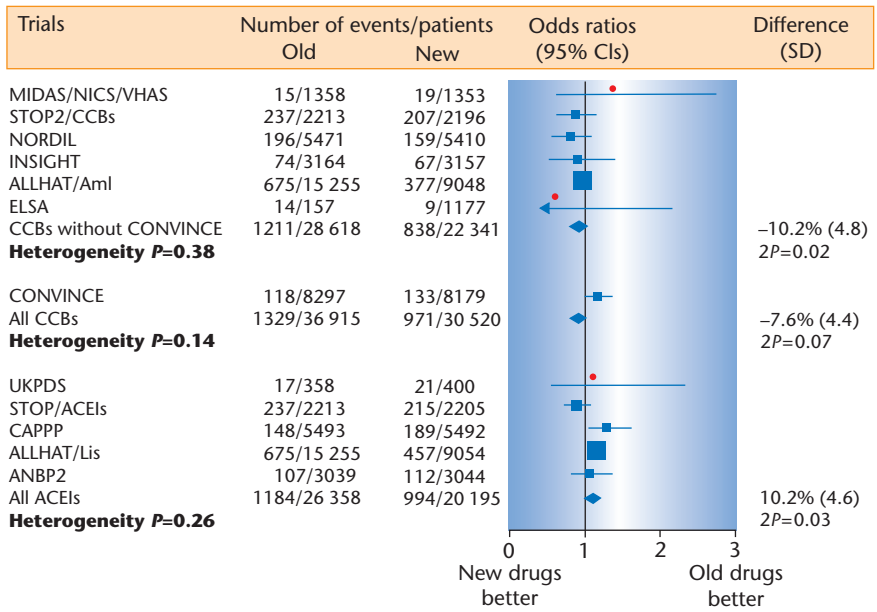

Figure 10.2 Fatal and non-fatal stroke in randomized clinical trials comparing 'newer' with 'old' antihypertensive drugs.

[138]. Although ALLHAT [139] stands out as the largest double-blind trial undertaken in hypertensive patients, interpretation of its results is difficult in several aspects, which may account for the heterogeneity of ALLHAT results with respect to those of the other trials.

1 In ALLHAT, 90% of the patients at randomization were already on antihypertensive treatment, most often diuretics, thus ALLHAT tested 'continuing a diuretic' vs. 'switching drug classes'. Patients on diuretics with latent or compensated heart failure were deprived of their therapy when they were not randomized to chlorthalidone.
2 The achieved systolic pressure was higher on doxazosin, amlodipine and lisinopril than on chlorthalidone. Presumably, these factors explain why the Kaplan–Meier curves started to diverge immediately after randomization for heart failure and approximately 6 months later also for stroke.
3 The sympatholytic agents used for step-up treatment (atenolol, clonidine and/or reserpine at the physician's discretion) led to a somewhat artificial treatment regimen, which does not reflect modern clinical practice, is not usually recommended and is known to potentiate the blood pressure response to diuretics much more than to ACE inhibitors or alpha-blockers.
4 ALLHAT did not include systematic end-point evaluation, which may have particularly affected evaluation of 'softer' end-points, such as congestive heart failure.

These limitations notwithstanding, ALLHAT [138,139], either alone or in combination with the other trials, supports the conclusion that the benefits of antihypertensive therapy largely depend on blood pressure lowering, thus being in line with the preliminary and most recent findings of the meta-analysis of the BPLTTC [107,150]. The conclusion that a substitution of portion of the benefit of antihypertensive treatment depends on BP reduction per se is also supported by the recent findings of the INVEST study [151], in which cardiovascular disease was similarly frequent in patients treated with verapamil compared with those treated with atenolol (± hydrochlorotiazide). It is not entirely supported by the data of the Second Australian Blood Pressure study [152], in which ACE inhibitor-based treatment was found to be more protective against cardiovascular disease than diuretic-based treatment. The difference was modest, however, and significant only when the second morbid event in the same patient was included in the analysis. Finally, the conclusion of the paramount importance of blood pressure control for prevention of cardiovascular complications is supported by the results of the recently published VALUE trial [153,154], in which cardiac disease (the primary end-point) was similarly frequent in high-risk hypertensive patients who were treated with valsartan or amlodipine. Amlodipine reduced blood pressure to a greater degree in the months that followed randomization than using two drug-regimens, and this was accompanied by a lower risk of events.

Apart from the VALUE trial, two other recent trials have studied the new class of angiotensin receptor antagonists. The LIFE study [155] has compared losartan with the beta-blocker atenolol in hypertensive patients with left-ventricular hypertrophy for an average of 4.8 years, and found a significant 13% reduction in major cardiovascular

events, mostly due to a significant 25% reduction in stroke incidence. There were no blood pressure differences between the treatment groups. The SCOPE study [156] was initiated as a comparison of elderly patients receiving candesartan or placebo but, because for ethical reasons 85% of the placebo-initiated patients received antihypertensive therapy (mostly diuretics, beta-blockers or calcium antagonists), the study is a comparison of antihypertensive treatment with or without candesartan. After 3.7 years of treatment there was a non-significant 11% reduction in major cardiovascular events, and a significant 28% reduction in non-fatal strokes among candesartan-treated patients, with an achieved blood pressure slightly lower (3.2/1.6 mmHg) in the candesartan group.

In the most recent meta-analysis of the BPLTTC [150], it was concluded that ARB-based regimens showed a greater effect than other control regimens on the risk of stroke, heart failure and major cardiovascular events, but not on coronary heart disease, cardiovascular death and total mortality. However, it is likely that only the effect on heart failure will persist when the results of the VALUE trial, which only became available after the BPLTTC publication, are considered together with the results from the BPLTTC meta-analysis.

Randomized trials based on intermediate end-points

LEFT-VENTRICULAR HYPERTROPHY

The studies that have tested the effects of various antihypertensive agents on hypertension-associated left-ventricular hypertrophy, mostly evaluated as left-ventricular mass at the echocardiogram, are almost innumerable, but only a few of them have followed strict enough criteria to provide reliable information. The very few studies adhering to these strict criteria do not yet provide uncontrovertible answers, although their most recent meta-analysis suggests that, for a similar blood pressure reduction, newer agents (ACE inhibitors, calcium antagonists and angiotensin II antagonists) may be more effective than conventional drugs [157]. The large and long-term (5 years) LIFE Study is particularly relevant, as the greater regression of electrocardiographically determined left-ventricular hypertrophy (LVH) with losartan was accompanied by a reduced incidence of cardiovascular events [155]. The same findings were obtained in a LIFE substudy in which LVH was determined by echocardiography. Future studies should investigate treatment-induced effects on indices of collagen content of the ventricular wall rather than on its mass only.

ARTERIAL WALL AND ATHEROSCLEROSIS

A number of randomized trials have compared the long-term (2–4 years) effects of different antihypertensive regimens on carotid artery wall intima media thickness. The most convincing evidence has been obtained for calcium antagonists, which comes from trials with different agents, concluding with a long-term study on more than 2000 patients [158]. The data show [158–160] that for a similar reduction in blood pressure these drugs slow down carotid artery wall thickening and plaque formations more than conventional drugs. Evidence of a greater benefit is also available for ACE inhibitors [161], although less consistently.

RENAL FUNCTION

The most abundant evidence concerns renal function in diabetic patients [162]. Progression of renal dysfunction can be retarded by adding an angiotensin receptor antagonist [135,136] (compared with placebo) in diabetic patients with advanced nephropathy. Consistent effects of more intensive blood pressure lowering were found on urinary protein, both overt proteinuria and microalbuminuria. Of several studies in diabetic patients comparing treatments initiated by different agents, some [101,145,148] did not show a difference in the renal protective effect of the drugs that were being compared, whereas one indicated the angiotensin antagonist irbesartan to be superior to the calcium antagonist amlodipine in retarding development of renal failure [136], and the other indicated the angiotensin antagonist losartan to reduce incidence of new overt proteinuria better than the beta-blocker atenolol [163].

As to patients with non-diabetic renal disease, a recent meta-analysis of 11 randomized trials comparing antihypertensive regimens including or excluding an ACE inhibitor [164] indicates a significantly slower progression in patients achieving blood pressure of 139/85 mmHg rather than 144/87 mmHg. It is not clear, however, whether the benefit should be ascribed to ACE inhibition or to the lower blood pressure achieved. Some light on the matter is shed by the recently completed AASK study [165]. ACE inhibitors were shown to be somewhat more effective than beta-blockers [165] or calcium antagonists [166] in slowing glomerular filtration rate decline. It appears, therefore, that in patients with non-diabetic renal disease the use of an ACE inhibitor may be more important than an aggressive blood pressure reduction, whereas in diabetic patients aggressive lowering of blood pressure may be equally important as blockade of the renin–angiotensin system.

NEW-ONSET DIABETES

Several trials have monitored the incidence of new-onset diabetes during the treatment follow-up (Fig. 10.3). With few exceptions [142,143], studies have shown a lower incidence in patients treated with an ACE inhibitor, a

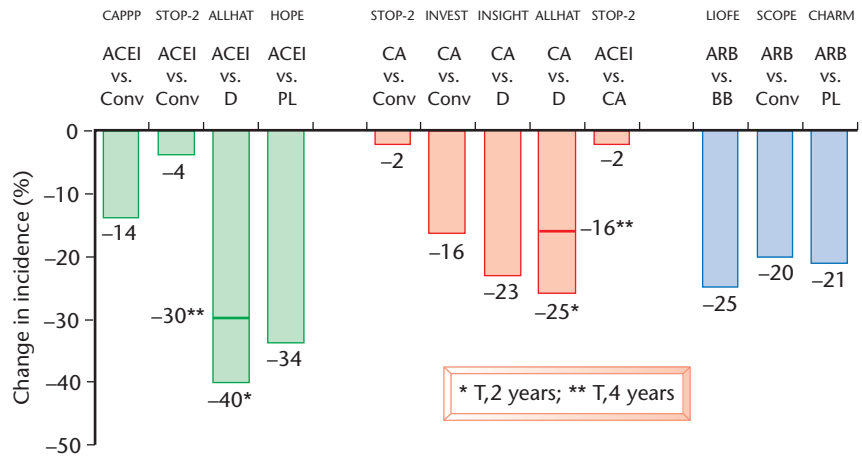

Figure 10.3 Prevention of new-onset diabetes with 'newer' vs. 'old' antihypertensive drugs in recent randomized clinical trials.

calcium antagonist or an angiotensin II antagonist compared with diuretics or beta-blockers [139,145,149,151, 156,167]; treatment with an ACE inhibitor has resulted in a lower incidence of new-onset diabetes than with placebo [100], and administration of the angiotensin II antagonist valsartan has been more beneficial on this end-point than administration of amlodipine [153]. There are thus differences between different antihypertensive drugs on this end-point. This is likely to be clinically relevant because, in the long term, treatment-induced diabetes is accompanied by an increased incidence of cardiovascular disease as much as native diabetes [168,169].

Therapeutic strategies

Principles of drug treatment: monotherapy vs. combination therapy

In most, if not all, hypertensive patients, therapy should be started gently, and target blood pressure values achieved progressively through several weeks. To reach target blood pressure, it is likely that a large proportion of patients will require combination therapy with more than one agent. The proportion of patients requiring combination therapy will also depend on baseline blood pressure values. In grade 1 hypertensives, monotherapy is likely to be successful more frequently [104,138,139]. In trials on diabetic patients, the vast majority of patients were on at least two drugs, and in two recent trials on diabetic nephropathy [135,136] an average of 2.5 and 3.0 non-study drugs were required in addition to the angiotensin receptor antagonist used as study drug.

According to the baseline blood pressure and the presence or absence of complications, it appears reasonable to initiate therapy either with a low dose of a single agent or with a low-dose combination of two agents (Fig. 10.4). If low-dose monotherapy is chosen and blood pressure control is not achieved, the next step is to switch to a low dose of a different agent or to increase the dose of the first compound chosen (with a greater possibility of eliciting adverse disturbances) or to make recourse to combination therapy. If therapy has been initiated by a low-dose combination, a higher dose combination can subsequently be used or a low dose of a third compound added.

The following two-drug combinations have been found to be effective and well tolerated, but other combinations are possible (Fig. 10.5):

- diuretic and beta-blocker;
- diuretic and ACE inhibitor or angiotensin receptor antagonist;
- calcium antagonist (dihydropyridine) and beta-blocker;
- calcium antagonist and ACE inhibitor or angiotensin receptor antagonist;
- calcium antagonist and diuretic;
- alpha- and beta-blockers;
- other combinations can be used if necessary, and three or four drugs may be required in special cases.

The use of long-acting drugs or preparations providing 24-h efficacy on a once-daily basis is recommended. The advantages of such medications include improvement in adherence to therapy and minimization of blood pressure variability, thus possibly providing greater protection against the risk of major cardiovascular events and the development of TOD [170,171].

Particular attention should be given to adverse events, even purely subjective disturbances, because they may be an important cause of non-compliance. Patients should always be asked about adverse effects, and dose or drug changes made accordingly. Even within the same drug class, there may be compounds less prone to induce a specific adverse effect (e.g. among beta-blockers, less fatigue or Raynaud's phenomenon with vasodilating

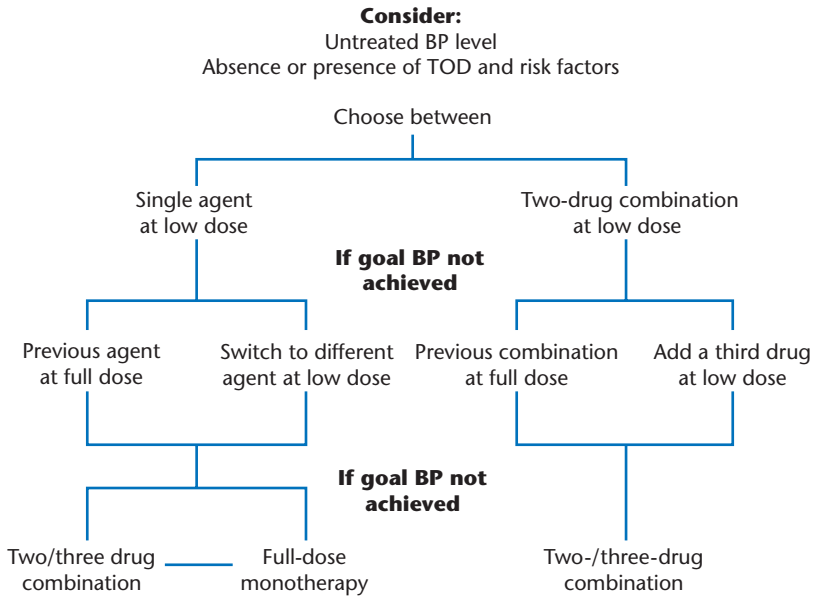

Figure 10.4 Monotherapy vs. combination therapy against hypertension.

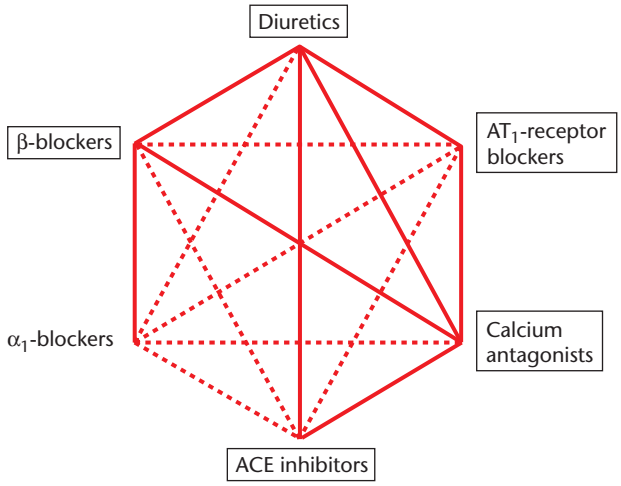

Figure 10.5 First-line treatments and choices of drug combinations.

compounds; among calcium antagonists, no constipation with dihydropyridines, no tachycardia with verapamil and diltiazem, variable degree of dependent oedema with different compounds).

CHOICE OF ANTIHYPERTENSIVE DRUGS

A large number of randomized trials confirm that the main benefits of antihypertensive therapy are due to lowering of blood pressure per se, largely independently of the drugs used to lower blood pressure.

There is also evidence, however, that specific drug classes may differ in some effect or in special groups of patients. Finally, drugs are not equal in terms of adverse disturbances, particularly in individual patients, and patients' preference is a prerequisite for compliance and therapy success.

It can therefore be concluded that the major classes of antihypertensive agents—diuretics, beta-blockers, calcium antagonists, ACE inhibitors and angiotensin receptor antagonists—are suitable for the initiation and maintenance of antihypertensive therapy. Evidence favouring the use of alpha-blockers is less than evidence of the benefits of other antihypertensive agents, and it appears prudent to use alpha-blockers mostly for combination therapy. Emphasis on identifying the first class of drugs to be used is probably outdated by the awareness that two or more drugs in combination are necessary in the majority of patients, particularly those with higher initial blood pressures or TOD or associated diseases, in order to achieve target blood pressure.

Within the array of available agents, the choice of drugs will be influenced by many factors including:

1. the previous, favourable or unfavourable experience of the individual patient with a given class of compounds;
2. the cost of drugs, either to the individual patient or to the health provider, although cost considerations should not predominate over efficacy and tolerability in any individual patient;
3. the cardiovascular risk profile of the individual patient;
4. the presence of TOD, clinical cardiovascular disease, renal disease and diabetes;
5. the presence of other coexisting disorders that may either favour or limit the use of particular classes of antihypertensive drugs;

Table 10.6 Indications and contraindications for the major classes of antihypertensive drugs

		Contraindications	
Class	**Conditions favouring the use**	**Compelling**	**Possible**
Diuretics (thiazides)	Congestive heart failure Elderly hypertensives Isolated systolic hypertension Hypertensives of African origin	Gout	Pregnancy
Diuretics (loop)	Renal insufficiency Congestive heart failure		
Diuretics (anti-aldosterone)	Congestive heart failure Post myocardial infarction	Renal failure Hyperkalaemia	
Beta-blockers	Angina pectoris Post myocardial infarction Congestive heart failure (up-titration) Pregnancy Tachyarrhythmias	Asthma Chronic obstructive pulmonary disease Atrioventricular block (grade 2 or 3)	Peripheral vascular disease Glucose intolerance Athletes and physically active patients
Calcium antagonists (dihydropyridines)	Elderly patients Isolated systolic hypertension Angina pectoris Peripheral vascular disease Carotid atherosclerosis Pregnancy		Tachyarrhythmias Congestive heart failure
Calcium antagonists (verapamil, diltiazem)	Angina pectoris Carotid atherosclerosis Supraventricular tachycardia	A-V block (grade 2 or 3) Congestive heart failure	
ACE-inhibitors	Congestive heart failure Left-ventricular dysfunction Post myocardial infarction Non-diabetic nephropathy Type 1 diabetic nephropathy Proteinuria	Pregnancy Hyperkalaemia Bilateral renal artery stenosis	
Angiotensin II-receptor antagonists (AT1-blockers)	Diabetic nephropathy Diabetic microalbuminuria Proteinuria Left-ventricular hypertrophy ACE inhibitor cough	Pregnancy Hyperkalaemia Bilateral renal artery stenosis	
Alpha-blockers	Prostatic hyperplasia (BPH) Hyperlipidaemia	Orthostatic hypotension	Congestive heart failure

6 the possibility of interactions with drugs used for other conditions present in the patient.

The physician should tailor the choice of drugs to the individual patient, after taking all these factors, together with patient preference, into account. Indications and contraindications of specific drug classes are listed in Table 10.6, and therapeutic approaches to be preferred in special conditions are discussed in the next section.

Therapeutic approaches in special conditions

Elderly

There is little doubt from randomized controlled trials that older patients benefit from antihypertensive treatment in terms of reduced cardiovascular morbidity and mortality, whether they have systolic–diastolic hypertension

[133] or isolated systolic hypertension [132]. Whereas trials in the elderly usually include patients who are at least 60 years old, a recent meta-analysis concluded that fatal and non-fatal cardiovascular events combined were significantly reduced in participants in randomized, controlled trials of antihypertensive drug treatment, who were aged 80 years and over, but all-cause mortality was not reduced [172]. The larger randomized controlled trials of antihypertensive treatment vs. placebo or no treatment in elderly patients with systolic–diastolic hypertension used a diuretic or a beta-blocker as first-line therapy [133]. In trials on isolated systolic hypertension, first-line drugs consisted of a diuretic [12] or a dihydropyridine calcium channel blocker [13,173,174]. In all of these trials, active therapy was superior to placebo or no treatment. Other drug classes have only been used in trials in which 'newer' drugs were compared with 'older' drugs [139,142,155,156,175]. It appears that benefit has been shown in older patients for at least one representative agent of several drug classes, i.e. diuretics, beta-blockers, calcium channel blockers, converting enzyme inhibitors and angiotensin receptor antagonists.

Initiation of antihypertensive treatment in elderly patients should follow the general guidelines. Many patients will have other risk factors, TOD and associated cardiovascular conditions, to which the choice of the first drug should be tailored. Furthermore, many patients will need two or more drugs to control blood pressure, particularly due to the fact that it is often difficult to lower systolic pressure to below 140 mmHg [109,176].

Diabetes mellitus

The prevalence of hypertension is increased in patients with diabetes mellitus [177]. Type 2 diabetes is by far the most common form, occurring about 10–20 times as often as type 1. Hypertensive patients frequently exhibit a condition known as 'metabolic syndrome', i.e. a syndrome associating insulin resistance (with the concomitant hyperinsulinaemia), central obesity and characteristic dyslipidaemia (high plasma triglyceride and low HDL-cholesterol) [23,178]. These patients are prone to develop type 2 diabetes.

In type 1 diabetes, hypertension often reflects the onset of diabetic nephropathy [179], whereas a large fraction of hypertensive patients have still normoalbuminuria at the time of diagnosis of type 2 diabetes [180]. The prevalence of hypertension (defined as a blood pressure ≥ 140/90 mmHg) in patients with type 2 diabetes and normoalbuminuria is very high, at 71%, and increases even further to 90% in the presence of microalbuminuria [181].

The coexistence of hypertension and diabetes mellitus (either of type 1 or 2) substantially increases the risk of macrovascular complications, including stroke, coronary heart disease, congestive heart failure and peripheral vascular disease, and is responsible for an excessive cardiovascular mortality [179,182]. The presence of microalbuminuria is both an early marker of renal damage and an indicator of increased cardiovascular risk [183,184]. There is also evidence that hypertension accelerates the development of diabetic retinopathy [185]. The level of blood pressure achieved during treatment greatly influences the outcome of diabetic patients. In patients with diabetic nephropathy, the rate of progression of renal disease is in a continuous relationship with blood pressure until a level of 130 mmHg systolic and 70 mmHg diastolic is reached. Aggressive treatment of hypertension protects patients with type 2 diabetes against cardiovascular events. The primary goal of antihypertensive treatment in diabetics should be to lower blood pressure below 130/80 mmHg whenever possible, the best blood pressure being the lowest one that remains tolerated.

Weight gain is a critical factor in the progression to type 2 diabetes. It is therefore key to fight against overweight by all possible means, particularly by calorie restriction and a decrease in sodium intake, as a strong relationship exists between obesity, hypertension, sodium sensitivity and insulin resistance [186].

No major trial has been performed to assess the effect of pharmacological blood pressure lowering on cardiovascular morbidity and mortality in hypertensive patients with type 1 diabetes. There is, however, good evidence that beta-blocker and diuretic-based antihypertensive therapy delays the progression of nephropathy in these patients [187]. In albuminuric patients with type 1 diabetes the best protection against renal function deterioration is obtained by ACE inhibition [188]. It remains unknown whether angiotensin II receptor antagonists are equally effective in this indication.

As to antihypertensive treatment in type 2 diabetes [162], evidence of the superiority or inferiority of different drug classes is still vague and contradictory. Superiority of ACE inhibitors in preventing the aggregate of major cardiovascular events is limited to two trials, one against diuretics/beta-blockers [149] and the other against a calcium antagonist [106], or on analyses of cause-specific events for which the trial power was even less. The recent ALLHAT trial [139] has also failed to find differences in cardiovascular outcomes in the larger number of type 2 diabetes patients included in the trial, randomized to a diuretic, a calcium antagonist or an ACE inhibitor. Recent evidence concerning angiotensin II receptor antagonists has shown a significant reduction of cardiovascular events, cardiovascular death and total mortality in diabetics when losartan was compared with atenolol [163], but not when irbesartan was compared

with amlodipine [136]. If renal end-points are also considered, the benefits of angiotensin II receptor antagonists become more evident, as the IDNT [136] showed a reduction in renal dysfunction and failure by the use of irbesartan rather than amlodipine, and LIFE [163] indicated losartan reduced incidence of new proteinuria better than atenolol. In conclusion, in view of the consensus that blood pressure in type 2 diabetic patients must be lowered, whenever possible, to < 130/80 mmHg, it appears reasonable to recommend that all effective and well-tolerated antihypertensive agents can be used, generally in multiple combinations in diabetic patients. Available evidence suggests that renoprotection may be improved by the regular inclusion of an angiotensin receptor antagonist in these associations, and that in patients with high normal blood pressure, who may sometimes achieve blood pressure goal by monotherapy, the first drug to be tested should be an angiotensin II receptor antagonist.

Concomitant cerebrovascular disease

Evidence of the benefits of antihypertensive therapy in patients who had already suffered a stroke or a transient ischaemic attack (TIA) (secondary prevention) was equivocal [189], and no definite recommendation could be given until recent trials have clearly shown the benefits of lowering blood pressure in patients with previous episodes of cardiovascular disease, even when their initial blood pressure was in the normal range [99].

The other issue, whether elevated blood pressure during an acute stroke should be lowered at all, or to what extent and how, is still a disputed one, for which there are more questions than answers, but trials are in progress. A statement by a special International Society of Hypertension (ISH) panel has recently been published [190].

Concomitant coronary heart disease and congestive heart failure

The risk of a recurrent event in patients with coronary heart disease is significantly affected by the blood pressure level [191], and hypertension is frequently a past or present clinical problem in patients with congestive heart failure [192]. However, few trials have tested the effects of blood pressure lowering in patients with coronary heart disease or congestive heart failure. The HOT Study showed a significant reduction of strokes when the target blood pressure in hypertensives with previous signs of ischaemic heart disease was lowered, and found no evidence of a J-shaped curve [104,108].

Apart from the INVEST study [151], many of the more common blood pressure-lowering agents have been assessed in patients with coronary heart disease or heart failure with objectives other than reduction of blood pressure. Beta-blockers, ACE inhibitors and anti-aldosterone compounds are well established in the treatment regimens for preventing cardiovascular events and prolonging life in patients after an acute myocardial infarction and with heart failure, but how much of the benefit is due to concomitant blood pressure lowering and how much to specific drug actions has never been clarified. There are also data in support of the use of angiotensin receptor antagonists in congestive heart failure as alternatives to ACE inhibitors, especially in ACE inhibitor intolerance or in combination with ACE inhibitors [193,194]. The role of calcium antagonists in prevention of coronary events has been vindicated by the ALLHAT trial, which showed a long-acting dihydropyridine to be equally effective as the other antihypertensive compounds [139]. Calcium antagonists are possibly less effective in prevention of congestive heart failure, but a long-acting compound such as amlodipine may be used, if hypertension is resistant to other compounds [195].

Hypertensive patients with deranged renal function

Renal vasoconstriction is found in the initial stages of essential hypertension and this is reversed by the administration of calcium channel blockers and angiotensin-converting enzyme inhibitors. In more advanced stages of the disease, renal vascular resistance is permanently elevated as a consequence of structural lesions of the renal vessels (nephrosclerosis). Before antihypertensive treatment became available, renal involvement was frequent in patients with primary hypertension. Renal protection in diabetes requires two main accomplishments: first, to attain a very strict blood pressure control (< 130/80 mmHg and even lower, < 125/75 mmHg, when proteinuria > 1 g per day is present) and, second, to lower proteinuria or albuminuria (micro- or macro-) to values as near to normalcy as possible. In order to attain the latter goal, blockade of the effects of angiotensin II (either with an ACE inhibitor or with an angiotensin receptor blocker) is required. In order to achieve the blood pressure goal, combination therapy is usually required, even in patients with high normal blood pressure [162]. The addition of a diuretic as second-step therapy is usually recommended (a loop diuretic if serum creatinine > 2 mg/dl), but other combinations, in particular with calcium antagonists, can also be considered. To prevent or retard development of nephrosclerosis, blockade of the renin–angiotensin system has been reported to be more important than attaining very low blood pressure [165]. On the whole, it seems prudent to start antihypertensive therapy in patients (diabetic or non-diabetic) with reduced renal function, especially if accompanied by proteinuria, by

an ACE inhibitor or an angiotensin receptor antagonist, and then add other antihypertensive agents in order to further lower blood pressure.

Resistant hypertension

Hypertension may be termed resistant to treatment, or refractory, when a therapeutic plan that has included attention to lifestyle measures and the prescription of at least three drugs in adequate doses has failed to lower systolic and diastolic blood pressure sufficiently. In these situations, referral to a specialist should be considered.

There are many cases for resistance to treatment including cases of previous hypertension, such as isolated office (white coat) hypertension, and failure to use large cuffs on large arms. One of the most important causes of refractory hypertension may be poor compliance or adherence to therapy, and in this situation, after all else fails, it can be helpful to suspend all drug therapy while continuing to monitor blood pressure frequently. A fresh start with a new and simpler regimen may help break a vicious cycle.

High risk in general

In the VALUE trial [153], as many as 15 245 hypertensive patients with high cardiovascular risk for various reasons were randomized to valsartan- vs. amlodipine-based treatment for an average of 4.2 years and until 1599 primary end-points, defined as the composite of serious cardiac morbidity or cardiac mortality. There was no difference between the treatment arms with respect to the primary end-point; however, amlodipine lowered blood pressure more effectively than valsartan, and the difference in blood pressure was associated with less stroke and myocardial infarction early in the study. Towards the end of the study, valsartan reduced new-onset diabetes [153] and serious heart failure, particularly if the data were adjusted for the difference in blood pressure [154].

Personal perspective

Modern antihypertensive treatment should usually be given as a combination of well-tolerated drugs, not withholding lifestyle changes when appropriate. There is solid documentation of cardiovascular protection; although most benefit is related to the blood pressure reduction per se, there is evidence in certain patient groups, such as diabetics and patients with left-ventricular hypertrophy, that benefits may be better with certain drugs. However, blood pressure control among patients is still on average suboptimal or even poor, and this applies even more so to patients with complicated hypertension and particular high risk. The challenge for the future is to implement the knowledge from the research and provide equal levels of care for all hypertensive patients. Newer drugs seem better tolerated than the old ones, but they have not been studied in the vast majority of patients, namely those with mild blood pressure elevation only. It is a challenge for all to document more solid prognostic improvements among these patients, including examining the cost–benefit of treating these patients. Full implementation of ambulatory and home blood pressure assessments in clinical practice still needs better documentation. Isolated office or white coat hypertension, and also the reversed phenomenon in patients with high ambulatory but low office blood pressure, need better understanding. Prevention of certain not so 'hard' but still important end-points, such as new-onset diabetes, atrial fibrillation and vascular dementia, needs extensive investigations. The breakthrough of genetic stratification in the field of hypertension research is also still to come.

Acknowledgement

Henrik M. Reims, MD, is a recipient of a Norwegian Council of Cardiovascular Diseases scholarship.

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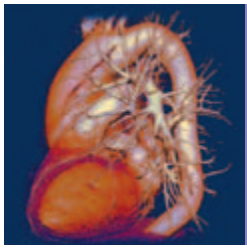

11 Diabetes Mellitus and Metabolic Syndrome

Francesco Cosentino, Lars Ryden and Pietro Francia

Summary

This chapter reviews an evidence-based approach to diagnosis and treatment of diabetes mellitus and metabolic syndrome according to the most recent scientific evidence, recommendations of the European Society of Cardiology, and world-wide institutional guidelines. The pathophysiology and clinical management of atherosclerotic complications of diabetes and metabolic syndrome are considered as a continuum rather than separate issues, according to the need for merging basic and clinical sciences into a real 'bench-to-bedside' approach.

Diabetes mellitus affects more than 150 million people world-wide, with an expected doubling of this number in the next 25 years. Furthermore, approximately 50% of persons above the age of 60 years will meet current diagnostic criteria for metabolic syndrome in the near future. Hyperglycaemia, insulin resistance and the consequent cellular shift to an increased oxidative stress metabolism carry a high risk for the development of comorbidities and cardiovascular risk factors, mainly hypertension, lipid disorders, proinflammatory state, and impairment of coagulation and thrombosis. As a consequence, the incidence of and mortality from all forms of cardiovascular disease are two- to eightfold higher in persons with diabetes, and coronary artery disease accounts for 75% of all deaths in individuals with diabetes. The impressive burden of the disease supports the employment of highly sensitive risk stratification systems to identify patients who will benefit from pharmacological interventions aside from glycaemic control (mainly statins, aspirin, and renin–angiotensin system antagonists) to prevent cardiovascular and cerebrovascular events, and new percutaneous intervention strategies, including drug-eluting stents and anti-thrombotic agents, that currently provide evidence of efficacy in treating target vessels and reducing the rate of restenosis.

Modification of diabetes-associated risk factors for cardiovascular disease, together with a combined approach of medical and interventional strategies to increase long-term vessel patency after percutaneous intervention, is our challenge for the future.

Introduction

Diabetes mellitus is characterized by a state of long-standing hyperglycaemia, hyperinsulinaemia and excess circulating free fatty acids resulting from environmental and genetic factors. The prevalence of diabetes is increasing rapidly, and individuals with diabetes are at high risk for cardiovascular disorders that affect the heart, brain and peripheral vessels. Although cardiovascular disease (CVD) accompanying diabetes is on the rise, many open issues remain concerning the temporal relations between diabetes and CVD, the contribution of conventional risk factors, and the role of diabetes-specific risk factors. The major CVD risk factors, including elevated low-density lipoprotein (LDL)-cholesterol, hypertension, smoking, remain important determinants of CVD in patients with diabetes. In addition, the emerging risk factors—hyperglycaemia, insulin resistance, albuminuria, fibrinogen and enhanced inflammatory activation—further appear to affect risk in individuals with diabetes. Hence the significant clustering of atherogenic risk factors links the current epidemic of diabetes and CVD. Indeed, diabetes

mellitus magnifies the risk of cardiovascular morbidity and mortality [1]. Besides the well-recognized microvascular complications of diabetes, such as nephropathy and retinopathy, macrovascular complications, including diseases of coronary, peripheral and carotid vessels, cause important and common problems in the type 2 diabetic population.

This chapter will consider the pathophysiology and management of atherosclerotic complications of diabetes as a continuum and not—traditionally—as separate sections. Nowadays, physicians caring for patients with CVD must have a working knowledge of the effects of diabetes mellitus and the morbid constellation of risk factors on the heart and blood vessels. Therefore, early detection and intervention with regard to the atherogenic metabolic abnormalities and glucose intolerance that precede development of diabetes is mandatory. A high priority is given to the modification of the major risk factors for CVD. Increasing evidence indicates that controlling CVD risk factors will reduce onset of CVD and its complications in patients with diabetes.

Diagnostic criteria

The clinical diagnosis of diabetes is often prompted by symptoms such as increased thirst, urine volume, recurrent infections, unexplained weight loss and glycosuria. A single blood glucose estimation in excess of the diagnostic values indicated in Table 11.1 establishes the diagnosis in such cases [2]. A blood glucose determination after an 8-h fast (fasting plasma glucose, FPG) of < 6.1 mmol/l (< 110 mg/dl) is considered normal. Impaired fasting glucose encompasses FPGs > 6.1 mmol/l but < 7 mmol/l (< 126 mg/dl). An FPG > 7.0 mmol/l establishes the diagnosis of diabetes mellitus. Among routine tests of glucose metabolism, the 2-h oral glucose tolerance test (OGTT) most closely reflects postprandial glucose disposal. Patients fast overnight, then have blood drawn for serum glucose immediately before and 2 h after the ingestion of an oral load of 75 g of dextrose. Impaired glucose tolerance (IGT) corresponds to a 2-h glucose concentration between 7.8 mmol/l (140 mg/dl) and 11.1 mmol/l (199 mg/dl), while diabetes is defined as a value > 11.1 mmol/l (> 200 mg/dl) [2,3]. For clinical purposes, an OGTT to establish diagnostic status should be considered if causal blood glucose values lie in the uncertain range (i.e. between the levels that establish or exclude diabetes) and FPG levels are below those which establish the diagnosis of diabetes. In this regard, despite the recent lowering by the American Diabetes Association [4] of the value of normal FPG concentration to 5.5 mmol/l and impaired fasting glucose (IFG) (from > 5.5 mmol/l to < 7.0 mmol/l), there is evidence that some of the individuals identified by the new fasting values differ from those identified from their 2-h post-glucose challenge values. Indeed, in less obese subjects and the elderly, lower fasting glucose levels may be seen in persons who have 2-h post-load glucose values that are diagnostic for diabetes. On the other hand, middle-aged, more obese patients are more likely to have diagnostic fasting values. Diagnosis requires the identification of people at risk for development of complications in whom early preventive strategies are indicated. Ideally therefore both the 2-h and the fasting value should be used [2]. These recommendations contrast with those of the American Diabetes Association Expert Committee which gives primacy to

	Venous glucose concentration in mmol/l (mg/dl)	
	Whole blood	**Plasma**
Diabetes mellitus		
Fasting	≥ 6.1 (≥ 110)	≥ 7.0 (≥ 126)
or		
2-h post glucose load	≥ 10.0 (≥ 180)	≥ 11.1 (≥ 200)
or both		
Impaired glucose tolerance		
Fasting (if measured)	< 6.1 (< 110)	< 7.0 (< 126)
and		
2-h post glucose load	≥ 6.7 (≥ 120) and < 10.0 (< 180)	≥ 7.8 (≥ 140) and < 11.1 (< 200)
Impaired fasting glycaemia		
Fasting	≥ 5.6 (≥ 100) and < 6.1 (< 110)	≥ 6.1 (≥ 110) and < 7.0 (< 126)
and (if measured)		
2-h post glucose load	< 6.7 (< 120)	< 7.8 (< 140)

Table 11.1 Values for diagnosis of diabetes mellitus and other categories of hyperglycaemia. Modified from [2].

the FPG. IGT or IFG are not clinical entities, but rather risk categories for future diabetes and/or cardiovascular disease. IGT is often associated with the metabolic syndrome (insulin-resistance syndrome). Thus, IGT may not be directly involved in the pathogenesis of cardiovascular disease, but rather may serve as a marker of enhanced risk. Self-evidently, those individuals with IGT manifest glucose intolerance only when challenged with an oral glucose load.

In this chapter, the focus is on type 2 diabetes, characterized by insulin resistance and/or inadequate beta-cell insulin secretion, because these patients represent more than 90% of those with diabetes and atherosclerosis. However, those with type 1 diabetes (previously known as insulin-dependent or juvenile diabetes) also have an independently higher risk of cardiovascular events, and their disease generally develops at a much younger age than in the type 2 diabetic population.

Atherosclerotic burden associated with diabetes

Diabetes mellitus is estimated to affect more than 150 million people world-wide, with an expected doubling number in the next 25 years, reaching 5.4% of the total adult population [5]. In the United States 17 million people are diabetics, 95% of whom have type 2 diabetes. Among these, 5–6 million are unaware of their condition and do not receive treatment [6,7]. An additional 35 million—20% of all people in the middle-adult years and 35% of the entire older population—have some degree of abnormal glucose tolerance and show signs of insulin resistance; this higher-risk group will account for a significant proportion of CVD and premature mortality. The increasing frequency of obesity and sedentary life-styles, major underlying risk factors for type 2 diabetes in both developed and developing countries, portends that diabetes will continue to be a growing world-wide entity. The incidence of and mortality from all forms of CVD are two- to eightfold higher in persons with diabetes than in those without diabetes. Coronary artery disease (CAD) accounts for 75% of all deaths in individuals with diabetes [8,9] and as many as 30% of patients presenting with acute coronary syndromes have the disease [7]. Both in-hospital and long-term mortality rates after an acute myocardial infarction (MI) are twice as high for patients with diabetes as for those without diabetes (Fig. 11.1). In one population-based study [10], the 7-year incidence of first myocardial infarction or death for patients with diabetes was 20% but was only 3.5% for non-diabetic patients. A history of myocardial infarction increased the rate of recurrent myocardial infarction or cardiovascular death events for both groups (18.8% in non-diabetic persons and 45% in those with diabetes). Thus patients

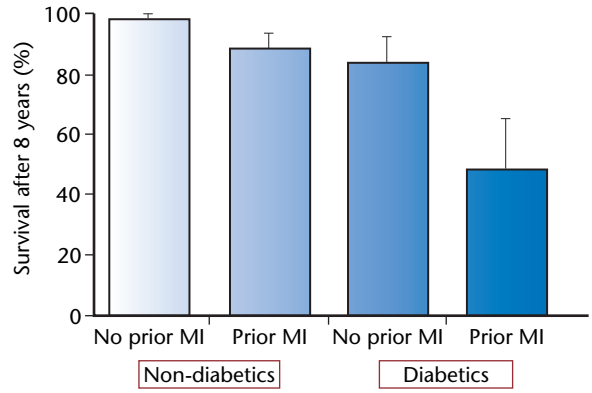

Figure 11.1 Mortality in diabetics after myocardial infarction. Redrawn with permission from [10].

with diabetes but without previous myocardial infarction carry the same level of risk for subsequent acute coronary events as non-diabetic patients with previous myocardial infarction. Such results led the Adult Treatment Panel III of the National Cholesterol Education Program to establish diabetes as a CAD risk equivalent mandating aggressive antiatherosclerotic treatment [11]. Comorbidities —including renal insufficiency, peripheral and cerebral vascular disease—that are more prevalent in patients with diabetes often worsen outcomes. The increase in the incidence of diabetes, its association with CVD, and the accompanying high morbidity and mortality make diabetes a serious public-health issue.

Vascular disease risk factors: from pathophysiology to clinical management

Hyperglycaemia, insulin resistance and oxidative stress

Hyperglycaemia

Hyperglycaemia characterizes both type 1 and type 2 diabetes mellitus. Since a number of studies closely linked elevated blood glucose levels to excess mortality and morbidity from vascular disease [12], growing efforts currently focus on clarifying the effects of glucose on vascular function, in particular endothelial function and nitric oxide (NO) bioavailability.

Indeed, the endothelium contributes to the control of vascular smooth muscle tone by the release of NO. The NO causes vasodilatation and platelet inhibition and thereby prevents vasoconstriction and thrombus

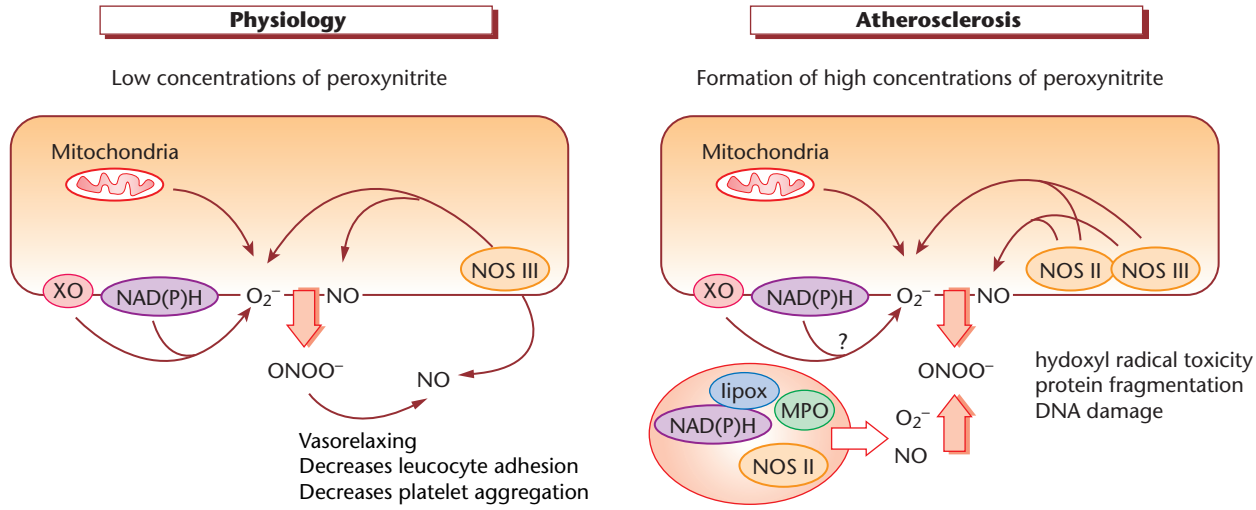

Figure 11.2 In the atherosclerotic setting, an excessive production of O_2^- occurs. O_2^- rapidly inactivates NO, leading to the formation of high concentrations of peroxynitrite ($ONOO^-$), a condition associated with cellular toxicity. Please note the putative sources of O_2^- in the left panel. Reproduced with permission [192].

formation. It is generated from a terminal guanidino nitrogen of L-arginine and is catalysed by a family of enzymes called NO synthases [13,14]. One of these enzymes, endothelial NOS (eNOS), is Ca^{2+}-dependent and is constitutively present in various cell types, including endothelial cells. The activity of the L-arginine/NO pathway is a balance between synthesis and breakdown of NO by its reaction with the superoxide anion (O_2^-). Under physiological conditions the production of this molecule is not markedly affected by O_2^-. Hence, NO may exert its well-known vascular protective effects favouring an antiatherosclerotic environment. However, in the presence of cardiovascular risk factors, an excessive production of O_2^- occurs rapidly, inactivating NO and leading to the formation of high concentrations of peroxynitrite ($ONOO^-$), a very powerful oxidant (Fig. 11.2).

Several lines of evidence support the concept that hyperglycaemia decreases endothelium-derived NO availability and affects vascular function [15,16] via a number of mechanisms mainly involving overproduction of reactive oxygen species (ROS), namely O_2^- [17] (Fig. 11.3).

The mitochondrial electron transport chain is probably one of the first targets of high glucose, with a direct net increase in superoxide anion formation. A further increase in superoxide production is driven by a vicious circle involving ROS-induced activation of protein kinase C (PKC) [15] and vice versa. Indeed, activation of PKC by glucose has been implicated in the regulation and activation of membrane-associated NAD(P)H-dependent oxidase, this latter leading to subsequent production of superoxide anion [18]. Indeed, NAD(P)H activity and subunit protein expression are enhanced in the internal mammary arteries and saphenous veins of diabetic patients [19]. Moreover, high glucose-dependent PKC activation induces an upregulation of inducible cyclo-oxygenase 2 and eNOS expression as well as a selective increase of thromboxane production and reduced NO release. Hence, activation of the PKC pathway represents a proximal node in the intracellular signalling leading to hyperglycaemia-induced oxidative stress and endothelial dysfunction [20] (Fig. 11.4).

Oxygen-derived free radical excess affects endothelial function via a number of different pathways:

- Superoxide anion rapidly inactivates NO to peroxynitrite [21], a powerful oxidant which easily penetrates across phospholipid membranes and produces substrate nitration, thereby inactivating regulatory receptors and enzymes, such as free radical scavengers [22,23] and key NOS co-factors, for instance tetrahydrobiopterin [24].
- Mitochondrial production of superoxide increases intracellular formation of advanced glycation end-products (AGEs) which adversely affect endothelial function by increasing ROS production and inflammatory cytokines from vascular cells thereby enhancing endothelial expression of various adhesion molecules implicated in atherogenesis [25].
- Activation of the receptor for AGEs (RAGE) increases intracellular superoxide anion production [26] and seems to represent a key step in atherosclerotic lesion development [27].
- Superoxide anion production activates the hexosamine pathway, which lowers protein kinase Akt-induced NOS activation [28]. Akt activation is

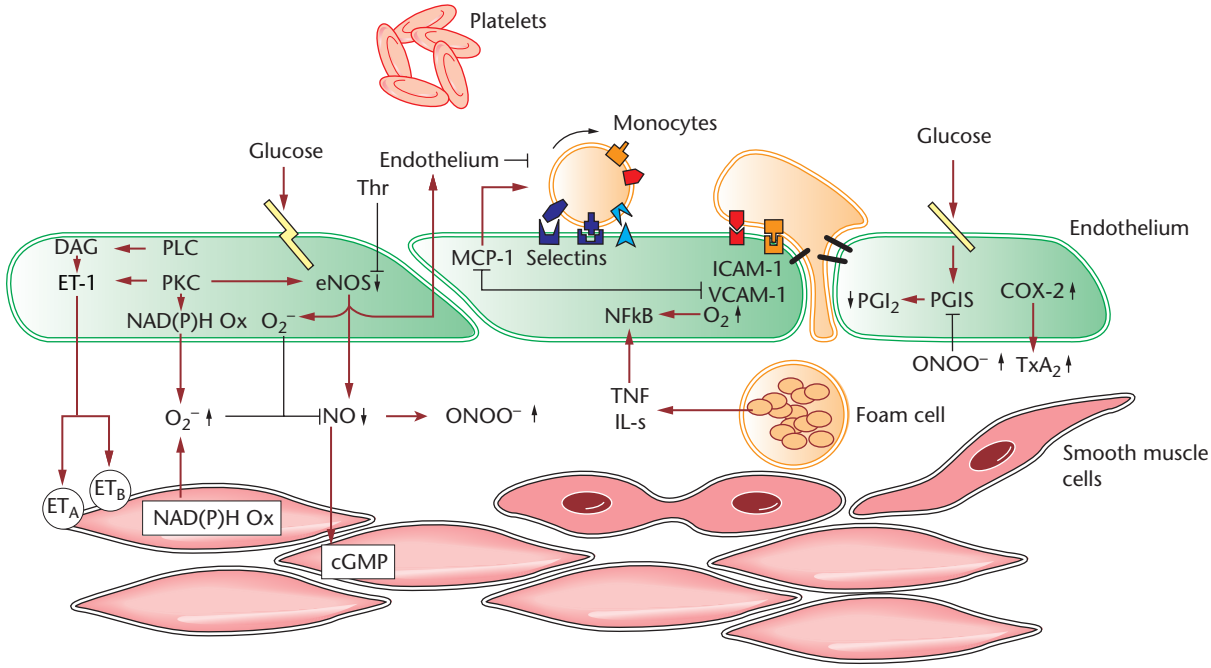

Figure 11.3 Hyperglycaemia and endothelium-derived vasoactive substances. DAG, diacylglycerol; ET-1, endothelin-1; PKC, protein kinase C; PLC, phospholipase C; eNOS, endothelial nitric oxide synthase; Thr, thrombin; NADPH Ox, nicotinamide adenine dinucleotide phosphate oxidase; O_2^-, superoxide anion; $ONOO^-$, peroxynitrite; MCP-1, monocyte chemoattractant factor-1; NF-κB, nuclear factor kappa B; TNF, tumour necrosis factor; ILs, interleukins; ICAM-1, intercellular adhesion molecule 1; VCAM-1, vascular adhesion molecule 1; PGI_2, prostaglandin I_2; PGIS, prostacyclin synthase; COX-2, cyclo-oxygenase-2; TxA_2, thromboxane A_2. Reproduced with permission from [193].

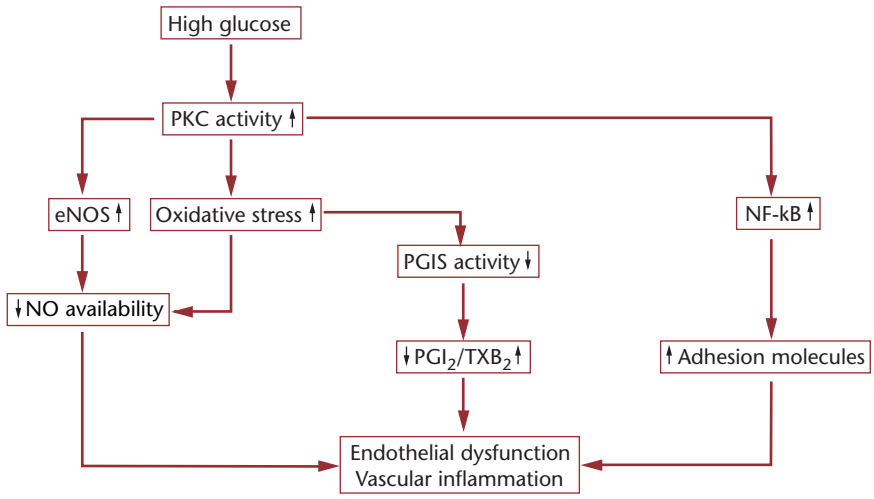

Figure 11.4 A single unifying protein kinase C (PKC)-dependent mechanism is the triggering step by which hyperglycaemia induces endothelial dysfunction and vascular inflammation. PGIS, prostacyclin synthase; PGI_2/TXB_2, prostaglandin I_2/thromboxane B_2.

further limited by PKC-dependent inhibition of phosphatidylinositol-3 kinase (PI-3K) pathway.

- High glucose-induced oxidative stress increases the levels of dimethylarginine, a competitive antagonist of NOS [29].

The impact of diabetes mellitus on vascular function is not limited to the endothelium. In patients with type 2 diabetes mellitus, the vasodilator response to exogenous NO donors is diminished [30]. Dysregulation of vascular smooth muscle function is further enhanced by impairments in sympathetic nervous system function. Diabetes increases PKC activity, NF-κB production, and generation of oxygen-derived free radicals in vascular smooth muscle, akin to these effects in endothelial cells.

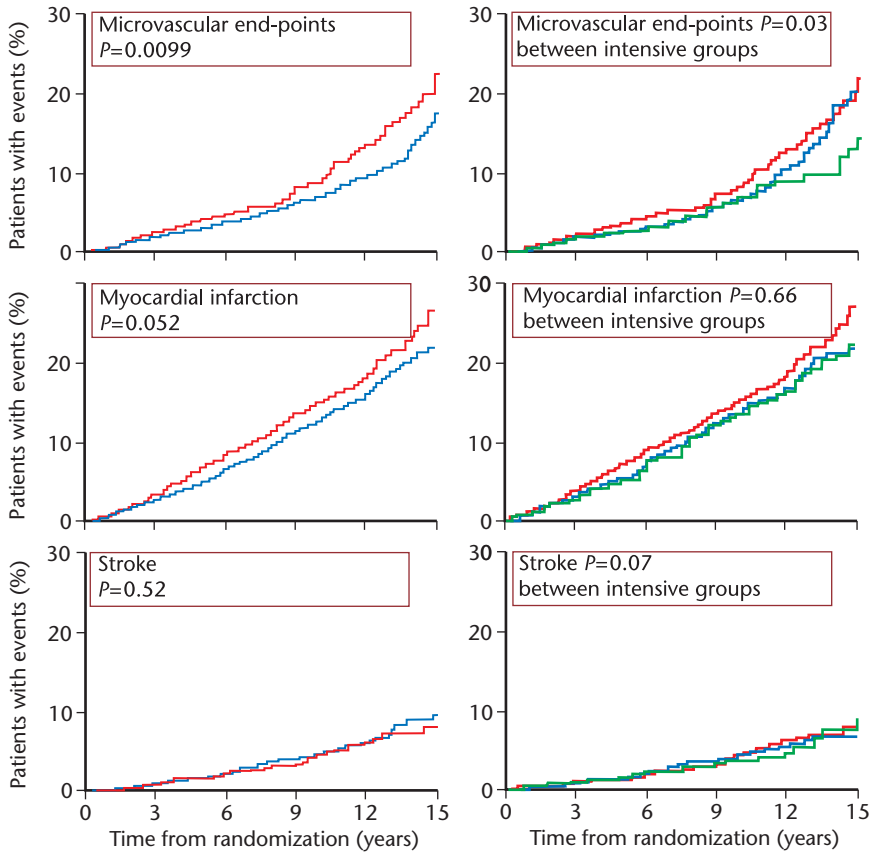

Figure 11.5 Kaplan–Meier plots of aggregate end-points: microvascular disease, myocardial infarction and stroke for intensive and conventional treatment and by individual intensive therapy. Microvascular disease = renal failure, death from renal failure, retinal photocoagulation, or vitreous haemorrhage. Myocardial infarction = non-fatal, fatal, or sudden death. Stroke = non-fatal and fatal. Reprinted with permission [33].

Moreover, diabetes heightens migration of vascular smooth muscle cells into nascent atherosclerotic lesions, where they replicate and produce extracellular matrix —important steps in mature lesion formation [31]. Vascular smooth muscle cell apoptosis in atherosclerotic lesions is also increased, such that patients with diabetes tend to have fewer smooth muscle cells in the lesions, which increases the propensity for plaque rupture [32]. In persons with diabetes, elaboration of cytokines diminishes the vascular smooth muscle synthesis of collagen and increases production of matrix metalloproteinases, yielding an increased tendency for plaque destabilization and rupture.

Given the above-mentioned effects of hyperglycaemia on vascular function, one might speculate that tight glycaemic control warrants preservation from micro- and macrovascular damages and favourably impacts prognosis in diabetic patients. Epidemiological studies support the notion that increasing blood glucose levels proportionally relates to cardiovascular events. Less is known on the effect of a really strict glycaemic control. In the United Kingdom Prospective Diabetes Study (UKPDS) [33] the risk of death, stroke, or amputation did not change while there was a trend towards fewer myocardial infarctions in the most actively treated group. Glycaemic control was, however, rather modest, with a glycated haemoglobin A1c (HbA1c) of 7% in the intervention group and only a small difference of 0.9% between the intervention and the control groups. Still, improved treatment of hyperglycaemia lowered the incidence of diabetic retinopathy and nephropathy (Fig. 11.5). Considering the established close relationship between glucose levels and cardiovascular risk, a strict control of glycaemia is at present highly recommended in diabetic patients. A HbA1c < 6.0% (Diabetes Control and Complications Trial standard), fasting glucose < 6.0 mmol/l (venous plasma, < 110 mg/dl) and postprandial glucose < 10.0 mmol/l (< 180 mg/dl) should be considered as targets for glycaemic control [34]. Risks and benefits of more stringent goals are currently under evaluation.

Insulin resistance

Insulin resistance is a typical characteristic of type 2 diabetes. Insulin stimulates NO production from endothelial cells by increasing the activity of NOS via activation of PI-3K and Akt kinase. Thus, in healthy subjects, insulin increases endothelium-dependent (NO-mediated)

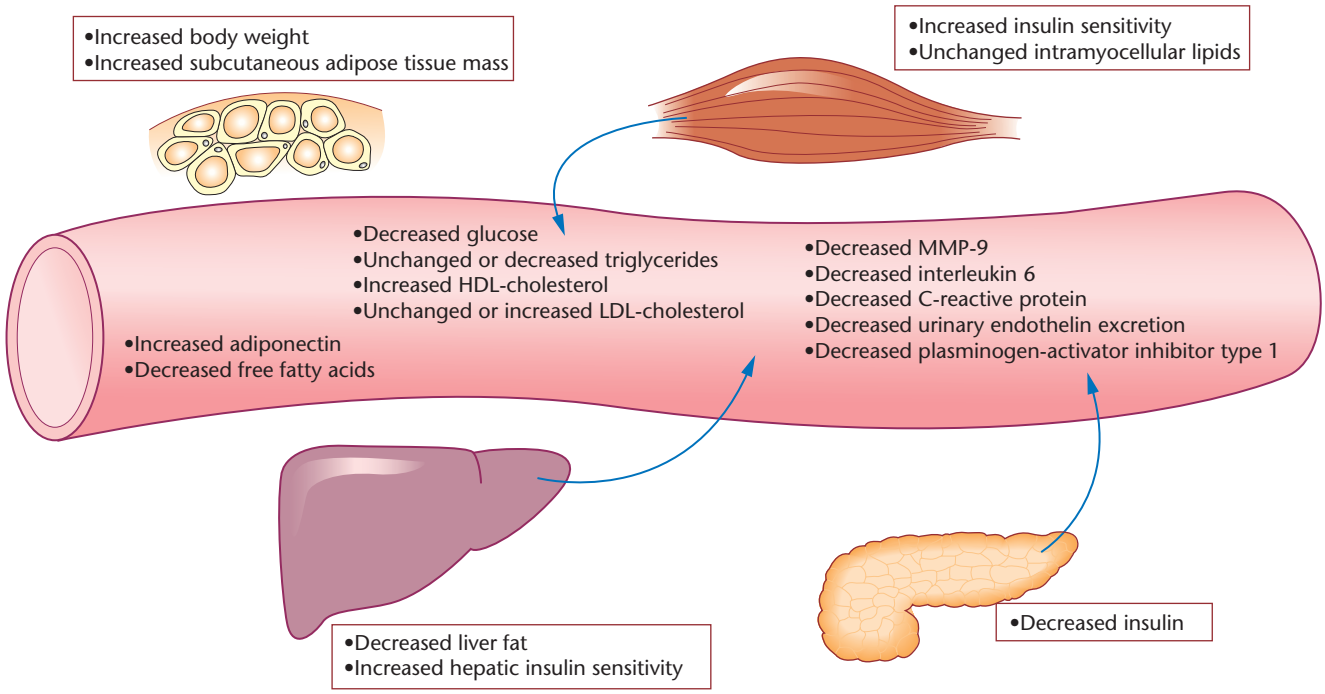

Figure 11.6 Mechanism of action of thiazolidinediones *in vivo* in humans. MMP-9, matrix metalloproteinase-9; HDL, high-density lipoprotein; LDL, low-density lipoprotein. Reproduced with permission [38].

vasodilatation. On the contrary, endothelium-dependent vasodilatation is reduced in insulin-resistant subjects. Furthermore, insulin-mediated glucose disposal correlates inversely with the severity of the impairment in endothelium-dependent vasodilatation. Abnormal endothelium-dependent vasodilatation in insulin-resistant states may be explained by alterations in intracellular signalling that reduce the production of NO. Insulin signal transduction via the PI-3K pathway is impaired and insulin is less able to produce NO. On the other hand, insulin signals via the mitogen-activated protein kinase pathway (MAPK) remain intact. MAPK activation is associated with increased endothelin production and a greater level of inflammation and thrombosis.

Insulin resistance is a distinct trait of diabetes mellitus, and its magnitude directly relates to cardiovascular outcomes [35,36]. In the UKPDS, a likely reason that the biguanide metformin decreased macrovascular events is enhanced insulin sensitivity. However, the addition of metformin to a sulphonylurea increased cardiovascular risk [37].

The recently introduced thiazolidinediones offer another approach to decrease insulin resistance [38] (Fig. 11.6). These compounds activate the peroxisome proliferator-activated receptor-γ (PPAR-γ), a nuclear receptor that takes part in vascular cell and adipose differentiation [39]. They also seem to have an anti-inflammatory property, a feature that may favourably impact the natural history of the atherosclerotic process [40]. Drug therapies that increase insulin sensitivity, such as metformin and the thiazolidinediones, improve endothelium-dependent vasodilatation. At present, and after elimination of troglitazone because of hepatotoxic effects, rosiglitazone and pioglitazone are approved in most countries for the treatment of hyperglycaemia in patients with type 2 diabetes. Whether the hypothetical benefits of these drugs hold true in clinical practice is presently being studied in large clinical trials.

Oxidative stress

Given the pivotal role of oxidative stress in endothelial function and atherosclerotic processes in diabetes, growing efforts focus on the putative effects of antioxidant therapy. Despite evidence indicating the reversal of endothelial dysfunction by different antioxidant agents [41], data from clinical trials are still inconclusive and do not support compelling indications for antioxidant therapy in diabetes mellitus [42,43]. These data would seem to refute a role of oxidative stress in the pathogenesis of atherosclerosis. There are several reasons to believe that this conclusion is not justified but rather that treatment with antioxidative is perhaps not the best approach for reducing oxidative stress. First, the rate of costant for

reactions between vitamin E and superoxide is several orders of magnitude less than the rate of constant for the reaction of superoxide with NO. Second, many of the oxidative events occur in the cytoplasm and in the extracellular space, and would not be affected by lipid-soluble antioxidants, which are concentrated in lipid membranes and lipoproteins. Third, antioxidants may become pro-oxidants after scavenging a radical, vitamins E and C become tocopheroxyl and ascorbyl radicals, respectively. The tocopheroxyl radical can be regenerated by other antioxidants such as vitamin C or co-enzyme Q10. For this reason, the use of cocktails of antioxidants rather than high doses of a selected one may be more effective. Given the above considerations, it is quite possible that use of antioxidant vitamins will never prove to be the best approach to limit vascular oxidant stress. To prevent the development of the earliest stages of diabetic vascular disease, future research should focus on identifying substances which have antioxidant effects not because they scavenge radicals but because they block their production.

Lipid disorders

Classically, diabetes mellitus induces elevation of triglycerides and LDL-cholesterol, and decline of high-density lipoprotein (HDL) plasma levels. These changes clearly affect the natural history of the atherosclerotic disease, and render patients with diabetes more prone to developing CAD, stroke and peripheral vascular disease. Recent evidence confers to diabetes-related enhanced free fatty acid liberation a crucial role in producing the well-described changes in lipid profile. Excess circulating levels of free fatty acids result from both enhanced release from adipose tissue and reduced uptake from skeletal muscle [44]. The liver responds to free fatty acid excess by increasing very-low-density lipoprotein (VLDL) production and cholesteryl ester synthesis [45]. The accumulation of triglyceride-rich lipoproteins, depending also on their reduced clearance by lipoprotein lipase, triggers hypertriglyceridaemia and lowers HDL levels by promoting exchanges from HDL to VLDL via cholesteryl ester transfer protein [45]. HDL are not only reduced in quantity, but also impaired in function. Indeed, HDL from poorly controlled type 2 diabetic patients are less effective in preventing LDL oxidation compared to those from non-diabetic subjects [46]. Moreover, increased VLDL production and abnormal cholesterol and triglyceride transfer between VLDL and LDL enhance the plasma levels of small and dense proatherogenic LDLs [47], which are in addition more prone to oxidation because of impaired antioxidant defence mechanisms in the plasma of diabetics [48]. Since their pro-atherosclerotic effects on coronary, carotid and peripheral arteries, the above-mentioned changes in lipid profile have important clinical consequences, thus representing an important treatment target. Non-pharmacological approaches, including glycaemic control, dietary modifications, weight loss, physical exercise and cessation of smoking [49] represent the first mode of therapy. However, life-style modifications are mostly inadequate and a drug-based therapeutic regimen is mandatory, especially in patients who experience poor glycaemic control. The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (or statins), by increasing LDL clearance and decreasing VLDL secretion, currently represent the cornerstone of lipid-lowering therapy. In the Scandinavian Simvastatin Survival Study [50], simvastatin reduced the risk of total mortality and myocardial infarction by 43% and 55%, respectively, in diabetic patients, compared to 29% and 32% in non-diabetic patients. Accordingly, the Cholesterol and Recurrent Events (CARE) trial [51] demonstrated a 24% reduction in cardiovascular events in diabetic patients with CAD and elevated or average LDL-cholesterol with statins. In the Heart Protection Study (HPS) [43], which enrolled 3000 diabetic subjects without evidence of atherosclerosis at entry, simvastatin reduced the combined end-point of acute coronary syndrome, stroke or revascularization by 34% over a 5-year follow-up period in the diabetic subgroup. The primary preventive Collaborative Atorvastatin Diabetes Study (CARDS) [52] assessed atorvastatin for primary prevention of major cardiovascular events in patients with type 2 diabetes and LDL-cholesterol below 4.14 mmol/l. In this study, 2838 patients without a history of cardiovascular disease were randomized to placebo or 10 mg of atorvastatin daily if they had at least one further risk factor (retinopathy, albuminuria, current smoking, or hypertension). The trial was terminated after a median duration of follow-up of 3.9 years because of the beneficial effects of atorvastatin. Acute coronary heart disease events were reduced by 36%, coronary revascularizations by 31% and stroke by 48%. Moreover, atorvastatin reduced the death rate by 27%, which was borderline significant.

As a result of its ability to increase HDL and decrease triglyceride levels without affecting glucose control, niacin would be an ideal drug in dyslipidaemic diabetic patients [53]. However, the effect on cardiovascular outcomes is still unproven in diabetics. This and well-known side-effects [54] still make niacin a second-line agent.

Fibric acid derivatives, as PPAR-α agonists, also raise HDL and lower triglyceride levels. The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) [55] showed a 24% risk reduction in death from

CAD, non-fatal myocardial infarction and stroke in diabetic patients with normal LDL and low HDL levels treated with gemfibrozil. As a result of the potential risk of myositis [56] the joint use of fibric acid derivatives and statins requires careful monitoring and should be considered only in selected patients.

Hypertension

Hypertension is a common comorbidity of diabetes. Indeed, high blood pressure is more common in patients with type 2 diabetes than in matched controls [57]. While in type 1 diabetes hypertension is often the result of underlying nephropathy, the association of type 2 diabetes and high blood pressure is a typical feature of the metabolic syndrome. In 1998, UKPDS [58] first documented the benefits of tight blood pressure control in diabetic patients. Both atenolol and captopril decreased the risk of stroke and death with comparable magnitude [59]. Of note, the majority of enrolled subjects required two or three drugs to control blood pressure at follow-up.

According to the European Society of Cardiology guidelines on cardiovascular disease prevention, a target blood pressure < 135/80 mmHg is the goal in diabetic hypertensive patients [34]. Although diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and calcium-channel blockers are all effective in lowering blood pressure in diabetics (Table 11.2), the modern approach in diabetic patients starts with modulation of the renin–angiotensin system (Fig. 11.7). Modulation of the renin–angiotensin system by ACE inhibitors, and more recently by ARBs, seems to exert vascular protective effects beyond blood pressure control, and to limit target organ damage [60–63]. In the HOPE trial, ramipril significantly reduced death, myocardial infarction and stroke in more than 3000 high-risk non-hypertensive diabetic patients [64]. Interestingly, ramipril treatment was also associated with a 34% reduction in new-onset diabetes [65]. More recently, the LIFE study showed that losartan was superior to atenolol in reducing the combined end-point of cardiovascular death, stroke, or myocardial infarction and total mortality in a large subgroup of hypertensive diabetic patients [66,67]. Of note, because the blood pressure-lowering of the two drugs was equivalent, the reported effect seems to be largely independent of blood pressure lowering. Such benefits support the front-line use of ACE inhibitors and ARBs in high-risk diabetic patients, probably regardless of whether they are hypertensive. A further reason to stress the key role of renin–angiotensin system modulation in diabetic hypertensive patients is the well-demonstrated ability of ACE inhibitors and ARBs to slow the deterioration of renal function and rate of progression to end-stage renal disease [60,62]. The putative added value of combining an ACE inhibitor with an ARB in diabetic patients is still under evaluation [68].

From a practical perspective, prehypertensive (systolic blood pressure of 130–140 mmHg or diastolic blood pressure of 80–90 mmHg) diabetic patients may benefit from life-style and behavioural therapy for a maximum

Table 11.2 Relationship between blood pressure lowering and risk of cardiovascular disease in patients with diabetes

Trial	No. of patients	Duration (years)	Blood pressure control		Initial therapy	Outcome	Risk reduction (%)
			Less tight	Tight			
SHEP, 1996	583	5	155/72*	143/68*	Chlorthalidone	Stroke CVD events CHD	NS 34 56
Syst-Eur, 1999	492	2	162/82	153/78	Nitrendipine	Stroke CV events	69 62
HOT, 1998	1501	3	144/85*	140/81*	Felodipine	CV events MI Stroke CV mortality	51 50 NS 67
UKPDS, 1999	1148	8.4	154/87	144/82	Captopril or atenolol	Diabetes-related end-points Deaths Strokes Microvascular end-points	34 37 44 37

Table 11.2 (*cont'd*)

Trial	No. of patients	Duration (years)	Blood pressure control		Initial therapy	Outcome	Risk reduction (%)
			Less tight	Tight			
HOPE, Micro-HOPE, 2000	3577	4.5	Changes in SBP 2.4 mmHg DBP 1.0 mmHg	–	Ramipril vs. placebo	CV events CV mortality MI Stroke Total mortality New-onset diabetes	25 37 22 33 24 34
CAPP, 2001	572	7	155/89 vs. 153/88	–	Captopril vs. diuretics or beta-blockers	Fatal + NFMI + stroke + CVD deaths	41
IDNT, 2001	1715	2.6	≤ 135/85 144/83	–	Irbesartan vs. amlodipine (am.) placebo (pl.)	Doubling of serum creatinine + end-stage renal disease + death from any cause	23 vs. am. 20 vs. pl.
IRMA, 2001	590	2	143/83 141/83	–	Irbesartan 150 or 300 mg vs. placebo	Onset of diabetic nephropathy	35 (150 mg) 65 (300 mg)
RENAAL, 2001	1513	3.4	152/82 vs. 153/82	–	Losartan vs. placebo in addition to conventional therapy	Doubling of serine serum creatinine End-stage renal disease Death CV events	25 28 NS 22
LIFE, 2002	1195	4.8	146/79 vs. 148/79	–	Losartan vs. atenolol	Total mortality in diabetics New-onset diabetes	39 25
INSIGHT, 2003	6321	4	145/82 144/82	–	Nifedipine 30 mg or hydrochlor-thiazide 25 mg + amiloride 2.5 mg	CV death + MI + heart failure + stroke Composite of primary end-point including all-cause mortality and death from vascular and non-vascular causes	NS 24 (Nif.)
VALUE, 2004	15 245	4	139/79 vs. 137/78	–	Valsartan vs. amlodipine	Cardiac deaths + morbidity	NS

SHEP, Systolic Hypertension in the Elderly Program; Syst-Eur, Systolic hypertension in Europe; HOT, Hypertension Optimal Treatment; CAPP, CAptopril Prevention Project; IDNT, Irbesartan Diabetic Nephropathy Trial; IRMA, IRbesartan MicroAlbuminuria in type 2 diabetes; RENAAL, Reduction in End-points in NIDDM with Angiotensin II antagonist Losartan; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVD, cardiovascular disease; CHD, coronary heart disease; CV, cardiovascular; MI, myocardial infarction; NFMI, non-fatal MI; NS, not significant.
*Blood pressure in diabetic and non-diabetic population because blood pressure was not reported for diabetic patients alone.
Data derived from [194] and modified from [195].

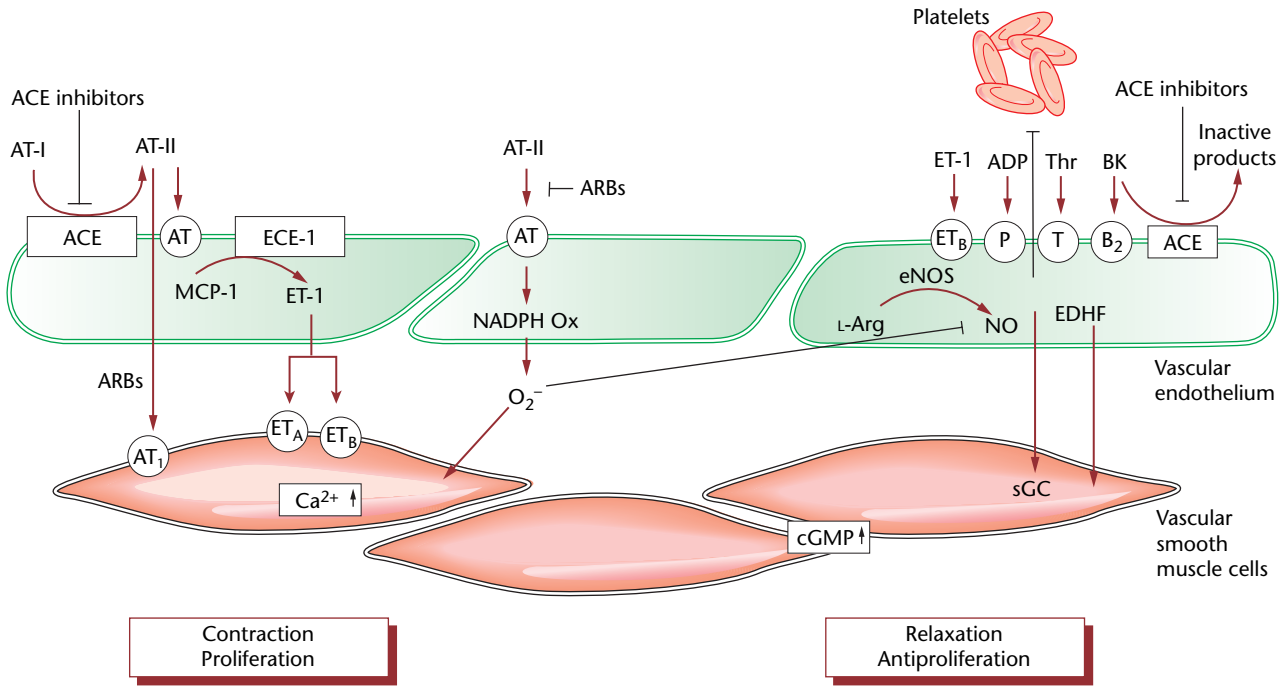

Figure 11.7 Effects of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) on endothelium-derived vasoactive substances. AT-I, angiotensin-I; AT-II, angiotensin-II; ECE-1, endothelin-converting enzyme-1; bET-1, big endothelin-1; ET-1, endothelin-1; ET_A and ET_B, endothelin receptor subtypes; AT_1, angiotensin receptor-1; Thr, thrombin; BK, bradykinin; L-Arg, L-arginine; eNOS, endothelial nitric oxide synthase; EDHF, endothelium-derived hyperpolarizing factor; sGc, soluble guanylate cyclase; cGMP, cyclic guanosine monophosphate.

of 3 months. If target blood pressure < 135/80 mmHg is not achieved, a pharmacological intervention with a regimen that includes either an ACE inhibitor or an ARB should be established. Careful monitoring of potassium serum levels is necessary in diabetics treated with ACE-inhibitors, particularly in those with moderate-to-severe impairment of glomerular filtration rate.

Thrombosis and coagulation

Platelet function is crucial in determining the natural history of atherosclerosis and the consequences of plaque rupture. It is therefore not surprising that cardiovascular risk is closely linked to platelet function abnormalities and coagulation disorders in the diabetic patient. The intracellular platelet glucose concentration mirrors the extracellular environment and is associated with increased superoxide anion formation, PKC activity and decreased platelet-derived NO [69,70]. Moreover, diabetic patients show increased expression of glycoprotein Ib and IIb/IIIa, which enhances both platelet–von Willebrand factor and platelet–fibrin interactions [69] (Fig. 11.8). Hyperglycaemia further affects platelet function by impairing calcium homeostasis [71] and thereby altering platelet conformation, secretion and aggregation, and thromboxane formation. Further abnormalities affecting platelet function include impaired endothelial production of nitric oxide and prostacyclin, and increased production of fibrinogen, thrombin and von Willebrand factor [69].

Moreover, blood coagulability is enhanced in diabetic patients. Indeed, plasma coagulation factors (e.g. factor VII and thrombin), lesion-based coagulants (e.g. tissue factor) and atherosclerotic lesion content of plasminogen activator inhibitor-1 (a fibrinolysis inhibitor) are increased, and endogenous anticoagulants (e.g. thrombomodulin and protein C) are decreased [72–76]. Thus, a propensity for platelet activation and aggregation, coupled with a tendency for coagulation, amplify the risk that plaque rupture results in thrombotic occlusion of arteries (Fig. 11.8).

Results from several trials have consistently demonstrated that increased propensity for platelet aggregation in diabetics strongly relates to cardiovascular outcomes. The Antiplatelet Trialists' Collaboration analysed the results of 195 trials of > 135 000 patients at high risk of arterial disease and found that platelet antagonists lowered the risk of stroke, myocardial infarction and vascular death [77] (Fig. 11.9). In the Early Treatment of Diabetic Retinopathy Study (ETDRS), aspirin reduced the risk of myocardial infarction in patients with type 1 or

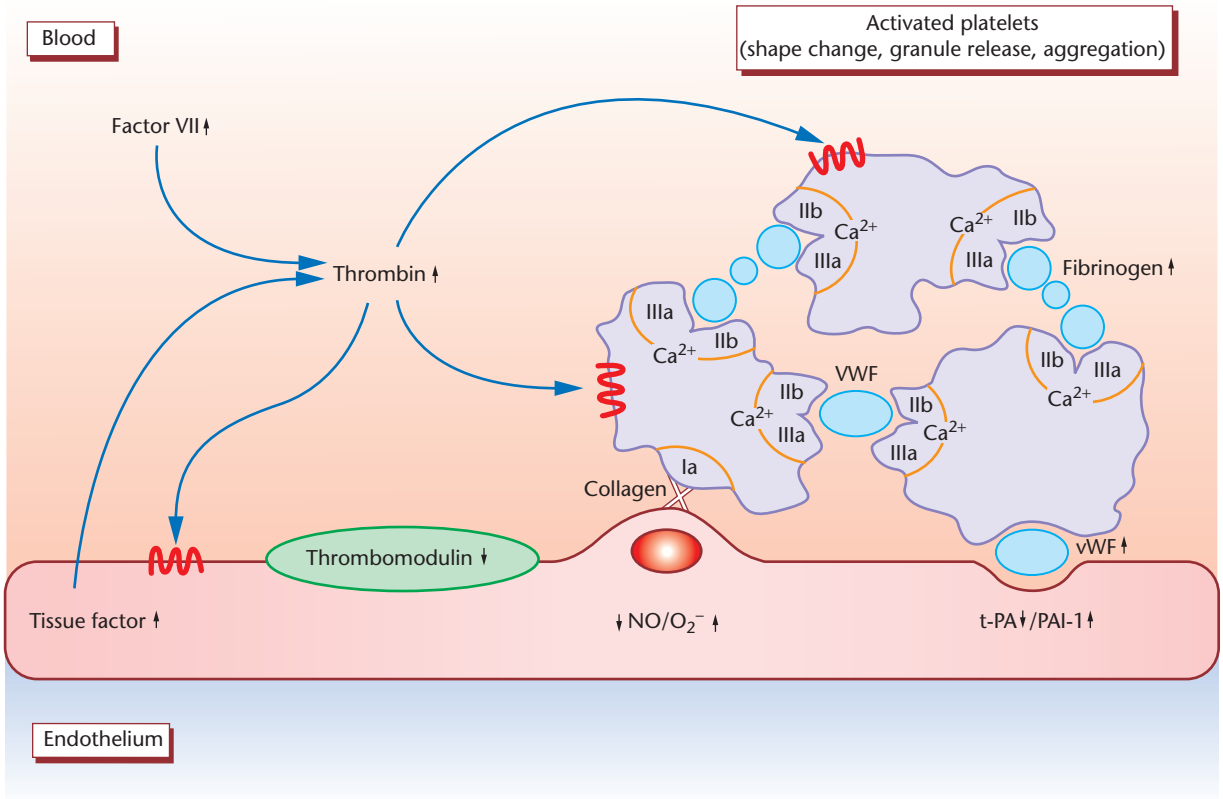

Figure 11.8 Platelet function and plasma coagulation factors are altered in diabetes, favouring platelet aggregation and a propensity for thrombosis. There is increased expression of glycoprotein Ib and IIb/IIIa, augmenting both platelet–von Willebrand factor (vWF) and platelet–fibrin interaction. The bioavailability of NO is decreased. Coagulation factors, such as tissue factor, factor VII and thrombin, are increased; plasminogen activator inhibitor (PAI-1) is increased; and endogenous anticoagulants such as thrombomodulin are decreased. t-PA, tissue plasminogen activator. Reproduced with permission from [193].

Category of trial	No. of trials with data	Allocated antiplatelet	Adjusted control	Observed expected	Variance	Odds ratios (CI) Antiplatelet–control	% Odds reduction (SE)
Previous myocardial infarction	12	1345/9984 (13.5)	1708/10 022 (17.0)	–159.8	567.6		25 (4)
Acute myocardial infarction	15	1007/9658 (10.4)	1370/9644 (14.2)	–181.5	519.2		30 (4)
Previous stroke/transient ischaemic attack	21	2045/11 493 (17.8)	2464/11 527 (21.4)	–152.1	625.8		22 (4)
Acute stroke	7	1670/20 418 (8.2)	1858/20 403 (9.1)	–94.6	795.3		11 (3)
Other high risk	140	1638/20 359 (8.0)	2102/20 543 (10.2)	–222.3	737.0		26 (3)
Subtotal: all except acute stroke	188	6035/51 494 (11.7)	7644/51 736 (14.8)	–715.7	2449.6		25 (2)
All trials	**195**	**7705/71912 (10.7)**	**9502/72 139 (13.2)**	**–810.3**	**3244.9**		**22 (2)**

Figure 11.9 Effects of antithrombotic therapy in myocardial infarction, stroke and vascular death in the Antithrombotic Trialists' Collaboration. Reproduced with permission [77].

type 2 diabetes without increasing the risk of vitreous or retinal bleeding, even in patients with retinopathy [78]. In acute coronary syndromes, platelet antagonists seem to be particularly effective in diabetics. The PRISM-PLUS study showed that addition of tirofiban (a platelet glycoprotein IIb/IIIa antagonist) to heparin decreased the risk of death and myocardial infarction particularly in diabetics [79]. A meta-analysis of six large-scale trials of intravenous glycoprotein IIb/IIIa inhibitors in the management of acute coronary syndromes in diabetics showed that these agents reduce mortality by 25% at 30 days in diabetic patients [80]. In the Clopidogrel in Unstable Angina to Prevent Recurrent Ischaemic Events (CURE) study the addition of clopidogrel to aspirin led to a reduction in death, myocardial infarction, or stroke in patients with unstable angina/non-ST-segment-elevation myocardial infarction (NSTEMI), irrespective of their diabetes status [81]. In addition, specific and amplified benefits of clopidogrel treatment have been reported in diabetics [82].

Given the above reported evidence, it is appropriate to recommend the use of aspirin both as a secondary prevention strategy in diabetics already affected by myocardial infarction, cerebrovascular disease or peripheral artery disease, and as a primary prevention strategy in diabetics who have additional risk factors for cardiovascular disease.

Clinical presentation and management of cardiovascular disease

Coronary artery disease

The short- and long-term prognosis in patients with diabetes presenting with acute coronary syndrome (ACS) has been evaluated in several randomized clinical trials. The first Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial (GUSTO I) enrolled 41 021 patients presenting with STEMI, including insulin-treated and non-insulin-treated patients with diabetes [8]. The 30-day mortality rate was significantly higher for diabetic than non-diabetic patients. A meta-analysis was also performed with data from six large-scale trials enrolling patients without and with diabetes hospitalized for NSTEMI and/or unstable angina [80]. The 30-day mortality rate was found to be significantly higher in the diabetic subgroup. In the Organization to Assess Strategies for Ischaemic Syndromes (OASIS) registry, a six-nation NSTEMI/unstable angina outcome study, diabetes increased mortality by 57% [9]. The recently published Euro Heart Survey on diabetes and the heart [83] studied the prevalence of abnormal glucose regulation in adults with CAD. The survey involved 110 centres in 25 countries recruiting 4196 patients with CAD. An OGTT was used for the characterization of glucose metabolism. In patients with acute CAD, 36% had impaired glucose regulation and 22% had newly detected diabetes. In patients with stable CAD these proportions were 37% and 14%, respectively. The survey showed that normal glucose regulation is indeed less common than abnormal glucose regulation in CAD patients. Based on these studies, an aggressive treatment strategy with maximization of life-saving therapies is crucial for patients with diabetes and CAD. The importance of this is underlined by recently published follow-up data from the Glucose Abnormalities in patients with Myocardial Infarction (GAMI) study. This study demonstrated that abnormal glucose regulation detected a few days after an acute myocardial infarction is an independent predictor of a dismal prognosis [84].

Glycaemic control

The Diabetes and Insulin–Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study [85] demonstrated that tight glycaemic control can further improve outcomes in diabetic individuals after acute myocardial infarction. Of 620 diabetic patients with acute myocardial infarction, 306 were randomly assigned to a ≥ 24-hour insulin–glucose infusion followed by multidose subcutaneous insulin. Three hundred and fourteen patients were randomized as controls, receiving routine glucose-lowering therapy. During an average follow-up of 3.4 years, 33% of patients in the intensive insulin group and 44% in the control group died ($P = 0.011$). Metabolic control, mirrored by blood glucose and HbA1c, improved significantly more in patients on intensive insulin treatment than in the control group. Therefore, intensive insulin treatment reduced long-term mortality in addition to standard therapy with aspirin, ACE inhibitors, and beta-blockers. While the intensive-treatment group had a lower mortality than the usual-care group, it was unclear whether the benefit was the result of the initial insulin–glucose infusion or the chronic insulin therapy.

The second DIGAMI trial [86] compared the following three management protocols: acute insulin–glucose infusion followed by insulin-based long-term glucose control; insulin–glucose infusion followed by standard glucose control; and routine metabolic management according to local practice, in 1253 patients with type 2 diabetes and suspected acute myocardial infarction. The DIGAMI 2 trial did not show that an acutely introduced,

long-term intensive insulin treatment strategy improves survival in type 2 diabetic patients following myocardial infarction and did not demonstrate that initiating treatment with an insulin–glucose infusion is superior to conventional management. However, the overall mortality in DIGAMI 2 was lower than expected, probably because of the very aggressive use of evidence-based treatment, including revascularization. Moreover, glucose control was better than in DIGAMI 1 at the onset and continuation of DIGAMI 2 and the three glucose management strategies did not result in significantly different metabolic control. Indeed, target glucose levels were not reached in the intensive insulin group. The DIGAMI 2 trial did, however, clearly confirm that glucose level is a strong, independent predictor of long-term mortality following myocardial infarction in patients with type 2 diabetes.

Taking these studies together, it is reasonable to initiate glucose control by means of insulin infusions, at least in patients with high blood glucose levels on admission. Furthermore, continued strict glucose control is mandatory, but the therapeutic regimen to accomplish this goal may be oral agents or insulin. Yet there is no definite answer to which is the best choice, so today this decision is based on practical reasons from patients and physicians but most importantly on the effect of the long-term glucose levels.

Revascularization strategies

Over the last 25 years, percutaneous coronary intervention (PCI) has evolved considerably from its early use in patients with focal lesions in the proximal coronary vessels to its application in more complex lesions and in patients with multivessel disease. In the National Heart, Lung and Blood Institute PTCA registry [87], patients with diabetes had a greater incidence of three-vessel disease and more diffuse disease in both proximal and distal coronary artery segments when compared with patients without diabetes. In the Fast Revascularization during Instability in Coronary Artery Disease (FRISC-II) trial it did, however, seem as if the presence of diabetes in itself, rather than a diffuse or multivessel disease, was related to an unfavourable prognosis as regards new coronary events or mortality [88].

Randomized controlled trials comparing PCI with coronary artery bypass grafts (CABG) [89,90] have not revealed any difference in terms of mortality between the two revascularization strategies within non-diabetic populations. In contrast, data from randomized trials and non-randomized studies suggest that diabetics have a higher mortality with PCI than with CABG. The Bypass Angioplasty Revascularization Investigation (BARI) [89] is the largest of the randomized trials. BARI enrolled 1829 patients with multivessel disease of whom 19.5% were medically treated diabetic patients. In patients without diabetes the cumulative survival was virtually identical for CABG and PCI. Patients with diabetes did, however, have a clinically and statistically significant survival advantage after CABG compared with PCI. The 7-year survival rate was 76% for diabetic patients assigned to CABG and 56% for those assigned to PCI. Moreover there was a significantly higher need for repeated revascularization among diabetic PCI-treated patients than in the group without diabetes (Fig. 11.10). Following CABG the survival rate was better in diabetic patients who received an internal mammary artery graft than those given saphenous vein grafts only.

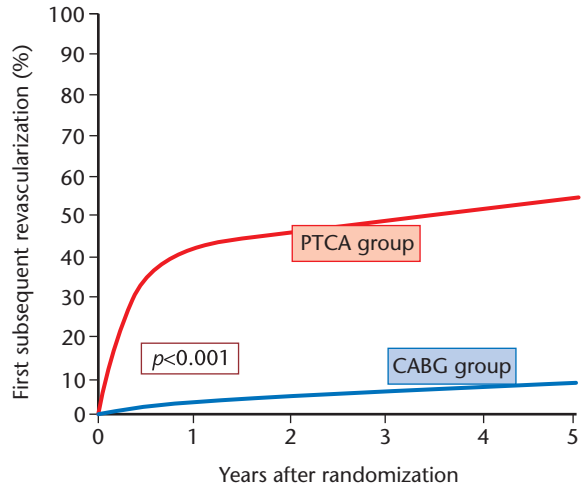

Figure 11.10 In the BARI trial, percutaneous transluminal coronary angioplasty (PTCA) patients had significantly higher need for repeated revascularization than did CABG patients. CABG, coronary artery bypass graft. Reproduced with permission from [89].

In the Emory Angioplasty versus Surgery Trial (EAST) [91], 392 patients with multivessel CAD were randomized to PCI or CABG. The survival rates were nearly identical after 3 years and the long-term survival at 8 years was not significantly different between the PCI and the surgical groups (79.3% vs. 82.7%, $P = 0.40$).

Revascularization of diabetic patients in the setting of acute coronary syndromes has been evaluated in a subgroup analysis of the FRISC-II trial. This revealed that early revascularization, either by CABG or PCI, was at least as effective among diabetic as in non-diabetic patients, with an almost 40% reduction of the combined endpoint re-infarction and mortality during the first year of follow-up. Since the risk for events was higher in the diabetic subgroup, fewer diabetic than non-diabetic patients needed to be treated to save one event (11 vs. 32).

A management strategy based on early coronary angiography and, if possible, an early coronary intervention is therefore recommended for diabetic patients [88].

Diabetes restenosis and coronary stenting

Coronary stenting has become the predominant method of PCI. Currently, up to 80% of interventions are accomplished with stent placement. Better angiographic results and prevention of adverse coronary remodelling despite the increase in neo-intimal hyperplasia justify the expectation of better outcome in diabetic patients; however, there are conflicting reports to date.

Short-term angiographic success rates of stenting in diabetics (92–100%) are often similar to those observed in non-diabetic patients [92]. The composite end-point of mortality, non-fatal myocardial infarction and urgent CABG is similar in diabetic and non-diabetic patients in most series. These in-hospital complications after stent implantation compare favourably with the rates reported after balloon PCI in diabetics. However, a clear trend toward higher rates of subacute stent thrombosis was found in diabetics. It was also reported that insulin-treated diabetics were at higher risk for in-hospital mortality when compared with non-insulin treated type 2 diabetics and non-diabetics.

Turning to long-term results, Van Belle *et al*. [93] found a lower angiographic restenosis rate in diabetic patients treated with coronary stents compared with those treated with balloon angioplasty and restenosis rates were similar in diabetics and non-diabetics treated with stents. Event-free survival is, however, often lower in diabetics. As reported by Elezi *et al*. [94], diabetics have a less favourable clinical outcome and a lower event-free survival than non-diabetic patients even after successful stent placement. The incidence of both restenosis and stent-vessel occlusion was significantly higher in diabetic patients. Diabetes was identified as an independent risk factor for adverse clinical events and restenosis in multivariate analysis. A subgroup analysis of the Arterial Revascularization Therapy Study (ARTS) trial [95], including 112 diabetic patients, revealed that surgical revascularization with routine use of arterial bypass conduits provides a superior 1-year clinical outcome compared with PCI in patients with diabetes and multivessel CAD even when a strategy of stented angioplasty is applied. Diabetic patients treated with stenting had the lowest event-free survival rate (63.4%) because of the higher demand of repeated revascularization compared with diabetic patients treated with CABG (84.4%, $P < 0.001$) and non-diabetic patients treated with stents (76.2%, $P < 0.04$) (Fig. 11.11).

Thus, long-term outcome after PCI is hampered in the diabetic population even after stenting, mainly because restenosis remains a major limitation. Several studies did indeed reveal that diabetes is an independent risk factor for in-stent restenosis after balloon angioplasty, ranging from 35% to 71% [96]. Coronary stenting with bare metal stents reduces this risk, but restenosis remains more frequent in diabetics with a restenosis rate of 24–40% [93]. Tight glycaemic control, aggressive risk factor modification, and the use of glycoprotein IIb/IIIa inhibitors have been attempted to improve the outcome of coronary stenting in diabetics, with some success. Different percutaneous interventions have been used to treat in-stent restenosis, including balloon angioplasty, repeat stenting, rotational or directional atherectomy, and intracoronary radiation (brachytherapy).

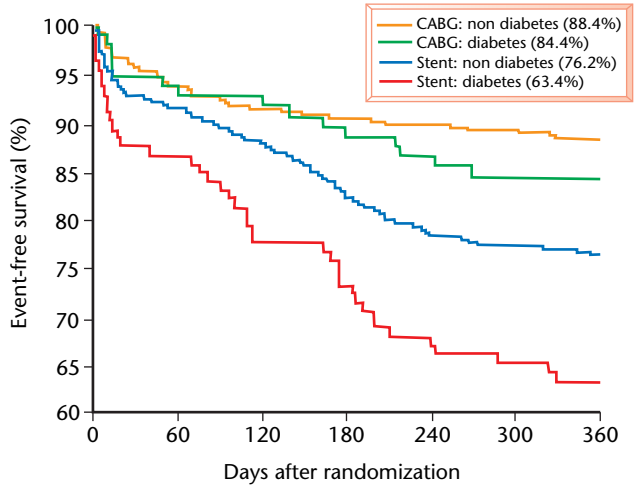

Figure 11.11 In the ARTS Trial, diabetic patients treated with stenting had the lowest event-free survival rate (63.4%) because of a higher incidence of repeat revascularization compared with both diabetic patients treated with coronary artery bypass grafts (CABG) (84.4%, $P < 0.001$) and non-diabetic patients treated with stents (76.2%, $P < 0.04$). Reproduced with permission from [95].

Stents coated with biodegradable and non-biodegradable polymers for local delivery of pharmacological agents have been proposed as a method to reduce in-stent restenosis. Sirolimus (rapamycin), a cytostatic macrocyclic lactone with both anti-inflammatory and antiproliferative properties, reduces restenosis significantly in several prospective, multicentre, randomized trials [97,98]. However, among patients receiving sirolimus-eluting stents, there remains a trend toward a higher frequency of repeat intervention in diabetic patients compared with non-diabetic patients, particularly in the insulin-requiring group. A recent meta-analysis comparing drug-eluting stents to bare metal stents in diabetic subpopulations in several clinical trials revealed that drug-eluting stents

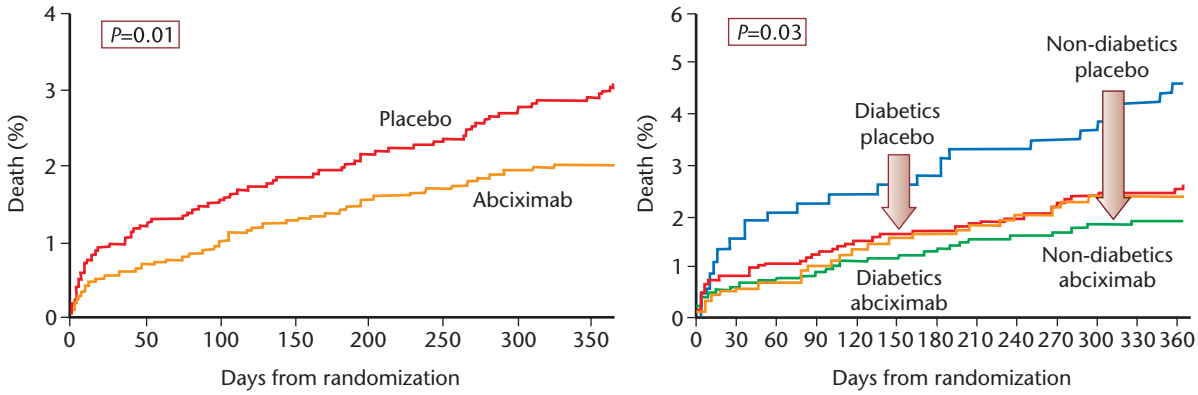

Figure 11.12 Pooled data from the EPIC, EPILOG and EPISTENT trials showed that abciximab decreases the 1-year mortality of diabetic patients to that of placebo-treated non-diabetic patients. Reprinted from [104], with permission from American College of Cardiology Foundation.

were associated with an 80% relative risk reduction for restenosis during the first year of follow-up [99]. Future clinical trials comparing drug-eluting stents with coronary arterial bypass surgery are certainly needed to determine the optimal revascularization strategy in diabetic patients with multivessel disease.

Diabetes and glycoprotein IIb/IIIa inhibitors

Potent platelet inhibition by glycoprotein IIb/IIIa inhibitors has been demonstrated to improve outcomes after PCI. There is evidence to suggest that glycoprotein IIb/IIIa receptor blockade has an even greater effect in diabetics with less need for repeat intervention among stented patients [100]. Abciximab, tirofiban and eptifibatide achieved similar levels of inhibition of platelet aggregation and similar reduction in the platelet–monocyte interaction in patients undergoing coronary stenting. Their effects in patients undergoing PCI have been reported in numerous trials.

The EPISTENT trial was the largest study evaluating the benefit of abciximab therapy in patients undergoing coronary stenting [100]. It demonstrated a significant reduction of major cardiac events at 30 days and at 6 months in the abciximab groups compared with the stent-plus-placebo group. In addition, the combination of stenting and abciximab therapy among diabetic patients resulted in a significant reduction in 6-month rates of death, myocardial infarction and target vessel revascularization compared with stent plus placebo or balloon angioplasty plus abciximab therapy. Abciximab has not been consistently shown to reduce angiographic restenosis in prior balloon angioplasty studies. In the EPIC trial, abciximab therapy showed a 35% reduction in the primary end-point of death, myocardial infarction and urgent revascularization at 1 month, with a similar risk reduction in diabetic and non-diabetic patients [101]. At 3 years, however, the clinical benefits were sustained in the total population [102], whereas diabetics experienced a progressive deterioration with more clinical events than non-diabetics. In the EPILOG trial, abciximab therapy in diabetic patients undergoing elective PCI led to a significant reduction of death and myocardial infarction at 30 days and at 6 months [103]. However, target vessel revascularization at 6 months was reduced only in the non-diabetic subgroup, and diabetics treated with abciximab and standard-dose heparin had a marginally greater benefit than those assigned to abciximab and low-dose heparin.

Pooled data from the EPIC, EPILOG and EPISTENT trials [104], including 1462 diabetic patients, showed that abciximab decreases the 1-year mortality of diabetic patients to that of placebo-treated non-diabetic patients (Fig. 11.12). In the PRISM-PLUS Study, a comparison of treatment outcomes in the diabetic subgroup revealed that the combination therapy (tirofiban and heparin) compared with heparin alone was associated with reductions in the incidence of cardiac adverse events, but these results did not reach statistical significance [105]. Furthermore, there is increasing evidence that glycoprotein IIb/IIIa inhibitors are of particular value in the diabetic patients with non-ST-elevation acute coronary syndromes during PCI [80].

Cerebrovascular disease

Diabetes increases the risk of stroke [106]. As an example, the risk of stroke among patients taking hypoglycaemic medications was increased three-fold among the nearly 350 000 men in the Multiple Risk Factor Intervention

Trial [107]. In the Baltimore-Washington Cooperative Young Stroke Study, stroke risk increased more than 10-fold in diabetic patients younger than 44 years, ranging as high as 23-fold in young Caucasian men [108]. Diabetes also increases stroke-related mortality and doubles the rate of recurrent stroke [109,110].

Diabetic patients with cerebrovascular atherosclerosis should receive platelet antagonists, statins and ACE inhibitors. A strategy of surgical revascularization combined with medical therapy for asymptomatic and symptomatic patients with haemodynamically significant internal carotid artery atherosclerosis resulted in fewer strokes than medical therapy alone [111,112]. Diabetic subjects represented 23% of the total population in the Asymptomatic Carotid Atherosclerosis Study (ACAS) [111] and 19% in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [112]. Consequently, they should be managed in accordance with non-diabetic patients with carotid artery disease. Cardiovascular mortality following carotid endarterectomy is increased in diabetic patients after both 30 days and 1 year because of an increased rate of coronary events [113,114]. The rates of perioperative major and minor stroke, however, do not differ between diabetic and non-diabetic patients [115] even if the need for hospitalization was somewhat longer. Thus, despite a lack of direct outcome data in diabetic patients, evidence suggests that the use of stenting for the treatment of carotid artery atherosclerosis is as rational in patients with diabetes as in those without diabetes [116].

Peripheral arterial disease

Diabetes increases the incidence and severity of limb ischaemia approximately two- to fourfold [117]. Data from the Framingham cohort and Rotterdam studies show increased rates of absent pedal pulses, femoral bruits, and diminished ankle–brachial indices [118]. Diabetic peripheral arterial disease often affects the distal limb vessels, such as the tibial and peroneal arteries, limiting the potential for collateral vessel development and reducing options for revascularization [119]. As such, patients with diabetes are at a particularly high risk to develop symptomatic forms of peripheral artery disease, such as intermittent claudication and critical limb ischaemia, and to undergo amputation. In the Framingham cohort, the presence of diabetes increased intermittent claudication more than threefold in men and more than eightfold in women. Diabetic persons have a particular propensity to develop foot ulcers with male sex, hyperglycaemia and diabetes duration as important risk factors. Foot ulcers often result from severe macrovascular disease, and diabetic neuropathy exacerbates the risk [120,121]. Once ulceration occurs, patients with diabetes have a much higher risk of amputation, highlighting the importance of prevention. Two non-invasive therapies have demonstrated benefit in improving walking distance in patients with peripheral artery disease: exercise and cilostazol [122,123]. Supervised exercise therapy produces impressive increases in walking distance. Patients with progressively disabling claudication and those with critical limb ischaemia should be considered for revascularization. Decisions regarding endovascular or open surgical procedures depend in large part on the severity and distribution of the arterial lesions. Outcomes of iliac artery percutaneous transluminal angioplasty and stenting in patients with diabetes have been reported as being similar to or worse than those in non-diabetic patients [124] and the long-term patency rates after femoral-popliteal percutaneous transluminal angioplasty are less in diabetic than non-diabetic patients [125]. The long-term patency rates of tibio-peroneal artery percutaneous transluminal angioplasty are low in both diabetic and non-diabetic patients, but may be sufficient in the short term to facilitate healing of foot ulcers. Graft patency rates are similar in diabetic and non-diabetic patients following surgical revascularization. Still there is a greater rate of limb loss in diabetic patients with critical limb ischaemia as a result of persistent foot infection and necrosis [126]. Moreover, the risk of perioperative cardiovascular events is increased in patients with diabetes [127].

Selected issues

Cardiac autonomic neuropathy and silent myocardial ischaemia

Autonomic neuropathy is a serious and common complication of diabetes. It has been estimated that about 20% of asymptomatic diabetic patients have abnormal cardiovascular autonomic function [128,129]. The risk for cardiovascular autonomic neuropathy depends on the duration of diabetes and the degree of glycaemic control. It is caused by injury to the autonomic nerve fibres that innervate the heart and blood vessels. The hypotheses concerning its aetiology include metabolic insult to nerve fibres, neurovascular insufficiency, neurohormonal growth factor deficiency and autoimmune damage [130]. The main consequences are dysfunctional heart rate control, abnormal vascular dynamics and cardiac denervation, which become clinically overt as exercise intolerance [131], orthostatic hypotension [132],

intraoperative cardiovascular lability [133] and silent myocardial ischaemia.

The earliest sign is often a vagal deficiency leaving sympathetic innervation unopposed. A manifestation of this is that diabetic patients tend to have higher resting heart rate and less heart rate variability during the day than their non-diabetic counterparts. A clinical setting where this may be particularly unfavourable is at the onset of a myocardial infarction causing unnecessary myocardial oxygen consumption in a situation with decreased nutritional blood supply.

The autonomic nervous system influences coronary blood flow regulation independently of endothelial cell function. Diabetic patients with sympathetic nervous system dysfunction have impaired dilatation of coronary resistance vessels in response to cold pressure testing when compared with diabetics without defects in cardiac adrenergic nerve density. Global myocardial blood flow and coronary flow reserve, studied by positron emission tomography in response to adenosine provocation, were subnormal in diabetics with cardiovascular autonomic neuropathy. It is obvious that cardiovascular autonomic neuropathy may provoke ischaemic episodes by upsetting the balance between myocardial supply and demand. As a result of autonomic neuropathy, silent myocardial ischaemia is prevalent in diabetic patients but is often symptomatically apparent only in advanced stages of disease. Instead of typical angina, patients often complain of shortness of breath, diaphoresis, or profound fatigue.

Knowledge on the actual prevalence of cardiovascular autonomic neuropathy and its related mortality rates is conflicting. However, different studies and meta-analyses reveal that mortality rates among diabetic subjects with cardiovascular autonomic neuropathy are many times higher than among those without. Subjects with diabetes and low levels of autonomic function parameters (baroreflex sensitivity, heart rate variability and classical Ewing tests) had an approximately doubled risk of mortality in the Hoorn Study [134]. In the Detection of Ischaemia in Asymptomatic Diabetics (DIAD) study [135], cardiac autonomic dysfunction, assessed by the Valsalva manoeuvre, was a strong predictor of ischaemia, whereas traditional and emerging risk factors were not. Impaired angina perception largely accounts for such an increased mortality. Indeed, silent myocardial ischaemia delays treatment of acute coronary events and makes it more difficult to monitor anti-ischaemic treatment or determine whether restenosis has occurred after a coronary intervention. Although silent myocardial ischaemia has a reported prevalence of 10–20% in diabetic populations compared with only 1–4% in non-diabetic populations, routine screening for silent myocardial ischaemia in diabetics remains debatable. In the DIAD study [135], 22% of 522 type 2 diabetic patients randomized to adenosine stress testing with myocardial perfusion imaging by means of single photon emission computerized tomography (SPECT) had silent ischaemia. This would indicate that asymptomatic diabetic patients have at least an intermediate probability of CAD, a prevalence that may justify routine screening for CAD by non-invasive testing. In a series of 203 diabetic patients [136], the prevalence of functional silent myocardial ischaemia, assessed by stress ECG and thallium myocardial scintigraphy, was 15.7%. In this study, the positive predictive value of exercise ECG was 90%, compared with 63% of thallium myocardial scintigraphy. Thus, available evidence highlights the need for non-invasive screening by means of stress-testing in diabetic subjects, especially considering the high sensitivity, feasibility and low costs of exercise ECG.

Based on cardiovascular autonomic neuropathy-associated coronary blood flow impairment, misdiagnosed CAD, and the consequently higher risk of mortality, it is presently recommended that a baseline determination of cardiovascular autonomic function is performed upon diagnosis in type 2 diabetes and within 5 years of diagnosis for type 1 diabetes, followed by yearly repeated tests [137].

The diabetic cardiomyopathy

The existence of a unique diabetic cardiomyopathy has been debated for decades. In the early 1970s, epidemiological evidence from the Framingham Heart Study [138] showed that, after adjustment for age, blood pressure, blood cholesterol, obesity and a history of CAD, the presence of diabetes quadrupled the risk for chronic heart failure in men aged from 35 to 64 years and doubled the risk in men aged 65 years or older. In women aged 35–64 years, diabetes entailed an eightfold increase in chronic heart failure and this increase was fourfold in older women. Further analysis of the Framingham Cohort showed that diabetic individuals, particularly women, had greater left ventricular wall thickness and cardiac mass than control subjects [139]. More recent studies reported a solid link between diabetes and some forms of 'idiopathic' dilated cardiomyopathy [140,141], and confirmed that diabetes-related cardiac myopathy is independent from CAD [142].

Diabetic cardiomyopathy often manifests itself with diastolic dysfunction. Doppler echocardiographic studies have demonstrated that diastolic dysfunction is an early feature of diabetes in animal models [143] and in humans [144,145]. The reduction of left ventricular compliance is associated with severity and duration of diabetes, and negatively correlates with the ability to

perform treadmill exercise. The frequent coexistence of hypertension and diabetes does, however, cloud the actual contribution of the diabetic state to the diastolic dysfunction. The fact that impaired left ventricular diastolic filling in animal models of type 2 diabetes occurs early, even before the onset of hypertension and vasculopathy, suggests that diastolic dysfunction is an effect of diabetes itself. After the onset of diastolic dysfunction, progressive myocardial dysfunction occurs in a time-dependent fashion, leading not only to a cardiomyopathy characterized by increased ventricular stiffness, but also to cavitary dilatation, mural thinning and depressed contractile behaviour. Because of the common coexistence of diabetes, hypertension and CAD, it is currently being debated whether left ventricular dilatation and systolic dysfunction are primarily triggered by the glucometabolic disorder itself rather than by the synergistic action of these factors. From a clinical perspective, prevention of the development of left ventricular systolic dysfunction and subsequent heart failure is currently focused on pharmacological treatment of the comorbidities. It may also explain why meticulous antihypertensive treatment seems to be particularly effective in the diabetic subject. More specific, metabolically oriented treatment modalities are, however, tested.

Further evidence for the existence of a distinct diabetes-specific cardiomyopathy emerges from basic reports of changes in cardiac structure and cardiomyocyte ultrastructure plausibly attributable to the diabetic milieu. In diabetic patients, as well as in animal models, the heart displays a reduction in cardiac mass, myocardial hypertrophy, interstitial fibrosis, and cell loss over time [146]. Although similar patho-anatomical changes may be seen even in the hypertensive heart, cardiac cell death is still believed to be a direct consequence of hyperglycaemia-induced metabolic abnormalities, subcellular defects and abnormal gene expression [147]. A prominent role is currently conferred to enhanced intramyocardial deposition of collagen [148], abnormalities in calcium handling [149], changes in troponin T [150], and PKC-mediated cardiac hypertrophy and failure [151]. Moreover, recent evidence in diabetic patients [152] and in streptozotocin-induced diabetic mice [153] suggests that increased incidence of cell apoptosis occurs in the diabetic heart, mainly as a consequence of oxidative stress-triggered receptor-independent cell death pathway activation [154]. Thus, oxidative stress rather than hyperglycaemia per se may account for subcellular remodelling, cardiomyocyte apoptosis and the subsequent onset of cardiomyopathy. Accordingly, a significant increase in 3-nitrotyrosine-containing proteins, typical end-products of the reaction of peroxynitrite with biological compounds [155], has been reported in cardiomyocytes from diabetic patients and streptozotocin-induced diabetic animals. This evidence suggests a causative link between hyperglycaemia, oxidative/nitrosative stress, cardiomyocyte apoptosis and diabetic cardiomyopathy.

The metabolic syndrome

Insights from pathophysiology for better clinical management

In 1988, Reaven [156] noted that several risk factors (e.g. dyslipidaemia, hypertension, hyperglycaemia) commonly cluster together. He defined this clustering as syndrome X, and identified it as a risk factor for cardiovascular disease.

Nowadays, extended panels of metabolic risk factors have been identified to better understand pathogenesis, predict outcomes and improve clinical management of the so-called metabolic syndrome (MS). Two independent efforts to identify definition criteria have been carried out by the National Cholesterol Education Program's Adult Treatment Panel III (ATP III) [157] and the World Health Organization (WHO) [158].

ATP III identified six components of the MS that relate to CVD:

- abdominal obesity;
- atherogenic dyslipidaemia;
- raised blood pressure;
- insulin resistance and/or glucose intolerance;
- proinflammatory state;
- prothrombotic state.

All of these components are part of a larger body of risk factors for CVD that ATP III identifies as underlying (obesity, physical inactivity, atherogenic diet), major (cigarette smoking, hypertension, elevated LDL-cholesterol, low HDL-cholesterol, family history of premature coronary heart disease, aging) and emerging (elevated triglycerides, small LDL particles, insulin resistance, glucose intolerance, proinflammatory state and prothrombotic state).

To facilitate diagnosis and preventive interventions, ATP III proposed a clinical definition based on having at least three of five criteria (Table 11.3) [159]. Using ATP III definition, the estimated prevalence of the MS among men and women in NHANES III [160] ranges from 5% (normal weight) to 60% (obese) in men, and from 6% (normal weight) to 50% (obese) in women. Currently it exceeds 20% of individuals who are at least 20 years of age, and 40% of the population > 40 years [161].

Table 11.3 ATP III clinical identification of the metabolic syndrome

Risk factor	Defining level
Abdominal obesity (given as waist circumference)*†	
men	> 102 cm (> 40 inches)
women	> 88 cm (> 35 inches)
Triglycerides	≥ 150 mg/dl
HDL-cholesterol	
men	< 40 mg/dl
women	< 50 mg/dl
Blood pressure	≥ 130/≥ 85 mmHg
Fasting glucose	≥ 110 mg/dl‡

*Overweight and obesity are associated with insulin resistance and metabolic syndrome. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated body mass index. Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.
†Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g. 94–102 cm (37–39 inches). Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.
‡The American Diabetes Association has recently established a cut-off point of ≤ 100 mg/dl, above which persons have either pre-diabetes (impaired fasting glucose) or diabetes. This new cut-off point should be applicable for identifying the lower boundary to define an elevated glucose as one criterion for the metabolic syndrome.
Reproduced with permission [159].

The WHO criteria (Table 11.4) require insulin resistance for diagnosis, by demonstrating the presence of type 2 diabetes, IFG or IGT by OGTT in patients without IFG. In addition to insulin resistance, two other risk factors are sufficient for a diagnosis of MS.

On the contrary, ATP III claims that information obtained from an OGTT does not outweigh the inconveniences and costs of applying this test in the clinical routine.

Notably, both ATP III and WHO recognize CVD as the primary outcome of the MS. In the Framingham Study the MS alone predicted 25% of all new-onset CVD. In the absence of diabetes the MS generally did not raise the 10-year risk for CAD to > 20% (the threshold for the CAD risk equivalent in ATP III). Notably, the 10-year cardiovascular risk in men with MS ranged from 10 to 20%, whereas it did not exceed 10% in most women, who also displayed a lower rate of CAD events during the eight-year follow-up.

Table 11.4 WHO clinical criteria for metabolic syndrome

Insulin resistance, identified by one of the following:
- type 2 diabetes
- impaired fasting glucose
- impaired glucose tolerance
- or for those with normal fasting glucose levels (< 110 mg/dl), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinaemic, euglycaemic conditions

Plus any two of the following:
- Antihypertensive medication and/or high blood pressure (≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic)
- Plasma triglycerides ≥ 150 mg/dl (≥ 1.7 mmol/l)
- HDL-cholesterol < 35 mg/dl (< 0.9 mmol/l) in men or < 39 mg/dl (< 1.0 mmol/l) in women
- Body mass index > 30 kg/m^2 and/or waist : hip ratio > 0.9 in men, > 0.85 in women
- Urinary albumin excretion rate ≥ 20 mg/min or albumin : creatinine ratio ≥ 30 mg/g

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In this section, specific risk factors and new emerging and contributing conditions will be analysed in the attempt to identify a continuum between pathogenesis, clinical management and treatment of MS risk factors.

Obesity

In ATP III, abdominal obesity, recognized by increased waist circumference, is the first criterion listed. Its inclusion reflects the pivotal role assigned to abdominal obesity as a contributor to the MS: obesity contributes to hypertension, high serum cholesterol, low HDL-cholesterol and hyperglycaemia, and it associates with higher CVD risk. Excess visceral adipose tissue releases several products that apparently exacerbate these risk factors, including:
- non-esterified fatty acids, which overload muscle and liver with lipid, thus enhancing insulin resistance
- plasminogen activator inhibitor type 1 (PAI-1), which contributes to a prothrombotic state
- C-reactive protein (CRP), which may signify cytokine excess and a proinflammatory state.

The strong connection between abdominal obesity and risk factors led ATP III to define the MS essentially as a cluster of metabolic complications of obesity.

As stated by the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) [162], overweight and obesity are defined by a body mass index (BMI) of 25–29.9 kg/m^2 and ≥ 30 kg/m^2, respectively.

Abdominal obesity, defined as a waist circumference ≥ 102 cm (≥ 40 inches) in men and ≥ 88 cm (≥ 35 inches) in women, is associated with several of the components of the MS. In ATP III, the rationale for using waist criteria rather that BMI arises from data showing that measures of overall obesity are relatively insensitive indicators of the risk for metabolic and cardiovascular complications of obesity, as compared with measures of central or abdominal adiposity [163]. Waist circumference reflects both abdominal subcutaneous adipose tissue and abdominal visceral adipose tissue. The visceral adipose tissue is supposed to be the major determinant of metabolic and cardiovascular complications of obesity [164]. It is presently unclear whether more accurate measures of specific abdominal subcutaneous and visceral adipose tissue using computerized tomography or magnetic resonance imaging may provide superior information regarding obesity complications [165].

It is generally accepted that obesity should be the primary target of intervention in MS. First-line therapy should be weight reduction obtained by lowering caloric intake and reinforcing physical activity. Weight loss lowers serum cholesterol and triglycerides, raises HDL-cholesterol, lowers blood pressure and glucose, and reduces insulin resistance. Recent data further show that weight reduction can decrease serum levels of CRP and PAI-1.

Extreme diets are often ineffective in producing long-term results. More effective and healthful for long-term weight loss are reduced-energy diets, consisting of a modest calories/day reduction. General recommendations for diet composition include low intake of saturated fats, trans fats and cholesterol; reduced consumption of simple sugars; increased intake of fruits, vegetables and whole grains. Regular physical activity is highly recommended, with a daily minimum of 30 minutes of moderate-intensity activity [166]. More exercise (i.e. 1 hour daily) is even more efficacious for weight control. A realistic goal is to reduce body weight by 7–10% over 6–12 months. Long-term maintenance of weight loss is best achieved when regular exercise is included in the weight-reduction regimen, and professional support (such as nutrition counselling) and group training is often helpful (see Chapter 9).

Insulin resistance

Insulin resistance per se is believed to play a significant role in the pathogenesis of MS, and many investigators claim that insulin resistance is the pathophysiological process behind the clustering of cardiovascular risk factors in the MS [167]. Insulin resistance predicts atherosclerosis and cardiovascular events independently of other risk factors, including fasting glucose and lipid levels [168]. However, so far there is little evidence that a reduction in insulin resistance will substantially improve any of the components of the MS other than glucose intolerance. Moreover, identifying a unique role for insulin resistance is complicated by the fact that it is often linked to obesity. Thus, the putative mechanistic link between insulin resistance and most of the components of the MS remains unclear and does not meet general consensus. Mechanisms by which insulin resistance impacts other MS risk factors are:

- diversion of excess non-esterified fatty acids from lipid-overloaded insulin-resistant muscles to the liver, thus promoting fatty liver and atherogenic dyslipidemia;
- enhanced output of very-low-density lipoprotein;
- predisposition to glucose intolerance, which can be worsened by increased hepatic gluconeogenesis in the insulin-resistant liver;
- blood pressure raising, by a variety of mechanisms (see below for details).

Insulin resistance generally rises with increasing body fat and most people with a BMI ≥ 30 kg/m^2 have postprandial hyperinsulinaemia/reduced insulin sensitivity [169] while persons with a BMI between 25 and 29.9 kg/m^2 exhibit a spectrum of insulin sensitivities as well. In some populations (such as South Asians), insulin resistance is common even with BMI < 25 kg/m^2, a condition termed primary insulin resistance.

Various measures have been used to define insulin sensitivity [170]. While hyperinsulinaemic clamp and glucose tolerance testing-based approaches accurately define insulin resistance, prolonged insulin infusion and/or repeated blood sampling are required, which may be undesirable in routine clinical practice. Surrogate measures of insulin sensitivity including the Homeostasis Model Assessment (HOMA) and Quantitative Insulin Sensitivity Check Index (QUICKI) have been developed, showing a good correlation with direct gold-standard measures [171] and predicting the development of cardiovascular disease and type 2 diabetes mellitus [172].

The reduction of insulin resistance is an attractive pharmacological target to prevent CVD in MS patients and there are currently two classes of drugs available: metformin and insulin sensitizers, such as thiazolidinediones. Both drugs reduce insulin resistance and favourably impact different metabolic risk factors. However, no clinical trial has documented the efficacy of metformin and thiazolidinediones in reducing CVD risk, thus limiting recommendation for their use in preventing CVD in patients with either MS or diabetes.

Atherogenic dyslipidaemia

Atherogenic dyslipidaemia is often recognized in MS and manifests itself by raised triglycerides, low HDL-cholesterol, increased remnant lipoproteins, elevated apolipoprotein B, and small LDL and HDL particles. It is commonly believed that hypertriglyceridaemia is the result of enhanced triglyceride hepatic synthesis driven by an increased flux of free fatty acids from the periphery to the liver in an insulin-resistant setting [173]. The causes of hypertriglyceridaemia in the MS are, however, most likely multifactorial and the increased free fatty acid flux hypothesis is one side of this issue. In the same view, low HDL-cholesterol, often ascribed to elevated triglycerides because of increased transfer of triglycerides to HDL and cholesterol from HDL [174], are likely to have a more complex origin, because HDL-cholesterol levels are often reduced in patients with insulin resistance even when fasting triglyceride levels are normal.

More recently, activation of innate immunity and immunity-related inflammation have been proposed as potential links between insulin resistance and dyslipidaemia. In animal models activation of innate immunity leads to changes in lipoproteins, enzymes, transfer proteins and receptors [175] commonly seen also in human MS. Inflammation-driven increase in lipase production has been proposed as a mechanism promoting reduction of lipid content of HDLs [176].

While lipid-lowering therapy is mandatory in dyslipidaemic MS patients, most of them do not display elevated LDL-cholesterol levels, and there is no consensus on the appropriate LDL target in the MS. It is conceivable that in the presence of additional traditional (smoking, family history of CAD) or new (high CRP levels, evidence of a prothrombotic state) risk factors, the MS should be considered a cardiovascular disease equivalent rather than a 'sum' of risk factors. Statin therapy with a target LDL-cholesterol < 100 mg/dl (or even lower, based on evidence in 'very-high-risk patients') would then be the appropriate target.

Several drugs are available for patients with atherogenic dyslipidaemia. Statins reduce all apolipoprotein B-containing lipoproteins, often achieving ATP III goals for LDL/non-HDL-cholesterol. Their impact on CV events is well documented [158]. Fibrates improve all components of atherogenic dyslipidaemia, and *post hoc* analysis of recent trials strongly suggests that they reduce CVD end-points in patients with atherogenic dyslipidaemia and MS [177]. Since clinical studies demonstrate that abnormal lipoprotein patterns are better controlled by statin–fibrate therapy, a combined therapeutic strategy would seem attractive. However, both fibrates and statins have the potential to produce myopathy, and their combined use enhances this risk [55]. Nicotinic acid shares some features with fibrates, and is considered especially efficacious for raising HDL-cholesterol levels. Its combined use with statins is promising. Still awaiting proven efficacy confirmation from randomized clinical trials is the category of dual PPAR agonists. They are promising agents targeting both PPAR-α and PPAR-γ, thereby simultaneously treating insulin resistance, glucose intolerance, elevated triglycerides and low HDL-cholesterol levels.

High blood pressure

In obese patients, blood pressure is sensitive to sodium intake, and this sensitivity is related to fasting insulin levels [178]. The antinatriuretic effect of insulin, together with its ability to activate the sympathetic nervous system [179] and to drive abnormal vascular function, contributes to the development of hypertension. Moreover, both hyperglycaemia and insulin activate the renin–angiotensin system by enhancing the expression of angiotensin, angiotensin II, and angiotensin I receptor, which contribute to raising the blood pressure of patients with insulin resistance (Fig. 11.13).

The majority of MS patients fall into the categories of normal and high–normal blood pressure levels (systolic blood pressure: 120–139 mmHg or diastolic blood pressure: 80–89 mmHg) or stage 1 hypertension (systolic blood pressure: 140–159 mmHg or diastolic blood pressure: 90–99 mmHg). Life-style modification is the cornerstone of management in all patients with high–normal blood pressure levels or with the MS. If blood pressure exceeds 140/90 mmHg, pharmacological therapy is indicated according to both JNC7 [180] and ESH-ESC [181] recommendations. In patients with established diabetes, antihypertensive drugs should be introduced at even lower blood pressures (> 130/> 80 mmHg) (see Chapters 6 and 9). No class of antihypertensive drugs has been identified as being uniquely efficacious in patients with MS. Diuretics and beta-blockers in high doses can worsen insulin resistance and atherogenic dyslipidaemia. However, beta-blockers are cardioprotective in patients with established CAD and are no longer contraindicated in patients with type 2 diabetes.

As mentioned, a rationale for antagonizing the renin–angiotensin system in MS has been proposed [182]. ACE inhibition improves insulin sensitivity and glycaemic control in diabetic patients [183] and was shown to induce a 14% relative reduction in the incidence of new-onset type 2 diabetes in the Captopril Prevention Project (CAPPP) [184]. This was confirmed by the Heart Outcomes Prevention Evaluation (HOPE) trial, in which

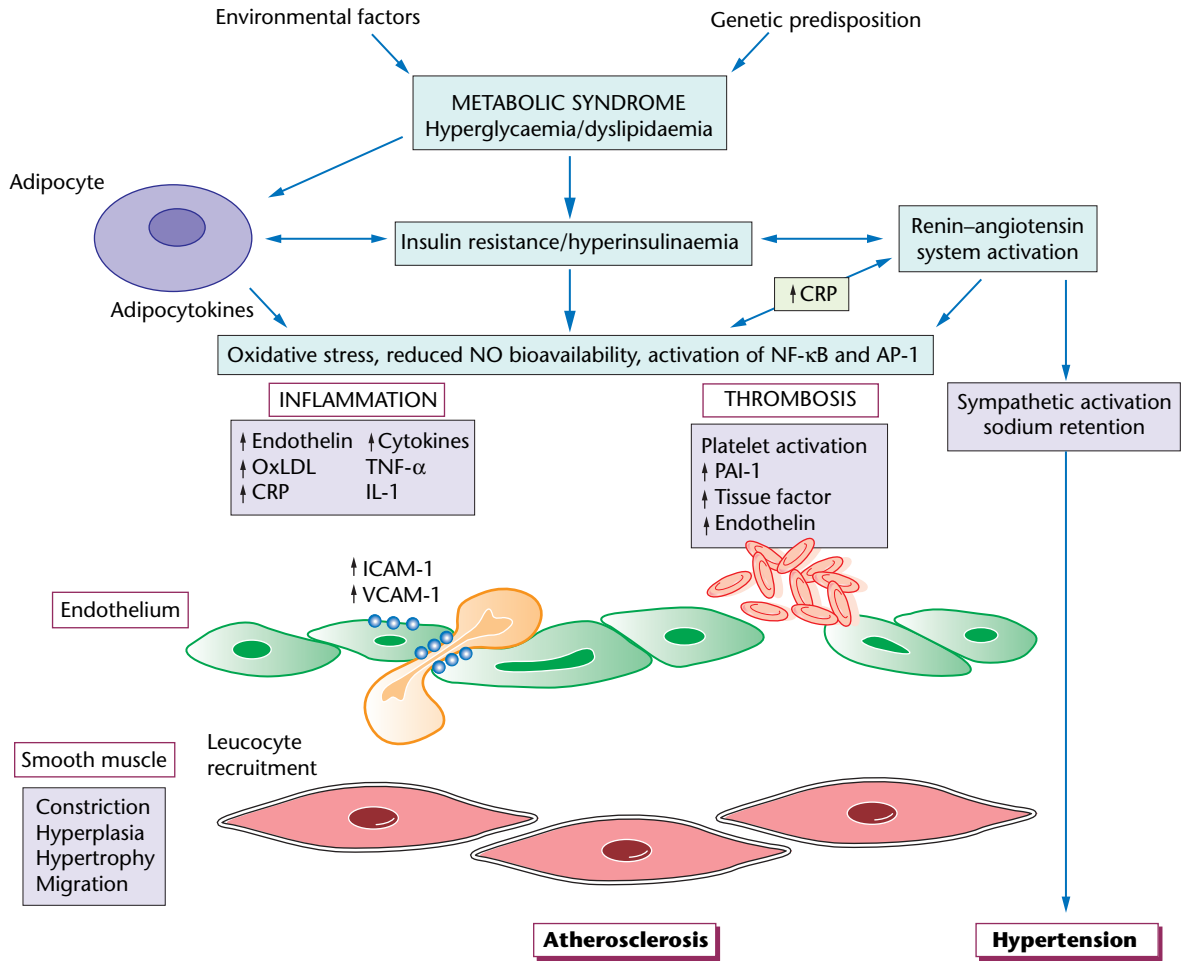

Figure 11.13 Pathophysiology of cardiovascular disease in metabolic syndrome. AP-1, activator protein-1; ICAM-1, intercellular adhesion molecule 1; OxLDL, oxidized LDL; VCAM-1, vascular cell adhesion molecule 1; CRP, C-reactive protein; TNF-α, tumour necrosis factor-α; IL-1, interleukin-1; PAI-1, plasminogen activator inhibitor-1. Reproduced with permission from [182].

ramipril significantly reduced by 34% the incidence of new-onset diabetes [185]. Moreover, in the Losartan Intervention for Endpoint Reduction (LIFE), conducted on patients with hypertension and left ventricular hypertrophy, losartan reduced the composite cardiovascular event rate by 13% and the incidence of new-onset diabetes by 25% compared with atenolol [66,67]. Similarly, treatment with valsartan, compared with amlodipine, was associated with a reduction in the incidence of diabetes in high-risk hypertensive patients in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) [186]. ACE inhibitors and angiotensin receptor antagonists also have a reno-protective capacity, not least in the diabetic patient.

In summary, ACE inhibitors and ARBs are useful, first-line antihypertensives. Some evidence exists that they carry advantages over other drugs in patients with diabetes.

Proinflammatory and prothrombotic state

Chronic subclinical inflammation is part of the MS [187]. This condition is characterized by elevated cytokines (e.g. tumour necrosis factor-α and interleukin-6) and acute-phase reactants (CRP and fibrinogen). Of interest, recent studies suggest that immunity and inflammation play a role in the development of insulin resistance and predict the development of type 2 diabetes mellitus [188,189]. Thus, the pathogenesis of insulin resistance and MS risk factors may have a common inflammatory basis which closely relates to the occurrence of atherosclerotic cardiovascular events. Since measures of inflammatory activity do not presently provide additional insights into the risk of events in MS patients, the current clinical approach to the MS does not incorporate measurement of inflammatory markers. However, as elevated CRP levels (≥ 3 mg/l) have been outlined as an emerging risk

factor for CVD, its inclusion together with traditional MS risk factors into a single algorithm is likely to provide a useful approach to risk prediction in MS patients. Indeed, in a recently published study [190], plasma CRP levels provided prognostic information regarding the risk of cardiovascular events in apparently healthy women at all levels of severity of the MS. From a practical perspective, the finding of high CRP levels in a MS patient should intensify life-style therapies, make certain that low-dose aspirin is used, and set lower LDL goals.

A prothrombotic state in patients with the MS is characterized by elevations of fibrinogen, PAI-1, and possibly other coagulation factors. In MS, activation of NF-κB promotes synthesis of PAI-1, a natural inhibitor of tissue plasminogen activator, and leads to impaired fibrinolysis. PAI-1 levels correlate with plasma insulin levels and insulin resistance, and appear to predict the likelihood of developing diabetes [191]. Since no drugs are available that target PAI-1 and fibrinogen, the alternative approach to the prothrombotic state is antiplatelet therapy. Use of aspirin is recommended in most patients whose 10-year risk for CHD is ≥10% as determined by Framingham risk scoring.

Personal perspective

The cardiology community should be aware of the important relationship between diabetes and atherosclerosis and be prepared to institute appropriate medical and interventional treatments to reduce the growing burden of cardiovascular disease and death among patients with diabetes. Unfortunately, the available evidence indicates that strict glycaemic control reduces microvascular disease to a greater extent than macrovascular manifestations. The relatively small reduction in glycaemia that can be achieved may explain the inability to show decreases in macrovascular events. Furthermore, interventions that improve glucose utilization or reduce insulin resistance have proven to be more promising for limiting cardiovascular complications. The multifactorial complexity of diabetic vascular disease may explain how pharmacological interventions that target dyslipidaemia, hypertension and the prothrombotic state associated with type 2 diabetes reduce the risk of macrovascular complications in such patients. Although we look forward to the development of new treatments for diabetic macrovascular disease, the implementation of aggressive medical management directed at optimizing glucose control, achieving normal blood pressure, correcting dyslipidaemia, and inhibiting platelet function is undoubtedly able to reduce the likelihood of adverse cardiovascular events.

Moreover, in the near future, approximately 50% of persons above the age of 60 years will meet current diagnostic criteria for metabolic syndrome with an estimated excess of cardiovascular risk which raises human, social and economic concerns. While a concerted effort with focus on dietary education and increased physical activity is mandatory to face off the medical and social burden of the disease, identifying and targeting primary pathogenetic abnormalities of metabolic syndrome is our challenging future. Statins, fibrates, metformin, thiazolidinediones, and possibly dual peroxisome proliferator-activated receptor agents will probably represent the cornerstone of pharmacological intervention. The increasing epidemic of metabolic syndrome is, however, not an isolated medical problem. To handle it on a population basis necessitates societal reforms including agricultural and food-processing political considerations.

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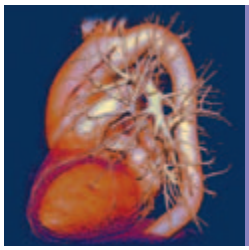

12 Acute Coronary Syndromes: Pathophysiology, Diagnosis and Risk Stratification

Christian W. Hamm, Christopher Heeschen, Erling Falk and Keith A.A. Fox

Summary

Acute coronary syndrome (ACS) is the clinical manifestation of the critical phase of coronary artery disease. Based on ECG and biochemical markers it is distinguished from ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina. The common underlying pathophysiology is related to plaque rupture or erosion with subsequent thrombus formation. Despite the decreasing age-adjusted mortality for myocardial infarction, the disease prevalence for non-fatal components of ACS remains high and the economic costs are immense. The effective treatment of ACS is guided by early diagnosis and risk stratification, and is based on the ECG and biochemical markers.

Introduction and definition

As early as 2600 BC, Egyptian papyrus scrolls recorded that patients with acute chest pain were at high risk of death. Today, the term acute coronary syndrome (ACS) is used to denote the acute phases of ischaemic coronary artery disease with or without myocardial cell necrosis. This term is preferred to earlier symptom-related terminology because it encompasses the common underlying pathophysiology.

ACS describes the spectrum of clinical manifestations which follow disruption of a coronary arterial plaque, complicated by thrombosis, embolization and varying degrees of obstruction to myocardial perfusion. The clinical features depend upon extent and severity of myocardial ischaemia. Complete coronary occlusion in the absence of collateral perfusion results in ST-segment elevation (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI). Transient or partial coronary occlusion may also result in myocyte necrosis as a result of embolization of thrombus and plaque fragments into the distal coronary circulation and changes in vascular tone. The release of sensitive markers of myocardial necrosis (e.g. troponins) is regarded as indicative of myocardial cell necrosis and fulfils the definition of myocardial infarction (NSTEMI) [1]. If no rise in markers is detected, the term unstable angina is used and non-cardiac differential diagnoses must be considered [2].

In the clinical setting the term 'acute coronary syndrome' is used as an initial working diagnosis (Fig. 12.1). According to the ECG and biomarker results the diagnosis is later refined. The first therapeutic steps are based on the ST-segment in the initial ECG.

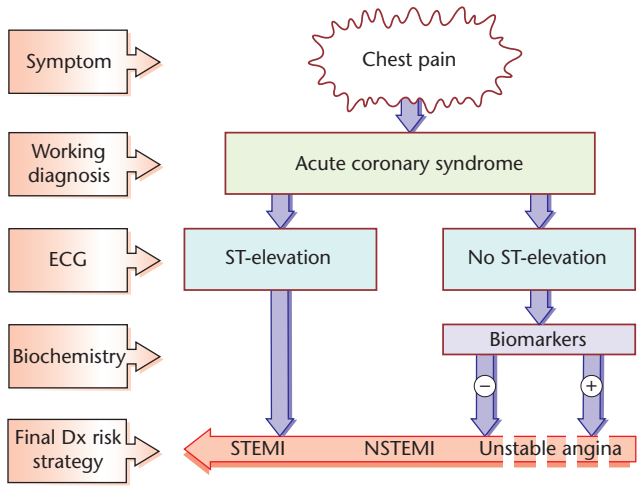

Figure 12.1 Spectrum and definition of the acute coronary syndrome. Dx, diagnosis.

Table 12.1 Deaths related to coronary heart disease per 100 000 of population in selected countries

Country	Men	Women
Ukraine	785	339
Russian Federation	715	254
Latvia	581	179
Czech Republic	317	117
Poland	291	91
United Kingdom	249	89
United States	203	95
Sweden	185	57
Germany	178	64
France	83	20
Japan	57	19

Adapted from British Heart Foundation [4].

Incidence and prevalence of acute coronary syndromes

Internationally, robust information is documented for coronary heart disease deaths and for acute myocardial infarction (AMI) with specific ECG and enzyme/marker characteristics (Table 12.1). The American Heart Association estimates that 1.1 million myocardial infarctions occur in the United States alone and that 40% of these patients will die. Approximately half of the deaths occur prior to the patient receiving medical attention [3]. Taken together with corresponding figures for myocardial infarction in the UK [4], these data suggest that the incidence of AMI is in the range of 1 per 250 to 1 per 500 of the population per year.

Based on registry data, the incidence for all ACS is approximately threefold the incidence of STEMI [5]. Thus, the annual incidence of ACS in Europe is estimated at between 1 per 80 to 1 per 170 of the population per year. However, the incidence of chest pain leading to hospital assessment, of suspected ACS, is substantially higher and varies regionally, depending on the threshold for referral or presentation to an emergency department.

An apparent paradox exists with respect to the prevalence of ACS. Although age-adjusted death rates from coronary artery disease are falling in many economically developed communities, the prevalence appears to be rising. This apparent contradiction is explained by increased awareness in both the public and primary-care physicians of ACS, especially suspected myocardial infarction, together with lowered thresholds for presentation and evaluation of suspected ACS. This now includes patients of advanced age and those with significant comorbidity. Previously, many of these patients may not have presented for evaluation of suspected ACS. Thus, although the true incidence of ACS may follow the declining trends for myocardial infarction, the higher prevalence is accounted for by more patients being evaluated for the condition.

Within the spectrum of ACS the relative prevalence of STEMI, NSTEMI and unstable angina can be determined from registry studies which include the entire spectrum of the disease condition. Among patients presenting with suspected ACS the working diagnosis is unstable angina in 44% and suspected or 'rule-out' AMI in 45%, with uncertain chest pain in the remainder [5]. By hospital discharge, STEMI is confirmed in 30%, NSTEMI in 25%, unstable angina in 38%, and other cardiac or non-cardiac diagnoses in the remainder. Thus, for each patient with STEMI there are approximately two further patients with either NSTEMI or unstable angina (the latter diagnosed by the presence of the clinical syndrome and ECG changes but without enzyme/marker elevations above the diagnostic threshold). The data on the prevalence of components of ACS are entirely consistent between the GRACE registry and the Euro Heart Survey [6]. In the Euro Heart Survey, 42% of the population had an initial diagnosis of ST-elevation ACS, and on discharge, Q-wave myocardial infarctions were identified in 33% of the patients, non-Q-wave myocardial infarction in 25% of patients, and unstable angina in 42% of the patients. Thus, the prevalence of ACS can be estimated in a specific population with reference to the frequency of STEMI or a Q-wave myocardial infarction in that cohort. Only one-third of patients with the syndrome manifest STEMI or Q-wave infarction by the time of hospital discharge.

In-hospital death rates are significantly higher among unselected registry populations (8% in GRACE and 8.4% in Euro Heart Survey for STEMI) compared with clinical trials (GUSTO V study: 5.6–5.9%) [7]. The incidence of myocardial infarction in the UK for men aged 30 to 69 years is approximately 6 per 1000, and 2 per 1000 for women [4]. Estimates for the prevalence of myocardial infarction vary across populations and study designs. However, the combined data from prevalence studies suggest that approximately 4% of men and 2% of women in the community have sustained a myocardial infarction [4]. In the UK in 2002/3, diseases of the circulatory system accounted for 1.1 million hospitalizations out of a total of 12.7 million hospitalizations (9%), and of these, coronary heart disease accounted for 4% [8].

Time trends

Analysis of data from the MONICA centres over a 10-year trend indicates an average 4% annual reduction

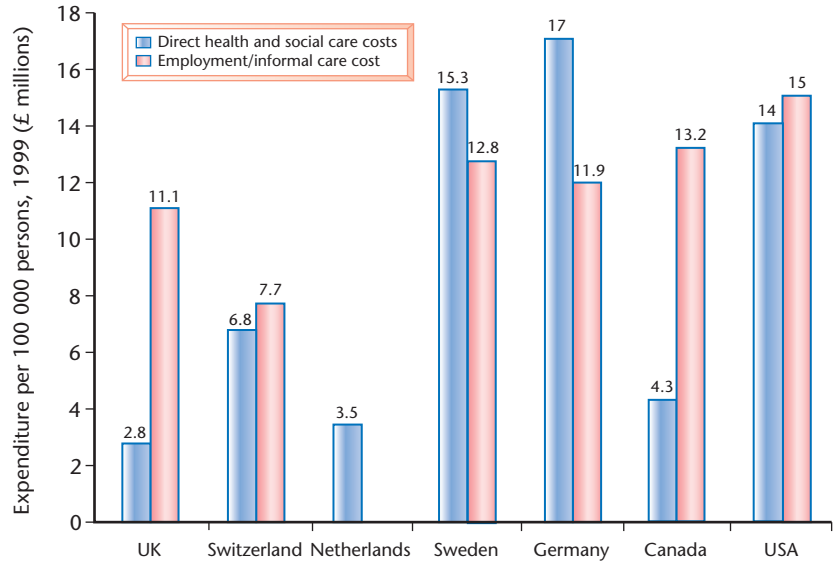

Figure 12.2 Expenditure on coronary heart disease per 100 000 persons in selected OECD countries. Adapted from Liu *et al*. [13].

in coronary artery disease mortality for men and women. However, this varies from a 7–8% annual reduction in some countries, for example Australia, Finland and Sweden, to annual increases in some geographic regions [9]. The decline in death rates from coronary heart disease amongst developed economies in Europe, North America, Australia and New Zealand (between 39 and 52% fall in age-adjusted death rates in men and women from 1989 to 1999) is contrasted with an increase in mortality in several countries of Eastern and Central Europe, most notably countries of the former USSR. For example, in Ukraine between 1989 and 1999 age-adjusted death rates rose by 60% in both men and women [4].

In the UK a 36% fall in age-adjusted death rates has occurred over the past decade; for men aged 35 to 74 years the death rate from coronary heart disease per 100 000 of the population fell from 364 to 199 [4]. The most rapid fall in death rates has occurred amongst men aged 55–64 years and women aged 55–64 years with lesser falls demonstrated in older and younger age groups. Recent large-scale multinational surveys and registries have used predefined case definitions and methods to minimize the influence of bias on patient inclusion and have provided robust information for the full spectrum of ACS [5,6].

Longitudinal studies within specific regions can provide important insights into changes over the course of time. In south-western France, for example, the 28-day case fatality rate has fallen between 1985 and 1993 by about 3% a year for first myocardial infarction [10]. It was concluded that this mainly reflects improvements in acute management rather than in prevention. Similarly, longitudinal studies in Sweden between 1984 and 1991 demonstrated that 2-year mortality after AMI fell from 36% to 25%. Most of the reduction in mortality occurred during the in-hospital phase [11]. In considering the decline in coronary heart disease mortality in Scotland, it was estimated that 40% of the decline was attributed to improved therapeutic treatments and 51% to measurable risk factor reductions [12].

Health economic implications

Despite the falling age-adjusted mortality for myocardial infarction, the disease prevalence for non-fatal components of ACS remains high and the economic costs are immense. The annual cost of coronary heart disease ranks highest of all diseases for which comparable analyses have been performed (Fig. 12.2) [13].

The economic cost of coronary heart disease relates not only to the direct cost to the health-care system but also to loss of productivity and to the provision of formal and informal care of patients. For example, in the UK, the economic burden of coronary heart disease has been estimated at 2.6 billion euros for direct health-care costs in 1999 and a further 3.6 billion euros for the provision of care for coronary artery disease subjects, and 4.4 billion euros for loss of productivity.

General risk factors for acute coronary syndromes

A series of modifiable risk factors (e.g. hyperlipidaemia, hypertension, diabetes and metabolic syndrome) and non-modifiable risk factors (e.g. gender and age) relate to

the development of atherosclerosis and the risk of presenting with ACS.

Age and gender

The most powerful independent predictor for the development of ACS, including presentation with myocardial infarction, is age. Among men, risk increases with each decile of age and comparisons between men and women demonstrate that for premenopausal women the risk corresponds with that of men approximately 10 years younger [4]. Post menopause, the risks increase for women but remain lower than for men of corresponding age [14]. However, interpretations of the impact of gender in ACS are complex and potentially influenced by referral bias and by differences in diagnostic sensitivity of the ECG and stress tests with gender. On angiography of suspected ACS a higher proportion of women do not have significant obstructive coronary heart disease. For example, in the RITA 3 study, 37% of women who fulfilled symptomatic and ECG criteria for non-ST elevation ACS did not have a stenosis greater than 50%, whereas the corresponding figure for men was 12%. Similarly, 26% of men but only 16% of women had significant disease in three or more vessels [15]. Adjusted for age, women have higher rates of diabetes and hypertension but are less frequently smokers [16].

Family history

Having accounted for all known risk factors, family history remains a significant independent risk factor for the development of coronary heart disease. In addition, genetic traits contribute to the specific risk phenotypes, including those related to hyperlipidaemia and hypertension. Twin studies reveal higher concordance among identical than non-identical twins.

Diabetes and metabolic syndrome

Clinical and animal studies demonstrate the importance of diabetes as a risk factor for the development of atherosclerosis as well as for ACS, and the increasing prevalence of obesity in specific populations is implicated in the increased frequency of metabolic syndrome and type 2 diabetes. Patients with type 2 diabetes mellitus have a risk of death from cardiovascular causes that is two- to sixfold elevated compared to those without diabetes. The development of ACS or cardiovascular death accounts for more than one-quarter of all new cardiovascular events among those with diabetes. Intensive intervention involving multiple risk factor reduction among patients with type 2 diabetes and microalbuminuria demonstrates that five patients need to be treated to prevent one cardiovascular event over the course of 8 years [17].

The dramatic increase in the prevalence of obesity among children and adolescents has been demonstrated across many economically developed and developing communities. In the year 2000, more than 20% of the US adult population from 22 states had a body mass index $> 30\ kg/m^2$. In contrast, none of the states had more than 20% of the population with this level of obesity in 1990 [18]. This rise has serious implications for future coronary events, including ACS. Among obese children and adolescents, the prevalence of metabolic syndrome approaches 50% (38.7% in moderately obese subjects and 49.7% in severely obese subjects) [19]. C-reactive protein (CRP) and interleukin-6 are markers of inflammation and their levels can be used as predictors for future cardiovascular events; the concentrations of these markers rise with the extent of obesity. In addition, adiponectin, a biomarker of insulin sensitivity which also has a role in preventing atherosclerosis development, is decreased in obesity [19]. The findings provide a link between obesity, metabolic syndrome and future risk of acute coronary events.

In the third National Health Nutrition Examination Survey (TNHNES) of more than 10 000 subjects, the presence of the metabolic syndrome independently increased the risk of myocardial infarction twofold [odds ratio (OR) 2.01; 95% confidence interval (CI) 1.53–2.64] [29]. Other independent predictors of cardiac events were low levels of high-density lipoprotein (HDL)-cholesterol (OR 1.35), hypertension (OR 1.44) and hypertriglyceridaemia (OR 1.66). A target-driven long-term intensified intervention aimed at modifying several risk factors in patients with type 2 diabetes and microalbuminuria reduces the risk of cardiovascular and microvascular events by approximately 50% [17].

Hypertension

There is a strong association between hypertension and coronary heart disease and there is a particularly strong influence of elevated blood pressure on stroke. Approximately two-thirds of cerebrovascular disease burden and half of ischaemic heart disease burden are attributable, at least in part, to elevated blood pressure [14]. The Blood Pressure Lowering Treatment Trialists' Collaboration has examined the influence of blood pressure lowering on mortality and the development of major cardiovascular events [20]. The overview examined data from 29 randomized trials ($n = 162\ 341$ patients) and the key finding was that the larger the reduction in blood pressure

(irrespective of the regimen used) the greater the reduction in risk of cardiovascular events. Thus, blood pressure lowering is critically important not only in secondary prevention but in the primary prevention of major cardiovascular events including the development of ACS.

Lipid abnormalities

Extensive studies have demonstrated that elevated low-density lipoprotein (LDL) cholesterol and very-low-density lipoprotein (VLDL) cholesterol are associated with atherogenesis and that lowering total cholesterol and LDL cholesterol is associated with reduced atherogenesis. Reduced cardiovascular complications have been demonstrated in primary and secondary prevention clinical trials [21]. Elevated levels of HDL-cholesterol are protective whereas reduced levels of HDL confer increased risk.

Multiple large-scale cholesterol-lowering trials have demonstrated a reduced number of cardiovascular events among treated individuals without manifest coronary artery disease at the time of inclusion (WOSCOPS, AFCAPS, TEXCAPS). Among those patients with hypertension at baseline, a 3-year treatment with a statin (atorvastatin) reduced the risk of major cardiovascular events by approximately one-third (hazard ratios for myocardial infarction or fatal coronary heart disease 0.64, $P < 0.01$) [22]. More detailed consideration of hyperlipidaemia and coronary risk is described elsewhere.

Other modifiable and potentially modifiable risk factors

Up-regulation of systemic inflammation provides a plausible mechanism for accelerating atherogenesis and its acute complications. A series of risk factors may be directly or indirectly related to increased coronary and vascular risk (for example elevated homocysteine, CRP, fibrinogen, plasminogen activator inhibitor type 1 and altered platelet reactivity).

A series of additional 'environmental factors' are influenced by life-style but may also interact with the genetically influenced factors listed above. These include high-fat, low-antioxidant diets (experimentally and clinically), smoking, a lack of exercise, and obesity. Infectious agents may also contribute to the up-regulation of the inflammatory response and acceleration of atherogenesis.

Individuals born with low birth weight exhibit a two- to threefold increased risk in later life of non-fatal coronary heart disease compared with normal birth weight infants [23]. Low birth weight is also associated with several coronary risk factors including the subsequent development of hypertension, type 2 diabetes and elevated cholesterol and fibrinogen concentrations. The risk factors are related not only to birth weight but to other indicators of restriction of fetal growth including small head circumference and altered placental development. The associations between size at birth and coronary heart disease are not explained by premature birth. They are also independent of the risks of subsequent obesity, smoking and socioeconomic classification. The findings have led to the hypothesis that coronary heart disease is programmed in fetal life ('the Barker hypothesis') [24]. *In-utero* programming of steroid metabolism may explain, at least in part, the re-setting of vascular tone in the arterial system and insulin sensitivity [25,26].

Based upon the INTERHEART case–control study in 52 countries, nine potentially modifiable risk factors account for more than 90% of the risk of AMI, consistently across geographic regions and ethnic groups [27]. Identified risk factors include abnormal lipids reflected by the apolipoprotein B–apolipoprotein A1 ratio, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits and vegetables, alcohol and regular physical activity. The findings suggest that these phenotypes are potentially amenable to modification across countries and diverse ethnic populations. This has major implications for primary and secondary prevention strategies.

Genetic influences in atherothrombosis and the initiation of acute coronary syndromes

Common forms of atherosclerosis are multifactorial and relate principally to polygenic disorders rather than to single gene defects. Nevertheless, rare Mendelian disorders have provided insights into disease mechanisms. These include familial hypercholesterolaemia with abnormalities of the LDL receptor and familial disorders of apolipoprotein B-100. Similarly, there are single gene defects associated with low HDL, including apolipoprotein A-1 deficiency and ABC transporter defects (Tangier disease). Specific genetic traits relate to disorders of haemostasis and elevated homocysteine is linked to a defect of cystathionine β-synthase (a regressive metabolic disorder with severe occlusive vascular disease). Type 2 diabetes is associated with altered expression of hepatocyte nuclear factor 4α, hepatocyte nuclear factor 1α and glucokinase. Hypertension is linked with 11β-hydroxylase abnormalities and mineralocorticoid receptor defects.

In contrast, a series of relatively common genetic variations contribute to coronary heart disease and to coronary heart disease risk factors. These include the apolipoprotein E defects which explain about 5% of the variance in cholesterol levels (LDL and VLDL). Various

polymorphisms influence HDL through hepatic lipase, lipoprotein lipase and defects in transfer proteins. A series of alleles explain more than 90% of the variance in lipoprotein (a). Polymorphisms influence tetrahydrofolate reductase and hence homocysteine levels. Specific polymorphisms influence fibrinogen, plasminogen activator inhibitor type 1 and coagulation factor VIII and hence defects in coagulation and endogenous fibrinolysis. Similarly, polymorphisms of angiotensinogen, the beta-2 receptor, and α-adducin affect blood pressure. Specific defects influence angiotensin-converting enzyme and endothelial nitric oxide synthase, contributing to vascular tone [28]. A series of polymorphisms influence the risk of plaque rupture, including those regulating matrix metalloproteinases. As further data emerge, unravelling the contribution of groups of polymorphisms may allow a more accurate genetic basis of risk for atherogenesis and its acute complications to be established. Genetic and environmental factors interact to produce specific clinical phenotypes where underlying genetic risk is amplified or modified by environmental and therapeutic interventions.

Many of the risk factors for the development of ACS also predict subsequent myocardial infarction and death. Such factors include increasing age, male gender, diabetes, hypertension and previous manifestations of coronary disease including angina, myocardial infarction and impaired contractile function heart failure.

Pathophysiology of acute coronary syndromes

Atherosclerosis is by far the most frequent cause of coronary artery disease, carotid artery disease and peripheral artery disease, but atherosclerosis alone is rarely fatal [29,30]. Life-threatening manifestations of atherosclerosis such as ACS are usually precipitated by acute thrombosis, superimposed on a ruptured or eroded atherosclerotic plaque, with or without concomitant vasoconstriction, causing a sudden and critical reduction in blood flow [30–32]. In rare cases, ACS may have a non-atherosclerotic aetiology such as arteritis, trauma, dissection, thromboembolism, congenital anomaly, cocaine abuse, or complications of cardiac catheterization.

Atherothrombosis

Atherosclerosis is a chronic and multifocal immunoinflammatory, fibroproliferative disease of medium-sized and large arteries mainly driven by lipid accumulation [33]. Atherosclerosis begins to develop early in life and progresses with time, but the speed of progression is unpredictable and varies markedly among different subjects. At every level of risk factor exposure, there is substantial variation in the amount of evolved atherosclerosis, probably because the individual vulnerability to atherosclerosis and its risk factors varies greatly. However, even in vulnerable individuals, it usually takes several decades to develop obstructive or thrombosis-prone plaques, so there should in principle be ample time to inhibit plaque development and its complications by timely screening and, where necessary, risk-reducing interventions (Fig. 12.3) [34,35].

Serial angiographic and pathoanatomical observations indicate that the natural progression of coronary artery disease involves two distinct processes: a fixed and hardly reversible process that causes gradual luminal narrowing slowly over decades (atherosclerosis), and a dynamic and potentially reversible process that punctuates the slow progression in a sudden and unpredictable way, causing rapid coronary occlusion (thrombosis or vasospasm, or both). Thus, symptomatic coronary lesions contain a variable mix of chronic atherosclerosis and acute thrombosis but, because the exact nature of the mix is unknown in the individual patient, the term atherothrombosis is frequently used. Generally, atherosclerosis predominates in lesions responsible for chronic stable angina, whereas thrombosis constitutes the critical component of culprit lesions responsible for the ACS [29,30,32].

Abnormal coronary vasoreactivity is common in ACS, but 'spasm' is usually confined to the culprit lesion, suggesting that it is caused by locally released vasoactive substances [36]. The plaque, particularly the inflamed and disrupted plaque responsible for an ACS, may contain potent vasoconstrictors such as endothelin-1, and superimposed thrombosis may also contain or generate vasoconstrictors such as thrombin and platelet-derived serotonin and thromboxane A.

Systemic and local inflammation

Three key pathophysiological mechanisms link vascular inflammation with the early development of ACS. Inflammation within the atherosclerotic plaque is reflected by monocyte recruitment, macrophage activation and the release of free radicals. The consequence is metalloproteinase activation and destabilization of plaques. Second, paradoxical vasoconstriction is linked with endothelial dysfunction, triggered by platelet aggregation, the release

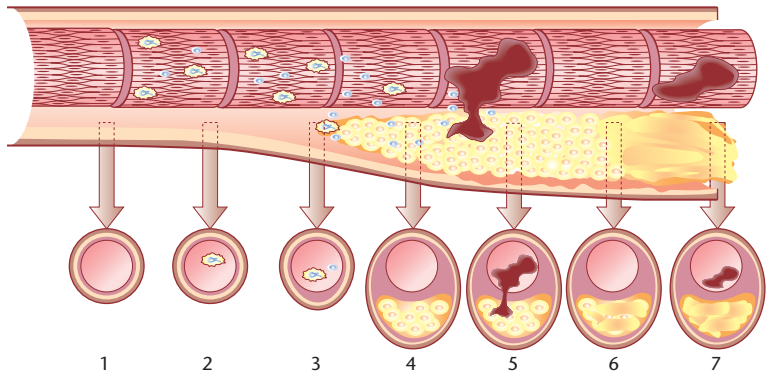

Figure 12.3 Development of the vulnerable plaque. Top, Longitudinal section of artery depicting 'timeline' of human atherogenesis from normal artery (1) to atheroma that causes clinical manifestations by thrombosis or stenosis (5, 6, 7). Bottom, Cross-sections of artery during various stages of atheroma evolution. 1, Normal artery. 2, Lesion initiation occurs when endothelial cells, activated by risk factors such as hyperlipoproteinaemia, express adhesion and chemoattractant molecules that recruit inflammatory leucocytes such as monocytes and T lymphocytes. Extracellular lipid begins to accumulate in intima at this stage. 3, Evolution to fibrofatty stage. Monocytes recruited to artery wall become macrophages and express scavenger receptors that bind modified lipoproteins. Macrophages become lipid-laden foam cells by engulfing modified lipoproteins. Leucocytes and resident vascular wall cells can secrete inflammatory cytokines and growth factors that amplify leucocyte recruitment and cause smooth muscle cell migration and proliferation. 4, As lesion progresses, inflammatory mediators cause expression of tissue factor, a potent pro-coagulant, and of matrix-degrading proteinases that weaken fibrous cap of plaque. 5, If fibrous cap ruptures at point of weakening, coagulation factors in blood can gain access to thrombogenic, tissue factor-containing lipid core, causing thrombosis on non-occlusive atherosclerotic plaque. If balance between prothrombotic and fibrinolytic mechanisms prevailing at that particular region and at that particular time is unfavourable, occlusive thrombus causing ACS may result. 6, When thrombus resorbs, products associated with thrombosis such as thrombin and mediators released from degranulating platelets, can cause healing response, leading to increased collagen accumulation and smooth muscle cell growth. In this manner, the fibrofatty lesion can evolve into an advanced fibrous and often calcified plaque, one that may cause significant stenosis, and produce symptoms of stable angina pectoris. 7, In some cases, occlusive thrombi arise not from fracture of fibrous cap but from superficial erosion of endothelial layer. Resulting mural thrombus, again dependent on local prothrombotic and fibrinolytic balance, can cause acute myocardial infarction. Superficial erosions often complicate advanced and stenotic lesions, as shown here. Superficial erosions do not necessarily occur after fibrous cap rupture. Adapted from Libby [32].

of thrombin and endothelin-1, and sympathetic stimulation. Third, thrombogenicity arises from an imbalance between endogenous concentrations of nitric oxide, prostacyclin, protein C/S and tissue plasminogen activator, and the prothrombotic stimulus from plaque components including tissue factor and apoptotic microparticles of endothelial origin [37].

The endothelium plays a critical role not only in the regulation of vasomotor tone, but is responsible for release of prostacyclin, endothelin-1, hyperpolarizing factor and nitric oxide, all of which influence thrombotic risk and vascular tone. Endothelial dysfunction is associated with enhanced oxidative stress and reduced nitric oxide bioavailability. Nitric oxide is synthesized from L-arginine under the influence of the enzyme nitric oxide synthase and is the key endothelium-derived relaxing factor, playing a pivotal role in the maintenance of vascular tone and reactivity [38]. In addition to being the main determinant of basal vascular smooth muscle tone, nitric oxide opposes the actions of potent endothelium-derived contracting factors such as angiotensin-II and endothelin-1. Furthermore, nitric oxide inhibits platelet and leucocyte activation and maintains the vascular smooth muscle in a non-proliferative state.

Although pathological findings associate ACS with the rupture or erosion of specific plaques, evidence exists for more widespread inflammation both in the systemic circulation and the arterial wall. Neutrophil activation has been demonstrated in both non-culprit and culprit coronary arteries in ACS, as evidence of general inflammatory up-regulation [39]. In contrast, such changes were not present in patients with stable angina, despite a similar extent of coronary artery disease. Furthermore, there is clinical evidence that acute systemic inflammation influences endogenous endothelium-dependent tissue plasminogen activator release in clinical studies [40]. The findings suggest that more extensive inflammation exists in the arterial wall in the context of ACS with increased susceptibility to ACS events in more than one vascular territory [41].

Although studies often report endothelial dysfunction as a loss of the vasodilatory capacity (in response to a

nitric oxide-releasing stimulus such as acetylcholine), the term encompasses a generalized defect in all the homeostatic mechanisms. Endothelial dysfunction is a broad term that implies diminished production of or availability of nitric oxide and/or an imbalance in the relative contribution of endothelium-derived relaxing and contracting factors (such as endothelin-1, angiotensin and oxidants). For example, endothelial dysfunction in diabetes may result from a decreased bioavailability of nitric oxide (secondary to insulin resistance) coupled with an exaggerated production of endothelin-1 (stimulated by hyperinsulinaemia or hyperglycaemia) [42]. Endothelial dysfunction has been implicated in the pathogenesis and clinical course of all known cardiovascular diseases and is associated with future risk of adverse cardiovascular events [43]. Systemic endothelial dysfunction is a major predictor of recurrence of instability in patients with acute coronary syndromes [44]. Assessment of the vascular phenotype might provide an integrated index of systemic inflammatory activation of the vascular wall and thus enable the identification of the inflamed, 'vulnerable' patient at risk. The implications are that treatment of obstructive target lesions in ACS should be accompanied by measures to reduce thrombotic consequences of up-regulated inflammation elsewhere in the arterial system.

In consideration of the important role that inflammatory processes play in determining plaque stability, recent work has focused on whether plasma markers of inflammation may help improve risk stratification in these patients. Even in the early phase of atherogenesis as well as after manifestation of atherosclerosis, elevated levels of inflammatory markers (e.g. intercellular and vascular adhesion molecules, selectins and pregnancy-associated plasma protein A) and downstream acute-phase reactants (e.g. CRP, serum amyloid A and fibrinogen) can be detected in the peripheral blood (Fig. 12.4).

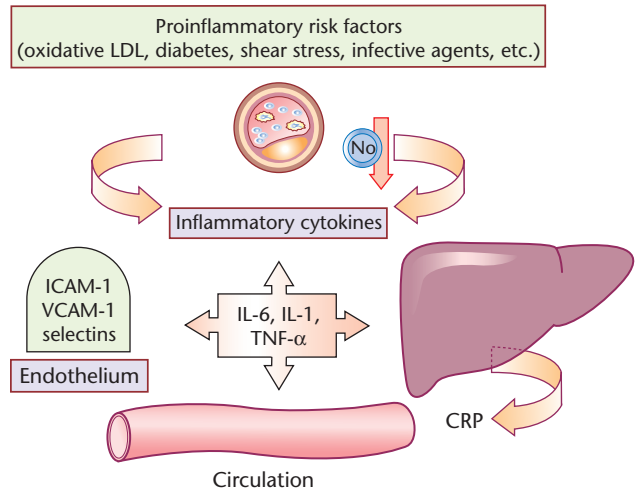

Figure 12.4 The pathophysiology of atherosclerosis with respect to lesion development, progression and destabilization. Biomarkers with distinct pathophysiological profile can be used to assess disease activity.

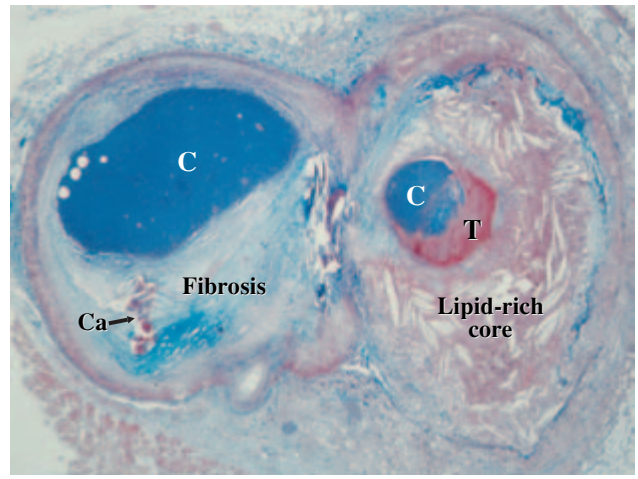

Figure 12.5 Atherothrombosis: a variable mix of chronic atherosclerosis and acute thrombosis. Cross-sectioned arterial bifurcation illustrating a collagen-rich (blue-stained) plaque in the circumflex branch (left), and a lipid-rich and ruptured plaque with a non-occlusive thrombus superimposed in the obtuse branch (right). Ca, calcification; T, thrombus; C, contrast in the lumen.

Vulnerable plaques

Coronary atherosclerotic plaques are very heterogeneous structurally as well as biologically, and even neighbouring plaques in the same artery may differ markedly (Fig. 12.5). The great majority of coronary plaques are, and will remain, quiescent, at least from a clinical point of view. In fact, during a lifetime, none or only few coronary plaques become complicated by clinically significant thrombosis, and these rare but dangerous thrombosis-prone plaques are called vulnerable. Thus, a vulnerable plaque is a plaque assumed to be at high short-term risk of thrombosis, i.e. causing an ACS [45]. The challenge is to find the thrombosis-prone plaques, treat them (or rather the patients harbouring them), and thus avoid ACS [46].

Approximately 75% of all coronary thrombi responsible for ACS are precipitated by plaque rupture [29,30]. In plaque rupture, there is a structural defect (a gap) in the fibrous cap that separates the lipid-rich core of an inflamed plaque from the lumen of the artery (Fig. 12.6). Based on the morphological appearance of ruptured plaques, it is assumed that a rupture-prone plaque will possess the features outlined in Table 12.2

Table 12.2 Features of ruptured plaques*

Thrombus
Large lipid-rich core (> 30–40% of plaque)
Fibrous cap covering the lipid-rich core
• thin (thickness < 100 μm)
• many macrophages (inflammation)
• few smooth muscle cells (apoptosis)
Outward remodelling preserving the lumen
Neovascularization from vasa vasorum
Adventitial/perivascular inflammation

*By inference, the same features, except thrombus, are assumed to characterize rupture-prone (vulnerable) plaques.

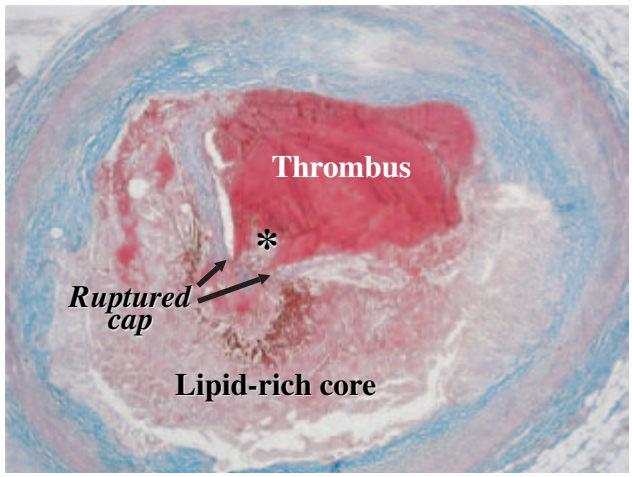

Figure 12.6 Plaque rupture. Cross-sectioned coronary artery containing a lipid-rich atherosclerotic plaque with occlusive thrombosis superimposed. The fibrous cap covering the lipid-rich core is ruptured (between arrows) exposing the thrombogenic core to the blood in the lumen. Atheromatous plaque content is displaced through the gap in the cap into the lumen (cholesterol crystals at asterisk), clearly indicating the sequence of events: plaque rupture preceded thrombus formation. Trichrome stain, rendering luminal thrombus and intraplaque haemorrhage red and collagen blue.

and illustrated in Figs 12.7 and 12.8. Lipid accumulation [47], thinning of the plaque's fibrous cap with local loss of smooth muscle cells [48] and inflammation with many macrophages and few mast cells and neutrophils [32,49,50], and intraplaque haemorrhage [51] destabilize plaques, making them vulnerable to rupture. In contrast, smooth muscle cell-mediated healing and repair processes stabilize plaques, protecting them against rupture [52]. Plaque size or stenosis severity reveals nothing, or only a little, about a plaque's vulnerability [53]. Many rupture-prone plaques are invisible angiographically, because of compensatory vascular remodelling, and they

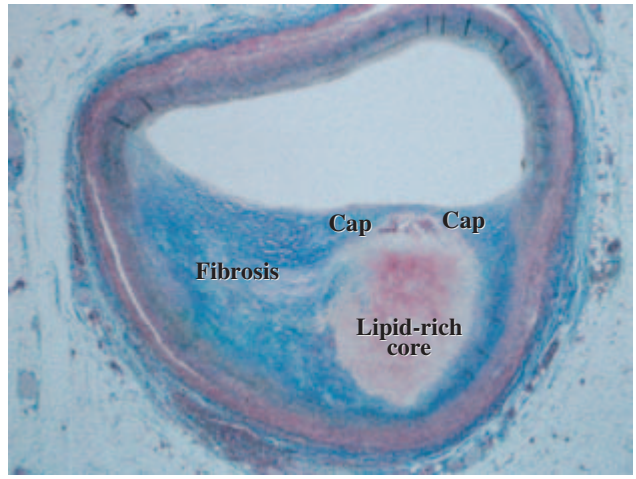

Figure 12.7 Vulnerable plaque. Cross-section of a coronary artery containing a plaque assumed to be rupture-prone, consisting of a relatively large lipid-rich core covered by a thin and fragile fibrous cap. Trichrome stain, rendering collagen blue and lipid colourless.

appear to be highly thrombogenic after rupture, probably because of a high content of tissue factor [54].

Clinical observations suggest that culprit lesions responsible for acute coronary syndromes generally are less calcified than plaques responsible for stable angina, indicating that calcium confers stability to plaques rather than the opposite [55]. The total amount of calcification (the calcium score) is a marker of plaque burden (and thus a marker of cardiovascular risk) rather than a marker of risk conferred by the individual calcified plaque [56].

The term plaque erosion is generally used for intact plaques with superimposed thrombosis, i.e. there is no underlying plaque rupture but the endothelium is missing at the plaque–thrombus interface (Fig. 12.9) [57]. These plaques have identified themselves as being relatively thrombogenic, but the precipitating factor or condition may, in fact, be found outside rather than inside the plaque (e.g. a hyperthrombotic tendency or so-called vulnerable blood).

Plaque vulnerability and remodelling

Arterial remodelling is bidirectional. Plaques responsible for ACS are usually relatively large and associated with compensatory enlargement that tends to preserve a normal lumen despite the presence of significant, and potentially dangerous, vessel wall disease [53,58]. Such lesions, hidden in the arterial wall, may not be seen by angiography. As many as three-quarters of all infarct-related thrombi appear to evolve over plaques causing only mild-to-moderate stenosis prior to infarction, partly because their propensity for outward remodelling, partly

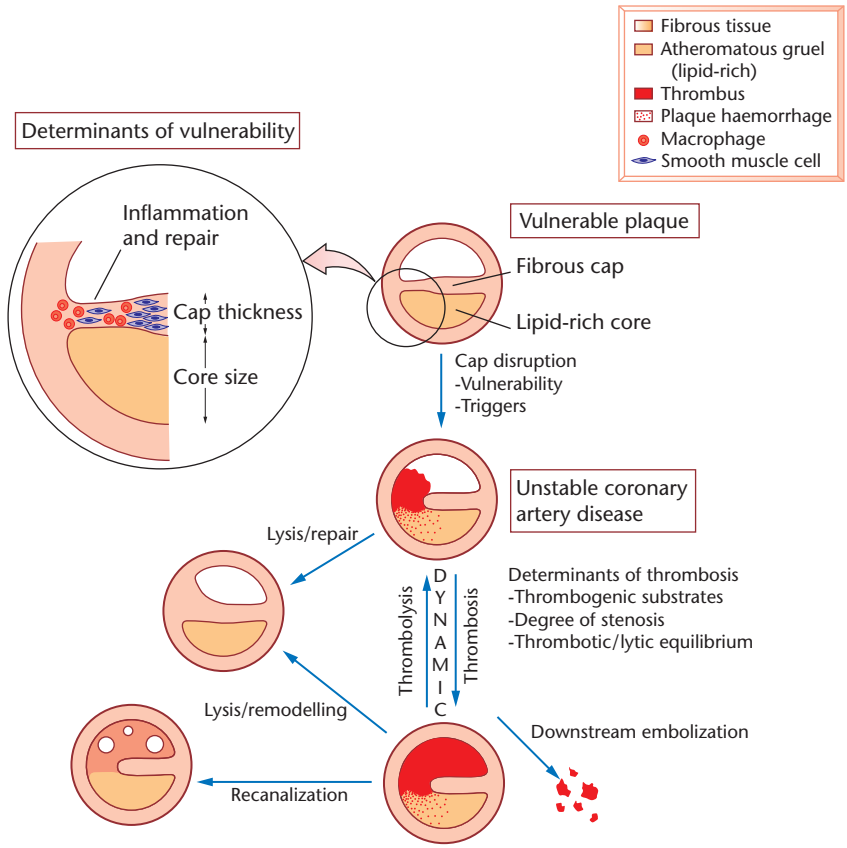

Figure 12.8 Plaque vulnerability, rupture and thrombosis. Lipid accumulation, cap thinning, macrophage infiltration, and local loss of smooth muscle cells destabilize plaques, making them vulnerable to rupture. It is unknown whether rupture of a vulnerable plaque is a random (spontaneous) or triggered event. The thrombotic response to plaque rupture is dynamic and depends on local (e.g. exposed substrate and shear forces) as well as systemic factors (e.g. platelets, coagulation and fibrinolysis).

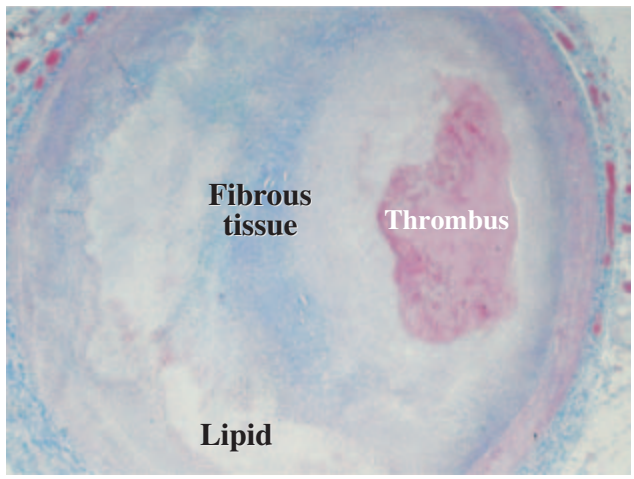

Figure 12.9 Plaque erosion. Cross-section of a coronary artery containing a severely stenotic atherosclerotic plaque with occlusive thrombosis superimposed. The lipid located deeply in the plaque is covered by a thick and intact fibrous cap. The endothelium is missing at the plaque–thrombus interface but the plaque surface is otherwise intact. Thus, there is no obvious local cause (no ruptured plaque) of thrombosis. Trichrome stain, rendering thrombus red, collagen blue, and lipid colourless.

because of their much greater prevalence compared to stenotic plaques [29]. Thus, the great majority of myocardial infarctions originate from atherosclerotic lesions that, prior to the acute events, were haemodynamically insignificant and probably asymptomatic. In contrast, plaques responsible for stable angina are usually smaller but, nevertheless, may cause more severe luminal narrowing because of concomitant local shrinkage of the artery (inward remodelling).

Onset of acute coronary syndrome: vulnerability versus triggers

Sudden rupture of a thin and inflamed fibrous cap may occur spontaneously but triggering could also play a role and thus help explain the non-random onset of ACS [59]. Potential triggers may include extreme physical activity, especially in someone unaccustomed to regular physical activity, severe emotional trauma, sexual activity, exposure to illicit drugs such as cocaine or amphetamines, cold exposure, and acute infections—or simply normal daily activities [59]. The fact that exercise stress testing in individuals with advanced coronary atherosclerosis rarely triggers an ACS suggests that plaque vulnerability

ultimately plays a more important role in plaque rupture than physiological stresses or other potential triggers.

After an ACS, the risk of a recurrent ischaemic event is high during the following 3–6 months. Many of these 'new' events are probably caused by reactivation of the original culprit lesion (rethrombosis), but both post-mortem and clinical observations indicate that patients with acute coronary syndromes often have many ruptured and/or 'active' plaques in their coronary arteries, indicating widespread disease activity [60]. The role of active non-culprit lesion (vulnerable plaques) for subsequent ischaemic events is unknown.

Coronary thrombosis caused by plaque rupture

A world-wide search revealed 18 autopsy studies in which 1460 coronary thrombi were identified and studied carefully with the purpose of characterizing the surface of the underlying atherosclerotic plaque [29]. Plaque rupture was the major cause of coronary thrombosis, being responsible for approximately 76% of the fatal thrombotic events world-wide, regardless of clinical presentation (myocardial infarction or sudden death). Plaque rupture is a more frequent cause of coronary thrombosis in males (81%) than in females (59%). It is rare in one extremely small subgroup of patients, namely premenopausal females, who constitute less than 1% of heart attack victims. A few studies have reported that diabetes (predominantly type 2), smoking and hyperlipidaemia tend to favour a particular type of thrombosis but, except for sex and menopause, no particular risk factors have consistently been connected with a particular type of plaque or mechanism of thrombosis [29]. Even in China, where the average plasma cholesterol level is low, rupture of a lipid-rich plaque is the major cause of coronary thrombosis [61].

Coronary thrombosis not caused by plaque rupture

The term plaque erosion has gained popularity for the minority of thrombi not precipitated by plaque rupture (~20% in males and ~40% in females) [29,57]. It refers to a heterogeneous group of atherothrombotic plaques where no deep injury is present to explain the overlying thrombus, only the endothelium is missing at the plaque–thrombus interface.

The precise mechanisms of thrombosis over eroded plaques are not known but probably reflect the heterogeneity of these plaques. It is conceivable that systemic thrombogenic factors such as platelet hyperaggregability, hypercoagulability, circulating tissue factor, and/or depressed fibrinolysis play a major role in thrombosis over plaques that are only eroded (vs. ruptured). Recent studies have suggested that activated circulating leucocytes may transfer active tissue factor by shedding microparticles and transferring them onto adherent platelets [54,62]. Accordingly, such circulating sources of tissue factor rather than plaque-derived tissue factor can contribute to thrombosis at sites of endothelial denudation as seen in plaque erosion.

Thrombotic response

Rupture of the plaque surface occurs frequently during plaque growth [63]. Most frequently, a small 'resealing' mural thrombus forms at the rupture site, and only occasionally does a major and life-threatening luminal thrombosis evolve. There are three major determinants of the thrombotic response to plaque rupture (or the amount of thrombosis formed on top of an eroded plaque): the local thrombogenic substrate, local flow disturbances, and the systemic thrombotic propensity.

Local thrombogenic substrate

Ongoing inflammation, in particular macrophage infiltration and activation, and lipid accumulation not only destabilize plaques, making them vulnerable to rupture, these plaque components also appear to be highly thrombogenic when exposed to the flowing blood after plaque rupture [64]. Activated macrophages express tissue factor, and the lipid-rich atheromatous core contains high amounts of active tissue factor, probably originating from dead macrophages [54,65]. Culprit lesions responsible for the acute coronary syndromes contain more tissue factor than plaques responsible for stable angina [66]. Oxidized lipids in the lipid-rich core may also directly stimulate platelet aggregation.

Local flow disturbances

In contrast to venous thrombosis, rapid flow and high shear forces promote arterial thrombosis, probably via shear-induced platelet activation [67]. A platelet-rich thrombus may indeed form and grow within a severe stenosis, where the blood velocity and shear forces are highest. Irregularities of the exposed surface also increase the platelet-mediated thrombus formation.

Systemic thrombotic propensity

The state (activation) of platelets, coagulation, and fibrinolysis is critical for the outcome of plaque rupture, documented by the protective effect of antiplatelet agents and anticoagulants in patients at risk of coronary thrombosis. Tissue factor probably plays an important

prothrombotic role both locally (expressed by macrophages in the culprit lesion) and systemically (expressed by activated leucocytes in the peripheral blood) [54,62,66].

Platelets, fibrin and thrombotic burden

In coronary thrombosis, the initial flow obstruction is usually caused by platelet aggregation, but fibrin is important for the subsequent stabilization of the early and fragile platelet thrombus. Thus, both platelets and fibrin are involved in the evolution of a stable and persisting coronary thrombus.

If the platelet-rich thrombus (macroscopically white) at the site of plaque disruption occludes the lumen totally —as is usually the case in STEMI—the blood proximal and distal to the occlusion will stagnate and may coagulate, giving rise to a secondarily formed venous-type stagnation thrombosis (macroscopically red) (Fig. 12.10). Stagnation thromboses may contribute significantly to the overall thrombotic burden, particularly in occluded vein grafts (no side branches), and thus hamper recanalization. Clinical observations indicate that it is indeed very difficult to recanalize an occluded vein graft rapidly by intravenous thrombolytic therapy alone.

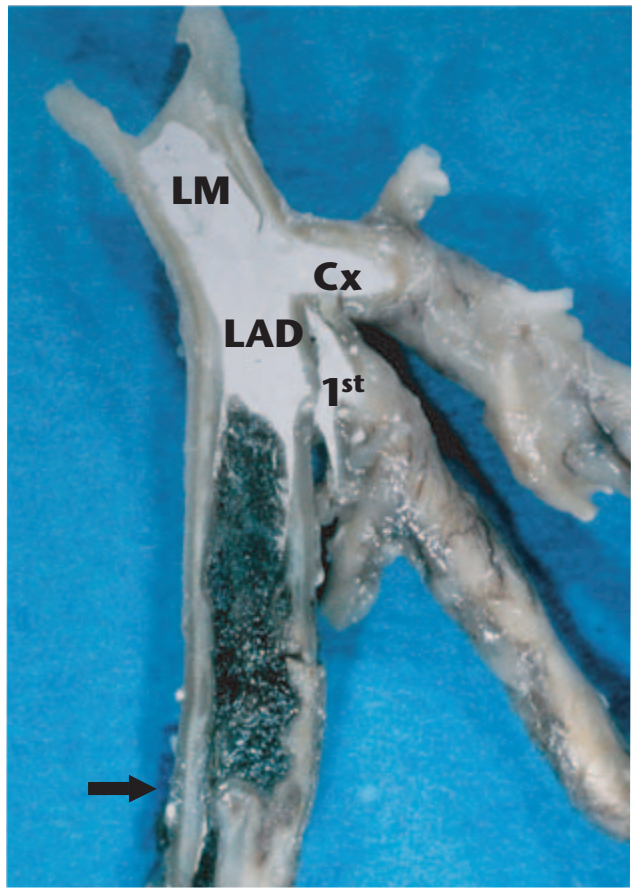

Figure 12.10 Thrombotic burden. Thrombosed coronary artery cut open longitudinally, illustrating a voluminous erythrocyte-rich stagnation thrombosis (dark black on screen) that has developed secondarily to blood stagnation caused by an occlusive platelet-rich thrombus (white) formed on top of a severely stenotic and ruptured plaque (arrow). The white material in the lumen is contrast medium injected post-mortem. LM, left main stem; LAD, left anterior descending coronary artery; Cx, circumflex branch; 1st; first diagonal branch.

Dynamic thrombosis and microembolization

The thrombotic response to plaque rupture is dynamic: thrombosis and thrombolysis, often associated with vasospasm, tend to occur simultaneously, causing intermittent flow obstruction and distal embolization (Fig. 12.11) [29]. The latter leads to microvascular obstruction which may prevent myocardial reperfusion despite a 'successfully' recanalized infarct-related artery [68].

The purpose of coronary recanalization is, of course, to provide oxygenated blood to the ischaemic myocardium, and 'successful' recanalization (a patent culprit artery with brisk flow angiographically) is assumed to improve the perfusion at the tissue level. However, mechanical crushing and fragmentation of atherothrombotic lesion during percutaneous coronary intervention has emerged as a major cause of intracoronary (micro) embolization leading to downstream microvascular occlusion and thus preventing optimal reperfusion of the ischaemic myocardium despite 'successful' recanalization of the infarct-related artery [68]. Both spontaneous as well as iatrogenic coronary microembolization appear to be associated with an unfavourable long-term prognosis.

Development of myocardial infarction

Myocardial infarction (i.e. irreversible injury) caused by complete coronary artery occlusion begins to develop after 15–20 minutes of severe ischaemia (no forward or collateral flow). Within the perfusion area of the occluded artery, flow deprivation and myocardial ischaemia are usually most severe subendocardially (apart from the innermost 10 or so cell layers nourished from the cavity) and, at least in dogs, cell death progresses from the subendocardium to the subepicardium in a time-dependent fashion, the 'wavefront phenomenon' (Fig. 12.12) [69]. Although the susceptibility to ischaemic necrosis differs significantly among patients (related to, for example, variability in preconditioning and oxygen demand/consumption), there are two well-characterized major determinants of the ultimate extent of infarction:

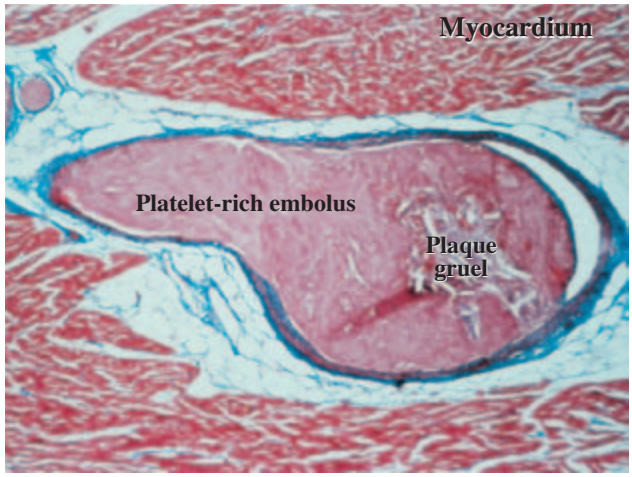

Figure 12.11 Distal embolization. Microvascular occlusion, caused by embolized platelet-rich thrombus and atheromatous 'gruel', in the myocardium downstream of a thrombosed epicardial coronary artery. If extensive, microvascular obstruction may prevent myocardial reperfusion despite 'successful' recanalization of the infarct-related artery.

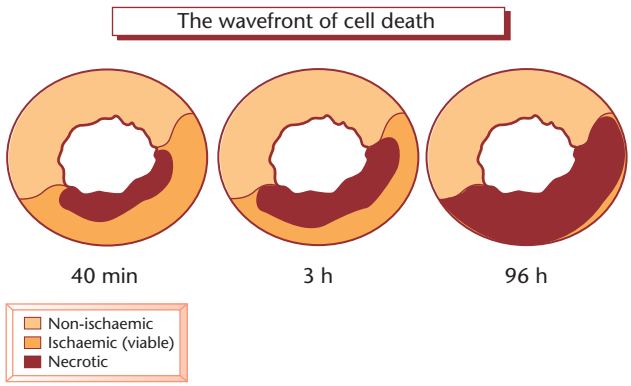

Figure 12.12 The wavefront phenomenon. Following coronary occlusion in dogs, ischaemic cell death progresses from the subendocardium to the subepicardium in a time-dependent fashion—the wavefront phenomenon. Adapted from Reimer and Jennings [69].

- Location of the occlusion, defining the 'area at risk' (amount of jeopardized myocardium).
- Severity and duration of myocardial ischaemia (residual flow and rapidity of recanalization).

The speed and completeness of infarct development and, consequently, the potential for myocardial salvage by reperfusion therapy is difficult to assess in the individual patient presenting with an evolving AMI. The amounts of residual or spontaneously restored forward flow and collateral flow differ substantially among AMI patients. Rapid recruitment of collateral flow at the time of coronary occlusion (via pre-existing collaterals) does not exist in some patients with myocardial infarction because they do not have such protective collaterals. They rapidly develop a transmural AMI, (like rabbits and pigs, which lack collaterals), whereas other myocardial infarction patients have collaterals, probably because of the presence of severe collateral-promoting atherosclerotic stenoses prior to the acute occlusion. Patients in this second set slowly develop a relatively small myocardial infarction, or possibly none at all, in the same way as cats and guinea-pigs, which possess native collaterals.

Collaterals

The available collateral flow, at the time of occlusion, may limit or even avert the development of myocardial infarction. In unstable angina with pain at rest, about 10% of patients have an occluded culprit artery at the time of presentation, but no definite infarction evolves because of well-developed collateral circulation [29]. In infarction without Q-wave development, about 25% of patients have an occluded culprit artery at early angiographic examination, increasing to 40% in the subsequent few days, but a significant amount of myocardium is salvaged because of parallel development of collateral vessels [29]. Conversely, in STEMI, nearly all patients initially have an occluded culprit artery. Unless recanalization occurs rapidly, these patients usually develop extensive transmural infarction with Q-waves on the ECG because of poor collateral circulation. Thus, collaterals may save myocardium at risk, and improve clinical outcome.

Reperfusion and no reflow

Timely, complete and sustained reperfusion may save myocardium at risk of undergoing necrosis in patients with evolving STEMI. Such infarcts nearly always remain anaemic and pale if not reperfused. Therapeutic reperfusion is, however, associated with extravasation of erythrocytes in the ischaemic tissues that have already passed the point of no return, giving rise acutely to a haemorrhagic red infarct. In addition, reperfusion is not homogeneous and, in particular, 'no reflow' may be a cause and/or a consequence of infarction [68].

No reflow in human AMI is more complex than that seen after ligation of a normal coronary artery in animals (classical no reflow model), because the clinical setting involves an atherothrombotic dynamic occlusion with both an innate risk of distal embolization and an embolization risk when crushed or fragmented mechanically during percutaneous coronary intervention [68]. Thus, coronary no reflow and myocardial hypoperfusion after

otherwise successful recanalization of infarct-related arteries do not simply represent non-reperfusion confined to myocardium that is already dead. No reflow may also result from percutaneous coronary intervention-induced (micro)vascular obstruction caused by distal (micro)embolization and/or microvascular spasm [68]. Because emboli necessarily stream preferentially to well-perfused and viable myocardium, potentially salvageable myocardium may vanish. Percutaneous coronary intervention-induced (micro)embolization may, in fact, not only prevent optimal reperfusion, it may worsen the ischaemia if distal branches receiving collateral flow are occluded. Thus, the vital question is, of course: how much of the coronary no reflow and myocardial hypoperfusion seen after primary percutaneous coronary intervention reflects the classical no reflow phenomenon caused by necrosis, and how much reflects percutaneous coronary intervention-induced distal microembolization (and perhaps microvascular spasm) causing more necrosis? The thrombotic burden may prove to be critical.

Clinical implications

Atherothrombosis with ruptured and eroded coronary plaques is common and can be clinically silent for long periods of time. However, acute thrombosis (with or without vasospasm) may cause sudden flow obstruction, giving rise to an ACS. The culprit lesion is frequently 'dynamic', causing intermittent flow obstruction, and the clinical presentation and the outcome depend on the location of the obstruction and the severity and duration of myocardial ischaemia. A non-occlusive or transiently occlusive thrombus—modified overall by vascular tone and collateral flow—most frequently underlies ACS without ST-segment elevation, whereas a more stable and occlusive thrombus prevails in STEMI. A critical thrombotic component is also frequent in culprit lesions responsible for out-of-hospital cardiac arrest and sudden coronary death.

For the prevention and treatment of the ACS, it is important to keep in mind that they are the result of an interaction between two distinct processes: atherosclerosis and thrombosis. Atherosclerosis is a chronic and fixed process that sets the limit for what is achievable by antithrombotic and thrombolytic therapies. Atherosclerosis persists after thrombolysis and may, if severe, prevent optimal and durable reperfusion. The atherosclerotic obstruction may, however, be eliminated by mechanical intervention or bypass surgery. In contrast, thrombosis is an acute and dynamic process that is highly susceptible to treatment with drugs. Thrombosis may appear and disappear rapidly, either spontaneously or accelerated by treatment. Vasospasm and thrombosis often coexist. Overall, drug therapy and mechanical intervention may complement each other in the treatment of the ACS, to obtain rapid, complete and sustained reperfusion.

An invasive approach (percutaneous coronary intervention) may be needed to obtain rapid, complete and sustained reperfusion of infarct-related arteries or to 'passivate' one or a few complex lesions that pose a particularly high short-term risk in ACS, but a target lesion-based approach alone will not eliminate the threat posed by all the other existing coronary plaques, and their overall risk determines the long-term prognosis. Therefore, lifelong systemic therapy is important in patients with diseases caused by atherosclerosis.

Diagnosis and risk stratification of ACS

Diagnosis and risk stratification in patients with ACS are closely linked. The leading complaint is usually chest pain which initiates a diagnostic cascade. Before an ECG is recorded or laboratory test results are available ACS remains the working diagnosis and the presence of a myocardial infarction must be considered.

Clinical presentation

An accurate history is essential in distinguishing the onset of ACS from alternative diagnoses. The prodrome is characterized by anginal type chest discomfort, but usually at rest or on minimal exertion. Of patients with STEMI and prodromal symptoms, two-thirds have symptoms in the preceding week and one-third have symptoms for up to 4 weeks. Overall, only 20% have symptoms for less than 24 hours.

The clinical presentation of patients with ACS encompasses a large variety of symptoms. The cardinal symptom is the ischaemic chest pain which is typically described by the patient as burning, tightness, or heaviness. Patients often have associated symptoms of nausea and fatigue. Chest pain can be graded according to the Canadian Cardiovascular Society Classification (CCS): prolonged (> 20 minutes) anginal pain at rest, new onset (*de novo*) severe (CCS Class III) angina, or recent destabilization of previously stable angina with at least CCS III angina characteristics (crescendo angina). Prolonged pain is observed in 80% of patients while *de novo* or accelerated angina is observed in only 20% of patients [70].

To recognize subgroups of patients with unstable angina who are at different levels of cardiac risk, the Braunwald classification was introduced [71]. This

Table 12.3 Braunwald classification of unstable angina

	Clinical circumstances		
Severity	**A—develops in presence of extracardiac condition that intensifies myocardial ischaemia (secondary UA)**	**B—develops in absence of extra-cardiac condition (primary UA)**	**C—develops within 2 weeks of acute myocardial infarction (post-infarction UA)**
I—new onset of severe angina or accelerated angina, no rest pain	IA	IB	IC
II—angina at rest within past month but not within preceding 48 h (angina at rest, subacute)	IIA	IIB	IIC
III—Angina at rest within 48 h (angina at rest, acute)	IIIA	IIIB-T_{neg} IIIB-T_{pos}	

Adapted from Hamm and Braunwald [74].

empirically developed classification is based on symptoms with respect to pain severity and duration as well as the pathogenesis of myocardial ischaemia and was validated in prospective studies [72,73]. Patients with unstable angina at rest within the last 48 hours (class IIIB) have been shown to be at highest risk of an adverse cardiac event (11% in-hospital event rate). The Braunwald classification has become an accepted standard for grading patients, designing study protocols, and improving the comparability of study results. For further risk assessment troponins have been introduced to this classification (Table 12.3) [74].

Patients with STEMI usually have severe chest pain with fear of dying, whereas in non-ST elevation ACS the pain is more waning and waxing, is dependent on the level of exertion, but usually lasts no longer than 20 minutes. The pain is typically located in the centre or the left lateral chest and radiates to the left shoulder, arm, neck and jaw. Pain may also be epigastric, particularly in inferior myocardial infarctions. Perception of pain in the right side of the chest does not exclude myocardial ischaemia. If the pain is related to inspiration (pleuritic pain), or radiates to the back, other differential diagnoses including aortic dissection must be considered (Table 12.4). Pain that persists over many days or pain that can be provoked mechanically is not ischaemic.

In up to one-half of patients with STEMI physical and or emotional factors are identified in the prodrome and may have influenced plaque rupture. A circadian periodicity of presentation with STEMI is observed. The peak incidence of events coincides with the early waking hours, possibly associated with rises in catecholamines and cortisol and increases in platelet aggregability.

Table 12.4 Differential diagnoses: acute chest pain

Cardiovascular diseases
- arrhythmias
- pericarditis
- myocarditis
- aortic dissection

Pulmonary diseases
- pulmonary embolism
- pleuritis
- pneumothorax

Skeletal disorders
- rip fracture/contusion
- spine diseases
- Tietze syndrome

Gastrointestinal disorders
- oesophagitis/oesophageal rupture
- pancreatitis
- gall bladder dysfunction

Others
- herpes zoster
- malignant diseases involving chest/bones

Population studies reveal that approximately 30% of myocardial infarctions occur silently or with less severe symptoms. They are detected only by chance on subsequent ECG recordings [75].

Atypical presentations of ACS are not uncommon. They are often observed in younger (25–40 years) and older (> 75 years) patients, diabetic patients and in women. In the Multicenter Chest Pain Study, acute myocardial ischaemia was diagnosed in 22% of patients presenting

to emergency departments with sharp or stabbing chest pain, 13% of those with chest pain that had some pleuritic features, and in only 7% of those whose chest pain was fully reproduced by palpation [76]. In addition, variant angina, as a result of coronary spasm, forms part of the spectrum of unstable angina and may not be recognized at initial presentation. Accordingly, the assessment of clinical symptoms alone is insufficient for risk stratification as symptoms may be difficult to assess objectively and can easily be subject to misinterpretation.

Physical examination

Physical examination of patients with chest pain includes chest examination, auscultation, and measurement of heart rate and blood pressure. The major purpose of the examination is to exclude non-cardiac causes of chest pain, non-ischaemic cardiac disorders (e.g. pericarditis, valvular disease), potential precipitating extracardiac causes, pneumothorax, and to look for signs of potential haemodynamic instability and left ventricular dysfunction. In patients with myocardial infarctions particular attention has to be drawn to systolic murmurs indicative of mitral regurgitation or ventricular septal defects.

The electrocardiogram

The resting ECG plays a central role in the early assessment of patients with suspected ACS. In all patients admitted with acute chest pain a 12-lead ECG should be recorded and evaluated by an experienced physician within 10 minutes. If a pre-hospital fibrinolysis programme exists a complete recording has to be obtained at the site of first contact with the patient. Exercise testing is contraindicated in symptomatic patients and in patients with elevated troponins. After stabilization and where there is a lack of high-risk features (Table 12.5), treadmill testing is useful for risk assessment.

The ECG remains an important screening tool also in patients with atypical presentations and it may provide evidence of alternative diagnoses such as pericarditis, pulmonary embolism, or cardiomyopathy. Ideally, a tracing should be obtained when the patient is symptomatic and compared with a tracing obtained when symptoms have resolved. Comparison with a previous ECG, if available, is extremely valuable, particularly in patients with coexisting cardiac pathology such as left ventricular hypertrophy or a previous myocardial infarction [76,77].

ST-segment shifts and T-wave changes are the most reliable electrocardiographic indicators of unstable coronary disease and associated with elevated risk [78,79]. Dynamic changes, particularly during episodes of chest pain, have a very high diagnostic value. Continuous ST-segment monitoring was shown to provide better ECG prediction, but should not delay invasive management in symptomatic patients [77].

ST-segment depression of > 1 mm in two or more contiguous leads, in the appropriate clinical context, are highly suggestive of ACS. Inverted T-waves (greater than 1 mm) in leads with predominant R-waves are also suggestive, although the latter finding is less specific. Deep symmetrical inversion of T-waves (≥ 0.2 mV) in the anterior chest leads is often related to significant proximal left anterior descending coronary artery stenosis. Non-specific ST-segment shift and T-wave changes of < 1 mm are much less specific. In the Multicenter Chest Pain Study such non-specific changes were often noted in patients in whom an ACS was ultimately ruled out. Transient episodes of bundle branch block occasionally may occur during ischaemic attacks.

Giant T-waves are a rare finding in the very early phase of AMI. New ST-segment elevations in the presence of appropriate symptoms indicates transmural ischaemia as a result of acute coronary occlusion. Persistent ST-segment elevation at the J-point with the cut-off points ≥ 0.2 mV in V1 through V3 and ≥ 0.1 mV in other leads characterizes evolving myocardial infarction (STEMI). The ST-segment vector points to the region of injury, which allows the infarct-related artery to be identified in many cases (Table 12.5). Right precordial leads (V3r to V6r) may be useful in identifying right ventricular involvement and V7 to V9 in detecting true posterior infarctions.

Transient ST-segment elevation may be observed in ACS and particularly in Prinzmetal's angina. To detect or to rule out transient ST-segment changes during recurrent episodes of chest pain or in silent ischaemia, continuous multi-lead ST-segment monitoring can be useful.

ST-segment depression may occur in reciprocal leads (Figs 12.13, 12.14) as an electrical mirror or as the result of true ischaemia in another territory ('ischaemia at a distance'). In the absence of ST-segment elevation, depression of the ST-segment is indicative of subendocardial ischaemia. Only biochemical markers of myocardial cell injury (e.g. troponins) will determine whether this patient is having a NSTEMI in the absence of typical ST-segment elevations. Isolated ST-segment depression in the right precordial leads may occur in strictly posterior myocardial infarctions. ST-segment elevations confined to leads V1 and V2 may be the result of early repolarization and should critically be interpreted when typical clinical symptoms are lacking.

During the evolution of cell necrosis the amplitude of the R-wave is reduced, T-waves become negative, and Q-waves develop. Clinically established myocardial infarction is defined by any Q-wave in leads V1 through V3, or

Table 12.5 Acute myocardial infarction based on electrocardiographic entry criteria with angiographic correlation

Location	Anatomy of occlusion	ECG	1-year mortality (%)*
Proximal left anterior descending	Proximal to first septal perforator	ST↑ V1–6, I, aVL and fascicular bundle or bundle branch block	25.6
Mid left anterior descending	Proximal to large diagonal but distal to first septal perforator	ST↑ V1–6, I, aVL	12.4
Distal left anterior descending or diagonal	Distal to large diagonal or to diagonal itself	ST↑ V1–V4 or ST↑ I,V5,6 aVL, V5–V6	10.2
Moderate to large inferior (posterior, lateral, right ventricular)	Proximal right coronary artery or left circumflex	ST↑ II, III, aVF and any or all of the following: 1) V1, V3R, V4R 2) V5V6 3) R > S in V1, V2	8.4
Small inferior sdsds	Distal righ coronary artery or left circumflex branch occlusion	ST↑ II, III, aVF only	6.7

*Based on GUSTO-I cohort population in each of the 5-year categories, all receiving reperfusion therapy.

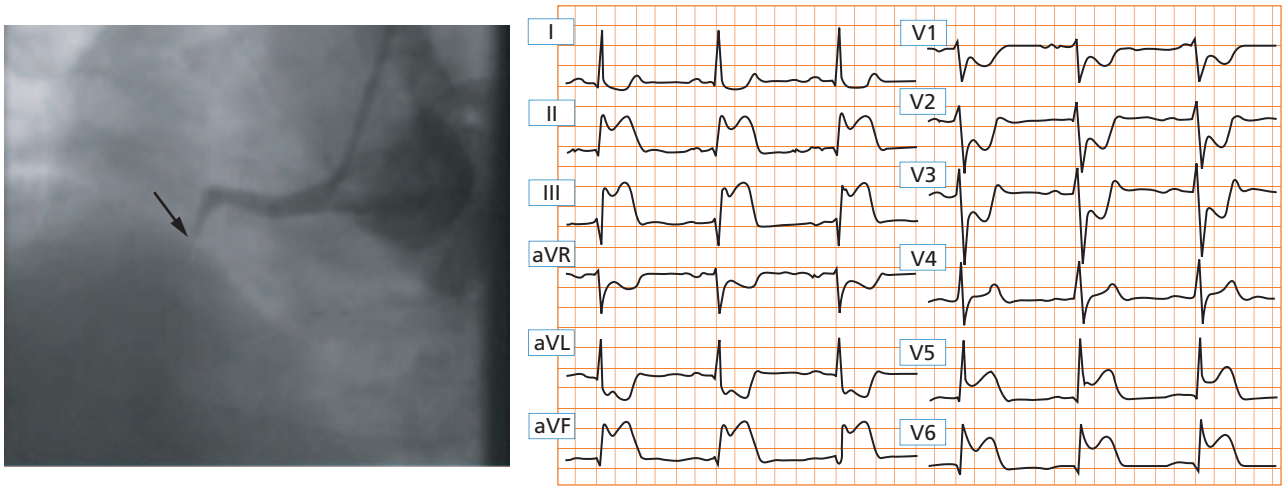

Figure 12.13 Inferior AMI: occluded right coronary artery, ST-segment elevation in leads II, III and aVF; ST depression in V1 to V4.

Q-wave ≥ 0.03 s and ≥ 0.3 mV in leads I, II, aVL, aVF, V4, V5, or V6. However, the absence or presence of Q-waves is not a reliable sign of a transmural or non-transmural infarct expansion. In addition, creatine kinase (CK) levels do not always correlate with the development of Q-waves. Accordingly, the terms Q-wave and non-Q-wave myocardial infarction should be used critically [80].

It is important to note that even a completely normal ECG in patients presenting with suspicious symptoms does not exclude the possibility of an ACS. In several studies about 5% of patients with normal ECG who were discharged from the emergency department were ultimately found to have either an AMI or unstable angina [81–83]. However, a completely normal ECG recording during an episode of significant chest pain should direct attention to other possible causes for the patient's complaints.

Biochemical markers

Biochemical markers play a central role in evaluating patients with chest pain. Besides routine laboratory measurements (haemoglobin, white blood cell count, thyroid hormones, etc.) special markers reflecting distinct pathophysiological processes must be obtained in this high-risk group of patients.

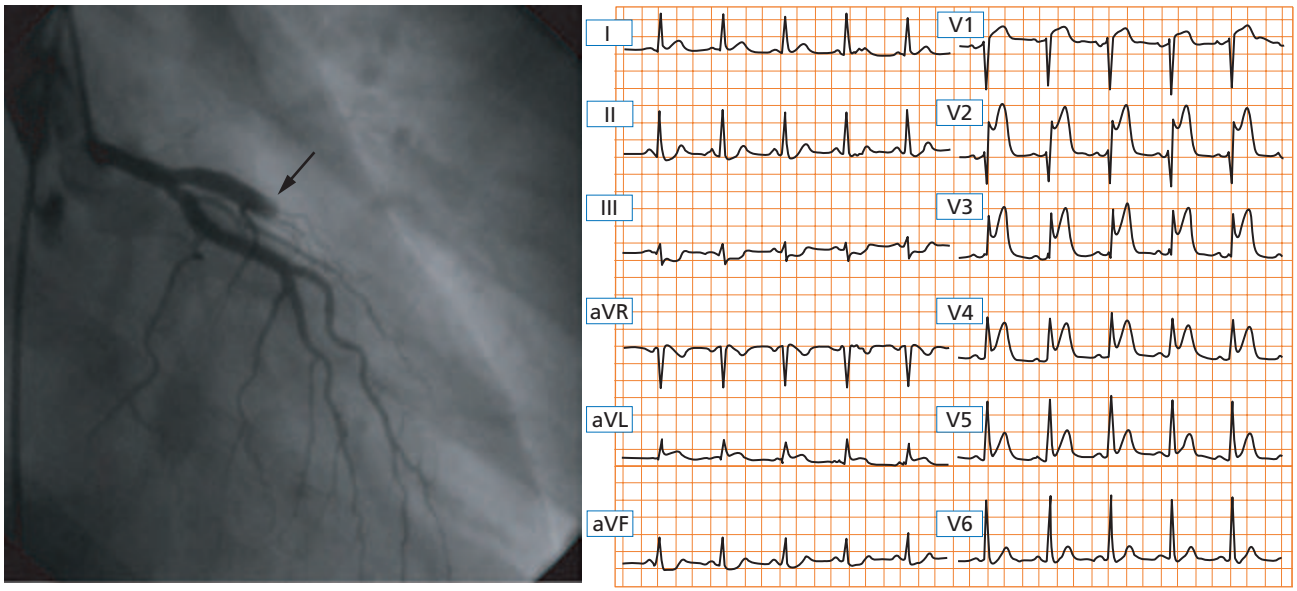

Figure 12.14 Anterior AMI: occluded left anterior descending coronary artery, ST-segment elevation.

Table 12.6 Biochemical markers for the detection of myocardial necrosis

	MW (kDa)	Specificity	Sensitivity	First rise after AMI	Peak after AMI	Return to normal
CK-MB mass	85.0	++	+	4 h	24 h	72 h
Myoglobin	17.8	+	+	2 h	6–8 h	24 h
Troponin T	33.0	+++	+++	4 h	24–48 h	5–21 days
Troponin I	22.5	+++	+++	3–4 h	24–36 h	5–14 days

Markers of myocardial necrosis

Pathohistological studies in patients with unstable angina have disclosed focal cell necroses in the myocardium distal to the culprit artery. These were attributed to repetitive thrombus embolization [84,85]. Focal cell necroses, or so-called minor myocardial injuries, are very infrequently detectable by routine creatine kinase (CK) and CK-MB measurements. Even improved test systems for the quantitative determination of CK-MB based on immunological determination, which are superior to enzyme activity measurements, did not substantially increase the sensitivity for the detection of minor myocardial injury. Myoglobin is a marker which rises earlier than CK-MB in AMI but has similar limitations with respect to specificity (Table 12.6).

These biochemical limitations of CK-MB and myoglobin measurements for the detection of minor myocardial injury have been overcome by the introduction of troponin measurements (Fig. 12.15). In the early 1990s, the cardiac isoforms of troponin T and troponin I were introduced into clinical practice. The troponin complex is formed by three distinct structural proteins (troponins I, C and T) and is located on the thin filament

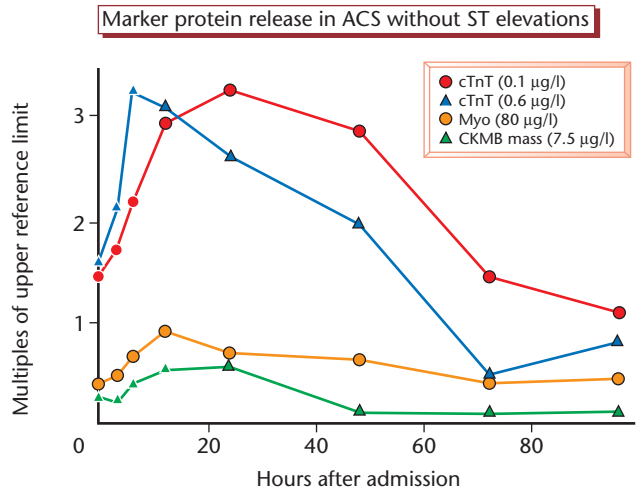

Figure 12.15 Biomarker levels in a typical patient with ACS without ST-segment elevation.

of the contractile apparatus in both skeletal and cardiac muscle tissue regulating the calcium-dependent interaction of myosin and actin. Cardiac isoforms for all three troponins, however, are encoded each by different genes

and can be distinguished by monoclonal antibodies recognizing the amino acid sequence distinct for the cardiac isoform [86]. However, only the cardiac isoforms of troponin T and troponin I are exclusively expressed in cardiac myocytes. Accordingly, the detection of cardiac troponin T and troponin I is highly specific for myocardial damage, attributing these markers the role of a new gold standard. In conditions of 'false-positive' elevated CK-MB, such as skeletal muscle trauma, troponins will clarify any cardiac involvement.

In patients with a myocardial infarction, a first rise of troponins in peripheral blood can be observed as early as 3–4 hours because of its release from a cytosolic pool, followed by a prolonged appearance of up to 2 weeks related to continuous proteolysis of the contractile apparatus in the necrotic myocardium. The high proportional rise of troponins, relative to the low plasma troponin concentrations in healthy controls, allows the detection of myocardial damage in about one-third of patients presenting with unstable angina even without elevated CK-MB [87–95].

Definition of acute myocardial infarction

The traditional clinical definition of myocardial infarction by WHO did not require elevations of biochemical markers, and hence was revised by the Joint European Society of Cardiology/American College of Cardiology Committee. Today, the AMI definition is based on biochemical criteria, namely troponin elevation as a result of irreversible cell damage, combined with clinical features (Table 12.7) [1]. This change in definition increases the frequency of the diagnosis of myocardial infarction and has important implications for the interpretation of epidemiological research and clinical trials as well as for clinical care. Although many physicians currently have conceptual difficulties with the translation of this change in paradigm into clinical practice, the increased risk in patients with elevated troponin levels justifies the revised criteria.

Table 12.7 Definition of AMI according to ESC/ACC/AHA consensus

Typical rise or fall of troponin or CK-MB with at least one of the following:
Ischaemic symptoms
New Q-waves on the ECG
ECG changes indicative of ischaemia (ST elevation/depression)
Coronary artery intervention (e.g. percutaneous coronary intervention)

Adapted from [1].

Troponins for risk stratification

It has been demonstrated in numerous clinical trials that troponin T and troponin I are strongly associated with increased risk both in the acute phase of hospitalization and during long-term follow-up. In the first report on troponin T in a small cohort of patients with unstable angina, it was demonstrated that the risk of death and myocardial infarction during hospitalization was increased even in the presence of antiplatelet therapy with aspirin and heparin [88]. In a substudy of the FRISC (FRagmin during InStability in Coronary artery disease) trial the prognostic value was shown to correlate with the absolute concentrations of troponin T over a 5-month period [91]. The peak value during the first 24 hours provided the best independent prognostic information and the absence of troponin T was superior to CK-MB for identification of the low-risk group [96]. Furthermore, the combination of the troponin T test with a predischarge exercise test represents an excellent risk assessment for unstable coronary disease [97]. During the 5-month follow-up, death and myocardial infarction occurred at a rate of only 1%, if both the troponin test and the predischarge exercise test were normal, whereas the event rate was as high as 50% when both tests were abnormal. Moreover, the prognostic potential of troponin T in the entire spectrum of patients with ACS, including myocardial infarctions, was evaluated in a substudy of the GUSTO (Global Use of Strategies To Open occluded coronary arteries) IIA trial [98]. A single measurement within 2 hours after admission was highly predictive of 30-day mortality and other major complications. The prognostic value was independent of ECG findings and was superior to CK-MB measurements.

For elevations of cardiac troponin I, a similar prognostic impact was evidenced as for troponin T elevations. In the TIMI IIIB trial including patients with unstable angina and non-Q-wave myocardial infarction, the mortality rate was closely related to troponin I levels reaching 7.5% after 42 days follow-up in patients with the highest troponin I values [90].

Analytical aspects of troponin measurements

Quantitative and semi-quantitative bedside troponin test systems for whole blood allow the prognostic potential of the troponins to be independent of clinical chemistry laboratory facilities. To establish the correct diagnosis and for prompt triage, point-of-care or bedside testing for biochemical markers may be advantageous. Point-of-care tests are characterized as assays to be performed either directly at the bedside or at 'near-patient' locations such as the emergency department, chest pain evaluation centre, or intensive-care unit. Therefore, the rationale

behind point-of-care testing is the improvement in analytical turnaround time. Suspected ACS represents a possibly life-threatening condition in which savings in time for therapeutic decision-making and further patient management may be decisive. The National Academy of Clinical Biochemistry as well as the ESC Task Force Report advise implementation of point-of-care testing systems if the hospital logistics cannot consistently deliver cardiac marker results within 1 hour [66,99–101]. Point-of-care techniques must be analytically accurate and equivalent to centralized laboratory methods. In large series, bedside tests results were validated against quantitative measurements and could be reliably performed by paramedical staff [92,93,102–104]. It was shown prospectively that risk stratification based on a protocol scheduling rapid testing of troponin on the patient's arrival in the emergency room, and again 4–6 hours later, provides a more reliable risk stratification than the previous more time-consuming protocols [92]. However, a single test result obtained on admission of the patient is inappropriate for risk stratification, because up to 10% of high-risk patients will be missed.

The difficulty with defining the appropriate diagnostic threshold for troponins is compounded by the availability of multiple assays for troponin I for which different reference ranges have been developed. For troponin I, many manufacturers report two decision limits: a 'diagnostic' limit for the definitive diagnosis of myocardial infarction based on prior comparisons to CK-MB and a lower limit 'suggestive' of myocardial injury that is important for the patients' prognosis. Though the challenge of developing terminology and diagnostic thresholds around low-level troponin elevation has been a source of debate, the clinical importance of increased troponin levels in suspected ACS is firmly established.

There is no fundamental clinical difference between troponin T and troponin I. Differences between study results are predominantly explained by varying inclusion criteria, differences in sampling patterns and use of assays with different diagnostic cut-offs. The decision limits must be based on carefully conducted clinical studies for individual troponin I assays and should not be generalized between different troponin I assays. For troponin T, levels as low as 0.01 μg/l have recently been shown to be associated with adverse cardiac outcomes in ACS [105]. From the FRISC studies a troponin T level of 0.03 μg/l appears to be the appropriate threshold [106]. Low levels of troponins appear to carry the highest risk in patients with ACS. However, the application of this threshold among more heterogeneous populations of patients presenting to the emergency department will require prospective evaluation. Currently, the diagnostic threshold for troponin T may be maintained between 0.06 and 0.10 μg/l, depending on the local laboratory performance.

Non-cardiac causes of elevated cardiac troponins

One initial barrier to the universal acceptance of troponins as the gold standard for the detection of myocardial injury has been the observation that troponin concentrations are increased rarely in non-cardiac conditions, but are more commonly elevated in patients with renal failure. Although measurements of cardiac troponins are generally assessed as highly specific for myocardial injury, elevated cardiac troponin, unrelated to myocardial damage, has been reported in a number of conditions including cerebrovascular accidents, subarachnoid haemorrhage, endocrine disease, polymyositis, dermatomyositis, and haematological malignancies [107,108]. Studies in intensive-care units have demonstrated increased troponin levels in septic patients. Importantly, troponin concentrations in these patients correlated with left ventricular dysfunction and the presence of multiorgan failure. However, it remains unclear whether troponin elevation affected either hospital length of stay or survival [109].

Elevated levels of cardiac troponins are also found in patients with end-stage renal disease in the absence of unstable heart disease. Even using more specific second-generation troponin T assays, up to 53% of asymptomatic patients with end-stage renal disease remain positive for cardiac troponin T [110–112]. An elevated concentration identifies patients at greater risk of all-cause mortality [110,113]. Given the lower frequency of abnormal troponin I in asymptomatic patients with end-stage renal disease, it has been suggested that this may be a more specific marker of cardiac ischaemia than troponin T for this group of patients [113,114]. Several factors are likely to explain the discrepancy between troponins I and T. Free cytosolic proteins are released earlier when cells are damaged, estimated to be 7% for troponin T as compared to 3.5% for troponin I [115]. There is roughly twice as much troponin T as troponin I per gram of myocardium [116]. Moreover, uraemia increases the free serum concentration and the clearance of protein-bound factors. As troponin I is released from the myocardium only as a complex and troponin T is released as a complex as well as free troponin T, it is possible that uraemia may affect the detection, release or clearance of different troponin subunits. Since free and bound troponin T are large molecules (37 and 77 kDa, respectively), it is unlikely that the kidney is responsible for clearance. Indeed, the half-life and clearance of troponin I after an AMI appear similar between patients with normal renal function and end-stage renal disease [117].

A number of studies investigated the prognostic role of serum troponins in patients with renal failure using the newer cardiac troponin assays. The largest of these trials enrolled a total of 733 patients with end-stage renal disease [118]. Troponin T was more commonly elevated than troponin I, and both an increased troponin T and an increased troponin I were predictive of increased mortality. In the setting of an ACS, a recent analysis of over 7000 patients from the GUSTO (Global Use of Strategies To Open occluded coronary arteries) IV trial found that troponin T is an important predictor for adverse outcome in both patients with and without renal failure [119]. In summary, serum cardiac troponin concentrations are frequently increased in asymptomatic patients with renal failure. This is likely to represent multifactorial pathology potentially including cardiac dysfunction, left ventricular hypertrophy, as well as subclinical myocardial infarction and is associated with an increased risk of morbidity and mortality in those patients.

Markers of inflammation

Of the numerous inflammatory markers that have been investigated over the past decade, CRP is the most widely studied. The exact source of elevated CRP levels among patients with unstable coronary syndromes remains unclear. Given that myocardial damage is also a major inflammatory stimulus, it is important to note that in a combined analysis of FRISC-II and GUSTO-IV, CRP elevation over a period of up to 120 hours was only found in patients with elevated troponin levels [120]. Similarly, in the CAPTURE (c7E3 Anti Platelet Therapy in Unstable REfractory angina) study, CRP levels were significantly higher in troponin-positive patients [94]. This suggests that an acute inflammatory process induced by myocardial damage is superimposed on a chronic inflammatory condition, both of which might influence long-term outcome in ACS. It is also important to note, however, that pro-inflammatory cytokines are also released from adipose tissue, tissue macrophages and injured myocardium.

There is robust evidence that, even among patients with troponin-negative ACS, elevated levels of CRP are predictive of future risk [94,125,126]. In the CAPTURE trial, only troponin T was predictive for the initial 72-hour period, but both CRP and troponin T were independent predictors of risk at 6 months [94]. The FRISC study confirmed that mortality is associated with elevated CRP levels at the time of the index event and continues to increase for several years [127]. In all studies the predictive value of CRP was independent of, and additive to, troponin. Most importantly, CRP has prognostic value among patients without evidence of myocyte necrosis; specifically, even among patients negative for troponin, an elevated CRP is predictive of future adverse events [94,126,127]. Recently, however, it was reported from the Reykjavik prospective cohort study, based on a large number of patients over a 20-year follow-up, that the predictive value of a single baseline measurement of CRP for the 20-year incidence of cardiovascular events was much less strong than previously estimated [128–131]. CRP added little to the predictive value provided by the assessment of traditional risk factors, including LDL-cholesterol. Accordingly, more research or more specific markers are necessary to clarify the use of CRP as a marker of cardiovascular risk in clinical practice.

Type 2 secretory phospholipase A_2 ($sPLA_2$) is also an acute-phase reactant, which accumulates in atherosclerotic arterial walls, elicits several effects on monocytes, and provides a link between inflammation and lipid accumulation in atherosclerotic plaques. It is present in the media of normal as well as diseased arteries, hydrolyses phospholipids, and contributes to the production of oxidized LDL-cholesterol which is taken up by macrophages resulting in enhanced transformation into foam cells. The $sPLA_2$ exhibits similar features to CRP as a marker of plaque inflammation as well as endothelial dysfunction [121,122] and may predict coronary events independently of other risk factors in patients with unstable angina [123]. Similarly, elevated levels of the lipoprotein-associated PLA_2 ($Lp\text{-}PLA_2$), using a different approach to determine PA_2 activation, have been shown to predict future coronary events in apparently healthy middle-aged men with moderately elevated total cholesterol, independent of CRP [124].

Current research activities focus on the identification of more upstream markers of the inflammatory cascade which may be more representative of vascular inflammation as opposed to systemic inflammation. These novel inflammatory markers include pregnancy-associated plasma protein A (PAPP-A). This zinc-binding metalloproteinase enzyme is a specific activator of insulin-like growth factor I, an important mediator of atherosclerosis. Among patients who died suddenly from cardiac causes, PAPP-A was abundantly expressed in ruptured and eroded unstable plaques, but was absent or minimally expressed in stable plaques [132]. In plaques with large lipid cores and cap rupture, staining for PAPP-A revealed that the enzyme occurred mostly in the inflammatory shoulder region. A clinical study suggests that measurement of plasma PAPP-A is an independent predictor of ischaemic cardiac events and the need of revascularization in patients who present with suspected myocardial infarction but remain troponin negative [133]. These data require validation in larger cohorts before they can enter routine use.

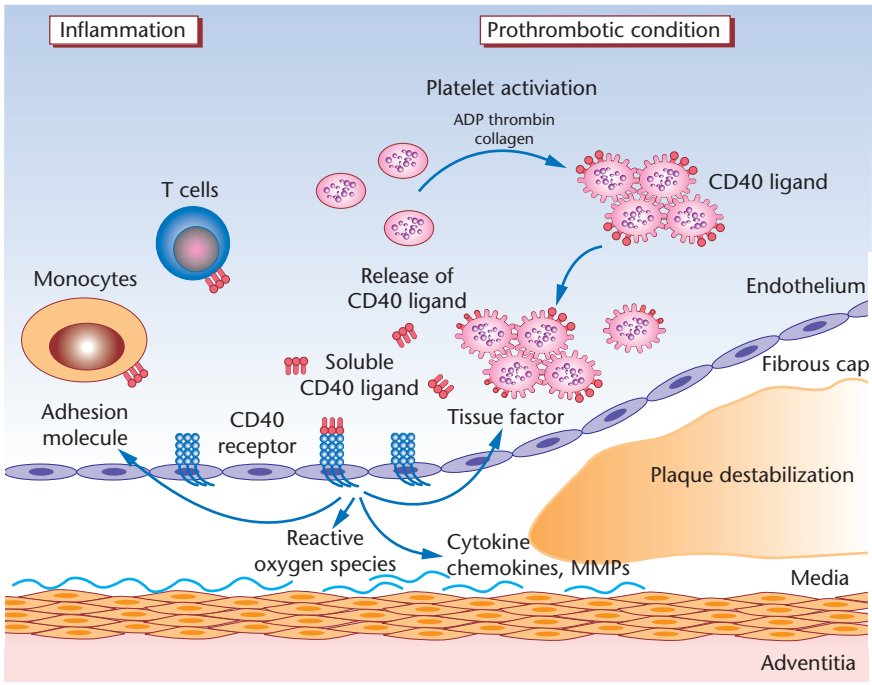

Figure 12.16 The pathophysiological role of soluble CD40 ligand in patients with acute coronary syndromes.

Biochemical markers of platelet activation

It has been shown that soluble CD40 ligand is a powerful biochemical marker of thrombotic inflammatory activation (Fig. 12.16) in patients with ACS, supporting the close relationship between inflammation and thrombotic activation in ACS [134,135]. Furthermore, studies have demonstrated that combining this marker with classical markers of necrosis (troponins) can help us to identify patients at the highest risk for subsequent cardiovascular events. Plaque rupture induces platelet activation through liberation of collagen, thrombin and ADP. The platelet activation results in an increased surface expression of CD40 ligand which subsequently is cleaved from the membrane surface. The released soluble CD40 ligand can activate CD40 on endothelial cells and, thereby, induce a pro-inflammatory cascade in the vessel wall. Moreover, soluble CD40 ligand can activate CD40 which is also expressed on inflammatory cells such as monocytes and T cells. The subsequent activation of these inflammatory cells and their invasion of the ruptured or eroded plaque results in a further inflammatory perturbation of the vessel wall. Importantly, blockade of the glycoprotein IIb/IIIa receptor on platelets inhibits the release of soluble CD40 ligand through inhibition of platelet aggregation via fibrinogen. It has been shown that levels of soluble CD40 ligand do not only identify patients with ACS that are at highest risk for ischaemic events but also predict which patient will derive major benefit from antiplatelet treatment with the glycoprotein IIb/IIIa receptor antagonist abciximab [135].

Inflammatory balance in patients with acute coronary syndromes

Several studies indicate an important role of inflammatory balance in patients with an ACS [136,137]. Interleukin-10 (IL-10) is secreted by activated monocytes/macrophages and lymphocytes [138]. It has multifaceted anti-inflammatory properties including inhibition of the prototypic pro-inflammatory transcription factor NF-κB leading to suppressed cytokine production, inhibition of matrix-degrading metalloproteinases, reduction of tissue factor expression, inhibition of apoptosis of macrophages and monocytes following infection, and promotion of the phenotypic switch of lymphocytes into the T helper type 2 phenotype [137]. All these inflammatory mechanisms have been shown to play a pivotal role for atherosclerotic lesion development and progression, suggesting a potential regulatory role of IL-10. Numerous recent experimental studies have shown that either systemic or local IL-10 gene transfer not only attenuates atherogenesis [138,139], but also affects processes associated with lesion progression [140]. Consistently, in the CAPTURE trial, elevated serum levels of the anti-inflammatory cytokine IL-10 were linked to patients with ACS having a significantly improved outcome [137]. The predictive value of IL-10 serum levels was independent of elevated troponin levels, which reflect the acute risk secondary to thrombotic complications during ACS. Thus, reduced IL-10 serum levels are not only a marker of plaque instability favouring the development of ACS, but—more importantly—are indicative of a poor prognosis even

after the occurrence of an acute ischaemic event caused by plaque instability. In addition, the beneficial effect of elevated serum levels of IL-10 was restricted to patients with elevated CRP serum levels indicative of an enhanced systemic inflammatory response. These data further support the concept that the balance between pro- and anti-inflammatory cytokines is a major determinant of patients' outcome in ACS.

Oxidative stress in acute coronary syndromes

There is growing evidence that myocardial cell injury is not only related to platelet activation but also preceded by recruitment and activation of leucocytes, most notably polymorphonuclear neutrophils [141]. Polymorphonuclear neutrophils have been shown to increasingly undergo degranulation within the coronary circulation in ACS [39]. One of the principal mediators secreted upon degranulation of polymorphonuclear neutrophils is myeloperoxidase, a haemoprotein traditionally viewed as a microbicidal enzyme [142]. There is accumulating evidence that myeloperoxidase displays potent pro-atherogenic properties. For example, myeloperoxidase can oxidize LDL-cholesterol, thereby propagating uptake by macrophages and perpetuating foam cell formation [143]. Furthermore, myeloperoxidase has been shown to activate metalloproteinases and promote destabilization and rupture of the atherosclerotic plaque surface [144]. Also, myeloperoxidase catalytically consumes endothelium-derived nitric oxide, thereby reducing nitric oxide bioavailability and impairing its vasodilatory and anti-inflammatory functions [145,146]. Two studies have revealed that myeloperoxidase is a powerful predictor of adverse outcome in patients with ACS [147,148]. Particularly in individuals with low troponin levels, myeloperoxidase identified patients at increased risk for early cardiovascular events that occur within days after the onset of symptoms [147]. This suggests that myeloperoxidase unmasks states of acute inflammation in the coronary circulation indicative of increased neutrophil activation, which ultimately precedes myocardial injury. While future prospective studies are warranted to confirm these results, the current findings support the rationale to further evaluate myeloperoxidase for risk stratification in patients with ACS and encourage the development of pharmacological strategies to modulate the catalytic activity of this enzyme.

Biochemical markers of neurohumoral activation

Neurohumoral activation of the heart can be monitored by measuring systemic levels of natriuretic peptides secreted from the heart. Atrial natriuretic peptides (ANP) are primarily produced in the cardiac atria, whereas brain (B-type) natriuretic peptides (BNP) are mainly synthesized in the ventricular myocardium [149]. Both peptides are generated as pro-hormones (proANP and proBNP), that upon secretion are cleaved into biologically active peptides (ANP and BNP) and N-terminal pro-hormone fragments (NTproANP and NTproBNP). Natriuretic peptides are released mainly in response to increased stretch or wall tension and are involved in the regulation of blood pressure, blood volume and sodium balance via modulation of natriuresis, vasodilatation and inhibition of the renin–angiotensin–aldosterone system as well as the sympathetic nervous system. In disease states, BNP and NTproBNP have a greater proportional rise than ANP and NTproANP, and have received most of the interest for a clinical application. Both natriuretic peptides are highly sensitive and fairly specific markers for the detection of left ventricular dysfunction. Therefore, investigators originally focused on the predictive value of natriuretic peptides in patients with congestive heart failure but more recently this focus has expanded to include ACS patients with unstable angina and NSTEMI. Patients with ACS and elevated NTproBNP or BNP levels, respectively, have a three- to fivefold increased mortality compared to those with lower levels of NTproBNP or BNP. More importantly, the level of NTproBNP was strongly associated with mortality even when adjusted for age, Killip class and left ventricular ejection fraction determined by echocardiography [150,151]. Moreover, in patients with stable coronary heart disease elevated levels of BNP are independently associated with inducible ischaemia and therefore provide the rationale for the hypothesis that NTproBNP levels in patients with ACS may also reflect ischaemia-induced left ventricular dysfunction even in the absence of myocardial necrosis [152].

Point-of-care testing

If patients with ACS without ST-segment elevations stabilize clinically, minor time delays may not be as critical as in STEMI. However, point-of-care assays are available for the determination of CK-MB, myoglobin and troponins [93,102–104,153–155]. These hand-held, disposable assays use small quantities of anticoagulated blood to determine the presence or absence of abnormal concentrations of cardiac proteins within 15 to 20 minutes. Based on immunochromatic methods these assays allow qualitative determination of myocardial proteins by utilization of mono- or polyclonal antibodies directed against the target protein. Application of a defined amount of whole blood or plasma onto the test strip initiates the assay process. From whole blood samples cellular blood components are separated by a permeable membrane. If abnormal concentrations of cardiac markers are present,

colour-labelled antibodies will bind to the proteins. By means of solid-phase technology the antibody–protein complex adheres to an immobilized ligand as part of the test kit and the process of antibody binding and migration finally results in an identifiable colour development at a specified region of the test kit.

Reading of point-of-care tests is performed visually and therefore is observer dependent. A further major limitation is that visual assessment only allows a yes or no statement without definitive information regarding the concentration of the marker in the blood. In general, a darker or earlier developing signal line indicates a higher concentration of the marker in the sample but remains subjective. Careful reading exactly at the assay-specific indicated time under good illumination is essential to avoid observer misinterpretation especially in cases of marginal antibody binding. Even the faintest colouring should be read as a positive test result. No special skill or prolonged training is required to read the result of these assays. Accordingly, these tests can be performed by a variety of members of the health-care team [156]. Numerous studies have shown that point-of-care test systems are reliable, provided the above precautions were taken into consideration [92,157]. Time to signal appearance (< 10 min) has been shown to identify a subgroup of patients that is at particular risk [158]. For troponin T an optical reading system is offered which also provides a printout of the quantitative result [104,159].

Multimarker approach in clinical practice

Since ACS is a complex event, several markers reflecting the respective pathophysiological pathways may be advantageous for risk stratification. Markers for the acute risk of myocardial infarction and for long-term mortality can be distinguished. The combined use of markers for myocardial necrosis, inflammation and neurohumoral activation may significantly add to our ability to correctly identify patients who are at high risk for future cardiovascular events (Fig. 12.17). Several studies have demonstrated clearly that a multimarker approach improves risk stratification [14,160]. The predictive value of CRP is strongly related to myocardial injury as evidenced by troponin elevation and is more related to the long-term outcome of these patients. Novel inflammatory markers such as myeloperoxidase and PAPP-A appear to be more closely related to the short-term risk of patients with ACS. These individuals with evidence for inflamed and unstable atherosclerotic plaque formation may benefit most from an aggressive medical treatment and the benefits of an early invasive strategy may also be greatest among those with elevated levels of inflammatory biomarkers.

Many of the above markers are not yet available for routine use to translate the complete potential of biochemistry to daily practice. Currently, it is advised to use troponins for the acute risk stratification on arrival of the patient in the hospital. During the subsequent days, BNP or NTproBNP allows estimation of the area that was at risk during the acute event and the impact on long-term outcome. For the detection of the underlying inflammatory activity responsible for the long-term mortality of the patients, currently only CRP is available on a routine basis and should be measured at the time of discharge.

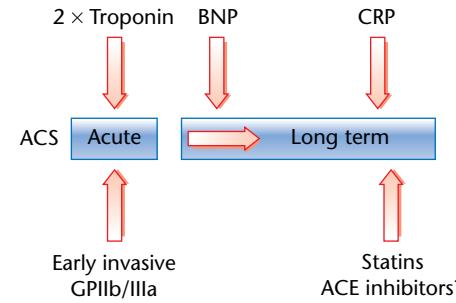

Figure 12.17 Multimarker testing in ACS during hospitalization.

Risk scores in acute coronary syndrome

The integration of underlying risks of coronary artery disease and risks of thrombosis is potentially challenging at the bedside. Accordingly, there is a need for simplified and widely applicable risk stratification tools facilitating the triage and management of patients with ACS.

Age, systolic blood pressure and heart rate

The simplest risk scoring systems have demonstrated that, in population analyses, a simple composite of age, systolic blood pressure and heart rate provides valuable prognostic information for patient groups. However, this information is less accurate and predictive for individual patients [161].

TIMI risk score

Based upon data from clinical trials, the TIMI risk score was derived and tested in STEMI populations [162]. This score allocates points on the basis of age, history of diabetes, hypertension or angina and examination features including blood pressure, heart rate, Killip class and weight. It also includes ST-segment elevation or left bundle branch block on the ECG and time to reperfusion of > 4 hours. Application of the data to the NRMI Registry demonstrates that the registry patients have a higher risk of death than the overall trial populations and the risk score showed strong prognostic capability (C index 0.74 overall). Among patients not receiving reperfusion therapy

the risk score underestimated death rates and offered lower discriminatory capacity (C index 0.65). Nevertheless, this score provides a simple and practical bedside tool for the triage of patients into high-risk, moderate-risk, or low-risk categories. In NSTEMI, the TIMI risk score was less accurate in predicting death (C index 0.61) [163]. The PREDICT score includes assessment of left ventricular function on discharge, with improved predictive accuracy [163].

GRACE risk score

Based upon a large unselected registry population of the full spectrum of ACS, eight variables were derived with independent predictive power for in-hospital death and for post-discharge death or myocardial infarction at 6 months post-discharge. The data were tested prospectively and against an external dataset (GUSTO-IIB). The eight variables contain more than 90% of the predictive capacity of the full multivariable model and the C statistic for in-hospital death was 0.84 and for post-discharge death or myocardial infarction was 0.71. The score can be used to provide a numerical risk of in-hospital death or post-discharge death or MI based upon a score card or using software running on palm devices or personal computers [164,165]. Thus, although the contributions of individual risk factors are difficult to estimate at the bedside for each individual patient, newly established risk-score tools provide simple methods to estimate the risk of death and MI, and hence guide in-hospital and post-discharge management.

Imaging modalities in ACS

Imaging modalities are secondary tools in the diagnosis of ACS. They usually only confirm or exclude the working diagnosis based on biochemical markers and the ECG.

Coronary angiography

This is the gold standard to prove or exclude coronary artery disease. In approximately 10–15% of patients presenting with chest pain no high-grade lesion can be identified, or coronary artery disease is excluded. The extent and location of lesions is useful for risk assessment and decision-making concerning revascularization by means of angioplasty or surgery. The culprit lesions that are responsible for the clinical symptoms frequently show filling defects, indicating intracoronary thrombus formation.

Echocardiography

Left ventricular systolic function is an important prognostic variable in patients with ischaemic heart disease and can easily and accurately be assessed by echocardiography. Two-dimensional echocardiography in experienced hands is a useful bedside technique in the triage of patients with acute chest pain. Regional wall-motion abnormalities occur within seconds after coronary occlusion well before necrosis. However, these are not specific for acute events and may be the result of old infarctions. Transient localized hypokinesia or akinesia in segments of the left ventricle wall may be detected during ischaemia, with normal wall motion on resolution of ischaemia. The absence of wall-motion abnormalities excludes major myocardial infarction. Echocardiography is of additional value for the diagnosis of other causes of chest pain such as acute aortic dissection, pericardial effusion, or massive pulmonary embolism.

Myocardial perfusion scintigraphy

This technology is usually not readily available and is therefore only infrequently used for the triage of patients presenting with acute chest pain. A normal resting technetium-99 myocardial perfusion scintigram effectively excludes major myocardial infarction. An abnormal acute scintigram is not diagnostic of acute infarction unless it is known previously to have been normal, but it does indicate the presence of coronary artery disease and the need for further evaluation.

Cardiac magnetic resonance imaging

This new technology is available in an increasing number of centres on an emergency basis. The multimodality characteristic of cardiac magnetic resonance imaging provides a comprehensive examination, combining regional contractile function, myocardial perfusion and viability. This allows identification of patients with ACS and differentiation of patients with myocardial infarction. In addition, cardiac magnetic resonance imaging can rule out other potential reasons for acute chest pain, such as myocarditis, pericarditis, aortic dissection and pulmonary embolism (Fig. 12.18) [80].

Risk stratification according to guidelines in ACS without persistent ST elevation

The Task Force Report of the European Society of Cardiology distinguishes between short-term and long-term risk in patients presenting with ACS. The short-term risk is related to the acute thrombotic event, whereas the long-term risk is determined by the progression of the underlying disease [101].

The algorithm for the work-up of patients presenting with chest pain to the emergency room is depicted in Fig. 12.19. At presentation patients can be assigned

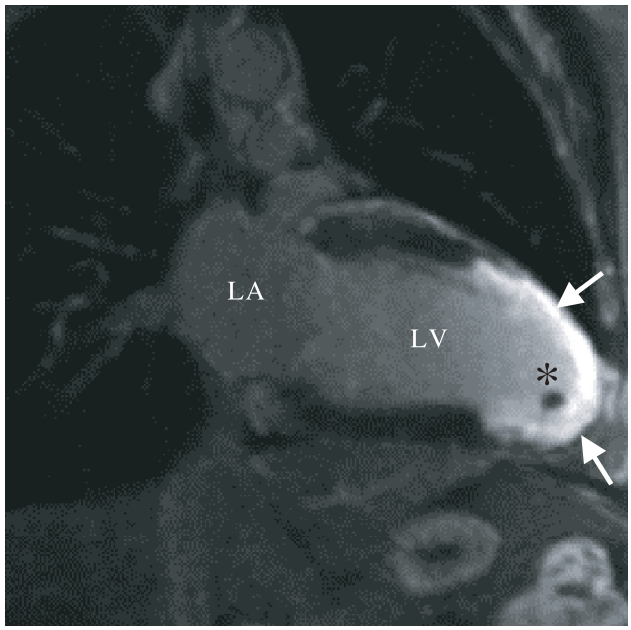

Figure 12.18 Vertical long axis of the left ventricle (LV) using an inversion recovery T_1-weighted gradient echo sequence 10 min after injection of gadolinium DTPA showing a large region of hyperenhancement in the anterior wall and the apex (i.e. late enhancement) representing a transmural infarction (arrow). An apical thrombus shows no contrast uptake (*). LA, left atrium.

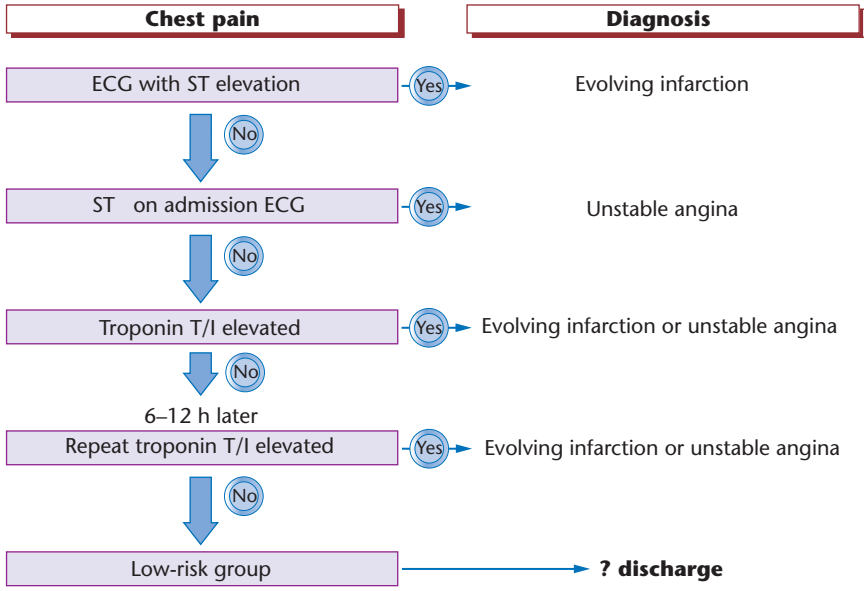

Figure 12.19 Algorithm of work-up of patients with chest pain.

to the high-risk or low-risk group according to several features that have been derived from large studies (Table 12.8). The therapeutic management is to be based on the risk assessment. Troponin elevations play the central role for the acute risk. In addition, dynamic ST-segment depression, critical arrhythmias (ventricular tachycardia, ventricular fibrillation), or haemodynamic instability (symptoms of shock) are linked to increased risk. Furthermore, the presence of diabetes is linked to a high likelihood of significant coronary artery disease and this alone places the patient in the high-risk group.

The long-term risk of mortality is related to well-established parameters. These include age and the established risk factors. From imaging modalities the extent of coronary artery disease (main stem lesion) and reduced left ventricular function are predictors of future outcome. Biochemical markers of inflammation (CRP) and of renal insufficiency (creatinine clearance) are further strongly associated with increased mortality.

Table 12.8 Parameters of high acute risk

Recurrent ischaemia/chest pain
Dynamic ST-segment changes
Elevated biomarkers: troponin, BNP or NTproBNP
Haemodynamic instability
Major arrhythmias (VF, VT)
Diabetes

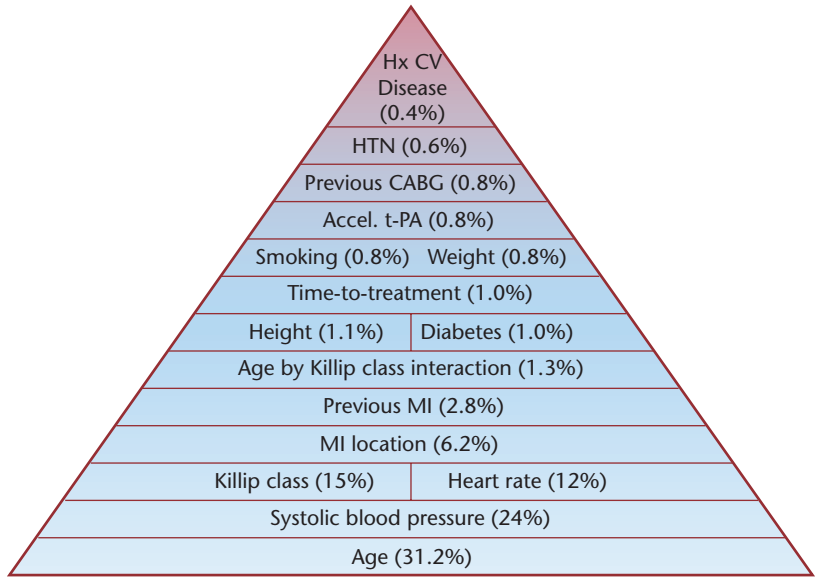

Figure 12.20 Multivariate model of 30-day mortality according to GUSTO I trial. Adapted from Lee *et al*. [166]. Hx, history.

Risk stratification in ST-segment elevation myocardial infarction

Whereas risk factors for the development of atherothrombosis provide insights into disease mechanisms and the opportunity for primary and secondary prevention therapy, analysis of the risk for adverse outcome after presentation with ST-segment elevations is critically important in guiding management and therapeutic decisions. Analysis usually uses a combination of clinical, ECG and biochemical parameters. Five rather simple baseline parameters can be used to predict more than 90% of the 30-day mortality: age, systolic blood pressure, Killip class, heart rate and infarct localization (Fig. 12.20) [166].

Killip class

The haemodynamic impact of the evolving myocardial infarction is clinically evident by the symptoms of shock. The Killip classification is widely used and linked to outcome. Killip class IV ('cardiogenic shock') is found in about 5% of AMI patients and is associated with extremely high mortality.

Infarct location

The prognosis of myocardial infarction is related to the extent of myocardium at risk and, related to this, to the site of coronary occlusion. The ECG reflects the infarct location (Table 12.5). Patients with main stem occlusion only rarely reach the hospital for reperfusion therapy. Occlusion of the proximal left anterior descending coronary artery proximal to the first septal branch is associated with high early and late mortality ('widow-maker'). Large inferior myocardial infarctions as a result of occlusion of a dominant right coronary artery are also a high risk, particularly when the right ventricle is involved. Other locations, such as apical (distal left anterior descending), lateral (diagonal branch), or small inferior infarctions (distal right or circumflex), show ST-segment elevations in only a few leads and have a better outcome. Strictly posterior myocardial infarctions (marginal branch of left circumflex) may escape routine ECG leads or only be evident through ST depression in V1 to V4, but usually have a good outcome.

ECG criteria

The ECG allows the rough location of the infarct artery and identification of the extent of the territory at risk. The development of a bundle branch block or atrioventricular block in anterior myocardial infarctions suggests involvement of a proximal septal artery and is associated with increased mortality. Atrioventricular blocks in inferior myocardial infarctions are frequent and mostly transient.

Biomarkers on presentation

Blood sampling for serum markers must be routinely performed in the acute phase, but one should not wait for the results to initiate reperfusion treatment. The finding of elevated markers of necrosis may sometimes be helpful in deciding to give reperfusion therapy (e.g. in patients with left bundle branch block), but should retard decision-making. Elevation of markers of necrosis (troponin) on arrival in hospital is associated with adverse outcome [167].

Personal perspective

The prevalence of coronary artery disease and consecutively the prevalence of ACS are continuously increasing as a result of growing life expectancy and increasing rates of obesity and diabetes. A further increase is expected not only in highly industrialized countries but also, and most pronounced, in the rapidly developing, densely populated regions of the world. It is already conceivable that diagnosis and risk assessment of individual patients in the near future will be guided by sophisticated biochemical markers that capture earlier stages of pathophysiology long before fatal events have occurred. Further contributions to the early detection of patients at risk are expected from improved non-invasive imaging techniques. There is little room for improvement in the outcome of ongoing ST-segment elevation myocardial infarctions with modern invasive management techniques, but health-education programmes directed towards better early identification may contribute most effectively to reducing fatal outcomes.

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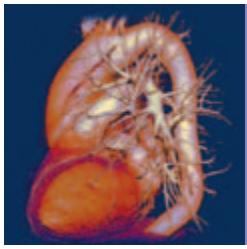

13 Management of Acute Coronary Syndromes

Eric Boersma, Frans Van de Werf and Felix Zijlstra

Summary

Optimal treatment of patients presenting with an acute coronary syndrome aims at immediate relief of ischaemia and the prevention of serious adverse events, including death, myocardial (re)infarction and life-threatening arrhythmias. Guidelines recommend that patients with suspected acute coronary syndrome be admitted to an in-patient unit with careful observation for recurrent ischaemia, continuous ECG monitoring, and frequent assessment of vital signs. Once the diagnosis has been established, patient management may include antiplatelet therapy, antithrombin therapy, fibrinolytic therapy, coronary angioplasty, or cardiac surgery.

In patients presenting without persistent ST-segment elevation, aspirin treatment is associated with a 53% (95% CI 39–63%) reduction in the incidence of death or non-fatal myocardial infarction, whereas heparin treatment is associated with a 34% (95% CI 1–56%) reduction in this composite end-point. The use of glycoprotein IIb/IIIa inhibitors in patients undergoing early percutaneous coronary intervention results in a 41% (95% CI 19–56%) reduction in periprocedural thrombotic complications. However, the optimal timing of coronary revascularization is still the subject of debate. The strategy of early invasive treatment was associated with a 15% (95% CI 3–26%) reduction in the composite end-point of death or myocardial infarction after a 1-year follow-up compared with conservative treatment, but the event reduction might be underestimated because of the large number of patients who crossed over to invasive treatment, and the restrictive use of stents and glycoprotein IIb/IIIa inhibitors.

In patients presenting with ST-segment elevation, fibrinolytic therapy is associated with an 18% (95% CI 4–23%) mortality reduction. In patients receiving fibrinolysis within 1 hour of symptom onset, a 48% event reduction can be obtained. A primary percutaneous coronary intervention results in an additional 30% (95% CI 16–42%) mortality reduction compared to fibrinolysis. Ongoing trials will reveal whether a strategy of planned, immediate angioplasty after an initial pharmacological regimen (so-called 'facilitated' angioplasty) will result in even further mortality reduction.

Introduction

Patients presenting with acute chest pain represent a broad clinical spectrum, ranging from atypical and non-cardiac diseases to a class of syndromes including unstable angina pectoris, myocardial infarction and sudden death, otherwise known as acute ischaemic heart diseases or acute coronary syndromes (ACS). In the latter, the chronic process of coronary atherosclerosis has suddenly progressed, with subsequent activation of the coagulation system. Coronary plaque vulnerability and destabilization have multifactorial aetiologies, with inflammation, cap matrix and necrotic lipid core remodelling, and intraplaque haemorrhage being important associated pathophysiological processes [1].

Diagnosis and medical decision-making in acute chest pain patients rest on two important pillars: the electrocardiogram (ECG) and biochemical testing (Fig. 13.1).

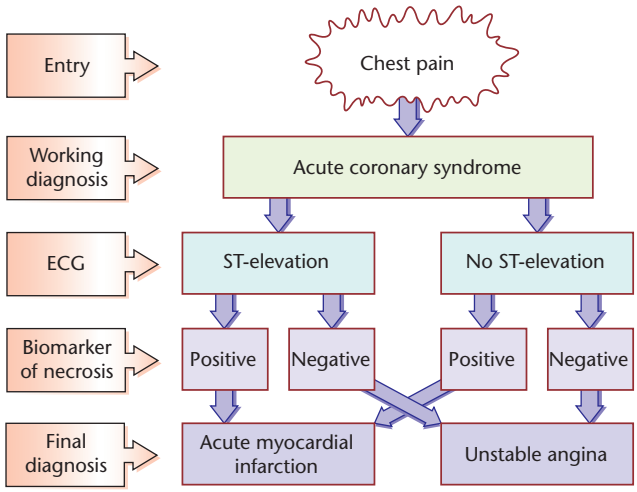

Figure 13.1 Terminology used in acute coronary syndromes. Reproduced with permission from Hamm *et al. Lancet* 2001; **358**: 1533–1538 [151].

Patients presenting with persistent ST-segment elevation (STE) or new onset left bundle branch block with subsequent elevation of serum levels of markers of myocardial necrosis usually have a totally occluded epicardial coronary artery. The therapeutic objective is rapid, complete and sustained reperfusion by fibrinolytic therapy or percutaneous coronary intervention (PCI). Patients with acute chest pain who present without persistent STE, but with ST-segment depression or T-wave abnormalities, are diagnosed as having either myocardial infarction or unstable angina pectoris, depending on the presence or absence of elevated serum levels of markers of myocardial necrosis. ACS patients without persistent STE are candidates for aggressive medical management, possibly followed by PCI.

This chapter presents a concise overview of the treatment options available for ACS patients. For the greater part, this review is limited to in-hospital treatment that has proven clinical benefits, based on evidence gained in randomized controlled clinical trials. Even then, a large number of pharmacological and mechanical interventions has to be discussed. For reasons of readability, with regard to medical therapies, we therefore mainly describe class (efficacy) effects, whereas details on applied dosages are omitted. Still, it should be emphasized that findings of clinical studies should be interpreted in relation to the pharmacological properties of the applied agents, and in relation to evidence that exists from other investigations. Clinicians should preferably use agents that have been proven effective in specific indications. Detailed advice for the treatment of ACS patients can be found in guidelines of the European Society of Cardiology (ESC) and the American College of Cardiology (ACC)/American Heart Association (AHA), in the remainder of this chapter referred to as 'guidelines' [2–5].

Methods

A computerized MEDLINE search identified 19 063 reports that were published in English between January 1980 and June 2004, with 'acute coronary syndromes', 'unstable angina pectoris', or 'myocardial infarction' as major topics, and 'therapy' as a secondary topic. Out of these, we reviewed the abstracts of reports labelled as 'clinical trial' (n = 3944), 'meta-analysis' (n = 134), 'review' (n = 2958), or 'practice guidelines' (n = 55). Relevant papers were selected, and their content was examined, whereas the corresponding bibliographies were manually searched. In addition, a search was performed of the scientific sessions abstracts published between January 2000 and June 2004 in *Circulation*, the *Journal of the American College of Cardiology* and the *European Heart Journal*.

Clinical trial results are summarized by figures that present the number of patients randomized, the absolute incidence of an important efficacy end-point, the relative risk reduction by experimental therapy compared with control therapy, and the absolute risk reduction. The relative risk reduction is expressed as an odds ratio together with the corresponding 95% confidence interval (CI). The pooled odds ratios of trials evaluating similar treatment strategies are determined by the method of Cochrane–Mantel–Haenszel, whereas the Breslow–Day test was applied to examine the statistical evidence of heterogeneity between the trial-specific odds ratios [6,7]. In the figures, individual trial odds ratios are indicated by solid black squares, whereas the stratified overview of the results of all trials is indicated by an open square. Within each figure, the area of these squares is proportional to the amount of statistical information contributed by the trial (i.e. approximately proportional to the number of events).

General care in acute coronary syndromes

Optimal treatment of patients presenting with an acute coronary syndrome aims for immediate relief of ischaemia, and the prevention of serious adverse events, including death, myocardial (re)infarction and life-threatening arrhythmias. The severity of symptoms dictates some of the general care that should be given during the initial treatment. In general, guidelines recommend that patients

with suspected acute coronary syndrome be admitted to an in-patient unit with careful observation for recurrent ischaemia, continuous ECG monitoring, and frequent assessment of vital signs. Once the diagnosis has been established, patient management may include anti-ischaemic therapy, antiplatelet therapy, antithrombin therapy, fibrinolytic therapy, coronary angioplasty or cardiac surgery.

Relief of pain is of paramount importance, not only for humane reasons, but also because the pain is associated with sympathetic activation, which causes vasoconstriction and increases the workload of the heart. Intravenous opioids (morphine or diamorphine) are the analgesics most commonly used in this context. Guidelines recommend the administration of oxygen (by mask or nasal prongs), especially to patients with cyanosis, respiratory distress, and those who have features of heart failure or shock.

Anxiety is a natural response to the pain and the circumstances surrounding an acute coronary syndrome. Reassurance of the patient and his relatives is of great importance. If the patient becomes excessively disturbed, administration of a tranquillizer may be considered, but opioids are frequently all that is required.

Treatment of non-ST-elevation acute coronary syndromes

Anti-ischaemic therapy

Beta-blockers

In non-ST-segment elevation acute coronary syndromes (NSTE-ACS), the primary benefits of beta-blockers are the result of their effects on 1-adrenergic receptors that cause a decrease in cardiac work and myocardial oxygen demand. Slowing of the heart rate also has a favourable effect, acting not only to reduce oxygen demand but also to increase the duration of diastole and diastolic pressure-time, a determinant of coronary flow and collateral flow.

Initial studies of beta-blocker benefits in NSTE-ACS were small and uncontrolled. A meta-analysis of the randomized controlled trials that are conducted in patients with 'threatened myocardial infarction' (i.e. characteristic chest pain but normal ECG, or only ST-segment depression) suggests that initial treatment with intravenous beta-blockers followed by oral treatment for a week leads to a 13% reduction in the risk of myocardial infarction compared with control therapy [8]. Although the trials in patients presenting with NSTE-ACS lack the power to assess reliably the effects of beta-blockers on mortality, randomized trials in patients presenting with stable angina, recent myocardial infarction and STE-ACS have all shown a statistically significant mortality reduction by these agents [9,10]. Guidelines therefore recommend beta-blockers as a routine part of care in acute coronary syndromes.

Nitrates

The therapeutic benefits of nitrates are related to their effects on the peripheral and coronary circulation. The major therapeutic benefit is related to the venodilatory effects, which lead to a decrease in myocardial preload and left ventricular end-diastolic volume, resulting in a decrease in myocardial oxygen consumption. In addition, nitrates dilate normal and atherosclerotic coronary arteries and increase coronary collateral flow.

Most studies of nitrate treatment in NSTE-ACS have been small and uncontrolled [11,12]. In fact, there are no randomized controlled trials that address the clinical efficacy of these agents. Thus, the rationale for the use of nitrates in NSTE-ACS is extrapolated from pathophysiological principles and clinical observations.

Calcium-channel blockers

Calcium-channel blockers are vasodilating drugs. In addition, some agents of this class have significant direct effects on atrioventricular conduction and heart rate. There are three subclasses, which are chemically distinct and have different pharmacological effects: the dihydropyridines (e.g. nifedipine), the benzothiazepines (e.g. diltiazem) and the phenylalkylamines (e.g. verapamil). The agents in each subclass vary in the degree to which they produce vasodilatation, decreased myocardial contractility and delayed atrioventricular conduction. Atrioventricular block may be induced by phenylalkylamines. Nifedipine and amlodipine produce the most marked peripheral arterial vasodilatation. Diltiazem has the least vasodilatory effect. All subclasses cause similar coronary vasodilatation.

There are several small randomized trials that evaluated the clinical effectiveness of calcium-channel blockers in NSTE-ACS. Generally, they demonstrated efficacy in relieving symptoms that appears equivalent to that of beta-blockers [13,14]. However, calcium-channel blockers were not associated with a reduction in mortality or morbidity in these patients. For dihydropyridines, randomized trial data provide evidence for an increased mortality risk when they are administered early as a rapid-release, short-acting preparation without a beta-blocker

[15]. In view of these data, guidelines recommend calcium-channel blockers for symptom relief in patients who do not respond to beta-blockers and nitrates.

Antiplatelet therapy

The primary role of platelets is to maintain vascular integrity through haemostasis. However, in patients with atherosclerosis, this normal process may become excessive and result in thrombosis. The role of platelets in the pathophysiology of atherothrombotic diseases has been confirmed as central. While atherosclerosis is the major underlying chronic pathology, platelet-dependent thrombosis initiated by acute plaque rupture is mainly responsible for the acute clinical event. Platelet adhesion and aggregation are the key processes. Platelets do not adhere to normal endothelium, but do adhere to disrupted endothelial surfaces. Following adhesion, platelets undergo shape changes, secrete the contents of their alpha and dense granules, transform endogenous arachidonic acid into thromboxane A_2, and undergo conformational changes in glycoprotein (GP) IIb/IIIa receptors that effect platelet-to-platelet aggregation. The central role of platelet activation and aggregation in the pathophysiology of ACS makes it an ideal therapeutic target.

Aspirin

Acetylsalicylic acid (aspirin) was the first effective platelet inhibitor to be identified. Aspirin results in an irreversible modification of the enzyme cyclo-oxygenase, rendering it incapable of converting arachidonic acid into thromboxane A_2. Between 1983 and 1990 four randomized trials were conducted that studied the effectiveness of aspirin compared with control therapy in 3096 patients with NSTE-ACS (Fig. 13.2) [16–19]. The daily dose of aspirin varied from 324 to 1300 mg, whereas the treatment period varied from < 1 to 24 months. At the completion of study medication, the composite end-point of death or myocardial infarction was observed in 6.2% of the patients randomized to aspirin and in 12.2% of controls. Thus, aspirin was associated with a 53% relative risk reduction (odds ratio 0.47 and 95% CI 0.37–0.61). In a meta-analysis of 142 randomized trials (73 247 patients) involving a wide range of patients considered to be at high risk of vascular events, prolonged antiplatelet therapy, including aspirin, was associated with a 25% relative risk reduction in the composite end-point of vascular death, myocardial infarction or stroke compared with control therapy (6.9% vs. 9.2% events; odds ratio 0.75 and 95% CI 0.72–0.78) [20]. Aspirin doses in the range 75 to 150 mg were as effective as higher doses. Accordingly, guidelines recommend starting low-dose aspirin (with a loading dose of at least 300 mg) in patients with NSTE-ACS during the acute phase, and continuing medication during long-term follow-up.

Glycoprotein IIb/IIIa inhibitors

Aspirin is a relatively weak antiplatelet agent because it inhibits only one of several pathways that result in platelet aggregation. Blockade of the cyclo-oxygenase pathway by aspirin can be overcome by activation of other agonist pathways. The final common pathway in the process of platelet aggregation is the activation of the GP-IIb/IIIa receptor. Activated GP-IIb/IIIa receptors connect with fibrinogen to form bridges between activated platelets, leading to the formation of platelet thrombi. Thus, inhibitors of platelet GP-IIb/IIIa are more potent agents than aspirin. Four intravenous GP-IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban and lamifiban) have been evaluated in clinical trials.

Between 1991 and 1997 GP-IIb/IIIa inhibitors were first evaluated in patients undergoing PCI for various indications, to confront the challenge of platelet aggregation caused by culprit plaque disruption. A meta-analysis of 10 randomized trials (13 166 patients) in this environment demonstrated a 36% reduction in the 30-day incidence of death or myocardial infarction by GP-IIb/IIIa inhibitors compared with control therapy [21]. The

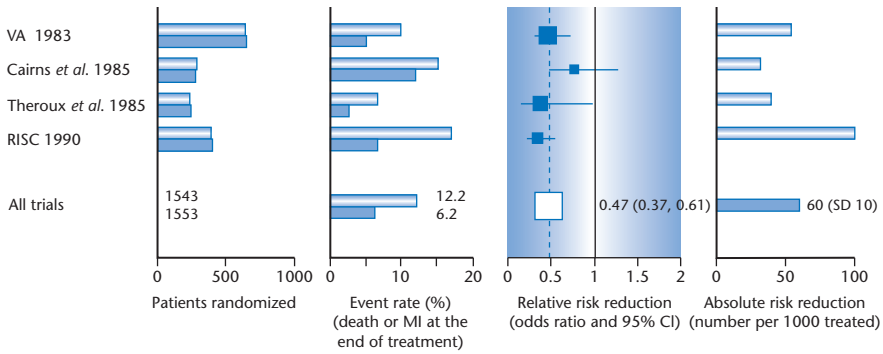

Figure 13.2 Death or myocardial infarction at the completion of study medication in randomized trials of aspirin (dark blue bars) versus control (light blue bars) in patients with non-ST-elevation acute coronary syndrome. Note the variable duration of study medication.

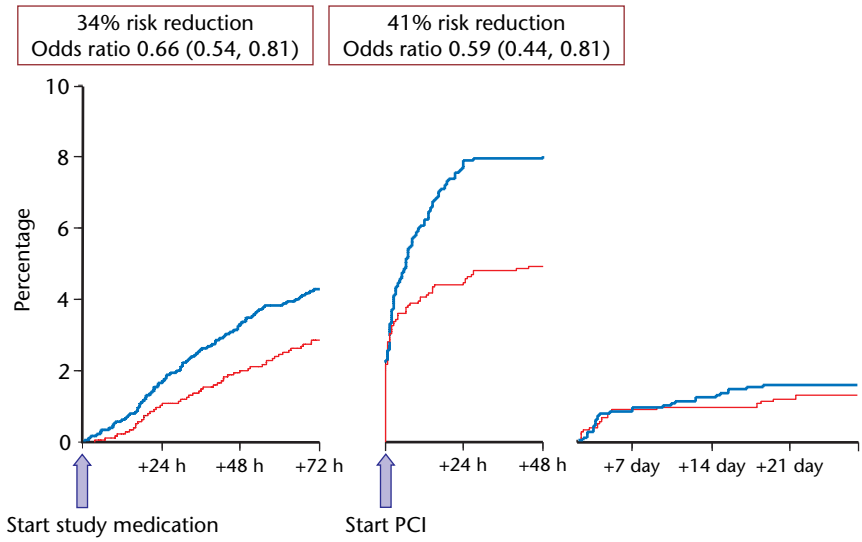

Figure 13.3 Cumulative incidence of death or non-fatal myocardial (re)infarction in patients with non-ST-elevation acute coronary syndrome randomly assigned to GP-IIb/IIIa inhibition (red lines) or placebo. Data were derived from CAPTURE, PURSUIT and PRISM-PLUS. Left panel: event rates during initial period of pharmacological treatment until moment of a PCI or coronary bypass grafting, if any. Middle panel: event rates among PCI patients during 48-hour period after procedure. During and shortly after PCI, all patients were on study medication. Right panel: event rates in period starting 48 hours after PCI, during which all patients were off study medication. At beginning of each period, event rates were (re)set at 0%. Any patient still alive contributes to event estimates in each period. Reproduced with permission from Boersma *et al.*, *Circulation* 1999; **100**: 2045–2048 [25].

CAPTURE trial, which was published in 1997, evaluated the effectiveness of GP-IIb/IIIa inhibitors (abciximab) in 1265 NSTE-ACS patients scheduled for early PCI [22]. The PRISM-PLUS (48-hour treatment with tirofiban; 1915 patients; published in 1998) and PURSUIT (72-hour treatment with eptifibatide; 10 948 patients; published in 1998) trials evaluated the effectiveness of GP-IIb/IIIa inhibitors in NSTE-ACS patients not scheduled for early PCI [23,24]. Still, a substantial number of patients underwent PCI during study medication. A meta-analysis that combined the CAPTURE, PRISM-PLUS and PURSUIT data demonstrated a 41% reduction in the periprocedural incidence of death or myocardial infarction in patients randomized to GP-IIb/IIIa-inhibitors compared with control therapy (4.9% vs. 8.0% events; odds ratio 0.59 and 95% CI 0.44–0.81; Fig. 13.3) [25]. A significant risk reduction was also observed in the short-term period before the intervention.

Several phase II trials have suggested that blockade of the platelet GP-IIb/IIIa receptor may also be useful in the treatment of NSTE-ACS patients not scheduled for early PCI. In this context, between 1994 and 2000 six phase III randomized trials (31 402 patients) were undertaken in aspirin-treated patients in whom early coronary revascularization was not recommended during study drug infusion (Fig. 13.4) [23,24,26–29]. Altogether 12 different treatment regimens were investigated, with a treatment duration that varied from 48 to 120 hours. In a meta-analysis of these trials, GP-IIb/IIIa inhibitors were associated with a modest, but statistically significant, 9% reduction in the 30-day incidence of death or myocardial infarction compared with control therapy (10.8% versus 11.8% events; odds ratio 0.91 and 95% CI 0.85–0.98) [30]. In patients with elevated cardiac troponins GP-IIb/IIIa inhibitors were associated with a 15% event reduction (10.3% versus 12.0% events; odds ratio 0.85 and 95% CI 0.71–1.0), whereas no risk reduction was seen in patients with negative troponins. This observation is in agreement with the notion that such elevated cardiac troponin levels reflect minimal myocardial damage resulting from platelet emboli. These patients seem to have active ongoing intracoronary thrombosis, which can be effectively reduced by powerful antiplatelet therapy.

In view of these data, guidelines recommend treatment with a GP-IIb/IIIa inhibitor in all NSTE-ACS patients scheduled for PCI. Treatment with a GP-IIb/IIIa inhibitor might also be considered early after admission in patients at high risk for thrombotic complications who are not routinely scheduled for early intervention, including those with elevated troponins or ST-segment depression, and diabetic patients. Treatment should then be continued until a decision to perform coronary intervention has been made. It should be noted that lamifiban is not registered for use in NSTE-ACS patients. In Europe,

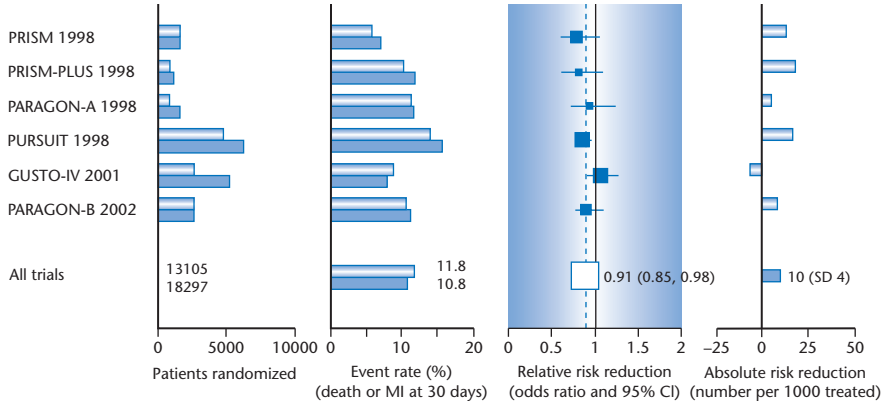

Figure 13.4 Death or myocardial infarction at 30-day follow-up in randomized trials of glycoprotein IIb/IIIa inhibitors (dark blue bars) vs. control (light blue bars) in patients with non-ST-elevation acute coronary syndrome who are not scheduled for early coronary intervention.

eptifibatide is not registered for use in patients undergoing PCI.

Four trials (33 404 patients; published in 2000) addressed prolonged treatment with oral GP-IIb/IIIa inhibitors in NSTE-ACS patients after coronary intervention [31]. Such prolonged treatment showed no evidence of benefit. In fact, a modest, but statistically significant increase in mortality was apparent in patients receiving oral GP-IIb/IIIa inhibitors [31].

Adenosine diphosphate receptor inhibitors

The thienopyridine derivatives, ticlopidine and clopidogrel, are agents that inhibit the platelet aggregation induced by adenosine diphosphate. Combining one of these agents with aspirin may therefore have an additive effect to reduce ischaemic events. Ticlopidine has been evaluated in NSTE-ACS patients by Balsano and colleagues [32]. In their randomized trial (652 patients; published in 1990) ticlopidine was associated with a significant reduction in the composite end-point of vascular death or myocardial infarction at 6 months compared with control therapy (7.3% versus 13.6% events; odds ratio 0.54 and 95% CI 0.30–0.85). However, intolerance of this drug is relatively frequent because of gastrointestinal disorders, or allergic reactions. In addition, neutropenia or thrombocytopenia may occur. Ticlopidine has been superseded by clopidogrel.

The CURE trial (12 562 patients), which was published in 2001, studied aspirin-treated NSTE-ACS patients, who were randomly allocated to treatment with clopidogrel (300 mg loading dose, followed by 75 mg daily) or placebo [33]. Study medication started in the acute phase, and was continued during a median follow-up of 9 months. In CURE, treatment with clopidogrel was associated with a 20% reduction in the incidence of cardiovascular death, myocardial infarction or stroke at the end of study-drug administration compared with control therapy (9.3% versus 11.4% events; hazard ratio 0.80 and 95% CI 0.72–0.90). The event reduction was already present at the 30-day follow-up, and little additional effect was seen beyond 30 days. Major bleeding complications were more common in patients randomized to treatment with clopidogrel than in controls (3.7% vs. 2.7% events; hazard ratio 1.4 and 95% CI 1.1–1.7) but no excess risk in life-threatening bleeding complications was observed. The risk of bleeding complications was relatively low in patients using aspirin doses below 100 mg (2.5% vs. 2.0% events). The clinical benefits of dual oral antiplatelet therapy with aspirin and clopidogrel were confirmed by the CREDO trial (published in 2002), which enrolled 2116 patients who were to undergo elective PCI or were deemed at high likelihood of undergoing PCI (approximately 50% of patients had NSTE-ACS) [34]. Therefore, guidelines recommend that clopidogrel be used in conjunction with a low maintenance dose of aspirin.

Antithrombin therapy

Exposure of blood to tissue factor in the necrotic core of the plaque activates the coagulation cascade and leads to the generation of thrombin. Thrombin is one of the most potent platelet agonists, and recruits additional platelets to the site of vascular injury. In addition to converting fibrinogen to fibrin, thrombin activates factor XIII, which stabilizes the fibrin clot. Thrombin also promotes its own formation via activation of factors V and VIII. Depending on the extent of activation of coagulation and the degree of stasis in the affected artery, a thrombus that is rich in fibrin and erythrocytes may develop and extend upstream and downstream from the ruptured plaque. Thus, unregulated thrombin generation may be an important trigger of (recurrent) ischaemic events.

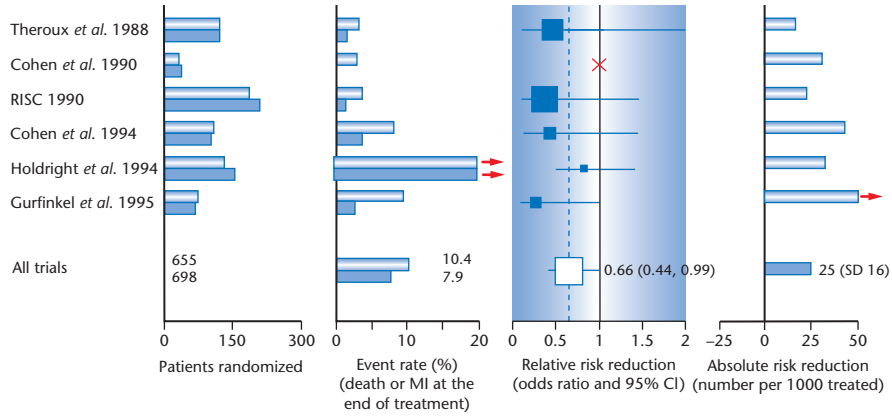

Figure 13.5 Death or myocardial infarction at the completion of study medication in randomized trials of unfractionated heparin (dark blue bars) vs. control (light blue bars) in patients with non-ST-elevation acute coronary syndrome.

Unfractionated heparin and low-molecular-weight heparin

Heparin binds to anti-thrombin III and induces a conformational change that results in rapid inhibition of thrombin, which may prevent propagation of an established thrombus and allows time for endogenous fibrinolysis to occur. In clinical practice, maintenance of therapeutic anti-thrombin control is hampered by unpredictable levels of heparin binding to plasma proteins. In addition, heparin has limited effectiveness against platelet-rich and clot-bound thrombin. Low-molecular-weight heparin (LMWH), which consists of fragments of the heparin molecule, has potential advantages over heparin as it has a greater activity against factor Xa, it produces a more predictable anticoagulant response, and it has a longer plasma half-life. [Note that heparin is also called 'unfractionated' heparin (UFH) to distinguish it from its low-molecular-weight fragments. We will use the term UFH in the remainder of this chapter.] LMWH can be administered subcutaneously based on a weight-adjusted dose and do not require laboratory monitoring. Different LMWH appear to have similar activities in prevention and treatment of venous thrombosis, despite some differences in pharmacology and half-life.

Between 1988 and 1996, six randomized trials (1353 patients) were conducted that compared UFH with control therapy and two trials (1639 patients) compared LMWH (dalteparin, nadroparin) with control in NSTE-ACS patients treated with aspirin (Fig. 13.5) [18,19,35–39]. Treatment duration varied from 2 to 7 days. In these trials, UFH was associated with a 34% reduction in the incidence of death or myocardial infarction at the completion of study medication compared with control therapy (7.9% vs. 10.4% events; odds ratio 0.67 and 95% CI 0.44–0.99). LMWH was associated with a 61% event reduction compared with control therapy (2.1% vs. 5.2% events; odds ratio 0.39 and 95% CI 0.22–0.86).

Between 1995 and 2004, nine randomized trials (27 034 patients) were conducted in NSTE-ACS that compared LMWH (dalteparin, enoxaparin, nadroparin) with UFH (Fig. 13.6) [40–48]. These trials together showed

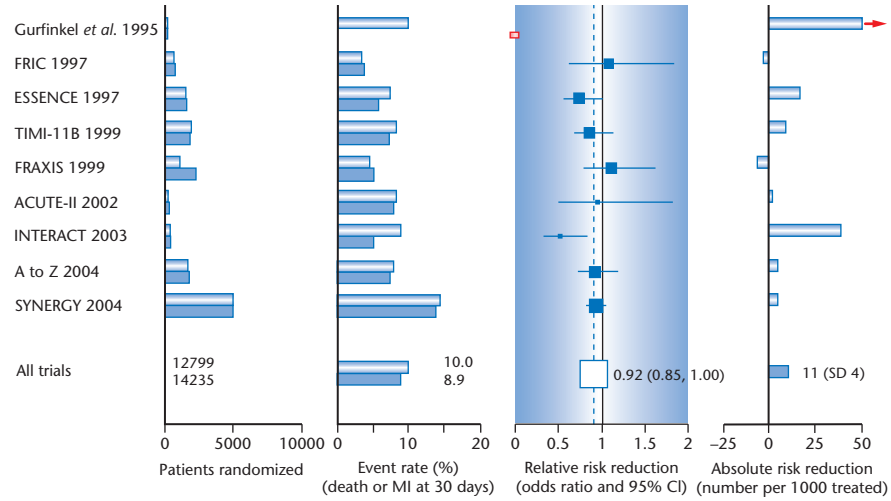

Figure 13.6 Death or myocardial infarction at 30-day follow-up in randomized trials of low-molecular-weight heparin (dark blue bars) vs. unfractionated heparin (light blue bars) in patients with non-ST-elevation acute coronary syndrome. Divergent follow-up duration in Gurfinkel *et al*. [38] was to hospital discharge; in FRIC was 6 days; in FRAXIS was 14 days.

that LMWH was associated with a modest, statistically non-significant, 8% reduction in the incidence of death or myocardial infarction at 30 days compared with UFH (8.9% vs. 10.0% events; odds ratio 0.92 and 95% CI 0.85–1.0). There was statistical evidence of heterogeneity ($P = 0.07$) between the separate trial results. The six enoxaparin trials, which enrolled 21 946 patients [41,42, 44–47], showed more homogeneous results (P-value for heterogeneity 0.3). Enoxaparin was associated with a 9% event reduction compared with UFH, which was just statistically significant (10.1% vs. 11.0% events; odds ratio 0.91 and 95% CI 0.83–0.99) [48]. The incidence of major bleeding complications was slightly higher in patients receiving enoxaparin, but no difference in blood transfusion was noted.

Between 1996 and 1997 five randomized trials (12 099 patients) evaluated the effectiveness and safety of long-term treatment with a LMWH (dalteparin, enoxaparin, nadroparin) in NSTE-ACS patients [49]. Taken together, these trials offer no evidence of a reduction in the incidence of death or myocardial infarction with the use of LMWH compared with control therapy (4.2% vs. 3.9% events; odds ratio 0.98 and 95% CI 0.81–1.2). However, long-term LMWH was associated with a significant increase in the risk of major bleeding.

In view of these data, guidelines recommend short-term antithrombin therapy with either UFH or LMWH as an adjunct to aspirin in NSTE-ACS patients. There is some evidence that enoxaparin is more effective than UFH in preventing death or myocardial infarction, at the cost of a slight excess in major bleeding complications. LMWHs offer significant practical advantages with simplicity of administration, more consistent antithrombin effects, and no need for monitoring. Observational studies have suggested that LMWHs can safely be used in combination with GP-IIb/IIIa inhibitors [50]. In this context, the INTERACT study (746 patients; published in 2003) suggested that efficacy and safety of enoxaparin were better than those of UFH in eptifibatide-treated patients [46].

Direct thrombin inhibitors

When bound to fibrin, fibrin degradation products, or subendothelial matrix, thrombin is resistant to inactivation by the heparin–antithrombin complex. Bound thrombin, which remains enzymatically active, triggers thrombus growth by factors V, VIII and XI, thereby amplifying thrombin generation. Bound thrombin also activates platelets, via thromboxane A_2-independent pathways that are not blocked by aspirin. In contrast to UFH and LMWH, which catalyse the inactivation of thrombin by antithrombin, direct thrombin inhibitors bind to the enzyme and block its interaction with its substrates.

Twelve randomized clinical trials (53 313 patients) were conducted from 1995 to 1998 that evaluated the efficacy and safety of the direct thrombin inhibitors compared with UFH [51–62]. Five trials enrolled patients with NSTE-ACS [51–55], five trials enrolled patients with STE-ACS [56–60], and two trials enrolled patients undergoing PCI [61,62]. The direct thrombin inhibitors under investigation included argatroban, bivalirudin (also known as hirulog), efegatran, hirudin and inogatran, whereas treatment duration varied from 48 to 168 hours. Taking the results of the ACS trials together, treatment with a direct thrombin inhibitor was associated with a modest, but statistically significant, 8% reduction in the incidence of death or myocardial infarction at 30 days (9.7% versus 10.6% events; odds ratio 0.92 and 95% CI 0.87–0.98; Fig. 13.7). There was no evidence of a differential treat-

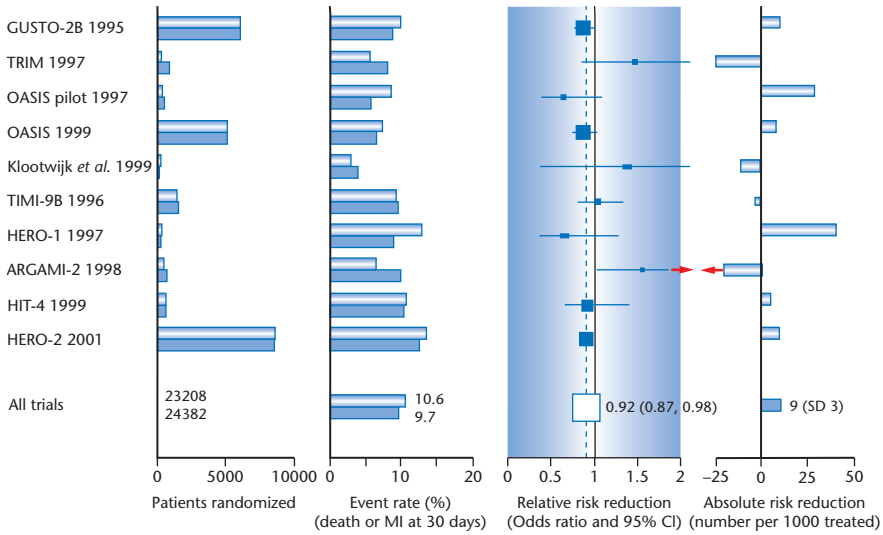

Figure 13.7 Death or myocardial infarction at 30-day follow-up in randomized trials of direct thrombin inhibitors (dark blue) vs. unfractionated heparin (light blue) in patients with acute coronary syndrome. GUSTO-2B, TRIM, OASIS pilot, OASIS and Klootwijk *et al.* [55] enrolled patients without ST-elevation; TIMI-9B, HERO-1, ARGAMI-2, HIT-4 and HERO-2 enrolled patients with ST-elevation.

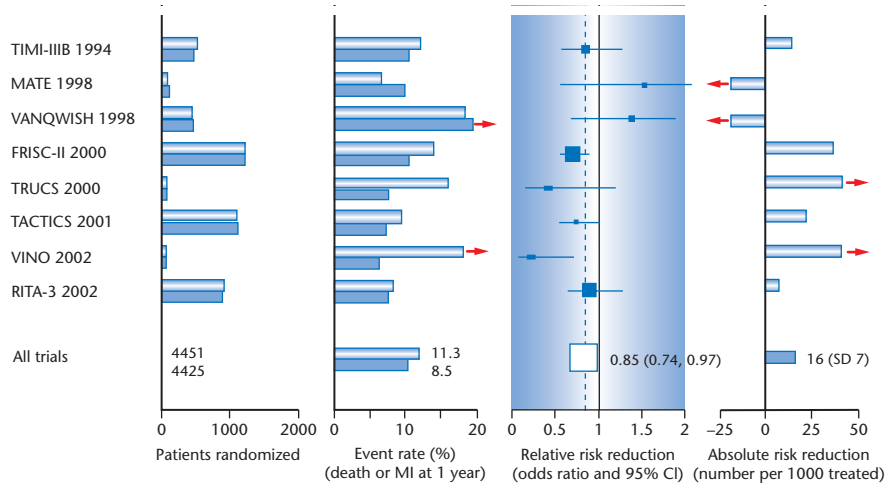

Figure 13.8 Death or myocardial infarction at 1-year follow-up in randomized trials of early invasive (dark blue bars) vs. conservative treatment (light blue bars) in patients with non-ST-elevation acute coronary syndrome. Data are derived from Fox *et al.*, *Lancet* 2002; **360**: 743–751 [73].

ment effect between the separate trials. Mortality as a single end-point was not reduced. Compared with UFH, direct thrombin inhibitors were associated with a lower risk of major bleeding overall. However, there was strong evidence of heterogeneity for major bleeding, which is consistent with the results of individual trials suggesting an increased bleeding risk associated with hirudin, but a risk reduction with bivalirudin [63].

In summary, direct thrombin inhibitors provide a modest clinical benefit over UFH. These agents are not registered for use in ACS patients in Europe.

Early invasive or conservative therapy?

Revascularization, including PCI or coronary artery bypass grafting (CABG), in NSTE-ACS patients is performed to treat ongoing myocardial ischaemia and to prevent recurrent ischaemia and progression to myocardial infarction or death. The indications for myocardial revascularization and the preferred approach depend on clinical characteristics, and the extent and angiographic characteristics of the lesions identified by coronary angiography. Guidelines recommend an early invasive strategy for patients at high risk, including patients with elevated cardiac troponins, patients with diabetes mellitus and those who develop haemodynamic instability during the observation period. For the remaining group of patients early invasive and conservative strategies are both judged appropriate. In clinical practice, however, early revascularization is only applied to a minority of patients. In large-scale international registries of NSTE-ACS patients only 20–25% underwent PCI or CABG during the initial hospitalization [64,65]. Apparently, the most appropriate revascularization strategy in patients presenting with NSTE-ACS is still the subject of debate.

Between 1994 and 2002 eight clinical trials (8876 patients) were undertaken that randomly allocated NSTE-ACS patients to an early invasive strategy or to conservative treatment (Fig. 13.8) [66–73]. Patients randomized to the early invasive strategy underwent cardiac catheterization during the first days after hospital admission (in the majority of patients cardiac catheterization was performed within 72 hours), and, if judged necessary, revascularization as soon as possible thereafter. Treatment decisions in patients randomized to the conservative treatment strategy were left to the discretion of the treating physician, and were mainly based on symptoms. Taking all trials together, early invasive treatment was associated with a 15% reduction in the composite end-point of death or myocardial infarction after a 1-year follow-up compared with conservative treatment (10.4% vs. 12.0% events; odds ratio 0.85 and 95% CI 0.74–0.97). There was, however, evidence of a differential treatment effect between the separate trials. In particular, divergent results were observed in the VANQWISH trial (920 patients; published in 1998), as patients randomized to early invasive treatment had significantly higher 1-year event rates (24.0% vs. 18.6% events; odds ratio 1.4 and 95% CI 1.0–1.9) [68]. The VANQWISH results have been challenged by several investigators, who emphasized the fact that a large proportion of patients allocated to the conservative strategy actually underwent coronary revascularization within 30 days after enrolment (33% compared with 44% in the early invasive arm). Also, in the earlier trials, of which VANQWISH was one, neither intracoronary stents nor GP-IIb/IIIa inhibitors were available for patients undergoing PCI [66–68]. Finally, in VANQWISH, an exceptionally high perioperative mortality was observed in the invasive arm (11.6% vs. 3.4% events; odds ratio 3.7 and 95% CI 1.0–13.6).

A meta-analysis of the five recent trials revealed a 27% event reduction by the early invasive strategy (8.5% vs. 11.3% deaths or myocardial infarction at 1 year; odds ratio 0.73 and 95% CI 0.62–0.86) [74].

Management of ST-elevation acute coronary syndromes

Pharmacological therapy

Fibrinolysis

Since it became clear that a myocardial infarction is caused by an acute intracoronary thrombotic occlusion, treatment strategies have been introduced that aim for rapid, complete and lasting restoration of the coronary blood flow. GISSI-1 (11 806 patients; published in 1986) and ISIS-2 (17 187 patients; published in 1988) are the major landmark studies of fibrinolytic therapy, by demonstrating a 23% reduction in 30-day mortality among patients randomized to streptokinase compared with control therapy (9.8% vs. 12.4% events; odds ratio 0.77 and 95% CI 0.72–0.83) [75,76]. Between 1986 and 1993 nine phase III trials were conducted that randomized at least 1000 STE-ACS patients (within 24 hours of symptom onset) to treatment with a fibrinolytic agent [alteplase, 100 mg over 3 hours; anisoylated purified streptokinase activator complex (APSAC), 30 U in 5 minutes; streptokinase, 1.5 MU over 1 hour; urokinase, two boluses of 1 MU each, 1 hour apart] or control therapy (Fig. 13.9) [75–83]. Taken together, these trials (56 462 patients) showed that fibrinolytic therapy was associated with an 18% reduction in the incidence of death at 30–35 days follow-up (9.3% vs. 11.1% events; odds ratio 0.82 and 95% CI 0.77–0.86) [84]. Fibrinolysis was also associated with a small, but significant excess risk of intracranial haemorrhage (0.4% vs. 0.1% events).

Streptokinase is the most frequently used fibrinolytic agent world-wide. However, because the GUSTO-1 trial demonstrated a further 15% mortality reduction by 'accelerated' or 'front-loaded' alteplase (100 mg infusion over 90 minutes, with over half of the dose within 30 minutes) over streptokinase (6.3% vs. 7.3% events; odds ratio 0.85 and 95% CI 0.78–0.94), front-loaded alteplase became the standard for pharmacological reperfusion therapy [85]. The disadvantage of this development is that front-loaded alteplase increased the risk of intracranial haemorrhage (0.7% vs. 0.5% events) when compared with streptokinase.

During the 1990s several wild-type alteplase mutants were developed with a longer half-life, so that these agents could be administered via bolus injection. Promising results were observed with these agents in phase II trials but subsequent phase III trials, which were published between 1997 and 2000, failed to show superiority of the new agents over front-loaded alteplase with regard to 30-day mortality [86–89]. In a combined analysis of the GUSTO-3 (15 059 patients; reteplase), COBALT (7169 patients; double bolus alteplase), ASSENT-2 (16 949 patients; tenecteplase) and InTIME-2 (15 060 patients; lanoteplase) trials, 7.0% of patients randomized to bolus fibrinolytic agents died within 30 days compared with 6.8% of patients randomized to front-loaded alteplase (odds ratio 1.0 and 95% CI 0.96–1.1). In ASSENT-2, tenecteplase was associated with a significant reduction in the risk of major non-cerebral bleeding complications

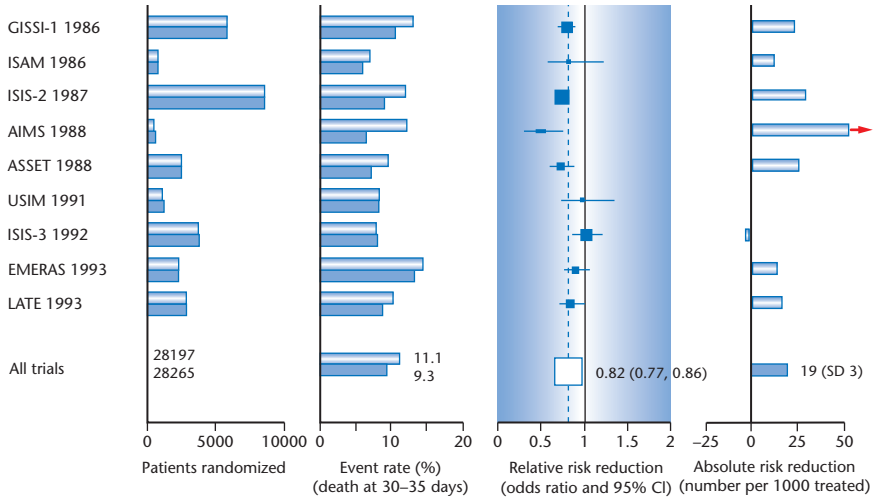

Figure 13.9 Death at 30-day follow-up in randomized trials of fibrinolytic therapy (dark blue bars) vs. control (light blue bars) in patients with ST-elevation acute coronary syndrome.

(26.4% vs. 29.0%), as well as in the need for blood transfusion (4.3% vs. 5.5%; odds ratio 0.76 and 95% CI 0.67–0.87). Some investigators argue that the use of bolus fibrinolytic agents was associated with an increased incidence of intracranial haemorrhage [90]. However, this increased risk was not evident in the group of patients treated with tenecteplase or reteplase. Furthermore, the intensity of adjunctive antithrombin therapy seems to be a confounding factor. In summary, the bolus fibrinolytic agents have a similar effectiveness to, and a slightly more favourable (tenecteplase) safety profile than, front-loaded alteplase.

Adjunctive antiplatelet therapy

Adequate vessel patency does not guarantee perfusion at the myocardial tissue level. There are three important caveats with fibrinolytic therapy in this respect. First, as a result of treatment, the occluding thrombus may fall apart into smaller fragments, causing distal microembolization. Second, treatment with a fibrinolytic agent only resolves the fibrin-rich part of the thrombus, whereas the platelet-rich part remains largely untouched. Finally, fibrinolysis generates elevated levels of free thrombin, and thus activates platelet aggregation, which may cause a further worsening of the microcirculation. To overcome these caveats, pharmacological reperfusion strategies were developed to combine fibrinolytic therapy with aggressive antiplatelet therapy.

The ISIS-2 trial provided undeniable evidence of the benefits of early aspirin therapy in patients presenting with STE-ACS [76]. In that trial, patients randomized to aspirin had a 23% reduced risk of 35-day mortality compared with controls (9.4% vs. 11.8% events; odds ratio 0.77 and 95% CI 0.70–0.85). ISIS-2 also demonstrated that the benefits of fibrinolysis (streptokinase) and aspirin were additive.

Phase II trials in STE-ACS that evaluated combined treatment with reduced-dose fibrinolytic therapy and GP-IIb/IIIa inhibitors provided indirect evidence of a more complete reperfusion with that strategy than with fibrinolytic therapy alone. In this respect, favourable results were observed in terms of ST-segment resolution, thrombosis in myocardial infarction (TIMI) frame count and myocardial blush. Additionally, shorter time periods to ST-segment resolution were observed, indicating improved early reperfusion. On account of these promising observations, two large phase III trials were undertaken to evaluate the clinical efficacy and safety of such combination therapy. In GUSTO-5 (16 588 patients; reported in 2001), combined treatment with reduced-dose reteplase and abciximab was not associated with a lower 30-day mortality compared with full-dose reteplase alone (5.6% vs. 5.9% events; odds ratio 0.95 and 95% CI 0.83–1.1) [91]. It is true that a significant reduction in myocardial re-infarction was observed at 30-day follow-up (2.3% vs. 3.5% events; odds ratio 0.65 and 95% CI 0.54–0.78) but this did not translate into a reduction in mortality during long-term follow-up [92]. Combination therapy was associated with an increased incidence of major bleeding complications (4.6% vs. 2.4% events; odds ratio 2.1 and 95% CI 1.7–2.4), particularly in elderly patients. The results of the ASSENT-3 trial (6095 patients; reported in 2001), which compared half-dose tenecteplase plus abciximab with full-dose tenecteplase alone (in a third arm, patients received tenecteplase plus enoxaparin) were similar to those of GUSTO-5: no effect on mortality, a significant reduction in the incidence of myocardial re-infarction at 30 days, and an increased risk of major bleeding complications [93]. In view of these data, guidelines for STE-ACS do not recommend the routine use of a reduced dose fibrinolytic in combination with a GP-IIb/IIIa inhibitor.

Adjunctive antithrombin therapy

The release of thrombin from the thrombus, as a result of fibrinolysis, contributes to a procoagulant state. Thus, it seems appropriate to combine fibrinolytic and antiplatelet therapy with antithrombin therapy. However, in the large GISSI-2 (20 891 patients; reported in 1990) and ISIS-3 (41 299 patients; reported in 1992) trials, combination therapy with a fibrinolytic agent, aspirin and UFH was not associated with a significant reduction in mortality during a 35-day follow-up, nor with a significant reduction in myocardial re-infarction, compared with combination therapy with fibrinolysis and aspirin [81,94,95]. In contrast, the incidence of major bleeding complications was increased. In the GUSTO-1 trial, no major differences were observed between subcutaneous and intravenous heparin among patients given streptokinase [85]. In view of these data, one could conclude that neither subcutaneous nor intravenous heparin adds much to the outcome in patients treated with streptokinase and aspirin. This opinion, however, is not commonly shared [96], and unfractionated heparin is often used in myocardial infarction patients treated with streptokinase. Apart from that, intravenous heparin as a component of the GUSTO-1 front-loaded alteplase regimen is widely accepted, although front-loaded alteplase without intravenous heparin has not been extensively studied.

As far as LMWHs are concerned, several phase II trials indicated a trend toward a better angiographic patency, improved ST-segment resolution, and lower reocclusion rates associated with enoxaparin compared with UFH, as an adjunct to streptokinase or front-loaded alteplase. In

the ASSENT-3 trial, in which tenecteplase was applied, patients randomized to enoxaparin had a significantly lower incidence of the composite end-point of 30-day death, myocardial re-infarction or refractory ischaemia compared with UFH (11.4% vs. 15.4% events; odds ratio 0.71 and 95% CI 0.59–0.85), without a significant increase in the risk of bleeding complications [93]. However, in the ASSENT-3 PLUS trial (1639 patients; published in 2003) pre-hospital administration of the same dose of enoxaparin resulted in a significant increase in intracranial haemorrhage compared with UFH [97]. Therefore, additional (and larger) studies are needed before reliable conclusions can be drawn on the use of enoxaparin or other LMWHs in combination with fibrinolytic agents.

A total of five randomized trials studied the efficacy and safety of direct thrombin inhibitors as an alternative for UFH in patients presenting with STE-ACS [56–60]. As has been demonstrated above, in patients presenting with ACS, direct thrombin inhibitors are associated with a modest 8% reduction in 30-day death or myocardial re-infarction compared with UFH, but mortality is not affected. In patients presenting with STE-ACS direct thrombin inhibitors were not associated with an increased risk of intracranial bleeding complications compared with UFH [60,63].

Percutaneous coronary interventions

Primary percutaneous coronary interventions

Recent studies have shown that fibrinolytic treatment is not capable of restoring coronary arterial patency in 20–45% of cases, depending on the fibrinolytic agent used [98]. In addition, 5–10% of patients experience an early reocclusion, whereas a late occlusion occurs in 30% of patients [99,100]. Mechanical reperfusion therapy by means of coronary angioplasty is associated with a significantly higher success rate. Furthermore, mechanical reperfusion is not associated with an increased risk of life-threatening intracranial bleeding complications. However, the major challenge of this approach is the treatment delay involved in mobilizing the interventional team and preparing the interventional facility. Under optimal circumstances, this will lead to a 30-minute treatment delay compared with in-hospital initiation of fibrinolytic therapy [101]. When compared with pre-hospital treatment, this delay may range from 60 to 90 minutes.

In light of these factors, the comparative effectiveness of 'primary' PCI (angioplasty without prior or concomitant fibrinolytic therapy) and fibrinolysis has been debated over the last decade. Twenty-two randomized trials (7437 patients), which were conducted between 1990 and 2003, addressed this issue (Fig. 13.10). In these trials, primary PCI was associated with a significant 30% reduction in 30-day mortality compared with fibrinolysis (5.3% vs. 7.4% events; odds ratio 0.70 and 95% CI 0.58–0.84) [102]. When compared with front-loaded alteplase, primary PCI was associated with a 19% mortality reduction (5.5% vs. 6.8% events; odds ratio 0.81 and 95% CI 0.64–1.0). Primary PCI was also associated with a significantly lower incidence of myocardial reinfarction, stroke and intracranial haemorrhage. The initial benefit of primary PCI over fibrinolysis is maintained during long-term follow-up, but no further enhancement of the treatment benefit was observed beyond the 30-day period [103,104]. The best results of primary angioplasty were predominantly achieved by experienced operators (> 75 cases per year), in high volume centres (> 200 cases per year) with door-to-balloon times of less than 90 minutes [104]. Additionally, three studies (2622 patients; published between 2000 and 2003) have confirmed the

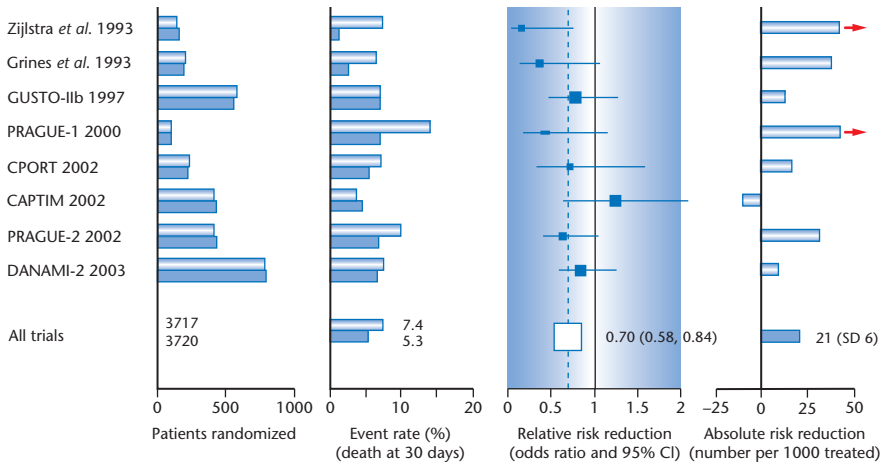

Figure 13.10 Death at 30-day follow-up in randomized trials of primary PCI (dark blue bars) vs. fibrinolytic therapy (light blue bars) in patients with ST-elevation acute coronary syndrome. Results are shown from selected trials that randomized at least 200 patients. Overall results are based on all 22 trials that were conducted between 1990 and 2003 (see text).

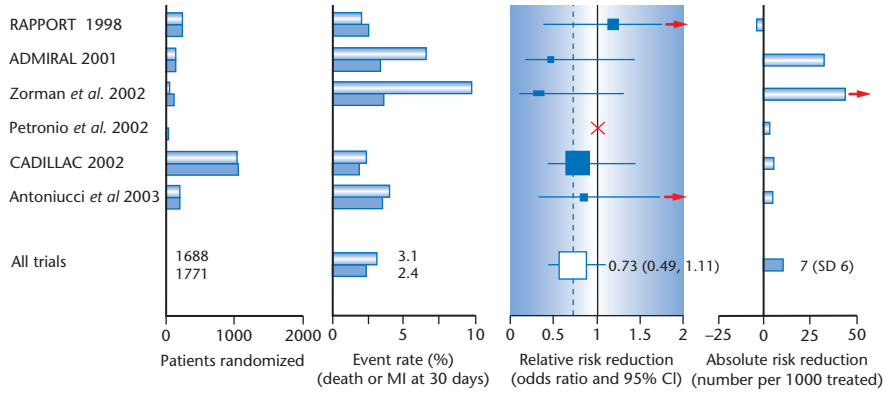

Figure 13.11 Death or myocardial infarction at 30-day follow-up in randomized trials of glycoprotein IIb/IIIa inhibitors (dark blue bars) vs. control (light blue bars) in patients with ST-elevation acute coronary syndrome undergoing primary PCI.

benefit of a transfer for primary PCI strategy over fibrinolytic therapy in acute myocardial infarction [105–107]. It remains unclear whether these excellent results could be applied and translated into daily practice. Still, guidelines consider primary PCI as the preferred therapeutic option when it can be initiated within 90 minutes of the first medical contact.

Rescue percutaneous coronary intervention

'Rescue PCI' is defined as PCI performed on a coronary artery which remains occluded despite fibrinolytic therapy. Limited experience from two randomized trials suggests a trend towards clinical benefit if the infarct-related vessel can be recanalized at angioplasty [108,109]. Although angioplasty success rates are high, an unsolved problem is the lack of reliable non-invasive methods for assessing patency of the infarct-related coronary artery. Coronary intervention in patients who received full-dose fibrinolytics and a GP-IIb/IIIa antagonist may lead to excessive bleeding complications.

Balloon or stent?

No statistically significant difference in mortality was observed between primary coronary stenting or balloon angioplasty. However, primary stenting was associated with a non-significant trend for reduction in the incidence of myocardial re-infarction and a significant reduction in target vessel revascularization [110]. Thus, coronary stenting has emerged as a safe alternative that appears to augment the angiographic and clinical results of primary balloon angioplasty.

Glycoprotein IIb/IIIa inhibitors

The use of GP-IIb/IIIa inhibitors in STE-ACS patients undergoing percutaneous intervention inhibits platelet aggregation at the site of plaque rupture and procedure-induced injury, potentially improving the clinical outcome. Between 1998 and 2003, six randomized trials (3459 patients) of abciximab versus control therapy in patients undergoing primary PCI (with or without stenting) examined this hypothesis (Fig. 13.11) [111–116]. In these trials, abciximab was associated with a non-significant trend for reduction in mortality and myocardial reinfarction at the 30-day follow-up compared with control therapy (2.4% vs. 3.1% events; odds ratio 0.73 and 95% CI 0.49–1.1), which is compatible with the benefit of GP-IIb/IIIa inhibitors as observed in other PCI studies [21]. In the RAPPORT trial (483 patients; published in 1998) [111] haemorrhagic complications were significantly increased in patients receiving abciximab, probably as a result of relatively high heparin doses. Therefore, guidelines recommend the use of abciximab in primary angioplasty only in combination with low-dose heparin.

Facilitated percutaneous coronary interventions

Facilitated PCI refers to a strategy of planned immediate PCI after an initial pharmacological regimen. PCI performed as a matter of policy immediately after fibrinolytic therapy, to enhance reperfusion or reduce the risk of reocclusion, has proved disappointing in a number of earlier trials all showing a tendency to an increased risk of complications and death. However, increased experience and the availability of stents have made PCI following pharmacological intervention safer. In the randomized trials that have been conducted so far, pretreatment with a fibrinolytic agent or with a GP-IIb/IIIa inhibitor resulted in improved pre-procedural coronary patency, whereas there was no evidence of an excess bleeding risk [117–120]. However, these trials did not demonstrate any benefit in reducing infarct size or improving outcomes. Several randomized trials of facilitated PCI are in progress [121].

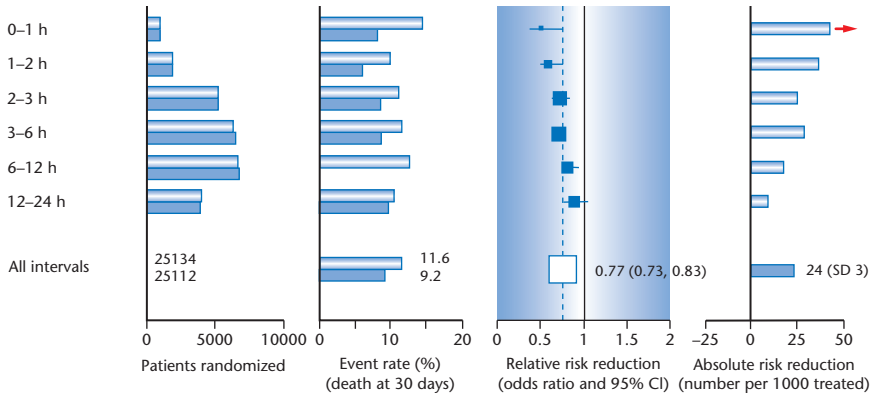

Figure 13.12 Death at 30-day follow-up in randomized trials of fibrinolytic therapy (dark blue bars) vs. control (light blue bars) in patients with ST-elevation acute coronary syndrome, in subgroups according to time from symptom onset to treatment.

Time to treatment and outcome

Time to treatment and outcome after fibrinolysis

Time from symptom onset to treatment is one of the most important determinants of the success of pharmacological reperfusion therapy. A detailed analysis of the relation between treatment delay and treatment effect in placebo-controlled trials indicated that the mortality reduction by fibrinolytic therapy is greatest in patients presenting within 1 hour of symptom onset (Fig. 13.12) [84,122]. The relative mortality reduction in this group was as high as 48% (8.2% vs. 14.7% events; odds ratio 0.52 and 95% CI 0.39–0.69), whereas the absolute mortality reduction was estimated at 65 per 1000 patients treated. Fibrinolytic treatment that was initiated within 2 hours resulted in a significantly higher mortality reduction (45% reduction; odds ratio 0.56 and 95% CI 0.47–0.68) than later treatment (20% reduction; odds ratio 0.80 and 95% CI 0.75–0.85), indicating that most benefit of fibrinolysis can be obtained during the ongoing process of myocardial cell death. Thus, to realize the full life-saving potential of fibrinolysis, treatment should be initiated as soon as possible after symptom onset, preferably within the first 1–2 hours.

Time to treatment and outcome after primary angioplasty

Primary angioplasty is unavoidably associated with an increased treatment delay compared with fibrinolytic therapy, but it is as yet unclear how much the angioplasty-related treatment delay nullifies its benefits. Data from randomized trials indicate that primary angioplasty and fibrinolytic therapy yield equivalent mortality reductions if the angioplasty is delayed by 50 minutes [123]. In other investigations, however, primary angioplasty was associated with a significant reduction in major cardiac end-points over fibrinolysis even after prolonged treatment delays [107]. In a large observational study of 27 080 patients treated by primary angioplasty, increased mortality rates were observed after door-to-balloon times exceeding 2 hours [124]. It should be realized that analyses are hampered by the fact that only a minority of patients undergoing primary angioplasty are treated within 2 hours from onset of symptoms.

Pre-hospital diagnosis and triage

The time that expires between the onset of chest pain and the initiation of reperfusion therapy has three main components. First, the patient needs time to recognize the cardiac nature and severity of the problems, and to seek appropriate medical aid. Unfortunately, most patients fail to react rapidly to symptoms. Several registries indicate that 50% of patients who are eligible for reperfusion therapy do not report their symptoms within 3 hours [65,125]. The time needed for transportation to the hospital is the second component of total treatment delay. Depending on the local infrastructure, the distance to the nearest hospital, and the hour of the day, transport delay may vary from 15 to 90 minutes [126–128]. The third component of treatment delay is the time that is needed inside the hospital for initial evaluation by an emergency room physician, ECG recording and interpretation, laboratory testing, further evaluation by an experienced staff cardiologist, and transport from the emergency room to the coronary care unit or catheterization laboratory where therapy is subsequently initiated. Data from a broad spectrum of European clinical practices demonstrate that the in-hospital delay is considerable: only 25% of patients receiving fibrinolysis are treated within the recommended 20 minutes after arrival at the emergency room, whereas only 50% of patients undergoing primary PCI receive this therapy within the recommended 90-minute time window [65].

These results can be improved by a treatment strategy that aims at diagnosis and triage prior to hospital admission, using 12-lead ECG [129]. In such a system, after myocardial infarction is confirmed, immediate, pre-hospital fibrinolytic therapy can be installed, or the patient can be directly transported to a catheterization laboratory, which will have been prepared before the arrival of the patient. Several investigations indicated that this approach may result in a reduction of the total ischaemic time by approximately 1 hour, regardless of the mode of reperfusion therapy [126–128,130].

Pre-hospital fibrinolysis versus in-hospital fibrinolysis

A meta-analysis of the 10 randomized trials (6607 patients) comparing pre-hospital versus in-hospital fibrinolysis demonstrated a significant 18% mortality reduction at 30 days by the pre-hospital treatment strategy (9.0% versus 10.7% events; odds ratio 0.82 and 95% CI 0.69–0.96; Fig. 13.13) [131]. Additionally, early, pre-hospital fibrinolysis is associated with a higher proportion of aborted infarctions than in-hospital treatment [132,133].

The safety of pre-hospital fibrinolysis is strongly dependent on the possibility of a correct diagnosis in the pre-hospital setting. To confirm ongoing myocardial infarction, a standard 12-lead ECG is required, which can either be transmitted via a telephone connection for interpretation by experienced cardiologists, or interpreted on-site by specifically designed computer programs. Both approaches are associated with similarly low false-positive rates.

Pre-hospital fibrinolysis versus primary percutaneous coronary interventions

The CAPTIM trial (reported in 2002) enrolled 840 patients with STE-ACS, who were randomly allocated to primary PCI or the strategy of pre-hospital fibrinolysis (front-loaded alteplase regimen) with subsequent transport to a centre with interventional facilities [134]. In this trial, primary PCI was associated with a lower incidence in the composite end-point of death, myocardial re-infarction or disabling stroke at 30-day follow-up, but statistical significance was not reached (6.2% vs. 8.2% events; odds ratio 0.75 and 95% CI 0.44–1.3). Interestingly, in CAPTIM, in patients randomized within the first 2 hours after symptom onset, primary PCI seemed to be associated with an increased mortality risk (5.7% vs. 2.2% events), whereas in patients randomized after 2 hours primary PCI seemed to be associated with reduced mortality (3.7% vs. 5.9% events) [135]. The interpretation of the CAPTIM results (especially the results observed in posterior defined subgroups) is complicated by the fact that the study had to be terminated prematurely because of lack of funding (initially, a sample size of 1200 patients was chosen). Also, the vast majority of patients randomized to pre-hospital fibrinolysis underwent coronary angiography (85%) and subsequent angioplasty (70%) within 30 days.

Prophylactic therapies

Beta-blockers

There is overwhelming evidence for the benefits of early beta-blockade in patients with STE-ACS. Benefits have been demonstrated for patients with and without concomitant fibrinolytic therapy, both early and late after symptom onset. Randomized trials revealed a 13% mortality reduction at 7 days by beta-blocker therapy compared with control (3.7% vs. 4.3% events; odds ratio 0.87 and 95% CI 0.78–0.99) [9]. Several observational

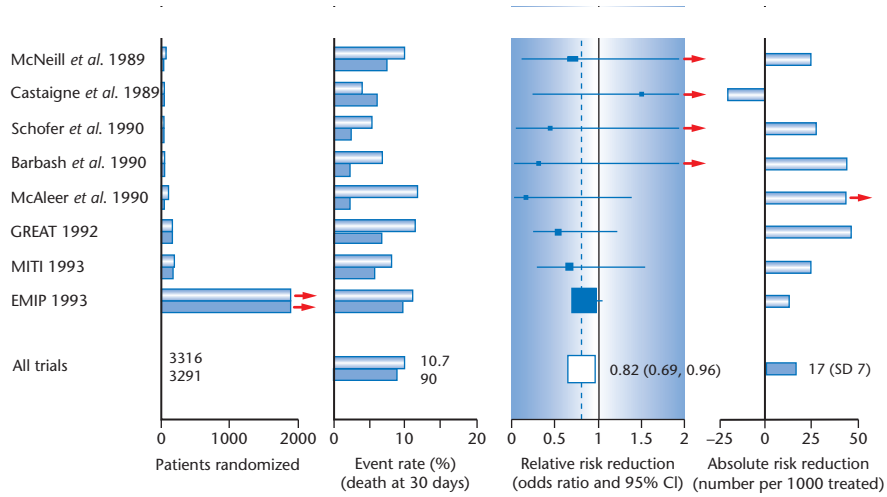

Figure 13.13 Death at 30-day follow-up in randomized trials of pre-hospital (dark blue bars) vs. in-hospital (light blue bars) fibrinolytic therapy in patients with ST-elevation acute coronary syndrome.

studies indicate that early beta-blocker therapy also improves the prognosis of STE-ACS patients undergoing primary PCI [136,137]. Thus, guidelines recommend that beta-blockers should be initiated early in the course of STE-ACS, and continued unless adverse effects have been observed.

Angiotensin-converting enzyme inhibitors

The GISSI-3 (19 394 patients; reported 1994), ISIS-4 (58 050 patients; reported 1995) and Chinese Study (13 634 patients; reported 1995) have shown that angiotensin-converting enzyme (ACE) inhibitors started on the first day reduce mortality in the succeeding 4–6 weeks by a small but significant amount [138–140]. The CONSENSUS II study (6090 patients; reported 1992) with intravenous enalapril, however, failed to show a benefit [141]. This may have been through chance, or because the treatment was initiated early with an intravenous formulation. A systematic overview of trials of ACE inhibition early in acute myocardial infarction indicated that this therapy is safe, well-tolerated and associated with a modest, but statistically significant, 6% reduction in 30-day mortality compared with control therapy (7.3% vs. 7.7% events; odds ratio 0.94 and 95% CI 0.89–0.98) [139]. There is now general agreement on starting ACE inhibitors in the first 24 hours if no contraindications are present. Opinions still differ as to whether to give ACE inhibitors to all patients or to high-risk patients only. In patients who do not tolerate an ACE inhibitor, the angiotensin receptor blocker valsartan is an equally effective alternative [142].

Nitrates

A meta-analysis of 10 trials of early intravenous nitrate therapy conducted in 2041 STE-ACS patients showed a significant mortality reduction compared to control therapy [143]. However, each of the trials was small and the results, although highly significant, had wide confidence limits. In the larger GISSI-3, ISIS-4 and ESPRIM (4017 patients; published in 1994) trials [138,139,144], no significant reduction in mortality was observed by the routine administration of nitrates. Thus, guidelines do not recommend the use of nitrates for the improvement in prognosis of STE-ACS patients.

Calcium-channel blockers

A meta-analysis of trials involving calcium antagonists early in the course of acute myocardial infarction showed a non-significant adverse trend [145]. There is no case for using calcium antagonists for prophylactic purposes in the acute phase of myocardial infarction.

Specific issues

Arrhythmias and conduction disturbances

Arrhythmias and conduction disturbances are extremely common during the early hours after presentation with STE-ACS. In some cases, such as ventricular tachycardia, ventricular fibrillation and total atrioventricular block, these are life-threatening and require immediate correction. Often arrhythmias are a manifestation of a serious underlying disorder, such as continuing ischaemia, pump failure, altered autonomic tone, hypoxia, and electrolyte and acid–base disturbances, that requires attention and corrective measures. Guidelines indicate that the necessity for treatment and its urgency depend mainly upon the haemodynamic consequences of the rhythm disorder.

Diabetic patients

Up to one-quarter of all patients with STE-ACS have diabetes and this figure is expected to increase [146]. Importantly, diabetic patients may present with atypical symptoms and heart failure is a common complication. Diabetic patients who sustain a myocardial infarction still have a doubled mortality risk compared with non-diabetic patients. There are indications that patients with diabetes do not receive the same extensive treatment as non-diabetic patients, presumably because the physician fears treatment complications. Diabetes is not a contraindication for fibrinolytic therapy, even in the presence of retinopathy. Furthermore, treatment with beta-blockers and ACE inhibitors seems to be even more effective than in non-diabetic patients and the risk for complications is negligible. The acute phase is often characterized by deterioration of the metabolic control and hyperglycaemia is an independent predictor of mortality. Strict attention to the glycaemic control by use of intravenous insulin infusion followed by multiple-dose subcutaneous insulin treatment has been shown to reduce long-term mortality [147,148].

There is experimental and limited clinical evidence that routine administration of glucose–insulin–potassium may favourably influence metabolism in the ischaemic myocardium and therefore confer a clinical benefit. Meta-analysis of the available data in 1928 patients suggests a 28% reduction in hospital mortality (16.1% vs. 21.1% events; odds ratio 0.72 and 95% CI 0.57–0.91) [149]. Additional mortality trials are currently being conducted.

Concluding remarks

During the last decades major progress has been made in the treatment of ACS, and this has been reflected in a decreased mortality and in a better quality of life. Ongoing and future research with anti-Xa agents (pentasaccharides), glucose–insulin–potassium infusion, adenosine, supersaturated aqueous oxygen (to reduce reperfusion injury in STE-ACS) and moderate systemic hypothermia may improve the patient's prognosis even further. However, such future treatment refinements will probably not lead to changes as dramatic as those of the past. On the other hand, treatment strategies proven to be effective are still largely underused. This was evident in two recent surveys of clinical practice. In GRACE up to one-third of eligible STE-ACS patients did not receive reperfusion therapy [64]. Similarly, in the Euro Heart Survey of ACS, only half of the patients enrolled with ST-segment elevation received reperfusion therapy [65]. Finally, despite compelling evidence on the importance of very early reperfusion therapy, the time from symptom onset to treatment of 2.7 hours as observed in clinical trials in the beginning of the 1990s has remained unchanged [150]. Therefore, our first aim should be to implement and expand the delivery of effective (acute) treatment in a timely fashion for all eligible ACS patients. In view of the imminent epidemic of cardiovascular disease, with ACS as its most prominent manifestation, adopting these measures from a global perspective will be a great accomplishment that will lead to a better life for patients with this disabling condition.

Personal perspective

During the last decades, major improvements have been achieved in the management and outcome of patients with acute coronary syndromes. The introduction of coronary care units in the 1960s, pharmacological reperfusion therapy in the 1980s, and the widespread application of catheter-based interventions—in combination with aggressive anti-platelet and anti-thrombin therapy—in the 1990s have contributed to a dramatic fall in in-hospital mortality rates in patients presenting with and without ST-elevation. Additionally, chronic treatment with aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, and statins have contributed to an improved long-term prognosis in survivors of the acute phase. Despite these promising developments, acute coronary syndromes will remain a major health issue during the decades ahead, for several reasons. Acute cardiac events will continue to occur at early ages in individuals with a genetic predisposition, and in those with an unhealthy life-style. Furthermore, survivors of an acute coronary syndrome constitute a population with chronic cardiac conditions, who remain at increased risk of future fatal and non-fatal cardiac events. Finally, it should be realized that the Western world is ageing, and (heart) diseases come with age. It is true that ongoing and future research may result in modern treatment options that may help to improve the patient's prognosis even further. However, such frontline research should not distract our attention from what is already known. Data are emerging that treatment strategies proven to be effective are still largely underused. Therefore, the first aim as of today should be to implement and expand the delivery of effective (acute) treatment in a timely fashion for all eligible patients. In view of the imminent epidemic of cardiovascular disease, with acute coronary syndrome as its most prominent manifestation, adopting these measures from a global perspective will be a great accomplishment that will lead to a better life for patients with this disabling condition.

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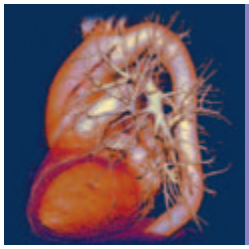


14 Chronic Ischaemic Heart Disease

Filippo Crea, Paolo G. Camici, Raffaele De Caterina and Gaetano A. Lanza

Summary

The coronary circulation serves the purpose of matching myocardial oxygen supply and consumption. A transient mismatch results in myocardial ischaemia, followed by left ventricular dysfunction and ECG changes, with or without angina. Four major clinical syndromes can be identified among patients presenting with chronic ischaemic heart disease. *Stable angina* is caused by critical epicardial coronary artery stenoses, responsible for stress-induced ischaemia. The exercise stress test remains the first-line test for diagnosis; when it cannot be performed or is not interpretable imaging stress tests are necessary. Prognosis is good, annual mortality being < 2%. Risk of major cardiac events is higher in patients with low workload myocardial ischaemia, reduced effort tolerance and multivessel coronary artery disease, in particular if left ventricular function is impaired. *Variant angina* is caused by coronary artery spasm and is characterized by angina at rest, with preserved effort tolerance. Diagnosis requires documentation of transient episodes of ST-segment elevation or of coronary artery spasm at angiography. Risk of major cardiac events is higher in patients with refractory spasm and/or with ischaemia-induced ventricular tachyarrhythmias or bradyarrhythmias. *Cardiac syndrome X* is characterized by anginal pain, predominantly during exercise but also at rest, despite a normal coronary angiogram. Diagnosis requires demonstration of angina and ST-segment depression during stress test, in the absence of wall motion abnormalities. Prognosis is good, but symptoms can be invalidating. *Ischaemic cardiomyopathy* is dominated by symptoms and signs of left ventricular dysfunction. Prognosis is mainly determined by the degree of left ventricular dysfunction.

The coronary circulation

The coronary circulation is composed of three vascular systems arranged in series: (1) the arterial system conveys blood from the aorta to the site of metabolite and gas exchanges with myocardial cells, and controls most of the resistance to flow; (2) the capillary system controls the regional microdistribution of blood flow and blood–tissue exchanges; and (3) the venous system controls intramyocardial blood volume at the end of diastole, thus influencing end-diastolic myocardial fibre length.

Although all the components of the coronary circulation are essential for its correct functioning, evidence accrued over the past few decades has proved that a number of different abnormalities in the arterial system are involved in the pathogenesis of many cardiac diseases and this is why this chapter focuses on this section of the coronary circulation.

Coronary arterial system

The coronary arterial system is composed of three compartments with different functions, although their precise borders cannot be clearly defined anatomically or histologically (Fig. 14.1) [1].

- The proximal compartment is represented by the large epicardial coronary arteries which have a capacitance function and offer little resistance to coronary blood flow. During systole, epicardial coronary arteries accumulate elastic energy as they increase their blood content up to about 25%. This elastic energy is transformed into blood kinetic energy at the

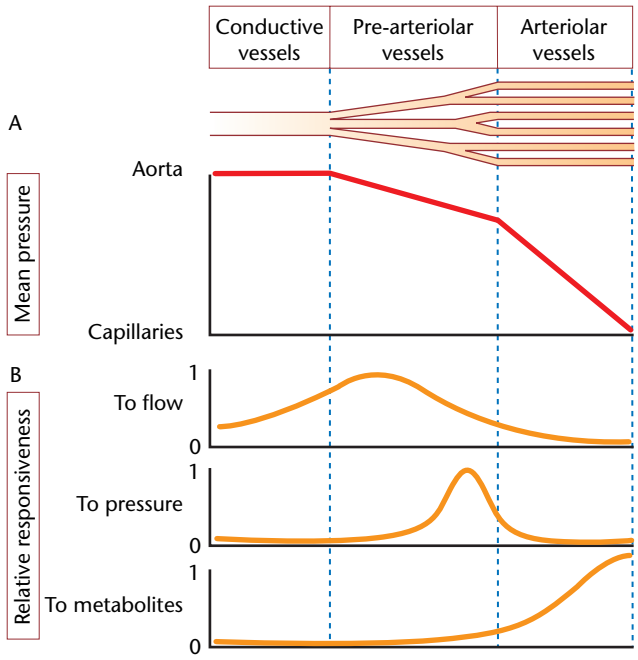


Figure 14.1 (A) Schematic representation of the functional subdivision of the coronary arterial system in conductive vessels, pre-arterioles and arterioles. The pressure drop along conductive vessels is negligible, that through pre-arterioles is appreciable and that through the arterioles is the largest. Pre-arterioles, by definition, are not exposed to myocardial dilator metabolites because of their extramyocardial position or their wall thickness. (B) Conductance vessels and, to an even greater extent, proximal pre-arterioles are more responsive to flow-dependent dilatation. Distal pre-arterioles are more responsive to changes in intravascular pressure and are mainly responsible for autoregulation of coronary blood flow. Arterioles are more responsive to changes in the intramyocardial concentration of metabolites and are mainly responsible for the metabolic regulation of coronary blood flow. Adapted from Maseri *et al.* [1].

beginning of diastole and contributes to the prompt reopening of intramyocardial vessels that are squeezed closed by systole.

- The intermediate compartment is represented by pre-arterioles. They are characterized by a measurable pressure drop along their length. They are not under direct vasomotor control by diffusible myocardial metabolites because of their extramyocardial position or arterial wall thickness. Proximal pre-arterioles are more responsive to changes in flow, while distal pre-arterioles are more responsive to changes in pressure. Their specific function is to maintain pressure at the origin of the arterioles within a narrow range when coronary perfusion pressure and/or flow change.
- The distal compartment is represented by arterioles. They are characterized by a considerable pressure drop along their length and represent the site of the metabolic regulation of myocardial blood flow, as their tone is influenced by substances produced during myocardial metabolism. Their specific function is the matching of myocardial blood supply and myocardial oxygen demand.

Large epicardial arteries have a diameter ranging from a few millimetres to ~500 μm and are visible at coronary angiography. Pre-arterioles (diameter from ~500 to ~100 μm) and arterioles (diameter < 100 μm) are below the resolution of current angiographic systems and hence are not visible at angiography. Notably, each compartment is governed by distinct regulatory mechanisms.

Distribution of coronary vascular resistance in series

The vascular resistance is distributed in series along the coronary vascular bed, but it also varies in parallel vascular segments in different layers of the ventricular wall.

The individual contribution of successive coronary vascular segments to total resistance can be inferred from the progressive drop in mean pressure from the aorta to the coronary sinus. About 10% of the pressure drop occurs in epicardial coronary arteries, 30% in pre-arterioles, 40% in arterioles and 20% from capillaries to large veins (Fig. 14.2) [2]. Notably, such an inference is an approximation as the vascular cross-section varies considerably during the cardiac cycle. Indeed, because the left ventricular wall compresses intramyocardial vessels during systole, most of the coronary blood flow to the left ventricle occurs during diastole. Thus, the contracting heart obstructs its own blood supply. At peak systole there is even backflow in the coronary arteries, particularly in the intramural and small epicardial vessels. During diastole the driving pressure is the pressure gradient between the coronary arteries and either the right atrium or the left ventricle (for veins that drain directly into the ventricle). If perfusion pressure is progressively lowered, diastolic blood flow ceases when the coronary driving pressure reaches 40–50 mmHg, the so-called *pressure at zero flow*, which is largely determined by diastolic compressive forces.

Distribution of coronary vascular resistance in parallel

The distribution of coronary resistance in parallel vascular segments in different layers of the ventricular wall can be studied by pressure/flow curves which provide information on the differences in vascular resistance between subendocardial and subepicardial layers of the ventricular

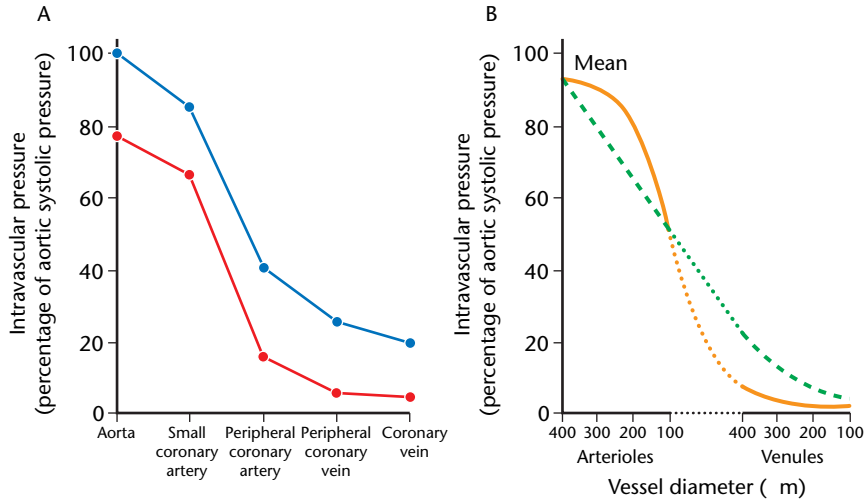


Figure 14.2 (A) Systolic (blue line) and diastolic (red line) pressures in a distal epicardial coronary artery, in a coronary arteriole, in a small coronary vein and in a large coronary vein of anaesthetized dogs, expressed as percentages of aortic pressure. The greatest pressure drop occurs through small coronary arteries. (B) Mean coronary pressure drop from the aorta to small coronary arteries and veins in a rabbit heart, measured on the surface of the epicardium (orange line). The greatest pressure drop occurs at the level of arterioles less than 100 μm in diameter. During intravenous dipyridamole infusion (green line) the pressure drop across pre-arteriolar vessels increases, indicating insufficient flow-mediated dilatation. Adapted from Klassen *et al*. [2] and Chilian *et al*. [33].

wall. In non-beating hearts, maximal conductance is higher in the subendocardial than the subepicardial layers. Conversely, in beating hearts, maximal conductance is lower in the subendocardial layers because of greater extravascular compressive forces during both systole and diastole. The extravascular systolic compressive forces have two components. The first is the intracavitary left ventricular pressure, which is transmitted fully to the subendocardium, but falls off to almost zero at the epicardial surface. The second is the vascular narrowing caused by compression and bending of vessels coursing through the ventricular wall from subepicardium to subendocardium (intramyocardial pressure). Hence, during ventricular contraction, subendocardial arterioles become more narrowed relative to those in the subepicardium and, at the onset of diastole, they present a higher resistance to flow, needing a longer time to resume their full diastolic calibre.

Tachycardia impairs the subendocardial blood flow, particularly in the presence of myocardial hypertrophy. In fact, the time constant of diastolic filling of intramyocardial vessels does not shorten with heart rate and becomes a limiting factor for the perfusion of subendocardial layers. Nevertheless, in conscious dogs, under normal resting conditions, the subendocardial flow is higher than the subepicardial flow (with a ratio of about 1.25:1), because of a greater conductance in the subendocardial arterioles. The latter finding is consistent with the higher subendocardial oxygen demand which is secondary to the greater wall stress in the subendocardial than in the subepicardial layers [3]. Thus, given a sufficiently high perfusion pressure, a sufficiently long diastole and an adequate systolic expansion of conductive arteries, the subendocardium is adequately perfused. However, when perfusion pressure at the origin of arteriolar vessels isreduced compared to that of the aorta (e.g. due to epicardial coronary stenosis or aortic stenosis) perfusion becomes jeopardized earlier in the inner compared to the outer layers of the left ventricle. The inner layers then become even more susceptible to underperfusion if diastolic time is short and in the presence of myocardial hypertrophy. Of note, selective constriction of subepicardial vessels can influence perfusion pressure in subendocardial vessels and hence subendocardial flow. Overperfusion of the subepicardial layers, in particular during exercise, when subendocardial perfusion is hampered by the shortening of diastolic time, might be prevented by sympathetic-system-mediated selective constriction of the subepicardial vessels, as proposed by Feigl [4]. Accordingly, potent constrictors, such as endothelin and α-adrenergic agonists, or adenosine antagonists, such as theophylline [5], cause selective subepicardial constriction which secondarily improves subendocardial perfusion.

Response of the coronary circulation to changes in flow

The shear stress, the tractive force that acts on the vascular wall, is proportional to the shear rate or velocity and to viscosity. Arteries exhibit an intrinsic tendency to maintain a constant shear stress, despite changes in shear rate or in viscosity. Indeed, very high or very low shear stress may jeopardize the interaction between blood elements and the endothelium. In the absence of changes in distending pressure, variations of flow in epicardial

coronary arteries can be achieved by intracoronary injection of arteriolar vasodilators such as adenosine. Angiographic studies in man have shown that epicardial coronary arteries dilate in response to an increase in coronary blood flow and that the increase in coronary diameter is proportional to the increase in flow, thus maintaining shear stress constant [6].

Flow-mediated dilatation occurs also in proximal pre-arterioles during the dilatation of distal pre-arterioles in response to a reduction in perfusion pressure and during arteriolar dilatation in response to an increased myocardial oxygen consumption or following myocardial ischaemia. In this setting, flow-mediated dilatation serves mainly to minimize any fall in pressure along the course of proximal pre-arterioles during dilatation of more distal vessels [7].

Mechanisms of flow-mediated dilatation

Flow-mediated dilatation is determined by vasodilators released by endothelial cells in response to an increase in shear stress, in particular nitric oxide (NO), endothelium-derived hyperpolarizing factor (EDHF) and prostacyclin. NO induces relaxation of smooth muscle cells by activating the formation of cyclic guanosine monophosphate from guanosine triphosphate. EDHF causes hyperpolarization and relaxation of smooth muscle cells by opening K^+ channels, whereas prostacyclin causes relaxation by activating adenylate cyclase, which leads to the formation of cyclic adenosine monophosphate.

NO appears to play a key role in flow-mediated relaxation of the large epicardial vessels, as the latter is prevented by N^g-monomethyl-L-arginine, a specific inhibitor of NO synthesis [8]. The contribution of EDHF to endothelium-dependent relaxation varies as a function of the size of the artery; indeed, it is more pronounced in resistance vessels and might play an important role in pre-arteriolar flow-mediated dilatation [9]. In contrast, the contribution of prostacyclin to flow-mediated relaxation appears to be modest. Yet, prostacyclin-mediated relaxation might be important in the presence of endothelial dysfunction with reduced bioavailability of NO, when it may provide a useful compensatory mechanism [10].

Response of the coronary circulation to changes in perfusion pressure: autoregulation

When metabolic requirements do not vary, the coronary circulation exhibits an intrinsic tendency to maintain blood flow at a constant rate despite changes in perfusion pressure, a mechanism known as autoregulation.

Variations of coronary perfusion pressure in the beating heart, in the presence of unaltered myocardial metabolic requirements, can be achieved by perfusing the coronary circulation independently from the aorta, so that aortic pressure (a determinant of myocardial oxygen consumption) remains constant when coronary arterial pressure is varied. In this setting, pressure/flow curves show that when perfusion pressure is varied, flow remains almost constant over a wide range of pressures, i.e. from 60 to 120 mmHg (Fig. 14.3). The level at which flow remains constant is determined by the level of myocardial oxygen consumption; when this is low the plateau of flow is low, when oxygen consumption is high the plateau is high [11]. Notably, for decreasing perfusion pressures, autoregulation is better maintained in the subepicardium than in the subendocardium, which, therefore, is more susceptible to the detrimental effects of very low perfusion pressures.

Mechanisms of autoregulation

The mechanism responsible for autoregulation is probably a myogenic response of distal pre-arteriolar vessels: they dilate in response to a reduction of perfusion pressure and constrict in response to an increase of perfusion

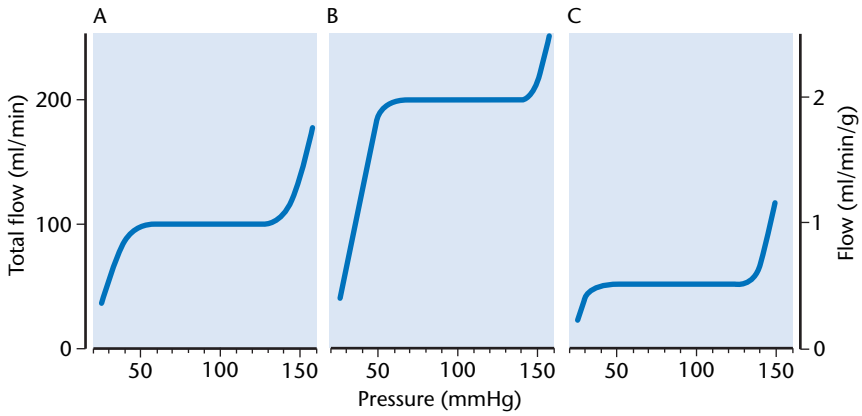


Figure 14.3 Autoregulation of coronary blood flow in anaesthetized dogs in the presence of normal (A), high (B), or low (C) oxygen consumption. In the presence of autoregulation, coronary flow is determined by the level of myocardial oxygen consumption, by the oxygen saturation of arterial blood and by neurohumoral modulation of coronary vasomotor tone. Autoregulation fails when perfusion pressure either decreases or increases beyond the range of pressures within which autoregulation acts. Adapted from Bache *et al.* [11].

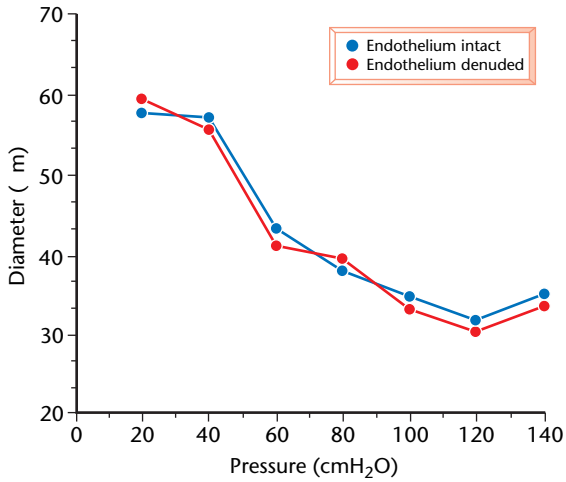


Figure 14.4 Effects of increasing pressures in a dog arteriole. Arteriolar dilatation and constriction were observed at lower and higher pressures, respectively. After mechanical denudation of the endothelium, spontaneous tone and myogenic responses were preserved. Thus, endothelium-independent pressure-induced myogenic constriction in arterioles is the main determinant of coronary autoregulation. Adapted from Kuo *et al*. [12].

pressure (Fig. 14.4) [12]. Myogenic responsiveness in the coronary microcirculation, independent of the endothelium, has been directly demonstrated *in vivo* in vessels that contribute to coronary microvascular resistance, and it is more pronounced in subepicardial than in subendocardial pre-arterioles. The mechanisms of the myogenic constriction in response to an increase in distending pressure are not well understood. They probably involve activation of a non-selective cation channel and subsequent influx of Na^+, K^+ and Ca^{2+} ions. The consequent membrane depolarization enables the recruitment of voltage-dependent calcium channels, which contributes to the increased calcium inflow. Furthermore, stretch initiates hydrolysis of membrane phospholipids, a process which contributes to increased intracellular calcium release. Myogenic contraction is ultimately caused by activation of myosin light chain kinase [13].

Response of the coronary circulation to changes in myocardial oxygen consumption: functional hyperaemia

The coronary circulation supplies the myocardium with blood for its widely and rapidly changing needs. It can supply oxygen in amounts up to five times the baseline consumption, and carries substrates and removes metabolic waste products, all to ensure optimal working conditions for myocardial cells. This demanding function takes place in an organ that generates its own perfusion pressure.

Under basal resting conditions the tone of coronary resistive vessels is high and coronary blood flow is at its lowest level. This intrinsically high resting tone provides the coronary circulation with the ability to increase flow by reducing vasomotor tone when myocardial oxygen consumption increases, a mechanism known as functional hyperaemia. This metabolic control of coronary blood flow is very precise and is fundamental for adequate myocardial oxygen supply. Indeed, in normal humans myocardial oxygen extraction is already considerably raised under resting conditions and does not change appreciably during increased cardiac work up to submaximal levels [14].

For any level of myocardial oxygen consumption, average coronary vascular resistance, and hence flow, can be modulated by a wide variety of neurotransmitters, by autacoids produced by the vessel wall, blood-borne substances, and drugs acting on different segments of resistive vessels. Neurotransmitters are released at nerve endings. Autacoids are generated locally by endothelial cells (NO, prostaglandins, EDHF, endothelin) or by adventitial cells (histamine, kinins, leukotrienes) while others are released by circulating platelets (thromboxane A_2, serotonin) or carried in the bloodstream (adrenaline). Notably, when myocardial oxygen consumption remains constant, any change in flow caused by neurohumoral modulation is mirrored by a change in oxygen extraction, so that vasodilatation or constriction are associated, respectively, with a proportional increase or decrease in coronary sinus Po_2 and oxygen saturation [15].

Determinants of myocardial oxygen consumption

The heart is an aerobic organ which relies almost exclusively on the oxidation of substrates for the generation of energy and can develop only a small oxygen debt. The most important determinant of oxygen consumption is cardiac work, as in the non-beating heart oxygen consumption is only 15–20% of that under normal resting conditions. Oxygen consumption, as for other tissues, is also influenced by the type of substrate used; indeed, it is higher when using predominantly fatty acids (which have a respiratory quotient of 0.7) than when using carbohydrates (which have a respiratory quotient of 1.0). Furthermore, myocardial oxygen consumption is about 15–20% higher in the subendocardium than the subepicardium.

Most of the time the factors that influence myocardial metabolic activity vary concurrently. However, when they are artificially separated under experimental conditions in a canine model, they rank in the following order [16].

1 *Heart rate*. Myocardial oxygen consumption approximately doubles during atrial pacing when heart rate is doubled. However, this is probably an underestimate, as during pacing (but not during exercise) the stroke volume decreases, also causing a decrease in ventricular volume and wall tension.
2 *Aortic pressure*. Myocardial oxygen uptake approximately doubles as mean aortic pressure is increased from 75 to 175 mmHg at constant heart rate and stroke volume.
3 *Myocardial inotropic state*. Myocardial oxygen consumption increases by about 30% when d*P*/dt (the first derivative of systolic left ventricular pressure over time) is doubled by extrasystolic potentiation or by noradrenaline administration at constant heart rate, aortic pressure and cardiac output.
4 *Stroke volume*. Myocardial oxygen consumption increases by about 20% when stroke volume is increased by 60% at constant rate–pressure product (i.e. heart rate times systolic blood pressure).

An accurate measurement of myocardial oxygen consumption requires the determination of coronary blood flow and of arterial–venous difference in blood oxygen content (which is generally achieved by sampling blood simultaneously from the aorta and the coronary sinus). As coronary sinus sampling is required, and as the measurement of coronary flow presents considerable methodological problems, a number of indirect indices have been proposed. Of these, the rate–pressure product is the simplest and yet it correlates closely in a wide range of values with measured changes in myocardial oxygen consumption [14].

Mechanisms of metabolic regulation of myocardial blood flow

By acting on coronary arterioles, adenosine is probably the key mediator of metabolic blood flow regulation. Adenosine is formed by degradation of adenine nucleotides under conditions in which adenosine triphosphate (ATP) utilization exceeds the capacity of myocardial cells to re-synthesize high energy compounds (a process dependent on oxidative phosphorylation in mitochondria). This results in the production of adenosine monophosphate, which is converted to adenosine by the enzyme 5′-nucleotidase. Adenosine then diffuses from the myocytes into the interstitial fluid, where it exerts powerful arteriolar dilator effects through the stimulation of A_2 adenosine receptors on smooth muscle cells. Several findings support the critical role of adenosine in the metabolic regulation of myocardial flow. Indeed, its production increases in cases of imbalance in the supply/demand ratio of myocardial oxygen, with the rise in interstitial concentration of adenosine paralleling the increase in coronary blood flow. Inhibition of adenosine, however, does not reduce the magnitude of functional hyperaemia entirely, thus suggesting that other substances can play a critical role [17].

It is worth emphasizing that the response of the coronary circulation to changes in myocardial oxygen consumption triggers a complex and integrated microvascular response. The arterioles dilate in response to the release of myocardial metabolites and this dilatation decreases both resistance in the overall network and pressure in distal pre-arterioles, which in turn induces myogenically sensitive vessels to dilate. Furthermore, dilatation of distal pre-arterioles and arterioles results in an increase in shear stress and triggers flow-dependent dilatation in larger pre-arterioles and in conductance arteries.

Thus, as proposed by Chilian [18], the coronary circulation matches blood flow with oxygen requirements by coordinating the resistances within different microvascular domains, each governed by distinct regulatory mechanisms. Such an integration appears advantageous because the system does not rely on a single mechanism of control. Accordingly, if a pathological process renders a mechanism dysfunctional, other mechanisms, at least to some extent, can compensate for it, although the price to pay is a reduction of regulatory mechanism reserve.

Response of coronary circulation to a brief coronary occlusion: reactive hyperaemia

When a major epicardial coronary artery is occluded for a short period of time, occlusion release is followed by a significant increase in coronary blood flow, a phenomenon known as reactive hyperaemia. The maximum increase in blood flow occurs within the few seconds after the release of the occlusion and the peak flow, which has been shown to reach four or five times the value of pre-ischaemic flow, is dependent on the duration of the ischaemic period for occlusion times up to 15–20 seconds. Although occlusions of longer duration do not modify further the peak of the hyperaemic response, they do affect the duration of the entire hyperaemic process, which increases with the length of the occlusion [19]. Generally, the excess flow that follows the occlusion, known as flow repayment, is larger than the flow debt incurred during the ischaemic period (Fig. 14.5) [20].

From the previous observations it is generally accepted that myocardial ischaemia, even of brief duration, is the most effective stimulus for vasodilatation of coronary resistive vessels and that, under normal circumstances, reactive hyperaemic peak flow represents the maximum flow available at a given coronary perfusion pressure.

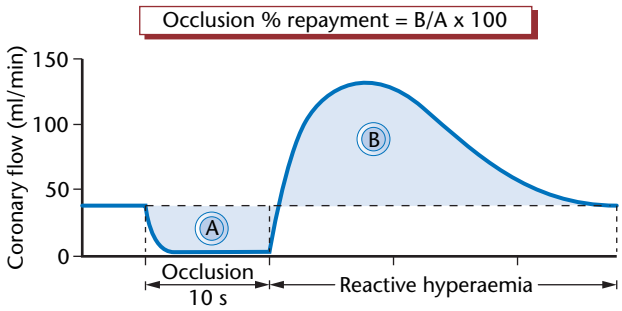


Figure 14.5 Mean coronary blood flow before, during and after coronary occlusion. Area A is the flow debt acquired during occlusion, whereas area B is its repayment following restoration of blood flow (see text for definitions). Typically, the repayment is larger than the flow debt incurred during the ischaemic period.

Values of coronary blood flow comparable to the peak flow of reactive hyperaemia can be achieved using coronary vasodilators such as adenosine or dipyridamole, which induce a 'near maximal' vasodilatation of the coronary microcirculation. This concept, however, has been challenged by studies in experimental animals, as well as in human subjects, that have demonstrated that reactive hyperaemic peak flow may not represent the true ceiling of blood flow achievable at a given perfusion pressure [21,22]. Reactive hyperaemia occurs also in denervated isolated hearts, thus suggesting that flow-mediated, myogenic and metabolic mechanisms (see previous sections) are the main determinants of this phenomenon [23].

Coronary flow reserve

The concept of coronary flow reserve was first introduced by Gould *et al.* in 1974 [24] as an indirect parameter to evaluate the global function of the coronary circulation. Coronary flow reserve is the ratio of coronary blood flow during near maximal coronary vasodilatation to resting flow and is an integrated measure of flow through both the large epicardial coronary arteries and the microcirculation (Fig. 14.6) [25].

Coronary flow reserve must be considered a relative, rather than absolute, value that depends on four main variables:

- resting blood flow
- cross-sectional area of arteriolar vessels per unit volume of myocardium
- extravascular coronary resistance
- arteriolar perfusion pressure.

Since resting blood flow is the denominator in the formula used to compute coronary flow reserve, any increase in resting blood flow (e.g. the increase in resting perfusion seen in patients with arterial hypertension)

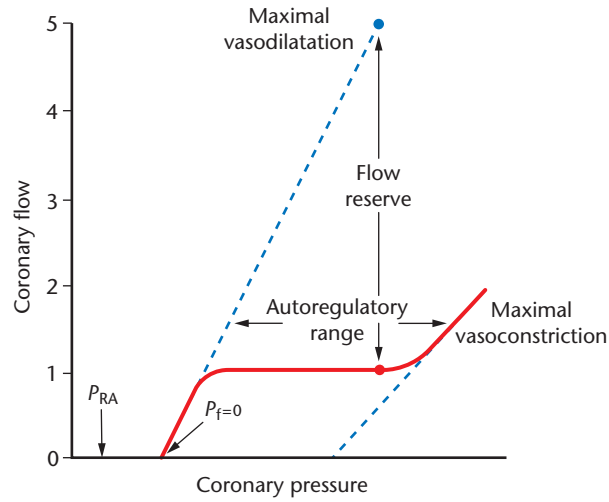


Figure 14.6 Relationship between coronary blood flow and coronary arterial pressure in the left ventricle. At a constant level of myocardial oxygen consumption, coronary blood flow is maintained constant over a wide range of coronary perfusion pressures (red line), included within the boundaries of maximal resistive coronary vessel dilatation or constriction (dashed lines). In the presence of maximal resistive vessel dilatation coronary blood flow and coronary arterial pressure are proportional (dashed line on the left). The red and blue circles represent the basal state and the maximal coronary blood flow, respectively, under normal conditions, giving a coronary flow reserve of 5.0. P_{RA} = right atrial pressure, $P_{f=0}$ = pressure at zero flow.

will lead to a net decrease in the available coronary flow reserve.

The total cross-sectional area of resistive vessels per unit volume of myocardium influences coronary flow conductance and hence the slope of the pressure/flow curve in inner and outer layers of the ventricular wall. The greater the vascular cross-sectional area, the steeper the slope of the pressure/flow curve (the greater the increase in flow per unit increase in pressure). In the presence of maximal vasodilatation the vascular conductance per unit volume of myocardium can be reduced because the total number of resistive vessels per unit volume is decreased or because the lumen of individual vessels is reduced.

Extravascular compressive forces reduce coronary flow reserve mainly in subendocardial layers, in particular during tachycardia and in the presence of elevated diastolic ventricular pressures (Fig. 14.7) [26].

The perfusion pressure that determines flow for any given level of vascular resistance is the pressure at the origin of arteriolar vessels. During maximal coronary dilatation, the slope of the pressure/flow curve is very steep; thus the increase of coronary flow reserve with increasing pressure is substantial. Under physiological conditions

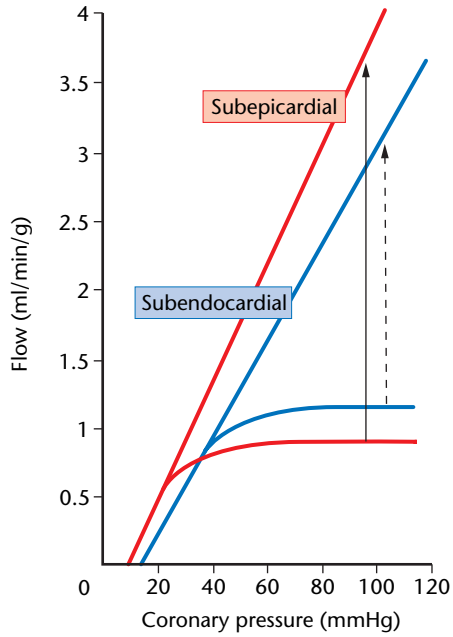


Figure 14.7 Coronary blood flow reserve in subendocardial and subepicardial layers. Under physiological conditions the coronary flow reserve is lower in the subendocardial layers, where there is a higher resting blood flow as a result of a higher oxygen consumption and a lower pressure/flow curve because of higher extravascular compressive forces. This difference between subepicardial and subendocardial layers increases progressively with tachycardia and with elevation of diastolic pressure. Adapted from Bache *et al*. [26].

the coronary perfusion pressure that determines myocardial blood flow corresponds closely to aortic pressure.

In patients, a reduced coronary flow reserve can be the result of a narrowing of epicardial coronary arteries or may reflect a dysfunction of the coronary microcirculation. The latter can be caused by structural (e.g. vascular remodelling with a reduced lumen to wall ratio) or functional (e.g. vasomotor abnormalities) changes, which may involve neurohumoral factors and/or endothelial dysfunction. An abnormal coronary flow reserve may also reflect changes in systemic haemodynamics (e.g. hypotension) as well as changes in extravascular coronary resistance (e.g. increased intramyocardial pressure).

Assessment of coronary flow reserve in man

The assessment of coronary flow reserve in humans implies the measurement of coronary or myocardial blood flow. Several techniques, including Doppler wires and coronary sinus thermodilution, are available for measuring coronary blood flow. These techniques are invasive and affected by serious limitations [27]. While coronary blood flow has units of volume per time (i.e. ml/min), Doppler measurements usually allow assessment of flow velocity (cm/s) and only a few techniques provide volumetric flow [28]. Measurement of inert tracer clearance, the assessment of which can be invasive (based on arterial–venous sampling) or non-invasive (based on external detection of radionuclide wash-out, e.g. ^{133}Xe) provides estimates of regional perfusion, although the mass of tissue subtended by the artery under study is unknown. Single-photon emission computerized tomography (SPECT) allows the non-invasive assessment of directional changes in regional tissue perfusion, but its physical limitations do not permit quantification of myocardial blood flow [29]. Positron emission tomography has been shown to allow non-invasive and accurate quantification of regional myocardial blood flow per gram of tissue, if suitable tracers are used and appropriate mathematical models are applied [30].

Resting and hyperaemic myocardial blood flows are heterogeneous both between and within individuals and exhibit a similar degree of spatial heterogeneity, which appears to be temporally stable. There is a significant linear association between age and resting myocardial blood flow, partly related to changes in external cardiac workload with age whilst hyperaemic myocardial blood flow declines in people over 65 years of age. Hyperaemic myocardial blood flow was found to reach higher values in subjects in whom the standard dose of adenosine (140 µg/kg/min) was used compared to those in whom dipyridamole (0.56 mg/kg infused over 4 min) was used as a hyperaemic stressor [31]. Thus, both age and type of vasodilator used determine the degree of hyperaemia achieved and, thus, are sources of variability. As a result, the inter-individual variability of hyperaemic myocardial blood flow is greater than that observed for resting myocardial blood flow. In normal humans, the range of regional coronary flow reserve is wide, with important clinical implications. Notably, a regional coronary flow reserve of less than 2.5 is often interpreted as abnormal. Yet, many normal left ventricular regions have a coronary flow reserve of less than 2.5 [32].

Myocardial ischaemia

Causes of myocardial ischaemia

Flow limiting stenosis

Under normal circumstances, large epicardial coronary arteries (conduit arteries) offer very little resistance to flow

whilst the pre-arterioles and arterioles, below 500 μm in diameter, are the principal determinants of coronary vascular resistance [33]. Atherosclerotic plaques which determine a reduction of luminal diameter add an extra resistance 'in series', that results in a post-stenotic pressure drop. The latter is compensated for by vasodilatation of resistive vessels and does not have any appreciable effect on coronary flow reserve for reductions of internal luminal diameter up to 50%. Thereafter, however, this compensatory mechanism is progressively exhausted for increasing values of stenosis severity and coronary flow reserve becomes close to unity (i.e. hyperaemic flow = resting flow) for reduction of luminal diameter > 80% (Fig. 14.8) [34]. Functionally, this process progressively limits the ability of the coronary circulation to increase blood flow to meet an increased metabolic demand and is the basis for exercise-induced myocardial ischaemia and angina pectoris in patients with obstructive coronary atherosclerosis.

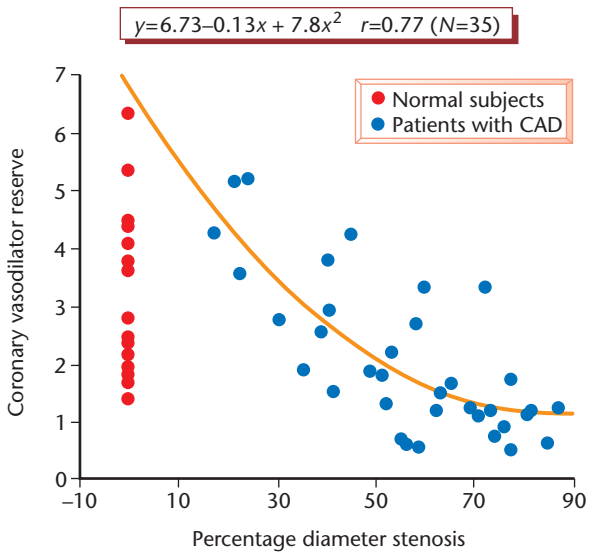


Figure 14.8 Relationship between severity of coronary stenosis (measured by quantitative coronary angiography) and coronary flow reserve (measured non-invasively by positron emission tomography and oxygen-15 labelled water) in patients with coronary artery disease (CAD, blue circles). There is a progressive decline in flow reserve for stenoses with a severity ≥ 50% and the flow reserve approaches unity for stenoses ≥ 80% (i.e. maximum flow, after adenosine, is not different from resting flow). When flow reserve is close to unity, any increase in cardiac workload cannot be met by an adequate increase in blood flow leading to myocardial ischaemia in the region subtended by the stenotic coronary artery. A massive interindividual variability of coronary flow reserve is noted, however, among apparently normal subjects (red circles), thus making the interpretation of coronary flow reserve in the presence of obstructive coronary atherosclerosis rather difficult. Adapted from Uren *et al*. [34].

Occlusive spasm and dynamic stenoses

Coronary artery spasm, consisting of a paroxysmal, intense occlusive vasoconstriction usually involving a segment of an epicardial coronary artery, which results in transmural myocardial ischaemia, is the unique pathogenetic mechanism of variant angina (see below) [35].

Coronary artery spasm may occur at the site of an obstructive coronary atherosclerotic plaque or in angiographically normal or near normal coronary arteries [36]. In some cases it may involve more segments in the same coronary artery branch or even more than one branch. Diffuse coronary spasm may also be observed, in particular in Japanese patients.

The substrate of coronary spasm is a hyperreactivity of smooth muscle cells of the involved coronary segment to vasoconstrictor stimuli [37]. This is likely to be related to alterations in intracellular transduction mechanisms [36], as indicated by the ability of different vasoconstrictor stimuli, acting through different membrane receptors (e.g. sympathetic and parasympathetic activation [38], ergonovine, histamine, dopamine, acetylcholine, serotonin, alkalosis) to precipitate coronary spasm, even in the same patient [37].

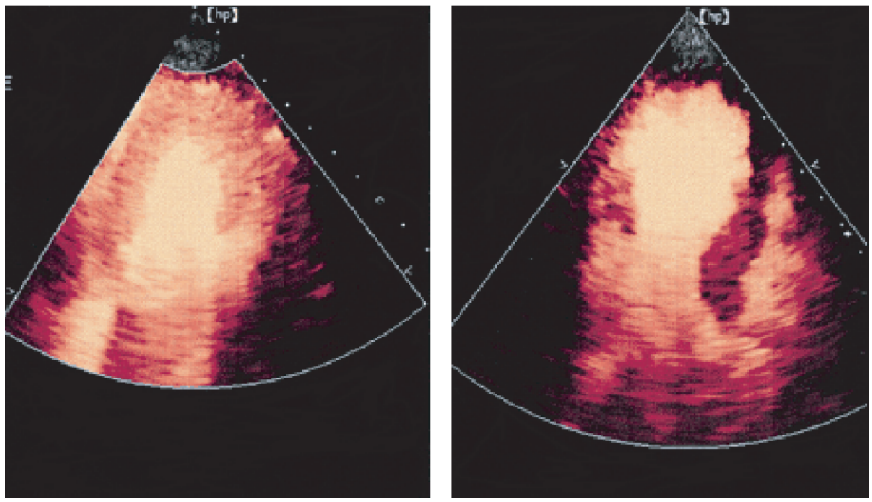
The causes of smooth muscle cell hyperreactivity are unknown, but several possible contributing factors have been suggested, including increased cellular rho-kinase activity [39], abnormalities in ATP-sensitive potassium channels [40] and membrane Na^+–H^+ countertransport [41].

Coronary spasm must be distinguished from dynamic stenoses observed in patients with stable angina. Coronary spasm is caused by hyperreactivity of smooth muscle cells of a localized coronary segment and is occlusive or subocclusive. Dynamic stenoses, instead, are mainly caused by endothelial dysfunction, which facilitates vasoconstriction at the site of pliable critical or subcritical coronary stenoses in response to sympathetic stimuli (such as exercise and mental stress), resulting in a transient worsening of stenosis severity. This may facilitate the occurrence of transient myocardial ischaemia in the presence of an increased myocardial oxygen consumption or even at rest [42].

It is worth noting that, although the main pathogenetic component of acute coronary syndromes is coronary thrombosis [43], abnormal coronary vasomotion of variable severity often plays a contributory role.

Thrombosis

Local thrombosis that occurs at the site of eroded or fissured plaques is central to the initiation of myocardial ischaemia in acute coronary syndromes. Notably, in



Reflow No reflow

Figure 14.9 Assessment of myocardial perfusion by myocardial contrast echocardiography in two patients treated by a primary percutaneous coronary intervention on the left anterior descending coronary artery, 24 hours after the event. Although both patients exhibited TIMI 3 flow in the infarct-related artery and had similar symptom onset to balloon time intervals, one patient exhibited excellent myocardial perfusion (left panel), whereas the other patient displayed 'no reflow' (right panel). The reasons for this different microvascular response to ischaemia–reperfusion are still largely unknown. (Courtesy of Dr Leonarda Galiuto, Cardiology Institute, Catholic University, Rome, Italy.)

about two-thirds of patients thrombus formation occurs at the site of atherosclerotic plaques which reduce lumen diameter by less than 50%, and in 97% of patients at the site of plaques which reduce lumen diameter by less than 70%. In this setting a crucial role is played by local tissue factor expression, and probably also by tissue factor transported by circulating leucocyte-derived microparticles, which interacts with factor VIIa to initiate a cascade of enzymatic reactions resulting in the local generation of thrombin and fibrin deposition. Furthermore, thrombin and collagen exposed by endothelial cell disruption, trigger platelet aggregation, followed by the release of powerful vasoconstrictors.

Microvascular dysfunction

Until quite recently, causes of transient myocardial ischaemia were investigated in conduit coronary arteries. However, recent advances have highlighted the crucial involvement of microcirculation in several clinical manifestations of ischaemic heart disease (IHD). Microvascular dysfunction can be the result of either functional (e.g. endothelial and/or smooth muscle cell dysfunction) or structural (e.g. remodelling of intramural coronary arteries with a reduced lumen to wall ratio) alterations.

A new concept is emerging where 'coronary microvascular disease' is a well-defined condition that often precedes the development of full-blown IHD and may have an independent prognostic value [44]. Indeed, coronary microvascular dysfunction has been documented in asymptomatic subjects with risk factors for IHD, including not only hypertension and diabetes [45], but also hypercholesterolaemia, obesity and smoking [46–48], and can be severe enough to cause angina even in patients with minimal to moderate disease of the epicardial coronary arteries.

Coronary microvascular dysfunction can be observed following percutaneous coronary interventions in patients with stable angina [49] and appears to play an important role also in patients with unstable angina [50]. The 'no reflow phenomenon' is an extreme form of microvascular dysfunction which can occur in the territory of an acute myocardial infarction despite restoration of epicardial blood flow by successful thrombolysis or primary percutaneous coronary interventions, thus negating the potential prognostic advantages of the treatment (Fig. 14.9) [51].

A dysfunction of the coronary microcirculation has also been demonstrated in some cardiac diseases unrelated to coronary artery disease, in particular dilated and hypertrophic cardiomyopathies (Table 14.1) [52,53]. It is worth noting that microvascular dysfunction has been suggested to be a strong predictor of major cardiac events at follow-up in these groups of patients [52,53], whereas it remains unclear whether it may have any prognostic value in other clinical conditions characterized by left ventricular hypertrophy.

Finally, microvascular dysfunction has been suggested to be involved in the pathogenesis of cardiac syndrome X (see below). The hypothesis that angina in cardiac syndrome X is of ischaemic origin was based on the presence of ST-segment depression during spontaneous chest pain episodes and on ECG stress tests, as well as on the evidence of reversible stress-induced myocardial perfusion defects [54], reduced endothelium-dependent and independent coronary vasodilation [55], and metabolic evidence of myocardial ischaemia in some studies [56]. Other

Table 14.1 Clinical conditions associated with evidence of coronary microvascular dysfunction

Spontaneous
Risk factors for ischaemic heart disease
Smoking
Hyperlipidaemia
Hypertension
Obesity
Diabetes
Secondary left ventricular hypertrophy
Primary cardiomyopathies
Acute coronary syndromes (no-reflow)
Syndrome X*
Iatrogenic
Percutaneous coronary interventions
Bypass surgery

*The pathogenetic role of microvascular dysfunction is still debated.

studies, however, failed to find evidence of abnormal myocardial blood flow or coronary flow reserve [57], or metabolic evidence of ischaemia during stress tests [58]. Therefore, the pathogenetic mechanisms of chest pain in these patients remain under debate [59]. An ischaemic origin of angina is contradicted also by the lack of transient wall motion abnormalities in the presence of angina and typical transient ST-segment [60]. Maseri *et al*. [1], however, proposed that focal ischaemia in small myocardial regions scattered throughout the myocardium caused by pre-arteriolar dysfunction might explain the paradox of angina and ST-segment depression in the absence of wall motion changes.

Extracoronary cardiac and non-cardiac causes of ischaemia

As described earlier in this chapter, 90% of myocardial blood flow occurs in diastole and this is because of the high extravascular compressive forces during systole. An increase of diastolic ventricular pressure causes an elevation of extravascular compressive force, which can limit myocardial perfusion, thus facilitating effort-induced myocardial ischaemia. An increase of diastolic ventricular pressure is typically observed in hypertrophic cardiomyopathy, in restrictive cardiomyopathy and in hypertensive heart disease. In aortic stenosis both an increase of diastolic left ventricular pressure and a reduction of coronary perfusion pressure contribute to the pathogenesis of effort-induced myocardial ischaemia.

Finally effort-induced myocardial ischaemia can be favoured by a reduction of oxygen content in arterial blood, as observed in anaemia or in patients with severe pulmonary diseases, or by increased metabolic requests, as in hyperthyroidism.

Consequences of myocardial ischaemia

Structural and ultrastructural alterations

Most of our understanding of the early cellular consequences of myocardial ischaemia is derived from experimental studies in animals. It is generally accepted that ischaemia for up to 15–20 minutes is associated with reversible injury, whereas ischaemia of longer duration leads to a progressively more extensive area of irreversible injury. Most of the ultrastructural alterations seen early in ischaemic myocardium, such as cell swelling, glycogen depletion, margination of nuclear chromatin and elongation of myofibrils, become progressively more severe in the irreversible phase. There are, however, two distinctive signs of irreversible damage: amorphous matrix densities in the mitochondria and breaks in the sarcolemma [61].

In the dog, irreversible damage is initially detectable (15–20 minutes after coronary occlusion) in subendocardial layers, which are more susceptible to ischaemia because of the higher myocardial oxygen consumption, and then propagates towards the subepicardial layers (the wavefront of necrosis). Apoptosis appears to be a significant complicating factor of acute myocardial infarction, increasing the magnitude of myocyte cell death associated with coronary artery occlusion, and might play an important role in cardiac remodelling [62].

Metabolic alterations

Under conditions of myocardial ischaemia, oxygen shortage leads to a reduced rate of substrate oxidation (both free fatty acids and glucose) resulting in ATP depletion and accumulation of reduced coenzymes, that are re-oxidized to some extent in the mitochondria by way of the maleate–aspartate cycle. Thus, despite greater glucose availability through both an increased uptake of exogenous glucose and activation of glycogen breakdown, glucose oxidation during ischaemia is negligible. Pyruvate formed through glycolysis cannot be oxidized and, in the presence of increased amounts of reduced nicotinamide adenine dinucleotide (NADH), is converted to lactate by lactate dehydrogenase, thus contributing to tissue acidosis. In addition, a greater amount of alanine, produced via transamination of pyruvate, is released from myocardial fibres. Finally, major changes involve K^+ and Ca^{2+} ions. Loss of intracellular K^+ begins within seconds of the onset of ischaemia and extracellular

concentration markedly increases during the first few minutes. The mechanisms of this loss, which begins before substantial ATP depletion, are still largely unknown. The decrease of transmembrane K^+ gradient is a major cause of abnormalities detectable on surface ECG. The early increase in cytosolic Ca^{2+} results from increased influx and decreased sequestration in the sarcoplasmic reticulum and is thought to be one of the mechanisms of irreversible cell death [63].

After an ischaemic episode, myocardial glucose utilization is higher than in resting conditions despite normalization of the haemodynamic conditions (Fig. 14.10) [64]. This extra glucose is probably used for rebuilding of the glycogen stores that had been depleted during ischaemia.

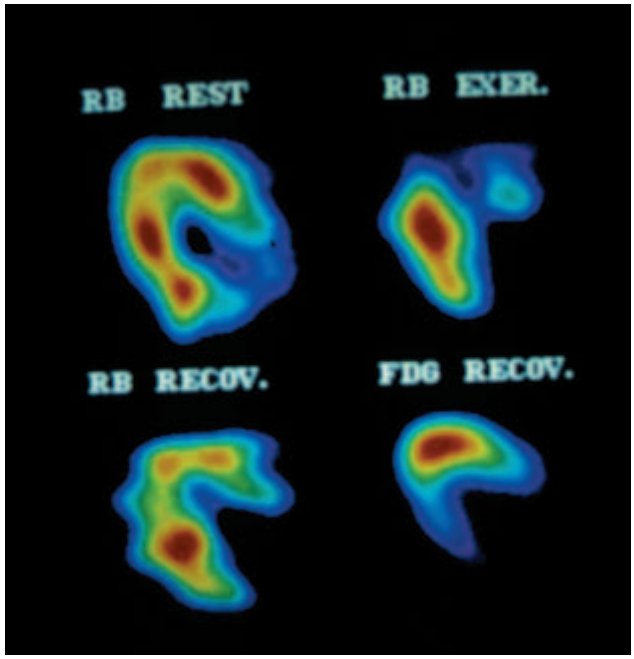


Figure 14.10 Positron emission tomography scans of rubidium-82 (^{82}Rb)- and ^{18}F-labelled deoxyglucose (FDG) uptake in the left ventricle of a patient with left anterior descending coronary artery disease. In each image, the left ventricular free wall is in the 6 o'clock to 10 o'clock position, the anterior wall and septum are in the 10 o'clock to 3 o'clock position, and the remaining open area is in the plane of the mitral valve. The scan at rest (top left) shows a homogeneous cation uptake in all myocardial walls. The ^{82}Rb scan recorded during exercise (top right) shows a severely reduced cation uptake in the anterior left ventricular wall, while the ^{82}Rb scan recorded in the recovery phase (when the patient had neither pain nor ECG changes) shows that perfusion is similar to baseline (bottom left). FDG was injected in the recovery phase after the last ^{82}Rb scan. The FDG scan, recorded 60 minutes after tracer injection, shows a greater FDG uptake in the previously ischaemic area (bottom right). FDG uptake in the anterior wall is 1.55 times higher than that in the non-ischaemic muscle. Adapted from Camici *et al.* [64].

Cardiac function alterations

Over 70 years ago Tennant and Wiggers [65] demonstrated that acute ischaemia rapidly impairs myocardial contractile function. For many years it was believed that relief of ischaemia led to an almost immediate normalization of function, provided that necrosis had not occurred. In 1975, Heyndrickx *et al.* [66] demonstrated, in a conscious dog model, that a 15-minute coronary occlusion (a time period generally not associated with cell death), followed by reperfusion, produced a marked depression in regional contractile function that persisted for at least 6 hours after reperfusion. The term 'myocardial stunning' was coined to describe this viable tissue that exhibited prolonged post-ischaemic ventricular dysfunction. More recently, stunning has been demonstrated to occur in patients with IHD both after exercise-induced and dobutamine-induced ischaemia (Fig. 14.11) [67,68]. Another more persistent form of post-ischaemic left ventricular dysfunction has been demonstrated in patients with chronic IHD: 'hibernated myocardium'. This can be defined as chronically dysfunctional myocardium, subtended by a stenotic coronary artery (with severe limitation of coronary flow reserve), that improves function upon coronary revascularization. The pathophysiology of myocardial hibernation in humans is more complex than initially postulated. The recent evidence that repetitive ischaemia in patients with IHD can be cumulative and leads to more severe and prolonged stunning, further supports the hypothesis that, at least initially, stunning and hibernation are two facets of the same coin [69].

Finally, a consequence of myocardial ischaemia is 'myocardial preconditioning', where a short episode of ischaemia can reduce the morphofunctional effects of a subsequent episode of ischaemia. The term was introduced by Murry *et al.* [70], who found a reduction in myocardial infarct size in dogs, when persistent coronary occlusion was preceded by one or more brief episodes of ischaemia. Preconditioning was subsequently demonstrated in other animal species, and further studies have also shown that a second window of protection can be demonstrated approximately 24 hours after the ischaemic stimulus, lasting for 48–72 hours [71]. In humans, ischaemic preconditioning has also been found to occur as a reduced myocardial suffering during repeated spontaneous or provoked (e.g. by balloon inflation during coronary angioplasty) transient ischaemic episodes [72].

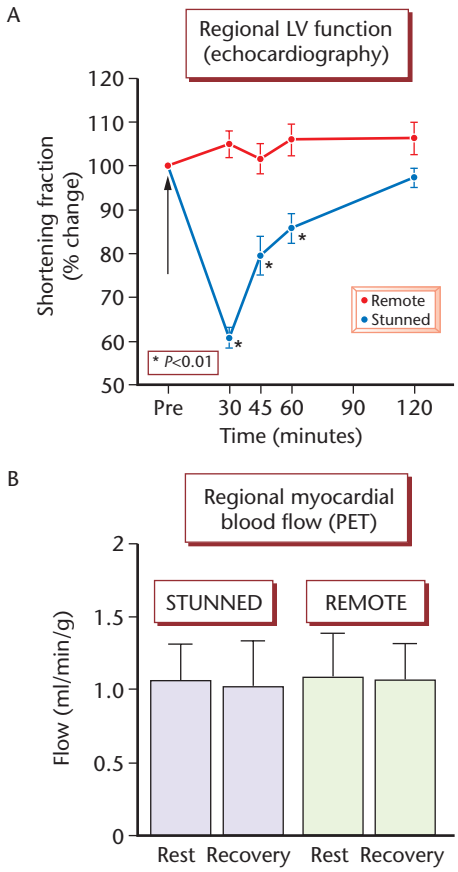


Figure 14.11 Demonstration of stunning in patients with single vessel coronary artery disease and exercise-induced ischaemia. (A) Regional left ventricular wall motion assessed by echocardiography at baseline and at different time points during dobutamine stress test. Shortening fraction in the recovery phase was unchanged in the control territory subtended by a non-diseased coronary artery (red line). By contrast, the shortening fraction was severely reduced in the ischaemic territory (blue line) and returned towards baseline only after 120 minutes from the cessation of dobutamine stress test. (B) In the ischaemic region, myocardial blood flow, as measured by positron emission tomography (PET) and ^{15}oxygen-labelled water, was comparable to blood flow in the non-ischaemic territory, both at baseline and also 30 minutes after dobutamine stress test, when shortening fraction was still severely depressed, thus demonstrating the occurrence of stunning in man. Adapted from Barnes *et al.* [67].

Arrhythmias

Myocardial ischaemia can trigger electrophysiological changes that favour the development of arrhythmias. These are rare during transient episodes of subendocardial ischaemia, whereas they are more common when myocardial ischaemia is transmural and in the setting of acute myocardial infarction. The most common forms of arrhythmia during ischaemia and infarction are ventricular tachyarrhythmias and fibrillation whilst atrioventricular block and asystole occur less frequently. In the canine model, but not in man, life-threatening ventricular arrhythmias are frequently found at the time of post-ischaemic reperfusion.

Reflex sympathetic activation

Ischaemia stimulates the terminal endings of both vagal and sympathetic fibres that innervate the myocardium. Sympathetic activation can further exacerbate myocardial ischaemia by increasing contractility and triggering vasoconstriction and ventricular arrhythmias. Following acute myocardial infarction continued sympathetic activation contributes to ventricular remodelling and hypertrophy and to myocardial β-adrenoceptor down-regulation [73].

Cardiac ischaemic pain

Cardiac ischaemic pain is a late consequence of myocardial ischaemia. Notably, transient myocardial ischaemia and even necrosis can occur in the absence of pain. More than 200 years after the original description of angina pectoris by Heberden [74], the mechanisms that lead to the genesis of cardiac ischaemic pain are still not fully elucidated. However, it now appears that substances released during myocardial ischaemia, that are able to stimulate afferent nerves, trigger the pain signal [75].

An important chemical stimulus is adenosine release by cardiomyocytes during ischaemia [76]. Adenosine plays a major role in the metabolic regulation of myocardial blood flow, because of its powerful vasodilator effect on arterioles. Interestingly, adenosine is also a powerful algogenic substance. Indeed, its intracoronary injection causes angina-like chest pain in the absence of signs of ischaemia. The algogenic effect of adenosine is mediated by A_1 receptors located on the membranes of afferent cardiac nerve fibres, whereas its vasodilator effect is mediated by A_2 receptors on vascular smooth muscle cells. Cardiac ischaemic pain, however, can still be induced after administration of adenosine inhibitors, suggesting that mechanisms other than adenosine are involved in its origin. In particular, bradykinin and substance P have been found to induce or modulate angina pain in man.

Cardiac pain signals are transmitted throughout sympathetic and, in part, vagal nerves to neurones in the dorsal horns of the spinal cord, from here to the thalamus, and from the thalamus to the cortex, where they are processed and decoded as pain [77] (Fig. 14.12).

The central transmission of pain signals generated from the heart is modulated in the central nervous system by both ascending and descending signals. An important

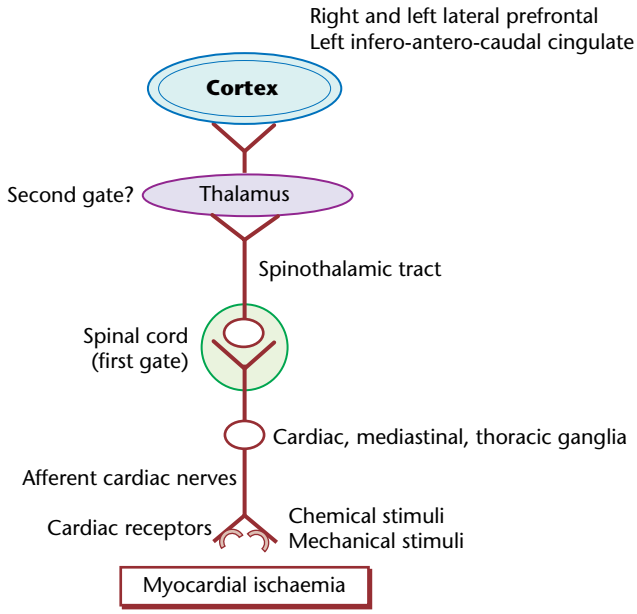


Figure 14.12 Transmission of cardiac ischaemic pain signals to cortical centres. Cardiac ischaemic pain signals generated by chemical stimuli (e.g. adenosine) or mechanical stimuli (e.g. stretching of intramyocardial or periarterial nerve fibres) travel throughout sympathetic and, in part, vagal nerves to neurones in the dorsal horns of the spinal cord. From there pain signals are transmitted to the thalamus and to the cortex where they are processed and decoded as pain. Profound modulation of pain signals occurs both at the spinal and, probably, at the supraspinal level.

modulation is believed to occur in the dorsal horns of the spinal cord, where, according to the gate theory, a group of intermediate neurones may inhibit the transmission of the pain signal [78].

The somatic location of cardiac ischaemic pain does not allow us to predict the site of myocardial ischaemia. Indeed, about 70% of patients who suffer from both anterior and inferior myocardial infarction at different times of their life experience pain in the same body region during the infarctions [79]. Accordingly, separate infusions of adenosine into the right or left coronary artery result in a similar distribution of pain in about 75% of the patients [80]. On the other hand, different locations of angina in the same patient at different times suggest ischaemia originating from different myocardial regions [81].

The ischaemic cascade

The clinical consequences of transmural myocardial ischaemia occur in a rather predictable sequence known as the 'ischaemic cascade' and are characterized by the following events:

- reduction in pH and increase in the concentration of K^+ ions in venous blood draining the ischaemic region;
- regional wall motion abnormalities and signs of global diastolic and systolic left ventricular dysfunction;
- development of ST-segment changes;
- cardiac ischaemic pain.

This sequence of events helps to explain why imaging techniques based on the assessment of regional wall motion are more sensitive than ECG in the detection of myocardial ischaemia.

It has been proposed that severe microvascular dysfunction might be followed by a different 'ischaemic cascade' characterized by the early onset of ECG changes and chest pain in the absence of regional wall motion abnormalities [1].

Coronary collateral circulation

Collaterals develop from pre-existing anastomotic channels (thin-walled structures ranging in diameter from 20 to 200 μm), as a result both of the establishment of a pressure gradient between their origin and termination and of chemical mediators released during tissue hypoxia, a process called arteriogenesis. A pressure gradient of about 10 mmHg has been shown to be sufficient to elicit the development of collateral flow. Intercoronary arterial anastomoses are present in variable numbers in different species: they are so numerous in guinea-pigs that they can prevent infarction following sudden coronary occlusion, whereas, at the other extreme, they are virtually absent in rabbits. In dogs the density of anastomotic channels can deliver 5–10% of preocclusional resting flow. Humans have a slightly worse collateral circulation than dogs, but with a marked interindividual variability [82].

Arteriogenesis occurs in three stages [83]:

- the first stage (first 24 hours) is characterized by passive widening of pre-existing channels and endothelial activation, followed by secretion of proteolytic enzymes which dissolve extracellular matrix;
- the second stage (from 1 day to about 3 weeks) is characterized by migration of monocytes into the vascular wall, followed by secretion of cytokines and growth factors, which trigger proliferation of endothelial and smooth muscle cells and of fibroblasts;

- the third phase (3 weeks to ~3 months) is characterized by thickening of the vascular wall as a result of deposition of extracellular matrix.

In its final stage the mature collateral vessels may reach ~1 mm in luminal diameter. Tissue hypoxia can favour collateral development by acting on the promoter gene of vascular endothelial growth factor (VEGF), but it is not an essential requirement for collateral development. There is no consistent evidence that exercise can favour collateral development. Among risk factors diabetes might impair the ability to develop collateral vessels [84].

Well-developed collateral circulation can be sufficient to prevent myocardial ischaemia in man in the presence of a sudden collateral occlusion, but it rarely provides blood flow adequate to meet myocardial oxygen consumption during maximal physical exercise.

Collateral vessels may also form through angiogenesis, which involves sprouting of new vessels from pre-existing vessels and usually results in the formation of capillary-like structures. This was clearly demonstrated following mammary artery implants in the myocardium of dogs with gradual total occlusion of a major coronary artery. The collateral blood supply provided by such newly formed vessels is rather small compared with that provided by arteriogenesis [85].

Epidemiology of chronic ischaemic heart disease

Population-based studies have shown that the prevalence of angina increases with age, being twice as common in men as it is in women. Indeed, in men angina prevalence increases from 2–5% in the 45- to 54-year-old age group to 11–20% in the age group 65–74 years, whereas in women angina prevalence increases from 0.5–1% to 10–14% for the same age groups. After 75 years angina prevalence is similar in the two sexes. According to these figures, it can be estimated that the prevalence of angina patients in Europe may be as high as 30 000–40 000 per 1 million total population [86].

In the Framingham study [87], among 5127 initially asymptomatic subjects (aged from 30 to 62 years) followed up for 14 years, the mode of first presentation of IHD was predominantly an acute coronary syndrome in men (68%) and predominantly a stable angina in women (56%). The common first presentation of IHD with an acute coronary syndrome is consistent with the observation that acute coronary occlusion usually occurs suddenly at the site of non-flow-limiting stenoses. These observations also suggest a different prevalence of pathogenetic mechanisms of angina in the two sexes.

In the Framingham study [87], among patients who presented with an acute myocardial infarction, 45% of men, but only 15% of women, developed a syndrome of stable angina at follow-up. This figure is probably even lower in the current era of primary coronary interventions.

Population-based studies, however, do not allow us to establish the mechanism of chronic stable angina. Indeed, although in the majority of patients chronic stable angina is associated with obstructive coronary artery disease, it may also be caused by coronary artery spasm or may occur in patients with angiographically normal coronary arteries (cardiac syndrome X).

There have been no systematic studies assessing the epidemiology of variant angina. In two surveys, coronary vasospasm was the presenting mechanism of angina in about 1.5% of patients admitted to hospital because of angina [88].

The prevalence of cardiac syndrome X can be inferred from angiographic studies. Among patients with chest pain that is suggestive of angina pectoris, who undergo coronary angiography, 10–30% are found to have normal or near normal coronary arteries at angiography and no evidence of coronary vasospasm. A sizeable proportion of these patients might present with cardiac syndrome X [89].

Another clinical presentation of chronic IHD is ischaemic cardiomyopathy. The latter can be a complication of myocardial infarction, often after multiple infarctions and in elderly patients, or can be, less frequently, the initial manifestation of IHD. In the GISSI-2 study, signs of cardiac failure at 6 months after a first myocardial infarction were present in 9% of 9860 patients who received thrombolysis [90]. However, the growing survival rate after a first myocardial infarction exposes patients to the natural progressive worsening of the underlying IHD, thus increasing the risk of evolution towards progressive heart failure. Notably, ischaemic cardiomyopathy, either associated or not with stable angina, is the leading cause of heart failure in developed countries, accounting for two-thirds to three-quarters of cases.

Assessment of angina pectoris

Characteristics of angina pectoris

Independent of its causes, the most typical clinical manifestation of myocardial ischaemia is represented by

angina pectoris (*angina*, from the Latin for anguish) [91]. The features of chest pain that should be investigated to diagnose and characterize angina pectoris include type, location, irradiation and duration of pain, modalities of pain onset and offset, and response to nitrate administration. Importantly, a careful assessment of characteristics of chest pain may help to establish the mechanisms responsible for myocardial ischaemia.

In its typical presentation, angina is referred as a constrictive, aching sensation, or pressure or tightness discomfort in the retrosternal area or in the anterior portion of the chest. Typically, the area of pain is indicated by the patient with a clenched fist or an open hand in the middle of the chest. Pain frequently radiates towards the neck, the left shoulder and the medial side of the left arm, and lasts no more than 10–15 minutes. Angina responds promptly to short-acting nitrates.

Several variants, however, exist to this typical presentation. Thus, pain can be represented by a heavy or burning sensation and can radiate towards the epigastrium, the right shoulder or arm, the interscapular area, the jaw and teeth, and, exceptionally, it can also be referred to the upper right abdominal quadrant or to the head [92]. Angina in atypical locations, although rarely, may represent the main or only symptom of IHD.

In most cases it is possible to identify conditions which trigger angina. These are more often represented by physical efforts, but they may consist of stressful or emotional states, exposure to cold, abundant meals or hypertensive episodes. Angina usually subsides by removing the triggering cause, but short-acting nitrates may be necessary to shorten angina duration. Finally, angina can also occur at rest without any apparent triggering cause.

Table 14.2 Differential diagnosis of chest pain

Cardiovascular causes
Ischaemic
Flow-limiting coronary stenosis
Coronary vasospasm
Coronary thrombosis
Microvascular dysfunction*
Non-ischaemic
Coronary arterial wall distension
Dyssynergic myocardial contraction
Aortic dissection
Pericarditis
Pulmonary embolism or hypertension
Non-cardiovascular causes
Gastrointestinal
Oesophageal spasm
Gastro-oesophageal reflux
Gastritis/duodenitis
Peptic ulcer
Cholecystitis
Respiratory
Pleuritis
Mediastinitis
Pneumothorax
Neuromuscular/skeletal
Chest wall pain syndrome
Neuritis/radiculitis
Herpes zoster
Tietze's syndrome
Psychogenic
Anxiety
Depression

*See Table 14.1.

Differential diagnosis of chest pain

Angina pectoris can be simulated by several non-ischaemic cardiac diseases or by extracardiac diseases. Indeed, somatic or visceral pain signals may converge on the same neurones in the spinal dorsal horns which also receive cardiac ischaemic pain signals, thus resulting in a pain sensation similar or indistinguishable, as to type and location, from angina (Table 14.2).

Cardiovascular causes of chest pain

In the absence of obstructive coronary stenoses, spasm or thrombosis, chest pain, usually related to effort or to other conditions of increased myocardial oxygen demand, may occur in patients with severe left ventricular hypertrophy, caused by aortic stenosis, hypertrophic cardiomyopathy, arterial hypertension, or, less frequently, by aortic regurgitation or dilated cardiomyopathy. In these conditions, the increased left ventricular mass is often not matched by a parallel growth of coronary microcirculation; thus, increased oxygen demand cannot be satisfied. Diastolic dysfunction, with increased diastolic pressure, is also present and facilitates subendocardial ischaemia. Finally, coronary microvascular dysfunction can contribute to myocardial ischaemia [53]. Distinction from angina caused by obstructive coronary artery disease may be difficult even after full non-invasive diagnostic investigation and may eventually require coronary angiography.

Notably, angina in the absence of signs of myocardial ischaemia is sometimes experienced by patients who have recently undergone coronary stent implantation [93]. Stretching of the coronary arterial wall at the site of stenting is the likely mechanism in these cases. In very rare cases, angina is triggered by the intermittent appearance of heart rate-dependent left bundle branch block, in the absence of any evidence of myocardial ischaemia [94]. Stretching of afferent nerve fibres caused by dyssynergic

myocardial contraction at the appearance of left bundle branch block is the likely mechanism of pain in these cases.

Aortic dissection must be carefully excluded in patients presenting with chest pain. In this condition chest pain is usually of sudden onset and severe, but in some cases it is subacute and atypical. It often radiates to the back, lasts for hours, is not influenced by breathing or turning and may tend to migrate. A history of hypertension or a marfanoid habitus in young patients should raise suspicions. Differences in peripheral pulses and an enlarged aorta on chest X-ray should also suggest the diagnosis of aortic dissection, which is then confirmed by trans-oesophageal echocardiography, computerized tomography (CT) or cardiac magnetic resonance (CMR).

Chest pain caused by pericarditis is usually easily recognized because of typical changes in breathing and exacerbation by assuming the supine position; pericardial rubs can be present and the ECG usually shows typical diffuse ST-segment elevation.

Chest pain caused by pulmonary embolism is frequently associated with dyspnoea and tachypnoea; the presence of typical predisposing conditions (e.g. recent surgery, prolonged bed rest) should raise suspicions. The ECG, laboratory investigation and imaging techniques usually allow the correct diagnosis.

Finally, pulmonary hypertension, either primary or secondary, may also be associated with chest pain, caused by increased stress on the pulmonary arterial wall or by right ventricular ischaemia. A careful physical examination and appropriate diagnostic tests (e.g. ECG, chest X-ray, echocardiography) usually allow the correct diagnosis of pulmonary hypertension.

Non-cardiovascular causes of chest pain

These include four major groups of clinical syndromes.

Gastro-intestinal disorders are among the most frequent disorders mimicking angina. Oesophageal spasm and reflux, in particular, may cause typical retrosternal or epigastric pain, which can radiate towards the neck, jaw and arms, and can occasionally be relieved by short-acting nitrates. Chest pain caused by gastro-oesophageal reflux usually appears immediately after a meal or at night. Yet, angina can occur under the same circumstances. Furthermore, both reflux and angina can be triggered by exercise. Of note, reflux and oesophageal spasm may coexist with angina, as the latter may be facilitated by autonomic reflexes and pain related to gastro-enteric disorders. The response to anti-acid treatment and endoscopy may help in the differential diagnosis.

Peptic ulcer and gastritis (and/or duodenitis) may sometimes mimic angina. However, the link to meals, the absence of a relation to effort and the response to anti-acid treatment suggest the diagnosis, which can be confirmed by endoscopy.

Acute or chronic cholecystitis can also sometimes simulate atypical angina, but the pain is not relieved by nitrates. Abdominal ultrasound examination is usually sufficient to document the presence of cholecystitis.

Respiratory diseases (pneumothorax, pleuritis, mediastinitis) may cause chest pain, but symptom features and an accurate physical examination usually establish the correct diagnosis, which can subsequently be confirmed by imaging techniques.

Neuromuscular disorders, including chest wall pain syndrome and neuritis, are among the most common causes of chest pain. Neuromuscular chest pain is usually modified by breathing and/or chest movement, and can be induced by pressure on specific points of the chest. Pain is usually long-lasting (hours, days), does not have any relation with effort and is not relieved by nitrates, whereas it is relieved by anti-inflammatory drugs. Tietze's syndrome (swelling and pain of left chondro-sternal joints) is a rare condition that can be easily recognized.

Psychogenic causes should, finally, be taken into account after organic causes of chest pain have all been excluded. Indeed, anxiety and depression are possible causes of chest pain simulating angina pectoris.

Angina equivalents

In some patients myocardial ischaemia is expressed by transient symptoms that are different from angina pectoris, including dyspnoea, arrhythmias and pre-syncope or syncope.

Dyspnoea may occur when transient ischaemia involves a large myocardial mass, thus resulting in severe left ventricular dysfunction and pulmonary congestion/oedema. In this case cardiac auscultation may reveal a third heart sound and basal pulmonary rales might be heard on thorax auscultation. Dyspnoea may also occur when myocardial ischaemia causes left ventricular papillary muscle dysfunction, resulting in severe mitral valve regurgitation. In this case, a new, or worsening of a previous, apical systolic murmur is appreciated on cardiac auscultation during ischaemia.

Arrhythmias induced by myocardial ischaemia can be appreciated by the patient as palpitation (e.g. correlated to effort). Severe tachyarrhythmias (e.g. ventricular tachycardia), but also bradyarrhythymias (e.g. atrioventricular or sino-atrial block) may result in

presyncope or syncope, as a result of a fall in left ventricular output.

Silent ischaemia

A large number of studies using Holter monitoring have consistently shown that most spontaneous episodes of myocardial ischaemia (i.e. 70–80%), regardless of their causes, are silent, as they are not associated with angina, or angina equivalents [95]. Furthermore, silent ischaemia can also be frequently documented during diagnostic stress tests. The proportion of silent ischaemic episodes is similar in the different coronary ischaemic syndromes, being unrelated to the causes of ischaemia. Of note, from a clinical point of view, prognosis of painful and silent myocardial ischaemia is similar, being dictated in both cases by the underlying causes of myocardial ischaemia.

The causes of silent ischaemia are not completely clear, but several mechanisms are likely to contribute to this phenomenon. A relation between extent and severity of myocardial ischaemia and the occurrence of angina has been suggested by some reports. Most studies, however, failed to find differences between patients with painful or painless ischaemia with regard to severity of ST-segment changes, wall motion abnormalities or haemodynamic changes during ischaemic episodes [96]. Thus, on the whole, the association between severity and extent of myocardial ischaemia and occurrence of pain is poor, even in the same patient.

The causes of painless ischaemia can be different in patients who present both painless and painful myocardial ischaemia during the same day, or even in a short period of time, despite similar duration and severity of ischaemia, and in those who predominantly or exclusively present silent ischaemia.

In the former group silent ischaemic episodes are probably the result of a dynamic peripheral and/or central modulation of cardiac pain signals [77,97]. Instead, in patients with predominant, or even only, silent myocardial ischaemia, the failure to develop pain could be because of a generalized defective perception of painful stimuli. Indeed, these patients, compared to those with predominantly painful ischaemia, have a higher threshold and tolerance for pain stimuli, including forearm ischaemia, cold pressor, skin electrical stimulation, intravenous adenosine infusion, and dental pulp stimulation [91]. Increased central release of endogenous opioids, which inhibit nociceptive dorsal horn-convergent neurones, has been proposed as a possible mechanism, but studies comparing plasma levels of endogenous endorphins in patients with predominantly painful or painless ischaemia have given controversial results [91]. Finally, psychological factors may play an important role, as patients exhibiting predominantly silent ischaemia have been found to present lower scores for nervousness, 'excitability' and tendency to complain.

In contrast with current beliefs, there is no definite evidence that silent ischaemia is more prevalent among diabetic patients [98].

Clinical syndromes of chronic ischaemic heart disease

Stable angina

Symptoms and physical examination

Stable angina is characterized by a pattern of angina which has remained stable for at least 2 months. It can be the first manifestation of IHD or can appear in patients who had suffered a previous acute coronary event. Typically, angina is induced by efforts or conditions that increase myocardial oxygen demand (e.g. emotional and psychological stresses, hypertensive episodes). Angina is promptly relieved by interrupting the precipitating event, although short-acting nitrates can accelerate pain relief.

The pathologic substrate of stable angina is the presence of coronary flow-limiting stenoses, which do not allow an adequate increase in coronary blood flow during increased myocardial oxygen demand. Typically, myocardial ischaemia is limited to the subendocardial layers, which is most frequently manifested by ST-segment depression in one or more ECG leads (more often V4–V6).

In stable angina, myocardial ischaemia can occur reproducibly for a given level of exercise or in specific conditions, suggesting fixed stenoses. In most patients, however, the ischaemic threshold is variable, and angina can occasionally occur at rest (mixed angina). This variability can be the result of vasomotion at the site of pliable stenoses, modulating their severity (dynamic stenoses) and/or of vasomotor changes in the coronary microcirculation or collateral vessels [99,100].

The Canadian Cardiovascular Society classification of stable angina is the most widely used to assess the severity of angina pectoris (Table 14.3) [101].

In patients with stable angina general physical examination is often unremarkable, but findings suggesting lipid disorders (i.e. cutaneous xanthomata, xanthelasma, corneal arcus) can be observed on visual inspection. Peripheral pulse examination may reveal bruits and murmurs suggesting arterial stenoses, in particular in the carotid and femoral arteries.

Table 14.3 Canadian Cardiovascular Society classification of angina pectoris*

I	Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina results from strenuous or rapid or prolonged exercise at work or recreation
II	Slight limitation of ordinary activity: walking or climbing stairs rapidly, walking uphill, walking or climbing stairs after meals, in cold, in wind, or when under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and under normal conditions.
III	Marked limitations of ordinary physical activity: walking one or two blocks on the level and climbing more than one flight under normal conditions.
IV	Inability to carry on any physical activity without discomfort. Anginal syndrome may be present at rest.

*Reproduced from [100].

In the absence of left ventricular dysfunction, cardiac examination may be uninformative. However, a rapid pulse may be a clue to thyrotoxicosis or anaemia which can exacerbate angina pectoris. A third and/or fourth heart sound can be heard during angina because of transient cardiac failure. A transient paradoxical splitting of the second heart sound appears in cases sof ischaemia-induced left bundle branch block, whereas a transient systolic murmur may indicate mitral regurgitation following papillary muscle dysfunction, in particular in patients with a dilated left ventricle. Finally, a systolic aortic murmur may suggest that aortic stenosis is a likely cause of angina.

Non-invasive diagnosis

Resting ECG In patients with suspected angina pectoris a resting 12-lead ECG should be recorded, although only occasionally it is of diagnostic value. Indeed, resting ECG is normal in about 50% of cases and, when abnormal, will show abnormalities (e.g. minor ST-segment/T wave changes, atrioventricular or intraventricular conduction disorders, supraventricular or ventricular arrhythmias) that are not sufficiently specific for the diagnosis of IHD because they can be frequently found in several other conditions. However, the detection of pathologic Q/QS waves, even in the absence of any history of previous myocardial infarction, or of typical negative symmetric T waves and/or ST-segment depression, strongly suggests an ischaemic origin of symptoms.

Chest X-ray Although routinely performed in mostpatients, chest X-ray has poor diagnostic value in suspected stable angina. The detection of coronary calcifications, however, is associated with a high probability of obstructive IHD [102].

Exercise stress test (EST) Treadmill or bicycle EST during 12-lead ECG monitoring is the test of choice to diagnose myocardial ischaemia in the majority of patients with suspected stable angina, because of its simplicity and the excellent cost : benefit ratio (Table 14.4) [103].

The main diagnostic ECG abnormality during EST consists of a rectilinear or downsloping ST-segment depression ≥ 0.1 mV, persisting for at least 0.06–0.08 seconds after the J-point, in one or more ECG leads. It is worth noting that in about 15% of patients diagnostic ST-segment changes appear during the recovery phase, rather than during the active phase, of exercise [104].

Table 14.4 Non-invasive tests for diagnosis and prognostic stratification of stable angina

Test	Recommended use	Comments
Exercise ECG	First choice in most patients	Difficult to interpret in presence of abnormal basal ECG
Exercise myocardial perfusion scintigraphy or echocardiography	Patients with non-interpretable ECG Non-conclusive exercise ECG results For accurate location of ischaemia	Imaging techniques more sensitive and specific than ECG Exercise more physiological than pharmacological stressors Echocardiography more informative than nuclear techniques and radiation free, but interpretation more operator-dependent and poor image quality in some patients
Myocardial perfusion scintigraphy or echocardiography during infusion of pharmacological stressors	Patients unable to exercise Preferable if assessment of viable myocardium is also needed	Echocardiography more informative than nuclear techniques and radiation free, but interpretation more operator-dependent and poor image quality in some patients

To obtain maximal diagnostic information from EST, the latter should be symptom/sign limited and performed without the influence of anti-ischaemic drugs. A meta-analysis of the most important studies which investigated the diagnostic value of EST for obstructive IHD reported average sensitivity and specificity of 68% and 75%, respectively [103]. However, a careful analysis of the data, taking into account selection biases of the patient cohorts, suggested that the sensitivity of EST may be lower (about 45%), but that specificity is even higher (about 90%) [105].

The positive predictive value for coronary artery disease of exercise-induced ST-segment depression increases up to 90% if it is accompanied by typical angina pain, if it occurs in the early stages of exercise or persists for more than 5 minutes in the recovery phase, and if it is > 0.2 mV [106,107]. Early appearance, extensive lead involvement and slow normalization after exercise are clues to the presence of multivessel IHD.

When assessing the accuracy of EST, as well as of other non-invasive techniques, for the diagnosis of obstructive IHD, intrinsic bias should be considered, which may account for a proportion of erroneous results. This bias consists of considering the presence or absence of obstructive coronary stenoses at angiography as the gold standard for diagnostic accuracy. Indeed, on the one hand non-invasive stress tests detect myocardial ischaemia, which may be caused by coronary spasm or microvascular dysfunction. On the other hand, obstructive atherosclerosis does not always cause myocardial ischaemia during stress (e.g. for the presence of well-developed collateral circulation).

Several other EST-related variables have been suggested to improve the diagnostic accuracy of EST, including QRS and U wave changes, ST/HR slope or ST/HR index and the ST/HR recovery loop, but their efficacy in improving the predictive value of EST remains doubtful [103].

In clinical practice the interpretation of ST-segment changes during EST should be individualized, particularly considering the pre-test probability for the patient to have obstructive coronary artery disease, which mainly depends on the characteristics of symptoms, but is also influenced by risk factors, in particular age (Table 14.5). Indeed, owing to the suboptimal sensitivity and specificity of EST, pre-test probability influences the predictive value for IHD, according to Bayes theorem (Fig. 14.13) [108]. (Bayes theorem allows the calculation of the probability of a subject to be affected by a disease in the presence of a positive or negative diagnostic test. According to Bayes theorem, the probability of the disease depends not only on the sensitivity and specificity of the test but also on the pre-test probability of the disease in the population of individuals to which the subject belongs [see Fig. 14.13]). According to this theorem, diagnostic tests are particularly useful and maximally informative in patients with an intermediate probability of disease. Indeed, in patients with estimated low pre-test probability of IHD (e.g. a 30-year-old woman with atypical angina), ST-segment depression has low predictive value for IHD, because of a high proportion of false-positive results. As a consequence, the test is not usually recommended for diagnostic purposes in asymptomatic individuals with a good risk factor profile. At the other extreme, in patients with estimated high pre-test probability of IHD (e.g. a 60-year-old diabetic man with typical angina) EST is only confirmatory, whereas a negative test does not allow obstructive coronary artery disease to be excluded. Nevertheless, EST is useful in these patients, providing additional information on the severity of ischaemia, the degree of functional limitation and prognosis [109]. The exact definition of the upper and lower boundaries of intermediate probability is a matter of physician judgement in individual patients, but values of 10% and 90%, respectively, have been suggested [110]. The post-test probability of coronary artery disease, according to characteristics of symptoms, age and magnitude of ST-segment depression induced during exercise stress test, is summarized in Table 14.5.

The exercise ECG stress test has limited value in patients with basal ECG abnormalities, including left bundle branch block, paced rhythm or Wolff–Parkinson–White syndrome, which preclude a correct interpretation of ST-segment changes. False-positive results are also more frequent in patients with resting ST-segment/T wave abnormalities, because of left ventricular hypertrophy, electrolyte imbalance, or drug effects (e.g. digitalis).

An important issue with EST is the diagnosis of obstructive IHD in women, in whom ST-segment depression has been found to have lower specificity (i.e. it is more often a false-positive result) than in men. However, when pre-test probability is accurately determined and patients with normal ECG at rest are selected, EST has the same reliability in women as in men [111].

Scintigraphic stress tests Exercise myocardial perfusion scintigraphy is a robust, non-invasive method of assessing regional myocardial perfusion and allows the diagnosis of myocardial ischaemia by showing a reversible reduction of isotope myocardial uptake at peak exercise, as compared to rest, in myocardial regions supplied by stenotic coronary artery branches (Fig. 14.14).

The three commercially available flow perfusion tracers, ^{201}thallium (^{201}Tl), and ^{99m}technetium-labelled sestamibi or tetrofosmin, have similar accuracies for the detection of IHD.

Table 14.5 Pre-test and post-test exercise stress test likelihood of ischaemic heart disease, according to chest pain features, sex and age

Age (years)		Typical angina		Atypical angina		Non-anginal chest pain	
		Male	Female	Male	Female	Male	Female
Pre-test							
30–39		69.7	25.8	21.8	4.2	5.2	0.8
40–49		87.3	55.2	46.1	13.3	14.1	2.8
50–59		92.0	79.4	58.9	32.4	21.5	8.4
60–69		94.3	90.1	67.1	54.4	28.1	18.6
Post-test							
30–39	0.00–0.04	25	7	6	1	1	< 1
	0.05–0.09	68	24	2	4	5	1
	0.10–0.14	83	42	38	9	10	2
	0.15–0.19	91	59	55	15	19	3
	0.20–0.24	96	79	76	33	39	8
	> 0.25	99	93	92	63	68	24
40–49	0.00–0.04	61	22	16	3	4	1
	0.05–0.09	86	53	44	12	13	3
	0.10–0.14	94	72	64	25	26	6
	0.15–0.19	97	84	78	39	41	11
	0.20–0.24	99	93	91	63	65	24
	> 0.25	> 99	98	97	86	87	53
50–59	0.00–0.04	73	47	25	10	6	2
	0.05–0.09	91	78	57	31	20	8
	0.10–0.14	96	89	75	50	37	16
	0.15–0.19	98	94	86	67	53	28
	0.20–0.24	99	98	94	84	75	50
	> 0.25	> 99	99	98	95	91	78
60–69	0.00–0.04	79	69	32	21	8	5
	0.05–0.09	94	90	65	52	26	17
	0.10–0.14	97	95	81	72	45	33
	0.15–0.19	99	98	89	83	62	49
	0.20–0.24	99	99	96	93	81	72
	> 0.25	> 99	99	99	98	94	90

Values represent the percentage of patients found to have significant obstructive coronary atherosclerosis at angiography. Adapted from Isner and Asahara [85].

Published figures of sensitivity and specificity for the diagnosis of coronary disease vary widely and depend upon the characteristics of the population studied (e.g. gender, presenting symptoms, medication, presence of previous infarction, etc.), the imaging technique used (planar or SPECT, qualitative or semi-quantitative analysis) and the experience of the centre. Overall, exercise myocardial scintigraphy is more sensitive than EST for IHD detection, while the specificity of the two tests have been found to be similar. Using SPECT imaging, sensitivity and specificity can be as high as 91% and 89%, respectively [30]. However, the average sensitivity and specificity of exercise ^{201}Tl-SPECT, uncorrected for referral biases, are approximately 89% and 76%, respectively, for qualitative analysis, and 90% and 70%, respectively, for quantitative analysis [105].

Athough scintigraphic exercise stress tests might be considered as an alternative to standard EST to detect ischaemia, they are more expensive and time-consuming, and less cost-effective. Thus, for diagnostic purposes they are only indicated in patients with non-conclusive results of ECG-EST or when ECG is not interpretable (Table 14.4).

Furthermore, scintigraphic studies are more accurate than EST in predicting the presence of multivessel IHD and in detecting the location and extent of myocardial ischaemia [112,113]. Thus, they can be indicated when this information is important.

Pharmacological stressors can be used as an alternative to exercise in patients who are unable to exercise adequately (e.g. elderly patients or patients with peripheral vascular disease or those limited by dyspnoea) [114].

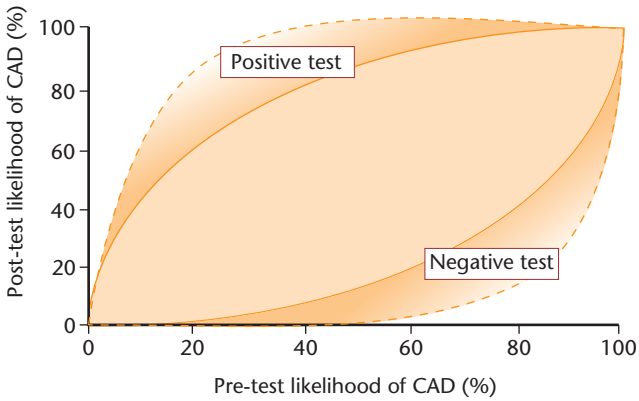


Figure 14.13 The relationship between pre-test probability of obstructive coronary artery disease and the post-test probability of the disease according to the result of a diagnostic non-invasive test with a sensitivity and specificity of 75% (solid lines) and a test with a sensitivity and specificity of 90% (dashed lines). In the former condition, it can be seen that, in the case of a positive test (upper solid line), the probability of disease becomes sufficiently high (50%) only when pre-test probability is at least 20%, and progressively increases with the increase of the pre-test probability. On the other hand, if pre-test probability is elevated, the probability of disease remains high, even in the case of a negative test (bottom solid line). Diagnostic accuracy improves significantly with a test with a very high sensitivity and specificity; indeed, in the case of a pre-test probability of 20%, such a test is associated with a positive predictive value of disease of 85%. However, it can be observed that, in this case also, when pre-test probability is very low (e.g. 5%) a positive test is associated with a presence of disease of only 45% (upper dashed line). At the other extreme, if the pre-test probability is high, post-test probability remains high even in the presence of a negative test (bottom dashed line). Adapted from Epstein [108].

They include the sympathetic agonist dobutamine, which causes an increase of myocardial oxygen consumption simulating physical exercise, and the arteriolar vasodilators dipyridamole and adenosine, which cause subendocardial underperfusion in myocardial regions supplied by stenotic coronary artery branches, because of coronary blood-steal phenomenon.

The diagnostic accuracy with pharmacological stressors has been reported to be similar to that with exercise [115]. The latter, however, is preferable because of the more obvious relation of exercise levels with real-life activities and to the additional diagnostic and prognostic information provided by the results of exercise stress per se.

Radionuclide angiography has been used in previous years to diagnose obstructive IHD, but it has now fallen out of favour because it adds no relevant diagnostic information to that provided by other non-invasive tests.

Echocardiographic stress tests Exercise echocardiography is an alternative to exercise myocardial perfusion scintigraphy as a second-tier test to standard ECG-EST, presenting similar indications and advantages, including a more reliable diagnosis of multivessel disease and location of myocardial ischaemia [116]. Its indications as a real first-step alternative to ECG-EST are similarly doubtful (Table 14.4).

Diagnosis of IHD on echocardiography is based on the detection of stress test-induced reversible regional left ventricular wall motion abnormalities. Compared to scintigraphy, inconveniences include poor image quality in about 15% of patients, higher operator-dependent interpretation, lower sensitivity (in particular for single-

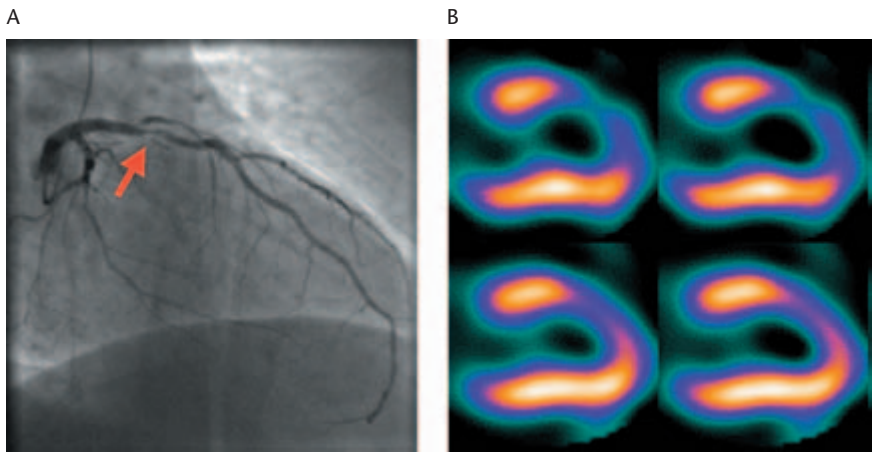


Figure 14.14 (A) severe stenosis is present in the left anterior descending coronary artery (arrow) at coronary angiography. (B) Single positron emission computed tomography (SPECT) identifies the ischaemic area as an exercise stress-induced perfusion defect (upper panels) obtained by either ^{99}technetium-labelled MIBI (left) or ^{201}thallium (right). Images at rest (bottom panels) show partial redistribution of radioisotopes. Taken together, these findings indicate the presence of a previous antero-apical myocardial infarction with inducible myocardial ischaemia in the peri-infarct region. (Courtesy of Dr Paolo Marzullo, Laboratory of Nuclear Cardiology, CNR Institute of Clinical Physiology, Pisa, Italy.)

vessel disease of the left circumflex coronary artery), the need for special training for a correct performance and interpretation, and more difficult assessment of ischaemia in the presence of basal left ventricular wall motion abnormalities. The inability to image at peak exercise is only a minor disadvantage because contractile abnormalities do not usually normalize immediately after peak exercise.

Exercise echocardiography, however, also has some advantages over exercise perfusion scintigraphy, including a slightly higher specificity, the possibility of a more extensive evaluation of cardiac anatomy and function, greater availability, lower cost, and a greater safety (being free of radiation exposure).

Pharmacological stressors are used more frequently than exercise in echocardiography. Indications and stressors for echocardiography are the same as those for pharmacological scintigraphic stress tests. In patients with negative tests, however, atropine is often added, either to dobutamine (especially in patients on beta-blockers) or to dipyridamole, to increase heart rate and the sensitivity of the test.

In a direct comparison of the different stress tests, sensitivity of exercise and dobutamine echocardiography for the diagnosis of obstructive coronary artery disease was similar, whereas sensitivity of dipyridamole echocardiography was lower and specificity did not differ among tests [117].

Ambulatory ECG Holter monitoring Holter monitoring may reveal myocardial ischaemia in up to 10–15% of patients with stable angina who do not develop diagnostic ST-segment depression during exercise testing [118]. This can occur in patients in whom coronary vasoconstriction plays an important role in the pathogenesis of myocardial ischaemia. Accordingly, ECG monitoring may be indicated for diagnostic purposes in a limited number of patients with symptoms suggestive of dynamic stenosis or coronary vasospasm.

Electron beam CT This allows the accurate detection and quantification of coronary artery calcifications, which correlate, through the elaboration of a calcium score, with the severity of coronary artery disease. However, its role in the diagnostic work-up of IHD remains doubtful [119].

Multislice CT angiography CT angiography with peripheral injection of contrast medium is an attractive technique for the non-invasive detection of coronary stenoses. However, its diagnostic accuracy is still uncertain and its routine use cannot be recommended yet [120].

Table 14.6 Indications for coronary angiography

To establish diagnosis
- Typical angina in patients with negative results of non-invasive stress tests
- Unexplained life-threatening ventricular arrhythmias or resuscitated sudden death
- Valvular or congenital heart disease in candidates for cardiac surgery in patients at moderate to high risk of ischaemic heart disease
- Need to establish the diagnosis for clinical or occupational reasons in patients at moderate to high risk of ischaemic heart disease

In candidates for myocardial revascularization
- Severe stable angina (Class 3 or 4 of CCS classification) despite optimal medical therapy
- Mild to moderate stable angina (CCS class 1 to 2) associated with high-risk criteria for adverse outcome on non-invasive testing*
- Mild to moderate angina in patients who are being considered for major non-cardiac surgery, especially vascular surgery (repair of aortic aneurysm, femoral bypass, carotid endarterectomy)
- Recurrence of angina pectoris in patients previously submitted to myocardial revascularization

*See Table 14.7. CCS classification, Canadian Cardiovascular Society Classification.

Invasive diagnosis

By definition, obstructive IHD is ultimately diagnosed by documenting flow-limiting coronary artery stenosis at angiography. Yet, because of the small, but definite, risk of complications and its cost, coronary angiography cannot be recommended as a routine diagnostic procedure to assess chest pain.

Coronary angiography is indicated in the diagnostic work-up in the following situations (Table 14.6):
- typical angina in patients with negative results of non-invasive stress tests;
- unexplained life-threatening ventricular arrhythmias or resuscitated sudden death;
- valvular or congenital heart disease in candidates for cardiac surgery with moderate to high risk of IHD;
- need to establish the diagnosis for clinical or occupational reasons (e.g. activities which would expose the patient himself and/or other people to significant risks in the case of an occurrence of acute ischaemic events) in patients with moderate to high risk of IHD.

Coronary angiography should not be performed in:
- anginal patients who refuse revascularization; and
- anginal patients whose symptoms are well controlled

by treatment and are not candidates for myocardial revascularization, according to prognostic stratification based on non-invasive investigations.

Prognosis and risk stratification

On average, the prognosis of stable angina is reasonably good. Annual mortality is < 2% and occurrence of myocardial infarction is also low [105]. It is possible, however, to identify subsets of patients who are at lower risk and subsets who are at higher risk of major coronary events.

Symptoms, resting ECG and chest X-ray The severity and frequency of chest pain, as expressed by Canadian Cardiovascular Society (CCS) classification, have prognostic implications. Indeed, a low anginal threshold is usually associated with severe coronary flow reserve reduction [121]. Symptoms of acute left ventricular dysfunction during angina, possibly indicating extensive myocardial ischaemia, also predict a worse outcome. However, the relationship between symptoms and IHD severity is less than optimal, thus limiting the value of symptoms for predicting clinical outcome.

The presence of abnormalities on standard 12-lead ECG (i.e. Q waves, persistent ST-T wave abnormalities) and left ventricular enlargement or pulmonary venous congestion on chest X-ray are also associated with a poorer outcome [122].

Non-invasive tests In patients with stable angina, the most important non-invasive prognostic markers include left ventricular function, physical capacity and severity and extent of coronary atherosclerosis. Left ventricular function can be easily assessed by two-dimensional echocardiography (or by radionuclide angiography). Good left ventricular function is usually associated with a good prognosis. Below 40%, further reductions of left ventricular ejection fraction are associated with an exponential increase in mortality [123]. Physical capacity and severity and extent of coronary atherosclerosis can both be assessed by EST. Thus, EST is the key test for risk stratification of patients with stable angina, being also of paramount importance for management decisions. A good effort tolerance in the absence of ischaemia is associated with a good outcome [124]. Indeed, in the Coronary Artery Surgery Study (CASS) registry, completing stage 2 of the Bruce protocol on treadmill EST, in the absence of ischaemia, was associated with a yearly mortality < 1%, even in the absence of treatment with antiplatelet agents and statins. Notably, very low mortality was also observed in patients who went beyond stage 4 of the Bruce protocol, despite three-vessel disease [125].

The occurrence of myocardial ischaemia during exercise, in particular if it appears at low workload and is associated with a low ejection fraction, portends an ominous prognosis [109]. High-risk features of EST are summarized in Table 14.7.

Composite scores, which take into account symptoms, ECG signs of ischaemia and other exercise parameters, have been proposed to improve prognostic stratification of stable angina patients. The Duke Treadmill Score [126], which has been prospectively validated in large cohorts of patients, is based on exercise capacity (as exercise duration), severity of myocardial ischaemia (as maximal ST-segment depression) and appearance of angina, and is calculated from the following formula: exercise duration (Bruce protocol, in min)—(5 × ST-segment depression during exercise test, in mm)—(4 × angina index), where the angina index assumes a value of '0' if there is no angina induced by exercise, '1' if non-limiting angina occurs during exercise, and '2' if angina is the reason for stopping the test. Among patients with suspected IHD, the two-thirds of patients with a Duke score > 5 had a 4-year survival rate of 99% (average annual mortality rate 0.25%), whereas, at the other extreme, the 4% of

Table 14.7 High-risk findings of major non-invasive stress tests

Exercise ECG	ST-segment depression ≥ 1 mm at Bruce stage 1 Slow ST depression recovery (> 5 minutes) after exercise Achievement of workload < 4 METs Abnormal blood pressure response Duke treadmill score ≤ –11
Stress myocardial scintigraphy	Multiple and/or large and/or severe reversible perfusion defects Stress-induced left ventricular dilatation Stress-induced lung thallium-201 uptake
Stress echocardiography	Multiple and/or large and/or severe regional wall motion abnormalities Stress-induced left ventricular dilatation

MET, Metabolic equivalents.

patients, with a score of –11 or less, had a 4-year survival rate of 79% (average annual mortality rate 5%).

In patients who can undergo exercise and exhibit an interpretable ECG, the additional prognostic value of imaging stress tests compared to that of EST is clinically limited [112]. The extent of perfusion defects and/or signs of left ventricular dysfunction on radionuclide scintigraphic tests and the extent of left ventricular wall motion abnormalities on echocardiography, induced by either exercise or pharmacological stressors, have been found to be associated with an adverse clinical outcome in stable IHD patients (Table 14.7) [127,128].

Frequent transient ischaemic episodes during daily life are also associated with a worse prognosis [129], although the information this finding adds to EST is not clear.

Invasive tests It is important to recognize that diagnostic techniques able to identify vulnerable plaques responsible for future acute coronary events are still lacking [130].

Several prognostic indices have been proposed to relate disease severity to the risk of subsequent cardiac events. The simplest and most widely used is the classification into one, two, three, and left main vessel disease. Recently, the extent of coronary atherosclerosis assessed at angiography has been found to be a better predictor of outcome than its severity (i.e. number of coronary artery branches presenting critical stenoses) [131]. Thus the higher mortality rates in patients with multivessel disease, as compared to those with one-vessel disease, are probably the consequence of a higher number of mildly stenotic, or even non-stenotic, plaques that are potential sites for acute coronary events.

The major current focus for risk stratification is on non-invasive techniques, the rationale being the identification of patients in whom revascularization might decrease mortality. Randomized trials of coronary bypass demonstrated that patients randomized to initial surgery had a lower mortality rate than those treated medically only if they were at moderate to high risk for major cardiac events. Accordingly, the use of coronary angiography to identify patients whose prognosis can be improved by revascularization procedures is inappropriate when the estimated annual mortality rate is not higher than 1%; in contrast, it could be appropriate for patients whose mortality risk is greater than 3% [132].

Coronary angiography is indicated for prognostic reasons in patients who are candidates for myocardial revascularization if they present with the following (Table 14.6):

- severe stable angina (CCS class 3 or 4) despite optimal medical treatment;
- mild to moderate stable angina (CCS class 1 to 2) associated with high-risk criteria for adverse outcome on non-invasive testing;
- mild to moderate angina in patients who are candidates for major non-cardiac surgery, especially vascular surgery (repair of aortic aneurysm, femoral bypass, carotid endarterectomy);
- recurrence of angina pectoris after myocardial revascularization.

Vasospastic angina

Prinzmetal's variant angina should be suspected in patients with angina occurring exclusively or predominantly at rest, without any apparent triggering cause. Angina is usually of short duration (2–5 minutes), sometimes recurs in clusters, frequently shows a typical circadian pattern, with a more frequent occurrence in the early morning or in the night hours, and promptly responds to short-acting nitrates. Effort tolerance is often well preserved, but exercise is a trigger of coronary artery spasm in about 25–30% of patients.

The clinical diagnosis is confirmed by the documentation of transient ST-segment elevation (from 1–2 mm up to 20–30 mm) on the ECG during an anginal episode (Fig. 14.15). When it is difficult to record standard ECG during angina, variant angina can usually be diagnosed by ambulatory ECG monitoring over 24–48 hours; this also allows assessment of the total ischaemic burden and the daily distribution of ischaemic episodes [133]. EST can allow the diagnosis of vasospastic angina in a minority of patients by inducing reversible ST-segment elevation during or immediately after the effort. The latter is typically prevented by pre-test assumption of short-acting nitrates.

In some patients a pharmacological provocation test of coronary spasm is necessary to confirm the diagnosis. Provocation tests of spasm can be performed non-invasively, under careful clinical and ECG monitoring, by administration of intravenous ergonovine, which induces typical symptoms and ECG changes. Alternatively, intracoronary administration of ergonovine or acetylcholine can be used to induce spasm during coronary angiography, which allows a direct documentation of coronary spasm (Fig. 14.16). The invasive procedure is warranted in patients in whom the use of systemic provocation tests of coronary spasm are associated with an increased risk of refractory spasm (e.g. prolonged angina, delayed response to short-acting nitrates). Coronary angiography also allows the assessment of coronary vessels. Critical coronary stenoses are found in about half of the patients.

In some patients severe ventricular tachyarrhythmias may develop during ischaemic episodes caused by

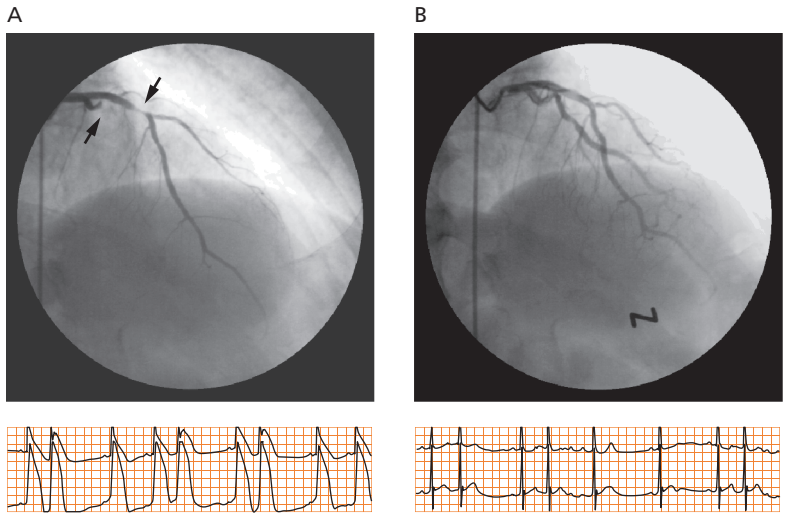


Figure 14.15 Documentation of occlusive coronary artery spasm of both left anterior descending coronary artery and circumflex coronary artery (arrows) following intracoronary administration of 16 μg of ergonovine in a patient with typical variant angina (left upper panel). Coronary spasm promptly resolves after intracoronary administration of 2 mg isosorbide dinitrate (right upper panel). The electrocardiogram shows marked ST-segment elevation up to 20 mm (left bottom panel) which resolves after administration of nitrates (right bottom panel).

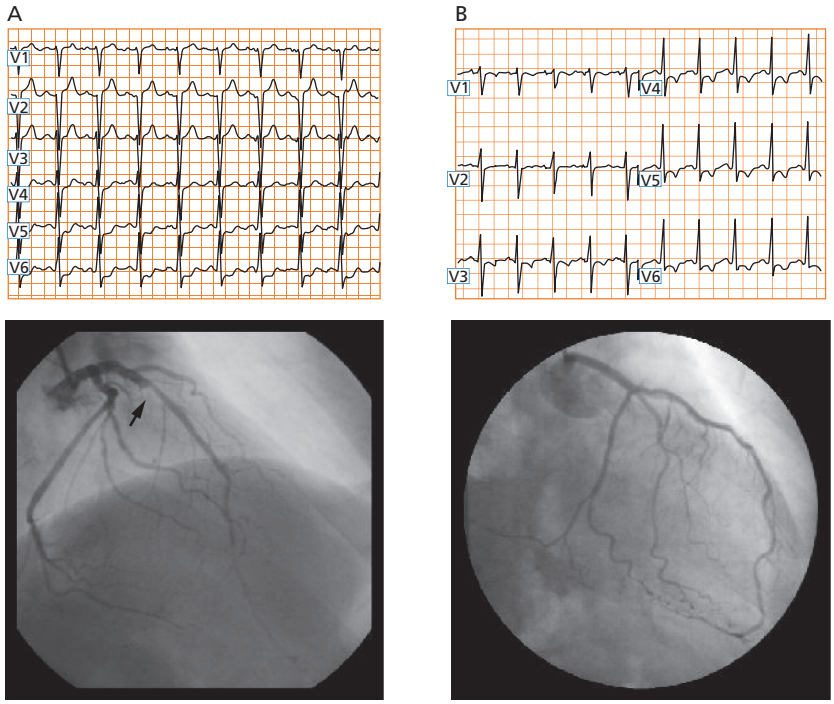


Figure 14.16 'Ischaemic' ST-segment depression (~1.5 mm) in anterior-lateral leads induced by treadmill exercise stress test (Bruce protocol) in two patients with stable effort angina (upper panels). The morphology and severity of ST-segment depression and the workload of exercise (Bruce stage 2) is similar in the two patients. Yet, in patient A (bottom left panel) coronary angiography shows a tight stenosis of proximal left anterior descending coronary artery (arrow), whereas in patient B (bottom right panel) angiography shows angiographically normal coronary arteries (syndrome X patient).

coronary spasm. These patients may present syncope or presyncope associated with angina and are at risk of sudden death [134]. The causes of the individual susceptibility to ventricular tachyarrhythmias are poorly known, but there is no strict relationship with the severity of ischaemic episodes. Severe bradyarrhythmias (sinus arrest, atrioventricular block) may also occur, in particular in patients with inferior transmural ischaemia.

Prognosis of variant angina, in early studies, was found to mainly depend on the presence of multivessel IHD [135]. Subsequent studies, however, showed that sudden death and cardiac arrest, as well as acute myocardial infarction, may occur also in patients with normal or near-normal epicardial arteries [133].

Prognosis of variant angina is strictly dependent on the time of diagnosis. Indeed, most events occur within days or months of symptom onset. Thus a prompt diagnosis is mandatory to initiate drug therapy with vasodilators, in particular with calcium antagonists, which prevent recurrence of spasm in about 90% of patients and have been demonstrated to improve long-term prognosis [136].

High risk factors include multivessel spasm, severe ischaemia-related bradyarrhythmias or tachyarrhythmias, prolonged spasm, in particular those not promptly responding to nitrates, and, finally, spasm that is refractory to high doses of calcium antagonists.

Cardiac syndrome X

Syndrome X is typically characterized by: (1) angina predominantly occurring on effort and typical enough to suggest IHD; (2) 'ischaemia-like' ST-segment depression during angina or provocation tests (Fig. 14.16); (3) normal coronary arteries at angiography; (4) absence of epicardial coronary artery spasm and of known causes of microvascular dysfunction.

There is still debate as to whether microvascular dysfunction is the cause of ischaemia and chest pain in cardiac syndrome X (see above in this chapter). However, there is consensus that enhanced pain perception is present in these patients. It remains controversial, however, whether increased cardiac pain perception is caused by a general nociceptive abnormality related to a cortical defect or rather by a specific peripheral cardiac neural alteration [137,138].

In most cases the features of chest pain do not allow us to distinguish patients with cardiac syndrome X from those with obstructive coronary atherosclerosis. Some features of angina, however, strongly suggest syndrome X, including a prolonged duration of chest pain after interruption of effort and a slow or inconstant response to sublingual nitrates.

Non-invasive diagnosis of syndrome X is not easy. Physical examination is typically unremarkable, whereas EST shows results similar to those observed in patients with obstructive IHD (Fig. 14.16). Exercise myocardial perfusion scintigraphy is positive in about half of the patients [88]. The absence of left ventricular contractile abnormalities during echocardiographic stress test (dipyridamole, dobutamine, or exercise), despite the induction of chest pain and ST-segment depression [139], strongly suggests cardiac syndrome X, as does the lack of improvement of exercise-induced angina and ST-segment changes by short-acting nitrates [140].

Prognosis of syndrome X has consistently been shown to be excellent, as no increase in the risk of major cardiac events has been reported [141]. A significant impairment of left ventricular function at follow-up has been found in the small subset of patients who present with resting or stress-induced left bundle branch block, who, however, are considered to be latent cases of dilated cardiomyopathy. Notably, recent data suggest that evidence of endothelial dysfunction in syndrome X women is associated with the development of clinically silent, but angiographically detectable, coronary artery disease at long-term follow-up [142].

Despite the excellent prognosis, several patients with syndrome X show persistence and even worsening of symptoms over time, with angina attacks becoming more frequent, severe, prolonged and poorly responsive to drug therapy. Symptoms may considerably restrict the patient's daily activities and lead to frequent non-invasive, and even invasive, diagnostic investigations, and to emergency room and hospital admissions. Thus, quality of life in these patients can be severely impaired, making syndrome X a socially and economically relevant cardiac disease [88].

Ischaemic cardiomyopathy

In a number of cases the clinical presentation of chronic stable IHD is dominated by symptoms and signs of left ventricular dysfunction, a condition defined as ischaemic cardiomyopathy [143]. This is the most common form of dilated cardiomyopathy and most often occurs in patients with a history, or evidence, of previous myocardial infarction [144]. Concomitant stable angina can be present in some of these patients.

Ischaemic cardiomyopathy can result from a single large infarction (usually > 20% of myocardial mass) or from multiple smaller infarctions, followed by progressive ventricular dilatation and dysfunction, which may develop over a number of years. The reasons why for a similar extent of myocardial infarction some patients, but not others, develop severe myocardial dysfunction are still largely debated [145].

Notably, some patients may have suffered from one or more silent myocardial infarctions, revealed by pathological Q waves on a routine ECG, developing symptoms of heart failure as the first manifestation of IHD. In other patients there is no clinical and ECG evidence of previous myocardial infarction, suggesting progressive ischaemia-related loss of myocytes, possibly involving apoptosis [62].

Symptoms of left ventricular dysfunction typically include dyspnoea on effort, paroxysmal nocturnal dyspnoea, fatigue, weight gain and reduced urinary output. Physical examination may reveal signs of heart failure, including a reduced first heart sound, presence of a third sound, ankle oedema and pulmonary rales. A systolic murmur can be present when mitral regurgitation occurs as a consequence of left ventricular dilatation or papillary muscle dysfunction.

Echocardiography shows left ventricular dilatation and reduced ejection fraction and, frequently, severe diastolic dysfunction. Coronary angiography usually exhibits multivessel coronary artery disease. In some patients the

Table 14.8 Non-invasive techniques for the assessment of myocardial viability

Test	Advantages	Limitations
SPECT imaging	High sensitivity Possibility of FDG imaging Quantification of left ventricular function Predictive of clinical outcome	Areas of attenuation as non-viability Impossibility to differentiate endocardial and epicardial viability No absolute measure of blood flow Less specific than dobutamine echocardiography and less sensitive than PET
PET imaging	Absolute quantification of myocardial blood flow and glucose utilization In conjunction with euglycaemic clamp allows interindividual and intercentre comparisons of glucose uptake More sensitive than other techniques No attenuation problem Predictive of outcome	Less specific than dobutamine echocardiography and CMR Not ideal to differentiate endocardial and epicardial viability High cost and limited availability
Dobutamine echocardiography	Higher specificity than nuclear techniques Assessment of both viability and ischaemia Assessment of left ventricular function Predictive of outcome Low cost, wide availability	Poor acoustic window in some patients Lower sensitivity than nuclear tests More operator-dependent
Contrast echocardiography	Simultaneous assessment of microvascular integrity and systolic thickening Better examination of extent of viability than echocardiography Possibility to discriminate subendocardial from subepicardial perfusion	Poor acoustic window in some patients Attenuation problems
Contrast CMR	Accurate measurement of wall thickness Assessment of microvascular integrity Assessment of transmural extent of myocardial necrosis Good sensitivity and specificity for viability detection	Need for faster automated techniques Information not in real time Patients with pacemaker or defibrillator* or who are claustrophobic cannot be studied High cost, limited availability

FDG, fluorodeoxyglucose; CMR, cardiac magnetic resonance; PET, positron emission tomography; SPECT, single-photon emission computerized tomography.
*Recent data, however, suggest that patients with electronic devices, including pacemakers, defibrillators and neurostimulators, can be studied by CMR without any significant increase in adverse events [153].

extent and severity of coronary atherosclerosis is much less than predicted by left ventricular dysfunction, thus suggesting that the latter could mainly be caused by a primary myocardial disease, such as myocarditis [146].

In patients with ischaemic cardiomyopathy it is important to establish the presence and extent of hibernated myocardium. Non-invasive imaging methods to assess myocardial metabolic activity, membrane integrity and inotropic reserve are ideally suited for this assessment. Indeed, nuclear techniques allow the identification of viable but dysfunctional myocardial regions, as viable myocardial fibres have intact cell membranes which take up specific labelled tracers like ^{201}Tl (used with SPECT) or ^{18}F-labelled deoxyglucose (used with positron emission tomography), while dobutamine echocardiography identifies regional inotropic reserve and contrast echocardiography allows the assessment of microvascular integrity. Contrast-enhanced CMR is emerging as an important method for viability assessment. The relative merits of nuclear techniques, echocardiography and CMR for myocardial viability assessment are summarized in Table 14.8. Cost, availability and local expertise will always affect, however, the clinical popularity of a given diagnostic approach [147].

The assessment of myocardial viability has relevant therapeutic and prognostic implications, as myocardial revascularization seems to improve symptoms and perhaps prognosis in patients exhibiting viability of several

hibernated myocardial regions, but not in patients without evidence of myocardial hibernation. A word of caution, however, is needed as, in the absence of properly designed randomized prospective trials, these recommendations are merely based on retrospective studies [148].

As already highlighted, ischaemic cardiomyopathy is associated with a poor outcome, compared to stable IHD without severe impairment of left ventricular function. The reasons for the worse clinical outcome include higher risks of (1) life-threatening ventricular arrhythmias, (2) severe left ventricular dysfunction during recurrence of ischaemia or a new myocardial infarction, (3) potentially fatal systemic complications, and (4) iatrogenic complications as a result of the multidrug therapy.

Among IHD patients with ischaemic cardiomyopathy, clinical outcome might be improved by implantation of an automated cardiac defibrillator [149]. However, efforts to identify patients at higher risk of sudden death are warranted because of the high cost of the device. Predictors of sudden death include ventricular arrhythmias, late potentials on signal-averaged ECG, and, finally, depressed heart rate variability [150], heart rate turbulence [151] and baroreflex sensitivity [152], all expressions of an impairment of cardiac sympatho-vagal balance.

Personal perspective

Chronic IHD has three classic clinical presentations, i.e. stable angina, vasospastic angina and ischaemic cardiomyopathy. In addition, a fourth clinical manifestation exists, cardiac syndrome X, which is characterized by typical angina with a normal coronary artery, and the pathophysiology of which remains under debate. Transient myocardial ischaemia results from the complex interplay of different factors including flow-limiting stenoses and abnormal vasomotion of the epicardial coronary arteries as well as dysfunction of the coronary microvasculature. The relevance of pathogenetic components is different in the different clinical syndromes. The anatomic assessment of coronary artery disease still strongly relies on coronary angiography. Improvements which were unthinkable just a few years ago are being made in non-invasive imaging modalities, including multislice computed tomography and cardiac magnetic resonance, which will probably substitute diagnostic angiography in the years to come. Furthermore, functional information provided by these new imaging modalities plays a key role in the assessment of microvascular dysfunction and in the quantification of hibernated myocardium in ischaemic cardiomyopathy. Notably, the quality of life of patients with chronic IHD, who do not need revascularization procedures for prognostic purposes or in whom myocardial revascularization is not feasible, is frequently limited by angina severity. The latter is modulated by central processing of afferent stimuli originating from the heart, resulting in silent ischaemia at one extreme or in enhanced pain perception at the other extreme. A better knowledge of the molecular mechanisms that are responsible for the functional alterations contributing to the determination of the severity of angina in each individual patient is strongly warranted to develop new forms of personalized treatments.

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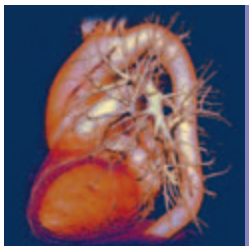


15 Management of Angina Pectoris

Kim Fox, Henry Purcell, John Pepper and William Wijns

Summary

The aims of treatment of chronic stable angina are to minimize or abolish symptoms and also to improve prognosis by preventing myocardial infarction and death. Major advances have been made in antianginal treatment since organic nitrates were first used clinically over a century and a quarter ago. Current drugs may afford prophylaxis as well as relief of symptoms and several agents appear to modify the underlying atherosclerotic disease process and improve prognosis. While much of the decline in ischaemic heart disease (IHD) may be explained by improved treatments, more than half of the decline is attributed to reductions in major risk factors, principally smoking [1]. This chapter reviews life-style, pharmacological and interventional treatments for secondary prevention and for symptomatic treatment of patients with chronic stable angina.

Interventions for secondary prevention

Smoking

Smoking is responsible for 50% of all avoidable deaths and half of these are due to cardiovascular disease [2]. Smoking already kills 1 in 10 adults and is expected to cause 10 million deaths annually world-wide by 2030 [3]. Long-term smoking is associated with impaired endothelium-dependent coronary vasodilatation [4]. Smoking-enhanced platelet aggregation and platelet thrombus formation may be important mechanisms for the increased risk of acute coronary events in smokers [5].

While quitting smoking is difficult, estimates of risk reduction from intervention programmes range from 18 to 65% [6]. Counselling should be available to all smokers on the benefits of smoking cessation in terms of cardiovascular disease (and cancer) prevention. Choice of pharmacotherapy for smoking cessation is dependent on the clinical history of the patient and patient preference. Nicotine replacement therapy (NRT) and sustained-release bupropion (bupropion SR) are first-line treatments for smoking cessation. The cardiovascular effects of nicotine, such as increases in heart rate with small rises in blood pressure, have provoked some concerns about the use of NRT in patients with IHD. However, nicotine patches have been used successfully in heart disease patients without any adverse effects [2]. Similarly, it is suggested that NRT may be initiated as early as 2–3 days after acute myocardial infarction and that it may be used in all patients with angina and cardiac arrhythmias. The growing consensus is that NRT is preferable to continued smoking among patients with stable IHD and that interventions such as NRT should be adopted sooner rather than later. In a randomized multicentre trial [7] of bupropion in smokers with cardiovascular disease, more than twice as many smokers had quit smoking at 1 year with this compound compared with placebo. The safety profile of the drug was similar to that seen in the general smoking population, the commonest adverse effects being insomnia and dry mouth. While further data are required, it is likely that bupropion is a valuable medication for patients with cardiovascular disease. It may be appropriate for heart disease patients to sign a

consent form to agree to undertake smoking cessation therapy following explanation of the immense benefits and the marginal risks involved.

Several novel pharmacological approaches to smoking cessation are currently being investigated including selective blockade of the endocannabinoid system, which is believed to play an important role in energy expenditure and tobacco dependence.

Dyslipidaemia and diet

Dietary modification is an essential part of the management of patients with coronary disease. A diet high in unsaturated and low in saturated fats ('Mediterranean diet') should become part of the life-style of such patients and their families. Patients with coronary disease should aim to bring their total cholesterol to 4.5 mmol/l or less, with low-density lipoprotein cholesterol (LDL-C) 2.5 mmol/l or less; a high-density lipoprotein cholesterol (HDL-C) greater than 25% of total cholesterol should be sought [2]. However, despite an excellent diet, these targets may often not be achieved, in which case pharmacological therapy will be needed.

First-line pharmacological treatment is with a statin, described later; indeed there is a growing consensus that statin treatment should be initiated in all patients irrespective of the level of cholesterol, and treatment titrated to achieve at least the recommendations above.

Other lipid-lowering therapies to consider in patients with angina who have low HDL-C and other features of the metabolic syndrome where LDL-C is below the treatment threshold according to guidelines include fibrates (e.g. bezafibrate, fenofibrate). Fibrates might also be considered when patients are intolerant of statins. Fibrates are especially beneficial in patients with a combination of hypertriglyceridaemia and low HDL-C [8]. Ezetimibe, a cholesterol absorption inhibitor that inhibits passage of cholesterol across the intestinal wall, may also be considered in patients who are intolerant of statins. It may also be co-administered with a lower dose of statin to improve tolerability [9]. A further option is niacin, which has been shown to confer a long-term survival benefit in patients recovering after myocardial infarction [10]; a more modern extended-release niacin preparation appears to be better tolerated than older formulations, which produced a high incidence of adverse effects, e.g. flushing and other cutaneous reactions.

Hypertension and diabetes

Hypertension contributes to all of the major atherosclerotic cardiovascular disease outcomes, increasing risk, on average, two- to three-fold [11]. Coronary disease is the most lethal and common consequence. Hypertension is also the most consistently powerful predictor of stroke. The risk of a recurrent event in patients with IHD is significantly affected by the blood pressure level [12]. Meta-analysis of 61 prospective observational studies has shown that even a 2-mmHg decrease in systolic blood pressure can produce a 7% reduction in risk of IHD mortality and a 10% reduction in risk of stroke mortality [13]. Treatment with any commonly used blood pressure-lowering regimen reduces the risk of total cardiovascular events and larger reductions in blood pressure produce larger reductions in risk [14]. Choice of blood pressure-lowering agent is reviewed in recent guidelines [12].

Diabetes is a cardiovascular disease equivalent and should be managed as such, the assumption being that all patients with type 2 diabetes already have vascular disease [15]. The risk of myocardial infarction in patients with diabetes and no evidence of IHD is similar to that of patients without diabetes who have had a myocardial infarction. Outcomes are worse in diabetic patients for all manifestations of IHD. For patients with known coronary disease and diabetes, rates of death approach 75% over 10 years [16]. Risk of cardiovascular events is further amplified in patients with the metabolic syndrome, where insulin resistance is seen as a key characteristic [17]. Aggressive medical management directed at optimizing glucose and blood pressure control, correcting dyslipidaemia and inhibiting platelet function reduces the likelihood of adverse cardiovascular events.

Other factors

The multifactorial nature of IHD and the multiplicative effect of risk factors, which also include obesity, sedentary life-style, psychosocial stress and so forth, make it important to assess the total cardiovascular risk in an individual patient and to take comprehensive action to address all risk factors.

Physical activity

Physical activity should be promoted for all, but for those with established IHD advice should be based on a preceding formal exercise test. The role of exercise alone in reducing cardiovascular events following myocardial infarction is not known but systematic reviews suggest that cardiac rehabilitation improves coronary risk factors and events in this population [18].

Stress and self-help programmes

Angina patients may also benefit from a self-help angina management programme. One such programme, which

consists of a patient-held 'work book' and audio-taped relaxation programme, has been shown to improve psychological, symptomatic and functional status of patients newly diagnosed with angina [19].

Psychological stress is a well-recognized trigger of myocardial ischaemia [20]. For these reasons stressful driving conditions should be avoided. Occupational stress is also common but pre-retirement patients should be encouraged to return to work and continue their occupation, with appropriate modifications if necessary.

Sexual activity and erectile dysfunction

Sexual intercourse may also become anxiety provoking, particularly for patients recovering after myocardial infarction. Studies have shown that stable, optimally treated angina patients are not at greater relative cardiovascular risk during coitus [21]. Men with cardiovascular disease are more likely to have erectile dysfunction than the general population and may be prescribed agents such as sildenafil (Viagra) or tadalafil (Cialis). One study has shown a lack of any important influence of sildenafil on the development of ischaemia [22], while a further study has shown that sildenafil is well tolerated and produces favourable trends in terms of exercise duration and time to angina on treadmill testing [21]. As dramatic decreases in blood pressure may occur with administration of nitrates within 24 hours of taking sildenafil, their combination is contraindicated.

Hormone replacement therapy

Although oestrogen has antiatherogenic properties, including the potential to improve the lipid profile, hormone replacement therapy is associated with an early increased risk of cardiovascular events. Available evidence suggests that hormone replacement therapy is not indicated for either primary or secondary prevention of IHD, and any potential long-term benefits in lipid profile will be exceeded with statin treatment [23].

Drugs to improve outcomes in angina (secondary prevention)

Antiplatelet agents

Aspirin is the prototypical platelet antagonist and has been available since the end of the nineteenth century. Aspirin was the first drug recognized to have important platelet-inhibitory effects. Its major antithrombotic effect is to irreversibly inhibit platelet thromboxane A2 synthesis, which has pro-aggregatory and vasoconstrictive properties. Aspirin's antiplatelet effects last for the life of the platelet (9–10 days). Aspirin is a mainstay in the treatment and prevention of vascular events. The efficacy of aspirin has been clearly demonstrated in the Antithrombotic Trialists' Collaboration meta-analysis [24]. Its ability to prevent platelet aggregation appears to be its predominant mode of action but a recent study shows that aspirin reduces the incidence and frequency of ischaemic episodes as well as systemic concentrations of haemostatic and inflammatory markers [25]. High-risk patients derive the most benefit from aspirin, with a proportional risk reduction in serious vascular events of 46% in those with unstable angina and 33% among those with stable angina. The benefits were clearly demonstrated in the Swedish Angina Pectoris Trial (SAPAT) [26]. This randomized double-blind trial compared aspirin 75 mg/day and placebo with concomitant treatment of sotalol (mean 160 mg/day) in over 2000 patients with stable angina over a mean period of 50 months. Compared with sotalol and placebo, the aspirin plus sotalol group had a 34% reduction in myocardial infarction and sudden death (P = 0.003). There was also a significant 22–32% reduction in vascular events, vascular death, stroke and total mortality in this latter group.

Daily low doses of aspirin (75–325 mg) seem to be as effective as higher doses for long-term administration, but in an acute setting 150 mg or upwards may be required. Thus aspirin 75 mg daily is the current recommended dose for prevention of serious vascular events in patients with established IHD [24]. There is a two-fold increase in the risk of upper gastrointestinal bleeding associated with aspirin use in the range 75–100 mg daily [27]. Aspirin should not be used in individuals without IHD in whom any potential benefits of therapy are outweighed by the small risk of gastrointestinal bleeding.

Up to one-quarter of individuals may exhibit 'aspirin resistance'. However, no test of platelet function is recommended in order to assess the antiplatelet effect of aspirin in the individual patient [27]. It is difficult to assess the clinical significance of *in vitro* platelet function studies. In patients with contraindications to aspirin or if they are non-responders (aspirin failures) who may experience a cardiac event while taking aspirin, and also in those intolerant of aspirin, clopidogrel 75 mg daily is a suitable alternative. Antiplatelet regimens are needed that are more effective than aspirin alone. Clopidogrel, a thienopyridine, acts by blocking adenosine diphospate (ADP)-dependent activation of platelets. Clopidogrel and ticlopidine are structurally related, although ticlopidine

use has now been eclipsed by clopidogrel as the former has a slower onset of antiplatelet effect and can cause bone marrow toxicity and other adverse effects. Clopidogrel has an established role in acute coronary syndrome (unstable angina and Non ST-segment elevation myocardial infarction (NSTEMI)) and in percutaneous coronary intervention (PCI). It has also recently been approved for use 'as early as possible after symptoms start . . .' in patients with ST segment elevation myocardial infarction (STEMI). The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) study has established that there is no benefit overall of the combination of clopidogrel and aspirin in the long-term in patients with stable vascular disease. Adverse effects with clopidogrel are not dissimilar to aspirin but the frequency of severe rash is higher. Dipyridamole or anticoagulants such as warfarin or thrombin inhibitors are not indicated in stable angina.

Lipid-lowering therapy

Reduction of serum cholesterol is increasingly recognized as essential for the prevention of cardiac events in individuals with IHD. For patients with clinically established cardiovascular disease and diabetes, total plasma cholesterol should be < 4.5 mmol/l (175 mg/dl) and LDL-C < 2.5 mmol/l (100 mg/dl) [2]. Dietary intervention is an important initial treatment in patients with elevated lipids, but only modest reductions (3–5%) in total cholesterol have been achieved in general population studies. However, randomized trials have found that advising people with IHD to adopt a more Mediterranean diet, eating more fish (particularly oily fish), more fruit and vegetables, bread, pasta, olive oil and so forth, may result in a substantial survival benefit [28]. Concentrated fish oil, high in omega-3 fatty acids, reduces high triglyceride levels. One preparation (Omacor) has been shown to reduce sudden cardiac death by 45% when administered as a daily 1-g capsule in survivors of myocardial infarction [29].

There is a considerable body of evidence from randomized clinical trials with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins, e.g. simvastatin, pravastatin) showing that they significantly improve survival, prevent myocardial infarction and reduce the need for costly hospitalizations and revascularization procedures in IHD patients with a range of cholesterol values. Key trials [30–33] of statins in secondary prevention are summarized in Table 15.1 [34]. Such findings support the view that therapy stabilizes lipid-rich atherosclerotic plaques of mild to moderate severity and therefore makes them less vulnerable to rupture. Intensive lipid lowering with a statin provides greater protection against death and cardiac events than does a standard regimen [35]. Statins appear also to exert anti-inflammatory and antithrombotic effects and may modulate endothelial dysfunction independently of their lipid-lowering effect.

Beta-blockers

Beta-adrenergic receptor antagonists (beta-blockers) reduce myocardial ischaemia, improve exercise tolerance and provide symptomatic relief in angina. Beta-blockers act predominantly by competitive inhibition of β-adrenoceptors, particularly β_1 receptors, which are more prevalent in the heart. Their principal antianginal actions are considered to be slowing of heart rate in response to exercise and emotion, and reducing cardiac output; thus myocardial oxygen demand is reduced and coronary blood flow is increased via increased filling time in diastole. They also reduce blood pressure in response to reductions in heart rate and contractility rather than by reducing peripheral resistance, which also conserves energy expenditure. The so-called cardioselective agents (e.g. atenolol and bisoprolol) bind to β_1 receptors and generally cause less frequent adverse effects such as bronchoconstriction and Raynaud's phenomenon, which are mediated by β_2-receptor blockade. However, β_1 selectivity is only a relative characteristic, and at moderate to high doses β_2-receptor blockade occurs with the cardioselective agents. Beta-blockers are then best avoided in patients with asthma or chronic obstructive airways disease but can be used effectively in patients with diabetes, although they may mask or prolong hypoglycaemia. The recently reported Glycemic Effects in Diabetes Mellitus: Carvedilol–Metoprolol Comparison in Hypertensives (GEMINI) trial [36] showed that carvedilol improved cardiovascular risk factors and stabilized glycaemic control, while worsening of glycaemic control was observed with metoprolol. Such findings highlight potentially important metabolic effects that exist between beta-blockers and which may have important consequences in patients with diabetes.

While they share general β-receptor blocking properties, beta-blockers have pharmacological differences (Table 15.2). For example, drugs that have intrinsic sympathomimetic activity (ISA), also called partial agonist activity (PAA), have less effect on resting heart rate and not only block β-receptors but also stimulate them, depending on the prevailing level of sympathetic activity. These agents cause less bradycardia and may offer advantages to patients who also have peripheral vascular

Table 15.1 Major statin clinical event trials in secondary prevention

Trial and agent	Follow-up (years)	Baseline LDL-C, mg/dl (mmol/l)	Changes in lipids	Primary end-point	Statin	Placebo	RRR	ARR*	NNT	Other clinical effects
4S Simvastatin 20–40 mg/day	5.4	188 (4.9)	LDL-C ↓ 35% HDL-C ↑ 8% TG ↓ 10%	All-cause mortality	182/2221 (8.2%)	256/2223 (11.5%)	30% ($P < 0.001$)	3.3%	30	CABG or PTCA ↓ 37% ($P < 0.001$)
				Non-fatal MI, CHD death or resuscitated cardiac arrest (secondary)	431/2221 (19.4%)	622/2223 (28%)	34% ($P < 0.001$)	8.6%	12	Post hoc: stroke or TIA ↓ 30% ($P = 0.024$)
CARE Pravastatin 40 mg/day	5	139 (3.6)	LDL-C ↓ 32% HDL-C ↑ 5%† TG ↓ 14%	Non-fatal MI or CHD death		274/2078 (13.2%)	24% ($P = 0.003$)	3.0%	33	Non-excess non-CVD death CABG or PTCA ↓ 27% ($P < 0.001$) Stroke ↓ 31% ($P = 0.03$)
LIPID Pravastatin 40 mg/day	6.1	150 (3.9) median	LDL-C ↓ 25%† HDL-C ↑ 5%† TG ↓ 11%†	Non-fatal MI or CHD death	557/4512 (12.3%)	715/4502 (15.9%)	24% ($P < 0.001$)	3.6%	28	Total mortality ↓ 22% ($P < 0.001$) CABG or PTCA ↓ 20% ($P = 0.001$) Stroke ↓ 19% ($P = 0.048$)
HPS‡ Simvastatin 40 mg/day	5	131 (3.4)	LDL-C ↓ 29%† HDL-C ↑ 3%† TG ↓ 14%†	All-cause mortality	1328/10 269 (12.9%)	1507/10 267 (14.7%)	13% ($P < 0.001$)	1.8%	56	Revascularization procedures ↓ 24% ($P < 0.001$)
				Fatal or non-fatal vascular events	2033/10 269 (19.8%)	2585/10 267 (25.2%)	24% ($P = 0.001$)	5.4%	19	Stroke ↓ 25% ($P < 0.001$)

*ARR was calculated as the placebo event rate minus the statin event rate.
†Percentage average difference between statin and placebo.
‡The HPS enrolled many types of high-risk patient, 35% of whom had not experienced a prior coronary event.
ARR, absolute risk reduction; CABG, coronary artery bypass graft; CHD, coronary heart disease; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NNT, number needed to treat; PTCA, percutaneous transluminal coronary angioplasty; RRR, relative risk reduction; TG, triglycerides; TIA, transient ischaemic attack. See text for full names of trials.
Reproduced with permission from Gotto *et al*. [34].

Table 15.2 Properties of beta-blockers

Drug	PAA	Cardioselective	Lipophilicity	Plasma half-life (h)
Acebutolol	+	Yes	++	3–4
Atenolol	–	Yes	–	6–9
Betaxolol	–	Yes	++	14–22
Bisoprolol	–	Yes	+	13–14
Carvedilol*	–	No	++	6–7
Celiprolol†	+	Yes	–	4–5
Labetalol*	+?	No	+++	3–4
Metoprolol	–	Yes	++	3–7
Nadolol	–	No	+	20–24
Nebivolol	–	Yes	++	21
Oxprenolol	+	No	++	1–3
Pindolol	++	No	++	3–4
Propranolol	–	No	+++	3–5
Sotalol	–	No	–	9–10
Timolol	–	No	++	4

*Labetalol and carvedilol have additional α_1-blocking properties.
†Selective β_2 agonist.
PAA, partial agonist activity.

disease, although they tend to be less effective in angina prophylaxis. About 15–20% of patients will not tolerate long-term use of beta-blockers. The most common adverse effects include fatigue, dizziness, weakness, depression and, particularly with the lipid-soluble agents, central nervous system problems such as vivid dreams and insomnia. Care must be taken to observe the contraindications to beta-blockade and it should be noted that sudden withdrawal of beta-blockers may occasionally result in rebound angina and an increase in cardiac events.

Meta-analysis of randomized controlled trials after myocardial infarction shows that beta-blockers reduce the odds of death by 23% in long-term trials and by 4% in short-term trials [37]. Most evidence is available for propranolol, timolol and metoprolol, and it cannot be assumed that prognostic benefit will be achieved with other agents; although atenolol is widely used, it has been inadequately evaluated in this setting. A recent meta-analysis of placebo-controlled trials of atenolol in hypertensives [38] suggests no advantage of the beta-blocker over placebo in terms of reducing all-cause cardiovascular mortality or myocardial infarction, and casts doubts about its suitability for hypertensive patients. Beta-blockers have become an important treatment for several supraventricular (e.g. atrial fibrillation) and ventricular (e.g. ventricular tachycardia) arrhythmias. Use of beta-blockers in heart failure is now firmly established but there are no large long-term studies assessing their effect on mortality in patients with angina pectoris [39].

Calcium antagonists

Calcium antagonists are structurally and pharmacologically heterogeneous compounds that share a common property: they inhibit entry of calcium into cells resulting in vasodilatation of vascular smooth muscle and relaxation of myocardial muscle [40]. They have also been shown to be effective in the treatment of coronary artery spasm. Their antianginal effects appear to be mediated through a reduction of myocardial oxygen demand secondary to decreased afterload and myocardial contractility. There are three main classes: verapamil and diltiazem (the non-dihydropyridines) and the dihydropyridines (e.g. nifedipine, amlodipine) (Table 15.3). All these agents and their analogues are effective antianginals. Dihydropyridines may cause reflex tachycardia and are normally prescribed with a beta-blocker. The principal adverse effect is ankle oedema. Diltiazem may cause bradycardia, while constipation and flushing are sometimes seen with verapamil, which can also cause significant depression of myocardial contractility, requiring caution when used with beta-blockade. These latter two agents should not be used in patients with pulmonary congestion/heart failure.

There is evidence that calcium antagonists may retard the atherosclerotic process [41], but more complete clinical data are required to establish whether calcium antagonists have any role other than symptom control in patients with angina. There has been considerable

Table 15.3 Cardiovascular effects of calcium antagonists

	Amlodipine	Diltiazem	Verapamil
Heart rate	↔	↓	↓
AV node conduction	↔	↓	↓
Myocardial contractility	↔	↓↓	↓↓↓
Peripheral vasodilatation	↑↑	↑	↑
Myocardial oxygen demand	↓	↓	↓

AV, atrioventricular; ↑, increase; ↓, decrease; ↔, unchanged.
Adapted with permission from Purcell *et al*. [40].

controversy about the safety of calcium antagonists. The Angina Prognosis Study in Stockholm (APSIS), which examined the long-term treatment effects of metoprolol and verapamil on the combination of death and non-fatal cardiovascular end-points including myocardial infarction [42], showed no statistically significant difference in treatment effects between both drugs. Similarly, the International Verapamil–Trandolapril Study (INVEST) [43] examined mortality and morbidity outcomes in hypertensives with coronary artery disease by comparing this combined calcium antagonist and angiotensin-converting enzyme (ACE) inhibitor strategy with a non-calcium antagonist treatment strategy (atenolol–hydrochlorothiazide) and showed both strategies to be equally effective. The Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis post-Thrombolysis (INTERCEPT) showed the safety, and to some degree the benefit, of diltiazem in patients with acute myocardial infarction but without heart failure, who had received thrombolysis [44]. Diltiazem was associated with a relative decrease in the combined event rate for non-fatal myocardial infarction and refractory ischaemia. Although diltiazem has not been studied in an outcome trial in chronic stable angina, the above trial and other supplementary findings [45] suggest that diltiazem has a useful role, potentially improving prognosis, in this population, in the absence of heart failure.

Both verapamil and diltiazem reduce heart rate, unlike the dihydropyridine calcium antagonists such as nifedipine and amlodipine. With the older short-acting formulation of nifedipine, for example, there was a rapid onset of action and pronounced dose-related fluctuations in the vasodilator effect that provoked stimulation of the sympathetic nervous system and reflex tachycardia, causing *increased* risk of cardiac events. A Coronary Disease Trial Investigating Outcome with Nifedipine GITS (ACTION) using a long-acting nifedipine formulation reported recently [46]. This showed that the administration of nifedipine GITS, compared with conventional antianginal treatment (i.e. beta-blockers, nitrates, etc.), had no effect on major cardiovascular event-free survival in patients with stable coronary artery disease. Therefore, although nifedipine GITS does not affect outcomes, it is now shown to be safe in this population.

The Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT) [47] compared the effects of amlodipine or enalapril or placebo in patients with coronary artery disease and normal blood pressure. Results showed that both drugs reduced events including cardiovascular death and non-fatal myocardial infarction (and hospitalization for angina). Results were directionally similar for both drugs but smaller and non-significant treatment effects were seen with enalapril.

Further reviews are available on the use of long-acting calcium antagonists in the management of hypertension and angina [48,49].

ACE inhibitors

ACE inhibitors have been available for over 20 years, initially for hypertension and then for treatment of heart failure. ACE inhibitors act to prevent vasoconstriction by inhibiting the production of the vasoactive octapeptide angiotensin II from the decapeptide angiotensin I. This inhibition results in vasodilatation due to lowering of systemic vascular resistance and natriuresis from inhibition of aldosterone secretion. Inhibition of degradation of bradykinin may also lead to increases in circulating bradykinin, which can contribute to the vasodilator effects. Inhibition of angiotensin II may also reduce sympathetic tone. ACE inhibitors are now recommended for all patients with left ventricular dysfunction (even in the absence of heart failure) following myocardial infarction. These drugs are generally well tolerated. The main adverse effect is to produce a dry cough in up to 20% of individuals. Angio-oedema is one comparatively rare but more serious adverse effect. Subsequent studies suggested that inhibition of the renin–angiotensin system has important effects on improving endothelial dysfunction and other properties that could translate into benefits in IHD [50]. This was confirmed in the Heart Outcomes Prevention Evaluation (HOPE) trial [51], which was conducted

in patients aged 55 years or more, at high risk of cardiovascular complications, characterized by a high prevalence of diabetes, hypertension, stroke and peripheral vascular disease. HOPE showed a significant 22% reduction in the composite end-point of myocardial infarction, stroke or death from cardiovascular disease among the patients assigned to ramipril. This was followed by the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) [52], conducted in a 'broad-risk' population, all with documented stable IHD without left ventricular dysfunction. The majority were on background therapy of aspirin, statins and beta-blockers. Perindopril treatment was associated with a 20% relative risk reduction in cardiovascular death, myocardial infarction or cardiac arrest. Such findings make a compelling indication for use of one or other of these ACE inhibitors in all patients with IHD.

These findings are in contrast to the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial [53]. This compared the effects of the ACE inhibitor trandolapril and placebo added to current standard therapy in patients with stable coronary artery disease and preserved left ventricular function. The incidence of the primary end-point, cardiovascular death, myocardial infarction or coronary revascularization, was almost identical for trandolapril and placebo. The reason why no benefit was demonstrated with the ACE inhibitor is not fully explained. Overall event rates in PEACE were lower than in HOPE or EUROPA, perhaps because of differences in prior medications or revascularization between the different study populations. Similarly, we cannot assume that 'all ACE inhibitors are the same' and important pharmacological differences exist between them; also the dose is likely to be important since both HOPE and EUROPA used higher doses of ramipril and perindopril.

At present we have little information on the effects of angiotensin II receptor antagonists in the treatment of chronic stable angina.

Nicorandil

Adenosine triphosphate (ATP)-sensitive potassium channels are ubiquitous in the heart and blood vessels and are important modulators of cardiovascular function. Nicorandil is a hybrid compound that comprises a potassium channel opener and a nitrate moiety [54]. Nicorandil has a dual mechanism of action on both preload and afterload, producing a dose-related improvement in haemodynamics. Angiographic studies have shown that the drug dilates both stenotic and non-stenotic coronary arteries and it is indicated for prophylaxis and treatment of angina, normally at a dose of 20 mg twice daily. Nicorandil may mimic ischaemic preconditioning, which is a powerful protection against myocardial necrosis. Unlike classical nitrates there appears to be an absence of haemodynamic tolerance to nicorandil. Headache is the problem most commonly encountered, usually occurring early on commencement of treatment and disappearing with chronic dosing. Nicorandil appears to have comparable efficacy to other standard antianginals. Its role in symptomatic treatment is discussed later.

The Impact Of Nicorandil in Angina (IONA) study [55] showed that nicorandil 20 mg twice daily, in addition to standard antianginal therapy, improved outcomes in terms of reducing events related to acute coronary disease and the associated requirement for admission to hospital. The drug may therefore have a useful role in treatment of angina unresponsive to initial medical treatment.

Revascularization

The indications for coronary revascularization and the effects of PCI and coronary artery bypass graft (CABG) surgery on outcomes are discussed later in this chapter.

Drugs for the symptomatic treatment of angina

Nitrates

Both short-acting and long-acting preparations are widely employed. While sublingual tablets are rapidly effective for treating an acute attack, many patients find the nitrate spray more convenient.

Short-acting agents

All patients with angina pectoris should be offered sublingual glyceryl trinitrate (GTN) for symptomatic relief. In patients with minimal symptoms, intermittent use of sublingual GTN may suffice. The precise mechanism of action of nitrates remains to be established but principally involves relaxation of vascular smooth muscle, leading to vasodilatation and unloading of the heart. This is achieved with increased production of nitric oxide, an endogenous vasodilator released by the endothelium. Nitrates reduce both the preload and afterload on the heart. Such combined action results in reduced ventricular filling pressures, cardiac dimensions and

wall tension and, ultimately, reduced energy needs. Nitrates also relax large coronary arteries, can reduce coronary spasm and may also enhance coronary collateral flow, thereby redistributing flow from epicardial to subendocardial ischaemic territory. Although nitrates can cause a reflex increase in heart rate and contractility, such effects are usually not sufficient to negate their beneficial effects.

Long-acting nitrates

Long-acting nitrates are only for symptomatic relief of angina. There are no data showing that long-term treatment with nitrates reduces mortality or the incidence of myocardial infarction in patients with stable angina [56]. Long-term dosing with oral slow-release isosorbide dinitrate does not reduce cardiac events in patients recovering after myocardial infarction [57]. Tolerance to continuous oral or transdermal nitrates develops rapidly [58] and, in order to overcome this, nitrate-free intervals or a modified delivery system designed to provide a low-nitrate period have been recommended. The worry about intermittent nitrate therapy is that rebound exacerbation of symptoms may occur.

The safety of nitrates has been established with long-term use. Adverse effects include headache and occasionally postural hypotension. Only about 10% of patients are non-responders to nitrate therapy and a further 10% experience adverse effects requiring withdrawal of therapy [59].

Also available in certain countries is molsidomine, a vasodilator with an action similar to organic nitrates (i.e. increases levels of nitric oxide) and which has antianginal activity similar to long-acting nitrates without causing tolerance.

Beta-blockers

The mode of action and use of beta-blockers has been described in detail above. Beta-blockers should be considered first-line treatment for the relief of angina. All angina patients who require regular symptomatic treatment should be treated, unless contraindicated, with a beta-blocker [60]. Beta-blockers without ISA/PAA are titrated to achieve resting heart rates of between 55 and 60 b.p.m., although 50 b.p.m. may be required in more severe angina.

Calcium antagonists

There is no evidence suggesting superiority of one calcium antagonist over another in the treatment of angina. The heart rate-lowering effects of diltiazem and verapamil are considered to offer similar advantages to beta-blockers and they may be used as first-line treatment when beta-blockers are inappropriate. Dihydropyridines may be useful in combination with a beta-blocker. The sequence of use of beta-blockers and calcium antagonists is outlined in the treatment algorithm shown in Fig. 15.1.

Metabolic agents

A number of antianginal drugs exert their anti-ischaemic effects primarily by altering myocardial metabolism [61]. Such drugs may be useful in patients with refractory angina who are already receiving 'optimal' medical treatment or who may not be suitable for revascularization.

Trimetazidine, which is available in some European countries, is a metabolic agent that has no haemodynamic effects. It has been shown to preserve energy balance and prevent disturbance of ion haemostasis during ischaemia. Its specific mechanism of action is unknown but its antianginal effects are attributed to modulatory effects on intracellular calcium [62]. Trimetazidine also stimulates glucose oxidation and acts as a partial fatty acid oxidation inhibitor (pFox inhibitor). Antianginal efficacy has been established with immediate-release formulations of trimetazidine three times daily [63] and, more recently, with a modified-release formulation of trimetazidine 35 mg daily. The most commonly reported adverse effects with clinical doses are fatigue/drowsiness.

Ranolazine, a new anti-ischaemic drug, is a selective inhibitor of the late sodium current that has the potential to reduce intracellular sodium-dependent calcium overload and its detrimental effects on cardiomyocyte function. It is currently undergoing the European approval process. Benefits have been shown in the Monotherapy of Ranolazine in Stable Angina (MARISA) trial [64] and the Combination Assessment of Ranolazine in Stable Angina (CARISA) trial [65]. Ranolazine as monotherapy in the dose range 500–1500 mg twice daily and in combination with other antianginals and ranolazine 750–1000 mg sustained release twice daily, increases exercise tolerance and reduces ischaemia and also provides additional symptomatic relief in addition to atenolol, amlodipine or diltiazem at standard doses, without adverse long-term survival consequences over 1–2 years of therapy. The most commonly reported adverse effects with ranolazine are constipation, dizziness, nausea and asthenia.

Other metabolic agents include L-carnitine, dichloroacetate [66], glucose–insulin–potassium (GIK), perhexiline, and etomoxir, an investigational carnitine-palmitoyl transferase 1 inhibitor. While it is early days for some of these compounds, others described above have been available for a number of years and although they are

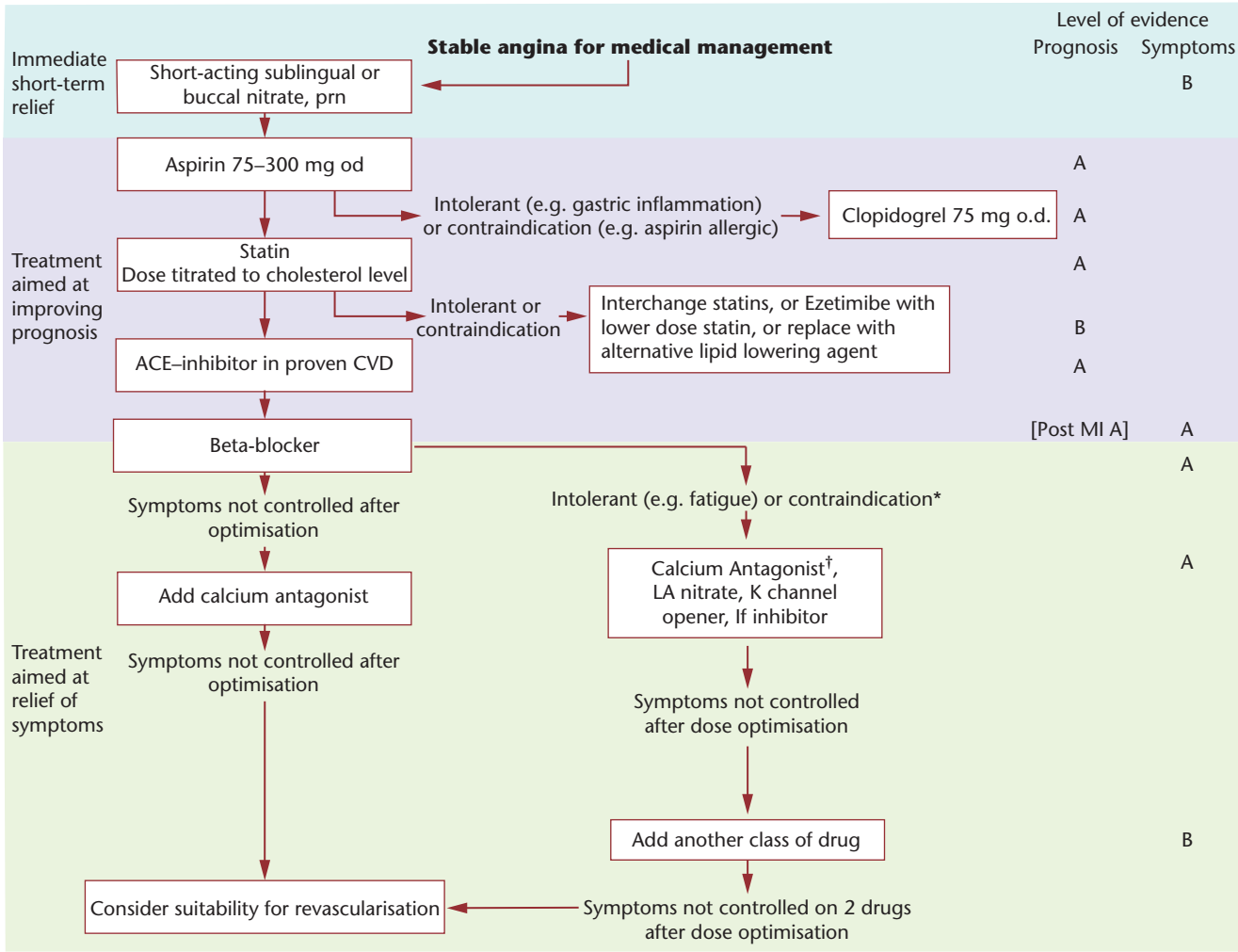


Figure 15.1 Algorithm for medical management of stable angina. High-risk candidates for revascularization on prognostic grounds alone should be identified and referred appropriately. Evidence for prognosis refers to evidence of reduction in CV death or CV death/MI. Evidence for symptoms includes reduction in need for revascularization and hospitalization for chest pain. *Relative contraindications to beta-blockade include asthma, symptomatic peripheral vascular disease and first-degree heart block. †Avoid short-acting dihydropyridine formulations when not combined with a beta-blocker.

promising, longer-term safety and outcome trials are eagerly awaited.

Specific bradycardic agents

A high resting heart rate is associated with an increased risk of IHD [67]. Drugs that lower heart rate, such as beta-blockers, have been shown to reduce the risk of sudden death and re-infarction in patients with IHD. Beta-blockers also play an important role in prevention of anginal attacks as described above. Because beta-blockers have haemodynamic effects other than lowering of heart rate and blood pressure (e.g. they are negatively inotropic), they are not well tolerated by all patients. The question remains whether agents which have a pure bradycardic action without other haemodynamic effects might also have clinical benefits in angina. There are a number of agents that have a direct action on the sinoatrial node [68], including zatebradine, which is no longer being developed because of its propensity to cause QT prolongation and dose-related ocular adverse effects.

Ivabradine specifically inhibits I_f, a primary pacemaker current, and does not induce significant prolongation of repolarization over the dose range 2.5–10 mg twice daily.

A recent randomized controlled trial over a 4-month period [69] showed that ivabradine produces dose-dependent improvements in exercise tolerance and time to ischaemia during exercise. There was an increase in the incidence of mild visual symptoms, mainly with ivabradine 10 mg, which resolved spontaneously or with drug cessation. These may be linked to the presence of retinal ion channels similar to those mediating I_f. There were no 'rebound' phenomenon with ivabradine withdrawal.

Specific heart rate modulating agents may have an important role in the future. Ivabradine has recently received approval for use from the European Agency for the evaluation of medicinal products (EMEA).

Treatment strategies

Figure 15.1 provides an algorithm for the treatment of patients with angina. The strategy involves mainstay drugs for improving prognosis (i.e. aspirin, statin, ACE inhibitor and beta-blocker) and then a tiered system to introduce specific antianginals, calcium antagonists and so forth. The levels of evidence for these drugs are also provided. In patients with minimal symptoms, intermittent sublingual GTN may suffice. No one drug has shown consistently greater efficacy in relieving chest pain or reducing exercise-induced ischaemia. In general, optimal dose regimens of a given class of drug are preferable to routine use of combination therapy. Many patients respond to monotherapy when drugs are used at the appropriate doses; when monotherapy fails it is often advisable to add another class of antianginal. Patients who do not have adequate control of symptoms on maximal doses of two drugs should be referred for cardiological assessment rather than be given a third drug.

A number of other therapies have been proposed for the treatment of angina. These include dietary supplementation with antioxidants, for example. Space does not allow comprehensive review here but, while patients may benefit from these, this issue is still unresolved. We also concur with guidelines in the USA that chelation therapy has no role in the treatment of chronic stable angina.

Conclusions

We have reviewed the evidence for treatments providing symptomatic relief of stable angina and life-style and pharmacological interventions that may be disease modifying. The majority of angina patients will be treated medically. There are very extensive data following long experience with many of the current antianginals. Newer classes have become available and other investigational agents are in the pipeline. It may be that patient treatment will be optimized more readily using a combination of an antianginal that has haemodynamic effects and a compound which has metabolic effects only. The first requirement is to ensure the safety of treatments employed and, secondly, to reduce myocardial ischaemia and improve patient outcome.

Revascularization

All patients thought to have angina should be referred to a cardiologist to identify whether they might benefit from prognostic investigation and treatment [70]. Criteria for access to coronary angiography and revascularization have been developed (Tables 15.4 and 15.5). The criteria stratify patients into four different classes: 1, 2a, 2b and 3. Class 1 includes patients for whom there is very strong evidence of effectiveness. Class 2a includes those with indications for which there is strong evidence of effectiveness and for which most cardiologists would offer treatment. Class 2b includes patients with indications where there is no clear evidence of benefit and class 3 includes patients where there is strong evidence that they should not have angiography or revascularization. Table 15.4 indicates patients who should be referred for a coronary angiogram, ranging from those with chronic disabling angina to those who are at lower risk. Similarly, Table 15.5 outlines those patients who warrant revascularization, ranging from those with significant main-stem disease to those with borderline stenoses but no ischaemia on exercise testing.

Coronary bypass surgery

Coronary artery surgery is the most documented, evaluated and audited operation in the history of medicine. There are two main indications for operation: symptomatic and prognostic. The former involves patients whose angina is not controlled by medical treatment. The latter is the presence of coronary artery disease, which has been shown to have a better prognosis with surgery than with medical treatment. Such disease includes: (1) significant stenosis of the left main stem, (2) significant proximal stenosis of the three major coronary arteries, and (3) significant stenosis of two major coronary arteries, including high-grade stenosis of the proximal left anterior

Table 15.4 Indications for coronary angiography in chronic stable angina

Class 1
A Patients with disabling (CCS class 3–4) chronic stable angina particularly if the symptoms are inadequately responding to medical therapy
B Patients with high-risk criteria on non-invasive testing regardless of angina severity
C Patients who have survived sudden cardiac death or serious ventricular arrhythmia
D Patients with angina and symptoms and signs of congestive cardiac failure
E Patients with clinical characteristics that indicate a high likelihood of severe coronary artery disease, e.g. patients awaiting renal transplantation, those with dilated cardiomyopathy of unknown cause, those with chronic stable angina being considered for major vascular surgery
F Patients previously treated by myocardial revascularization (PCI or CABG) who develop recurrence of moderate or severe angina

Class 2a
A Patients with inadequate prognostic information after non-invasive testing
B Patients with significant left ventricular dysfunction (EF < 45%) or history of myocardial infarction, CCS 1 or 2 angina and demonstrable ischaemia but less than high-risk criteria on non-invasive testing
C Chronic stable angina in patients with bundle branch block if readily induced ischaemia is demonstrable by myocardial perfusion scintigraphy/dobutamine stress echocardiography
D Patients in whom it is essential to establish the diagnosis for clinical or occupational reasons
E Patients with CCS class 1 or 2 angina but intolerance to adequate medical therapy

Class 2b
A Patients with CCS class 1 or 2 angina, preserved left ventricular function and less than high-risk criteria on non-invasive testing who are rendered symptom-free on medical therapy
B Asymptomatic patients awaiting major surgery with a good exercise tolerance and/or less than high-risk criteria on non-invasive testing
C Patients with ventricular ectopics/asymptomatic non-sustained ventricular tachycardia with normal echocardiogram and low-risk non-invasive testing
D Asymptomatic patients with incidental left bundle branch block, normal echocardiogram and low-risk non-invasive testing
E Patients with atrial fibrillation/atrial flutter with normal echocardiogram and low-risk non-invasive testing

Class 3: patients who generally do not need coronary angiography
A Patients with CCS class 1 or 2 angina who respond to medical therapy and who have no evidence of ischaemia on non-invasive testing
B Asymptomatic low-risk patients with no evidence of ischaemia on non-invasive testing
C Patients who prefer to avoid revascularization

CABG, coronary artery bypass graft; CCS, Canadian Cardiovascular Society; EF, ejection fraction; PCI, percutaneous coronary intervention.
Adapted from various sources courtesy of Dr C. Baker, Hammersmith Hospitals NHS Trust.

descending artery. The presence of impaired left ventricular function increases the prognostic advantage of surgery over medical treatment in all categories. This information comes from two major randomized studies: the European Coronary Artery Study and the North American CASS study. Early reports demonstrated a symptomatic advantage of CABG over medical treatment. As follow-up lengthened, the prognostic advantages began to emerge in a number of subgroups [72].

The overall operative mortality for elective first-time CABG is 2–4% [73]. There are well-developed risk stratification models available for the assessment of risk in individual patients. There is the paradox that the higher the risk of operation, the greater the benefit of surgical over medical treatment. In patients with three-vessel disease, the completeness of revascularization is a significant determinant of the relief of symptoms over a 5-year period [74]. Approximately 80% of patients are angina-free 5 years after surgery and 63% at 10 years, but by 15 years only 15% are free of an ischaemic event [75].

Choice of conduit

The acceleration in adverse events after 10–15 years is due to gradual occlusion of vein grafts in addition to progressive disease in the native coronary vessels. Independent predictors of recurrence of angina are female gender, obesity, preoperative hypertension and lack of use of the left internal mammary artery (LIMA) as a conduit to the left anterior descending artery (LAD) [76]. Over the last

Table 15.5 Indications for coronary revascularization for chronic stable angina

Class 1

A CABG for patients with significant LMS disease

B CABG for patients with three-vessel disease: the survival benefit is greater in patients with abnormal left ventricular function

C CABG for patients with two-vessel disease with significant proximal LAD disease and either left ventricular dysfunction or demonstrable ischaemia on non-invasive testing

D PCI for patients with two- or three-vessel disease with significant proximal LAD coronary artery disease who have anatomy suitable for catheter-based therapy

E PCI or CABG for patients with one- or two-vessel coronary artery disease without significant proximal LAD disease but with a large area of viable myocardium and high-risk criteria on non-invasive testing

F CABG or PCI for patients with one- or two-vessel coronary artery disease without significant proximal LAD disease who have survived sudden cardiac death or sustained ventricular tachycardia

G In patients with prior PCI, CABG or PCI for recurrent stenosis associated with a large area of viable myocardium and high-risk criteria on non-invasive testing

H PCI or CABG for patients who have not been successfully treated by medical therapy and can undergo revascularization with acceptable risk

Class 2a

A Repeat CABG for patients with multiple SVG stenoses, especially when there is significant stenosis of a graft supplying the LAD. It may be appropriate to use PCI for focal SVG stenoses

B Use of PCI or CABG for patients with one- or two-vessel coronary artery disease without significant proximal LAD disease but with a moderate area of viable myocardium and/or demonstrable ischaemia on non-invasive testing

C Use of PCI or CABG for patients with one-vessel coronary artery disease with significant proximal LAD disease

D Use of PCI for patients with symptomatic LMS disease and/or evidence of myocardial ischaemia on non-invasive testing who are not candidates for CABG

Class 3

A Use of PCI or CABG for patients with one- or two-vessel coronary artery disease without significant proximal LAD coronary artery disease, who have no symptoms or mild symptoms that are unlikely to be due to myocardial ischaemia, or who have not received an adequate trial of medical therapy and (a) have only a small area of viable myocardium or (b) have no demonstrable ischaemia on non-invasive testing

B Use of PCI or CABG for patients with borderline coronary stenoses (50–60% diameter in locations other than the LMS) and no demonstrable ischaemia on non-invasive testing

C Use of PCI or CABG for patients with insignificant coronary stenoses (< 50% diameter)

D Use of PCI for patients with significant LMS disease who are candidates for CABG. Those with significant LMS disease have a class 1A indication for CABG

Note: in this context the term 'non-invasive testing' includes exercise stress testing, dobutamine stress echocardiography, myocardial perfusion scanning, positron emission tomography assessment of myocardial blood flow and intravascular ultrasound and assessment of fractional flow reserve.

CABG, coronary artery bypass graft; LAD, left anterior descending; LMS, left main stem; PCI, percutaneous coronary intervention; SVG, saphenous vein graft.

20 years the standard procedure has been to graft the LAD with the LIMA and use saphenous vein for the other bypass grafts. By 10 years, 60% of vein grafts are stenosed or occluded. Since at least 70% of patients are alive 10 years after surgery, the recurrence of symptoms from vein graft disease remains a clinical problem. Large observational studies have shown that the use of the LIMA graft improves survival and reduces the incidence of late myocardial infarction and recurrent angina and the need for further cardiac interventions. There appears to be significant survival benefit when using bilateral internal mammary artery (IMA) grafts irrespective of age, ventricular function and the presence of diabetes [77,78] (Fig. 15.2). Furthermore, the benefit of using bilateral IMAs increased with the duration of follow-up, particularly in terms of the need for repeat surgery, which at 10 years was 40% for single IMA grafting and 8% for bilateral IMA grafting in well-matched patients. Ten years after CABG, 90% of IMA grafts continue to function well. With the use of skeletonized IMA pedicles, the risk of sternal devascularization and subsequent dehiscence is much reduced, even in diabetics. Other arterial grafts include the radial artery and the right gastroepiploic artery. The greatest experience has been with the radial

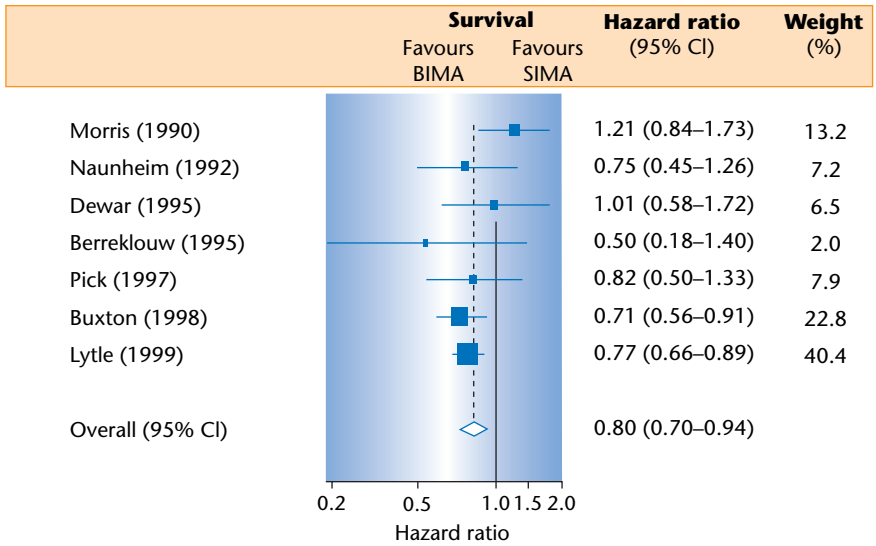


Figure 15.2 Meta-analysis of single internal mammary artery (SIMA) and bilateral internal mammary artery (BIMA) grafts [78].

artery, where reports have indicated patency rates of greater than 90% at 3 years. There is a learning curve with radial artery grafts and it is now clear that they should only be used for coronary vessels with high-grade stenosis or occlusion.

A prospective, randomized, single-centre trial in 438 patients investigated whether angiographic patency of the radial artery was superior to that of the free right internal mammary artery (RIMA) or saphenous vein and whether radial artery grafts have superior outcomes to free RIMA or saphenous vein grafts [79]. No evidence emerged of a greater freedom from untoward events with radial artery use. A recent report in which the post-operative angiograms of 310 symptomatic patients were reviewed showed disappointing results for medium-term patency of the radial artery [80]. At 5 years the patency results were 92% for LIMA, 85% for RIMA, 64% for saphenous vein and 53% for radial artery grafts. There was a gender difference for the radial graft patency, with elderly females faring worse.

Beating heart surgery ('off-pump')

The use of an extracorporeal circulation (cardiopulmonary bypass) for performing coronary artery surgery remains the most commonly used approach. However, there are risks, including a whole-body inflammatory response and the production of microemboli. The need for aortic cannulation and manipulation of the ascending aorta may lead to release of emboli, especially in elderly atheromatous patients, who constitute an increasing proportion of the patient pool accepted for coronary surgery. So-called 'off-pump' surgery may lead to a reduction in perioperative mortality and morbidity. The recent introduction of stabilization devices has enabled surgeons to treat patients with three-vessel disease in this way (Fig. 15.3). Randomized trials comparing off-pump with the standard procedure are now available. Although the use of blood products was reduced in the off-pump group (3% vs. 13%) and the release of creatine kinase (CK)-MB isoenzyme was 41% less in the off-pump group, there were no differences in perioperative complication rates. There was no difference in outcome in the first 1–3 years after surgery between off-pump and standard groups [81,82]. A meta-analysis of six studies including 558 patients randomized to on-pump and 532 to off-pump found no significant difference in the combined end-point of death, stroke or myocardial infarction [83]. More recently, Khan and colleagues [84] in a further

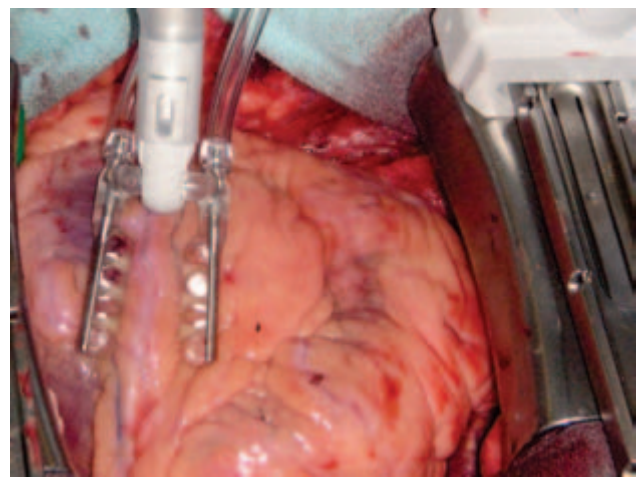


Figure 15.3 Use of a stabilizer to enable anastomosis of left internal mammary artery to left anterior descending artery on the beating heart.

randomized trial with angiographic follow-up at 3–6 months showed a significant reduction in graft patency (90% vs. 98%) in the off-pump group. These studies suggest that the use of off-pump surgery is not a panacea but should be applied cautiously and selectively to patients with good target vessels and significant comorbidity.

In the debates about on-pump and off-pump surgery, on-pump is usually treated as a single commodity. However, cardiopulmonary bypass can be conducted in several distinct ways. Cardioplegic arrest may be employed using a variety of solutions at different temperatures and by different routes, antegrade or retrograde or a combination of the two. Non-cardioplegic methods have a long pedigree and can be very effective. With the use of stabilizers, cardiopulmonary bypass can be employed without the insult of global ischaemia caused by aortic cross-clamping, and used to empty the heart while local stabilization of the target vessel is secured. When the vessel is opened a shunt may be placed, thus minimizing any regional ischaemia. This approach has proved effective in patients with hibernation and dilated hearts, and in repeat coronary surgery.

Repeat coronary artery surgery

The incidence of repeat coronary artery surgery, as a proportion of all coronary artery surgery, is less in Europe (5–10%) than in North America (10–15%). There is a higher morbidity and a two to three times higher mortality [85]. Although the relief of angina is less predictable and less complete than after first-time surgery, the long-term outcome is encouraging, with 73% of patients free of angina at 5 years. The indications for reoperation have not been defined by randomized trials, but the same principles apply as for first-time surgery. Stenosis in a vein graft to the LAD is associated with a reduction in survival [86]. A major improvement in survival after reoperation was especially evident for patients in this category. Among these patients, survival rates were 84% and 74% for the reoperation group at 2 and 4 years compared with 76% and 53% for the medically treated group.

Surgery in the presence of impaired left ventricular function

In the early 1980s, Rahimtoola [87] reviewed the results of coronary bypass surgery trials and identified patients with coronary artery disease and chronic left ventricular dysfunction that improved with revascularization. The results of medical treatment for ischaemic cardiomyopathy have been poor. Coronary revascularization provides superior long-term survival but may be associated with a high operative mortality and significant morbidity for certain patient subgroups with heart failure and very low ejection. At one time heart transplantation provided an attractive alternative, but the severe and worsening shortage of donor organs has made this option largely impractical, as the mortality while waiting for a transplant reduces the overall survival for patients assigned to this form of treatment.

Coronary artery disease is the major cause of heart failure. It accounts for 95% of cases of congestive heart failure in patients aged 25–75 years. More than 50% of patients with congestive heart failure and coronary artery disease have evidence of stress-induced ischaemia or hibernation [88]. The pathophysiology underlying this disease includes myocyte loss with scar formation, chronic dysfunction in viable myocardium associated with stunning and hibernation, and structural changes in remote myocardium. The potential benefits of revascularization are to reduce the ischaemic burden, reduce the arrhythmic potential, reduce maladaptive growth and restore the coordinated movement in dysfunctional segments [89].

Data from the CASS registry for patients with left-ventricular ejection fraction (LVEF) below 35% involved 651 patients [90,91]. The 5-year survival was significantly better in surgical patients (68%) than in the medical group (54%). The contrast became more marked in patients with LVEF less than 26%, whose 5-year survival was 63% with surgery but 43% with medical treatment. This information is the cornerstone of our current approach to patients with coronary artery disease and congestive heart failure.

With recent improvements in anaesthesia and myocardial management, the operative mortality has been reduced to less than 10% in most series [92–94]. Perioperative care has been enhanced by the increased use of balloon counterpulsation and short-term ventricular assist devices. Angina often present in these patients can be successfully ameliorated by surgery [94] as can symptoms of heart failure, particularly if there is careful selection of patients [95–98].

Clearly, revascularization can improve functional status in patients with ischaemic cardiomyopathy, but viability assessment is crucial for the appropriate selection of patients.

Conclusions

Coronary artery surgery remains the gold standard for the alleviation of symptoms in patients with coronary artery disease. In addition there are small subsets in whom surgery will improve prognosis, notably those with left main-stem or proximal anterior descending disease, as well as those with impaired left ventricular function and three-vessel coronary disease. In addition, it is an

important form of treatment for patients with ischaemic cardiomyopathy, including those for whom angina is a minor component of their symptoms. New approaches are likely to reduce the morbidity of the procedure, particularly in respect of stroke in elderly patients.

Percutaneous coronary intervention

Introduction and historical background

Balloon angioplasty is aimed at restoring blood flow through stenotic coronary arteries by mechanical dilatation, i.e. inflation of a balloon catheter steered percutaneously to the narrowed site under fluoroscopic guidance. The procedure was introduced in 1977 by Grüntzig [99] and has gained increasing clinical application since then [100,101]. In Europe, PCI is presently preferred over CABG in a ratio of 3 : 1 [102]. Ease of use and convenience of PCI weighs heavily against the greater durability of the more invasive bypass operation. Also, both the safety and efficacy of PCI have continuously improved further to technological progress and advances in adjunctive pharmacological management. Following the availability of miniature and highly steerable guidewires, which have permitted access to virtually any branch of the epicardial coronary tree, the next decisive improvement resulted from the development and successful application of endovascular metallic scaffolds, called stents [103–105]. Stents are presently used in more than 80% of all PCI procedures [100–102]. The stent implantation technique itself has been optimized by proper stent expansion and apposition against the wall, as learned from intravascular ultrasound imaging [106]. Stented angioplasty is superior to balloon angioplasty for the following reasons.

1 Plaque fracture and dissection caused by balloon inflation often resulted in a pseudo-successful procedure while limited luminal enlargement was actually obtained.
2 The dilated lesion shows greater stability after stenting, while abrupt closure within 48 h following balloon treatment was not uncommon (up to 15% in the presence of severe residual dissection).
3 The angiographic result obtainable after stenting is predictable irrespective of stenosis complexity.
4 Stent implantation results in fewer vessel reocclusions and lower rate of reintervention.

Several randomized clinical trials support the above-mentioned statements, particularly the Benestent family of trials, which represent the foundations of the practice of PCI, at least in Europe [107–110] (Fig. 15.4). For instance, Benestent II tested the hypothesis that use of a heparin-coated stent (plus aspirin and ticlopidine) would result in a better event-free survival than standard balloon angioplasty [108]. After stenting, 87.2 and 84.3% of patients were event-free at 6 and 12 months respectively, as opposed to 80.7 and 77.6% after balloon angioplasty. Despite allocation to balloon treatment, bail-out stenting was unavoidable in 13% of patients. The rates of stent thrombosis were as low as 0.2%. The best outcome (89.3% event-free rate at 6 months) was observed in patients randomized to clinical follow-up, in which repeat angiography was only performed on clinical grounds [109] (Fig. 15.4). Other randomized clinical trials have shown that this benefit was maintained up to 5 years after the initial procedure [110,111]. The results of PCI have thus greatly improved over the last few years due to a number of factors acting in synergy [111]. However, until fairly recently, restenosis after stented angioplasty had remained the Achilles heel of PCI.

Advances in the treatment and prevention of restenosis after PCI

Prior to the stent era, numerous mechanical and pharmacological approaches to the prevention of restenosis were tested and shown to be failures. Although a variety of devices have been developed to crack, break, stretch, scrape, shave or burn the atherosclerotic plaque, the durability of an initially successful procedure has been hindered by an incidence of angiographic restenosis within 6 months as high as 50%. This is because restenosis after balloon angioplasty or any other mechanical intervention except stenting is a complex wound healing process that results in exuberant neo-intimal proliferation as much as in constrictive remodelling of the vessel [112]. Implantation of a metallic stent cage virtually eliminates vessel shrinkage and thereby significantly reduces clinical restenosis, i.e. the need for repeat intervention due to recurrent symptoms. At the same time, implantation of metallic stents exacerbates the neo-intimal proliferative reaction such that there remain a number of lesion subsets associated with poor short-term outcome and angiographic restenosis rates above 30%, specifically small vessels, long lesions, saphenous vein graft disease and ostial lesions [113]. Restenosis inside a previously deployed metallic stent is difficult to treat because of recurrence rates ranging from 19 to 83% after any new intervention, albeit plain balloon angioplasty or a combined procedure involving plaque debulking [114]. This is particularly the case when diffuse or proliferative in-stent restenosis is present. Because in-stent restenosis has been shown to be almost exclusively due to neo-intimal

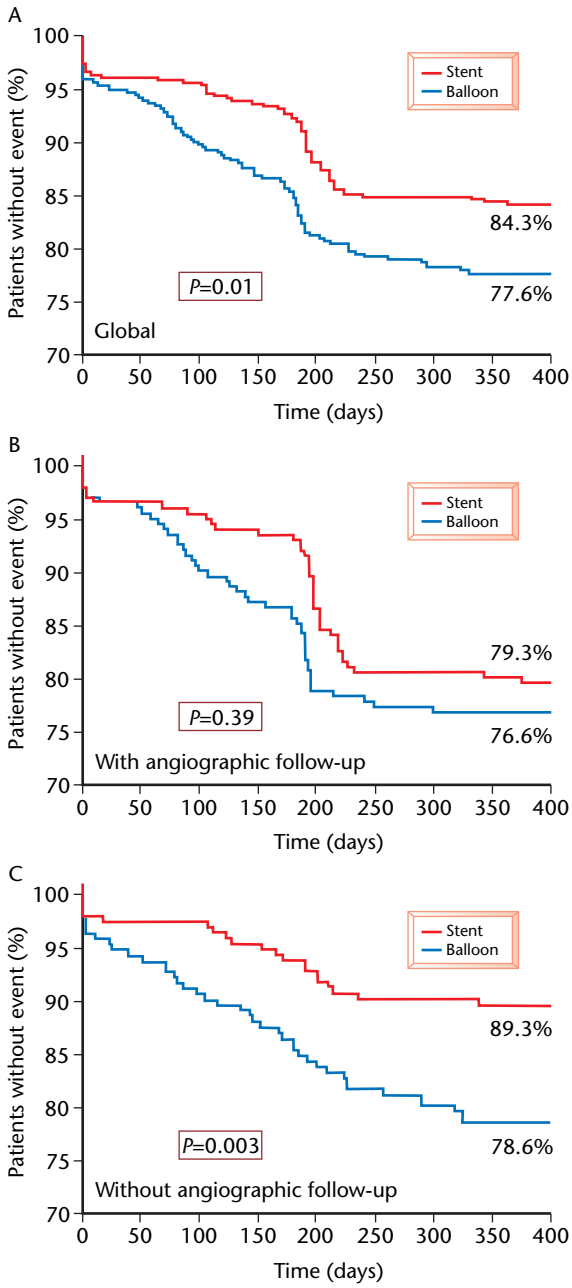


Figure 15.4 Major adverse clinical event (MACE)-free survival in patients randomized to balloon angioplasty vs. implantation of bare metal stenting (Benestent II trial). In the global population (A), most of the events occur at 6 months after randomization. In the subgroup randomized to angiographic follow-up (B), these events represent mostly reinterventions that are triggered at least in part by angiography. In the patient subgroup randomized to clinical follow-up (C), the outcome in both balloon and stent groups is driven by clinical needs. This study design documented for the first time the extent to which systematic repeat angiography interferes with regular patient care.

proliferation, intracoronary irradiation was successfully applied, with either gamma or beta radiation [115]. However, long-term results of brachytherapy have been plagued with exceedingly high rates of stent thrombosis and late vessel occlusion [116–118], presumably due to delayed re-endothelialization. Vascular brachytherapy applied at the time of the initial stented angioplasty, in an attempt to prevent later proliferation of in-stent neointima, has been abandoned as well, due to a number of unexpected problems: subacute and late stent thrombosis, edge failure and geographical miss, acquired stent malapposition against the vessel wall due to vessel expansion and late recurrence [119]. Presently, drug-eluting stents (DES) are replacing metallic stents. These metallic scaffolds are covered with polymers from which less than 0.1 mg of cytotoxic and anti-inflammatory compounds (e.g. paclitaxel, sirolimus, everolimus) are progressively eluted over the first weeks after stent implantation. Both angiographic restenosis rates and the need for repeat intervention due to symptom recurrence have been reduced by over 60%, at least with the use of the currently approved devices (Table 15.6) [120]. Another development is the increasingly frequent use of direct stenting, i.e. stent implantation without balloon pre-dilatation. Animal experiments have suggested that direct stenting reduces endothelial and vessel wall damage and produces less neo-intimal proliferation [121]. When applicable with DES, restenosis rates as low as 2% have been observed [122,123]. Clinical follow-up for up to 4 years after DES seems to indicate durability of this result and additional long-term data are accumulating [124]. In addition to their favourable impact on restenosis and symptom recurrence, the use of DES will likely cause an expansion of the indications for PCI, as indicated by the evaluation of 'real world' practice in centres where DES have already completely replaced metallic stents [125,126]. Registries and surveillance data suggest that results obtainable in 'real life' are indeed comparable to those reported in randomized clinical trials, even in patient and lesion subsets considered at higher risk for poor outcome and which are usually excluded from such trials [125,126].

Indications for PCI in patients with chronic IHD

Mechanical revascularization vs. medical treatment

The obvious goal of revascularization in patients with stable coronary artery disease is to relieve angina, improve quality of life and revert signs of inducible ischaemia [127]. In patients with severe ischaemia, such as those included in the ACIP trial (patients had both stress-inducible ischaemia and at least one episode of silent ischaemia on 48-h Holter monitoring), revascularization

Table 15.6 Meta-analysis of 11 randomized clinical trials on drug-eluting stents combining sirolimus and paclitaxel, polymeric and non-polymeric delivery

	Drug-eluting stents ($n = 2641$)*	Bare metallic stent ($n = 2449$)*	Odds ratio	95% confidence interval
All-cause mortality	0.95 (26)	0.86 (21)	1.11	0.61–2.06
Myocardial infarction	2.69 (71)	2.94 (72)	0.92	0.65–1.25
Target lesion revascularization	4.20 (111)	13.19 (323)	0.26	0.14–0.45
Major adverse cardiac events	7.84 (207)	16.37 (401)	0.42	0.32–0.53
Angiographic restenosis†	8.91 (155)	29.37 (457)	0.18	0.06–0.40

Note: odds ratio < 1.00 favours drug-eluting stent, odds ratio > 1.00 favours bare metallic stent.
*Values are percentages with numbers in parentheses.
†Drug-eluting stent ($n = 1739$) and bare metallic stent ($n = 1556$).
Adapted with permision from Babapulle *et al*. [120].

significantly reduced death and infarction rates at 2 years follow-up compared with medical treatment [128,129]. However, in the vast majority of patients with stable angina, prognosis is excellent and unlikely to be improved by PCI. Instead, the AVERT trial [130], in which patients were randomized to PCI or medical care including high-dose atorvastatin (80 mg daily), strongly challenged the idea that every epicardial stenosis should be 'fixed'. In fact, outcome was better in patients treated medically and at 1.5 years the incidence of any ischaemic event was 13.4% after atorvastatin vs. 20.9% after PCI. Given the incremental benefit of statins [131,132] and ACE inhibitors [133] in patients with chronic IHD undergoing revascularization, the COURAGE trial was initiated in order to reassess the role of aggressive medical therapy alone and in combination with PCI. While the results are awaited, revascularization should be triggered by the symptomatic status and/or the documented evidence of inducible ischaemia, not just by the presence of a seemingly significant stenosis. Unless the stenosis appears critical at coronary angiography, even experienced interventional cardiologists cannot accurately predict the haemodynamic significance of most narrowings based on visual assessment or quantitative coronary angiography [134]. Although non-invasive stress imaging (with a sensitivity of 76–88% and specificity of 80–88%) should ideally be applied prior to cardiac catheterization, a majority of patients in the real world undergo coronary angiography without prior functional testing [135]. When exercise-induced ischaemia has not been documented for any reason, the measurement of pressure-derived fractional flow reserve (FFR) can be applied during the invasive examination. This test is simple, easily obtained and lesion specific, and an FFR below 0.75 is a robust surrogate for inducible ischaemia [136–138]. In the DEFER trial [137,138], PCI was either performed or deferred based on the FFR value. Event-free survival was similar between the deferral and PCI groups (92% vs. 89% at 12 months and 89% vs. 83% at 24 months), indicating that PCI does not improve outcome when performed on stenoses that are non-flow-limiting.

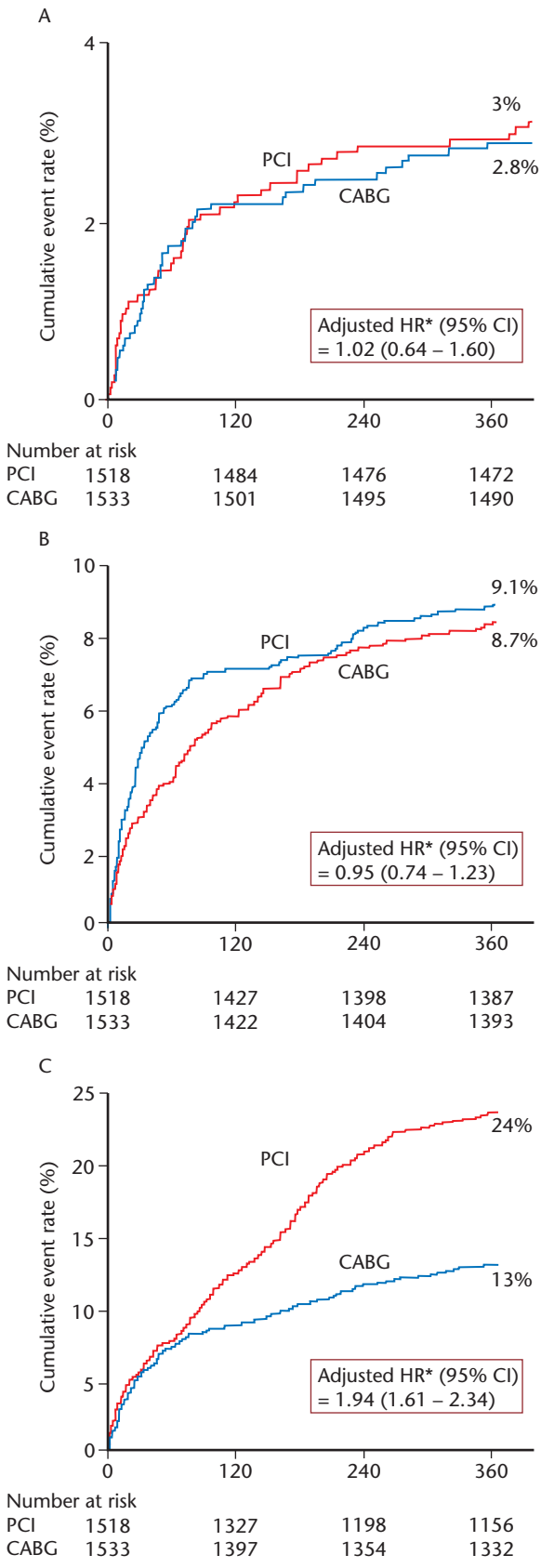
PCI vs. CABG

Meta-analysis of 7964 patients randomized between 1987 and 1999 showed no statistically significant risk difference for irreversible adverse events (death, myocardial infarction and stroke) between the two revascularization strategies at 1, 3 or 8 years [139]. Mortality at 3 years was 5.2% in early trials on balloon angioplasty vs. 3.5% in recent trials on stented angioplasty [139,140]. Symptomatic relief was equivalent at the expense of an increased need for repeat revascularization in patients allocated to PCI. Compared with the balloon era, stented angioplasty using metallic stents has halved the risk difference for repeat revascularization at 1 year [139,140], which however remains at 18% after PCI vs. 4.4% after CABG (95% CI hazard ratio 3.3–5.9) (Fig. 15.5). The value of DES in treating patients with multivessel disease who would otherwise be candidates for bypass surgery was evaluated in the ARTS II registry [141]. At 1 year, clinical outcome was equivalent to the results obtained with bypass surgery in the surgical arm of ARTS I. These results provided the rationale and the design of prospective randomized clinical trials comparing CABG with DES in patients with multivessel disease (FREEDOM, SYNTAX).

PCI in specific patient and lesion subsets

Chronic total occlusion

Chronic total occlusion still represents the anatomical subset where PCI is associated with low technical success and high complication rate, including extensive



dissection, side-branch occlusion, distal embolization and coronary perforation [142]. When the occlusion can be crossed with a guidewire and the distal lumen has been reached, satisfactory results are obtainable with stent implantation albeit at the expense of a high restenosis rate (32–55%) [143]. The use of DES has been shown to improve these results in a significant way [144,145].

PCI in patients with multivessel disease and/or diabetes mellitus

In patients with multivessel IHD and high-risk profile, CABG was associated with better survival than PCI after adjustment for risk profile [146]. Initial differences in cost and quality of life between CABG and PCI were no longer significant at 10–12 years of follow-up [147]. Although a direct comparison of PCI with CABG in diabetics is not yet available, every subgroup or *post hoc* analysis has invariably shown that the outcome for diabetics is worse following PCI [148]. In the ARTS I trial [149], outcome for diabetics was poor in both treatment arms, but even more so following PCI. After 3 years, mortality was 7.1% in the PCI and 4.2% in the CABG group, with a still significant difference in event-free survival of 52.7% in the PCI group and 81.3% in the CABG group [150]. Preliminary data from ARTS II, a prospective registry [141], suggest that the use of DES in patients with multivessel disease and/or diabetes mellitus may change this situation, a possibility that is currently being evaluated in randomized trials.

PCI for unprotected left main disease

The presence of unprotected left main coronary artery stenosis identifies an anatomical subset that benefits from revascularization by CABG. Stenting for unprotected left main disease is considered in the absence of other revascularization options [151]. Initial data on the use of DES seem promising but remain observational [152].

PCI in patients at high surgical risk

The AWESOME trial [153] showed that PCI is a safe and effective alternative to CABG for patients with refractory

Figure 15.5 Meta-analysis of ARTS I, SoS, ERACI-2 and MASS-2 shows no significant difference in total mortality (A) or in combined irreversible events including death, myocardial infarction and stroke (B) between patients with multivessel disease randomized to percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). However, the need for repeat revascularization procedures at 1 year following PCI remains nearly twice that after CABG (C).

ischaemia who are at high surgical risk. The 'patient choice registry' revealed that PCI, including PCI of protected left main (i.e. partially bypass protected), is a valuable option for many post-CABG patients, rather than repeat bypass surgery [153]. Other high-risk groups include the elderly [154] and patients with renal failure [155]. Both the SYNTAX and FREEDOM trials will capture the outcome data of these patient subgroups that are usually excluded from randomized clinical trials.

PCI for saphenous vein graft disease

Although stented angioplasty yields better immediate results than balloon angioplasty [156,157], later outcome is affected by further progression of graft atherosclerosis and thrombosis. PCI of *de novo* stenoses in vein grafts is a high-risk procedure due to the high likelihood of distal embolization of thrombotic or atheromatous debris, which is not reduced with the use of glycoprotein IIb/IIIa inhibitors [158]. The no-reflow phenomenon that follows is characterized by inadequate flow at tissue level despite a fully dilated/reopened epicardial conduit. The embolized areas undergo microvascular disruption, endothelial dysfunction, myocardial oedema or inflammation that may cause critical haemodynamic deterioration [159]. Prevention of embolization and no-reflow phenomenon entails the use of distal protection systems, some of which are of proven efficacy [160,161].

Adjunctive pharmacological treatment

Antithrombotic and antiplatelet regimen

The mechanical trauma induced by PCI to the endothelium and deeper layers of the vessel wall is a strong stimulus for platetet activation and clotting, which necessitates careful combined antiplatelet and anticoagulant treatment [162]. An increasingly aggressive pharmacological approach portends the risk of an excess in bleeding and vascular complications. Technical advances such as arterial access through the radial artery, the use of smaller size femoral sheaths and closure devices have permitted the safe use of multiple agents.

Since most PCI procedures are accompanied by stent implantation, all patients should receive aspirin and thienopyridine treatment [163,164]. To ensure full antiplatelet activity, clopidogrel should be initiated at least 6 h prior to the procedure with a loading dose of 300 mg, ideally administered the day before a planned PCI [165–167]. Prolonged treatment with clopidogrel (beyond 1 month) in patients with stable IHD is recommended after use of DES. There is presently no consensus on the optimal duration of dual antiplatelet therapy after DES but many physicians empirically recommend prolonged treatment up to 1 year, particularly after stenting of complex or multiple lesions. The impact of possible resistance to antiplatelet agents requires further investigation [168]. Glycoprotein IIb/IIIa inhibitors, the most potent antiplatelet drugs that block the fibrinogen receptor, were proven beneficial in high-risk PCI, particularly during acute coronary syndromes [169,170]. Given the overall low risk of PCI in stable IHD patients, the potential of glycoprotein IIb/IIIa receptor inhibitors of increasing the risk of bleeding complications and the considerable cost of their systematic use, they are not a part of standard periprocedural medication but should be considered in complex or high-risk procedures [171,172]. Unfractionated heparin is given as an intravenous bolus either under activated clotting time guidance or in a weight-adjusted manner (usually 100 IU/kg or 50 IU/kg if glycoprotein IIb/IIIa receptor inhibitor is given). Continued heparinization after completion of the procedure, either preceding or following arterial sheath removal, is not recommended. Low-molecular-weight heparins are considered to be more predictable anticoagulants than unfractionated heparin but data on their use as sole anticoagulant during PCI in stable IHD patients are limited. Bivalirudin is a direct thrombin inhibitor with short-lasting effect that should be used in patients with heparin-induced thrombocytopenia [173]. Bivalirudin monotherapy and provisional glycoprotein IIb/IIIa blockade provided comparable outcome to heparin plus planned glycoprotein IIb/IIIa inhibition [174–176]. The value of bivalirudin as first-choice anticoagulant during PCI is being assessed (ACUITY trial).

Post-procedural pharmacological treatment

Patients with chronic IHD undergoing PCI should benefit from secondary prevention measures [177] and hospital admission should be taken as an opportunity to implement changes in risk profile and to optimize pharmacological treatment. Surveys indeed indicate that ACE inhibitors and statins are underused in patients undergoing PCI [102].

Special devices and adjunctive technology

Atheroablative and debulking techniques

High-speed (140 000–180 000 rpm) diamond-burr rotablation pulverizes the atheroma. This technology is helpful in fibrotic or heavily calcified lesions that cannot be crossed by a balloon or adequately dilated before planned stenting [178]. Directional coronary atherectomy can remove obstructive plaque but has not proven clinically

beneficial [179,180]. The procedure is technically demanding, potentially associated with increased complication rates and of questionable value in specific lesion subsets (ostial and bifurcation stenoses). Cutting balloons create longitudinal plaque incisions and are marginally useful during the treatment of in-stent restenosis to avoid slippage of balloons at inflation.

Vascular brachytherapy

In-stent restenosis is due to intimal hyperplasia within metallic stents. In several randomized clinical trials, intracoronary brachytherapy showed significant improvement in angiographic and clinical outcome in native coronary arteries and in saphenous venous bypass grafts [115]. However, late thrombosis and late recurrence progressively reduce the initial benefit [116–118]. With the use of DES for both *de novo* stenting and the treatment of restenosis after bare-metal stenting, the indications for the more complex brachytherapy procedure are disappearing.

Intravascular ultrasound

By providing a cross-sectional quantifiable image of the lumen, plaque and vessel wall, intravascular ultrasound is a valuable adjunct to angiography, but its systematic use did not translate into a measurable reduction of major adverse clinical endpoints after PCI [181–183]. New developments include the analysis of the differential radiofrequency signals emitted by the various plaque components, a potentially useful application for plaque characterization [184].

Drug-eluting stents

DES using a wide variety of drugs and polymers have yielded opposing results indicating that not all approaches will uniformly prevent restenosis. Randomized clinical trials have shown positive angiographic and clinical results with the sirolimus- and the paclitaxel-eluting stents, initially in low-risk subjects and favourable lesion subsets (see Table 15.6) [120]. Compared with the use of bare metal stents, DES reduce the rate of major adverse cardiac events by 58% from 16.4 to 7.8%, a difference driven by a 74% reduction in the need for repeat revascularization. As the evidence is accumulating, indications for the use of DES are extended to small vessels, chronic total occlusions, bifurcational and ostial lesions, vein graft disease and in-stent restenosis.

Because stenting with DES now seems to confer durable results from the onset, indications for PCI are expanding to patient and lesion subsets that would otherwise require bypass surgery. Indeed, randomized clinical trials comparing PCI using DES with CABG in patients with unprotected left main stenosis and multivessel disease, particularly in the presence of diabetes, are ongoing. Similar to metallic stents, the major drawback of DES is (sub)acute stent thrombosis, an unpredictable event that is often accompanied by acute ischaemia and myocardial infarction. In pivotal randomized trials the rate of stent thrombosis varies between 0.6 and 1.6%, no different from the rate with bare stent controls [185,186]. Case reports of late (beyond 1 year) thrombosis shortly after interruption of clopidogrel, ticlopidine or aspirin treatment [187,188] suggest that the time window might be longer for DES than for metallic stents. Because of the perceived need for prolonged (3–6 months) prescription of aspirin and clopidogrel in order to avoid stent thrombosis, metallic stents are still preferred in patients scheduled to undergo extracardiac surgery.

Conclusions

PCI can be considered a valuable initial mode of revascularization in all patients with stable IHD and objective ischaemia in the presence of almost every lesion subset, with one exception: chronic total occlusions that cannot be crossed. The use of metallic stents and newer adjunctive medications has improved the procedural outcome after PCI. With DES, greater durability of the initial result is granted, now that the angiographic restenosis rate has declined below 10%. Until the results of proper randomized clinical trials become available, PCI should be used with reservation in diabetics with multivessel disease and in patients with unprotected left main stenosis. Therefore the decision to recommend PCI or CABG will continue to be guided by technical improvements in cardiology or surgery, local expertise and patients' preference [189].

Personal perspective

Angina is a common and disabling condition. We believe that secondary prevention is the way forward. Not only drugs but life-style modification is where the major opportunities lie in terms of preventing cardiovascular events in this patient population. We must also make every endeavour to develop new strategies and treatments to improve outcome, but we must ensure that properly tested measures and treatments are put into clinical practice. Undoubtedly there will be significant technological advances in operative techniques and in the deployment of new devices for percutaneous coronary intervention and cardiac surgery. However, although of considerable importance in improving symptoms and quality of life, these will be unlikely to play a major role in delaying or preventing cardiac events. While gene/stem-cell therapy provides a 'new frontier' and an exciting approach to treatment of atherosclerotic disease, any investment in this research has so far paid few dividends and we believe that it is unlikely to do so for some years to come.

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Chapter 15: Management of Angina Pectoris - UPDATES

Since the publication of the book, the following updates have been made to the online version of this chapter.

In the final paragraph under the heading:

Drugs to improve outcomes in angina (secondary prevention)
Antiplatelet agents

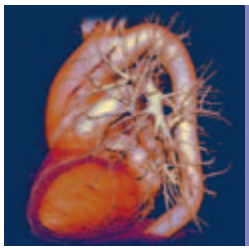
The text:

'Clopidogrel has an established role in acute coronary syndrome . . . thrombin inhibitors are not indicated in stable angina.'

has been updated with the following text:

Clopidogrel has an established role in acute coronary syndrome (unstable angina and Non ST-segment elevation myocardial infarction (NSTEMI)) and in percutaneous coronary intervention (PCI). It has also recently been approved for use 'as early as possible after symptoms start . . .' in patients with ST segment elevation myocardial infarction (STEMI). The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) study has established that there is no benefit overall of the combination of clopidogrel and aspirin in the long-term in patients with stable vascular disease. Adverse effects with clopidogrel are not dissimilar to aspirin but the frequency of severe rash is higher. Dipyridamole or anticoagulants such as warfarin or thrombin inhibitors are not indicated in stable angina.

2 January 2007



16 Myocardial Disease

Otto M. Hess, William McKenna and Heinz-Peter Schultheiss, with co-authors Roger Hullin, Uwe Kühl, Mathias Pauschinger, Michel Noutsias and Srijita Sen-Chowdhry

Summary

Diseases of the myocardium can be divided into three different forms: primary myocardial disease (the cardiomyopathies), inflammatory myocardial disease (myocarditis) and secondary myocardial diseases. There is a large overlap between the three different forms. Furthermore, primary myocardial diseases are mainly genetically transmitted, whereas inflammatory and secondary myocardial diseases are mostly acquired.

Definition and classification

Primary myocardial diseases are described as cardiomyopathies. These are defined as disease of the myocardium associated with cardiac dysfunction. They are divided into five different groups (Fig. 16.1).

Inflammatory myocardial disease is defined as inflammation of the myocardium and its structures caused by infectious and non-infectious agents. The inflammation may involve the myocytes, interstitium, vessels and/or pericardium. However, inflammation of the endocardium (endocarditis) is a disease on its own and is described in Chapter 22.

Secondary myocardial diseases are defined as disease of the myocardium of known origin. There are seven subgroups:

1 ischaemic cardiomyopathy;
2 hypertensive cardiomyopathy;
3 valvular cardiomyopathy;
4 alcoholic cardiomyopathy;
5 metabolic cardiomyopathy;
6 muscular dystrophy cardiomyopathy;
7 peripartum cardiomyopathy.

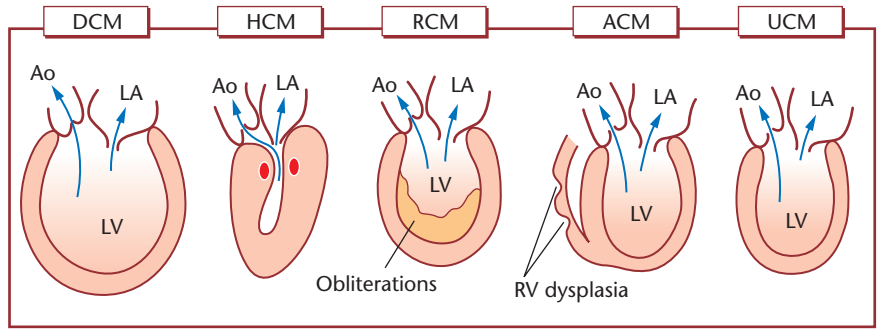


Figure 16.1 Classification of cardiomyopathies based on a report of the World Health Organization and International Society and Federation of Cardiology [38]. DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy; ACM, arrhythmic cardiomyopathy; UCM, unclassified cardiomyopathy.

Primary myocardial disease (cardiomyopathies)

Hypertrophic cardiomyopathy

Definition, aetiology and prevalence

The first account of hypertrophic cardiomyopathy (HCM) dates back to Donald Teare in 1958 who reported a common finding of asymmetric hypertrophy in the hearts of nine victims of sudden death from six families. Histological assessment of the myocardium revealed muscle bundles in different orientations separated by connective tissue. This seminal case series highlighted four cardinal features of the disease: unexplained hypertrophy of the left ventricle, myocyte disarray, familial occurrence and an association with sudden cardiac death (SCD). The pathological description coincided with growing awareness of left ventricular outflow tract obstruction (LVOTO) in young people without aortic valve disease, an entity then termed 'idiopathic hypertrophic subaortic stenosis'. Over the next two decades it became clear that neither the asymmetric distribution nor the presence of obstruction was necessary for a diagnosis of HCM; concentric, apical and eccentric patterns of hypertrophy are well recognized, while LVOTO has both clinical and prognostic importance but is present in less than one-quarter of these patients.

A milestone in the understanding of HCM came with the identification of mutations in the cardiac β-myosin heavy chain gene [1] (see Chapter 7). Later, other sarcomeric proteins were implicated in HCM, including α-tropomyosin, cardiac troponin T, troponin I, myosin-binding protein C, regulatory myosin light chain, essential myosin light chain, cardiac actin, titin, cardiac α-myosin heavy chain and troponin C. This led to the concept that HCM is a disease of the sarcomere, the contractile apparatus of the cell. Analysis of genotype–phenotype correlations demonstrated that hypertrophy is not essential for diagnosis, e.g. mutations in troponin T may be associated with subtle or no hypertrophy but a high incidence of SCD [2]. This established the view of HCM as an inherited heart muscle disorder caused by mutations in sarcomeric proteins, resulting in myocyte disarray, with or without fibrosis, myocardial hypertrophy and small-vessel disease (narrowing of intramural coronary arteries by medial thickening). The most common pattern of inheritance is autosomal dominant. Penetrance is incomplete and age-related: 55% for those aged 10–29 years, 75% for those aged 30–49, and 95% in gene carriers over the age of 50 [3].

Recently, attention has focused on non-sarcomeric variants of HCM, termed 'phenocopies'. The prevalence of HCM in the adult population is estimated at 1 in 500. However, only about 60% of adults with HCM have mutations in sarcomeric genes. A small proportion of the remainder may have unknown defects in components of the sarcomere, but this is unlikely to fully account for the discrepancy. Indeed, the majority of young children with left ventricular hypertrophy (LVH) do not have sarcomeric disease but rather metabolic disorders, mitochondrial cytopathies and syndromes with characteristic extracardiac features, disease states that may exist in adults with apparent HCM. Routine measurement of plasma α-galactosidase A levels among adult male HCM patients demonstrated a 4% prevalence of previously undiagnosed Anderson–Fabry disease [4]. Similarly, Danon's disease, another X-linked lysosomal defect, was identified in 1% of HCM index cases by DNA testing [5].

Timely detection of cardiac phenocopies of HCM is important. First, the cardiac profile is frequently distinct from that of sarcomeric HCM, with an increased incidence of conduction disease and progression to cavity dilation and heart failure. Management of these disorders also requires vigilance for extracardiac complications, such as skeletal myopathy, renal impairment and neurological involvement. Furthermore, specific therapies such as enzyme replacement in Fabry's disease may alter the natural history of the disease. Finally, recognition of recessive, X-linked and mitochondrial patterns of inheritance has major implications for familial assessment.

Towards a unifying hypothesis for the pathogenesis of HCM

The clinical, pathological and genetic diversity of HCM therefore precludes a comprehensive definition. LVH may be subclinical; myocyte disarray is present in Noonan's syndrome and Friedreich's ataxia but otherwise rare among the phenocopies; and a broad spectrum of genetic defects can give rise to HCM (Table 16.1).

That a single unifying mechanism may underlie sarcomeric HCM and the cardiac phenocopies is an attractive concept. One of the first attempts to define the primary dysfunction in HCM was the contractile deficit hypothesis [6]. It was theorized that the various sarcomeric mutations result in diminished contractility of cardiac myocytes. This in turn leads to increased cell stress, which induces production of trophic and mitotic factors that ultimately cause hypertrophy, myocyte disarray and fibrosis. Cytoskeletal function is impaired in dilated cardiomyopathy and after myocardial infarction, but preserved in HCM, accounting for the absence of cavity dilation in the latter. Early supporting evidence

Table 16.1 Disease-causing genes in hypertrophic cardiomyopathy (HCM) and phenocopies

Sarcomeric mutations (?ineffective ATP utilization)
β-Myosin heavy chain
α-Tropomyosin
Troponin T
Troponin I
Myosin-binding protein C
Regulatory myosin light chain
Essential myosin light chain
Cardiac actin
Titin
α-Cardiac myosin heavy chain
Troponin C
Metabolic diseases
?Reduced substrate for ATP synthesis
Glycogen storage diseases
Phosphorylase B kinase deficiency
CD36 and carnitine deficiencies
?Reduced activity of respiratory chain enzymes
Anderson–Fabry disease
?Impaired regulation of ATP
AMP kinase
Other
Danon's disease (LAMP-2 mutation)
Mitochondrial cytopathies
?Interference with ATP synthesis
MELAS, MERRF, LHON
Friedreich's ataxia (deficiency of frataxin, a key activator of mitochondrial energy conversion)
?Interference with ATP transport
Senger's syndrome
Syndromic HCM
Tyrosine phosphatase (Noonan's and LEOPARD syndromes)

LEOPARD, *l*entigines, *e*lectrocardiogram abnormalities, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormalities of the genitalia, *r*etardation of growth, and *d*eafness; LHON, Leber's hereditary optic neuropathy; MELAS, mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes; MERRF, myoclonic epilepsy and ragged red fibres.

came primarily from *in vitro* studies demonstrating reduced contractility of cells expressing β-myosin heavy chain and troponin T mutations [7,8]. Conversely, several mutations in β-myosin heavy chain are associated with enhanced enzymatic and mechanical properties [9], troponin T mutants show enhanced thin filament motility [10,11], and mutant α-tropomyosin may allow increased force output at submaximal calcium concentrations [12]. Non-sarcomeric HCM is also less easily explained on the basis of diminished contractile performance.

More recently, Ashrafian *et al*. [13] have postulated a central role for compromised cellular energetics in the development of HCM and related phenotypes. The energy deficit may result from an aberration at any point along the pathway of ATP synthesis, transfer, regulation and expenditure.

- Abnormalities in the handling of glycogen (e.g. phosphorylase B kinase deficiency), glucose or fatty acids (e.g. CD36 and carnitine deficiencies) reduce the substrate available for ATP production.
- The mitochondrial cytopathies and Friedreich's ataxia may interfere with ATP synthesis [14].
- Senger's syndrome, characterized by HCM, congenital cataracts and lactic acidosis, is associated with low activity of mitochondrial adenine nucleotide translocator 1, responsible for ATP transport out of the mitochondria.
- Mutations in AMP-activated protein kinase, the cellular fuel gauge, have been linked to HCM with pre-excitation, conduction system disease and a propensity towards early cavity dilation and systolic impairment [15].
- Emerging data suggest that lysosomal storage of glycosphingolipids in Fabry's disease may cause reduced activity of respiratory chain enzymes [16].
- The sarcomeric mutations have differing effects on contractility, but inefficient ATP utilization is a shared consequence.

Finally, the cellular energy deficit impairs the functioning of the sarcoplasmic reticulum calcium reuptake pump. The prolonged cytosolic calcium transient may serve as the signal that triggers cellular hypertrophy, although the exact pathway remains to be unravelled. Indeed, genetic defects that produce an HCM-like phenotype by an unknown mechanism may turn out to be components of the downstream signalling pathway. An example is tyrosine phosphatase non-receptor-type II protein, which has been implicated in both Noonan's syndrome and LEOPARD syndrome (*l*entigines, *e*lectrocardiogram abnormalities, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormalities of the genitalia, *r*etardation of growth, and *d*eafness).

The energy depletion hypothesis represents an attempt to reconcile the contrasting effects of the sarcomeric mutations on cellular contractility, and additionally succeeds in accounting for many of the cardiac phenocopies of HCM. Supporting evidence is emerging; magnetic resonance spectroscopy of mutations in β-myosin heavy chain, troponin T and myosin-binding protein C found significant reductions in the cardiac phosphocreatine to ATP ratio, an indicator of myocardial energy status [17]. Energetic abnormalities are also observed in ischaemic heart disease and heart failure, and have been considered

a consequence of hypertrophy rather than the primary defect. However, the presence of the bioenergetic deficit in non-penetrant gene carriers without hypertrophy argues against a secondary phenomenon [18]. Nevertheless, the value of any unifying paradigm is contingent on its relevance in the clinical arena. Grouping the sarcomeric mutations together remains meaningful owing to similarities in clinical presentation, risk stratification and management. Accordingly, validation of the energy depletion hypothesis awaits diagnostic and therapeutic applications. From a clinical standpoint, many disorders associated with unexplained hypertrophy have little in common with sarcomeric HCM, and are more usefully approached as distinct disease entities.

Pathophysiology

The main functional consequences of HCM are as follows.

DIASTOLIC DYSFUNCTION

Both the active and passive phases of diastole are abnormal in HCM. Isovolumetric relaxation in early diastole requires energy-dependent calcium uptake in the sarcoplasmic reticulum and is prolonged in HCM. Myocyte disarray, cellular energy deficit and altered affinity of mutant sarcomeric proteins for Ca^{2+} are all potential factors. Increased pressures are a corollary of ventricular filling prior to completion of active relaxation. Subendocardial ischaemia is both a contributor to diastolic dysfunction and a consequence of it, since the delay in pressure decay may result in diminished endocardial coronary blood flow.

Passive relaxation during ventricular filling in late diastole is determined by compliance. Both hypertrophy and interstitial fibrosis cause increased chamber stiffness in HCM, again resulting in increased filling pressures and reduced coronary blood flow.

Limited exercise capacity is common in HCM. Decreased time for filling at high heart rates, combined with impaired compliance, leads to a reduction in end-diastolic volume. This limits the ability of the left ventricle to augment stroke volume via the Frank–Starling mechanism. Chronotropic incompetence is common in HCM.

ISCHAEMIA

Reduced coronary flow reserve is well recognized in HCM; baseline coronary velocity is elevated compared with normal subjects, while velocities during hyperaemia are similar [18]. Systolic extravascular compression may play a role but does not wholly account for the deficiency, since the diastolic coronary vasodilator reserve is also diminished [19]. Changes in the coronary microcirculation have been implicated: arteriolar lumen area is smaller and capillary density is less, both parameters showing an inverse relationship with LVH [18]. Increased coronary conductance is thought to be related to higher oxygen demands of LVH. However, vascular medial hypertrophy and lack of capillary growth preclude increments in coronary conductance during hyperaemia.

LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

LVOTO, once the defining feature, is present in around 25% of HCM. Obstruction may also occur at mid-cavity level, or distally in the form of apical obliteration. Subaortic LVOTO, with systolic anterior movement (SAM) of the mitral valve, is the commonest form and the most amenable to treatment.

Mechanism of SAM Current thinking dictates that two conditions facilitate SAM: (1) abnormal valve apparatus with sufficient slack in the leaflets to allow movement; and (2) a haemodynamic force with an anterior component during systole.

Primary structural abnormalities of the mitral valve apparatus have been observed in patients with obstructive HCM, the most important of which is anterior displacement of the papillary muscles (Figure 16.2) [20]. This predisposes to SAM by (1) reducing the posterior tension conferred by the papillary muscles on the mitral valve; (2) increasing the proximity of the leaflets to the

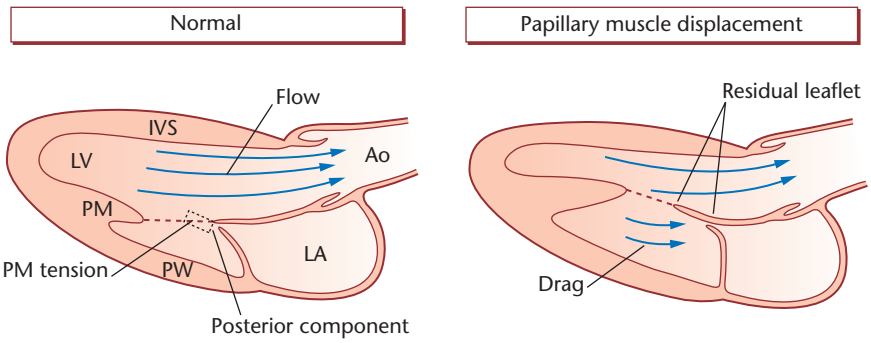


Figure 16.2 Anterior displacement of the papillary muscles in hypertrophic cardiomyopathy. Ao, aorta; IVS, interventricular septum; LA, left atrium; LV, left ventricle; PW, posterior wall. Reproduced with permission from Levine *et al.* [20].

left ventricular outflow stream; and (3) pulling the posterior leaflet upwards so that it meets the anterior leaflet near its mid-portion, thereby leaving a long portion of the distal leaflet unrestrained and susceptible to anterior forces. Incomplete coaptation of the leaflets also results in posteriorly directed mitral regurgitation. A central or anterior mitral regurgitant jet raises suspicion of intrinsic mitral valve disease.

The nature of the haemodynamic force has been subject to much debate [21]. Originally, SAM was thought to be due to the Venturi effect, which refers to the increase in velocity and concomitant decrease in pressure that occurs as fluid flows through a constriction. An object in the path of the fluid is subject to a force perpendicular to the direction of flow that pulls it into the stream. Thus, as blood is ejected into the narrow outflow tract in systole, it accelerates and a reduction in the static pressure occurs. The pressure difference thereby created pulls the mitral valve leaflet towards the septum.

Alternatively, the flow drag effect, i.e. the force exerted by a fluid in the direction of flow, may be involved. Thus, blood ejected into the LVOT pushes the free residual leaflet anteriorly. Doppler echocardiography suggests that SAM begins very early in systole, when the outflow tract velocity is normal [20]. The relatively low velocity is unlikely to generate significant Venturi forces; conversely, there will be increased contact of the flowing blood with the valve, augmenting the drag effect. Flow drag may therefore be the dominant hydrodynamic mechanism for SAM, although Venturi forces may also contribute as blood velocity in the outflow tract increases during systole.

ABNORMAL VASCULAR RESPONSES

In normal subjects, cardiac output rises during exercise. At high heart rates, filling time is reduced and augmentation of left ventricular end-diastolic volume requires increased venous return. This is dependent on constriction in non-exercising venous capacitance beds, which compensates for the vasodilation occurring in exercising muscle. The importance of this mechanism may be greater with HCM and diastolic dysfunction, which precludes adequate ventricular filling at high heart rates. Peripheral vasoconstriction is mediated by increased sympathetic stimulation during exercise, and partially attenuated by a number of vasodilatory influences, including stretch-induced activation of arterial baroreceptors and cardiac mechanosensitive receptors, and release of atrial and brain natriuretic peptides.

Around 30% of patients with HCM fail to increase their systolic blood pressure by ≥ 25 mmHg during exercise, or show a paradoxical fall in blood pressure of ≥ 20 mmHg. The inappropriate vasodilator response has been ascribed to excess stimulation of left ventricular mechanoreceptors by abnormal wall stress, due to myocyte disarray and fibrosis, exaggerated sensitivity of arterial baroreceptors and raised levels of natriuretic peptides [22].

ARRHYTHMIA

Triggers for ventricular arrhythmia in HCM include ischaemia, LVOTO, vascular instability and cellular energy depletion, while myocyte disarray and fibrosis provide the arrhythmogenic substrate. Non-sustained ventricular tachycardia (VT) occurs in around 20%. In contrast, sustained VT is rare and raises suspicion of a left ventricular apical aneurysm, sometimes seen in patients with mid-cavity obstruction.

Atrial fibrillation (AF) is linked with left atrial dilation, which is often associated with mitral regurgitation and LVOTO. As the most common sustained arrhythmia in HCM, chronic or paroxysmal AF is observed in 20–25%; subclinical AF may occur even more frequently. The prevalence of AF increases with advancing age.

WALL THINNING AND CAVITY DILATION

A decrease in left ventricular wall thickness was previously documented in up to 15% over 3 years [23]. Over a longer follow-up period, wall thinning ≥ 5 mm was noted in 60% of patients with severe LVH, accounting for the rarity of marked LVH in the elderly [24]. The mechanisms underlying left ventricular remodelling in HCM remain to be elucidated, although it is likely that ischaemia, compromised energetics and injury from abnormal haemodynamic loading lead to myocyte loss and fibrosis. However, cavity dilation and systolic impairment are infrequent, occurring in less than 5% of patients with HCM.

Clinical presentation

Clinicians should be alert to the possibility of HCM in a variety of circumstances (Table 16.2).

Diagnostic testing

Diagnostic testing should include a 12-lead ECG and echocardiography (Table 16.3). Family members will require assessment. Annual review is recommended from early adolescence, since the clinical manifestations of HCM frequently develop during pubertal growth. Relatives without evidence of disease at physical maturity were traditionally considered to be unaffected. However, growing recognition of late-onset HCM has led to the recommendation that adult relatives are offered continued evaluation on a 5-yearly basis [25]. Children below the age of puberty are usually assessed only if they are

Mode of presentation	Common aetiologies
Chest pain	Ischaemia, LVOTO
Exertional dyspnoea	Diastolic dysfunction
Reduced exercise capacity	LVOTO, systolic impairment, atrial fibrillation with uncontrolled ventricular response rate
Palpitation	Supraventricular arrhythmia (SVT, AF), ventricular arrhythmia (frequent VPBs, NSVT)
Syncope/presyncope	Supraventricular arrhythmia, LVOTO, vasovagal, ventricular tachyarrhythmia, vascular instability
Cardiac arrest	Ventricular tachyarrhythmia, supraventricular arrhythmia (e.g. AF) triggering VF, bradyarrhythmia, electromechanical dissociation
Incidental finding on health screen	
Familial evaluation	

AF, atrial fibrillation; LVOTO, left ventricular outflow tract obstruction; NSVT, non-sustained ventricular tachycardia; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VPB, ventricular premature beat.

Table 16.2 Clinical presentation of hypertrophic cardiomyopathy and underlying mechanisms

Echocardiography

Major criteria

LV wall thickness ≥ 13 mm in the anterior septum or
≥ 15 mm in the posterior septum or free wall
Severe SAM (septum–leaflet contact)

Minor criteria

LV wall thickness of 12 mm in the anterior septum or posterior wall or of 14 mm in the posterior septum or free wall
Moderate SAM (no septum–leaflet contact)
Redundant mitral valve leaflets

Electrocardiography

Major criteria

Left ventricular hypertrophy and repolarization changes
T-wave inversion in leads I and aVL (≥ 3 mm) (with QRS–T wave axis difference ≥ 30°), V3–V6 (≥ 3 mm) or II and III and aVF (≥ 5 mm)
Abnormal Q (> 40 ms or > 25% R wave) in at least two leads from II, III, aVF (in absence of left anterior hemiblock), V1–V4; or I, aVL, V5–V6

Minor criteria

Complete bundle branch block or (minor) interventricular conduction defect (in LV leads)
Minor repolarization changes in LV leads
Deep S V2 (> 25 mm)
Unexplained chest pain, dyspnoea or syncope

Guidelines are applicable only to first-degree relatives of index cases with confirmed hypertrophic cardiomyopathy, all of whom have a 50% probability of carrying the mutation. Diagnosis is established in the presence of 1 major criterion, or 2 minor echocardiographic criteria, or 1 minor echocardiographic plus 2 minor electrocardiographic criteria. Other causes of left ventricular hypertrophy (e.g. athletic training and hypertension) may confound diagnosis.
LV, left ventricular; SAM, systolic anterior motion of the mitral valve.

Table 16.3 Guidelines for the diagnosis of familial hypertrophic cardiomyopathy

Table 16.4 Characteristic ECG findings in hypertrophic cardiomyopathy (HCM)

Left-axis deviation
Left bundle branch block
Pathological Q waves in inferolateral leads
T-wave inversion (commonly in inferolateral leads)
ST-segment changes
Criteria for left atrial enlargement
Giant negative T waves in V3–V5 or V4–V6 (distal HCM)

symptomatic, have a high-risk family history, participate in competitive sports, or when there is heightened parental anxiety.

The other issue pertaining to familial assessment is the need for sensitive diagnostic criteria. Systematic evaluation of patients with known disease-causing mutations has identified a sizeable subset (20–50%) who do not fulfil conventional echocardiographic criteria for HCM, but who nevertheless show discernible abnormalities on ECG and echocardiography. Since autosomal dominant inheritance implies a 50% probability of any first-degree relative carrying the gene, minor abnormalities are more likely to represent disease expression than in the general population (Table 16.3) [26].

Characteristic ECG findings in HCM are summarized in Table 16.4. Voltage criteria for LVH seldom occur in isolation in HCM, but are common in normal adolescents and young adults. Pre-excitation is a recognized feature, particularly in conjunction with mutations in AMP kinase; however, a short PR interval with a slurred QRS upstroke is not infrequently observed in HCM patients without accessory pathways.

Echocardiography is the first-line investigation for assessing wall thickness, cavity dimensions, systolic and diastolic function, and outflow tract obstruction. Exercise echocardiography is of value in patients with chest pain, dyspnoea or presyncope for determining dynamic LVOTO. Tissue Doppler imaging is a useful adjunct for identifying regional abnormalities in systolic and diastolic function and changes in long-axis function, particularly in subclinical forms of the disease. Although the original diagnostic criteria for HCM stipulated left ventricular wall thickness ≥ 15 mm, any degree and distribution of LVH may be present. Considerable attention has been focused on the difficulty in distinguishing morphologically mild HCM (wall thickness 13–14 mm) from hypertrophy in athletes. Diagnosis of HCM is facilitated by the presence of repolarization abnormalities or pathological Q waves on the ECG. Echocardiography may be helpful as the left ventricular cavity is commonly enlarged in athletes but small in HCM; diastolic function is normal or enhanced in athletes but usually impaired in HCM; and left atrial size is normal in athletes but often increased in HCM.

Patients with a confirmed diagnosis of HCM should undergo exercise testing on an annual basis. An abnormal blood pressure response is a risk factor for sudden death, although its prognostic impact appears to be greatest in patients under 40 years of age. Simultaneous metabolic gas exchange measurements are useful for obtaining an objective assessment of exercise capacity. Metabolic exercise testing may be important in differentiating HCM from cardiovascular adaptation to training; athletes frequently demonstrate peak oxygen consumption > 120% of predicted, while over 98% of HCM patients show abnormal indices.

Holter ECG monitoring is recommended annually. Findings include paroxysmal AF, which merits antiarrhythmic therapy for suppression and/or anticoagulation, and non-sustained VT, a risk factor for sudden death. Extended monitoring with an event recorder or implantable loop recorder may be warranted in patients with symptoms suggestive of arrhythmia.

Management

Management of patients with HCM (Fig. 16.3) aims to alleviate symptoms, prevent complications (e.g. AF) and reduce sudden cardiac death.

MEDICAL THERAPY

Asymptomatic patients with mild LVH should not receive drug therapy, whereas asymptomatic patients with severe LVH should be treated with verapamil to improve relaxation and diastolic filling thereby lowering diastolic filling pressure [27–29].

Symptomatic patients should be first treated with verapamil, a calcium channel blocker that improves diastolic filling (positive lusitropic effect; Table 16.5) and reduces systolic outflow tract obstruction (negative inotropic

Table 16.5 Common agents and doses for treating hypertrophic cardiomyopathy

Calcium channel blockers
Verapamil 120 mg two to three times daily
Diltiazem 180 mg once or twice daily
Beta-blockers
Inderal 80 mg two to three times daily
Metoprolol 100–200 mg daily
Bisoprolol 5–10 mg daily
Antiarrhythmic drugs
Amiodarone 100–200 mg five times weekly
Disopyramide 100 mg three times daily or 200 mg twice daily

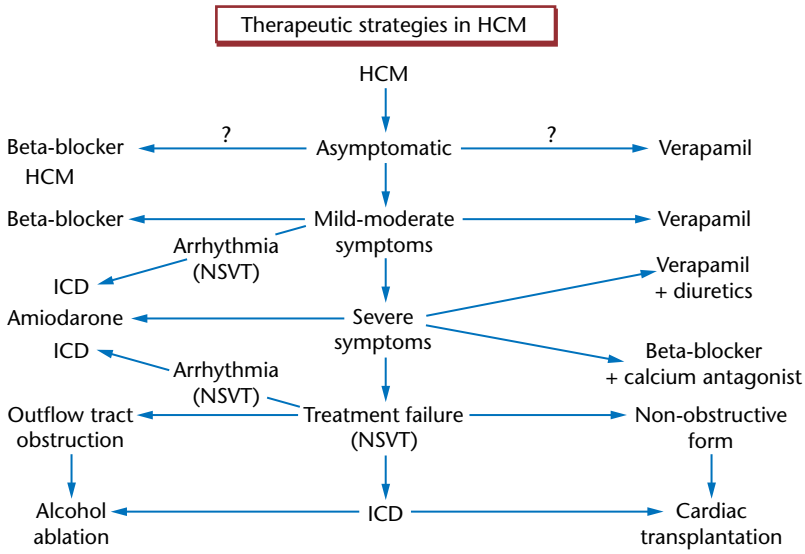


Figure 16.3 Treatment strategy in hypertrophic cardiomyopathy (HCM). ICD, implantable cardioverter-defibrillator; NSVT, non-sustained ventricular tachycardia. Reproduced with permission from Hess and Sigwart [30].

effect). As an alternative diltiazem may be used, although documentation is less extensive. If these drugs fail to improve symptoms, beta-blockers may be used either alone or in combination with a calcium channel blocker. Beta-blockers reduce outflow tract obstruction by their negative chronotropic and inotropic actions. Furthermore, the decrease in heart rate increases left ventricular size, which further reduces outflow tract gradient and increases diastolic filling time. However, these drugs exert no positive lusitropic effect and do not effectively improve diastolic function as do calcium channel blockers. Diuretics may be used in severely symptomatic patients to reduce filling pressure, although caution is recommended because these patients are sensitive to sudden volume changes. Volume sensitivity can be explained by the steep left ventricular pressure–volume curve, when a small drop in filling pressure reduces stroke volume and cardiac output dramatically. Diuretics may be used in combination with a beta-blocker or calcium channel blocker in order to reduce symptoms of pulmonary congestion.

Disopyramide, an antiarrhythmic drug that alters calcium kinetics, has been associated with symptomatic improvement and abolition of systolic pressure gradient. This effect has been attributed to its negative inotropic action and peripheral vasoconstriction. Nevertheless, long-term experience with this drug is limited.

Beta-blockers, calcium antagonists and the conventional antiarrhythmic drugs do not appear to suppress serious ventricular arrhythmias in HCM. However, amiodarone, which prolongs action potential duration and refractoriness of cardiac fibres, is effective in the treatment of both supraventricular and ventricular arrhythmias. Although it is believed that amiodarone improves prognosis and symptoms in HCM, only limited and inconclusive data are available. Amiodarone may be used in patients with supraventricular (AF) and ventricular tachyarrhythmias, although in severe cases implantation of a defibrillator may be mandatory.

Contraindications to medical treatment with calcium channel blockers or beta-blockers may be prolongation of the atrioventricular (AV) interval (risk of second- or third-degree AV block). Treatment with beta-blocking agents may be contraindicated in the presence of asthma bronchiale or chronic obstructive pulmonary disease.

Timing of therapy Treatment is indicated when the patient becomes symptomatic or LVH is severe. Refractoriness to medical therapy usually indicates progression of the disease. At this point more aggressive therapies such as alcohol ablation of the septum [30] or surgical septal myectomy are indicated. Double-chamber pacing for symptomatic relief and reduction of outflow tract obstruction has been used previously but is not recommended at present. However, insertion of an implantable cardioverter-defibrillator (ICD) is strongly advised in high-risk patients with severe LVH and a history of non-sustained or sustained tachyarrhythmias or syncopes [31]. Patients with severe LVH, recurrent syncopes, sustained and non-sustained ventricular tachyarrhythmias, a history of familial sudden cardiac death and a genetic phenotype for an increased risk of premature death should receive an ICD.

SURGICAL TREATMENT

Until recently, septal myectomy has been considered the treatment of choice for therapy-refractory patients with obstructive HCM [32,33]. Long-term follow-up after surgical myectomy has shown excellent results (Fig. 16.4)

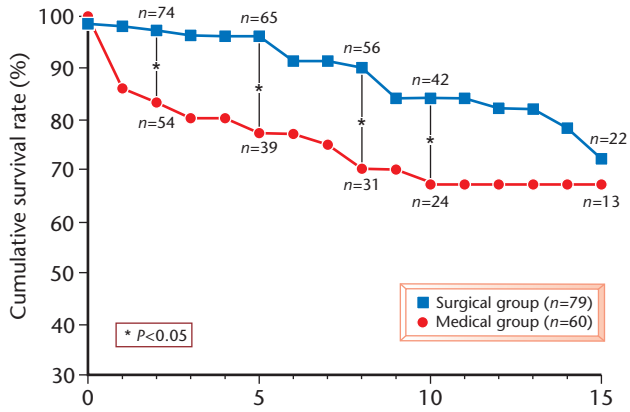


Figure 16.4 Cumulative survival rates of 139 patients with hypertrophic cardiomyopathy. Group 1, medical therapy ($n = 60$); Group 2, surgical therapy ($n = 79$). The average follow-up was 8.9 years for the entire study group, 8.2 years for Group 1 and 9.4 years for Group 2. Group 2 had higher 2-, 5-, 8- and 10-year survival rates than those of Group 1.

but ventricular remodelling with dilatation of the left ventricle may occur in 15–20% of patients. Alcohol ablation has changed this treatment strategy and surgical resection of the septum is reserved for selected cases with combined procedures such as coronary bypass grafting or mitral valve repair.

ALCOHOL ABLATION OF THE SEPTUM

Alcohol ablation of the ventricular septum can be considered to reduce LVOTO [34–36]. Outflow tract gradients of more than 30–50 mmHg at rest and 75–100 mmHg after provocation (extrasystole, isoproterenol infusion or amyl nitrite inhalation) are considered to qualify for septal ablation. With a small over-the-wire balloon catheter, 1–3 ml of pure alcohol are injected over 5 min into the first or second septal branch (Fig. 16.5) after identification of the correct ablation site by contrast echocardiography (Fig. 16.6).

Alcohol injection leads to a small myocardial infarction with a rise in creatine kinase (CK) of 500–1500 U/l. There is alcohol-induced septal hypokinesis, which leads to a reduction in outflow tract gradient (Fig. 16.7). In approximately one-third of patients the pressure gradient disappears immediately and in two-thirds after weeks or months (Fig. 16.8). Ventricular remodelling with a decrease in muscle mass and septal/posterior thickness takes 3–4 months.

Not all patients show a complete loss of outflow tract obstruction. Those who fail can be treated a second time. Complications include transient or permanent third-degree AV block (Fig. 16.9). Therefore, the procedure should not be done without a temporary pacemaker; 3–5% of all patients require definitive pacemaker implantation.

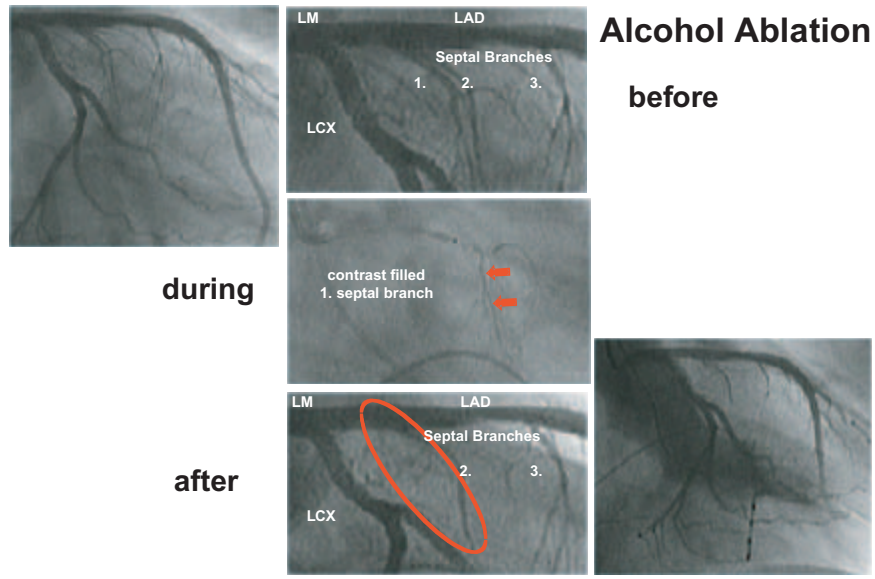


Figure 16.5 Coronary angiogram of the left coronary artery at high magnification. The left anterior descending (LAD) and left circumflex (LCX) coronary arteries can be clearly seen (top left) as well as the first (1), second (2) and third (3) septal branches (top middle). An over-the-wire balloon catheter is introduced into the first septal branch. The balloon is inflated and contrast material is injected (red arrows, middle panel) through the balloon catheter to identify the area at risk. Next, echocontrast (Levovist, Schering SA) is injected through the balloon catheter to identify the myocardial region in the two-dimensional echocardiogram. Pure ethanol is infused over 3–5 min, which leads to reduction or elimination of outflow tract obstruction. The last angiogram (bottom right) shows that the first septal branch has disappeared after alcohol injection (circle). LM, left main stem.

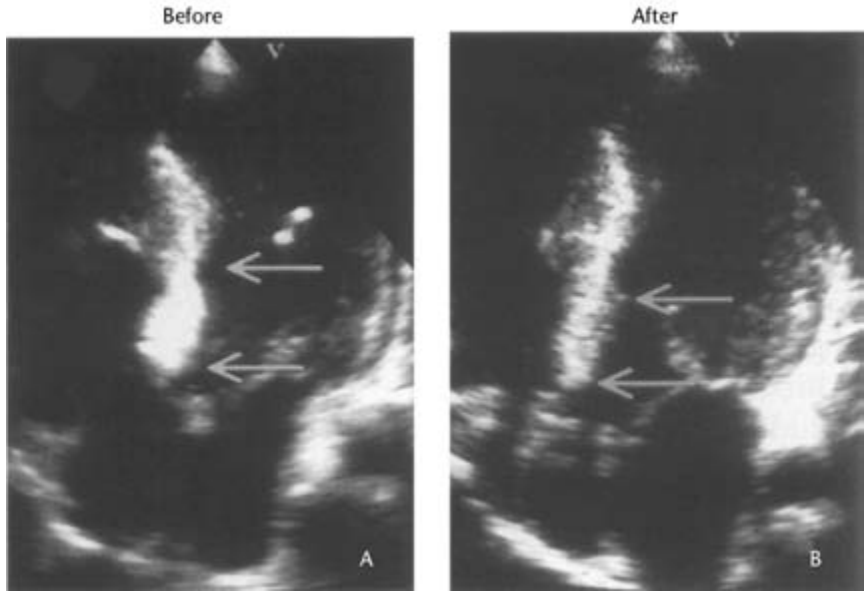


Figure 16.6 Two-dimensional echocardiogram before and after alcohol ablation. (A) Arrows indicate septal hypertrophy after injection of echocontrast medium. (B) Normalization of septal thickness 1 month after the intervention (arrows). Reproduced with permission from Faber *et al.* [36].

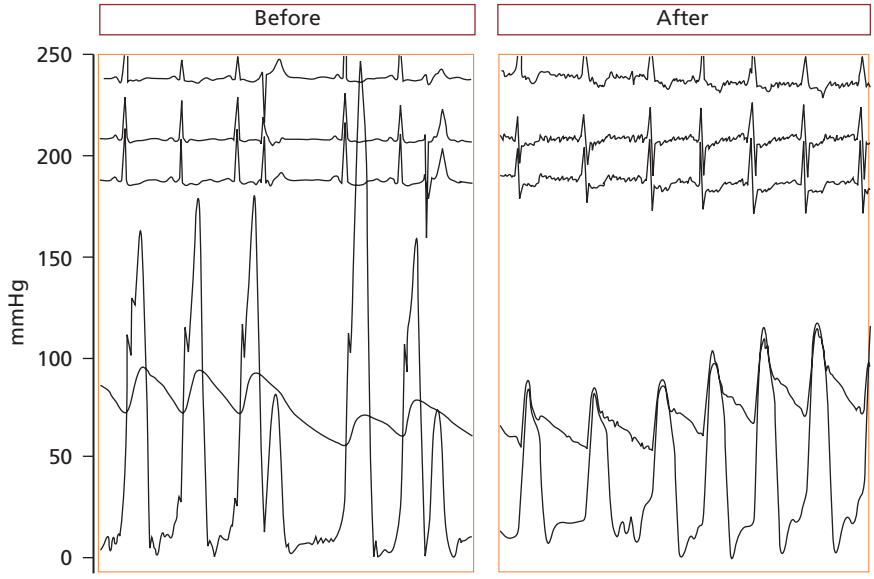


Figure 16.7 Pressure recording in a patient with hypertrophic cardiomyopathy before and after alcohol ablation of the septum. Before the intervention there is a large pressure gradient at rest (75 mmHg) and after post-extrasystolic potentiation (150 mmHg). The systolic pressure gradient disappears completely after alcohol ablation.

Complications

Sudden death is the most important threat for patients with HCM. Approximately 50–60% of those who die do so suddenly. Sudden death is assumed to be due to ventricular tachyarrhythmias, but haemodynamic factors and myocardial ischaemia may contribute. Young age (< 30 years) and a positive family history for cardiac arrest are risk factors for sudden cardiac death [37].

Syncopes may occur as a result of either arrhythmias or a sudden increase in outflow tract obstruction. Rapid changes in body position or strenuous exercise may lead to an increase in outflow tract obstruction because of a decrease in venous return with a decrease in cardiac volumes and an increase in outflow tract obstruction ('ASH-crash') or as a result of an increase in cardiac contractility with hypercontraction of the left ventricle (increase in outflow tract obstruction) and elimination of the left ventricular cavity (drop in cardiac output).

Strenuous exercise or competitive sports should be avoided because of the risk of sudden death. Typically, sudden death occurs during or after strenuous physical exercise.

AF as a cause of diastolic dysfunction, with increased filling pressure and dilatation of the atria, should be pharmacologically or electrically converted because of

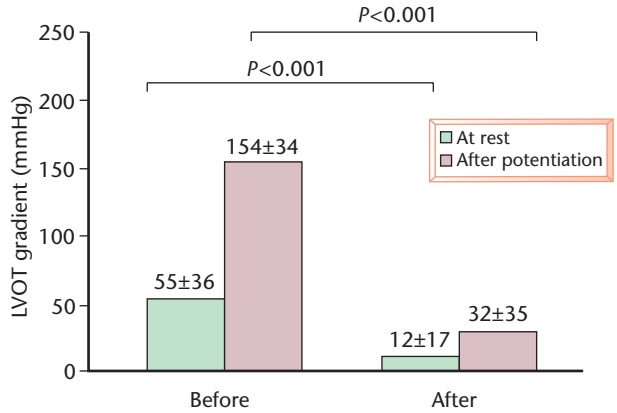


Figure 16.8 Left ventricular pressure gradient before and after alcohol ablation. Maximal pressure gradients are indicated at rest (first bar) and after post-extrasystolic potentiation (second bar). Data are shown at baseline (left bars) as well as 6 months after alcohol ablation (right bars). After the intervention there is a significant decrease in pressure gradients to one-quarter of the initial values.

the haemodynamic consequences of the loss of atrial contraction on cardiac output. If sinus rhythm cannot be reached, oral anticoagulation is mandatory when no contraindications exist.

Infective endocarditis may occur in about 5% of patients with HCM and antibiotic prophylaxis is indicated. Infection typically occurs on the aortic or mitral valve or on the septal contact site of the anterior mitral leaflet.

Prognosis and outcome

The clinical course in HCM is variable and may remain stable over years. However, HCM patients with risk factors such as a familial history of premature death, recurrent syncopes, septal thickness > 30 mm or a genetic phenotype with an increased risk of premature death may show a poor outcome [37]. Annual mortality rates have been reported to range between 2 and 3% but may be higher in children. Clinical deterioration is often slow but clinical symptoms are poorly related to the severity of outflow tract obstruction. Generally, symptoms increase with age. The occurrence of AF is an indicator of diastolic dysfunction with increased filling pressures and dilated atria. Timely conversion of AF is indicated.

Randomized clinical trials have not been undertaken, possibly because of the relatively low prevalence and the variability of the disease as well as the presence of symptomatic and asymptomatic patients. There is an urgent need for such randomized multicentre treatment trials.

Dilated cardiomyopathy

According to the WHO/ISFC Task Force on the Definition and Classification of Cardiomyopathies, the diagnosis of 'idiopathic' dilated cardiomyopathy (DCM) should only be made after exclusion of the specific cardiomyopathies [38]. Clinical evaluation alone does not allow reliable

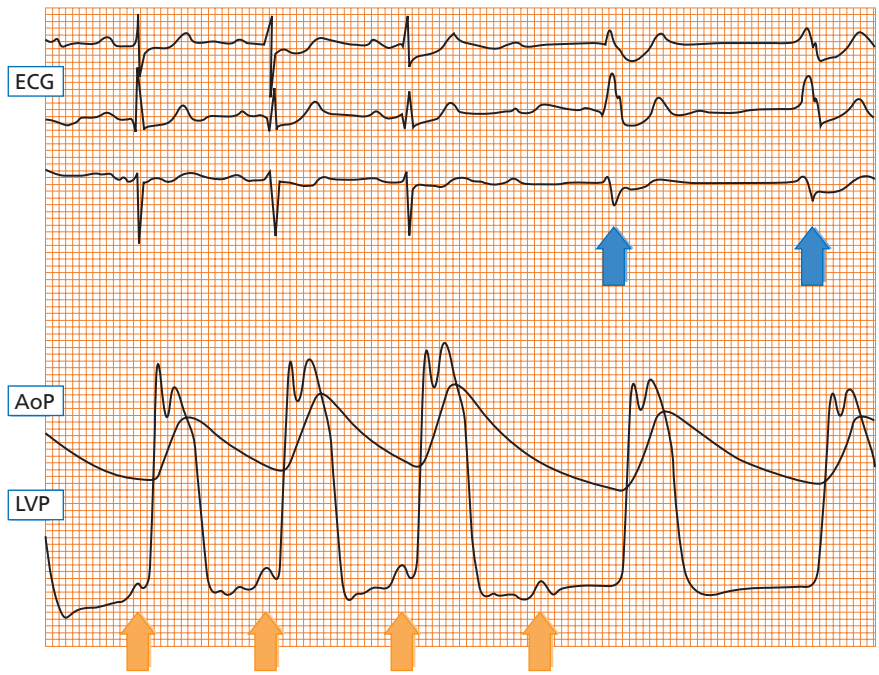


Figure 16.9 Simultaneous ECG and pressure recordings in a patient during alcohol ablation. Arrows indicate atrial contraction in the pressure curve (lower row). Occurrence of third-degree atrioventricular (AV) block can be seen after the fourth atrial beat, with a left ventricular escape rhythm (bundle branch block, dark arrows). Three to four minutes after the occurrence of third-degree AV block, normal sinus rhythm was restored. AoP, aortic pressure; LVP, left ventricular pressure.

segregation of specific cardiomyopathies, i.e. inflammatory, ischaemic and alcoholic cardiomyopathy, or cardiomyopathies associated with metabolic disorders [39–46].

Definition and prevalence

DCM is a chronic heart muscle disease characterized by cavity enlargement and impaired systolic function of the left or both ventricles (Table 16.6). The extent of myocardial dysfunction is not accounted for by abnormal loading conditions such as systemic hypertension or valve disease, previous infarction, ongoing ischaemia or sustained arrhythmia. The age-adjusted prevalence of DCM in the USA is 36 per 100 000 population.

Aetiology

Once considered idiopathic or sporadic, DCM is now recognized to be familial in at least 40–60%. Other factors linked with pathogenesis include anthracycline derivatives such as doxorubicin, and malnutrition, particularly thiamine and protein deficiencies. Many apparently secondary forms of DCM, notably alcoholic cardiomyopathy and peripartum cardiomyopathy, probably arise when incompletely penetrant genetic disease is unmasked by an additional insult to the myocardium (alcohol) or stress upon the cardiovascular system (pregnancy).

Table 16.6 Diagnostic criteria for dilated cardiomyopathy

1 Left ventricular ejection fraction < 0·45 (> 2SD) and/or fractional shortening < 25% (> 2SD), as ascertained by echocardiography, radionuclide scanning or angiography *and*
2 Left ventricular end-diastolic diameter > 117% of the predicted value corrected for age and body surface area, which corresponds to 2SD of the predicted normal limit + 5%
Exclusion criteria, which can lead to phenocopies
Systemic arterial hypertension (> 160/100 mmHg documented and confirmed at repeated measurements and/or evidence of target-organ disease)
Coronary heart disease (obstruction > 50% of the luminal diameter in a major branch)
History of chronic excess alcohol consumption, with remission of heart failure after 6 months of abstinence
Clinical, sustained and rapid supraventricular arrhythmias
Systemic diseases
Pericardial diseases
Congenital heart disease
Cor pulmonale

Reproduced with permission from Mestroni *et al*. [48].

The prevalence of familial DCM has been underestimated, because disease expression is frequently incomplete in family members. Prospective evaluation of the asymptomatic relatives of DCM patients revealed isolated left ventricular enlargement in 20%, mild contractile impairment in 6% and frank DCM in 3% [47]. Asymptomatic relatives with left ventricular enlargement showed histological and immunohistochemical changes similar to those with established disease, including myocyte pleomorphism, interstitial fibrosis and markers of inappropriate immune activation [41]. A proportion of relatives with minor abnormalities progressed to overt DCM, underscoring their importance as markers of early disease. Thus, relying on the family history alone is not adequate, and clinical screening of relatives is requisite for identification of familial cases.

A further issue is the variability of the phenotype in familial DCM, which may include arrhythmia, stroke, conduction system disease and sudden death in addition to ventricular dilation and dysfunction. Since the most common pattern of inheritance is autosomal dominant, first-degree relatives of DCM index cases have a 50% probability of being genetically affected, and the likelihood that mild unexplained features represent disease expression is high. Specific diagnostic criteria have been proposed for familial DCM [48]. Variable and age-related penetrance is a second impediment to recognition of familial cases. In one Italian series, penetrance was 10% in those less than 20 years old, 34% in those aged 20–30 years, 60% in those aged 30–40 and 90% in those over 40 [48]. This is compounded by the fact that the families seen in clinical practice are often small. Estimation of the true prevalence of familial DCM will therefore necessitate serial assessment of extended families over lengthy follow-up periods.

In those with no family history, DCM has been thought to be due to acute myocarditis. A triphasic model has been proposed, with an initial insult to the myocardium, followed by chronic inflammation, leading to ventricular remodelling and dysfunction [49]. The primary insult is believed to be a viral infection. Enteroviruses and adenoviruses are most commonly implicated. Although acute viral myocarditis is rapidly fatal in a small subset of patients, predominantly children, the majority recover without complications. Some will develop chronic inflammation as a corollary of viral persistence or triggered autoimmunity, with endomyocardial biopsies demonstrating lymphocyte infiltration and histological markers of immune activation. Studies employing polymerase chain reaction (PCR) techniques to detect viral ribonucleic acid in cardiac tissue have reported positive findings in up to 35% of DCM patients [49]. More recently, it was reported that a high proportion of patients with

the acute or healing phase of myocarditis or DCM have immunohistochemical evidence of enterovirus capsid protein VP1 in myocardial tissue, indicating translation of viral epitopes and a role for latent viral infection in pathogenesis [50]. In a small cohort of patients with left ventricular failure and viral persistence, 6-month therapy with β-interferon resulted in elimination of viral genomes and improvement in left ventricular function [44]. However, the demonstration of viral presence in DCM does not amount to a causal link, particularly as enteroviral genome has also been detected in patients with ischaemic heart disease [51].

The autoimmune model of DCM invokes a central role for the immune system in causing continued myocardial injury. During the initial viral infection, an effective immune response is critical in preventing fulminant myocarditis, with clinical markers of immunity such as anti-cardiac IgG correlating with a favourable outcome [49]. Unfortunately, tissue damage during this initial insult may result in the presentation of previously sequestered myocardial peptides to the immune system. Alternatively, molecular mimicry between viral proteins and endogenous myocardial antigens may result in an organ-specific autoimmune response. A third potential mechanism involves viral-induced expression of class II major histocompatibility complex (MHC) molecules in cardiac tissue, leading to presentation of self-peptides to infiltrating T cells and activation of organ-specific immunity. Evidence for inappropriate class II MHC expression has been found in endothelial and endocardial cells from cardiac biopsies of patients with DCM. Lending further support to the autoimmune hypothesis is the presence of circulating heart-reactive antibodies in 25–30% of patients with DCM and symptom-free relatives [52]. Of note, cardiac antibodies were more commonly found among relatives who showed disease progression, but frequently became undetectable during follow-up and in advanced DCM. A possible role as early markers of disease susceptibility is therefore suggested. From a therapeutic standpoint, a 3-month course of steroids and azathioprine for immunosuppression was associated with early and lasting improvement in left ventricular function in DCM patients with evidence of MHC up-regulation on cardiac biopsy [46].

It should be noted that the familial preponderance of DCM is compatible with autoimmune pathogenesis, since susceptible self-antigens may bind more avidly to certain MHC alleles than others. The HLA-DR4 allele, for example, appears to confer a predilection for autoimmune disorders such as rheumatoid arthritis and multiple sclerosis, and does in fact show a weak association with DCM. Similarly, viruses may act as a trigger factor for the development of DCM in subjects with a genetic predisposition. The absence of viral nucleic acids in the hearts of patients with familial DCM [53] argues against this possibility, implying that viral DCM and familial DCM are indeed distinct patient populations. Furthermore, DCM behaves as a single gene disorder in many affected families, and the identification of disease-causing mutations has provided insight into its pathogenesis. Autosomal dominant transmission predominates in adult-onset DCM, although recessive, mitochondrial and X-linked forms are also recognized.

Genetics

Elucidation of the molecular aetiology of DCM has proved challenging because of its exceptional genetic heterogeneity. One of the first major breakthroughs was the identification of dystrophin as the causative gene in X-linked familial DCM [54]. Defects in dystrophin are also responsible for Duchenne and Becker muscular dystrophy [55]. While muscular dystrophy patients frequently develop DCM, skeletal muscle involvement is rare among sufferers with X-linked DCM, although serum CK muscle isoforms are elevated in both [54] (see also Chapter 7).

A 427-kDa rod-shaped protein, dystrophin, localizes to the inner aspect of the myocyte cytoplasmic membrane (sarcolemma). Its large size is thought to predispose to a high rate of spontaneous mutations [56]. Dystrophin binds to actin at its N-terminus and to the transmembrane dystrophin–glycoprotein complex at its C-terminus (Fig. 16.10), thereby providing a link between the cytoskeleton and sarcolemma. Most of the mutations isolated in X-linked DCM affect the N-terminal domain [54].

The first disease-causing gene in autosomal dominant DCM to be discovered was cardiac actin and was localized to chromosome 15q14 [55]. Actin is a sarcomeric thin filament with a dual function in myocytes: it interacts with other components of the sarcomere (β-myosin heavy chain, α-tropomyosin, troponins) and has a key role in force generation within the contracting myocyte. At its other end, actin binds to the anchoring proteins dystrophin and α-actinin (which resides in Z-bands and intercalated discs), thereby facilitating transmission of the contractile force to the sarcolemma and adjacent myocytes. Interestingly, mutations in the sarcomeric end of actin are associated with HCM [57], while defects in its anchoring end cause DCM, presumably via impaired force transmission. A similar mechanism has been invoked for the DCM-related α-tropomyosin mutations, which may cause localized charge reversal at the surface of the tropomyosin protein. This may affect stability of the tropomyosin molecule and disrupt its

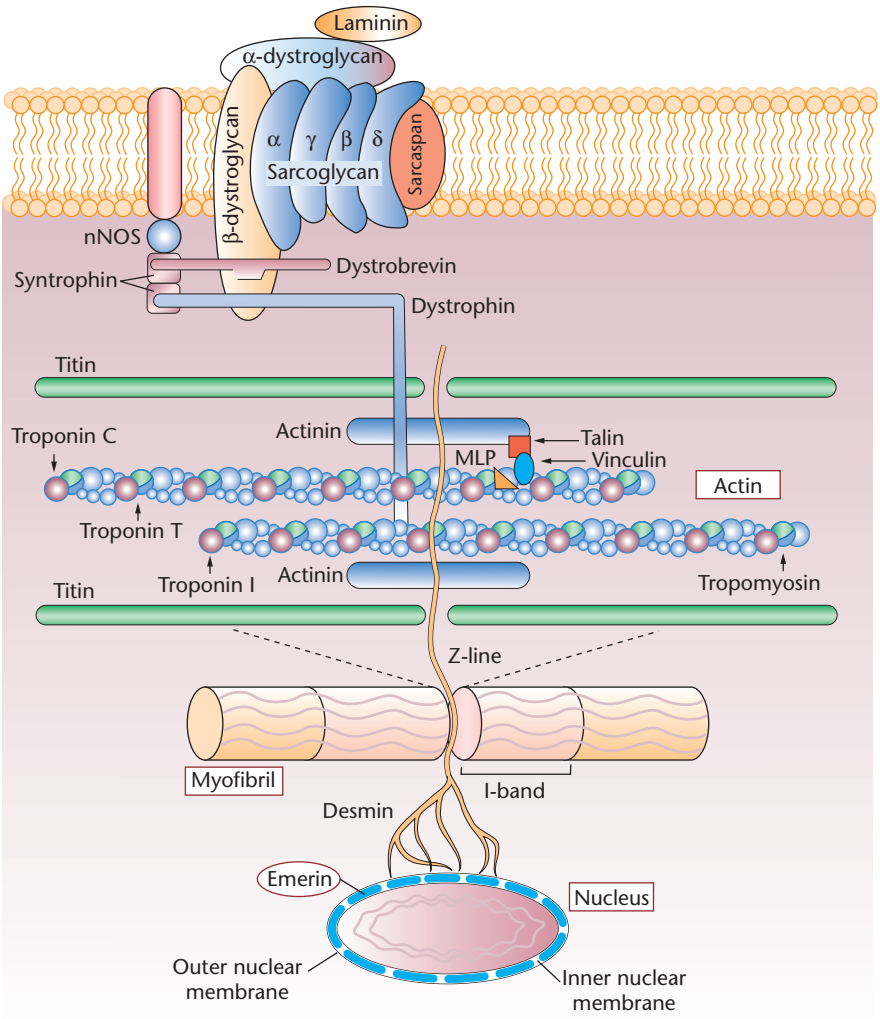


Figure 16.10 Proteins and pathways involved in the development of cardiomyopathy. nNos, neural nitric oxide synthase; MLP, muscle LIM protein. Reproduced with permission from Towbin and Bowles [54].

electrostatic interaction with actin within the thin filament [58]. The role of the thin filament in transmitting force to adjacent sarcomeres will be compromised [54]. In contrast, the tropomyosin mutations isolated in HCM cause an increase in isometric force output; inefficient sarcomeric ATP utilization is the likely consequence.

A missense mutation in the intermediate filament desmin has also been identified in a family with DCM [59]. The association of desmin, actin and dystrophin suggests that disruption of cytoskeletal function might be the final common pathway of disease expression [59]. In line with this, DCM mutations in δ-sarcoglycan [54], β-sarcoglycan [54] (both components of the dystrophin–glycoprotein complex), Cypher/Zasp (a Z-line protein that bridges the sarcomere to the cytoskeleton) [60] and metavinculin [59] (which connects actin filaments to the intercalated disc) have been found. Skeletal myopathy, which varies from subclinical to overt, may be an associated feature of some of these mutations.

Mutations in a number of other sarcomeric genes, including β-myosin heavy chain [61], cardiac troponin T and troponin C [62], may result in DCM. A recessive missense mutation in troponin I has also been isolated in a DCM family [63]. Early-onset disease expression and adverse prognosis have been reported in many families with sarcomeric DCM. The discovery of sarcomeric mutations in DCM raises two important issues. First, the mechanism by which these mutations induce ventricular dilation and impairment merits investigation; their functional effect is not readily explained by impaired transmission of force. Second, an explanation must be sought as to why certain sarcomeric mutations cause DCM, while other defects in the same genes produce the distinct phenotype of HCM. It has been proposed that the mutations associated with DCM may result in a deficit in force generation by the sarcomere. Conversely, the sarcomeric mutations that cause HCM may enhance mechanical function, and induce ventricular remodelling (i.e. hypertrophy) through ineffective utilization of ATP.

Impaired generation and transmission of force are therefore considered the key mechanisms underlying disease expression in DCM. Both may be relevant in the case of titin, a giant sarcomeric protein recently implicated in autosomal dominant DCM [61]. Titin binds to α-actinin, stabilizes the myosin filament and confers elasticity to the sarcomere. The position of the mutation is likely to be the main determinant of the functional effect.

Further gene identification studies have elicited mutations that are less easy to fit into the above model. An example is phospholamban, a transmembrane sarcoplasmic reticulum phosphoprotein that regulates the activity of the calcium reuptake pump. A missense mutation in phospholamban has been isolated in a family with autosomal dominant DCM [64], leading investigators to speculate that abnormal calcium handling, with consequent contractile impairment, may be an additional mechanism for the development of heart failure.

DCM in conjunction with conduction system disease is recognized in several kindreds. The autosomal dominant form is linked to mutations in the *LMNA* gene on chromosome 1q21 [61], which encodes two main isoforms, lamin A and C, by alternative splicing. The lamins are intermediate filament proteins of the inner nuclear membrane that are thought to contribute mechanical strength to the nuclear envelope. A role in transcription regulation is also postulated [65]. The phenotypic spectrum associated with mutations in lamin A/C is broad, encompassing skeletal myopathies, progeria, Charcot–Marie–Tooth disease and familial partial lipodystrophy, as well as progressive AV block and DCM. Disruption of the integrity of the nuclear envelope, resulting in premature cell death, has been suggested as the molecular basis for these diseases. However, the functional effect of specific mutations remains an area of active research. DCM with conduction system disease may also be inherited as an X-linked trait, in which emerin [66], another component of the nuclear membrane, has been implicated.

Despite the remarkable diversity of molecular mechanisms in DCM, the consequences at a cellular level are similar: neuroendocrine activation and local production of cytokines, maladaptive myocyte hypertrophy, apoptosis, fibrosis, and progressive ventricular dilation and impairment. Thus, the premise of a final common pathway may hold true. Recent studies demonstrate disruption of the N-terminus of dystrophin in both DCM and ischaemic heart failure, implying that loss of cytoskeletal integrity may be central to myocyte dysfunction in the failing heart. Of note, dystrophin remodelling was reversible following support with a left ventricular assist device (LVAD), suggesting that reduction of mechanical stress is critical to recovery of cellular and cardiac function [67].

Clinical presentation

CLINICAL COURSE

The natural history of DCM is heterogeneous and most patients are not critically ill. The prognosis of DCM has improved significantly in the last decades as a consequence of optimized treatment with angiotensin-converting enzyme (ACE) inhibitors and beta-blockers and, generally, is not different between sporadic or familial cases of DCM [68,69]. However, patients with DCM can be separated into two groups according to disease progression [68]:

1 patients with a more favourable outcome (group 1);
2 patients with a rapidly progressive downhill course, high mortality and urgent indication for heart transplantation (group 2).

More favourable outcome in DCM is associated with improvement in left ventricular function under medical treatment, a shorter duration of clinical symptoms, younger age, a worse NYHA class and a history of hypertension [70] (Fig. 16.11).

In patients with DCM, medical treatment with ACE inhibitors and/or beta-blockers improves left ventricular pump function in 50% of cases, while normalization occurs in 16%. In the remaining 33%, however, disease progresses long term, even independent of the initial response to treatment [68]. As many as 20% of patients with DCM will die within 1 year after diagnosis [71], most frequently due to sudden death (64%), with terminal

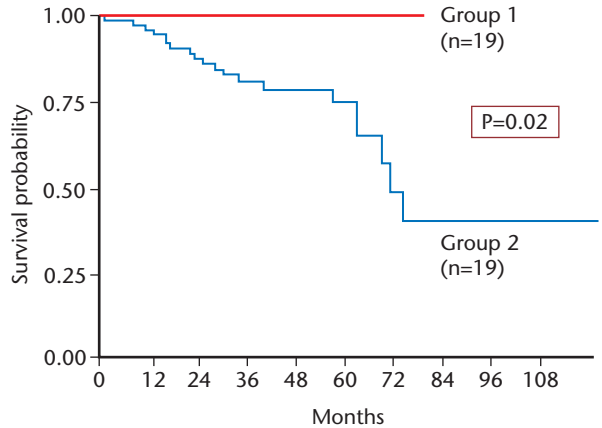


Figure 16.11 Kaplan–Meier survival curves of two groups of patients with dilated cardiomyopathy. Group 1, improvement of left ventricular ejection fraction (LVEF) with medical treatment; group 2, no improvement in LVEF. The survival probability was significantly different ($P = 0.02$).

heart failure accounting for most other cases. The 8-year transplant-free survival is as follows:

- 94% in those with normalized left ventricular ejection fraction (LVEF);
- 83% in those with functional NYHA class I–II and LVEF > 40%;
- 64% in those with NYHA class I–II when combined with LVEF ≤ 40%;
- 31% in those with persisting functional NYHA class III–IV.

CLINICAL SYMPTOMS

Clinical symptoms in patients with DCM are no different to those in patients with heart failure of other aetiology (see Chapter 21). Most often, DCM patients are less symptomatic and present with higher exercise tolerance when compared with other cardiomyopathies. Clinical symptoms in patients with DCM and systolic dysfunction of other aetiology can be grouped into major (specific) and minor (unspecific) criteria according to the Framingham study [72] and occur at different frequencies (Table 16.7).

Information from physical examination and medical history are not only valid and cost-effective for management decisions in heart failure but also relevant with respect to prognosis. Because of effective medical treatment, many patients with systolic pump dysfunction present with no or minor clinical symptoms. Nevertheless, the hepatojugular reflux and the third heart sound provide clinical information on the prognosis of the individual patient even in the context of best modern medical management [73].

Table 16.7 Clinical symptoms in patients with congestive heart failure: percentage occurrence of major and minor criteria

Major criteria	
Pulmonary rales	81%
Cardiomegaly	70%
Elevated jugular pressure	55%
Radiological signs of congestion	48%
Paroxysmal nocturnal dyspnoea	32%
Orthopnoea	31%
Third heart sound	19%
Minor criteria	
Exertional dyspnoea	93%
Peripheral oedema	56%
Depression	46%
Pleural effusion	32%
Hepatomegaly	14%
Nocturnal coughing	12%
Heart rate > 120 b.p.m.	4%
Weight loss < 4.5 kg in 6 months	2%

Pathophysiology

The initial stimuli that induce DCM are diverse: arterial hypertension, familial or genetic factors, myocarditis of viral or toxic origin, tachyarrhythmias, abnormal immune response. The consequent increased wall stress in combination with neurohumoral activation causes maladaptive changes in myocardial structure (remodelling), with complex molecular and cellular modifications. Histologically, remodelling is associated with cellular hypertrophy of cardiomyocytes, together with changes in the quantity and nature of the interstitial matrix. Biochemically, expression of the adult gene programme decreases and re-expression of fetal genes increases. Finally, the number of viable, functionally active cardiomyocytes decreases via programmed cell death (apoptosis) (Fig. 16.12). Several factors known to be present in the failing myocardium have been shown to cause apoptosis of cardiomyocytes *in vitro*:

- catecholamines via β-adrenergic signalling and reactive oxygen species [74];
- wall stress and angiotensin II [75];
- nitric oxide and inflammatory cytokines [76].

Thus it is not surprising that almost all the drugs used in heart failure have an antagonistic action on these pathways. All these drugs reduce and, potentially, reverse

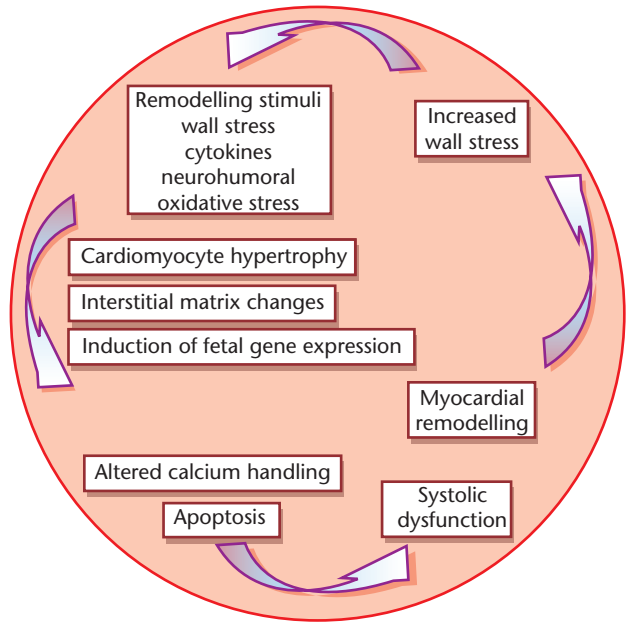


Figure 16.12 Vicious cycle in systolic dysfunction. Different remodelling stimuli induce complex cellular changes, ultimately resulting in systolic and/or diastolic dysfunction and increased wall stress, thereby promoting pathological remodelling.

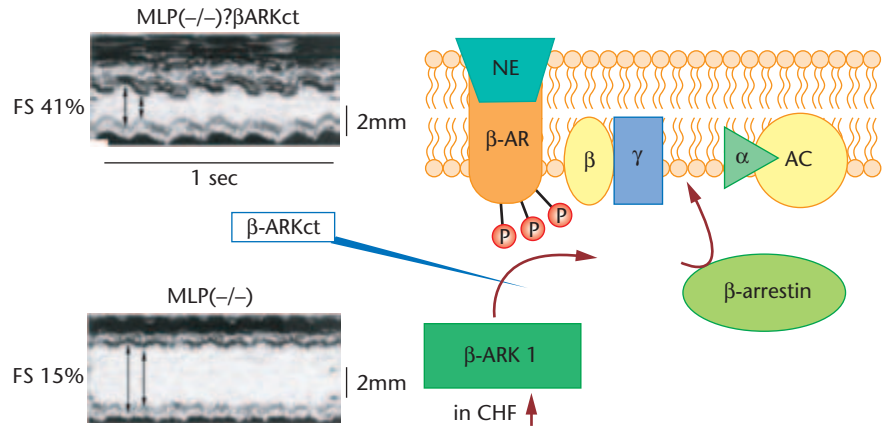


Figure 16.13 Signalling through the β-adrenergic receptor (βAR) in heart failure. βARK1 binds to the βγ-subunit of activated G-proteins, translocates to the sarcolemmal membrane and phosphorylates the agonist-occupied receptor. Phosphorylation allows binding of β-arrestin, uncoupling the receptor from further G-protein stimulation and downstream effectors such as adenylyl cyclase (AC). Both βARK1 and β-arrestin are required for homologous βAR desensitization, a phenomenon that occurs after the persistent agonist (noradrenaline, NE) stimulation characteristic of chronic heart failure. Expression of the C-terminal truncated, ineffective βARK1 in MLP (–/–) rescues myocardial function (see M-mode echocardiogram) and restores β-adrenergic responsiveness.

pathological cardiac remodelling and improve survival by attenuating stress signalling in the heart.

THE β-ADRENERGIC SYSTEM

Prolonged increased sympathetic activity results in both desensitization and down-regulation of sarcolemmal cardiac β-adrenergic receptors. Desensitization of β-adrenergic receptors is promoted by increased β-adrenoreceptor kinase (β-ARK) expression in the failing heart; this enzyme phosphorylates the β-adrenergic receptor [77]. Phosphorylated β-adrenergic receptors are then internalized and sequestered in the failing cardiomyocyte [78]. In the transgenic dominant-negative MLP mouse model of heart failure, cardiac expression of a dominant-negative β-ARK mutant restores β-adrenergic signalling and prevents progression to heart failure in several models of animal heart failure (Fig. 16.13). These results suggest that the loss of β-adrenergic signalling in the failing heart is a key mechanism, although the mechanism responsible for the salutary effects of beta-blockade still remain unclear.

CALCIUM HOMEOSTASIS

Calcium is vital for contractile function, and therefore it is not surprising that abnormalities in calcium handling have been implicated in the systolic dysfunction of DCM. Calcium ions enter the cardiac muscle cell through L-type calcium channels during each heart beat and trigger calcium release through ryanodine receptors. This raises the intracellular calcium concentration about tenfold. Reuptake of calcium into the sarcoplasmic reticulum via the sarcoplasmic reticulum Ca^{2+}-ATPase allows cardiac relaxation. The ability of the Ca^{2+}-ATPase to pump calcium back into the sarcoplasmic reticulum is governed by its interaction with phospholamban, a small modulatory protein within the membrane of the sarcoplasmic reticulum [79] (Fig. 16.14). In the failing heart, calcium release and uptake is diminished owing to a decrease in expression and activity of the Ca^{2+}-ATPase, resulting in diastolic and systolic dysfunction. The notion that aberrant calcium handling contributes to the pathogenesis of systolic dysfunction in DCM is supported by the finding that in mice lacking the cardiac LIM domain (double-zinc finger domain found in Lin1, Isl1 and Mec3 protein MLP, the heart failure phenotype is completely abrogated by homozygous deletion of the gene encoding phospholamban, which allows for enhanced calcium reuptake by the sarcoplasmic reticulum. However, the apparently beneficial effects of phospholamban ablation can be observed only in a subset of mouse models of DCM and heart failure because the phospholamban knockout does not rescue cardiomyopathic hearts resulting from sarcomere abnormalities [80].

NATRIURETIC PEPTIDES

Heart failure in DCM is accompanied by the up-regulation and secretion of atrial and B-type natriuretic peptides by the heart that signal through cell-surface receptors coupled to guanylate cyclase [81]. The resultant activation of protein kinase G by cGMP has been shown

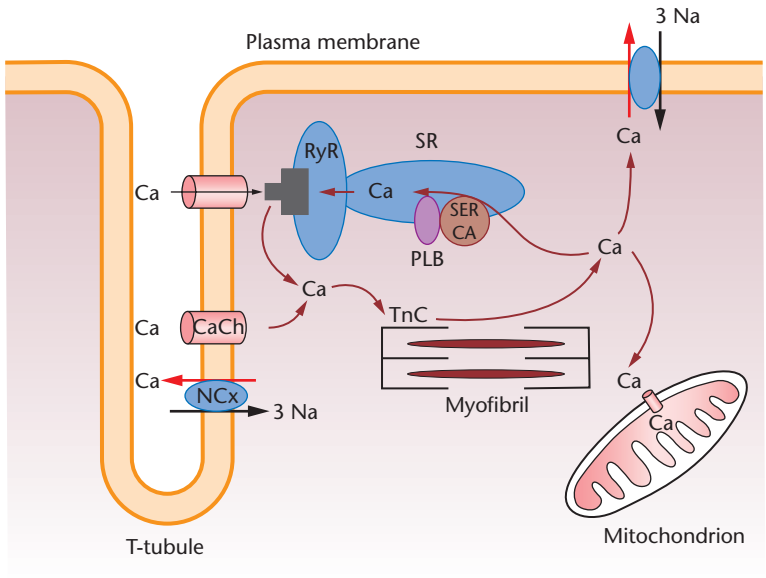


Figure 16.14 Calcium homeostasis. Membrane depolarization opens voltage-activated L-type calcium channels (CaCh), extracellular Ca^{2+} ions enter the cardiomyocyte and induce Ca^{2+} release by ryanodine receptors (RyR). Cytosolic Ca^{2+} concentration rises and intiates contraction. ATP-driven reuptake of Ca^{2+} ions into the sarcoplasmic reticulum (SR) by the sarcoplasmic Ca^{2+}-ATPase (SERCA) or extrusion of Ca^{2+} via the sodium–calcium exchanger (NCx) lowers cytosolic Ca^{2+} concentration and terminates contraction.

to suppress fetal gene activation through mechanisms that are only beginning to be unveiled. Nevertheless, the observation that gender influences the severity of cardiomyopathic phenotypes [82] suggests the presence of other underlying but not yet identified pathogenetic mechanisms.

Diagnostic testing

Clinical examination in patients with DCM is frequently of limited value in the assessment of haemodynamics and prognosis. Therefore, plasma biomarkers and physical examinations such as echocardiography, QTc interval or maximal exercise testing are often used to obtain additional objective information.

NEUROHORMONES

B-type natriuretic peptide, which is released in response to myocyte stretch [83], has become an established biomarker for guiding medical treatment [84]; furthermore, plasma concentrations approximately twice above normal are predictive of increased long-term mortality in patients with heart failure.

The plasma concentration of interleukin 6 correlates with the severity of symptoms and is an identified predictor of cardiovascular mortality in stable severe chronic heart failure [85]. Plasma concentrations of noradrenaline (norepinephrine) are predictive of cardiovascular morbidity and mortality.

ELECTROCARDIOGRAPHY

Electrocardiography provides no specific diagnosis in DCM. However, AF is associated with increased mortality or heart failure progression in all types of cardiomyopathy with chronic heart failure. In DCM, a decrease in heart rate variability due to chronic excessive sympathetic stimulation is related to an adverse prognosis [86], and prolonged QTc intervals predict mortality [87]. In addition, complex ventricular arrhythmias and decreased heart rate variability during 24-h Holter monitoring, when associated with low ejection fraction, place DCM patients at higher risk of death. Left bundle branch block with QRS duration of 130–150 ms reflects high intra-left ventricular dyssynchrony and has been proposed as a criterion for selecting patients for resynchronization therapy.

ECHOCARDIOGRAPHY

In DCM, LVEF < 30%, left ventricular end-diastolic pressure (LVEDP) ≥ 15 mmHg, and onset or worsening of mitral regurgitation are associated with increased cardiac mortality [87]. Furthermore, the size and shape of the left ventricle and the Doppler findings predict the development and severity of heart failure symptoms. A restrictive physiology with high atrial filling pressures is associated with a higher mortality rate. However, if the abnormal filling is reversed into one of pseudo-normal or impaired relaxation, the survival of DCM patients with this pattern is much better, whereas persistence of restrictive filling after 3 months despite optimal medical treatment is associated with a high mortality. Mitral valve insufficiency in DCM is associated with adverse prognosis; however, surgical mitral valve repair by undersized annuloplasty in combination with coaptation of the

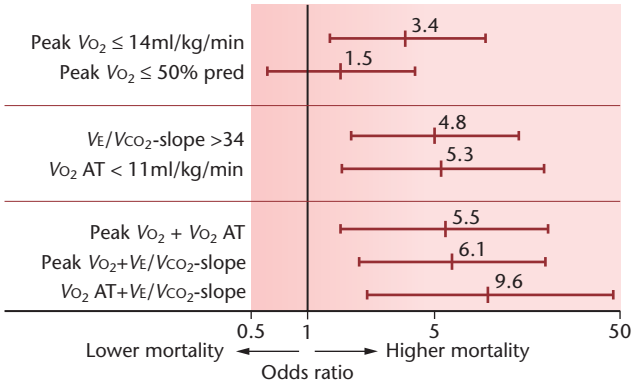


Figure 16.15 Cardiopulmonary exercise testing: predictors of death within 6 months in patients with ischaemic or dilated cardiomyopathy given as odds ratios (univariate analysis). Bars are 95% confidence intervals. Reproduced with permission from Gitt *et al*. [90].

Table 16.8 Survival in patients with ischaemic or dilated cardiomyopathy depends on the percentage achieved of predicted peak oxygen uptake

Percentage Vo_2max	1-year survival	2-year survival
≤ 50%	74%	43%
> 50%	98%	90%

mitral valve leaflets has a favourable outcome [88]. Thus, transoesophageal echocardiography plays an important role with respect to treatment of the mitral valve insufficiency in DCM.

CARDIOPULMONARY EXERCISE TESTING

Cardiopulmonary exercise testing measures the adequacy of the cardiac response to strenuous exertion and is an established predictor of risk in DCM [89] (Fig. 16.15 and Table 16.8). In addition, Vo_2 of anaerobic threshold (when < 11 ml/kg/min) and ventilatory efficiency (slope of VE vs. VCO_2) > 34 in combination are reliable predictors for 6-month mortality [90]. Prediction of prognosis is no different between ischaemic or dilated cardiomyopathy, although patients differ with respect to their neurohumoral profile.

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) has become a new standard for the assessment of ventricular volumes, ejection fraction, myocardial mass and regional wall motion (Fig. 16.16). Paramagnetic contrast detects regional abnormalities in myocardial contraction [91]. In addition, late

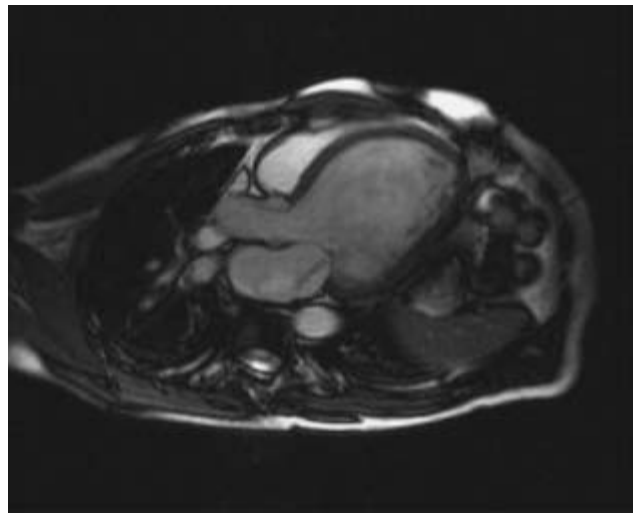


Figure 16.16 Cardiac magnetic resonance image in a patient with dilated cardiomyopathy. Horizontal transection of the dilated left ventricle with mitral jet due to mitral regurgitation.

enhancement marks areas of non-viable myocardium with higher sensitivity when compared with thallium scintigraphy [92].

LEFT AND RIGHT HEART CATHETERIZATION

Coronary angiography is required to exclude coronary atherosclerosis when the diagnosis of idiopathic DCM is considered. Additional information regarding cardiac output, wall stress, distensibility, compliance and pulmonary artery pressure can be obtained, and pulmonary wedge pressure or pulmonary resistance may add to risk stratification. Cardiac catheterization should not be considered when instituting chronic therapy.

ENDOMYOCARDIAL BIOPSY

Frequently, the histology of endomyocardial specimens is non-specific, with cardiomyocyte hypertrophy, enlarged nuclei and increased interstitial fibrosis. However, most asymptomatic relatives of patients with DCM with left ventricular enlargement have histopathological and immunopathological findings similar to those of patients with established disease [41]. In addition, *in situ* hybridization allows detection of persisting viral genome in endomyocardial biopsy (EMB) and thus the diagnosis of chronic myocarditis, even when microscopic examination does not demonstrate lymphocytic infiltration.

Management

Independent of the aetiology and possible specific

therapeutic options (e.g. anti-inflammatory, antiviral or immunomodulatory agents), the general guidelines for the treatment of heart failure apply equally to DCM, i.e. ACE inhibitors, angiotensin (AT)II receptor blockers, beta-blockers, diuretics, aldosterone antagonists, digitalis and cardiac transplantation [93,94]. Potentially cardiotoxic agents (i.e. alcohol, anthracyclines) should be discontinued [95]. In addition, exercise training can contribute to alleviation of heart failure symptoms and improve prognosis [96]. Similarly, in DCM with left bundle branch block and QRS duration > 120 ms and NYHA III–IV, cardiac resynchronization therapy may be considered [97–99] (see Chapter 21).

Cardiac transplantation remains the ultimate treatment option in patients with DCM with terminal heart failure refractory to conventional treatment [100]. LVADs may improve left ventricular function until cardiac transplantation ('bridge to transplantation') or until sustained improvement of left ventricular function occurs ('bridge to recovery') [101–103]. The value of partial ventriculectomy is limited [104].

Risk assessment and primary prevention of SCD is a challenge in DCM, especially since programmed ventricular stimulation has no predictive value as opposed to its use in ischaemic heart disease [105]. Aborted SCD is an indication for ICD (secondary prevention). Syncope is a strong predictor of SCD in DCM [106]. The combination of left ventricular end-diastolic diameter > 70 mm and non-sustained VT on Holter monitoring, and the combination of LVEF < 30% and non-sustained VT on Holter monitoring may identify patients at higher risk for SCD [107,108]. Conventional heart failure treatment also reduces mortality due to prevention of SCD (see Chapter 24) [109,110]. Microvolt T-wave alternans constitutes a promising method for the prediction of arrhythmic events [111]. ICD appears superior in the primary prevention of SCD compared with amiodarone: whereas the AMIOVIRT study showed no significant difference between amiodarone or ICD [112], the COMPANION trial [99] and the SCD-Heft trial demonstrated the superiority of ICD [113]. Rate control and/or rhythm control should be achieved in DCM patients with AF.

Anticoagulation is indicated in DCM patients with AF [114]. In light of the thromboembolic complications in DCM patients with substantially impaired left ventricular function [115–117], anticoagulation should be prescribed. However, evidence from the ongoing randomized WATCH trial on the benefit of anticoagulation in DCM patients with sinus rhythm must be awaited [118].

Genetic counselling is advisable in patients with familial DCM and their first-degree relatives. Since a high proportion of affected relatives are asymptomatic despite left ventricular enlargement, screening (ECG, echocardiography) should be performed in first-degree relatives [119].

Prognosis and outcome

The 5-year survival of DCM patients averages between 36% [120] and 30% [121]. After the initial diagnosis of DCM, clinical courses are highly heterogeneous. Identification of modifiable prognostic factors and elaboration of effective interventions is important for the outcome of DCM patients. Detailed prospective investigations have been elucidated by the Heart Muscle Disease Study Group. A subgroup characterized by a rapidly progressive course with high mortality rates, need for inotropic and/or LVAD support and urgent transplantation can be distinguished from the subgroup with more favourable outcome responding to concurrent heart failure medication (about 50% of patients). Less frequently (about 16%), healing courses can be observed [68], especially in the setting of acute DCM/fulminant myocarditis [122–124]. Transplant-free survival, as well as SCD, in

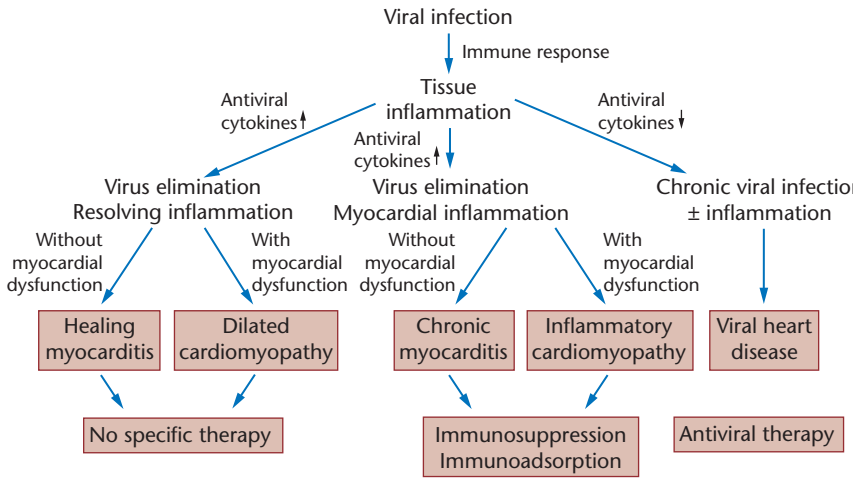


Figure 16.17 Pathophysiology of inflammatory cardiomyopathy and specific treatment options.

DCM patients is significantly associated with the course of NYHA/LVEF improvement under optimized heart failure medication [68].

Evidence emerging confirms the decrease in mortality and hospitalization of DCM patients undergoing heart failure treatment [68,125]. However, this treatment does not specifically target the cause of the disease, and some DCM patients do not respond (Fig. 16.17). Pathogenic substrates of DCM, namely inflammation and especially cardiotropic viral persistence/viral replication, are associated with adverse outcome [126–129], whereas histological morphometric analyses have no predictive value [130,131]. There is an emerging role for gene mutations, which are associated with a worse prognosis in DCM [132].

Several immunomodulatory trials have demonstrated sustained beneficial effects in DCM patients with chronic progressive courses despite full-scale heart failure medication [44–46]. However, results from ongoing multicentre trials must be awaited.

Restrictive cardiomyopathy

Definition and classification

Restrictive cardiomyopathy is characterized by abnormal diastolic function with either thickened or rigid ventricular walls leading to elevated filling pressures of the left- or right-sided cardiac chambers. In contrast to constrictive pericarditis, left- and right-sided diastolic filling pressures are discordant in restrictive cardiomyopathy but concordant in constrictive pericarditis. 'Discordant' describes the haemodynamic phenomenon of dissociation between left and right ventricular diastolic filling pressures during respiration, whereas 'concordant' describes parallel changes in both left and right ventricular diastolic pressures during respiration (Fig. 16.18).

The classification of restrictive cardiomyopathy is based on aetiological and clinical findings.

1 Primary forms
- (a) Löffler's endocarditis
- (b) Endomyocardial fibrosis

2 Secondary forms
- (a) Infiltrative diseases
- (b) Storage diseases
- (c) Post-radiation disease

Primary forms are associated with inflammation and hypereosinophilia and are due to chronic inflammatory processes, i.e. parasite infections, autoimmune diseases or eosinophilic leukaemia. Primary forms are rare in Western industrialized countries but may be endemic in some African or South American countries [133–137]. Secondary forms are caused by a variety of systemic diseases which are associated with thickening of the myocardial wall by infiltration, storage or excessive fibrosis.

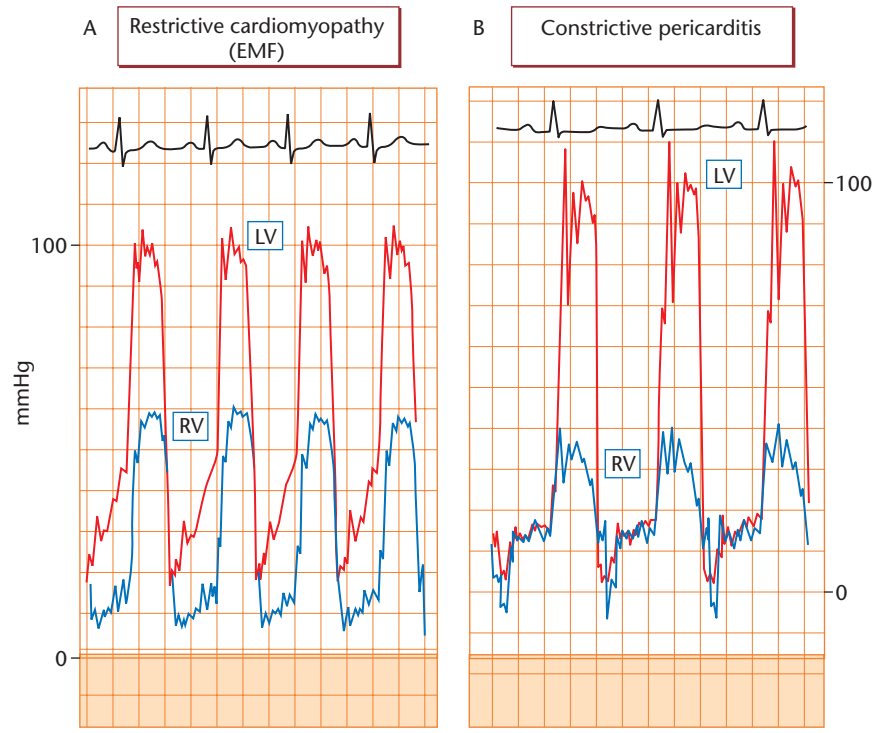


Figure 16.18 Simultaneous pressure recordings of the left ventricle (LV) and right ventricle (RV) in restrictive cardiomyopathy (A) and constrictive pericarditis (B). Diastolic pressures are discordant in (A) but concordant in (B).

Secondary forms are classified by the specific type of material deposition, i.e. infiltration, storage or replacement. Depending on the degree of infiltration or storage, clinical course in restrictive cardiomyopathy is often mitigated [137–140].

Primary forms

There are two primary forms of restrictive cardiomyopathy: the acute form, which is called Löffler's endocarditis, and the chronic form, which is termed endomyocardial fibrosis.

Löffler's endocarditis

The acute form of primary restrictive cardiomyopathy was described for the first time by Wilhelm Löffler in Zurich in 1936 [141]. He observed two patients who died from endocarditis, with extensive fibrosis of the endocardium and thrombotic thickening with severe blood eosinophilia. The fibrotic process is usually located at the apex of one or both ventricles and extends into the inflow tract, frequently involving the chordae tendineae [142–146]. These obliterations cause mitral and/or tricuspid regurgitation. Histological examination shows acute eosinophilic myocarditis involving both the endocardium and myocardium, with mural thrombosis often containing eosinophils and fibrotic thickening.

PATHOPHYSIOLOGY

The pathophysiological mechanism is not clear but eosinophils are thought to play a major role. Any process associated with hypereosinophilia for several weeks or months may lead to eosinophilic myocarditis [139,140]. Patients may die ultimately from cardiogenic shock, thromboemboli, or renal or respiratory dysfunction. Hypereosinophilia may be due to autoimmune disease, rheumatoid arthritis, parasite infections or eosinophilic leukaemia [147]. The patient shown in Fig. 16.19 suffered from eosinophilic leukaemia that was stabilized by medical therapy. Because of severe congestive heart failure, the patient underwent left ventricular decortication, which was associated with a dramatic clinical improvement. One year after the operation, the patient died from recurrence of eosinophilic leukaemia.

CLINICAL MANIFESTATIONS

The typical clinical symptoms include weight loss, fever, cough, rash and congestive heart failure. Although early cardiac involvement may be asymptomatic, cardiac dysfunction can be found in more than 50% of all patients. Cardiomegaly may be present on the chest radiograph, with lung congestion. Mitral or tricuspid regurgitation is common in most patients. Systemic embolism is frequent and often associated with neurological and renal dysfunction. Death is usually due to congestive heart failure.

DIAGNOSIS

Chest radiography may show cardiomegaly and pulmonary congestion, with dilatation of one or both atria. The ECG usually shows non-specific ST-segment and T-wave abnormalities. Arrhythmias are often present, especially AF [138]. The most important tool for diagnosis is echocardiography, which shows localized thickening of one or both ventricles at the apex (Fig. 16.19) with involvement of the chordae tendineae. Typically the atria are enlarged, associated with mitral and/or tricuspid regurgitation. Systolic function is usually preserved, with a typical restrictive mitral inflow pattern [143]. Cardiac catheterization shows markedly elevated ventricular filling pressures in the presence of a small ventricle with typical obliterations of the apex. Most patients have mild to moderate tricuspid or mitral regurgitation. The diagnosis may be confirmed by right or left ventricular EMB.

MANAGEMENT

Cardiac therapy is based on treatment of restrictive cardiomyopathy, including diuretics and after-load reduction with ACE inhibitors or AT1 receptor blockers. Beta-blockers may be used for reducing heart rate, or digitalis in the case of AF. Because of the risk of cardiac embolization, low-molecular-weight heparin or oral anticoagulation is mandatory.

Medical therapy depends on the aetiology of the hypereosinophilic syndrome: autoimmune disease may be treated with corticosteroids or immunosuppressive agents, rheumatoid arthritis with anti-tumour necrosis factor α, or eosinophilic leukaemia with antiproliferative agents [144].

Surgical therapy may be considered in patients who remain symptomatic but have been stabilized medically (Fig. 16.19). Endocardial decortication of one or both ventricles may be performed and may improve cardiac symptoms and reduce cardiac mortality.

PROGNOSIS

The classic syndrome of Löffler's endocarditis is associated with a poor prognosis and most patients die within 6–12 months. Since the cause of hypereo-sinophilia remains unknown in most patients, clinical outcome is often poor, although corticosteroids may suppress hypereosinophilia. Those patients with a known aetiology for hypereosinophilia may do better [145].

DIFFERENTIAL DIAGNOSIS

In a subacute phase, Löffler's endocarditis may mimic

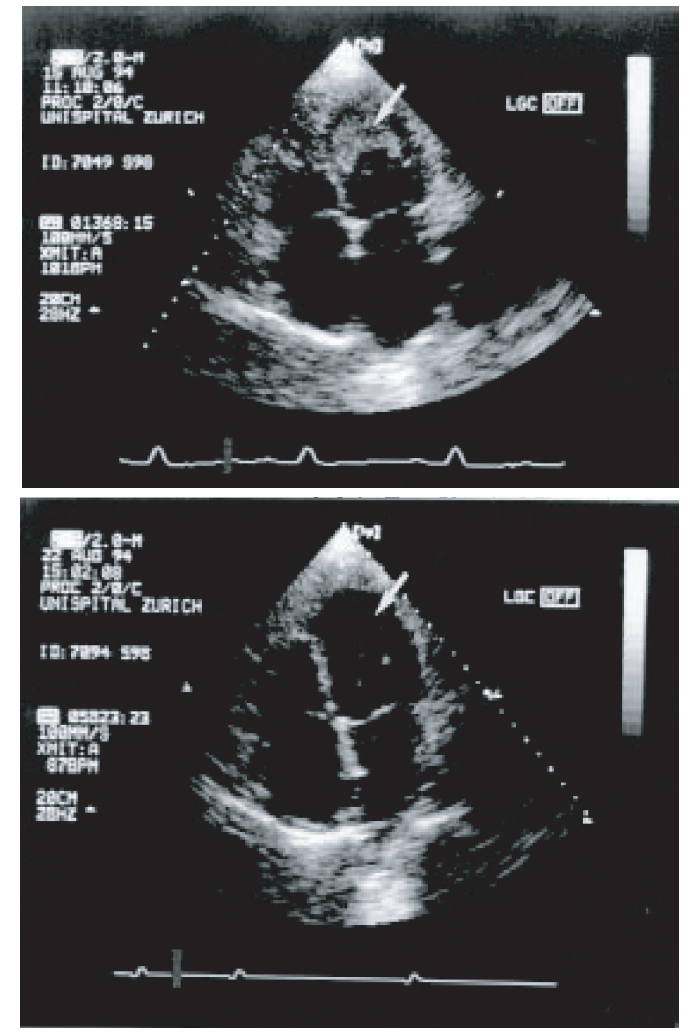


Figure 16.19 (A) Preoperative and (B) postoperative two-dimensional echocardiograms (four-chamber view) of a patient with eosinophilic leukaemia and Löffler's endocarditis of the left ventricle. Preoperatively, the left ventricle is globular and small but regains normal size with a clear decrease in left atrial chamber volume after surgical decortication.

chronic endomyocardial fibrosis. However, the clinical picture of acute illness, fever, cough, congestive heart failure and hypereosinophilia is so typical that correct diagnosis should not be missed.

Endomyocardial fibrosis

Endomyocardial fibrosis was first described in 1936. Since then, the endemic or equatorial African and the sporadic European form have been characterized. Endomyocardial fibrosis is marked by intense endocardial thickening of the apex and subvalvular apparatus of one or both ventricles [137,138]. The fibrotic thickening of the apex leads to obliteration of one or both ventricles, with obstruction to filling producing restrictive and, in some biventricular forms, constrictive physiology.

Three types of endomyocardial fibrosis have been described: right ventricular (10%), left ventricular (40%) and biventricular (50%) (Fig. 16.20). The African form is associated with a mean age of approximately 30–40 years and a male-to-female ratio of 2 : 1. The European form is associated with a mean age of 30–50 years and a male-to-female ratio of 1 : 2.

AETIOLOGY

The term 'primary restrictive cardiomyopathy' suggests idiopathic pathophysiology without a clear infective agent or autoimmune disease. In fact, aetiology appears to be multiple, such as parasite infections in equatorial Africa (filariasis) or autoimmune diseases associated with glomerulonephritis or rheumatoid arthritis.

The common pathophysiological pathway for both Löffler's endocarditis and endomyocardial fibrosis is probably excessive blood eosinophilia [139,145]. Hypereosinophilia of any cause (parasite infection, autoimmune disease, eosinophilic leukaemia, etc.) may also be responsible for the occurrence of endomyocardial fibrosis. It is believed that eosinophils are mechanically

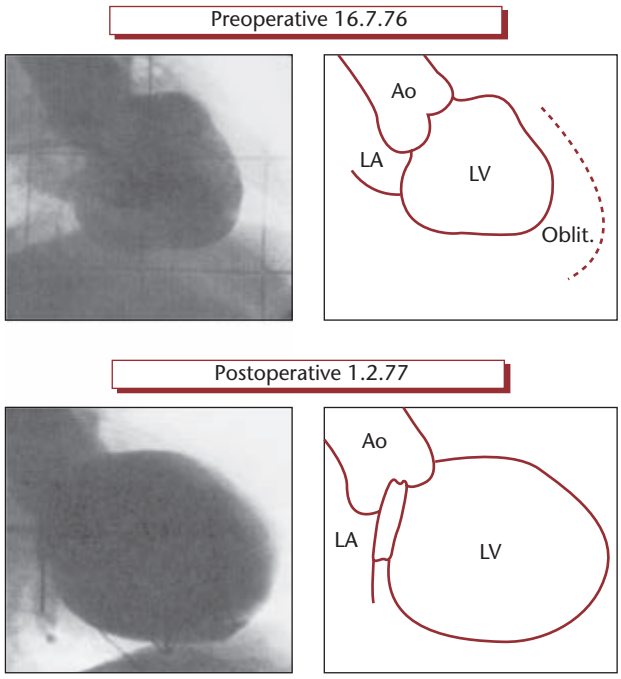


Figure 16.20 Preoperative (top) and postoperative (bottom) angiograms in a patient with biventricular endomyocardial fibrosis. The left ventricle (LV) is of globular shape with severe regurgitation into the left atrium (LA). After surgical decortication, the ventricle is significantly larger and mitral regurgitation is no longer present due to prosthetic valve replacement. Ao, ascending aorta. Reproduced with permission from Hess [137].

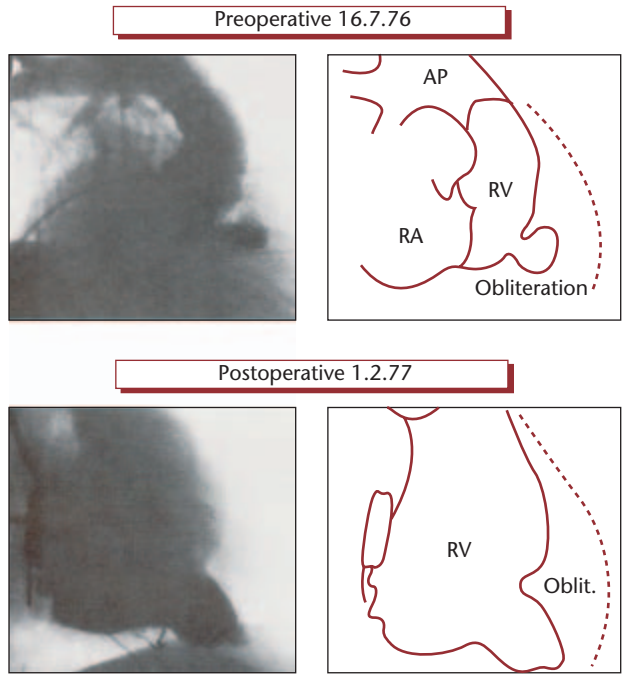


Figure 16.21 Preoperative (top) and postoperative (bottom) right ventricular angiograms in a patient with biventricular endomyocardial fibrosis (same patient as in Fig. 16.20). A characteristic, almost pathognomonic finding is obliteration of the right ventricular apex with a residual bay-like formation. After decortication, the right ventricle becomes larger but the bay-like formation persists. Prosthetic valve replacement has been performed because of severe tricuspid regurgitation. AP, arteria pulmonalis; RA, right atrium; RV, right ventricle. Reproduced with permission from Hess [137].

destroyed in the ventricles, which release fibroblast-stimulating factors that cause the typical lesions in the inflow tract and apex. The obliteration leads to a reduction in chamber volume (Figs 16.20 and 16.21, top panels), typically associated with mitral or tricuspid regurgitation because the chordae tendineae are often involved. Haemodynamically, the obliterations are associated with diastolic dysfunction and increased filling pressures, leading to lung congestion and right-sided heart failure. Typically the chambers are small but systolic contractions are maintained [137]. The clinical course is chronic and may be stable for several years or decades. However, progression to severe heart failure may be fast. The only treatment is surgical decortication [137].

DIAGNOSIS

The most important tool for diagnosis is two-dimensional Doppler echocardiography. The typical obliterations of the left ventricular apex can be seen (Fig. 16.19), with normal contractions of the basal regions. The haemodynamic consequence of diastolic dysfunction is atrial dilation, and AF may occur [143,144].

Chest radiography may not be very helpful but mild to moderate enlargement of the cardiac silhouette with signs of pulmonary congestion may be present. Pleural effusion may be seen. In patients with slow progression, diffuse calcifications of the endocardium may be found.

Laboratory findings are usually unspectacular but there may be increased C-reactive protein, electrolyte imbalance due to diuretic treatment and haematological changes according to the underlying disease.

MANAGEMENT

Heart failure treatment for diastolic dysfunction is appropriate in patients with mild to moderate restriction. Diuretics and ACE inhibitors may be helpful. Digitalis can be used in patients with atrial flutter or fibrillation. Beta-blockers are appropriate in patients with tachycardia but bradycardia is not well tolerated in these patients with small ventricles and high filling pressures.

Endocardial decortication has to be considered in advanced disease. Typically one or both ventricles are decorticated, with mitral or tricuspid valve replacement

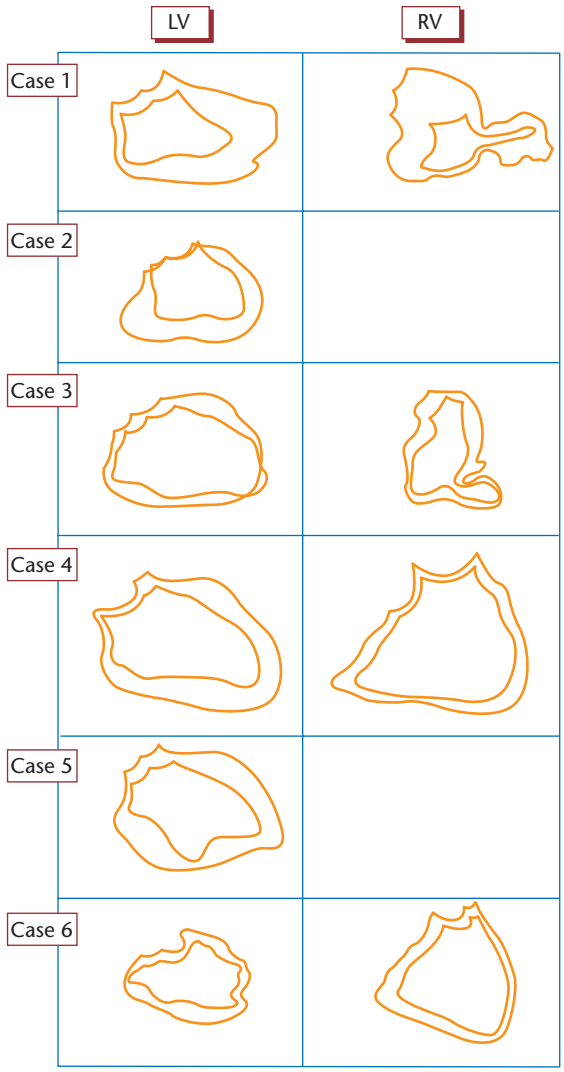


Figure 16.22 Typical angiographic findings (end-diastolic and end-systolic silhouettes) in six patients with endomyocardial fibrosis. LV silhouettes are shown on the left, RV silhouettes on the right. Please note the irregular shapes of the left and right ventricles with bay-like formations of the RV in cases 1 and 3.

because of involvement of chordae tendineae and papillary muscles. Good to excellent surgical results have been reported by several groups but slow progression to systolic heart failure may become a problem [148–156]. After decortication most patients show an increase in cardiac volumes (Figs 16.20 and 16.21), with a decrease in LVEDP (Fig. 16.22).

PROGNOSIS

Clinical course may be stable over years. When restriction becomes clinically apparent, a downhill course begins with a decrease in quality of life. After surgical decortication the clinical course may remain stable when the remaining myocardium is not severely fibrotic and

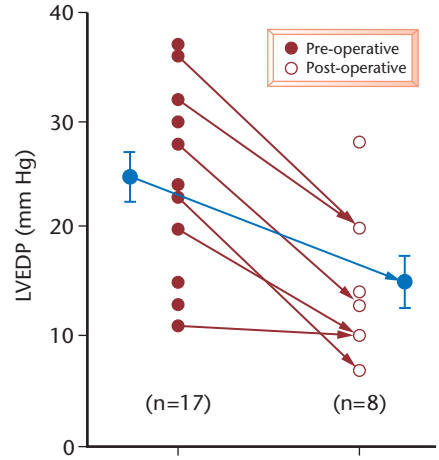


Figure 16.23 Left ventricular end-diastolic pressure (LVEDP) in 17 patients with endomyocardial fibrosis before (left) and 6–12 months after (right) successful decortication of the left ventricle ($n = 8$). LVEDP decreases from 25 to 15 mmHg as a consequence of improved diastolic function. Reproduced with permission from Hess *et al.* [155] and Schneider *et al.* [156].

dysfunctional. In rare cases recurrence of an acute Löffler's endocarditis may occur. At our institution a female patient developed Löffler's endocarditis, with marked blood eosinophilia and fibrotic thickening of the endocardium, 1 year after successful biventricular decortication [155]. The patient died a few days later in cardiogenic shock. Cardiac transplantation may be considered in patients with severe biventricular endomyocardial fibrosis but secondary pulmonary hypertension may be a limiting factor.

DIFFERENTIAL DIAGNOSIS

Primary restrictive cardiomyopathy can be difficult to differentiate from post-viral constrictive pericarditis, carcinoid syndrome of the right ventricle and amyloidosis [155,156]. There is a triad of key features of endomyocardial fibrosis.

1 Apical obliterations of one or both ventricles (echocardiogram or angiocardiogram).
2 Mild cardiomegaly with severe pulmonary congestion.
3 Mitral and/or tricuspid regurgitation; diastolic heart failure.

Secondary forms

Infiltrative diseases

In infiltrative diseases, a product of metabolism, inflammation or carcinomatosis pervades the cardiac interstitium and increases stiffness of the myocardium, thereby restricting ventricular relaxation, increasing filling pressures and reducing stroke volume.

Site of amyloid deposition	Clinical manifestations
Myocardium	Myocardium becomes firm, thickened and poorly compliant Diastolic dysfunction predominates early in disease course Systolic impairment occurs with disease progression
Valves and papillary muscles	Focal thickening of valves may be seen Valvular dysfunction rare but recognized
Conduction system	Conduction abnormalities (e.g. atrioventricular block) Atrial arrhythmia Ventricular arrhythmia Sudden arrhythmic death
Coronary arteries and other vessels	Deposits occur in media and adventitia, rarely in lumen Ischaemia, infarction, sudden death

Table 16.9 Clinical consequences of amyloid deposition in the cardiovascular system

AMYLOIDOSIS

Amyloidosis refers to a large group of disorders in which soluble extracellular proteins are misfolded and deposited as insoluble fibrils in the tissues, leading to disruption of tissue architecture and organ dysfunction. The disease may be acquired or hereditary, and is classified according to the nature of the fibril precursor protein and clinical features.

Acquired amyloidosis In primary (or AL) amyloidosis, the fibrillar protein is composed of κ and λ immunoglobulin light chains, produced by a proliferating clone of plasma cells. A systemic disease that tends to follow a rapidly progressive course, primary amyloidosis is often seen in conjunction with plasma cell dyscrasias such as multiple myeloma or the monoclonal gammopathies.

Secondary (or AA) amyloidosis occurs in association with chronic inflammatory disorders such as rheumatoid arthritis, ankylosing spondylitis and familial Mediterranean fever. Nephrotic syndrome and renal failure are common at presentation. The amyloid fibrils are composed of protein A.

β_2-Microglobulin amyloidosis is a complication of long-term haemodialysis that usually occurs in localized peri-articular form but is occasionally systemic.

Senile systemic amyloidosis is seen in patients over the age of 60 years. The fibril precursor is normal wild-type transthyretin. Congestive heart failure, heart block, AF and ventricular arrhythmia are recognized manifestations. Progression is slow and prognosis better than that of other acquired forms.

Hereditary amyloidosis Hereditary amyloidosis is the result of a mutation in one of a number of fibril precursor proteins, including transthyretin, apolipoprotein AI or AII, lysozyme, fibrinogen Aα chain, gelsolin and cystatin C. The phenotype varies according to the protein affected. Autosomal dominant inheritance is typical.

Cardiovascular involvement Amyloidosis frequently affects the heart. The propensity for cardiovascular involvement is greatest in primary, senile systemic and certain hereditary forms of the disease. Cardiac disease is relatively less common in AA amyloidosis but is a marker of unfavourable prognosis when present [157]. Amyloid fibrils may be deposited in the myocardium, papillary muscles, valves, conduction system and/or vessels, with consequent clinical manifestations (Table 16.9).

Clinical presentation of cardiac amyloidosis Clinical suspicion of cardiac amyloidosis arises in the following circumstances:

1. cardiac disease in the setting of established AL amyloidosis and/or plasma cell dyscrasia;
2. ventricular dysfunction or arrhythmia and long-standing connective tissue disease or other chronic inflammatory disorder;
3. any patient with restrictive cardiomyopathy of unknown aetiology;
4. LVH on echocardiography but a low-voltage ECG;
5. congestive heart failure of unknown cause refractory to standard medical therapy.

Diagnosis of cardiac amyloidosis The preliminary work-up for a patient with suspected cardiac amyloidosis includes a 12-lead ECG and two-dimensional echocardiography, with or without Holter monitoring. Characteristic findings are summarized in Table 16.10 [158]. A low-voltage ECG with increased septal and posterior left ventricular wall thickness on echocardiography is specific for

Table 16.10 Clinical investigations in cardiac amyloidosis

12-lead ECG
Low voltage*
Interventricular conduction delay/bundle branch block
Varying degrees of atrioventricular block
Poor R-wave progression ('pseudo-infarct pattern')*
Left-axis deviation

Holter
Atrial fibrillation
Other tachyarrhythmia or bradyarrhythmia

Two-dimensional echocardiography
Concentric or asymmetric thickening of the left ventricular wall
Occasional thickening of the right ventricle
Sparkling/granular appearance of myocardium*
Thickened interatrial septum*
Thickened valves and/or papillary muscles
Left atrial or biatrial dilation
Pericardial effusion
Diastolic dysfunction in early disease (E/A reversal)
Restrictive physiology (E >> A)
Systolic impairment with normal end-diastolic volume

Histology
Apple-green birefringence under polarized light microscope after staining with Congo red*
Immunoperoxidase stains to differentiate light chains/transthyretin/protein A, etc.

Cardiac catheterization
Raised filling pressures

Protein electrophoresis
Serum and urine electrophoresis for presence of monoclonal protein in patients with suspected AL amyloidosis

Genetic testing
Commercially available to detect common mutations

*Features considered relatively more specific for amyloidosis.

cardiac amyloidosis on non-invasive testing [158]. Other investigations that are of value include protein electrophoresis and genetic testing. EMB is often diagnostic, although multiple specimens may have to be obtained to avoid sampling errors.

Management and outcome Treatment is directed at both the underlying disease process and the cardiac complications. Systemic therapy is type-specific, underscoring the importance of determining the precise aetiology of amyloidosis. Prognosis of AL amyloidosis is poor; however, in subgroups of patients, combined treatment with high-dose melphalan and autologous stem cell transplantation has resulted in haematological remission, improved 5-year survival and reversal of amyloid-related disease [159]. In contrast, senile systemic amyloidosis is characterized by slow progression not requiring alkylating agents [160]. Reactive AA amyloidosis may respond to anti-inflammatory and immunosuppressive drugs that reduce production of acute-phase reactant serum amyloid A protein.

Ventricular dysfunction secondary to amyloidosis may be difficult to treat. Diuretics and vasodilators are used judiciously owing to the risk of hypotension with excessive falls in preload. Digoxin is contraindicated because it binds to amyloid fibrils and toxicity may develop at ordinary therapeutic doses. Complex ventricular arrhythmia has been documented in patients with cardiac amyloidosis and may be a predictor of SCD. Beta-blockers are administered with caution as they may promote AV block and their negative inotropism is often poorly tolerated. Implantation of a permanent pacemaker is indicated in patients with symptomatic bradyarrhythmias or complete AV block.

SARCOIDOSIS

Sarcoidosis is a multisystem disease characterized by non-caseating granulomas. Familial aggregation [161] suggests that genetic factors are involved. The lungs and lymphatic system are frequently affected. Cardiac involvement is uncommon; myocardial granulomas were detected in 27% of patients in one study [162]. It should be noted that microscopic granulomas within the heart may be overlooked at autopsy, resulting in underestimation of their prevalence. Indeed, cardiac disease has been reported in 58% of patients with sarcoidosis [163]. The most common sites of sarcoid granulomas are the left ventricular free wall (96%), septum (73%), right ventricle (46%), right atrium (11%) and left atrium (7%) [164].

Early treatment with corticosteriods and, if required, additional immunosuppressive agents improves outcome. Timely diagnosis is critical. Unfortunately, the perception that cardiac involvement is rare may lead to a delay in detection and therapy; in one study an ante-mortem diagnosis was made in only 65% of subjects [162]. Left ventricular diastolic dysfunction was present in 14% of patients with biopsy-proven pulmonary sarcoidosis but no other clinical features of cardiac disease [165], suggesting that subclinical sarcoid cardiomyopathy may be under-recognized.

Cardiovascular manifestations The cardiac complications of sarcoidosis and probable underlying mechanisms are summarized in Table 16.11.

Clinical presentation of cardiac sarcoidosis cardiac involvement should be considered in any sarcoidosis with symptoms of arrhythmia (i.e. palpitation, presyncope or syncope). Also worth investigating are patients with

Table 16.11 Cardiovascular manifestations of sarcoidosis

Abnormality	Manifestations	Proposed mechanism(s)
Conduction defects (common)	Primary AV block Bundle branch block Complete AV block Sudden death	Granulomatous or fibrous involvement of the basal interventricular septum and conduction system
Ventricular arrhythmia (common)	Frequent PVCs Non-sustained VT Sustained VT Sudden death	Associated with involvement of the LV free wall and aneurysm formation Granulomas and scarring create substrate for re-entry VT is frequently inducible by PVCs
Restrictive cardiomyopathy	Diastolic dysfunction	Myocardial infiltration by granulomas results in poor compliance
Dilated cardiomyopathy	Systolic impairment	Fibrogranulomatous replacement of the myocardium
Isolated right heart failure	RV hypertrophy RV dysfunction	Extensive fibrotic pulmonary sarcoidosis with secondary pulmonary hypertension
Myocardial hypertrophy	Asymmetric septal LVH Localized septal LVH Apical LVH	Inflammation in the septum or at the LV apex
Valvular dysfunction	Mitral regurgitation	Papillary muscle involvement
Atrial arrhythmia	SVT or AF	Atrial dilation secondary to LV dysfunction or cor pulmonale Granulomatous involvement of the atria
Pericarditis	Pericardial effusion	Fibrogranulomatous infiltration of pericardium
Coronary artery disease	Stenosis	Granulomatous vasculitis

AF, atrial fibrillation; AV, atrioventricular; LV, left ventricle; LVH, left ventricular hypertrophy; PVC, premature ventricular contraction; RV, right ventricle; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

dyspnoea out of proportion to pulmonary disease, particularly if physical signs of heart failure are present. Since sudden death may be the first manifestation of cardiac sarcoidosis, periodic screening with 12-lead ECG and echocardiography, with or without Holter monitoring, may be indicated.

Isolated cardiac sarcoidosis is rare and usually followed by systemic involvement. Alternatively, cardiac manifestations may develop after pulmonary sarcoidosis has resolved. In many cases, medical attention is not sought for mild respiratory complaints, or cough and dyspnoea are misattributed to infection or allergy. Thus, cardiac complications may be the presenting feature of the sarcoidosis. In patients without a diagnosis, the following cardiac abnormalities should raise suspicion:

1 the young patient with conduction system disease;
2 DCM with AV block, abnormal wall thickness, regional wall motion abnormalities, or perfusion defects in anteroseptal and apical regions that improve with stress [166];
3 sustained re-entrant VT [167], non-specific ECG abnormalities and echocardiogram, and angiographically normal coronary arteries;
4 restrictive cardiomyopathy of unknown aetiology;
5 presumed arrhythmogenic right ventricular cardiomyopathy and AV block, or signs and symptoms of chronic respiratory disease [168].

Diagnosis of cardiac sarcoidosis The minimum work-up for any patient with suspected cardiac sarcoidosis comprises a 12-lead ECG, echocardiography and Holter monitoring (Table 16.12).

Management and outcome Corticosteroids are first-line therapy for cardiac sarcoidosis. Prevention of disease progression necessitates early treatment, preferably at the time of diagnosis. Improvement or resolution of arrhythmia, conduction defects or perfusion abnormalities is well documented [169]. Left ventricular systolic impairment may respond, although steroids should ideally be commenced prior to the development of heart failure. The combination of pacemaker implantation for bradyarrhythmia and steroid therapy may improve prognosis and reduce mortality from SCD. Heart failure is now the main cause of death from cardiac sarcoidosis [170]. Once established, systolic heart failure may be

Table 16.12 Clinical investigations in cardiac sarcoidosis

12-lead ECG
Non-specific depolarization or repolarization abnormalities
Poor R-wave progression ('pseudo-infarct pattern')
Varying degrees of atrioventricular block
Arrhythmia

Two-dimensional echocardiography
Mild thickening of the left ventricular wall, concentric or asymmetric
Thinning of the myocardium with or without aneurysms in later stage, resulting from fibrosis
Right ventricular hypertrophy, dilation, and/or dysfunction
Increased pulmonary artery pressure
Mitral regurgitation secondary to papillary muscle dysfunction
Pericardial effusion
Systolic and/or diastolic dysfunction
Biatrial enlargement with restrictive physiology

Holter monitoring
Frequent PVCs, sustained or non-sustained VT
Bradyarrhythmias or conduction system disease

Myocardial perfusion scan
Perfusion defects affecting the anteroseptal and apical regions that improve with stress on thallium scanning
Gallium uptake in areas of inflammation

Magnetic resonance imaging
Structural and functional changes described above
Focal enhancement following administration of gadolinium, indicating fibrosis

Chest radiography/computed tomography
Detects pulmonary features of sarcoidosis in patients with cardiac presentation

Cardiac catheterization
Angiographically normal coronary arteries in presence of perfusion defect
Coronary artery stenosis secondary to vasculitis
Increased pulmonary artery pressure

Endomyocardial biopsy
High specificity but low sensitivity because of patchy disease involvement and likelihood of sampling errors

PVC, premature ventricular contraction; VT, ventricular tachycardia.

treated with ACE inhibitors and/or AT2 receptor antagonists and beta-blockers. The use of beta-blockers in patients with early conduction system disease warrants careful monitoring.

Antiarrhythmic therapy for recurrent VT remains largely empirical. Placement of an ICD should be considered for all sarcoidosis patients with ventricular tachyarrhythmia. Besides offering optimal protection against sudden death, the ICD may enable control of refractory VT by antitachycardia pacing. VT storm that is resistant to drug therapy may require catheter ablation as a last resort.

Table 16.13 Systemic manifestations of haemochromatosis

Cutaneous hyperpigmentation
Diabetes mellitus
Hepatomegaly, cirrhosis, hepatocellular carcinoma
Hypogonadotropic hypogonadism
Arthropathy

Storage diseases

The storage disorders are inborn errors of metabolism that result in the accumulation of the substrate or byproduct of the affected pathway. The intracellular location of the metabolite distinguishes storage disease from infiltrative disorders, in which deposition is confined to the interstitium. Accretion of the abnormal metabolite in the heart is toxic to myocytes and induces either concentric (HCM-like phenotype) or eccentric (DCM-like phenotype) hypertrophy.

HAEMOCHROMATOSIS

Haemochromatosis refers to genetically determined disorders of iron metabolism that result in iron overload and deposition. Organ dysfunction is due to the toxic effects of redox-active iron. Most commonly affected are the liver, pancreas, joints and heart (Table 16.13). The adult-onset form of haemochromatosis has been linked to mutations in the *HFE* gene on the short arm of chromosome 6 and, less commonly, the gene encoding transferrin receptor 2 (*TfR2*) [171]. Autosomal recessive inheritance with variable penetrance is typical. Heterozygosity is present in 8–10% of people of European descent, while 5 in 1000 are homozygous. Overt disease expression is rare in women of child-bearing age owing to protective blood loss during menstruation.

Three stages are recognized in the natural history of adult-onset haemochromatosis. In the initial biochemical phase, iron overload is confined to the plasma compartment, with increased transferrin saturation. More than 50% of *HFE* homozygotes with the most common disease-causing mutation (C282Y) will progress to the second deposition phase, in which iron accumulates in parenchymal tissues, with concomitant elevation of serum ferritin levels. Few patients progress to the final stage, with impairment of target organ function.

This pattern of gradual iron loading is in marked contrast to juvenile hereditary haemochromatosis, in which organ dysfunction ensues by the age of 30, with hypogonadism and glucose intolerance. Cardiac complications are also common and may result in premature death from

intractable heart failure. Mutations have been identified in the genes encoding hepcidin (*HAMP*) and hemojuvelin (*HJV*) [171].

Cardiovascular involvement Although haemochromatosis seldom affects the heart in isolation, cardiac complications are occasionally the presenting feature of the disease. The site and quantity of iron deposition within the heart determines the type and extent of cardiac dysfunction. The ventricles are commonly involved, leading in most cases to DCM, although a restrictive picture may be present. Subclinical cardiac disease can be identified by echocardiography.

On histology stainable iron is localized to the sarcoplasm but is generally absent from the interstitium. Cardiac haemochromatosis is therefore a storage disorder rather than infiltration, as evidenced by the normal ventricular wall thickness [172]. Ultrastructural studies reveal the presence of iron in the cytoplasm, nucleus and mitochondria; at least part of the toxicity of iron is ascribed to oxidative damage to the mitochondrial genome, with progressive mitochondrial dysfunction [173]. Consistent with this hypothesis is the predilection of haemochromatosis for organs with high mitochondrial activity: liver, pancreas and heart.

Of note, degenerative changes and fibrosis are minimal within the myocardium, probable accounting for the infrequency of ventricular tachyarrhythmia. Nevertheless, heart failure is often accompanied by ventricular extrasystoles or even VT, which may be difficult to treat [174]. In some patients, intravenous lidocaine (lignocaine), procainamide and propafenone fail to terminate sustained VT, as might DC cardioversion. Amiodarone may be successful in restoring sinus rhythm [175]. In a case of haemochromatosis presenting with recurrent syncope, both spontaneous and inducible polymorphic VT was present but there was no evidence of impaired ventricular function or diabetes, although liver function tests were mildly elevated. Marked signal loss in the liver was detected on MRI, a technique also useful for monitoring myocardial iron overload [176].

Commonly observed in cardiac haemochromatosis are atrial flutter or fibrillation and supraventricular tachycardia, possibly due to iron deposition in the atrium or related to increased pressures from ventricular dysfunction. Involvement of the conduction system may manifest as varying degrees of AV block or sick sinus syndrome.

Management and outcome Regular phlebotomy is the mainstay of treatment for cardiac haemochromatosis, and may effect partial or complete reversal of ventricular dysfunction and suppression of arrhythmia. Depletion of myocardial iron has been documented by serial EMB. Cardiac MRI offers a non-invasive means of assessing the response to therapy. Blood count, serum ferritin and transferrin saturations should also be monitored; excessively rapid mobilization of iron is thought to carry a risk of aggravating end-organ damage. Standard medical therapy is indicated for heart failure and arrhythmia.

Unfortunately, the correlation between cardiac iron load and function may decline in advanced disease [177]. It has been suggested that there is a threshold beyond which the toxic effects of iron accumulation in the myocardium result in permanent ultrastructural or metabolic derangements. Reduction in myocardial iron deposits at this stage do not result in improvement of cardiac function. Thus early diagnosis and initiation of prophylaxis or venesection remain critical. Screening of first-degree relatives for the disease is imperative and may be facilitated by increased availability of genetic testing.

GLYCOGEN STORAGE DISEASE

Glycogen storage disease (GSD) is a group of inherited metabolic disorders characterized by abnormalities in the enzymes that regulate the synthesis or degradation of glycogen. Glycogen storage occurs in the liver, heart, skeletal muscle and/or central nervous system. The heart is affected in types II, III and IV [178]. Cardiac manifestations often include severe LVH, which may mimic HCM or demonstrate a restrictive pattern. Cavity dilation and systolic impairment develop in advanced stages, producing a DCM-like phenotype. Conduction system disease is also described.

Glycogen storage disease type II Type II GSD, or Pompe's disease, is caused by deficiency of acid α-glucosidase (acid maltase) [179], which cleaves α-1,4 and α-1,6 glycosidic linkages of glycogen. The mode of inheritance is autosomal recessive. Genetic counselling and family screening are paramount once the diagnosis has been established.

The infantile form of type II GSD usually presents in the first months of life with failure to thrive, generalized hypotonia and weakness. Macroglossia and moderate hepatomegaly are associated features. Cardiomegaly is evident on chest radiography and may raise suspicion of the disease. Plasma CK levels are markedly elevated. The diagnosis is confirmed by enzyme assay of muscle or skin fibroblasts; acid α-glucosidase activity is virtually undetectable.

ECG findings in type II GSD include left-axis deviation, short PR interval, high-voltage QRS complexes and repolarization abnormalities. Echocardiography confirms severe concentric biventricular hypertrophy [180], which initially resembles HCM and may be associated with LVOTO. Systolic function is normal or hyperdynamic in

the initial stages, but deteriorates with disease progression as the ventricles dilate. Weakness of the diaphragm and intercostal muscles may necessitate mechanical ventilation, but high airway pressures may reduce ventricular filling and are poorly tolerated [181]. Death usually results from cardiorespiratory failure.

At post-mortem, the heart may be three times normal size. Fibroelastic thickening of the endocardium is often present. Histology reveals glycogen accumulation in cardiomyocytes, contained within membrane-bound vacuoles and free in the cytoplasm. Skeletal muscle shows a similar appearance.

In the past, infantile-onset Pompe's disease was almost uniformly fatal by 1 year of age. However, enzyme replacement therapy is promising and emphasizes the importance of early recognition, since the therapeutic window is short. In limited clinical trials of recombinant human acid α-glucosidase, treated infants showed decreased cardiomegaly, motor improvement and prolonged survival [181,182].

Late-onset type II GSD, in which disease develops after the age of 12 months, is associated with residual acid α-glucosidase activity (≤ 10% of normal in toddlers and children, and up to 40% in adults). Presentation in the elderly has been documented [183]. Interestingly, the clinical picture is dominated by proximal myopathy and respiratory insufficiency. Cardiac involvement is rare, suggesting that partial enzyme activity may be sufficient to protect the heart.

Glycogen storage disease type III Type III GSD, also known as Cori's or Forbe's disease, is caused by deficiency of the enzyme amylo-1,6-glucosidase, which is involved in 'debranching' the glycogen molecule during catabolism. This results in arrest of glycogen breakdown when the outermost branch points are reached. Phosphorylase limit dextrin, an abnormal form of glycogen, accumulates in affected tissue [184].

Type III GSD is also transmitted in autosomal recessive fashion. The clinical heterogeneity is explained at least in part by the variety of mutations identified. Fasting hypoglycaemia and hepatomegaly predominate. While liver dysfunction usually resolves during adolescence, worsening dysfunction and cirrhosis are also described. Cardiac involvement generally takes the form of LVH resembling HCM, which may be accompanied by SAM and LVOTO [185]. Many patients with echocardiographic abnormalities are asymptomatic. However, biventricular dilation, recurrent sustained VT and sudden death have also been reported. Late gadolinium enhancement has been observed on cardiac MRI, suggesting that progressive fibrosis may be the substrate for cavity dilation and re-entrant VT.

Glycogen storage disease type IV Type IV GSD is an autosomal recessive disorder linked to deficiency of the 'branching' enzyme amylo-1,4-1,6 transglucosidase [186]. The accumulation of polyglucosan bodies (an abnormal form of glycogen) in the liver may cause cirrhosis and hepatic failure in early childhood. However, non-progressive forms have also been documented [187]. Skeletal myopathy may occur and cardiac involvement characteristically manifests as congestive heart failure. A late-onset variant of type IV GSD is also described, with complete deficiency of branching enzyme and presentation in adolescence with DCM [188].

Fabry's disease

Anderson–Fabry disease is a metabolic storage disease in which deficiency of the enzyme α-galactosidase (α-Gal A) results in progressive tissue deposition of glycosphingolipids. Glycosphingolipids are components of the cytoplasmic membrane that consist of an outer saccharide component attached to a lipid called ceramide; the B blood group antigen is an example. Their ultimate breakdown inside lysosomes requires the action of a number of hydrolytic enzymes. α-Gal A is a lysosomal hydrolase responsible for the degradation of glycolipids with a terminal α-galactosamine residue. This substrate accumulates within cells owing to lack of α-Gal A activity in Fabry's disease.

The α-Gal A gene is located in the Xq22 region of the X chromosome. X-linked inheritance accounts for the male predominance, with incidence estimated at 1 in 40 000 to 1 in 60 000. Varying degrees of disease expression may nevertheless occur in female carriers as a result of random X-chromosome inactivation [189,190].

Fabry's disease predominantly affects the skin, endothelium, kidneys, liver, pancreas and nervous system (Table 16.14). Cardiac involvement is also common. In the classic phenotype, clinical manifestations begin in childhood or adolescence, on average at 10 years of age. Unfortunately, the non-specific symptoms may be misattributed to 'growing pains' or rheumatological diseases. Relentless progression is usual; neurological, cardiac and renal complications develop from late adolescence to adulthood. The average lifespan of 40 years improved by about a decade following introduction of renal dialysis. However, a major advance in Fabry's disease has been enzyme replacement therapy, which underscores the importance of early recognition. Clinical trials of gene-activated and recombinant human α-Gal A showed marked and rapid reduction in plasma and tissue levels of globotriaosylceramide, diminished pain and improved renal function [189].

Atypical variants of Fabry's disease may manifest after the age of 40. The phenotype is milder and may be

Table 16.14 Systemic manifestations of Fabry's disease

Pain
Chronic burning tingling pain in hands and feet
Fabry's crisis (acute severe pain precipitated by stress, exertion, concurrent illness/fever)

Skin
Angiokeratomas, lymphoedema

Eyes
Corneal opacity

Gastrointestinal
Diarrhoea, abdominal discomfort, vomiting

Neurological
Tinnitus, vertigo, headache, transient ischaemic attacks, cerebrovascular accidents

Pulmonary
Obstructive airways disease

Renal
Proteinuria, lipiduria, uraemia, hypertension, end-stage renal failure

Other
Reduced saliva and tear production; exercise and heat intolerance

confined to one organ system; isolated cardiac or renal manifestations are recognized. Residual enzyme activity is present in these patients, whereas α-Gal A levels are virtually undetectable in the classic form.

Cardiovascular involvement Intracellular accumulation of glycosphingolipids has been observed in the myocardium, conduction system, valves and vascular endothelium. Myocardial involvement typically manifests as LVH resembling HCM. Concentric hypertrophy is the most frequent distribution (37%), followed by asymmetric septal hypertrophy (10%). Eccentric and distal patterns of hypertrophy occur less frequently [4,191, 192]. The degree of hypertrophy shows a positive correlation with age and an inverse relationship with the level of α-Gal A activity; blood pressure does not appear to be a major determining factor. SAM and LVOTO may be present. As in HCM, systolic function is generally preserved, but mild to moderate diastolic impairment is common. A restrictive picture is rare. The deposits account for only around 1% of the increase in left ventricular mass, suggesting that the metabolic derangement induces compensatory hypertrophy by a mechanism that is still to be elucidated (see p. 483).

Thickening of the papillary muscles and mitral valve leaflets, with mild accompanying regurgitation, occurs in over half of patients with Fabry's disease. Mitral valve prolapse appears less common. Minor structural abnormalities of the aortic valve were observed in a smaller subset [191].

AF and non-sustained VT may occur in Fabry's disease, although the exact prevalence is uncertain. Varying degrees of AV block are a corollary of conduction system involvement.

Preferential storage of glycosphingolipids in the endothelium of cerebral vessels is associated with premature strokes. The vertebrobasilar circulation is predominantly affected. Endothelial dysfunction of coronary capillaries contributes to subendocardial ischaemia. Hypertension and dyslipidaemia related to chronic renal failure may also predispose patients with Fabry's disease to coronary artery disease. A relatively high prevalence of cigarette smokers has been reported among the Fabry population; it has been suggested that smoking may alleviate the neuropathic pain associated with the disorder.

Clinical management Patients with Fabry's disease experience the same cardiac symptoms as those with sarcomeric HCM, including anginal chest pain, exertional dyspnoea, palpitation, syncope and presyncope. In the isolated cardiac form of Fabry's disease, systemic manifestations are absent and diagnosis is dependent on enzyme assay and/or EMB. Affected males have reduced or undetectable levels of α-Gal A in plasma and peripheral leucocytes. Assessment of α-Gal A activity in 79 consecutive patients with late-onset HCM revealed a 6% prevalence of Fabry's disease [4]. X-linked inheritance will raise suspicion. Routine screening for Fabry's disease has therefore been advocated in male patients with HCM.

Female heterozygotes, in contrast, may have relatively high residual α-Gal A activity, limiting the value of enzyme assay in establishing the diagnosis. Confirmation of Fabry's disease in a male relative is strongly suggestive. Where this is not possible, EMB may elicit the diagnosis. Among 34 consecutive women with late-onset HCM, histology and/or electron microscopy showed features consistent with Fabry's disease in 12% [192]. Genetic testing may facilitate familial evaluation. Most affected families have private mutations, accounting in part for the variability in disease expression and prognosis. *De novo* mutations are uncommon.

Enzyme replacement is now the mainstay of disease-specific treatment. The cardiac manifestations of Fabry's disease respond to standard management strategies.

Post-radiation disease

Radiation may cause damage to any structure, including the pericardium, myocardium, valves, conduction system and coronary arteries. Much of our knowledge of radiotherapy-induced cardiovascular disease arose from

experience with survivors of Hodgkin's disease, many of whom are young and may develop sequelae. Chest irradiation is also used to treat breast cancer, lung cancer and seminomas [193]. The clinical impact of post-radiation cardiovascular disease will become more significant as long-term survival from cancer improves.

Myocardial involvement At least two mechanisms are thought to underlie myocardial injury from irradiation: microcirculatory damage and free-radical toxicity. Work with experimental animals suggests that the former is a three-stage process. The first acute phase occurs shortly after exposure to radiation and is characterized by acute inflammation of small and medium-sized arteries. In the latent phase that follows, damage to capillary endothelial cells causes thrombotic occlusion and ischaemia. Progressive myocyte death and fibrosis occurs over time. Experimentally, the end-result is extensive fibrosis and death. Fortunately, myocardial disease is generally milder in patients who have received radiotherapy, most of whom remain asymptomatic. Clinically overt cardiomyopathy is uncommon and generally shows a restrictive pattern. A DCM-like phenotype may occur with anthracycline derivatives, the cardiotoxicity of which is increased by radiation.

Pericarditis Pericardial disease may occasionally present during irradiation, although delayed onset is far more common. Early acute pericarditis is usually associated with radiation-induced necrosis of a large tumour adjacent to the heart. Radiotherapy is continued and long-term sequelae are rare (see also Chapter 15).

Delayed pericardial disease may present months to years after radiation exposure in two overlapping forms: (1) an acute pericarditis that evolves, in around 20% of patients, into chronic constrictive pericarditis; and (2) chronic pericardial effusion, which often resolves spontaneously over years. Patients with symptoms and/or evidence of haemodynamic compromise may benefit from total parietal pericardiectomy, which is associated with a more favourable outcome than pericardiocentesis alone.

Arrhythmia/conduction system disease The prevalence of conduction defects after radiotherapy is unknown, and delayed onset may preclude corroboration of a causal link. However, sick sinus syndrome and varying degrees of AV block have been reported. The level of the block is commonly infranodal rather than within the AV node. Supraventricular and ventricular arrhythmia have also been documented.

Valvular disease Among 294 asymptomatic patients previously treated with mediastinal irradiation for Hodgkin's disease, 29% had valve disease of sufficient clinical importance to justify antibiotic prophylaxis. The aortic valve was more commonly affected than the mitral and tricupsid valves, owing perhaps to its proximity to the radiation field. Both regurgitation and stenosis have been reported, although their relative frequency is unresolved. The prevalence of valve dysfunction increased with the time elapsed from radiotherapy.

Coronary artery disease Increased risk of coronary artery disease has been reported in patients previously treated with mediastinal irradiation. The left anterior descending and right coronary arteries fall within the typical radiation mantle field and are frequently affected. Proximal narrowing involving the ostia is typical [194]. Coronary artery disease generally occurs in patients with at least one other recognized risk factor besides exposure to radiation.

Clinical management Patients with radiation-induced cardiovascular disease may present with symptoms characteristic of the particular complication. Thus, acute pericarditis is accompanied by pleuritic chest pain and fever, while myocardial disease may manifest as chronic progressive dyspnoea. However, many radiotherapy recipients are asymptomatic. Subclinical myocardial dysfunction, pericardial effusion and valvular abnormalities are far more common than overt disease. Possibly silent myocardial infarction occurs more commonly in this subgroup than in the general population, owing to damage to cardiac nerve endings by irradiation.

Periodic cardiovascular evaluation of radiotherapy recipients has been advocated in order to identify clinically occult abnormalities [195]. A non-invasive work-up should include 12-lead ECG, echocardiography, exercise testing, Holter monitoring and a fasting blood lipid profile. Cardiac MRI may also be useful (see Chapter 3). Risk factors for coronary artery disease should be monitored and primary prevention measures instituted where necessary. Patients with valvular dysfunction may need endocarditis prophylaxis. Pregnancy is associated with increased cardiovascular demand and women should be encouraged to undergo cardiac assessment during antenatal care.

Contemporary radiotherapy techniques that involve lower total radiation doses and which minimize cardiac exposure by subcarinal shielding may diminish the risk of most types of cardiac disease. The antioxidant and iron chelator dexrazoxane confers protection against the cardiotoxic effects of anthracyclines, while amifostine reduces radiation-induced toxicity. Concurrent administration of cardiotoxic chemotherapeutic agents during radiotherapy should be avoided if at all possible. Aggressive treatment of hypertension and hyperlipidaemia

in this population may also reduce the likelihood of coronary artery disease developing in later life.

Arrhythmogenic cardiomyopathy

Definition

The 1996 WHO classification of cardiomyopathies defines arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) as a group of heart muscle diseases characterized by structural and functional abnormalities of the right ventricle due to localized or diffuse atrophy with replacement of the myocardium by fatty and fibrous tissue [38]. Preferred areas include the outflow tract, the apex and the subtricuspid area of the free wall. Usually, the ventricular septum is spared [196]. Generally, men aged 15–35 years are affected [197]. Clinically, these morphological alterations are associated with regional or global right ventricular dysfunction and life-threatening arrhythmias of right ventricular origin (e.g. premature ventricular beats, sustained VT or ventricular fibrillation), occasionally causing SCD in young patients with apparently normal hearts [196,198]. Since its first description by Fontaine *et al*. in 1977, considerable progress has been made in understanding its pathogenesis, morbid anatomy and clinical presentation [199–204]. Genetic background, natural history, exact clinical diagnosis including risk stratification, and treatment of high-risk patients are still poorly defined.

Aetiology and prevalence

Progressive loss and fibrofatty replacement of right ventricular myocardium in ARVD/C may be due to apoptosis of cardiomyocytes [205], myocardial inflammation [196,202,206], genetically determined myocardial atrophy [202] and possibly viral involvement [207]. Furthermore, regional clustering in Greece or northern Italy and familial history suggests an inherited disease usually with autosomal dominant inheritance and variable penetrance and phenotypes [197,208–210]. Because the disease is difficult to diagnose and because many patients may be asymptomatic until their first presentation with sudden death, the true incidence and prevalence of ARVD/C are unknown [211].

Genetics

Familial background has been demonstrated in 30–50% of ARVD/C cases [197]. Sporadic development or familial disease with incomplete penetrance and variable phenotypic expression may constitute for the remaining cases. Both males and females can carry the disease and transmit it. At present, 10 chromosomal loci on seven chromosomes have been identified (Table 16.15) [212]. Three involved gene products have been identified. In a rare inherited disease with a recessive form of transmission and 90% penetrance, mapped to chromosome 17, a defect in the gene encoding the cytoskeletal protein plakoglobin has been identified [213]. Genetic analysis of a similar disease with keratoderma and woolly hair at infancy and development of heart failure during adolescence revealed a mutation on chromosome 6p23–p24 encoding for desmoplakin, a protein important for attachment of intermediate filaments to the desmosome [214]. Mutations in the cardiac ryanodine receptor gene (chromosome 1q23–q24) may impair intracellular calcium release and trigger electrical instability and VT.

Table 16.15 Genetics of arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C)

Chromosome	Gene	Reference
Autosomal dominant forms of ARVD/C		
14q23–q24	–	Rampazzo *et al*. [208]
1q42–q43	Ryanodine receptor	Rampazzo *et al*. [219]
14q12–q22	–	Severini *et al*. [220]
2q32.1–q32.3	–	Rampazzo *et al*. [221]
3p23	–	Ahmad *et al*. [222]
10q22.3	–	Melberg *et al*. [223]
10p12–p14	–	Li *et al*. [224]
6p24	Desmoplakin	Rampazzo *et al*. [225]
Autosomal recessive forms of ARVD/C		
14q24–q	Plakoglobin	Frances *et al*. [226]
17q21	(Naxos disease)	Coonar *et al*. [213]

Adapted with permission from Paul *et al*. [212].

Pathophysiology

Acquired replacement of the right ventricular anterolateral free wall myocardium by fatty or fibrofatty tissue extending from the epicardium towards the endocardium in a wave-like manner is characteristic. Fatty replacement of the myocardium may be diffuse (80%) or segmental (20%). Transmural infiltration is often associated with increased wall thickness. Saccular aneurysms of the apex, infundibulum or postero-inferior wall are detected in 50% in the fibrofatty variant. Histomorphological findings with atrophic myocardium and focal myocyte necrosis in association with infiltrating lymphocytes resemble chronic myocarditis. Myocardial inflammation [206,215], viral infections [207] and genet-

ically determined dystrophy may be involved in the apoptotic loss of cardiac myocytes [205,216]. Islands of surviving myocardium interspersed with fatty or fibrofatty tissue may predispose to re-entrant tachycardia.

Clinical presentation

Exercise-triggered symptomatic VT of right ventricular origin (left bundle branch block configuration) is the most common clinical presentation. Palpitations and syncope are not uncommon due to sustained or non-sustained VT. With respect to VT morphology, it may be difficult to differentiate ARVD/C from benign and non-familial idiopathic right ventricular outflow tract tachycardia or pre-excitated AV re-entry tachycardia. In untreated patients, prolonged VT may degenerate into ventricular fibrillation. Because many patients are asymptomatic until their first presentation with sudden death, the true incidence and prevalence of VT-derived ventricular fibrillation leading to sudden cardiac arrest remains unknown. Patients presenting with congestive heart failure with or without ventricular arrhythmias are often misdiagnosed as having DCM.

Diagnostic testing

Clinical history may provide diagnostic and prognostic information if clinical events including palpitations, dizziness, presyncope, syncope and arrhythmias or a positive familial history are present.

ECG abnormalities are detected in up to 90%. Most commonly, right ventricular involvement is associated with T-wave inversion in V1–V3 without right bundle branch block. Repolarization abnormalities in leads beyond V3 may suggest left ventricular involvement [200]. Right bundle branch block, prolongation of QRS duration in V1–V3, and epsilon wave caused by ventricular postexcitation (in about 30%) reflect delayed right ventricular activation and are distinct ECG markers of the disease. Epsilon waves may be atypical and look like a smooth potential forming an atypical prolonged R' wave in leads V1–V3 if increased numbers of myocardial fibres are activated with delay. Therefore, any QRS duration in V1–V3 that exceeds QRS duration in V6 by more than 25 ms should be considered an epsilon wave [200].

Right ventricular angiography, which reveals right ventricular dilatation and regional or segmental wall movement abnormalities or dyskinesia typically detected in the infundibular, apical and subtricuspid region (bulgings and aneurysms), is the gold standard for the diagnosis of ARVD/C. These features, which have a diagnostic specificity of 90%, may also be detected non-invasively by MRI and echocardiography. MRI allows accurate characterization of right ventricular function and anatomy. Limitations of MRI in the detection of characteristic structural changes include exact determination of right ventricular free wall thickness and estimation of the amount of fatty tissue in comparison with the normally present epicardial and pericardial fat tissue. Differential diagnostic exclusion of other heart diseases, quantification of left and right ventricular function and structural abnormalities, non-invasive serial examinations of disease progression and screening of family members constitute the enormous potential of echocardiography as the preferential first-line diagnostic procedure. In minor forms of ARVD/C, localized abnormalities of the right heart cavities are difficult to detect. Subtle lesions may be missed by all imaging techniques.

The *in vivo* documentation of the typical histological changes of ARVD/C by EMB may be of diagnostic value but is limited by low sensitivity, especially in mild forms. EMB cannot prove transmural replacement of the myocardium by fatty or fibrofatty tissue. Moreover, the focal or segmental nature of lesions, the lack of involvement of the ventricular septum and the natural content of fatty tissue in older healthy patients may contribute to the low sensitivity of biopsy-derived diagnosis. The increased content of fatty and fibrotic tissue in older individuals or other cardiomyopathic conditions also interferes with the diagnostic accuracy of MRI.

Based on clinical and morphological findings, diagnostic criteria have been established for ARVD/C (Table 16.16) [217]. The diagnosis is based on two major criteria, one major plus two minor criteria, or four minor criteria, respectively, encompassing histological, electrocardiographic and arrhythmic factors [218].

Risk stratification

Prevention of fatal arrhythmic events and SCD is the main goal of management of ARVD/C. The development of often stress-induced ventricular fibrillation or haemodynamically intolerable VT is difficult to predict, especially in asymptomatic young subjects and athletes. Guidelines for prophylactic treatment of identified patients with minor symptoms or minor morphological changes are not available. Asymptomatic patients at high risk of sudden death are characterized by familial background and complex ventricular arrhythmias at young age or during competitive sport activities, syncope, or left ventricular involvement. In spite of ECG, Holter monitoring, exercise stress testing and signal-averaged ECG analysis, the predictive value of these non-invasive diagnostic tools for fatal events remains insufficient. Symptomatic patients should undergo a more detailed invasive analysis including left ventricular angiography, programmed ventricular stimulation and EMB.

Table 16.16 Major and minor criteria of arrhythmogenic right ventricular dysplasia/cardiomyopathy

Major criteria
Familial disease confirmed at necropsy or surgery
Epsilon wave or QRS duration > 110 ms in V1–V3
Severe RV dilatation and systolic dysfunction with no/mild LV involvement
Localized RV aneurysms (akinetic/dyskinetic areas with diastolic bulgings)
Severe segmental RV dilatation
Fibrofatty replacement of myocardium (endomyocardial biopsy)
Minor criteria
Family history of premature sudden death (< 35 years)
Family history based on clinical diagnostic criteria
Late potentials (signal-averaged ECG)
Inverted T waves in V2 and V3, no RBBB, in patients > 12 years
LBBB-type tachycardia (sustained or non-sustained) on ECG, Holter monitoring or during exercise testing
Ventricular extrasystoles (> 1000 in 24 h) on Holter monitoring
Mild global reduced RV dilatation and/or RV dysfunction with preserved LV function
Mild segmental RV dilatation
Regional right heart hypokinesia

LBBB, left bundle branch block; LV, left ventricle; RBBB, right bundle branch block; RV, right ventricle.
Adapted with permission from McKenna *et al*. [217].

Management of heart failure

Treatment of severe right ventricular or biventricular systolic dysfunction consists of current heart failure therapy, including ACE inhibitors or AT1 receptor antagonists, beta-blockers, diuretics, digitalis, spironolactone and anticoagulants. Heart transplantation may be considered in patients with refractory congestive heart failure.

Management of arrhythmias

Since the risk of sudden death in patients with ARVD/C is still poorly defined, pharmacological and non-pharmacological therapy is individualized. In patients with preserved systolic ventricular function, treatment of well-tolerated and non-life-threatening ventricular arrhythmias empirically includes amiodarone, beta-blockers, sotalol or propafenone. In patients with left ventricular dysfunction, pharmacological treatment is limited to amiodarone, possibly in combination with class I antiarrhythmics or beta-blocking agents.

The insertion of an automatic ICD is the treatment of choice in patients with syncope, cardiac arrest, documented VT or ventricular fibrillation, or positive familial history of SCD. The use of an ICD is limited by the progressive morphological changes within the right ventricular myocardium with low endocardial signals and increased pacing threshold.

Since new arrhythmic foci may develop over time due to the progressive nature of the disease, VT recurrences are reported in over 50% after catheter ablation. Nevertheless, monomorphic VT may be terminated by radiofrequency ablation in unstable patients with otherwise not effectively controlled arrhythmias. Sustained VT with ineffective drug control despite ICD may require heart transplantation.

Prognosis and outcome

Biventricular dysplastic involvement resulting in substantial left ventricular dysfunction mimicking DCM is rare. Progressive right ventricular failure may be a serious problem in a minority of patients, as may ventricular arrhythmias. Untreated sustained or non-sustained VT may be well tolerated by the majority of patients over a number of years but may degenerate to ventricular fibrillation and to sudden death (incidence of 1–2% per year) [196,204].

Unclassified cardiomyopathy: left ventricular non-compaction

Left ventricular non-compaction (LVNC) is a myocardial disease with a genetic basis that may result in heart failure, arrhythmia, thromboembolism and sudden death. It has only recently been recognized as a distinct cardiomyopathy and is defined by the presence of the following structural abnormalities.

1. A two-layer myocardium with thin compacted myocardium adjacent to the epicardium and thicker non-compacted myocardium near the endocardium. The ventricular wall appears markedly thickened overall. Current diagnostic criteria rely on measurement of the maximal end-systolic thickness of the non-compacted layer (N) and compacted layer (C). The diagnosis is confirmed with a ratio of N/C ≥ 2 in adults or N/C ≥ 1.4 in children [227]. The X/Y ratio, a measure of the relation between the depth of intertrabecular recesses and the overall wall thickness, is significantly higher in patients with LVNC compared with normal subjects; however, differentiation between the two layers in end-diastole is difficult [228].
2. Prominent and excessive trabeculations (usually three or more) in the non-compacted layer.
3. Deep intertrabecular recesses that fill with blood directly

from the left ventricular cavity, as demonstrated by colour flow Doppler.

4 Predominant localization of non-compacted regions to the lateral, apical and/or inferior walls of the left ventricle. The distribution is segmental rather than diffuse in LVNC. In contrast, heavy trabeculation coursing from the free wall to the septum is characteristic of normal hearts [229].

5 These stipulations serve to distinguish LVNC from prominent trabeculations of normal hearts, and in association with other diseases such as hypertension, valve lesions or DCM. Ventricular dilation and/or systolic impairment are common associated findings but are not requisite for diagnosis.

Prevalence and aetiology

Perhaps more so than any other cardiomyopathy, LVNC has been misdiagnosed as distal HCM, DCM or left ventricular apical thrombus [230]. It was only with the advent of superior echocardiographic technology that discrimination of two separate layers within the myocardium became possible. At lower resolutions, it is difficult to distinguish trabeculation from hypertrophy. Conversely, growing awareness of this new entity has led to over-diagnosis of prominent trabeculation or false tendons as LVNC, underscoring the need for standardized diagnostic criteria. The true prevalence of LVNC therefore remains difficult to estimate.

LVNC is thought to arise from arrest of normal myocardial maturation during embryogenesis. The early myocardium is composed of a loose network of interwoven fibres separated by deep recesses that communicate with the left ventricular cavity. During the fifth to eighth week of development, this spongy meshwork of fibres gradually becomes 'compacted', a process that advances from the epicardium to the endocardium and from the base of the heart to the apex. At the same time, the coronary circulation is being established and the intertrabecular recesses are reduced to capillaries [231]. While it is apparent that interruption of normal myocardial compaction would produce the characteristic LVNC phenotype, evidence for this mechanism is presently lacking.

LVNC is generally distinguished from persistent intramyocardial sinusoids, which are observed in the setting of congenital obstructive lesions of the right and left ventricular outflow tracts [232]. Ventricular pressure overload prevents regression of the embryonic sinusoids, resulting in deep recesses that communicate with both the ventricular cavity and the coronary circulation. This is considered a sporadic phenomenon. However, LVNC may occur in conjunction with congenital heart defects as a distinct inherited syndrome. Mutations in α-dystrobrevin have been identified in a Japanese family with LVNC, one or more ventricular septal defects and other congenital anomalies [233]. α-Dystrobrevin is a component of the dystrophic-associated glycoprotein complex that links the cytoskeleton of cardiac myocytes to the extracellular matrix.

Isolated LVNC, defined by the absence of coexisting cardiac abnormalities, has been linked with mutations in the gene *G4.5* at Xq28 [233], which has also been implicated in Barth's syndrome [234]. Barth's syndrome is an X-linked recessive disease that presents in infancy with the clinical triad of DCM, neutropenia and skeletal myopathy. The *G4.5* gene encodes a family of proteins known as tafazzins, the function of which is still being elucidated.

Mutations in Cypher/ZASP have been identified in both familial DCM and isolated LVNC [60]. Cypher/ZASP is a novel Z-line protein found in both cardiac and skeletal muscle that appears to play a role in bridging the sarcomere to the cytoskeleton.

Pathophysiology

Examination of post-mortem and explanted hearts from patients with LVNC confirms the anatomical features observed on imaging. Histology further demonstrates focal ischaemic necrosis within the thickened endocardial layer and trabeculations, but not in the epicardial zone. Interstitial fibrosis is also observed, of varying severity. Chronic myocarditis has been reported [227].

The pathological findings suggest possible mechanisms for the arrhythmia and progressive left ventricular failure that may accompany LVNC. The intertrabecular recesses receive blood directly from the left ventricular cavity. However, the epicardial and endocardial layers of the myocardium, including the trabeculations themselves, rely on the coronary arteries for their blood supply [235]. Failure of the coronary microcirculation to grow in step with the numerous trabeculae will result in capillary mass mismatch. The thickened myocardium may additionally compress intramural coronary vessels. The end-result of both of these processes is diminished subendocardial perfusion despite the presence of unobstructed coronary arteries. Reduced coronary flow reserve has indeed been documented in patients with LVNC by positron emission tomography [236]. Progressive ischaemia and consequent fibrosis may lead to systolic impairment and provide a substrate for arrhythmia.

The excessive trabeculation may also contribute to diastolic dysfunction by limiting the compliance of the myocardium; restrictive physiology occurs in 35% of adults with LVNC [235]. The frequency of thromboembolic events is as high as 24%. Thromboembolism is thought to result from stagnation of blood within the intertrabecular recesses and may manifest as

cerebrovascular accidents, transient ischaemic attacks, mesenteric infarction or pulmonary embolism.

Clinical presentation

Clinical onset ranges from the neonatal period to senescence. Patients with LVNC may present with symptoms of left ventricular failure, arrhythmia or, less commonly, thromboembolism. Cyanosis, failure to thrive and dysmorphic features are also described in childhood [237]. An increasing proportion of cases are identified via familial evaluation or incidentally during routine cardiac imaging.

Whether sudden death may be the first clinical manifestation of LVNC remains unresolved. LVNC is seldom represented in post-mortem series of victims of SCD, possibly due to a lack of awareness of the disease. It has been speculated that LVNC may account for a proportion of deaths ascribed to myocarditis or 'sudden arrhythmic death syndrome' with a structurally normal heart.

Diagnosis

The diagnostic work-up for a patient with suspected LVNC comprises 12-lead ECG, transthoracic echocardiography and Holter monitoring. Cardiopulmonary exercise testing with metabolic gas exchange measurements may also be useful for obtaining an objective assessment of functional capacity.

Most patients with LVNC have non-specific ECG findings. Shifts in the QRS axis, high QRS voltages, intraventricular conduction delay, bundle branch block and varying degrees of AV block have been described. Repolarization abnormalities include inverted T waves and ST-segment changes [231]. Up to 17% of paediatric patients have ECG features typical of Wolff–Parkinson–White syndrome [237], although this is rare among adults.

Considerable attention has focused on the role of cardiovascular MRI in the diagnosis of LVNC. Cardiovascular MRI is not restricted by acoustic windows and has the additional benefit of delineating areas of myocardial fibrosis following administration of gadolinium. However, two-dimensional echocardiography remains the mainstay of diagnosis. Use of intravenous contrast agents may improve definition of the endocardial border.

Management

Standard heart failure therapy is indicated for left ventricular dysfunction. Reports of the prevalence of arrhythmia vary widely. VT may occur in up to 41% of adult patients with LVNC [235]. In contrast, VT was rare in a study of Japanese children [238]. Extrapolating from the DCM population, treatment with beta-blockers and/or amiodarone may be sufficient for those with non-sustained VT and preserved left ventricular function. ICD placement should be considered in LVNC patients with sustained VT, recurrent unexplained syncope or LVEF < 35% on optimal medical therapy and non-sustained VT on Holter monitoring.

Similar discrepancies have been observed with regard to the frequency of thromboembolic events. At present, a pragmatic approach may involve anticoagulation of LVNC patients with ventricular dilation and/or significant systolic impairment. There is less evidence to support routine anticoagulant therapy for asymptomatic patients with normal ventricular function.

The most common pattern of inheritance in LVNC is autosomal dominant [239], which translates into a 50% probability of any first-degree relative carrying the disease-causing gene. Offering prospective cardiac evaluation to family members is therefore mandatory.

Prognosis and outcome

In a series of 34 adults with LVNC the mortality rate was high at 35% after 44 months; half of these deaths occurred suddenly. One patient died from refractory sustained VT and another from pulmonary embolism. End-stage heart failure accounted for one-third of the deaths and a further 12% of the patients in this cohort underwent cardiac transplantation. Unfavourable clinical outcomes were frequent [235].

However, this does not imply that LVNC has a uniformly poor prognosis. Preliminary surveys of any newly recognized disorder tend to be dominated by experience with symptomatic index cases with clinically severe disease. Adverse events among patients with HCM, for example, are far less common in community-based populations than originally predicted from tertiary centre studies. Many patients with LVNC are asymptomatic at initial diagnosis and may remain so for extended periods. Timely detection and judicious use of ICDs may improve outcomes in the remainder. The clinical course of LVNC in large populations without selection bias is still being defined.

Inflammatory myocardial disease

Myocarditis and viral cardiomyopathy

Definition

The term 'myocarditis' was first introduced by Sobernheim

in 1937. However, myocardial inflammation is no longer restricted to the early phase of 'acute myocarditis' since it is acknowledged that DCM may represent a sequel of chronic intramyocardial inflammation evoked by viral infection. With the expanding knowledge on the pathogenic link between myocarditis and DCM, the 1995 WHO/ISFC Task Force Report on the Definition and Classification of Cardiomyopathies introduced, among other specific cardiomyopathies, the new entity 'inflammatory cardiomyopathy' (DCMi), which is characterized by myocarditis in association with cardiac dysfunction [38]. Myocardial inflammation can be established by histological, immunological and immunohistochemical criteria. Idiopathic, autoimmune and infectious forms of DCMi are recognized.

Aetiology and prevalence

Several cardiotropic viruses have been identified in myocarditis and DCMi (Table 16.17). In patients with DCMi, parvovirus B19, human herpesvirus type 6 (HHV-6), enteroviruses (i.e. coxsackievirus), adenovirus and Epstein–Barr virus (EBV) are frequently detectable (Fig. 16.24). In the Western world, non-viral aetiologies (i.e. *Borrelia*, Chagas' disesae, diphtheria) are of minor importance. Evolution from myocarditis to DCM occurs in 21% of patients within a mean follow-up of 33 months.

The annual prevalence of DCM is 29 per million persons, and the annual prevalence of viral myocarditis is 131 per million persons. Considering that intramyocardial inflammation and/or viral persistence can be detected in about 60% of DCM patients, an annual prevalence of around 80 cases per million can be estimated. Detailed epidemiological data regarding acute myocarditis are not available.

Table 16.17 Cardiotropic viruses involved in myocarditis and inflammatory cardiomyopathy

Coxsackievirus
Adenovirus
Parvovirus B19
Human herpesvirus type 6
Epstein–Barr virus
Cytomegalovirus
Echovirus
Mumps virus
Influenza A and B viruses
Flavovirus
Human immunodeficiency virus
Measles virus
Polio virus
Hepatitis C virus
Rabies virus
Rubella virus
Variola virus
Varicella-zoster virus

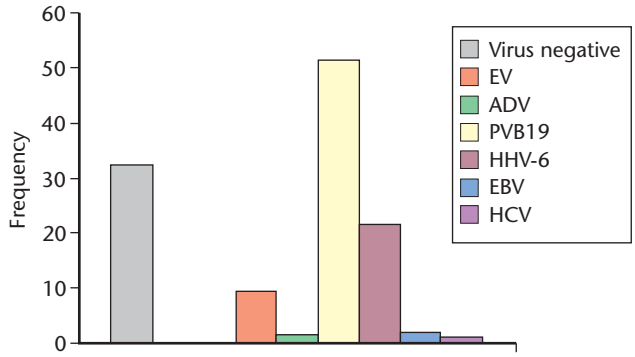


Figure 16.24 Spectrum of cardiotropic viruses in inflammatory cardiomyopathy. Frequencies of cardiotropic viruses proved by nested polymerase chain reaction in endomyocardial biopsies from patients with dilated cardiomyopathy. Results comprise in parts multiple viral infections. ADV, adenovirus; EBV, Epstein–Barr virus; EV, enterovirus; HCV, hepatitis C virus; HHV-6, human herpesvirus type 6; PVB19, parvovirus B19. Adapted with permission from Kühl *et al.* [42].

Genetics

At present, there is no evidence for monogenic inheritance of myocarditis or DCMi. It is hypothesized that a genetic predisposition might be associated with increased susceptibility for cardiotropic viruses and/or chronic myocardial inflammation in response to a viral infection. A well-investigated link is the disequilibrium of HLA haplotypes, with elevated HLA-DR4 frequencies (51% in DCM vs. 27% in controls, $P < 0.001$) and decreased HLA-DRw6 frequencies (9% in DCM vs. 24% in controls) [240]. However, the genetic inheritance of certain mutations and interference with modifier genes identified in familial cardiomyopathy does not preclude immunological pathomechanisms. In line with this, almost equally high rates of DCMi were reported in patients with familial DCM and their asymptomatic relatives and those with non-familial DCM [41].

Pathophysiology

Several viruses can be detected in biopsies from patients with clinically suspected myocarditis and DCM/DCMi, especially enteroviruses (i.e. coxsackievirus), adenovirus, parvovirus B19, HHV-6 and EBV (Fig. 16.24) [42,241]. The most detailed pathogenic pathways have been unravelled with respect to coxsackievirus. The *de novo* induction of coxsackie–adenovirus receptor in about 60% of DCM hearts, colocalized with the co-receptors for adenovirus internalization $\alpha_v\beta_3$ and $\alpha_v\beta_5$ (Fig. 16.25), indicates an important molecular determinant for the

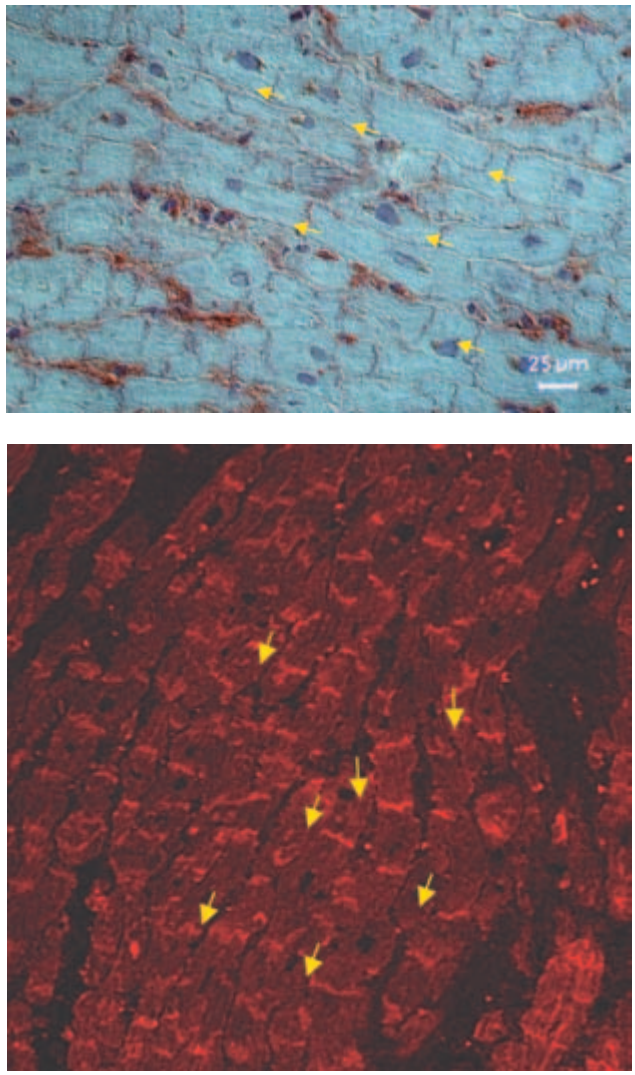


Figure 16.25 Coxsackie–adenovirus receptor (CAR) expression in dilated cardiomyopathy (DCM). (A) CAR induction in DCM with embryological expression pattern on the cardiomyocyte sarcolemma and the intercalated discs (arrows) (original magnification ×400). (B) Confocal laser scanning microscopy (Cy3 labelling) of CAR induction in DCM on the cardiomyocyte sarcolemma and the intercalated discs (arrows) (original magnification ×400). Reproduced with permission from Noutsias *et al*. [242].

cardiotropism of both coxsackievirus and adenovirus [242]. Basically, two different pathways of virus infection can be differentiated: (1) direct cytopathic effects and (2) secondarily induced effects, for example coxsackievirus protease 2A cleaves dystrophin, leading to disruption of the cytoskeleton [243]. Even non-replicating coxsackie viral genomes at low expression levels can exert cytopathic effects.

With regard to indirect pathways related to the host's immune response, the presentation of viral antigens evokes the antiviral immune response that aims at viral elimination and which is not necessarily detrimental to the heart. However, this immune response is a 'double-edged sword': molecular mimicry and perhaps genetically predisposing conditions can secondarily target cryptic myocardial antigens. In the case of postviral (auto)immunity, this immune response can continue despite possible elimination of the viral genome. On the other hand, chronic viral persistence maintains the anti-cardiac immune response. Activated B lymphocytes produce antibodies that can cross-react with myocardial antigens and may thus also contribute to impairment of cardiac contractility. Numerous autoantibodies have been identified in patients with DCM, targeting the ADP/ATP carrier, the β_1 adrenoreceptor, and further mitochondrial and contractile proteins. While the pathogenic relevance of autoantibodies may have been questioned in the past as epiphenomena of the immune response, recent experiments have proved the pathogenic principle of stimulating antibodies directed against the second extracellular β_1-receptor loop, since sera transferred from immunized rats induces DCM in healthy littermates [244]. Furthermore, results from immunoadsorption studies clearly indicate a causative role for autoantibodies in DCM [245].

Cardiodepressive cytokines induced by the immune system can directly impair cardiac contractility. Cytokines promote an imbalance between metalloproteinases (MMP) and their tissue inhibitors (TIMP), thus contributing to remodelling [246]. Preliminary results indicate a relationship between MMP/TIMP expression patterns and left ventricular function. Moreover, cytokines induce cell adhesion molecules (CAMs) on the endothelium, which mediate transendothelial migration of immunocompetent cells into the myocardium [39]. CAM interactions are also involved in the continuous loss of cardiomyocytes, mediated specifically by cytotoxic T lymphocytes [247]. This pathogenic model of myocarditis and DCMi is illustrated in Fig. 16.26.

There is growing evidence for the vasculotropism of parvovirus B19 and HHV-6. This may be responsible for the endothelial dysfunction and diastolic dysfunction observed in DCM, and possibly for the infarct-like presentation in the acute setting of myocarditis [241,248]. These data indicate additional virus-specific pathogenic mechanisms, which warrant further elucidation.

Clinical presentation

The clinical symptoms of myocarditis and DCM/DCMi comprise chest discomfort, heart failure symptoms, palpitations, syncope and SCD. Patients with acute myocarditis may report a close temporal association

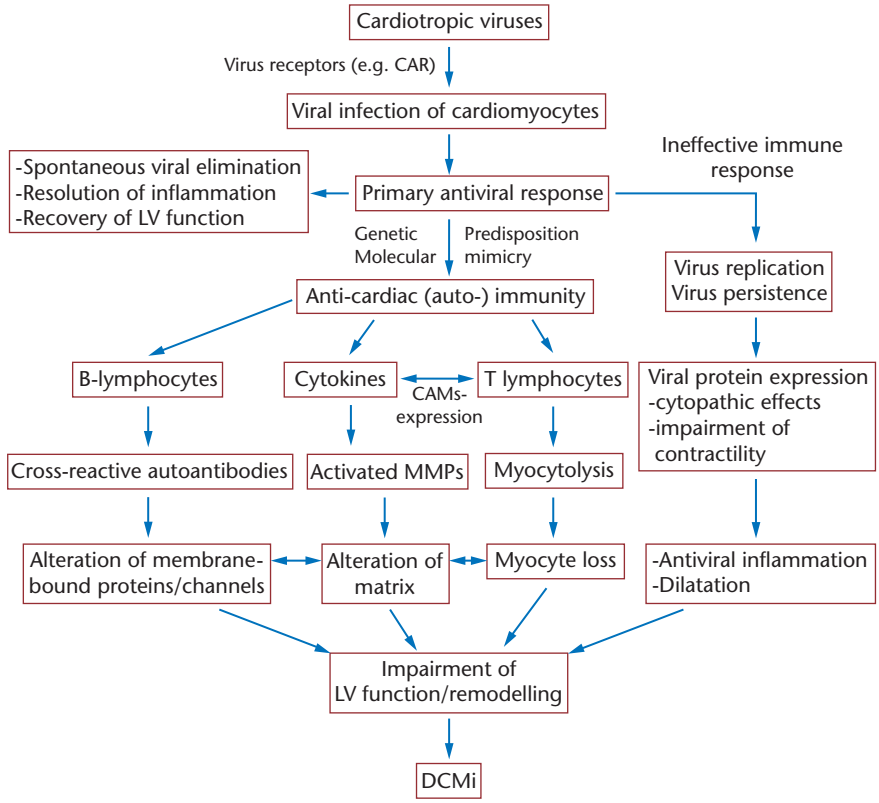


Figure 16.26 Pathophysiology of myocarditis and inflammatory cardiomyopathy (DCMi). CAMs, cell adhesion molecules; CAR, coxsackie–adenovirus receptor; MMP, matrix metalloproteinase.

(days to weeks) with an antecedent flu-like illness (upper respiratory or gastrointestinal tract infection) before the onset of symptoms. However, acute myocarditis, with its often subtle or virtually absent symptoms, may be frequently missed. Two different presentations of acute myocarditis can be differentiated.

1 In the setting of acute fulminant myocarditis, patients complain of acute onset and rapidly progressive (within hours to days) heart failure symptoms (i.e. dyspnoea at rest, peripheral oedema). Left ventricular function is severely impaired in concert with left ventricular dilatation, and possibly pulmonary oedema. Patients may require inotropic or mechanical support (i.e. LVAD). Left ventricular function in acute fulminant myocarditis usually improves dramatically and may even normalize completely at follow-up examinations [122], which is consistent with the hypothesis that left ventricular function can improve after viral elimination and resolution of myocarditis. Acute fulminant myocarditis is less frequent than acute non-fulminant myocarditis.
2 In comparison, patients with acute non-fulminant myocarditis typically present with acute onset of symptoms of angina pectoris and ST-segment elevation/depression or T-wave inversions as well as elevated CK-MB/troponin levels, mimicking acute myocardial infarction in the absence of coronary artery stenoses. Creatine phosphokinase/troponin levels usually normalize within 60 h. C-reactive protein is often increased. Global systolic function is often preserved in acute non-fulminant myocarditis, although regional wall motion abnormalities and diastolic dysfunction can be frequently observed. Furthermore, pericardial effusions and wall oedema can be detected by echocardiography [241].

The clinical presentation of patients with DCM is characterized by dyspnoea on exertion or at rest and peripheral oedema with often progressive course. Interestingly, some patients demonstrate a high exercise capacity despite severely depressed left ventricular contractility. Cardiomegaly, pulmonary congestion/oedema and pleural effusions are frequently observed on chest radiography. Systolic and diastolic dysfunction as well as left ventricular or biventricular dilatation can be confirmed by echocardiography. Furthermore, dilatation of the left atrium and often (relative) mitral insufficiency can be found. Rather rarely, left ventricular thrombi occur that can cause thromboembolic complications.

Both acute myocarditis and DCM/DCMi can present with various types of ECG abnormalities (right or left bundle branch block, ST-segment depression, Q waves and

T-wave inversions, AV block) and rhythm disturbances on Holter monitoring (sinus tachycardia/bradycardia, supraventricular/ventricular extrasystoles, atrial fibrillation/flutter, ventricular tachycardia/flutter/fibrillation). Myocarditis is a frequent cause of SCD (up to 40%), especially in the young, and is often associated with strenuous physical exertion.

Coronary artery stenoses are excluded by coronary angiography in both myocarditis and DCM/DCMi. Coronary artery vasospasm can be often induced by vasoconstrictor challenge, especially in the setting of acute non-fulminant myocarditis [241,248].

Symptoms and clinical findings in acute myocarditis and DCM/DCMi are summarized in Table 16.18. Notice-

Table 16.18 Clinical findings in patients with acute myocarditis and dilated/inflammatory cardiomyopathy (DCM/DCMi)

Investigation	Findings	Acute non-fulminant myocarditis	Acute fulminant myocarditis	DCM/DCMi
Clinical symptoms	Antecedent flu-like illness	+	+	–
	Febrile temperature	+	+	–
	Acute onset of angina pectoris ('infarct-like')	+	(+)	–
	Acute onset of heart failure	–	+	–
	Chronic progressive heart failure	–	–	+
	Palpitations	+	+	+
	Syncope	+	+	+
	Sudden cardiac death	+	+	+
Laboratory findings	CK-MB elevation	+	(+)	–
	Troponin elevation	+	(+)	–
	CRP elevation	+	+	–
Chest radiography	Cardiomegaly	(+)	+	+
	Pulmonary congestion	(+)	+	+
	Pleural effusion	(+)	+	+
Holter monitoring	ST elevation	+	(+)	–
	ST depression	+	+	+
	T-wave inversion	+	+	+
	Bundle branch block	+	+	+
	Atrioventricular block	+	+	+
	Sinus tachycardia/bradycardia	+	+	+
	Supraventricular/ventricular extrasystoles	+	+	+
	Atrial fibrillation/flutter	+	+	+
	Ventricular flutter/tachycardia, ventricular fibrillation	+	+	+
Echocardiography	Wall oedema	+	+	–
	Regional wall motion disturbances	+	(+)	(+)
	Diastolic dysfunction	+	+	+
	Global LV systolic dysfunction	(+)	+	+
	Ventricular dilatation	(+)	+	+
	Atrial dilatation	(+)	+	+
	Mitral insufficiency	(+)	+	+
	Pericardial effusion	+	+	–
	LV thrombus	–	(+)	(+)
Cardiac catheterization	Exclusion of coronary artery disease	+	+	+
	Coronary vasospasm	+	(+)	(+)
	Regional wall motion disturbances	+	(+)	(+)
	Global LV systolic dysfunction	(+)	+	+
	Mitral insufficiency	(+)	+	+

CK-MB, creatine kinase, myocardial bound; CRP, C-reactive protein; LV, left ventricle.

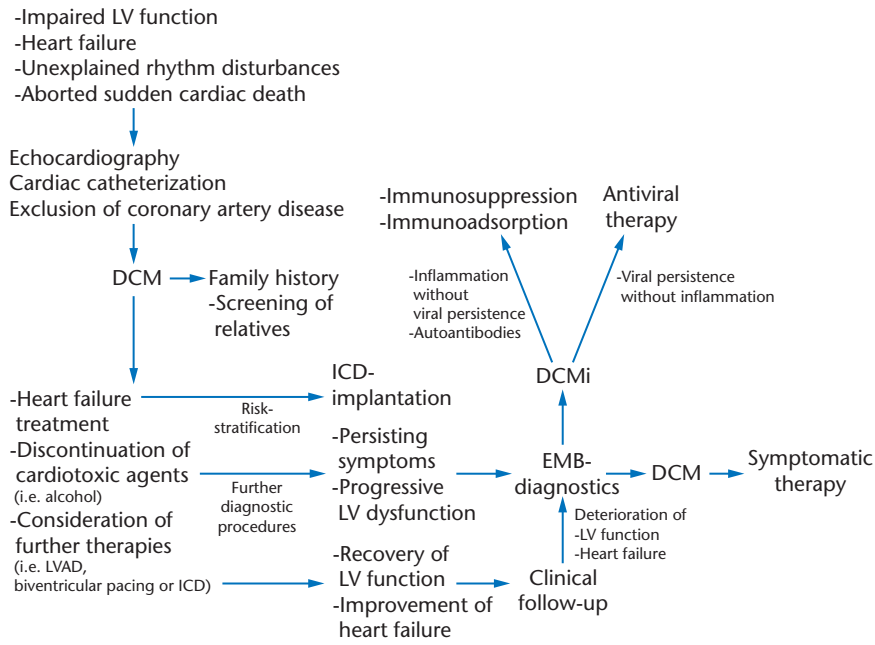


Figure 16.27 Diagnostic and therapeutic algorithms in dilated cardiomyopathy (DCM) and inflammatory cardiomyopathy (DCMi). EMB, endomyocardial biopsy; ICD, implantable cardioverter-defibrillator; LVAD, left ventricular assist device.

ably, none of these characteristics is valuable for the determination of viral/inflammatory aetiology and the differentiation between DCM and DCMi.

Management

In patients with clinically suspected acute myocarditis and those with DCM/DCMi, secondary causes of heart failure (i.e. coronary artery disease, arterial hypertension, significant valvular heart disease) should be excluded. The diagnostic procedures for and treatment of heart failure (i.e. ACE inhibitors, AT1 receptor blockers, beta-blockers, diuretics, aldosterone antagonists, digitalis; cardiac transplantation as ultimate option) apply also to myocarditis and DCM/DCMi. In addition, cardiac resynchronization and LVAD have provided substantial improvement in patients with myocarditis and DCM. Risk stratification and primary prevention of SCD imposes a clinical challenge, especially since programmed ventricular stimulation is not predictive. Based on the recently published SCD-Heft trial, the same criteria apply to both ischaemic and non-ischaemic cardiomyopathies: chronic heart failure, NYHA > II and LVEF < 35%. There are no conclusive data with respect to acute myocarditis. Patients should be monitored at least during the phase of elevated CK-MB/troponin levels. Screening of relatives in the case of positive family history can reveal early disease stages.

If patients with myocarditis/DCM improve with heart failure regimens, patients should be monitored clinically and by non-invasive ECG, Holter and echocardiography. Especially in patients with acute myocarditis, courses with spontaneous recovery of left ventricular function can be observed. However, if left ventricular function progressively deteriorates despite symptomatic heart failure medication, immunomodulatory treatment should be considered additionally (see p. 498). EMB should be obtained in these patients and subjected to contemporary diagnostic techniques (immunohistological assessment of inflammation, molecular biological proof of cardiotropic viruses). In addition, cardiac autoantibodies and their functional activity should be ascertained.

The algorithm for the management of patients with myocarditis and DCMi is presented in Fig. 16.27.

Diagnostic EMB procedures

EMB can be obtained from the right or left ventricle or from the atrial septum. Procedural complications of EMB are fairly rare in experienced centres, and a fatal outcome due to perforation accounts for less than 0.4% in large studies [249]. EMB procedures are therefore justified, provided that a clinical impact results from investigation of the biopsy.

HISTOLOGICAL ASSESSMENT OF INFLAMMATION

The Dallas criteria differentiate 'active' (interstitial infiltrates with myocytolysis) from borderline myocarditis (increased infiltrates with or without fibrosis; Fig. 16.28) [250]. Myocarditis is only rarely revealed by histological assessment (5–10%, including both forms). However, histological assessment is hampered by sampling error

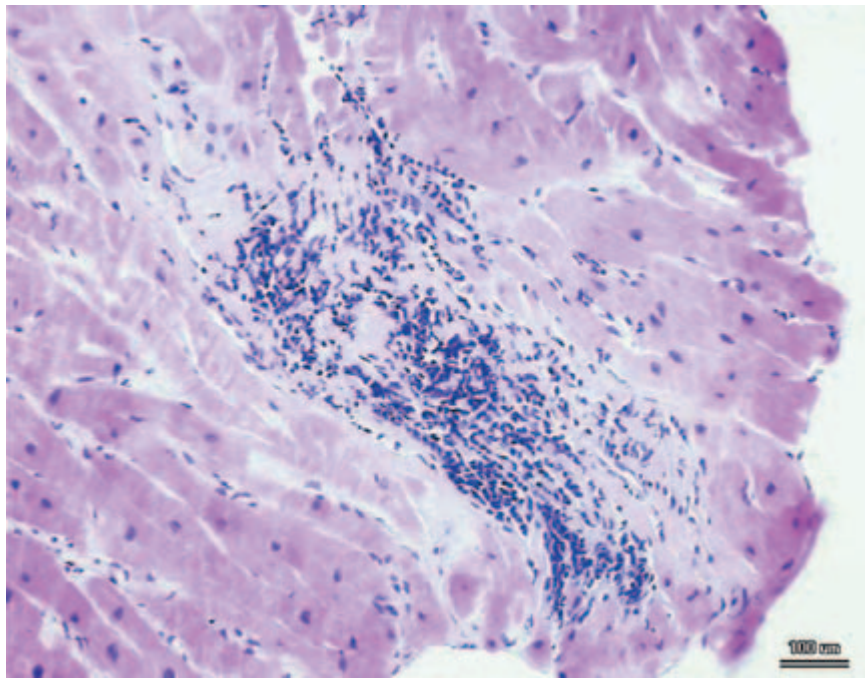


Figure 16.28 Histology of active myocarditis: focal lymphomononuclear infiltrate with adjacent myocytolysis (original magnification ×200).

and interobserver variability. Even Billingham, from the Dallas panel of expert pathologists, stated that 'these criteria have been misrepresented as a classification that is used as a *sine qua non* of the histological diagnosis of acute myocarditis'. Further characteristics of cardiomyopathies (i.e. hypertrophy, loss of myofibrils) are also detectable by histological assessment but are not pathognomonic for myocarditis or DCMi. Notwithstanding these pitfalls, histological assessment of EMB is still mandatory for the diagnosis of 'active myocarditis' and also for the differentiation from other conditions such as storage diseases.

IMMUNOHISTOLOGICAL EVALUATION OF INFLAMMATION

Immunohistological techniques have been established that are sensitive and specific and which provide quantification and phenotypic characterization of inflammation. These techniques have numerous advantages compared with the histological Dallas criteria (Table 16.19) and have helped elucidate many of the key players of the immune response in myocarditis and DCMi.

Increased T-lymphocyte infiltration (> 7/mm^2) is considered pathogenic (Fig. 16.29A). In addition, functional markers such as cytotoxic T lymphocytes (Fig. 16.29B) or activated T lymphocytes (i.e. CD45R0$^+$ or CD69$^+$) and macrophages can be specified. A further pivotal diagnostic hallmark is the endothelial abundance of CAMs, significantly related to the extent of infiltration due to specific receptor–ligand interactions; however, because of their homogeneous expression pattern, they are not prone to sampling error (Fig. 16.29C). Immunohistological staining can be quantified by digital image analysis, enabling observer-independent evaluation [39,242,249]. Commonly used target antigens for the immunohistological evaluation of intramyocardial inflammation are summarized in Table 16.20.

MOLECULAR BIOLOGICAL DETECTION OF VIRAL GENOMES

Molecular biological detection of viral genomes is pertinent for the differentiation of DCMi. Because of low sensitivity and specificity, serology or direct virus isolation from the myocardium has a negligible diagnostic value. PCR amplification of viral genomes has confirmed viral persistence in a major proportion of patients with myocarditis and DCM, and broadened the spectrum of cardiotropic viruses substantially.

The adverse prognostic impact of enteroviral persistence in DCM was identified early [126] and recent results indicate the importance of the replicative infection mode in many patients with DCM [127,251]. There is a growing importance of other cardiotropic viruses, especially parvovirus B19, HHV-6 and EBV (Fig. 16.24), and preliminary data indicate that these viruses also have adverse prognostic impact in DCM [45,241]. In addition, retrospective analysis has confirmed that patients with persistence of these recently identified viruses (except for hepatitis C) do not improve and may even deteriorate under immunosuppression [45], which infers that

Table 16.19 Synopsis of histological and immunohistological evaluation of intramyocardial inflammation

Histological evaluation of myocarditis (Dallas criteria)

Definition
Active myocarditis: increased infiltrates with adjacent myocytolysis
Borderline myocarditis: increased infiltrates without adjacent myocytolysis

Pitfalls
High interobserver variability
High sampling error
Substantial variability of myocarditis prevalence reported in DCM (0–63%)
No exact identification and quantification of immunocompetent infiltrates possible
No phenotypic characterization possible
Functionally important issues (i.e. CAM abundance, CTL-mediated myocytolysis) not accessible to histology
Subjective interpretation; observer-independent evaluation not possible
No discrimination of DCM patients who will benefit from immunosuppression in randomized trials

Immunohistological evaluation of inflammatory cardiomyopathy
Definition/classification
CD3+/CD2+ lymphocytes: > 7.0/mm^2
CAMs: three or more endothelial adhesion molecules (increased immunoreactivity compared with baseline expression in controls)
Perforin-positive CTLs: ≥ 7.0/mm^2

Advantages
Substantially lower interobserver variability and sampling error
Consistent prevalence of inflammatory cardiomyopathy in DCM (40–60%)
Exact identification and quantification of immunocompetent infiltrates feasible
Broad phenotypic characterization feasible (T lymphocytes, CTLs, macrophages, determination of activation status)
CAM abundance and CTL-mediated myocytolysis can be specified
Observer-independent quantification by digital image analysis has been established
Diagnostic discrimination of DCM patients who will benefit from immunosuppression and proof of treatment efficacy on the course of intramyocardial inflammation proven in several randomized studies

CAMs, cell adhesion molecules; CTL, cytotoxic T lymphocyte; DCM, dilated cardiomyopathy.
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Table 16.20 Commonly used target antigens for the immunohistological evaluation of intramyocardial inflammation

Target antigen	Recognized phenotypes/expression pattern
CD3	T lymphocytes
CD11a/LFA-1	T lymphocytes, large granular lymphocytes including CTLs; counter-receptor of ICAM-1
CD45R0	Memory T cells
Perforin	Specifically CTLs
CD11b/Mac-1	Macrophages; counter-receptor of ICAM-1
27E10	Specifically early activated macrophages
HLA class I	Expressed constitutively at baseline levels, induced in DCMi on endothelial and interstitial cells, occasionally also on the cardiomyocyte sarcolemma
CD54/ICAM-1	Expressed constitutively at baseline levels, induced in DCMi on endothelial and interstitial cells, occasionally also on the cardiomyocyte sarcolemma; endothelial receptor for both LFA-1+ and Mac-1+ infiltrates
CD106/VCAM-1	Expressed exclusively on endothelial cells; no constitutive expression; *de novo* induction in DCMi

CTLs, cytotoxic T lymphocytes; DCMi, inflammatory cardiomyopathy; ICAM-1, intercellular adhesion molecule 1; VCAM-1, vascular cell adhesion molecule 1.
Reproduced with permission from Noutsias *et al.* [249]

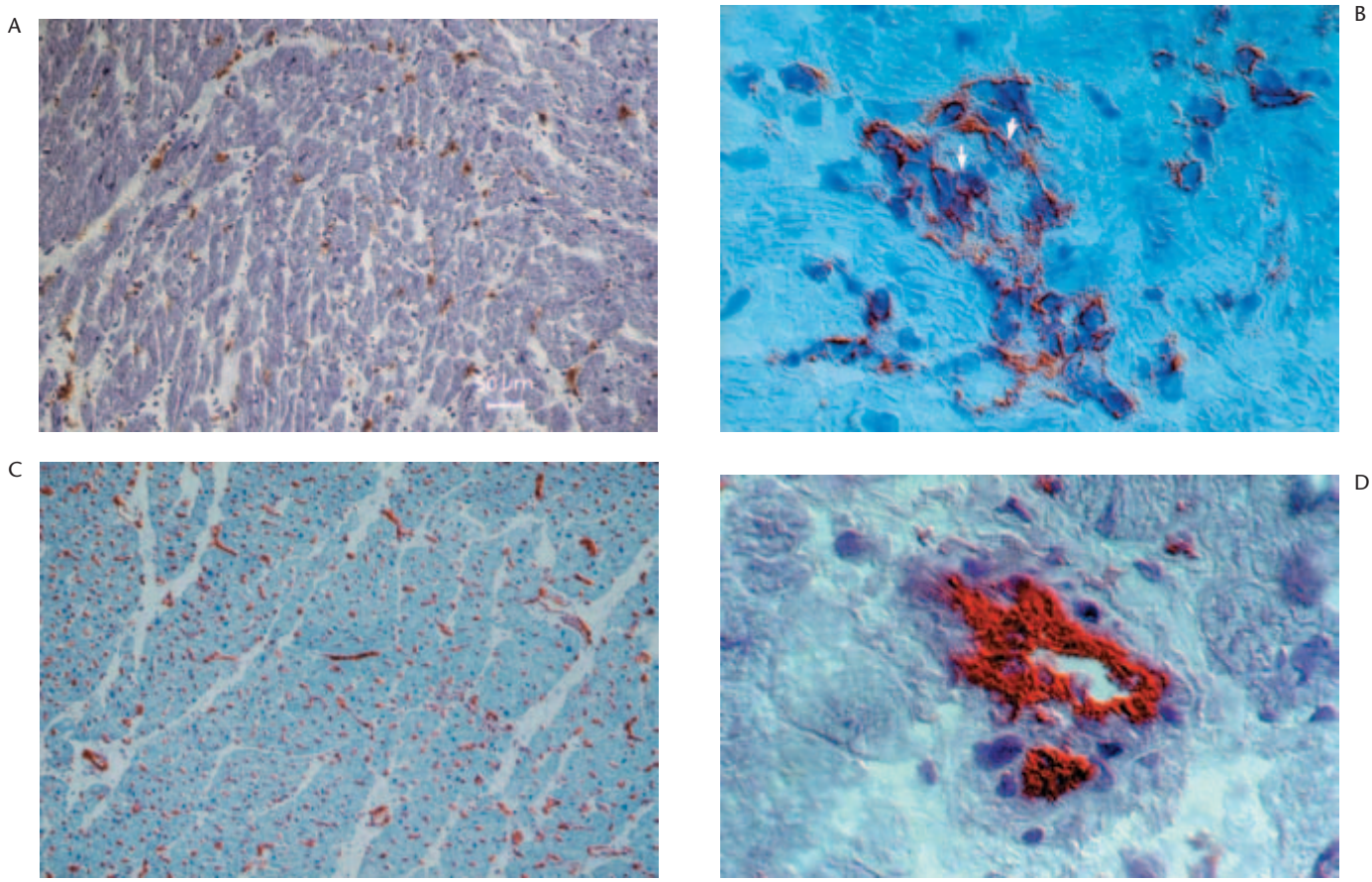


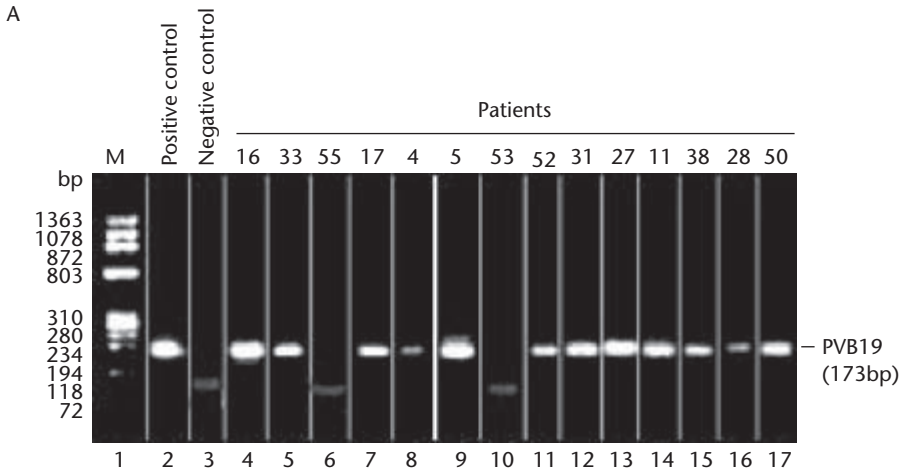
Figure 16.29 Immunohistological aspects of inflammatory cardiomyopathy (DCMi). (A) Typical diffuse infiltration pattern of LFA-1$^+$ lymphocytes in DCMi (original magnification ×200). (B) Focal cytotoxic T lymphocytes (perforin positive) encircling and entering a cardiomyocyte suggestive of myocytolysis in DCMi (original magnification ×630). (C) Homogeneous endothelial ICAM-1 abundance in DCMi (original magnification ×200). (D) Endothelial VCAM-1 expression in DCMi (original magnification ×630). Reproduced with permission from Noutsias *et al.* [247].

myocardial persistence of these viruses may have similar prognostic impact and therapeutic implications as for coxsackievirus infection.

In addition to nested PCR amplification of viral genomes, further methodological approaches are available to characterize viral infections. An important issue is the replicative mode of viral infection: viruses may exhibit either latent infection or active replication within the host tissue. Both infection modes have been reported in myocarditis and DCM with respect to enteroviral infection using strand-specific PCR, with minus-strand RNA indicating active viral replication [251]. It is noteworthy that patients with DCMi and active enteroviral replication have a substantially worse prognosis compared with those DCMi patients showing viral latency [127]. Real-time PCR approaches are suitable for quantifying the virus load. Direct sequencing of positive PCR results allows the identification of the virus genotype. Sequence analysis should be performed from the perspective of quality control in order to exclude contamination, which may occur especially during nested PCR methods (Fig. 16.30) [42,241,248].

Immunomodulatory treatment strategies

Immunomodulatory treatment should be considered as an additional treatment option in patients with DCM whose left ventricular function progressively deteriorates despite heart failure medication. This approach is based on the hypothesis that heart failure treatment does not affect the underlying pathogenic mechanisms of DCMi and that tailored immunomodulation will improve the progressive course of the disease by specific interaction with these pathways.



B

Patients	PVB19	CCCATTATGGGACTAATGGTGGAAACCTTTGCCTCCTTCGCAGTGGGATTATGGCAGCTACTTGCTGCGGGAGAAAACACCTT
	16	. . . . . T . . . . . T . . . . . A . . . . . A . . . . . T . .
	33	. . . . . A . . . . . T . . . . . A . . . . .
	17	. . . . . T . . . . . G . . . . . C . . . . .
	4	. . . . . A . . . . . A . . . . . T . . . . . G . . . . . T . . . . .
	5	. . . . . A . . . . . T . . . . . T . . T . . . . . A . . . . . A . . . . . T . .
	52	. . . . . T . . . . . G . . . . . C . . . . .
	31	. . . . . T . . . . . G . . . . .
	27	. . . . . A . . . . . T . . . . . A . . . . .
	11	. . . . . A . . . . . T . . . . . A . . . . .
	38	. . . . . T . . . . . T . . . . . G . . . . . C . . . . .
	28	. . . . . T . . T . . . . . A . . . . .
	50	. . . . . TC . . . . . T . . . . .

Figure 16.30 Polymerase chain reaction (PCR) and sequence analysis of parvovirus B19 (PVB19) in endomyocardial biopsies. (A) Qualitative proof of PVB19 genomes by nested PCR. (B) Sequence analysis of PVB19 genomes. Dots indicate sequence homologies and letters indicate point mutations after alignment with the reference PVB19 sequence. Reproduced with permission from Tschope *et al*. [248].

Several recent studies have demonstrated a clear benefit of tailored immunomodulatory regimens in selected patients with DCM when using contemporary diagnostic tools. EMB is mandatory in order to elucidate inflammation and/or viral infection, and the functional activity of autoantibodies should be assessed as well, since these pathogenic factors are important hallmarks for the choice of immunomodulatory strategy. According to current concepts, patients with DCMi with immunohistologically proven chronic inflammation but no viral persistence benefit from immunosuppression. Immunoadsorption is a treatment option in those patients with functionally active autoantibodies. Finally, patients with DCMi and cardiotropic viral persistence should not be subjected to immunosuppression, since these patients are candidates for antiviral treatment. At present, immunomodulation remains an option for expert centres.

Immunomodulation should be considered not only in DCMi patients with severely depressed LVEF but also in those patients with slightly impaired left ventricular function (in whom cardiac damage presumably did not progress to an irreversible stage) in order to halt and potentially reverse the pathogenically relevant process. The beneficial effects of immunomodulatory treatment are long-lasting in patients with DCMi, even after cessation of treatment.

IMMUNOSUPPRESSION

After exclusion of spontaneous recovery, a 6-month course of immunosuppression in 31 patients with DCMi with immunohistological diagnosis demonstrated significant positive effects on heart failure symptoms and haemodynamic measurements, paralleled by a significant decrease in infiltrates and CAM expression in 64% of the patients [252]. This substantial improvement in LVEF was observed irrespective of the initial LVEF at study entry, which implies that virtually all patients with DCMi can benefit from immunomodulatory treatment, even in cases with only slightly impaired left ventricular function

(e.g. regional left ventricular dysfunction), since these patients demonstrated almost a normalization of left ventricular function. Sustained beneficial effects of immunosuppression on heart failure symptoms, left ventricular dimensions and LVEF in immunohistologically EMB-proven DCMi have been confirmed in a randomized trial with 41 patients at 2 years follow-up after ≥ 3 months of treatment with corticosteroids and azathioprine [46]. Prednisone was started at a dose of 1 mg/kg/day and after 12 days the dose was tapered off every 5 days by 5 mg/day until reaching the maintenance dose of 0.2 mg/kg/day for a total of 90 days. Azathioprine was given at a dose of 1 mg/kg/day for a total of 100 days. This trial ultimately validates the diagnostic sensitivity and accuracy of CAM abundance for DCMi even in the absence of lymphocytic infiltration, possibly due to the close functional association between CAM induction and immunocompetent infiltration and cytokine induction [39], and thus constitutes an important criterion for selecting those patients who will likely benefit from immunosuppression. Furthermore, this study showed for the first time that a 3-month regimen is equally effective as previous trials that used 6 months of immunosuppression, and that the beneficial effects last for an extended period of time (2 years).

Viral persistence and lack of anti-cardiac autoantibodies were the key discriminators of those patients with DCMi who did not respond to a 6-month course of immunosuppression [45]. These compelling insights have confirmed the hypothesis that DCMi patients with viral persistence should not be subjected to immunosuppression, since inhibition of the antiviral immune response might perpetuate viral replication, and antiviral regimens should be favoured in these patients. However, this seems to be different in cases of hepatitis C virus-induced DCMi.

IMMUNOADSORPTION

The rationale for immunoadsorption is to extract cardiodepressive antibodies from the patient's plasma. The plasma is separated by a conventional plasmapheresis unit and passed through an immunoadsorber column. Total IgG is adsorbed during repetitive sessions at defined intervals, i.e. first course comprises daily immunoadsorption session on three consecutive days, followed by four courses at 1-month intervals. After every session, plasma IgG levels must be restored by injection of 0.5 g/kg polyclonal IgG.

The favourable haemodynamic results of immunoadsorption in patients with DCM may be related to removal of functionally active cardiac autoantibodies, since immunoadsorption leads to EMB-proven decrease in lymphocytic infiltration and CAM expression [253]. Using an *in vitro* bioassay that determines the cardiodepressant activity of antibodies on calcium transients and systolic cell shortening in adult rat cardiomyocyte cultures, patients with DCM of the 'cardiodepressant group' show improved haemodynamics whereas those in the 'non-cardiodepressant group' do not show amelioration [253]. This bioassay may thus differentiate those patients who will likely benefit from immunoadsorption. Immunoadsorption studies have been undertaken in DCM patients with severely depressed left ventricular function (LVEF < 35%), raising the average LVEF from about 20 to 30%. The beneficial effects of immunoadsorption on LVEF and heart failure symptoms last for up to 2.5 years after treatment and contribute to a significant reduction in hospitalization and morbidity, so that immunoadsorption may be an option as a 'bridge to transplantation'.

ANTIVIRAL TREATMENT

Type I interferons such as interferon-β are pivotal for the antiviral immune response. In a phase II study, 22 patients with DCMi with EMB-proven enteroviral (n = 15) or adenoviral (n = 7) persistence were treated with interferon-β for 24 weeks [44]. The subcutaneous administration followed a stepped regimen in order to limit the typical flu-like adverse effects of interferon, being initiated with 2 million units of interferon-β thrice a week on alternate days, and increased to 12 million units during the second and 18 million units during the third week. Complete elimination of viral genome was proven in follow-up biopsies in all patients. This was paralleled by a significant increase in LVEF (from 44.7 ± 15.5 to 53.1 ± 16.8%) and amelioration of heart failure symptoms. Noticeably, significant improvement in LVEF was observed both in patients with regional left ventricular dysfunction but preserved LVEF (> 50%) and especially in patients with global left ventricular dysfunction (LVEF < 50%). Concomitantly, there was a significant decrement in immunocompetent lymphocyte infiltration (from 19.2 ± 4.8 to 6.0 ± 3.1 cells/mm^2) in the follow-up evaluation. It is hypothesized that the interferon-β treatment augmented the antiviral immune response, which after complete elimination of the inducing viral agents finally subsided. Furthermore, termination of the virus-mediated direct cytopathic effects on cardiomyocytes may also have contributed to the observed beneficial effects. Interferon-β was safe and well tolerated, and flu-like adverse effects could be efficiently suppressed by non-steroidal anti-inflammatory drugs. Most importantly, there were no adverse cardiac effects such as deterioration of left ventricular function or arrhythmias [44]. Whether antiviral immunomodulation is a safe and effective treatment option in DCMi patients with

viral persistence (including further cardiotropic viruses) is being evaluated in the currently ongoing multicentre randomized BICC study (Betaferon in Patients with Chronic Viral Cardiomyopathy).

Prognosis and outcome

The 5-year survival of patients with DCM is approximately 36%. Myocarditis resolves in about 80% of patients spontaneously, but prospective studies have revealed a grave prognosis for patients with myocarditis as well, with a 10-year survival rate of 45%, mostly due to the manifestations of DCM and to SCD [122]. With coronary artery disease, DCM constitutes the leading indication for cardiac transplantation.

The initial clinical presentation of both myocarditis and DCM is highly variable as is their spontaneous prognosis. At present, no clinical parameter has proven prognostically useful for predicting the evolution from myocarditis to DCM/DCMi. Even LVEF, which in ischaemic heart disease serves as a strong predictor, has a seemingly inverse prognostic impact in acute myocarditis [122]. Furthermore, the maximum troponin and creatine phosphokinase levels in acute myocarditis, in contrast to myocardial infarction, have no prognostic impact.

Histological and morphometric EMB analyses have no predictive value. In contrast, immunohistological analysis of viral persistence in particular, but also chronic intramyocardial inflammation, have been associated with adverse prognosis in patients with DCM [126–128].

Secondary myocardial diseases

Myocardial disease that can be directly linked to an identifiable source is termed secondary. Acute ischaemia often precipitates left ventricular failure, while chronic ischaemia may induce hibernation of the myocardium. Both states may be reversible by revascularization owing to the presence of viable myocardium. Similarly, ventricular impairment frequently occurs in conjunction with valvular abnormalities; aortic stenosis is a classic example where timely correction may normalize ventricular function. Hypertension, diabetes and excess alcohol are common causes of secondary cardiomyopathy. A rare but important entity is peripartum cardiomyopathy. Tachycardia-induced cardiomyopathy is an underrecognized entity in which control of chronic atrial or ventricular tachyarrhythmia leads to restoration of normal ventricular function. Finally, cardiac involvement in the muscular dystrophies is also included under the umbrella term of secondary myocardial disease.

Hypertensive cardiomyopathy

Hypertension is a major predisposing factor for coronary artery disease, heart failure and cerebrovascular disease. Although LVH has been considered an adaptation to systolic overload in hypertensive patients, there is considerable evidence that it is independently associated with ventricular dysfunction, arrhythmia and sudden death. Hypertension-induced LVH may therefore be considered a cardiomyopathy in its own right.

Histological changes in hypertensive cardiomyopathy include enlargement and proliferation of cardiac myocytes [254]. Interstitial fibrosis is a key feature, characterized in particular by accumulation of type I and type III collagen [255]. The severity of myocardial fibrosis appears to correlate with heart weight, hypertrophy and systolic blood pressure [256]. As the collagen content of the interstitium increases to two to three times normal, the myocardium becomes non-compliant and diastolic dysfunction results. Hypertension is the leading cause of diastolic heart failure in clinical practice. Further progression of fibrosis ultimately leads to systolic impairment; myocyte apoptosis may also play a role.

During the course of hypertrophy, the coronary vasculature fails to enlarge at a rate sufficient to compensate for the increased myocardial mass. Abnormalities of the microcirculation are also recognized in the hypertensive heart. Endothelial dysfunction, medial thickening and perivascular fibrosis are all thought to contribute to diminished coronary reserve [257]. As a result, many patients with hypertensive cardiomyopathy have signs and symptoms of myocardial ischaemia despite unobstructed coronary arteries on angiography.

There is a significantly higher prevalence of AF and ventricular arrhythmia in patients with hypertension and LVH compared with the general population. Characteristic findings on Holter ECG include frequent multifocal ventricular extrasystoles and short runs of non-sustained VT; sustained ventricular tachyarrhythmia is rare [258, 259]. However, patients with hypertensive heart disease are at increased risk of sudden death, for which LVH and high-grade ventricular arrhythmia appear to be predictors [260]. The arrhythmogenic substrate is likely to be a product of myocardial fibrosis, ischaemia, autonomic imbalance and heterogeneous prolongation of the action potential in LVH [261].

Regression of LVH is accompanied by diminished ventricular arrhythmia, improved diastolic function, preservation of systolic function and resolution of microvascular ischaemia. Lowering of left ventricular mass

during antihypertensive treatment is associated with reduced incidence of cardiovascular events, additional to the effects of blood pressure control. However, not all antihypertensives are equipotent in this regard. ACE inhibitors and AT receptor antagonists appear most efficacious. Calcium channel antagonists also decrease left ventricular mass. Atenolol, in contrast, has been linked with increased cardiovascular mortality in comparison with other antihypertensives [262]. The hydrophilic profile of atenolol, and consequent low permeability into the central nervous system, may account for its apparent ineffectiveness in preventing VF.

Alcoholic cardiomyopathy

Alcoholic cardiomyopathy (ACM), by definition, is a form of dilated cardiomyopathy that occurs secondary to excess long-term alcohol consumption. The concept largely predates recognition of the genetic basis of DCM. Since the prevalence of heavy alcohol intake far exceeds that of ACM, it is likely that ethanol, as a known myocardial depressant, unmasks an underlying genetic predisposition to DCM. Intake of > 90 g of alcohol daily for over 5 years appears to confer an increased risk of ACM [263]. The effects of alcohol on the heart appear to be dose dependent but non-linear [264]. The threshold for the development of ACM is also lower in women, although reasons underlying this increased sensitivity to alcohol have not been elucidated [265].

Two phases are recognized in the natural history of ACM: an asymptomatic stage, characterized by isolated left ventricular enlargement with or without diastolic dysfunction; and a clinically overt stage, during which systolic impairment supervenes, together with signs and symptoms of heart failure. The incidence of AF and non-sustained VT appears similar to that of DCM. The sudden death rate is also comparable, although prognosis is noticeably more favourable in ACM patients practising abstinence [266].

In vitro experiments and animal models have suggested several potential mechanisms for the development of ACM, including ethanol-induced apoptosis of cardiac myocytes, impaired function of the mitochondria and sarcoplasmic reticulum, altered expression of sarcomeric proteins, and abnormal calcium handling. The contribution and interplay of these factors in the clinical setting remain to be clarified.

Heart failure therapy improves ventricular function in ACM, particularly in the presence of alcohol abstinence. Increased LVEF has also been documented in the context of continued heavy drinking, but pharmacological therapy does not confer any survival benefit in this subgroup [267]. The importance of abstinence in reducing mortality from ACM is therefore underscored. A recent study suggests that comparable outcomes may be achieved by controlled moderate drinking [268], although long-term follow-up data in a large cohort will be necessary before this approach can be recommended.

Metabolic cardiomyopathy

The term 'metabolic cardiomyopathy' refers to a heterogeneous group of disorders in which myocardial dysfunction occurs as a consequence of a derangement in metabolism. Covered previously in this chapter are the cardiac complications of the storage diseases and mutations in AMP kinase, the cellular fuel gauge. Nutritional deficits such as thiamine deficiency are well-known causes of a reversible DCM. Perhaps the most common form of metabolic cardiomyopathy is that seen in association with diabetes. Diabetes is a prominent risk factor for the development of ischaemic heart disease, but there is growing awareness of a direct effect on ventricular function that is independent of obstructed coronary arteries or concurrent hypertension. The prevalence of heart failure is considerably higher in diabetic patients than in age-matched controls, and a less favourable prognosis has also been reported [269,270]. Diabetic cardiomyopathy may account, at least in part, for the increased risk.

Profound changes in cardiac metabolism occur in diabetes (Table 16.21). Periodic evaluation of diabetic patients may be advisable to ensure early detection of subclinical ventricular dysfunction. Optimal glycaemic control and pharmacological therapy with ACE inhibitors/AT receptor antagonists and beta-blockers may attenuate ventricular remodelling and lead to improved survival.

Muscular dystrophy cardiomyopathy

The muscular dystrophies are primary disorders of skeletal and/or cardiac muscle that have a genetic basis. Originally defined by the presence of progressive muscle wasting and weakness, the dystrophies are classified according to the distribution and severity of skeletal muscle involvement. Many forms of muscular dystrophy are accompanied by myocardial disease, which was previously attributed to processes extrinsic to the heart. Weakness of the postural musculature causes lordosis and scoliosis, which impair thoracic movement during respiration. Intrinsic disease of the intercostal muscles and diaphragm is also well described. The combined result is restrictive lung disease, which may in turn lead to pulmonary hypertension and a secondary cardiomyopathy [271].

However, cardiomyopathy in the muscular dystrophies is a consequence of intrinsic myocardial dysfunction

Table 16.21 Factors that may contribute to myocardial dysfunction in diabetes

Obstructive epicardial coronary artery disease
Hypertension
Disturbances in calcium homeostasis
Decreased myosin ATPase activity
Decreased uptake of calcium by sarcoplasmic reticulum
Inhibition of Na^+/K^+-ATPase and Ca^{2+}-ATPase
Decreased Ca^{2+} sensitivity of actin–myosin complex
Alterations in sarcomeric proteins
Shifts in cardiac myosin heavy chain isoforms
Effects on myosin light chain-2, troponin I
Abnormalities of the microcirculation
Oxidative stress
Concomitant diabetic autonomic neuropathy
Myocardial ischaemia
Activated renin–angiotensin system
Reduced glucose utilization
Marked increase in fatty acid oxidation
Reduced rates of lactate oxidation
Inhibition of protein synthesis and increased catabolism of amino acids

Data from Avogaro *et al*. [270].

rather than skeletal muscle disease and respiratory complications. Several lines of evidence support this inference.

1 Duchenne and Becker muscular dystrophies have been linked to absolute or relative deficiency of the sarcolemmal protein dystrophin. Mutations in dystrophin have also been identified in X-linked DCM [272], underlining its role in primary myocardial disease. Molecular disruption of dystrophin in both ischaemic heart failure and DCM may be reversible by treatment with LVADs [67]. Thus it has been proposed that dystrophin remodelling may provide a final common pathway for contractile impairment in heart failure.
2 Histological examination of the heart in Duchenne and Becker muscular dystrophy reveals replacement of the myocardium with connective tissue and fat [273]. Similar findings in skeletal muscle suggest a common underlying disease process.
3 Equally compelling is the observation that female carriers of Duchenne and Becker muscular dystrophy may have left ventricular dilation in the absence of significant myopathic symptoms [274].
4 In some forms of muscular dystrophy, notably Emery–Dreifuss, locomotor involvement is mild and cardiac manifestations predominate [275].

Table 16.22 summarizes cardiac involvement in the muscular dystrophies and myotonic dystrophy. Periodic evaluation of affected patients and carriers with 12-lead ECG, two-dimensional echocardiography and ambulatory ECG monitoring is recommended. Myotonic dystrophy may occasionally present with cardiac manifestations and should be considered part of the differential diagnosis in a young patient with progressive conduction system disease. Treatment is tailored according to the nature of cardiac involvement; conduction defects may require pacing, while standard heart failure therapy is indicated for ventricular dilation and impairment. The presence of ventricular tachyarrhythmia in myotonic dystrophy may prompt the use of an ICD, as sudden death is a recognized complication.

Peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCM) is defined as left ventricular systolic impairment in the presence of the following additional criteria:

1 presentation within 1 month of delivery or during the first 5 months post-partum;
2 absence of pre-existing cardiac disease; and
3 no other cause for cardiac dysfunction.

Underlying cardiac disorders that are unmasked by the haemodynamic stress of a normal pregnancy are thereby excluded [276,277].

Prevalence and aetiology

The true incidence has not been established, although existing data suggest a frequency of between 1 in 3000 and 1 in 10 000 pregnancies [278]. This is likely to be an underestimate, as mild forms of PPCM probably remain unrecognized because of the prevalence of exertional dyspnoea and ankle oedema in the last trimester.

The aetiology of PPCM also remains uncertain (Table 16.23). Endomyocardial biopsies demonstrate features of myocarditis in up to 62% of cases [279], suggesting an inflammatory component. However, there does not appear to be any association between the presence of myocarditis and the clinical outcome. Malnutrition has been cited as a possible factor; women with PPCM in certain geographical areas have low plasma levels of selenium [280]. Others, however, appear to have good nutritional status. Viral infection has been postulated, although recurrence in subsequent pregnancies is less easy to explain on this basis. One intriguing possibility is that of an abnormal immune response during pregnancy [281], which has also been implicated in the pathogenesis of pre-eclampsia. Finally, familial occurrence of PPCM has been reported [282]. The most likely explanation is that PPCM is a manifestation of familial DCM, with the cardiovascular burden of pregnancy uncovering previously

Table 16.22 Cardiac involvement in muscular dystrophies

Type	Inheritance	Gene affected	Mechanism of disease expression	Extracardiac manifestations	Cardiac involvement
Duchenne	X-linked	Dystrophin gene at Xp21	Dystrophin serves as a bridge between the cytoskeletal protein actin (at the N-terminus) and the transmembrane protein β-dystroglycan (at the C-terminus). Absence of dystrophin leads to disruption of the mechanical link between the sarcolemma and the extracellular matrix	Childhood onset Progressive proximal myopathy Wheelchair-bound by teens	Dilated cardiomyopathy
Becker	X-linked	Dystrophin gene at Xp21	Dystrophin present but reduced in quantity or otherwise abnormal	Onset age 12 or later in life Proximal myopathy Slowly progressive	Dilated cardiomyopathy
Emery–Dreifuss	X-linked AD, rarely AR	STA gene at Xq28 LMNA gene at 1q21	Emerin is an integral protein of the inner nuclear membrane Lamins A and C are also nuclear envelope proteins	Contractures at ankles, elbows and neck Slowly progressive myopathy Humeroperoneal distribution	Atrial flutter/fibrillation 'Isolated atrial standstill'; low-amplitude or absent P waves; atria unresponsive to pacing. Ventricular pacing indicated Massive atrial dilation; anticoagulants advised Dilated cardiomyopathy Sudden death
Myotonic (type 1)	AD	DMPK gene at 19q13.3	Abnormal expansion of a trinucleotide cytosine-thymine-guanine sequence in the myotonin protein kinase gene (DMPK) 35 copies or less of CTG repeat in normal subjects; 50–2000 in myotonic patients May demonstrate genetic anticipation Exact function of DMPK unknown; localized to intercalated discs; can modify actin cytoskeleton	Myotonia Weakness of facial, pharyngeal and distal limb muscles Diabetes, thyroid dysfunction Cataracts	Conduction system defects (prolonged PR interval and/or wide QRS on ECG; pacing may be required) Atrial flutter/fibrillation Ventricular tachyarrhythmia Sudden cardiac death Mitral valve prolapse LV dilation and/or systolic impairment Left ventricular hypertrophy

AD, autosomal dominant; AR, autosomal recessive; LV, left ventricle.

unrecognized subclinical disease. This possibility is supported by anectodal evidence but warrants further prospective evaluation.

Clinical presentation

Patients with PPCM typically present with symptoms of left ventricular failure, such as orthopnoea and paroxysmal nocturnal dyspnoea. Repetitive monomorphic VT and systemic thromboembolism have also been reported. The findings on physical examination may be difficult to interpret as a third heart sound and ejection systolic murmur are present in more than 90% of normal pregnant women. Similarly, slight leftward deviation of the QRS axis is a normal ECG feature during pregnancy. Non-specific ST-segment changes and supraventricular

Table 16.23 Risk factors for the development of peripartum cardiomyopathy

Increasing maternal age
Multiparity
Multiple pregnancy
Pre-eclampsia
Gestational hypertension
Afro-Caribbean
Familial occurrence
Malnutrition
Cocaine use by mother
Long-term tocolytic therapy
Selenium deficiency
Chlamydia infection
Enterovirus infection

Data from de Beus *et al.* [276] and James [277].

or ventricular extrasystoles are often seen in PPCM. Two-dimensional echocardiography is the principal investigation. Left ventricular systolic impairment is requisite for diagnosis, with some authors recommending strict echocardiographic criteria: LVEF < 45% and/or fractional shortening < 30% plus left ventricular end-diastolic measurement of 2.7 cm/m^2 body surface area. Dilation of cardiac chambers may also be present, particularly in patients presenting more than 1 month after delivery.

Management

Standard therapy for left ventricular failure is employed in PPCM. Cardiogenic shock may necessitate insertion of an intra-aortic balloon pump. In the absence of significant decompensation, however, PPCM may be managed on an out-patient basis. ACE inhibitors and AT receptor antagonists are contraindicated after the first trimester owing to the potential for adverse effects on the fetus (oligohydramnios and its consequences, i.e. limb deformities, cranial ossification deficits, lung hypoplasia) and neonate (hypotension and renal failure). However, beneficial rescue therapy with a low-dose, short-acting ACE inhibitor has been reported in a small series of pregnant women with severe resistant vasoconstrictive hypertension [283]. Serial assessment of amniotic fluid volume was conducted and delivery was remote from maternal dosing. There were no fetal or neonatal complications; improved haemodynamics were observed in the mothers, with successful continuation of pregnancy. In a multicentre survey of the management of PPCM in current practice, 6% of perinatologists reported using ACE inhibitors during pregnancy [284]. In cases of severe refractory ventricular failure, the potential risks to the fetus from ACE inhibitor therapy should perhaps be balanced against the urgent need to optimize ventricular function to ensure a positive outcome for both mother and baby.

Pregnancy per se is a hypercoagulable state, and the risk of thromboembolism is further enhanced by bed rest, diuretic therapy and impaired ventricular function. Prophylactic doses of low-molecular-weight heparin are appropriate during pregnancy; warfarin may be instituted following delivery.

Prognosis and outcome

Reports of the long-term prognosis in PPCM are highly variable. Many patients experience symptomatic improvement, accompanied by complete or partial recovery of left ventricular function. However, a few progress to end-stage heart failure. In a retrospective series of 42 patients with PPCM followed up for an average of 8 years, death was recorded in 7% and a similar proportion underwent cardiac transplantation. Left ventricular function normalized in 43%. Earlier studies indicated a less favourable clinical outcome, with mortality rates of up to 56% [285]. Death usually results from worsening pump failure, although systemic thromboembolism and ventricular tachyarrhythmia have been documented. Predictors of high risk are lacking at present, but a combined strategy of early recognition and aggressive medical therapy is recommended.

Counselling patients with PPCM on the issue of future pregnancies poses a major clinical challenge because of potential recurrences of symptomatic heart failure. It has been suggested that subclinical ventricular dysfunction persists in many patients, and the haemodynamic burden of another pregnancy precipitates decompensation. Reactivation of a pregnancy-related disease process may also be invoked. Surveys of subsequent pregnancies in survivors of PPCM have elicited the following findings [286].

1. Left ventricular dysfunction and clinical deterioration may recur in the mother.
2. The incidence of complications is higher (up to 50%) in women with incomplete recovery of ventricular function. Maternal deaths are more likely to occur. An increased incidence of fetal prematurity and loss is also reported in this subgroup.
3. Women in whom ventricular function has normalized prior to pregnancy are at very low risk of death. Symptomatic heart failure may nonetheless recur in around 20% and result in persistent left ventricular impairment. Careful monitoring is therefore warranted.

Personal perspective

Myocardial diseases represent a large spectrum of inherited and acquired forms of heart muscle disease. The term 'cardiomyopathy' has been used in the past to describe primary forms of myocardial disease of unknown aetiology. However, in the past few years it has become evident that most of the primary forms are genetically transmitted, affecting the sarcomeric genes in HCM and the cytoskeleton-encoding genes in DCM. Secondary forms may represent HCM or DCM and are, as in the primary forms, most frequently genetically transmitted (e.g. amyloidosis, haemochromatosis, glycogen storage diseases, Fabry's disease). True secondary forms of myocardial disease are ischaemic, alcoholic or hypertensive heart disease, which are also genetically determined but which may mimic the cardiac phenotype of HCM or DCM. Thus most forms of myocardial disease today represent inherited forms of heart disease.

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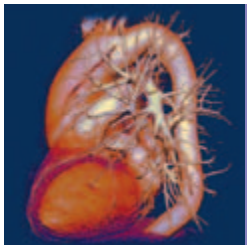

17 Pericardial Diseases

Bernhard Maisch, Jordi Soler-Soler, Liv Hatle and Arsen D. Ristic

Summary

The diagnosis of acute pericarditis is based on the clinical presentation (chest pain, pericardial friction rub) and typical ECG changes. Echocardiography is essential for the detection of pericardial effusion and for the determination of its physiological significance, signs of constriction, concomitant heart disease or paracardial pathology. A substantial proportion of patients classified as having 'idiopathic' pericarditis have disease that is the result of either viral or autoreactive pericarditis. To establish the aetiology pericardiocentesis, pericardioscopy and pericardial/epicardial biopsy may be necessary in these cases. Polymerase chain reaction or *in situ* hybridization in the pericardial effusion and/or pericardial/epicardial tissue are diagnostic for viral pericarditis but in routine clinical management these tests are applied infrequently. A diagnosis of tuberculous pericarditis can be established by conventional culture or polymerase chain reaction identification of *Mycobacterium tuberculosis* in the pericardial fluid or tissue or elsewhere. Pericardiocentesis is indicated for cardiac tamponade, is helpful for the diagnosis of suspected purulent, tuberculous or neoplastic pericarditis and in patients with large effusions without overt tamponade (> 20 mm in echocardiography in diastole). Electrical alternans and pulsus paradoxus are signs of an advanced stage of cardiac tamponade and indicate the need for prompt drainage. Aortic dissection is a major contraindication for pericardiocentesis. Relative contraindications include uncorrected coagulopathy, anticoagulant therapy, thrombocytopenia < 50 000/mm^3 and posterior and loculated effusions. In cardiac wounds, postinfarction myocardial rupture, or dissecting aortic haematoma cardiac surgery is life-saving. Loculated effusions may require open surgery or thoracoscopic drainage. Intrapericardial instillation of antineoplastic and/or sclerosing agents (e.g. cisplatin, thiotepa) can prevent recurrences of neoplastic pericardial effusions. Intrapericardial instillation of triamcinolone is efficient in preventing recurrences in patients with autoreactive pericardial effusion, mainly avoiding the side-effects of systemic corticosteroid therapy. Long-term colchicines (3–6 months) in combination with NSAIDs or aspirin is beneficial to prevent recurrences. Pericardiectomy is the only treatment for permanent constrictive pericarditis. However, surgery should not be carried out either too early, to avoid operating on patients with transient constriction, or too late, because myocardial fibrosis and/or atrophy significantly increase mortality.

Aetiology and classification of pericardial disease

The spectrum of pericardial diseases consists of congenital defects, pericarditis (dry, effusive, effusive–constrictive, constrictive), neoplasms, chylopericardium and cysts. The aetiological classification of pericarditis comprises: infectious, systemic autoimmune, postmyocardial infarction/postpericardiotomy syndrome, uraemic, toxic, metabolic and autoreactive forms [1–3].

Pericardial syndromes

Here we describe both disease entities (e.g. congenital defects) and syndromes, such as different clinical forms of pericarditis with various aetiologies.

Congenital defects of the pericardium

Congenital defects of the pericardium are detected in 1/10 000 autopsies. Pericardial absence can be partial (left

~70%, right ~17%) or total bilateral (rare) [4]. An association with other congenital cardiac, pulmonary or skeletal abnormalities is found in one-third of patients. Most patients with total pericardial absence are asymptomatic. Cardiac displacement and augmented mobility impose an increased risk for traumatic aortic dissection [4]. Partial left-side defects can be complicated by herniation of the heart, which can cause haemodynamic alterations or even angina, while partial right defects may cause compression of the vena cava. Pericardioplasty is indicated for imminent strangulation.

Acute pericarditis

Acute pericarditis can be dry, fibrinous or effusive. Major symptoms are retrosternal or left precordial chest pain (which radiates to the trapezius ridge, can be pleuritic or simulate ischaemia, and varies with posture, being more prominent when sitting than when lying) and sometimes shortness of breath. A prodrome of fever, malaise and myalgia is common. The pericardial friction rub can be transient, mono-, bi- or triphasic. Pleural effusion may be present. Heart rate is usually rapid and regular. ECG changes can be non-specific (including normal ECG) or very suggestive (Fig. 17.1). Echocardiography is essential to detect effusion and concomitant heart or paracardial disease.

Systematic approach to the aetiological diagnosis

Acute pericarditis may be a self-resolving benign disease but it can also be the first manifestation of neoplastic, purulent or tuberculous diseases that require prompt specific therapy. A systematic, stepwise approach to the aetiological diagnosis is essential to select the patients that can be effectively treated and on the other hand to spare those with self-resolving disease from unnecessary procedures (Table 17.1) [5–8]. If associated disease is present in acute pericarditis the likelihood that it is the cause of the pericardial syndrome is very high [9]. In these patients, and in patients with self-resolving forms, only non-invasive diagnostic tests are indicated. Many of them can be managed as out-patients [7]. However, in tamponade without findings of inflammation a

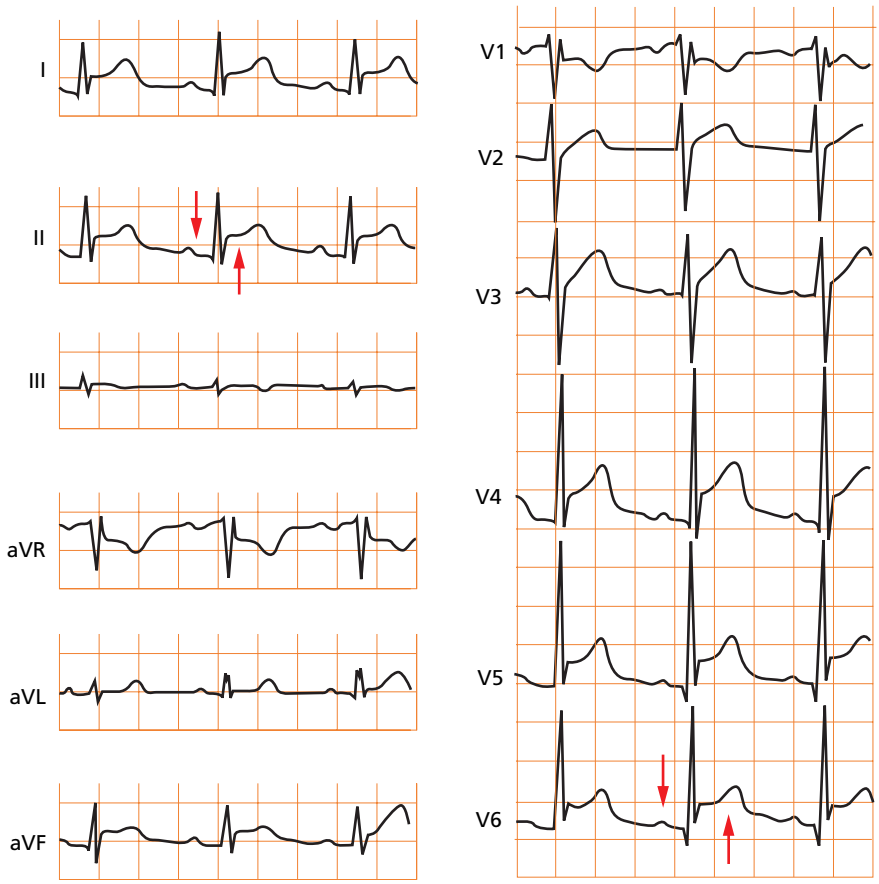

Figure 17.1 Typical ECG changes in acute pericarditis: PR depression (↓) and concave ST-elevation (↑).

Table 17.1 Diagnostic algorithm in acute pericarditis [2,3,5–8]

Diagnostic test	Characteristic findings
STEP I—tests obligatory in all patients	
History and physical examination	Identification of high-risk patients (should be hospitalized)* Pericardial rub (mono-, bi-, or triphasic)
ECG†	Stage I:—anterior and inferior concave ST segment elevation. PR segment deviations opposite to P waves Early stage II:—all ST junctions return to the baseline. PR segments deviated Late stage II:—T waves progressively flatten and invert Stage III:—generalized T wave inversions in most leads Stage IV:—ECG returns to prepericarditis state
Echocardiography	Effusion types B–D (Horowitz) Signs of tamponade or concomitant heart or paracardial disease
Laboratory analyses	Erythrocyte sedimentation rate, C-reactive protein, lactate dehydrogenase, leucocytes, parameters of renal and hepatic function, urine analyses Troponin I,‡ creatinekinase (muscle- and brain-specific form)
Chest X-ray	Ranging from normal to 'water bottle' shape To reveal pulmonary or mediastinal pathology
In self-limiting pericarditis (within 1 week) or known associate or systemic diseases no further diagnostic procedures are necessary. In patients symptomatic for more than 1 week despite the NSAID treatment, screening for systemic autoimmune disease (anti-nuclear antibodies, anti-ds-DNA, RF, C3, C4, immunoglobulins, immune complexes), thyroid disease, three sputum or gastric-aspirate cultures for *Mycobacterium* sp., serological tests (*Mycoplasma*, *Toxoplasma*, *Borrelia*, *Legionella*), and lymph node biopsy, tumour markers, and additional imaging (abdominal sonography, computerized tomography, magnetic resonance imaging) should be performed.	
STEP II—mandatory in tamponade, in large (> 20 mm) effusions and in suspected purulent, tuberculous or neoplastic aetiology, or if previous tests were inconclusive in symptomatic patients resistant to conventional treatment (see Table 17.2)	
Pericardiocentesis/ drainage	Analyses of pericardial effusion can establish the diagnosis of viral, bacterial, tuberculous, fungal, cholesterol and malignant pericarditis: *Analyses obligatory in all patients* • Cytology, cell counts • Acid-fast bacilli staining • *Mycobacterium* cultures (preferably with radiometric growth detection, e.g. BACTEC-460) and polymerase chain reaction for *M. tuberculosis* • Biochemical analyses: specific gravity, protein level, glucose, lactate dehydrogenase *Analyses in areas with high incidence of tuberculosis* • Adenosine deaminase, interferon-gamma, pericardial lysozyme *Analyses in suspected autoreactive or viral pericarditis* • Polymerase chain reaction analyses for cardiotropic viruses *Analyses in suspected bacterial or fungal pericarditis* • Cultures of pericardial fluid for aerobes, anaerobes and fungi (3×) • Blood cultures (3×) *Analyses in suspected chylopericardium* • Cholesterol, triglycerides
STEP III—Optional or if previous tests inconclusive in symptomatic patients who are resistant to conventional treatment	
Pericardial/epicardial biopsy (preferably by pericardioscopy)	Histology (neoplastic and tuberculous pericarditis) PCR for cardiotropic viruses, borreliosis and tuberculosis Immunohistochemistry (autoreactive forms)

*Indication for hospitalization: fever > 38°C, subacute onset, immunodepression, trauma, oral anticoagulant therapy, myopericarditis, severe pericardial effusion, or cardiac tamponade. Others can be treated as outpatients [7,8].
†Typical lead involvement: I, II, aVL, aVF and V3–V6. If ECG is first recorded in stage III, pericarditis cannot be differentiated by ECG from diffuse myocardial injury, 'biventricular strain', or myocarditis. Early repolarization is similar to stage I, but does not acutely evolve and J-point elevations are usually accompanied by a slur, oscillation, or notch at the end of the QRS just before and including the J point (best seen with tall R and T waves—large in early repolarization). Pericarditis is likely if, in V6, the J point is > 25% of the T wave height (using the PR segment as a baseline).
‡A cTnI rise was detectable in 32.2%, but > 1.5 ng/ml in 7.6%. It was not a negative prognostic marker regarding the incidence of recurrences, constrictive pericarditis, cardiac tamponade or residual left ventricular dysfunction [5].

likelihood ratio of 3.0 for neoplasia has been demonstrated [8,9]. A sustained clinical course (> 3 weeks) also increases the likelihood of specific disease. Importantly, purulent pericarditis should be considered in predisposing diseases (pleural empyema, mediastinal infection) [10]. Thus, in comparatively few patients with acute pericarditis (mainly those with haemodynamic compromise or protracted course) will specific pericardial investigations be needed for antiphlogistic therapy [6,10]. Probably, the most appropriate approach is a compromise between performing too many unnecessary invasive studies and missing too many specific diagnoses [1,6,8,10,11].

Management of acute pericarditis

Symptomatic treatment of acute pericarditis is based on chest pain management and anti-inflammatory therapy. The treatment of choice is aspirin (1–4 g/day). Ibuprofen (200–600 mg three times a day) and indomethacin (25–50 mg three times a day) are the preferred alternatives to aspirin because of its rare side-effects and the large dose range [3]. Colchicine (0.5 mg twice a day) as monotherapy or added to non-steroidal anti-inflammatory drugs (NSAIDs) is effective for the prevention of recurrences [12]. Systemic corticosteroids are indicated for connective tissue diseases, and autoreactive or uraemic pericarditis. Intrapericardial application may be effective and mainly avoids systemic side-effects in patients with large autoreactive and uraemic pericardial effusion that is resistant to conventional treatment [2].

Chronic pericarditis

A distinction should be made between chronic pericarditis (which implies inflammatory activity with pericardial pain, fever, and so on) and chronic pericardial effusion. Except for constrictive pericarditis, chronic (> 3 months) inflammatory pericarditis is rare. For instance, tuberculous pericarditis may show a subacute clinical course of several weeks, but not a persistent, sustained evolution. In contrast, pericardial effusion can exhibit a stable chronic course lasting for months or years.

Recurrent (relapsing) pericarditis

The term recurrent or relapsing pericarditis encompasses the intermittent type (symptom-free intervals without therapy) and the incessant type (discontinuation of anti-inflammatory therapy ensures a relapse). Massive pericardial effusion and overt tamponade are rare. Constriction rarely occurs as do relapses in postmyocardial/pericardial injury syndrome [13]. The management includes symptomatic treatment of acute episodes as for acute pericarditis and the prevention of recurrences. Colchicine is effective in the prevention of relapses [11–13]. Corticosteroids should be used only in refractory/highly symptomatic patients. The pericardial fluid should be analysed with cultures and polymerase chain reaction for the infective agents, if available, to exclude viral infection. A common mistake is to use a dose that is too low to be effective or to taper the dose too rapidly. The recommended regimen is: prednisone 1–1.5 mg/kg, for at least 1 month [8]. If patients do not respond adequately, azathioprine (75–100 mg/day) or cyclophosphamide can be added [3]. Corticoids should be tapered over a 3-month period. Towards the end of the taper colchicine (0.5 mg twice daily) or NSAID should be introduced for 3–6 months. Pericardiectomy is only indicated in patients with frequent and highly symptomatic recurrences that are unresponsive to any other therapy.

Pericardial effusion

Pericardial effusion may appear as transudate (hydropericardium), exudate, pyopericardium or haemopericardium. Large effusions are common with neoplastic, tuberculous, cholesterol, and uraemic pericarditis, myxoedema, and parasitoses [9]. Loculated effusions are more common in postsurgical, trauma and purulent pericarditis. Slowly developing large effusions can be remarkably asymptomatic, while rapidly accumulating small effusions can create tamponade. ECG may demonstrate low QRS and T wave voltages, PR-segment depression (Fig. 17.1), ST-T changes, bundle branch block and electrical alternans [3]. Microvoltage and electrical alternans are reversible after effusion drainage [13,14]. In chest radiography large effusions are depicted as globular cardiomegaly with sharp margins ('water bottle') (Fig. 17.2A). The size of effusion can be graded by echocardiography: (1) small (echo-free space in diastole < 10 mm), (2) moderate (10–20 mm) (Fig. 17.3A), (3) large (≥ 20 mm) (Fig. 17.3B), or (4) very large (≥ 20 mm and compression of the heart). Alternatively, the Horowitz classification [14], with the help of TM-echocardiography, distinguishes types A to F of pericardial effusion (Fig. 17.4). Within this classification, type A is normal motion of the adjacent pericardial and endocardial layers in systole and diastole, type B only shows a systolic separation of the epicardial and pericardial layers, the latter still with an inward movement in systole, type C shows clear-cut systolic separation of epi- and pericardium, type D demonstrates the separation of both layers in systole and diastole, type E shows a thickened pericardium and endocardium without fluid separation, and type F demonstrates some residual fluid between the thickened and concomitantly moving epi- and pericardial layers. In large effusions, the

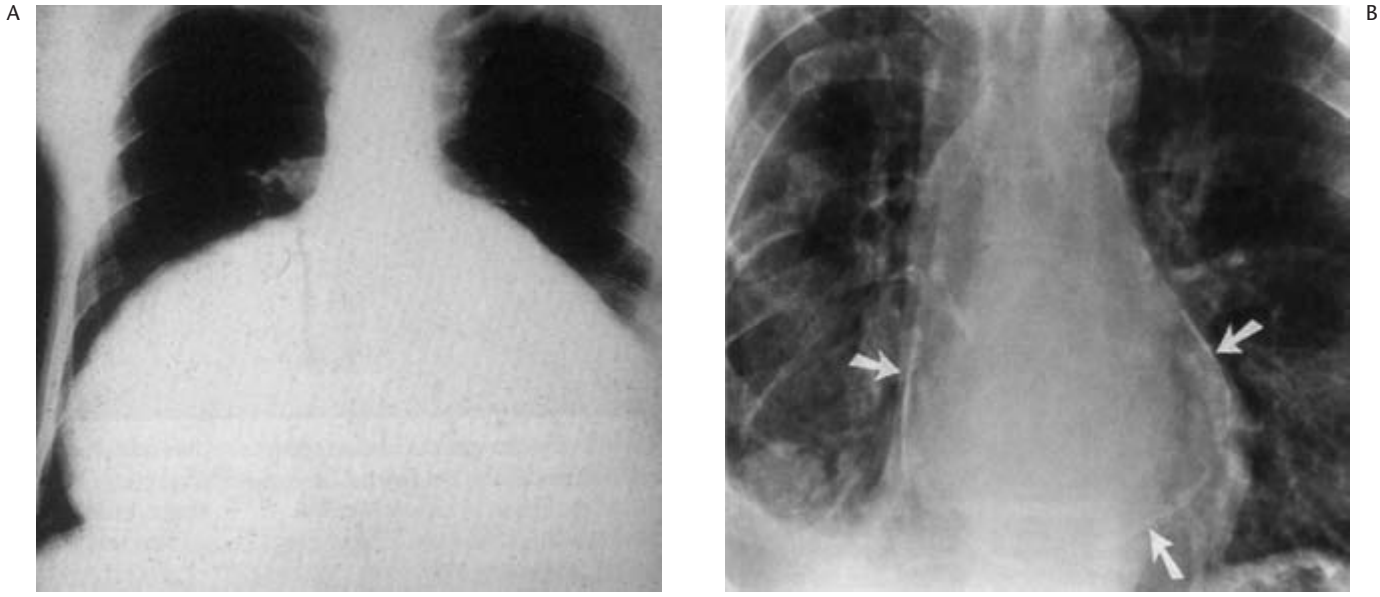

Figure 17.2 Chest X-rays in a patient with very large pericardial effusion—'water bottle' sign—(A) and in a patient with constrictive pericarditis and pericardial calcifications depicted by white arrows (B).

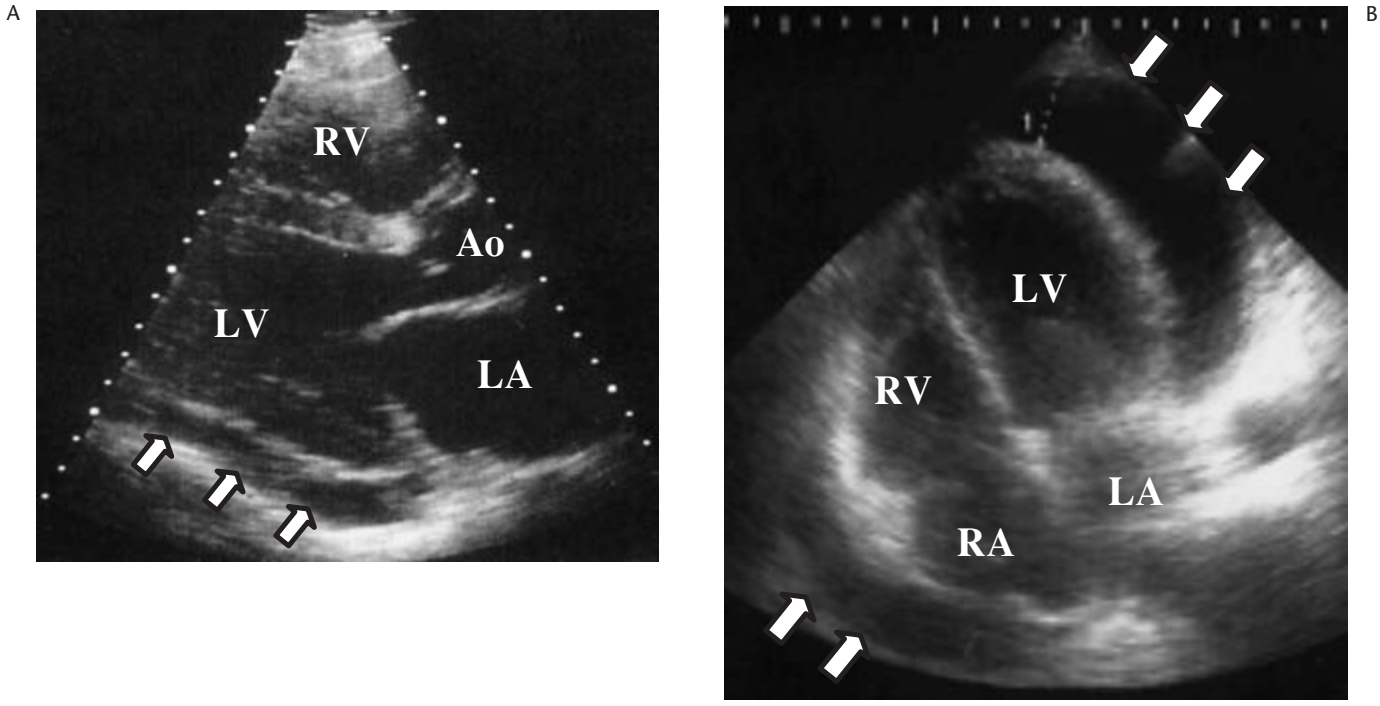

Figure 17.3 Echocardiography findings in a small-to-moderate pericardial effusion (white arrows). Long-axis parasternal view (A). Large pericardial effusion (B). Ao, aortic root; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

heart may move freely within the pericardium ('swinging heart') inducing pseudo-prolapse and pseudosystolic anterior motion of the mitral valve, paradoxical motion of the interventricular septum, and midsystolic aortic valve closure.

Cardiac tamponade

Cardiac tamponade is a compressive disorder of the heart (continuum ranging from a mild to a life-threatening condition), caused by effusion accumulation and the

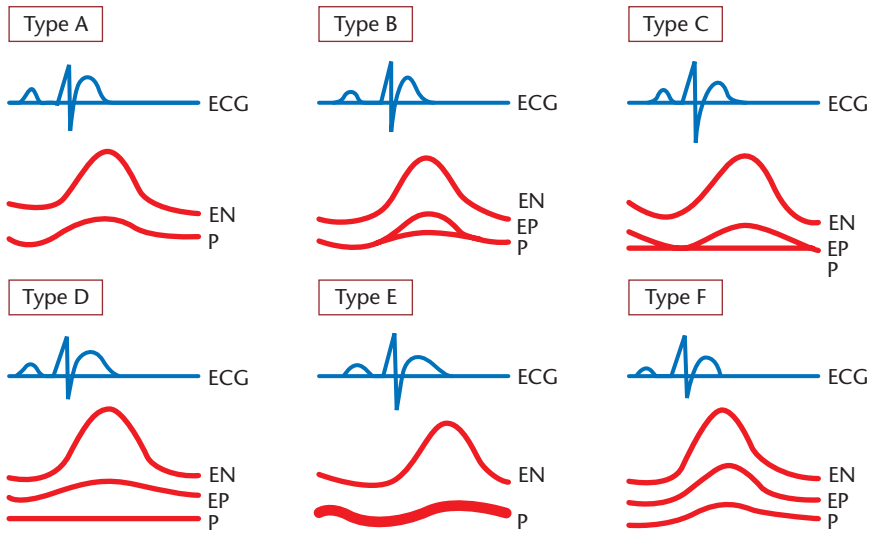

Figure 17.4 Schematic representation of various forms of epicardial and pericardial motion in pericardial effusion as seen with TM-echocardiography according to Horowitz [14].

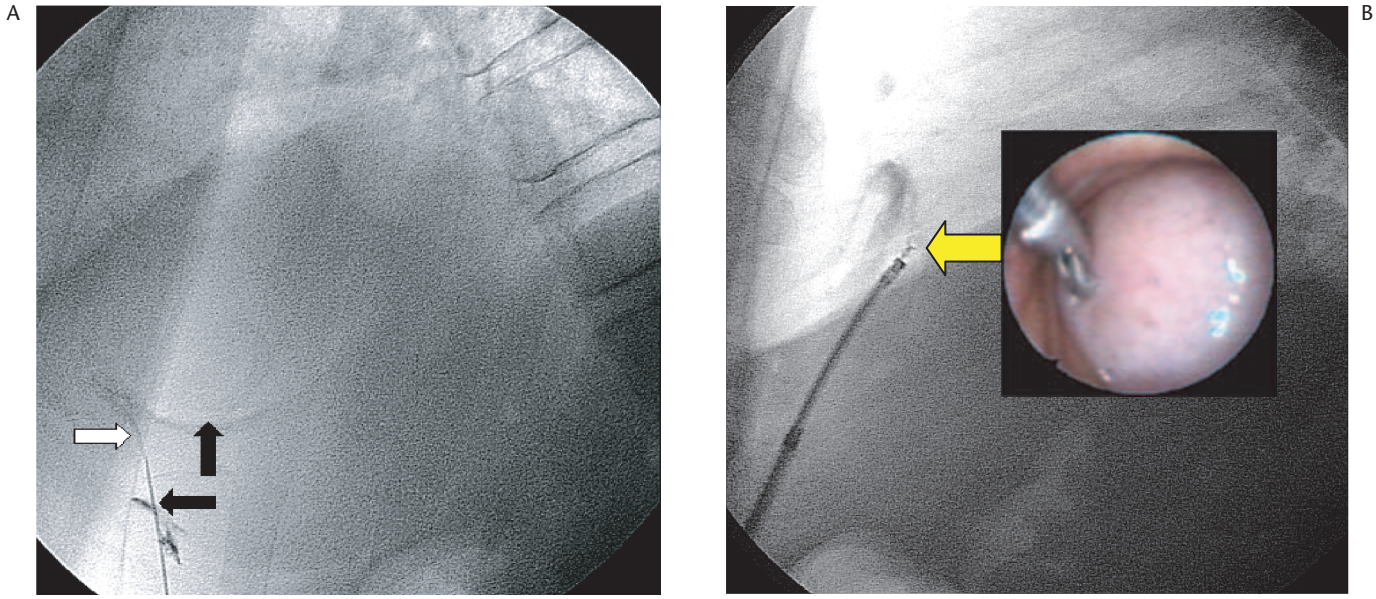

Figure 17.5 Subxiphoid, fluoroscopy-guided pericardiocentesis (A). The lateral view (90°) is most helpful in guiding the needle (white arrow: needle tip, black horizontal arrow: needle shaft) via the diaphragm to the epicardial 'halo' (black vertical arrow), which corresponds to the epicardial fat pad. Flexible percutaneous pericardioscopy and epicardial biopsy (arrow) are carried out via the same route. Here, as well, the lateral view is most informative (B).

increased intrapericardial pressure. In spite of the great value of echo-Doppler findings (see Chapter 2 on echocardiography), cardiac tamponade remains a clinical diagnosis. The classical clinical findings include features of venous hypertension and pulsus paradoxus (inspiratory reduction ≥ 20 mmHg in systolic blood pressure). Orthopnoea, cough and dysphagia, occasionally with episodes of unconsciousness, can be observed.

Up to one-third of patients with asymptomatic large pericardial chronic effusions develop unexpected cardiac tamponade [15]. Triggers for tamponade include hypovolaemia, paroxysmal tachyarrhythmia, and intercurrent acute pericarditis. Indications for pericardial drainage (Fig. 17.5) are listed in Table 17.2 [8,16].

Constrictive pericarditis

Constrictive pericarditis is a clinical syndrome brought about by impaired expansion of the heart by a rigid, chronically inflamed/thickened pericardium. It may, however, exist in the absence of pericardial thickening, with ultrastructural changes only (constriction with

Table 17.2 Indications for pericardiocentesis/pericardial drainage [8]*

Class I indications (Evidence and/or general agreement that the procedure is useful and effective)
- Cardiac tamponade.
- Effusions > 20 mm in echocardiography (diastole).
- Suspected purulent or tuberculous pericardial effusion.

Class II indications (Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment)

Class IIa indications (The weight of evidence or opinion is in favour of the procedure or treatment)
- Effusions 10–20 mm in echocardiography in diastole for diagnostic purposes other than purulent pericarditis or tuberculosis (pericardial fluid and tissue analyses, pericardioscopy, and epicardial/pericardial biopsy).
- Suspected neoplastic pericardial effusion.

Class IIb indications (Usefulness/efficacy is less well established by evidence or opinion)
- Effusions < 10 mm in echocardiography in diastole for diagnostic purposes other than purulent; neoplastic or tuberculous pericarditis (pericardial fluid and tissue analyses, pericardioscopy and epicardial/pericardial biopsy). In symptomatic patients diagnostic pericardial puncture should be reserved to dedicated centres.

Contraindications (Class III)
- Aortic dissection.
- Relative contraindications include uncorrected coagulopathy, anticoagulant therapy, thrombocytopenia < 50 000/mm^3, small, posterior and loculated effusions.
- Pericardiocentesis is not necessary when the diagnosis can be made otherwise or the effusions are small and resolving under anti-inflammatory treatment.

***How to perform pericardiocentesis**
- Recent and reliable echocardiography, best immediately before the procedure. The operator has to perform the echocardiography or to see the video himself.
- Pericardiocentesis guided by fluoroscopy should be performed in the cardiac catheterization laboratory under local anaesthesia. The subxiphoid approach has been used most commonly, with a 8–17 cm, long blunt-tip needle (e.g. Tuohy-17) permitting the passage of the guidewire, directed towards the left shoulder at a 30° angle to the frontal plane. Fig. 17.5 (left panel) shows the lateral view with the epicardial 'halo'. The same approach can be used for pericardioscopically guided epi-or pericardiac biopsies (Fig. 17.5 right panel).
- Pericardiocentesis guided by echocardiography can be performed in the intensive care unit, or at the bedside. Echocardiography should identify the shortest route to enter the pericardium intercostally (usually in the sixth or seventh rib space in the anterior axillary line). The intercostal arteries should be avoided by puncturing close to the upper margin of the rip.
- It is essential that the needle approach the pericardium slowly under steady manual aspiration (negative pressure). As soon as the pericardial effusion is aspirated a soft J-tip guidewire should be inserted and after dilatation this should be exchanged for a multi-holed pigtail catheter.
- Strict aseptic conditions, ECG and blood pressure monitoring have to be provided.
- Direct ECG monitoring from the puncturing needle is not an adequate safeguard.
- Right-heart catheterization can be performed simultaneously, allowing the assessment of tamponade, haemodynamic monitoring of pericardiocentesis, and exclusion of constriction.
- In large pericardial effusions it is prudent to drain < 1 litre at the time of the initial procedure to avoid the acute right ventricular dilatation.
- Prolonged pericardial drainage is recommended after pericardiocentesis until the volume of effusion obtained by intermittent pericardial aspiration (every 4–6 hours) falls to < 25 ml per day.

normal pericardial thickness) [17]. The predominant form is chronic constriction without pericardial effusion. Effusive–constrictive forms [18] are equally important. Acute/subacute forms, transient constrictive pericarditis [19], epicardial constriction [20] and occult/subclinical forms are rather rare.

Patients complain of fatigue, peripheral oedema, breathlessness and abdominal swelling. In decompensated patients venous congestion, hepatomegaly, pleural effusions and ascites may occur, aggravated by a protein-losing enteropathy. In few instances, haemodynamics can be additionally impaired by a systolic dysfunction (myocardial fibrosis or atrophy) [21,22]. Restrictive cardiomyopathy is the condition that may create the most serious differential diagnostic problems [8]. Much less frequently, pulmonary embolism, right ventricular infarction, pleural effusion, or chronic obstructive lung diseases can also be confused with constrictive pericarditis

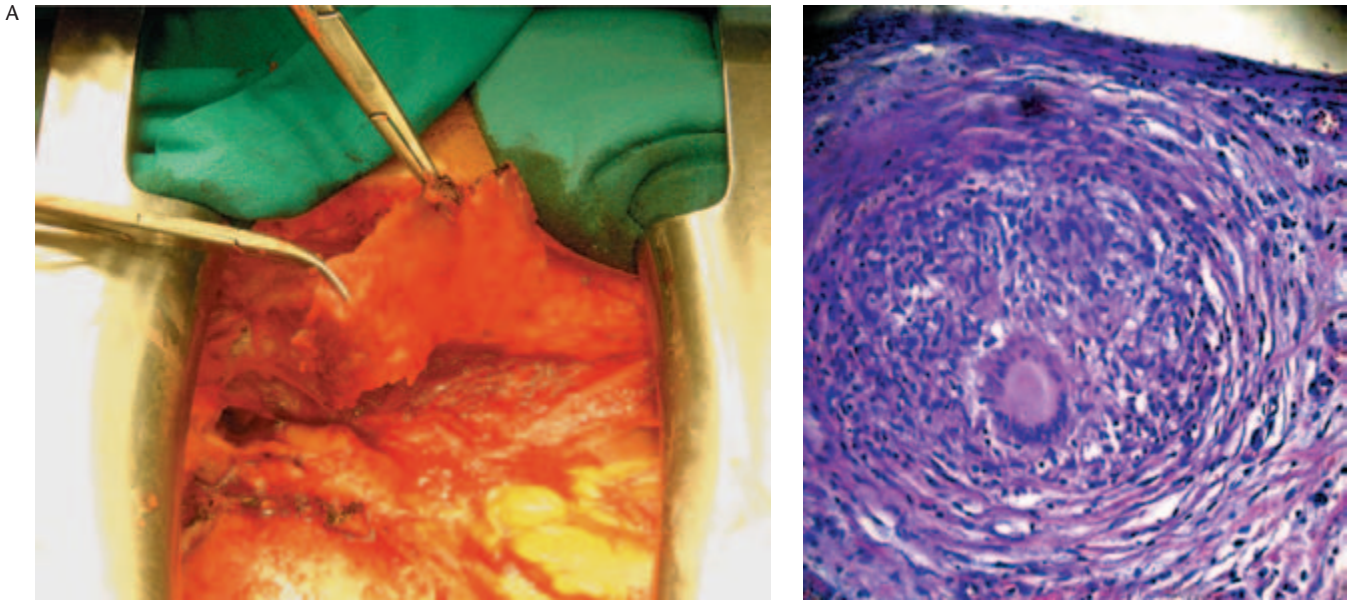

Figure 17.6 Pericardiectomy is the only treatment for permanent constriction (A). It is carried out after median sternotomy. Pathohistology revealed in this case granulomatous inflammation (HE ×160) (B).

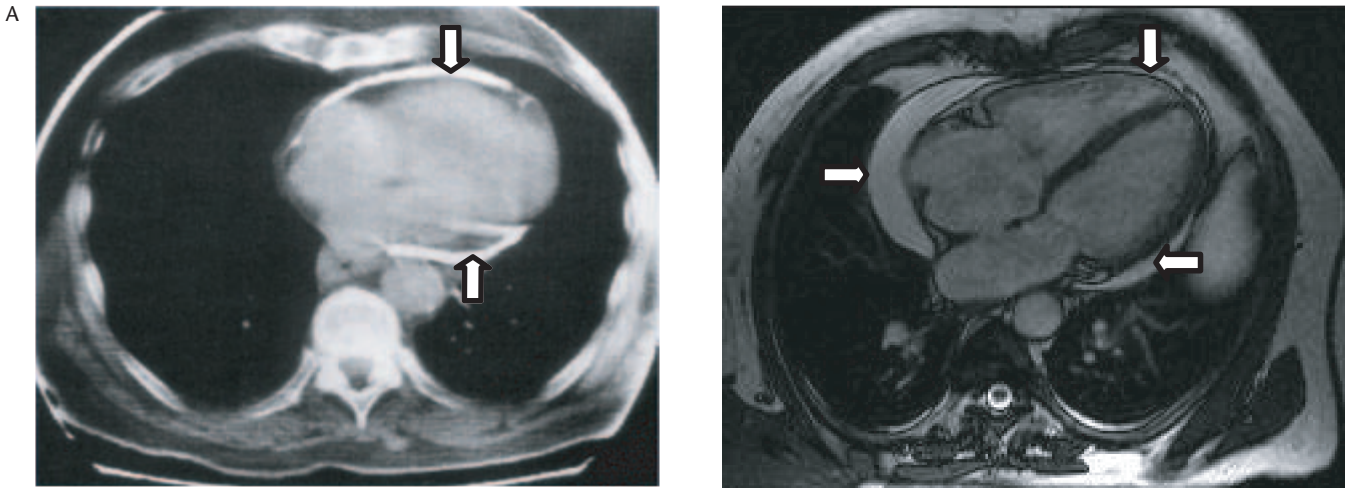

Figure 17.7 Computerized tomography finding in constrictive pericarditis (A). White vertical arrows depict thickened pericardium and pericardial calcification. Magnetic resonance imaging of a patient with effusive–constrictive pericarditis (B). Horizontal arrows show loculated pericardial effusion, and the vertical arrow indicates thickened pericardium.

[3]. Physical findings, chest radiography (Fig. 17.2 right panel), echocardiography [23], computerized tomography (Fig. 17.7A), magnetic resonance imaging (Fig. 17.7B), haemodynamics (Fig. 17.8), and endomyocardial biopsy contribute to establishing the diagnosis (Fig. 17.9).

Pericardiectomy (Fig. 17.6, left and right) is the only treatment for permanent constriction (Table 17.3). Symptomatic management (diuretics, digitalis, beta-blockers) diminishes congestion and tachyarrhythmias before surgery. Antituberculous treatment is mandatory in tuberculous constrictions for at least 2 months before the surgery [8].

Perioperative mortality is 6–12% in the current series [24–26], but can be up to 40% if patients with extensive

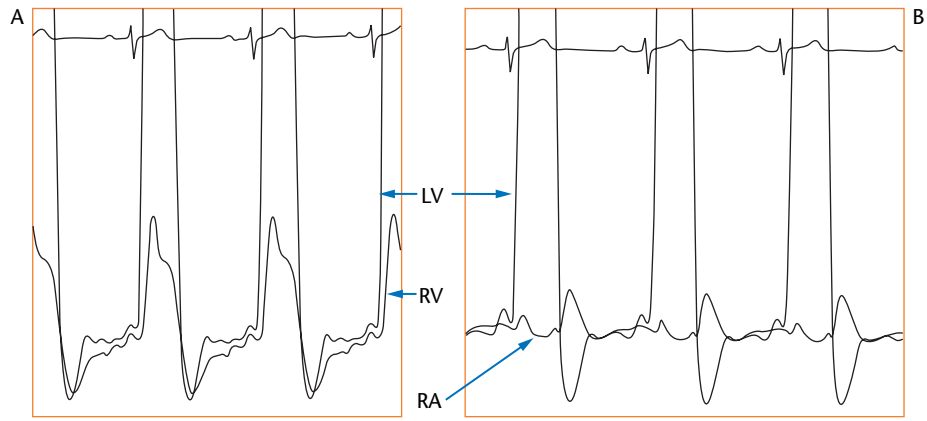

Figure 17.8 Cardiac catheterization in constrictive pericarditis. Equalization of pressures (B) and dip and plateau ('square root') sign in right and left ventricular end-diastolic pressures (A). LV, left ventricle; RV, right ventricle; RA, right atrium.

Physical examination
- Systemic venous congestion
- Low/fixed cardiac output
- Hypotension
- Low pulse pressure
- Abdominal distension
- Oedema
- Muscle wasting

ECG can be normal, or:
- Low QRS voltage
- Generalized T-wave inversion/flattening
- LA abnormalities
- Atrial fibrillation
- Conduction defects
- Pseudoinfarction pattern (rarely)

Chest X-ray
- Pericardial calcifications
- Pleural effusions

CT/MRI
- –Pericardial thickening
- –Calcifications
- –LV/RV tube configuration
- –Enlargement of atria
- –Narrowing of AV grooves
- –Caval veins congestion
- –Myocardial atrophy/fibrosis

Echocardiography

Two-dimensional mode
- –Pericardial thickening and calcifications[a]
- –Indirect two-dimensional signs of constriction:
- Increased respiratory change in LV size
- RA and LA enlargement with normal appearance of the ventricles, and normal systolic function
- Early pathological outward and inward movement of the interventricular septum
- Flattening waves at the LV posterior wall
- LV diameter is not increasing after the early rapid filling phase
- VCI and the hepatic veins are dilated with restricted respiratory fluctuations

Doppler echocardiography
- –Restricted filling of both ventricles with respiratory variation >25% over the AV-valves[b]

Transoesophageal echocardiography–pericardial thickening

Colour M-mode–rapid flow from left atrium to left ventricle

Tissue doppler echocardiography
- –Normal LV expansion velocity and rapid mitral annular velocity[c]

Cardiac catheterization

Haemodynamic assessment

Baseline
- –'Dip and plateau' or 'square route' sign in the RV/LV pressure curves
- –Equalization of LV/RV end-diastolic pressures in the range of 5 mmHg or less[d]
- –Low-normal cardiac output

Effects of respiration
- –Dissociation of LV/RV systolic pressure: decrease in RV pressure on expiration[e]
- –Positive Kussmaul's sign (inspiratory increase or lack of fall of the CVP or RA pressure)

Effect of exercise
- –Fixed cardiac output

Coronary angiography
- –To exclude coronary disease
- –Increased distance between the coronary arteries and the cardiac silhouette
- –Epicardial coronaries less mobile, septal coronaries hypermobile

LV/RV Angiography
- –The reduction of RV/LV size and increase of RA and LA size
- –During diastole a rapid early filling with stop of further enlargement ('dip-plateau')

Figure 17.9 Diagnostic approach in patients with constrictive pericarditis. AV, atrioventricular; LV, left ventricle; RV, right ventricle. [a]Thickening of the pericardium is not always equal to constrictive physiology. [b]Patients with increased atrial pressures or mixed constriction and restriction demonstrate < 25% respiratory changes. A provocation test with head-up tilting or sitting position with decrease of preload may unmask the constrictive pericarditis. Increased diastolic flow reversal in the hepatic veins on expiration is helpful in differential diagnosis with restrictive cardiomyopathy with increase in flow reversals during inspiration. In addition, filling is not restricted and superior vena cava flow increases with inspiration in chronic obstructive lung disease, whereas it does not change significantly with respiration in constrictive pericarditis. In chronic obstructive lung disease mitral inflow velocity will decrease nearly 100% during inspiration and will increase during expiration. The mitral E-velocity is highest at the end of expiration (in constrictive pericarditis mitral E-velocity is highest immediately after start of expiration). [c]Annular velocities except for the septum may be reduced because of calcifications. [d]Constrictive haemodynamics may be masked or complicated by valvular and coronary artery disease. [e]Highly specific for constrictive pericarditis in contrast to restrictive cardiomyopathy.

Table 17.3 Indications for pericardiectomy for constrictive pericarditis

Clinical findings supporting referral for pericardiectomy
- Presence of increasing jugular venous pressure
- Need for diuretic therapy
- Evidence of hepatic insufficiency
- Reduced exercise tolerance

Contraindications for pericardiectomy
- Very early constriction (asymptomatic patients, occult and functional class I) unless otherwise shown by:
  - Exercise testing (preferably with maximal O_2 consumption)
  - Jugular venous pressure
  - Liver function tests
- Transitory constriction
- Extensive myocardial fibrosis and/or atrophy in computerized tomography or magnetic resonance imaging
- Severe, advanced disease (NYHA Class IV) (operative mortality 30–40% vs. 6–19%)

myocardial atrophy/fibrosis are not excluded [21]. Major complications include acute cardiac insufficiency and ventricular wall rupture [3]. If surgery is carried out early, long-term survival after pericardiectomy corresponds to that of the general population [21,24–26]. Predictors of poor survival are prior radiation, worse renal function, higher pulmonary artery systolic pressure, abnormal left ventricular systolic function, lower serum sodium level, and older age [26]. Surprisingly, pericardial calcification had no impact on survival [26]. In a controlled study of 143 patients with constrictive tuberculous pericarditis, prednisolone therapy as an adjunct to streptomycin, isoniazid, rifampicin and pyrazinamide reduced the 2-year mortality (4% vs. 11%), decreased the need for repeated pericardial drainage or surgery (21% vs. 30%), and the incidence of late constriction (8% vs. 12%) [27]. The 10-year follow-up revealed adverse outcomes in 27% of patients treated with prednisolone in contrast to 38% on placebo, deaths from pericarditis being 3% vs. 11%, respectively. In a multivariate analysis prednisolone reduced the overall death rate, and substantially reduced the risk of death from pericarditis [28]. Further studies are needed to confirm the extrapolation to other populations.

Pericardial cysts

Congenital pericardial cysts are uncommon; they may be unilocular or multilocular, with a diameter from 1 to 15 cm [29]. Inflammatory cysts comprise pseudocysts and encapsulated, loculated pericardial effusions. Echinococcal cysts usually originate from ruptured hydatid cysts in the liver or lungs. Most patients with small cysts are asymptomatic, but chest discomfort, dyspnoea, cough or palpitations occur when the cyst becomes larger. On chest X-rays cysts are oval, homogeneous radiodense lesions, usually seen at the right cardiophrenic angle [30]. Echocardiography is useful, but computerized tomography (density readings) or magnetic resonance are often needed [31]. Cyst localizations can be the left, right, the posterior and anterior mediastinum. The congenital and inflammatory cysts can be treated by percutaneous aspiration and ethanol sclerosis [30,32], video-assisted thoracotomy, or surgical resection. Percutanous aspiration and instillation of ethanol or silver nitrate after pretreatment with albendazole is effective for echinococcal cysts [30].

Specific forms of pericarditis

The different aetiologies, the epidemiology, incidence and pathogenesis are given in Table 17.4.

Idiopathic pericarditis

In the general population of patients with acute pericarditis no aetiology has been demonstrated in a large number of patients in spite of a wide range of laboratory studies. To these patients the classical denomination of idiopathic pericarditis has been given [15]. It should be noted, however, that viral polymerase chain reaction studies of cardiac tissue or pericardial fluid to determine the aetiology have not been carried out routinely in these cases.

Viral pericarditis

Viral pericarditis is the most common infection of the pericardium. Inflammation is the result of direct viral attack [entero-, echo-, adeno-, cytomegalo-, Epstein–Barr, herpes simplex, influenza, parvo B19, hepatitis C, human immunodeficiency viruses (HIV), etc.] and the antiviral/anticardiac immune response, or both [3,32]. Cytomegalovirus pericarditis has an increased incidence in immunocompromised hosts [33]. The diagnosis of viral pericarditis is not possible without the evaluation of pericardial effusion and/or pericardial/epicardial tissue, preferably by polymerase chain reaction or *in-situ* hybridization. A four-fold rise in serum antiviral–antibody levels is suggestive but not diagnostic [8]. However, confirmation of suspected viral pericarditis may not be needed in everyday practice if resolution is effective with NSAIDs.

Table 17.4 Review of aetiology, incidence and pathogenesis of pericarditis

Aetiology	Incidence (%)	Pathogenesis
Infectious pericarditis		
Viral (Coxsackie A9, B1–4, Echo 8, mumps, Epstein–Barr, cytomegalo-, varicella, rubella, HIV, parvo B19 . . .)	30–50*	Multiplication and spread of the causative agent and release of toxic substances in pericardial tissue cause serous, serofibrinous or haemorrhagic (bacterial, viral, tuberculous, fungal) or purulent (bacterial) inflammation
Bacterial (pneumo-, meningo-, gonococcosis, *Haemophilus*, *Treponema pallidum*, borreliosis, chlamydia, tuberculosis . . .)	5–10*	
Fungal (*Candida*, *Histoplasma* . . .)	Rare	
Parasitary (*Entamoeba histolytica*, *Echinococcus*, *Toxoplasma* . . .)	Rare	
Pericarditis in systemic autoimmune disease		
Systemic lupus erythematosus	30†	Cardiac manifestations of the basic disease, often clinically mild or silent
Rheumatoid arthritis	30†	
Spondylitis ankylosans	1†	
Systemic sclerosis	> 50†	
Dermatomyositis	Rare	
Periarteritis nodosa	Rare	
Reiter's syndrome	~2†	
Familial Mediterranean fever	0.7†	
Type 2 (auto)immune process		
Rheumatic fever	20–50†	Secondary, after infection/surgery
Postcardiotomy syndrome	~20†	Mostly in acute phase
Post-MI syndrome	1–5†	10–14 days after surgery
Autoreactive (chronic) pericarditis	23.1*	DDg P. epistenocardica Common form
Pericarditis and pericardial effusion in diseases of surrounding organs		
Acute MI (P. epistenocardica)	5–20†	1–5 days after transmural myocardial infarction (MI)
Myocarditis	30†	Accompanying epimyocarditis
Aortic aneurysm	Rare	Dissection: haemorrhagic PE
Lung infarction	Rare	
Pneumonia	Rare	
Oesophageal diseases	Rare	
Hydropericardium in congestive heart failure	Rare	
Paraneoplastic pericarditis	Frequent	No direct neoplastic infiltrate
Pericarditis in metabolic disorders		
Renal insufficiency (uraemia)	Frequent	Viral/toxic/autoimmune
Myxoedema	30†	Serous, cholesterol-rich PE
Addison's disease	Rare	Membranous leak?
Diabetic ketoacidosis	Rare	
Cholesterol pericarditis	Very rare	Transudation of cholesterol (sterile serofibrinous PE)
Pregnancy	Rare	
Traumatic pericarditis		
Direct injury (penetrating thoracic injury, oesophageal perforation, foreign bodies)	Rare	
Indirect injury (non-penetrating thoracic injury, mediastinal irradiation)	Rare	Less frequent after introduction of topical convergent irradiation

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Table 17.4 (*cont'd*)

Aetiology	Incidence (%)	Pathogenesis
Neoplastic pericardial disease	35*	
Primary tumours	Rare	
Secondary metastatic tumours:	Frequent	Serous or fibrinous, frequently hemorrhagic effusion. Accompanying disease during the infiltration of malignant cells
• lung carcinoma	40‡	
• breast carcinoma	22‡	
• gastric and colon	3‡	
• other carcinoma	6‡	
• leukaemia and lymphoma	15‡	
• melanoma	3‡	
• sarcoma	4‡	
• other tumours	7‡	
Idiopathic	3.5*, in other series > 50*	Serous, fibrinous, sometimes haemorrhagic PE with suspect viral or autoimmune secondary immunopathogenesis

CHF, congestive heart failure; DDg, differential diagnosis; MI, myocardial infarction; P., pericarditis; PE, pericardial effusion.
*Percentage related to the population of 260 subsequent patients undergoing pericardiocentesis, pericardioscopy and epicardial biopsy (Marburg pericarditis registry 1988–2001) [1].
†Percentage related to the incidence of pericarditis in the specific population of patients (e.g. with systemic lupus erythematosus).
‡Percentage related to the population of patients with neoplastic pericarditis.
Reproduced with permission from the ESC Guidelines on the Management of Pericardial Disease [8].

Treatment is directed to resolving the symptoms and preventing recurrences (see Acute pericarditis). In chronic or recurrent symptomatic viral (myo)pericarditis the following specific treatment has been applied to eradicate the virus: (1) cytomegalovirus pericarditis: hyperimmunoglobulin—once a day 4 ml/kg on days 0, 4 and 8; 2 ml/kg on days 12 and 16; (2) Coxsackie B virus pericarditis: interferon-α or -β 2.5×10^6 IU/m^2 subcutaneously three times per week; (3) adenovirus and parvovirus B19 perimyocarditis: immunoglobulin treatment: 10 g intravenously on days 1 and 3 for 6–8 hours [35]. However, this is an ongoing study and the final results are not known at present.

Pericardial manifestation in HIV patients may be the result of infective, non-infective, or neoplastic disease (Kaposi sarcoma and/or lymphoma). Infective (myo)pericarditis results from the local HIV infection and/or from the other viral (cytomegalovirus, herpes simplex virus), bacterial (*Staphylococcus aureus*, *Klebsiella pneumoniae*, *Mycobacterium avium* and *Mycobacterium tuberculosis*) and fungal co-infections (*Cryptococcus neoformans*) [36]. In progressive disease the pericardial effusion occurs in ~40% [32]. Cardiac tamponade is rare. During the treatment with retroviral compounds, lipodystrophy can develop, leading to heart failure. Treatment is symptomatic, while in large effusions and cardiac tamponade pericardiocentesis is necessary. The use of corticosteroid therapy is contraindicated except in secondary tuberculous pericarditis, as an adjunct to tuberculostatic treatment [38].

Bacterial pericarditis

Purulent pericarditis is a rare, acute, fulminant illness that is always fatal if untreated. The mortality rate in treated patients is 40%, mostly because of cardiac tamponade, toxicity and constriction [10]. It usually arises by contiguous spread or haematogenous dissemination of an infection elsewhere in the body. Predisposing conditions are pericardial effusion, immunosuppression, chronic diseases (alcohol abuse, rheumatoid arthritis, etc.), cardiac surgery and chest trauma. Percutaneous pericardiocentesis must be promptly performed. The pericardial fluid obtained should undergo Gram, acid-fast, and fungal staining, followed by cultures of the pericardial and body fluids. Rinsing of the pericardial cavity, combined with effective systemic antibiotic therapy, is mandatory (antistaphylococcal antibiotic plus aminoglycoside, tailored according to pericardial fluid and blood cultures) [10]. Intrapericardial instillation of antibiotics (e.g. gentamycin) is useful but not sufficient. Open surgical drainage and pericardiectomy are required in patients with dense adhesions, loculated and thick purulent effusion, recurrence of tamponade, persistent infection and progression to constriction [8,10]. Surgical mortality is up to 8%. Instead of surgery, pericardiocentesis and frequent irrigation of the pericardial cavity with urokinase or streptokinase has been applied in a few patients [39,40]. However, the safety and efficacy of this approach in comparison to surgery remains to be investigated.

Tuberculous pericarditis

The clinical presentation is variable: acute pericarditis with or without effusion; cardiac tamponade, acute constrictive pericarditis, subacute constriction, effusive–constrictive, or chronic constrictive pericarditis, and pericardial calcifications [3,41,42]. The mortality rate in untreated effusive tuberculous pericarditis approaches 85%. Pericardial constriction in these cases is 30–50% [27,28,38]. The diagnosis is made by the identification of *M. tuberculosis* in the pericardial fluid/tissue, and/or the presence of caseous granulomas in the pericardium. Polymerase chain reaction methods can identify *M. tuberculosis* rapidly from 1 µl of pericardial fluid [43]. Increased adenosine deaminase activity and interferon-γ concentration in pericardial effusion are also suggestive. Pericardioscopy and pericardial biopsy improve the diagnostic accuracy (Fig. 17.5) [44].

Pericarditis in a patient with proven extracardiac tuberculosis is strongly suggestive of a tuberculous aetiology (several sputum cultures should be taken) [27]. The tuberculin skin test may produce a false-negative in 25–33% and a false-positive in 30–40% of patients [41]. The more accurate enzyme-linked immunospot (ELISPOT) test detects T cells that are specific for the *M. tuberculosis* antigen [45]. Perimyocardial tuberculous involvement is also associated with high serum titres of antimyolemmal and antimyosin antibodies [46].

Various antituberculous drug combination regimens of different durations (6, 9, 12 months) have been applied [27,28,47,48]. However, only patients with proven or very likely tuberculous pericarditis should be treated. Prevention of constriction in chronic pericardial effusion of undetermined aetiology by *ex iuvantibus* antitubercular treatment was not successful [49]. A meta-analysis of treatment results in effusive and constrictive tuberculous pericarditis suggested that tuberculostatic treatment combined with steroids might be associated with fewer deaths and less frequent need for pericardiocentesis or pericardiectomy [46,48]. If given, prednisone should be administered in high doses (1–2 mg/kg/day) because rifampicin induces its metabolism by the liver [3]. This is maintained for 5–7 days and progressively reduced in 6–8 weeks.

Pericarditis in renal failure

Renal failure produces large pericardial effusions in ~20% of patients [50]. It results from inflammation of the visceral and parietal pericardium and correlates with the degree of azotaemia (blood urea nitrogen > 60 mg/dl). Two forms have been described. (1) Uraemic pericarditis occurs in 6–10% of patients with advanced renal failure before dialysis has been instituted or shortly thereafter [3,50]. (2) Dialysis-associated pericarditis occurs in up to 13% of patients on maintenance haemodialysis, and occasionally with chronic peritoneal dialysis as a result of inadequate dialysis and/or fluid overload. Adhesions between the thickened pericardial membranes give a 'bread and butter' appearance. Fever, pleuritic chest pain and pericardial rubs may occur regardless of the size of the effusion. Autonomic impairment may occur in some uraemic patients, causing the heart rate to remain at 60–80 beats/min despite tamponade. Anaemia as a result of erythropoietin resistance worsens the symptoms [51]. The ECG does not show the typical diffuse ST/T wave elevations because of the lack of myocardial inflammation (otherwise, intercurrent infection should be suspected) [52].

Most patients with uraemic pericarditis respond to haemodialysis (heparin-free to avoid haemopericardium) with resolution of chest pain and pericardial effusion within 1–2 weeks [3]. Peritoneal dialysis may be therapeutic in pericarditis that is resistant to haemodialysis, or if heparin-free haemodialysis cannot be performed. NSAIDs and systemic corticosteroids have limited success when intensive dialysis is ineffective. Cardiac tamponade and large effusions resistant to dialysis must be treated with pericardiocentesis. Large, non-resolving symptomatic effusions can be treated with intrapericardial instillation of corticosteroids (triamcinolone hexacetonide 50 mg every 6 hours for 2 to 3 days) [8]. Pericardiectomy is indicated only in refractory, severely symptomatic patients. Colchicine may worsen the impaired renal function, but benefit was also noted in a resistant case of uraemic pericarditis [53].

Autoreactive pericarditis and pericarditis in systemic autoimmune diseases

An autoreactive or immunological mechanism can be implicated in many forms of pericarditis. However, the diagnosis of autoreactive pericarditis requires a complex work-up that includes the following criteria [2]:

- an increased number of lymphocytes/mononuclear cells > 5000/mm^3, or the presence of antibodies against heart muscle tissue in the pericardial fluid;
- inflammation in epicardial/endomyocardial biopsies (≥ 14 cells/mm^2);
- exclusion of active viral infection in pericardial effusion and endomyocardial/epimyocardial biopsies (no virus isolation, no immunoglobulin M titre against cardiotropic viruses in the pericardial effusion, and a negative polymerase chain reaction for major cardiotropic viruses);

- *Mycobacterium tuberculosis*, *Borrelia burgdorferi*, *Chlamydia pneumoniae* and other bacterial infections and excluded by polymerase chain reaction and/or cultures;
- neoplastic infiltration absent in pericardial effusion and biopsy samples; and
- exclusion of systemic, metabolic disorders and uraemia.

Intrapericardial treatment with triamcinolone is highly efficient with rare side-effects. This mechanism is of great interest from a pathophysiological point of view. The comprehensive invasive diagnostic protocol may not be necessary if symptoms and pericardial effusion decrease over time and resolve spontaneously or under anti-inflammatory treatment. The autoreactive mechanisms could be involved in patients with otherwise idiopathic pericarditis, recurrent pericarditis, postcardiac injury pericarditis, and pericarditis that occurs in systemic autoimmune diseases.

Pericarditis may also occur in several systemic autoimmune diseases: rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis, polymyositis/dermatomyositis, mixed connective tissue disease, seronegative spondyloarthropathies, systemic and hypersensitivity vasculitides, Behçet syndrome, Wegener's granulomatosis, and sarcoidosis [3]. Intensified treatment of the underlying disease and symptomatic management are indicated [8].

The post-cardiac injury syndrome: postpericardiotomy syndrome

Post-cardiac injury syndrome develops within days to months after cardiac/pericardial injury [3,54,55]. Pericardial effusion also occurs after orthotopic heart transplantation (21%), more frequently in patients receiving aminocaproic acid during the operation [56]. Cardiac tamponade after open heart surgery is more common following valve surgery than coronary artery bypass grafting and may be related to the postoperative use of anticoagulants [5]. Administration of anticoagulants in patients with early postoperative pericardial effusion imposes the greatest risk [57]. Symptomatic treatment is the same as for acute pericarditis and repeat surgery is rarely needed. Primary prevention using perioperative steroid treatment or colchicine is under investigation [58].

Postinfarction pericarditis

Postinfarction pericarditis occurs as an 'early' (pericarditis epistenocardica) or a 'delayed' form (Dressler's syndrome) [3,59]. Epistenocardiac pericarditis, caused by direct exudation, occurs in 5–20% of transmural myocardial infarctions within the first 7 days but is rarely discovered clinically. Dressler's syndrome arises from one week to several months after myocardial infarction, with manifestations similar to the post-cardiac injury syndrome. It does not require transmural infarction [3] and can also appear as an extension of epistenocardiac pericarditis. Its incidence was 0.5–5% in the past, particularly in the prethrombolytic era, but the syndrome has become a rarity most probably because of advances in treatment of acute myocardial infarction by cardiac interventions [3]. High doses of ibuprofen or aspirin should be given for 2–5 days. Steroids can be used for refractory symptoms but may delay the healing of infarction [3].

A postinfarction pericardial effusion larger than 10 mm is a predictor of ventricular wall rupture [60]. Urgent surgical treatment is life saving. If this is not feasible pericardiocentesis and intrapericardial fibrin-glue instillation could be an alternative [61].

Traumatic pericardial effusion

Iatrogenic tamponade occurs most frequently in percutaneous mitral valvuloplasty (transseptal puncture). Acute or subacute cardiac tamponade occurs very rarely during percutaneous coronary interventions and is successfully treated with membrane-covered graft stents [8]. A perforation rate of 0.3–5% was reported during right ventricular endomyocardial biopsy, leading to tamponade and circulatory collapse in less than half of the cases [62]. The incidence of pericardial haemorrhage in left ventricular endomyocardial biopsy is lower (0.1–3.3%). Procedure-related mortality was reported in only 0.05% in a worldwide survey of more than 6000 cases [62] and in none of the 2537 patients on the Marburg Heart Centre registry [63]. Pacemaker leads penetrating the right ventricle or epicardial electrodes may cause pericarditis with tamponade, adhesions, or constriction. A right bundle branch block instead of a usually induced left bundle branch block is a clue. Rescue pericardiocentesis is successful in 95–100% with a < 1% mortality [64]. The deceleration force in blunt chest trauma can lead to contusion with intrapericardial haemorrhage, cardiac or pericardial rupture or herniation.

Neoplastic pericarditis

The most common secondary malignancies of the pericardium are caused by the spread of lung cancer, breast cancer, malignant melanoma, lymphomas and leukaemia. Primary tumours are very rare. With small effusions most patients are asymptomatic. The onset of dyspnoea, cough, chest pain, tachycardia and jugular venous distension is observed when the volume of fluid exceeds 500 ml. The

diagnosis is based on the confirmation of the malignant infiltration within the pericardium by cytology or biopsy [65]. Notably, in almost two-thirds of the patients with documented malignancy pericardial effusion is caused by non-malignant diseases, e.g. radiation pericarditis, or opportunistic infections [66]. The chest roentgenogram, computerized tomography, and magnetic resonance imaging may reveal mediastinal widening, hilar masses, or pleural effusion [3]. The analyses of pericardial fluid, pericardial/epicardial biopsy are essential for the confirmation of malignant pericardial disease.

In neoplastic pericardial effusion without tamponade systemic antineoplastic treatment as baseline therapy can prevent up to 67% of recurrences [3]. Pericardial drainage is recommended in all patients with large effusions/tamponade (Table 17.2) [8]. Prevention of recurrences may be achieved by intrapericardial instillation of sclerosing, cytotoxic agents, or immunomodulators. Radiation therapy is effective in patients with radiosensitive tumours (lymphoma and leukaemia) [8]. Intrapericardial instillation of cisplatin is most effective in secondary lung cancer and thiotepa is valuable in breast cancer pericardial metastases [67–70].

Rare forms of pericardial disease

Fungal pericarditis

This may be endemic (*Histoplasma*, *Coccidioides*) or opportunistic (*Candida*, *Aspergillus*, *Blastomyces*, *Nocardia*, *Actinomyces*). Diagnosis is obtained by staining and culturing pericardial fluid or tissue or by determination of antifungal antibodies in serum [3]. NSAIDs can support the treatment with antifungal drugs (fluconazole, ketoconazole, itraconazole, amphotericin B) [8].

Radiation pericarditis

Radiation pericarditis may begin either during the exposure (very rare) or months and years later—with latency of up to 15–20 years. Its occurrence is influenced by the applied source, the dose, its fractionation, the duration, the radiation exposed volume, the form of mantle field therapy, and the age of the patient [3]. The effusion may be serous or haemorrhagic, and may later show fibrinous adhesions or constriction, typically without calcifications. Pericardial constriction occurs in up to 20% of patients, requiring pericardiectomy. The operative mortality is high (21%) and the postoperative 5-year survival is poor (1%) mostly as a result of myocardial fibrosis [22].

Chylopericardium

Chylopericardium is a very rare condition. It refers to a communication between the pericardium and the thoracic duct, predominantly as a complication of trauma, congenital anomalies, or surgery [3]. The pericardial fluid is sterile, odourless and opalescent with a milky white appearance and the microscopic finding of fat droplets. The chylous nature of the fluid is confirmed by Sudan III stain for fat and by high concentrations of triglycerides (5–50 g/l), and proteins (22–60 g/l) [3]. Enhanced computerized tomography, alone or combined with lymphography, can identify not only the location of the thoracic duct but also its lymphatic connection to the pericardium. Chylopericardium after thoracic or cardiac operation is preferably treated by pericardiocentesis and diet (medium-chain triglycerides). If production of chylous effusion continues, surgical treatment is mandatory. When the course of the thoracic duct can be precisely identified, its ligation and resection just above the diaphragm is effective.

Drug- and toxin-related pericarditis

Several drugs can induce this form of pericarditis [3]. Mechanisms include drug-induced lupus reactions, idiosyncrasy, ‘serum sickness’, foreign substance reactions, and immunopathy. Discontinuation of the causative agent and symptomatic treatment are indicated.

Pericardial effusion hypothyroidism

This occurs in 5–30% of patients [3]. Fluid accumulates slowly and tamponade occurs rarely. In some cases cholesterol pericarditis may be observed. The diagnosis is based on serum levels of thyroxin and thyroid-stimulating hormone. Therapy with thyroid hormone decreases the pericardial effusion.

Personal perspective

Technical advances in instrumentation, introduction of pericardioscopy and contemporary pathology, virology, and molecular biology techniques have improved the diagnostic armamentarium in pericardial diseases [44,65,66,71]. Visualization of epi- and pericardial layers is now possible *in vivo* using pericardioscopy that permits targeted biopsy with little risk and in turn gives an aetiopathogenetic diagnosis. This diagnostic tool will eventually change our management from symptomatic treatment of an idiopathic disease to causative therapy of an aetiological disease entity. Nevertheless, in many patients with acute pericarditis resolution occurs spontaneously or with NSAIDs. In these patients such a comprehensive approach is not clinically justified. In otherwise resistant forms of pericardial disease, however, aetiological diagnosis enables the administration of causative treatment. When access to the pericardium is facilitated, even in smaller effusions, the required treatment can be given intrapericardially in high dosage. This is particularly applicable to metastatic pericardial effusions, in which high-dose cisplatin or thiotepa prevent recurrence of a haemodynamically relevant or lethal tamponade. This will also be a promise for the future treatment of chronic symptomatic effusions with negative viral and bacterial work-up. In these patients, intrapericardial triamcinolone may reduce recurrences. Appreciating the clinical challenges raised by pericardial disease, the European Society of Cardiology has recently published guidelines on the diagnosis and management of pericardial diseases, available as full text, executive summary, slide collection, and pocket guidelines [8].

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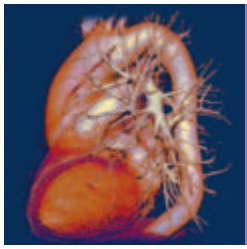

18 Tumours of the Heart

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Summary

Primary tumours of the heart are rare. Metastases are the most frequent tumours of the heart. Symptoms are very variable and can be the result of either local or systemic effects. Imaging with echocardiography and magnetic resonance plays an important role in diagnosis. Histology is important in determining tumour type with a role for endomyocardial biopsy in presurgical diagnosis. Most primary cardiac tumours are benign, the main benign tumour being myxoma (50–75% in most series). The main primary malignant tumour is the angiosarcoma. The majority of tumours occur in adulthood. Childhood tumours are mainly rhabdomyomas and fibromas. Surgery is successful for benign tumours when adequate resection margins are allowed. More extensive surgery, with possible resection or debulking for malignant tumours, has a more prominent role today. There is a role for chemotherapy and radiotherapy in lymphomas but their role in the treatment of other malignant tumours depends on the tumour type.

Introduction

Primary tumours of the heart, with the exception of atrial myxomas, occur rarely; metastatic tumours to or directly invasive of the heart are far more common. About 75% of primary tumours are benign and 75% of these are atrial myxomas. The benign tumours include rhabdomyomas, fibromas, papillary fibroelastomas, haemangiomas, pericardial cysts, lipomas, hamartomas, teratomas and paragangliomas/phaeochromocytomas. The last two can also be malignant. The malignant tumours consist of various sarcomas: myxosarcoma, liposarcoma, angiosarcoma, fibrosarcoma, leiomyosarcoma, osteosarcoma, synovial sarcoma, rhabdomyosarcoma, neurofibrosarcoma, malignant fibrous histiocytoma, undifferentiated sarcoma and lymphoma.

Primary tumours of the heart and pericardium have an incidence of between 0.0017% and 0.028% in collective series [1]. In the United States, based upon data from 22 large autopsy series, the prevalence of primary cardiac tumours is 0.02% (200 tumours per million autopsies). About 75% of primary tumours are benign and 50% of these benign tumours are myxomas, giving 75 cases of myxoma per million autopsies [2].

An Italian study reviewed 116 cases of cardiac tumours [3]. One hundred and thirteen were benign: myxoma being the most frequent (87 cases) followed by pericardial cyst (eight cases), endocardial papilloma (five cases), fibroma (three cases), rhabdomyoma (three cases), haematic cyst (two cases), teratoma (two cases), haemangioma (one case), coelothelioma (one case) and lipoma (one case). Twelve were malignant, including pericardial mesothelioma (three cases), myxosarcoma (three cases), angiosarcoma (two cases), fibrosarcoma (two cases) and leiomyosarcoma (two cases).

At the Royal Brompton Hospital, in London, during the last 20 years, we have resected 75 cardiac tumours in adults, the majority being myxomas (25 cases) but other benign tumours, as well as sarcomas and lymphomas, are included in our series (Fig. 18.1). Thus there is a large spectrum of cardiac tumours with myxomas predominating among benign tumours while sarcomas predominate among malignant tumours.

Cardiac tumours can also occur in infants and children but are extremely rare. In a study of 40 patients (mean age, 3.3 years; range, 2 days to 17 years; 65% female),

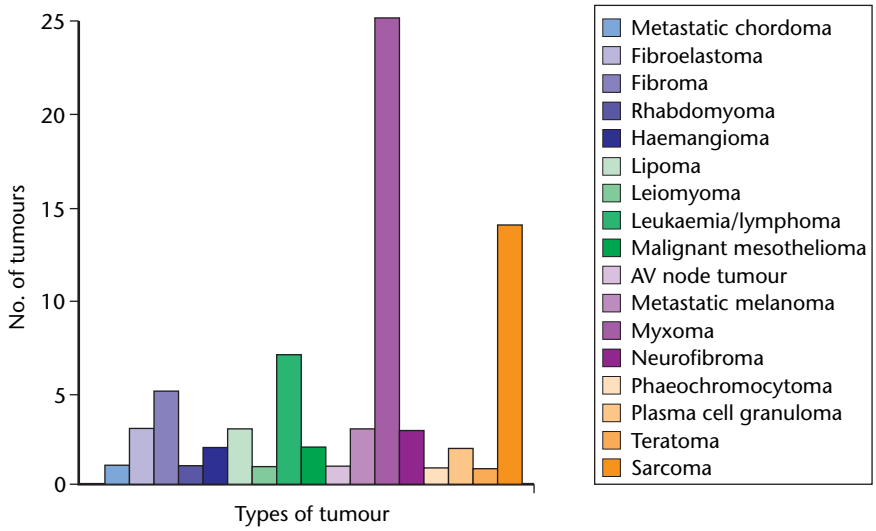

Figure 18.1 Cardiac tumours from Royal Brompton Series 1990–2005.

37 tumours (92%) were benign, mainly myxoma, fibroma and rhabdomyoma, while only three (8%) were malignant, rhabdomyosarcoma, germ-cell tumour and fibrosarcoma [4]. In 224 fetuses and neonates collected from the literature, most had a rhabdomyoma, followed by teratoma, fibroma, oncocytic cardiomyopathy, vascular tumours and myxoma [5].

Clinical presentation

Cardiac tumours produce a large variety of symptoms through many mechanisms (Table 18.1).

Intracavitary masses can impede intracardiac blood flow as a result of mechanical obstruction to ventricular filling or outflow leading to congestive heart failure. Depending on their location, intracavitary tumours may produce symptoms of right-sided heart failure, including hepatomegaly, ascites and superior vena cava obstruction, or left-sided heart failure associated with dyspnoea and orthopnoea from pulmonary congestion [6,7]. Intramural tumours can interfere with the mechanical performance of the ventricles, causing systolic dysfunction as the result of impaired contractility or diastolic dysfunction because of a restrictive physiological pattern.

Table 18.1 Clinical presentation of cardiac tumours

- Intracavitary obstruction and heart failure
- Intramuscular invasion and restrictive cardiomyopathy
- Impaired valve function
- Arrhythmias
- Pulmonary, cerebrovascular and peripheral embolism
- Pericardial effusion and tamponade
- General symptoms of malaise (pyrexia, weight loss, arthralgias, increased erythrocyte sedimentation rate)
- Mechanical haemolysis, anaemia

Tumours can also impair valve function. Mobile and pedunculated intracavitary left atrial myxomas may obstruct the blood flow through the mitral valve, producing intracardiac haemodynamics that resembles haemodynamics observed in mitral stenosis, often in combination with mitral regurgitation. However, mitral valve obstruction caused by left atrial myxomas often shows atypical clinical features, such as sudden onset and intermittent symptoms which can be associated with a certain body position. In contrast to mitral stenosis, left atrial enlargement and atrial fibrillation are less common, except in advanced disease. The auscultation findings may include a loud split first heart sound caused by the late onset of mitral valve closure and a typical early diastolic sound known as a 'tumour plop' produced as the tumour hits the ventricular wall or as its excursion is abruptly halted. The third heart sound, which is rare in mitral stenosis, can also be audible in the presence of left atrial myxoma. Left atrial myxomas can cause direct mechanical damage to the mitral valve as a result of the recurrent collisions between the tumour and the valve.

Right atrial myxomas may cause obstruction of the blood flow through the tricuspid valve and produce symptoms of right-sided heart failure. An early diastolic rumbling murmur of tricuspid stenosis and a pansystolic murmur of tricuspid regurgitation may change with respiration and with changes in the body position. Abrupt obstruction of intracardiac flow may cause syncope and seizure-like activity due to cerebral hypoperfusion.

Intramural tumours with extensive involvement of the ventricular myocardium, such as rabdomyomas, fibromas and rarely angiomas of the interventricular septum, may lead to a variety of ventricular arrhythmias including ventricular tachycardia, ventricular fibrillation and sudden cardiac death [8]. Tumours confined to the atria are usually associated with atrial fibrillation, flutter, and atrial tachycardia [9]. Large myxomas may obliterate the ventricular cavity and cause neurocardiogenic syncope. Tumours with conduction system involvement, such as angiomas and mesotheliomas of the atrioventricular node, may cause heart block and asystole and tumours confined to the interventricular septum with involvement of the His–Purkinje system may lead to intraventricular conduction delay and bundle branch block.

Left-sided intracavitary tumours, particularly myxomas with a friable irregular villous appearance, can be a source of emboli with tumour fragments or thrombi from the surface of a tumour travelling to cerebral, coronary, retinal, renal, visceral and peripheral arteries, resulting in embolic stroke, visceral infarction and peripheral vascular disease. Multiple recurrent emboli may mimic vasculitis or endocarditis and may lead to the formation of vascular aneurysms in the affected organs. Embolic stroke is the most common neurological manifestation and is often found in multiple sites (41%) [10]. Although coronary emboli are regarded as rare, cases of acute myocardial infarction have been described in individuals with normal coronary angiograms and no risk factors for ischaemic heart disease [11]. Right-sided tumours usually embolize to the pulmonary circulation, leading to pulmonary hypertension and to cor pulmonale in the event of multiple recurrent microemboli. Embolic event rates are 45–60% in left-sided myxomas and 8–10% in right-sided myxomas. Embolic stroke or systemic embolism can be the first manifestation of papillary fibroelastomas which otherwise may remain clinically silent. In a series of 26 patients with a prospective diagnosis of histologically confirmed papillary fibroelastoma of the heart, 23 patients showed symptoms attributable to embolization during a mean follow-up of 11 months, with stroke occurring in 19% and transient ischaemic attacks occurring in 35% [12].

Pericardial effusion and tamponade are common clinical manifestations of malignant, rapidly growing infiltrating cardiac tumours such as rhabdomyosarcomas, fibrosarcomas, malignant histiocytomas and angiosarcomas which often extend into the pericardial space. Pericardial effusions caused by sarcomas are typically haemorrhagic. Chest pain as a result of pericardial, pleural, or coronary involvement, is characteristic for malignant tumours. Epicardial and endocardial extension, diffuse pericardial involvement and local spread of the tumour to the pleura or mediastinum is typical for angiosarcoma. The superior vena cava syndrome, manifesting by cyanosis, distended neck veins, and oedema of the face and upper extremities, or obstruction of the inferior vena cava, resulting in visceral congestion, are commonly associated with malignant cardiac tumours. Metastases occur to distant organs, most frequently the lungs, mediastinum, vertebral column, brain, thyroid gland, bones and other internal organs.

Non-specific signs of disseminated malignancy, such as fever, weight loss and lassitude, are usually present. An increased paracrine synthesis of interleukin-6, specific for myxomas, may account for a variety of constitutional symptoms including fever, raised inflammatory markers and erythrocyte sedimentation rate, and rheumatic symptoms. However, some tumours produce no symptoms and become evident as incidental findings, especially today with the increased use of non-invasive imaging techniques. Approximately 20% of patients with cardiac myxoma are asymptomatic. Cardiac paragangliomas are extremely rare catecholamine-producing tumours that arise from intrinsic cardiac paraganglial (chromaffin) cells and produce symptoms typical of phaeochromocytoma (arterial hypertension, headache, palpitations and flushing). Elevated levels of urinary noradrenaline, vanillylmandelic acid, and total metanephrine or elevated levels of plasma noradrenaline and adrenaline are common diagnostic features.

Imaging

An increase in the incidence of primary cardiac tumours has been reported since the development of non-invasive imaging modalities. Earlier studies showed that most tumours were detected at autopsy. The introduction of imaging techniques has highlighted larger surgical series in the past 40 years. Among 27 640 patients assessed for cardiac disease, the incidence of tumours was 0.06% (1980–1984), 0.22% (1985–1989) and 0.32% (1990–1995) [13].

A number of imaging modalities are available for the assessment of cardiac tumours; each has advantages and limitations. Cardiac tumours rarely exhibit cardiomegaly on chest radiographs. Two-dimensional echocardiography has become the most important method for non-invasive detection. This establishes the presence of a mass in the majority of patients. While echocardiography is the first-line imaging technique for cardiac tumours, computerized tomography (CT) and magnetic

resonance imaging (MRI) are useful for further characterization and differential diagnosis. Transthoracic echocardiography is usually adequate for providing diagnostic information when the lesion is large and confined to the pericardium or a specific cardiac chamber. However, the technique has a limited acoustic viewing window in some patients, i.e. ultrasound is blocked by bone and lung tissue, limiting access to the heart. In addition, lesions confined to the atrial appendages and those with extracardiac extension are difficult to image. Myocardial contrast echocardiography with microbubbles imaged within the myocardial vascular bed allows better visualization of intracardiac mass perfusion and better differentiation between the tumour and an intramural thrombus. Transoesophageal echocardiography is excellent for imaging the left atrium, small cardiac lesions and extracardiac involvement, but is more invasive. Imaging of anterior structures, the aortic arch, and the left pulmonary artery is more difficult. A common reason for referral for MRI is determination of the presence of intracardiac filling defects. Tumours of the heart and surrounding structures are well demonstrated by MRI because of the inherent natural contrast between the cardiac structures and the intravascular lumen. The wide field of view of MRI, together with its ability to acquire images in multiple planes, make this method highly effective in demonstrating both intra- and extracardiac tumour extension. These advantages are particularly important in staging primary malignant cardiac neoplasms, such as sarcomas, which are frequently extensive in size and inoperable at initial diagnosis. Differentiation between benign and malignant cardiac tumours by their MR signal characteristics is usually disappointing because most tumours show low to intermediate signal intensity on T1-weighted images and high signal intensity on T2-weighted images. The exceptions are lipomas and fibromas. The lipoma produces a high-intensity signal on both T1- and T2-weighted images and a very low signal with fat-suppression images while fibromas have a characteristic delayed enhancement with the MRI contrast agent gadolinium DTPA. The morphological appearances are usually relied upon to give clues. Malignant primary tumours can be differentiated from benign primary tumours because of their large size, with wide points of attachment, involvement of more than one cardiac chamber or great vessel, and pericardial or extracardiac extension. Angiosarcomas and haemangiomas show signal enhancement after administration of an MR contrast agent. Electron beam and multidetector CT are alternative fast imaging methods but they involve X-ray radiation and the acquisition is usually limited to trans-axial plane.

As with all cardiac tumours, echocardiographic findings usually suggest the initial diagnosis but cross-sectional imaging with CT and MRI can help to resolve diagnostically challenging cases. With its direct multiplanar capability, excellent contrast resolution, and large field of view, MRI permits a detailed examination of the entire mediastinum, helping to rule out any mass that appeared ambiguous on echocardiography. CT provides superior resolution for detecting calcification or fat, while MRI with its direct multiplanar ability more completely characterizes the heart, pericardium, mediastinum and lungs. MRI also helps elucidate the pathophysiological effects of these tumours on cardiac function through gated cine-loop sequences. Beyond tumour characterization, both modalities can help confirm diagnosis through the addition of contrast, which helps distinguish tumour from myocardium, thrombus and blood flow artefacts.

Imaging is valuable for diagnosis, characterization, presurgical evaluation and follow-up [14]. Benign cardiac tumours typically manifest as intracavitary, mural, or epicardial focal masses. Myxomas are usually pedunculated and sometimes calcified. Malignant tumours demonstrate invasive features and present as infiltrative tumours that may involve the heart in a diffuse manner [14]. Lymphomas and metastases are usually recognized by the presence of known tumour elsewhere or by characteristic direct contiguous involvement. MRI is particularly useful for depiction of a tumour's contour and its relation to other cardiac structures, for determination of the location and border and for detection of pericardial invasion. MRI with gadolinium enhancement adds useful information for tissue characterization [15]. Malignant tumours usually have a wide point of attachment, are large and occupy almost the entire cardiac chamber. There can be involvement of more than one cardiac chamber or great vessel and pericardial or extracardiac extension is often noted. Tumour necrosis can be seen. Thus primary malignant cardiac tumours have distinctive features on MRI that can be used to differentiate them from primary benign cardiac tumours [16].

Ultimately, MRI best facilitates surgical planning and post-treatment follow-up, in large part because of its unparalleled ability to locate and delimit these tumours [17].

As better diagnostic techniques and new operative approaches are developed, pathologists will be called upon more often for intraoperative consultation to render a pathological diagnosis and assess adequacy of resection during surgery. Percutaneous endomyocardial biopsy prior to surgery is now commonly used with a low complication rate and use of different bioptomes or needle sizes. Intracavity right-sided masses can be approached using a transvenous catheter-directed technique and left-sided masses by transseptal atrial approaches. However,

biopsy, particularly of left-sided tumours, is associated with a significant risk of embolism, and for intramural tumours the diagnostic yield of endomyocardial biopsy is low. Biopsy is indicated when the extent of the tumour precludes surgical excision and the determination of histology is important to ensure appropriate chemotherapy. Some tumours, such as multiple rhabdomyomas in children, may regress spontaneously and the histological diagnosis is crucial for further management. Presurgical diagnosis is valuable, allowing a more appropriate surgical or oncological approach to the individual case. The widespread use of new imaging techniques has contributed significantly to earlier diagnosis and treatment and thus to improved survival.

Metastatic tumours

It must be remembered that metastatic tumours are more frequent than primary cardiac tumours. Up to 3% of patients with carcinoma have metastases in the heart at autopsy. Although there are exceptions, epithelial malignancies typically spread to the heart by the lymphatic system. Melanoma, sarcoma, leukaemia and renal cell carcinoma metastasize to the heart by a haematogenous route. Lymphomas may involve the heart by virtually any path, including direct extension, haematogenous seeding or lymphatic spread. Thymoma and oesophageal carcinoma involve the heart by direct extension. Melanomas, renal tumours including Wilms' tumour and renal cell carcinoma, adrenal tumours, liver tumours and uterine tumours are the most frequent intracavitary tumours, often spreading directly up the inferior vena cava (Fig. 18.2). However, tumours of virtually any type may result in intracavitary metastasis.

In a recent study of cardiac metastases five patients had lung cancer; two each had breast cancer, malignant melanoma, hepatoma and one each had gastric cancer, urinary bladder cancer, adrenocortical carcinoma, malignant lymphoma, angiosarcoma, fibrosarcoma, leiomyosarcoma, and two had cancers with unknown primaries. Tumour invasion was demonstrated echocardiographically. Massive pericardial effusion was observed in 11 of 20 patients; two with pericardial tumours including malignant lymphoma and lung cancer. Metastatic tumours in the right cardiac chambers come through the inferior vena cava and tumours in the left atrium, left ventricle and pericardium develop from direct extension of the primary lesions. There was an 80% mortality, and the average survival period after the diagnosis of cardiac metastases was 5.5 months [18].

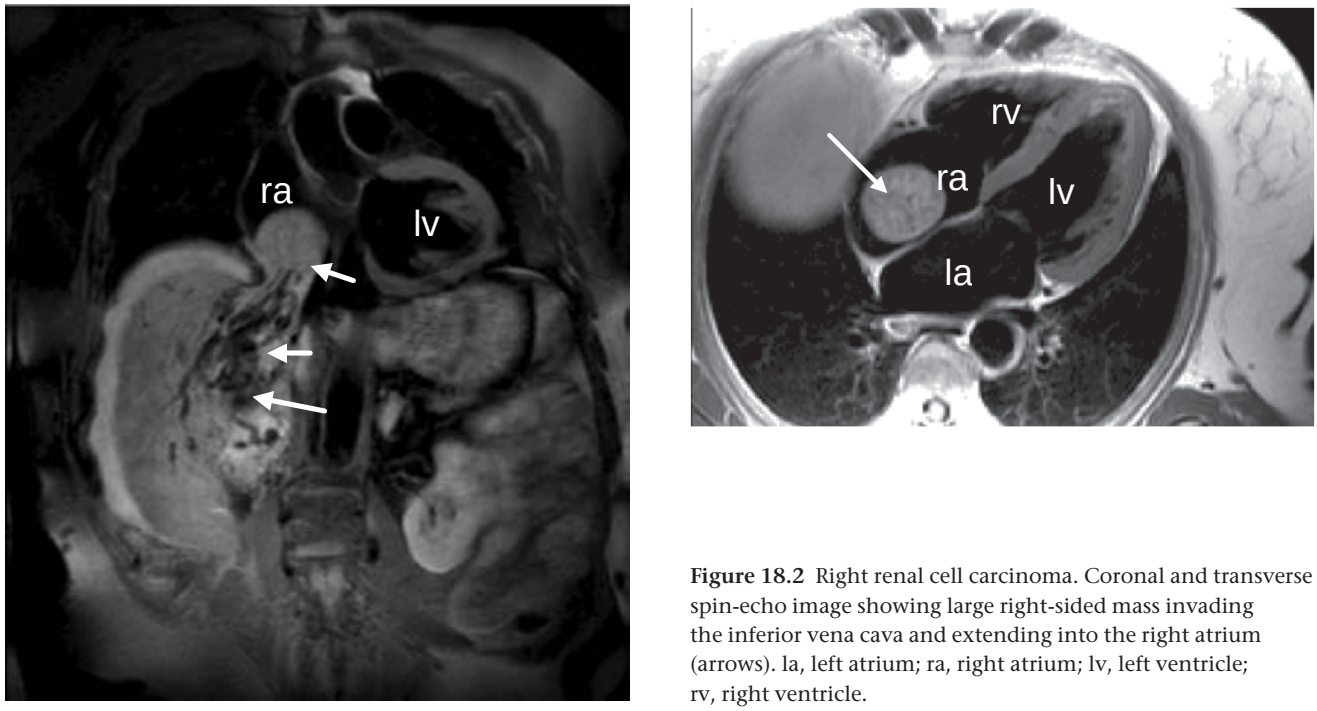

Figure 18.2 Right renal cell carcinoma. Coronal and transverse spin-echo image showing large right-sided mass invading the inferior vena cava and extending into the right atrium (arrows). la, left atrium; ra, right atrium; lv, left ventricle; rv, right ventricle.

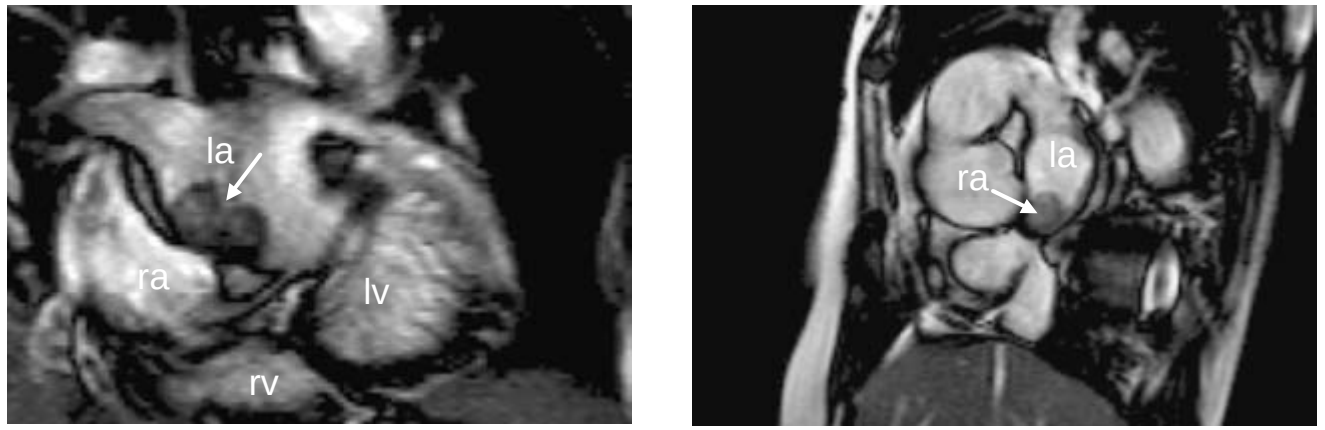

Figure 18.3 Atrial myxoma. Diastolic frame from dynamic cine-studies acquired in the left ventricular horizontal long axis (A) and in the short axis of the left atrium (B). A solid mass attached to the interatrial septum is clearly seen (arrow). la, left atrium; ra, right atrium; lv, left ventricle; rv, right ventricle.

Myxoma

The myxoma is the most frequent primary tumour of the heart and arises from the endocardium as a polypoid, often pedunculated, mass extending into the chamber. Symptoms are frequently non-specific, which poses a challenge in early diagnosis. The symptoms may vary from signs of congestive heart failure with murmurs and atrial arrhythmias to systemic findings such as elevated erythrocyte sedimentation rate and increase in gammaglobulin levels. The second most common clinical presentation is of embolic phenomena which can occur in both the pulmonary and systemic circulations. The majority of patients are usually in the 30- to 60-year age group. There is an equal sex distribution in most series but a predominance in women has been reported. Most cases are sporadic but 2.7% are familial and associated with syndromes. Familial patients are more likely to be young and to have right-sided lesions which are multiple. Family studies suggest an autosomal dominant pattern of inheritance with a variable phenotype. The acronyms LAMB (Lentiginosis, Atrial myxoma, Mucocutaneous myxomas, Blue naevi) and NAME (Naevi, Atrial myxoma, Myxoid neurofibroma, Ephelides) have been used to describe other physical associations with multiple myxomas. Carney described their association with cutaneous lentiginosis, fibroadenomas of the breast, pituitary and cortical adenomas, testicular Sertoli-cell tumours and psammomatous melanotic schwannoma. Recently, a specific mutation in the gene encoding the R1α regulatory subunit of cyclic adenosine monophosphate-dependent protein kinase A (PRKAR1α) has been discovered and found to be associated with a high risk of developing cardiac myxomas [19].

Macroscopic findings

Myxomas are located mainly in the atria (75% in the left and 15–20% in the right). They are attached to the atrial septum usually in the region of the rim of the fossa ovalis (Figs 18.3 and 18.4). However, 10% of atrial myxomas originate from sites other than the septum, the most common being the posterior atrial wall followed by the anterior wall and the atrial appendage. Myxomas do not usually arise from a cardiac valve and any tumour arising from such a location must be investigated thoroughly to rule out other tumours such as fibroelastoma or myxoid fibrosarcomas. Macroscopically, myxomas are usually polypoid, friable and pedunculated. Most have a short,

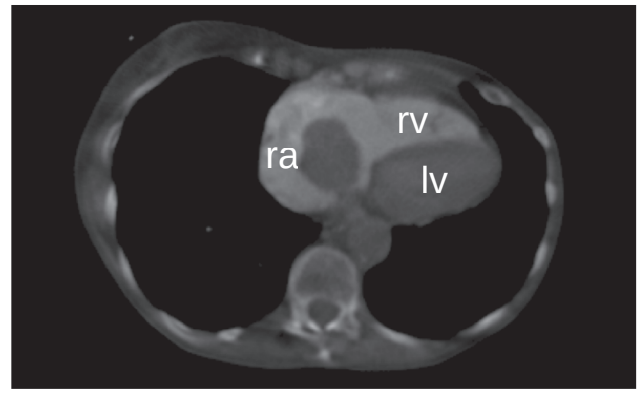

Figure 18.4 Atrial myxoma. Contrast-enhanced CT in transverse plane. ra, right atrium; lv, left ventricle; rv, right ventricle.

broad attachment. Flat sessile myxomas are rare and usually result from embolization, leaving only the broad base of the polypoid tumour attached to the endocardium. Myxomas are soft and gelatinous in consistency, often with areas of haemorrhage or thrombus. Their size varies enormously from 1 to 15 cm although the majority are in the 5–6 cm range. Polypoid myxomas are usually compact and show little tendency to embolize but the villous or papillary type with multiple friable polypoid fronds frequently embolize. Myxomas can be so large that they fill the atria and project through the valve into the ventricular cavity, producing a distinctive groove at the distal end. The tumours can calcify, which can be seen radiographically (the so-called litomyxoma). Up to 7% of myxomas arise in the ventricular cavities equally divided between the right and left ventricles and unlike the atria are not usually attached to the ventricular septum.

Microscopic appearance

Myxomas have extensive myxoid stroma composed of acid mucopolysaccharides within which are embedded polygonal cells with scanty eosinophilic cytoplasm (Fig. 18.5). These cells have round nuclei with open chromatin pattern and small nucleoli. The cytoplasm is abundant and eosinophilic with indistinct cell borders. They are often single with a stellate shape but small clusters also occur. Pleomorphism and multinucleate cells can be seen. The cells also form vascular-like channels and the cells cluster several layers thick around capillaries within the mass. Lymphocytes are often admixed with the myxoma cells. Foci of extramedullary haemopoiesis are occasionally found. Microscopic calcification is present in 10% of myxomas and areas of bone formation complete with haemopoietic tissue occasionally occur. The base of the myxoma extends into the underlying subendocardium. Wide local excision is needed to assure that the myxoma does not recur and complete excision of the atrial septum at the site of attachment is therefore important.

Histogenesis

Myxomas were originally believed to be the result of thrombi but are now considered as neoplasms. Ultrastructurally, the polygonal cells of myxomas resemble multi-potential mesenchymal cells which are found in the normal heart, predominantly in the subendocardial region and especially in the atria and atrial septum. The cells are generally cytokeratin negative (glandular inclusions can be positive) and vimentin positive. Markers for endothelial cells and smooth muscle are also positive in many myxomas. In addition, it has been suggested that they are neuroendocrine in origin based upon positivity with neuroendocrine markers. Because of this multiplicity of positive markers as well as electron microscopy, it is likely that they arise from multi-potential mesenchymal cells which are able to differentiate into fibroblasts, smooth muscle cells, endothelial cells and neuroendocrine cells and elaborate the acid mucopolysaccharide matrix of loose connective tissue. Some findings suggest

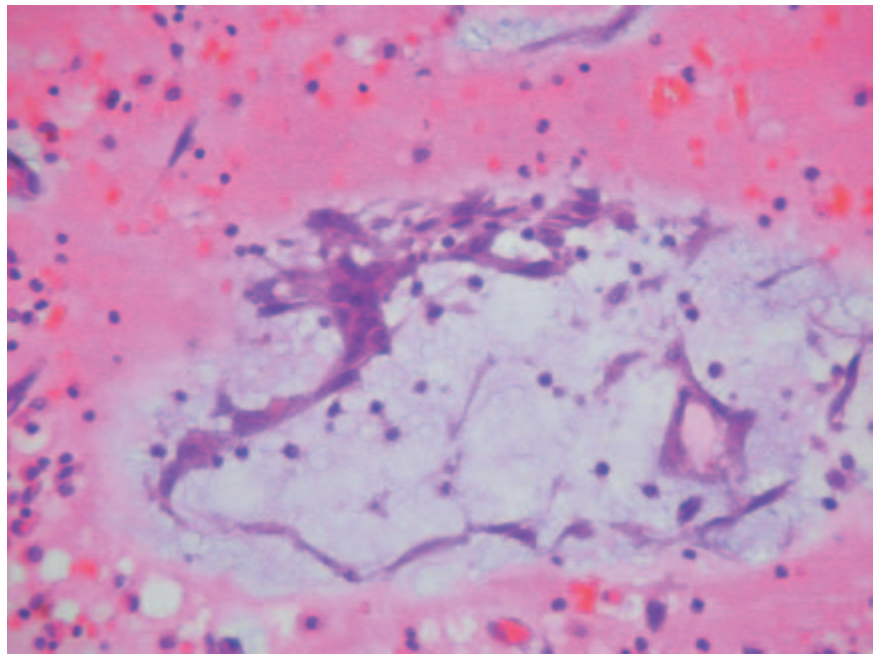

Figure 18.5 Section showing myxoma cells as dark clusters with a pale myxoid background. Haematoxylin and eosin stained section.

an infectious factor in cardiac myxoma. Herpes simplex virus type 1 (HSV-1) antigen has been detected in atrial myxoma suggesting that HSV-1 infection is associated with some cases of sporadic atrial myxoma [20].

Emboli

Emboli from cardiac myxomas are a frequent occurrence. They are gelatinous, soft and white/grey in appearance. Microscopically they contain the typical large polygonal cells embedded in a mucopolysaccharide matrix with admixed thrombus. It is therefore essential that all surgically removed emboli be sent for pathological examination. Because of the frequency of embolization with growth of the myxoma cells in blood vessels there is confusion concerning 'malignant myxomas', where these lesions are mistaken for metastases.

Behaviour

Most atrial myxomas are benign and can be removed by surgical resection. However, if they are not completely excised, they will recur and the incidence of recurrence is reported to be about 2%. Sometimes they recur at sites distant from the original resection and this is more likely to occur in the familial form of the disease where it is likely to be multiple primary tumours rather than recurrence of the original tumour. Where metastases have been reported, detailed histological review shows that many of these are examples of malignant tumours, i.e. liposarcomas or rhabdomyosarcoma, with extensive areas of myxoid degeneration or multiple benign myxomas. Recent reports of metastases to the brain probably represent growth of embolized material. Pulmonary, bone and skin lesions have also been described. Embolic myxomas do not possess malignant histological features and do not give rise to deposits in internal organs or lymph nodes.

Papillary fibroelastoma

Papillary fibroelastoma is the third most common primary tumour of the heart and is most likely to involve the cardiac valves. Like myxomas they arise from the endocardium. In most patients these tumours are incidental findings at echocardiography or autopsy and their true incidence is difficult to estimate. However, early diagnosis of this condition is important because it represents a surgically correctable cause of systemic emboli, stroke, myocardial infarction and sudden cardiac death. The echocardiographic findings should be confirmed by histology because the clinical differential diagnosis includes myxoma, vegetation, thrombi, and lipoma. Most patients are older than 60 years, which also contrasts with myxomas.

Macroscopic features

These tumours resemble what has been accurately described as 'a sea anemone' with multiple papillary fronds attached to the endocardium by a short pedicle. They are generally smaller than myxomas, usually 1 cm or less, and the fronds are longer, thinner and more delicate than those seen in papillary myxomas. Sometimes thrombus obscures the papillary structure, so a careful examination of all tumours, particularly those resected from the valves, must be made to find these delicate structures. Endocarditis can also complicate the appearance with vegetations obscuring the underlying architecture. They may arise anywhere in the heart but most frequently they occur on the aortic valve, either on the ventricular or arterial aspect. On the atrioventricular valves they are seen on the atrial aspect along the lines of closure or on the mid-portion. Occasionally they are multiple, being located on the mitral, aortic, pulmonary and tricuspid valves.

Microscopic appearance

These tumours consist of papillary fronds containing fibrous tissue, elastic fibres and smooth muscle cells set in a mucopolysaccharide matrix covered by hyperplastic endocardial cells. The papillary structures are avascular which contrasts with myxomas which are richly vascular. Histologically the papillary fronds consist of a central core of dense connective tissue surrounded by a layer of loose connective tissue and covered by endocardial cells. The amount of elastic is variable but usually a fine mesh work surrounds the central collagen core. Sometimes the entire central core may consist of elastic fibres.

Origin

This is considered to be either a hamartoma or to result from microthrombi. Microscopically the papillary fronds of these tumours are similar in structure to normal chordae tendineae, suggesting that the papillary fibroelastoma is a true hamartoma. Like the chondroid hamartoma of the lung they are much more frequent in older patients, many of whom have long-standing cardiovascular disease, which suggests that the tumours are secondary to mechanical wear and tear and represent a

degenerative process similar to Lambl's excrescences which are small filiform tags occurring along the contact surfaces of the heart valves of elderly patients. These excrescences are an incidental finding in many autopsies and are considered to be most probably the result of trauma with minute thrombus formation. Papillary fibroelastoma has been called giant Lambl's excrescence because of the resemblance in appearance and location.

Fibromas

In children and infants the most common cardiac tumour after the rhabdomyoma is a fibroma [21]. In surgical series taking in all age groups, it is the second most common benign primary cardiac tumour after myxoma. They are associated with Gorlin's syndrome in which patients develop odontogenic cysts, epidermal cysts, multiple naevi and basal cell carcinomas of the skin.

Fibromas of the heart are connective tissue tumours derived from fibroblasts and are very similar to soft tissue fibromas. These tumours occur at all ages and in both sexes, although they are more frequent in childhood. The symptoms depend on the location of the tumour, with either sudden death or cardiac failure developing. The majority of tumours causing sudden death extend into the ventricular conduction system.

Macroscopic description

Fibromas are almost always single and located in the ventricular myocardium, frequently in the ventricular septum (Fig. 18.6). Atrial fibromas are rare. The tumours are firm, grey/white with a whorled appearance and often reach a large size sometimes exceeding 10 cm in diameter. Central calcification is frequent and may even be seen on radiography. In contrast rhabdomyomas rarely calcify.

Microscopic features

These tumours are non-encapsulated and extend into the surrounding myocardium. This gives the impression of satellite nodules, but in fact these nodules connect to the main tumour mass. Central portions of the tumour are composed of hyalinized fibrous tissue, often with multiple foci of calcification and myxoid cystic degeneration. Normal cardiac muscle cells are frequently entrapped in the growing edge and may at times be found deep within the tumour. Solitary fibrous tumours of the pericardium may look similar but they usually occur in adults, are attached to the pericardium and do not infiltrate the myocardium. Inflammatory pseudotumours can occur in the heart but are extremely rare and contain a prominent inflammatory and vascular component while fibromas usually contain only small foci of lymphocytes and plasma cells, usually at the tumour–myocardium interface.

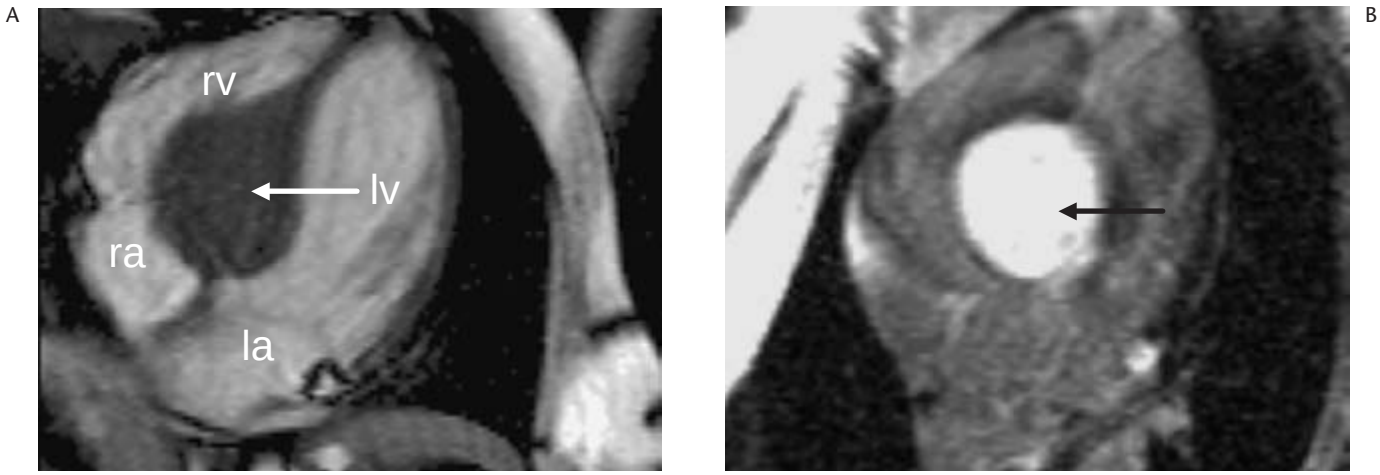

Figure 18.6 Fibroma. (A) Diastolic frame from cine acquisition in the left ventricle horizontal long axis showing mass involving the basal interventricular septum. (B) Delayed contrast-enhanced image in a similar plane to (A) showing homogeneous uptake of the contrast agent gadolinium indicating fibrous tissue. la, left atrium; ra, right atrium; lv, left ventricle; rv, right ventricle.

Rhabdomyoma

Rhabdomyomas are the most common primary benign tumour of the heart in the paediatric age group of less than 15 years. These tumours are present in the myocardium and are often multiple. They are considered to represent fetal hamartomas. In approximately 50% of patients, these tumours are associated with tuberous sclerosis. Clinically patients with rhabdomyomas can be divided into three groups: neonatal, asymptomatic and juvenile.

Neonatal

Approximately one-third of patients may be either stillborn or die within the first few days of life. Seventy-five per cent of these patients have large intracavity tumours with obstruction of at least one cardiac valve. Tuberous sclerosis is difficult to diagnose at this stage. Recent series have shown regression of these tumours with increasing age in those who survive into childhood. Rhabdomyomas can also be seen in children with congenital heart disease, such as hypoplastic left heart, transposition of the great vessels, Ebstein's anomaly, tricuspid and pulmonary atresia.

Asymptomatic cases

In the second group, again representing about one-third of patients, the majority have clinical evidence of tuberous sclerosis. The rhabdomyomas are an incidental finding at autopsy, being small and embedded in the myocardium.

Juvenile cases

The third group of patients present with cardiac symptoms of congestive cardiac failure, cardiac murmurs, arrhythmias and cardiomegaly. The majority of these patients have single large intracavity tumours with marked obstruction of blood flow in at least one cardiac chamber and, clinically, there is no evidence of tuberous sclerosis. The patients are usually under 15 years of age.

Macroscopic findings

Cardiac rhabdomyomas are multiple in most cases and occur throughout the heart but never on a cardiac valve. Most frequently they are located in the myocardium of the left and right ventricles including the septum and protrude into the cardiac chamber. The tumours are usually white to yellow/tan in colour and can vary in size from 1 mm to 9 cm. On imaging, these tumours are usually better defined and more echodense than fibromas.

Microscopic features

The tumours are usually well defined and circumscribed but not encapsulated and are easily distinguished from the surrounding myocardium as nodules of highly cellular tissue. The appearance of the cells is unique to this tumour. These are the 'spider cells' which are pathognomonic of the rhabdomyoma. The typical rhabdomyoma cells are large, up to 18 μm in diameter, and appear vacuolated, being filled with glycogen. The spider cells have centrally placed nuclei with elongated cytoplasmic projections of slender myofibrils extending to the periphery of the cell. The cells are immunopositive for myoglobin, desmin, actin and vimentin.

Prognosis

Partial or complete regression occurs in many of these tumours (24 of 44 patients; 54%). Overall, the prognosis is excellent. Individualized surgery allows early safe treatment of symptomatic tumours [13].

Lipoma

Lipomas can occur in the heart including the visceral and parietal pericardium. Parietal pericardial lipomas are often mistaken clinically for pericardial cysts. Multiple myocardial lipomas have been described in tuberous sclerosis. Most lipomas occur in the epicardium but with multiple tumours they can occur anywhere and have been reported on cardiac valves. The pericardial and intracavity lipomas are bosselated and may reach up to 10 cm in diameter. Grossly they are identical in appearance to adult fat or lipomas elsewhere in the body.

Lipomatous hypertrophy of the atrial septum and lipoma

The interatrial septum consists largely of an invagination of the atrial roof and contains epicardial fat. This fat is the source of the entity known as lipomatous hypertrophy of the atrial septum which is in fact a lipoma characterized by excess accumulations of mature adipose tissue forming a recognizable mass which exceeds 2 cm in diameter (Figs 18.7 and 18.8). These tumours are

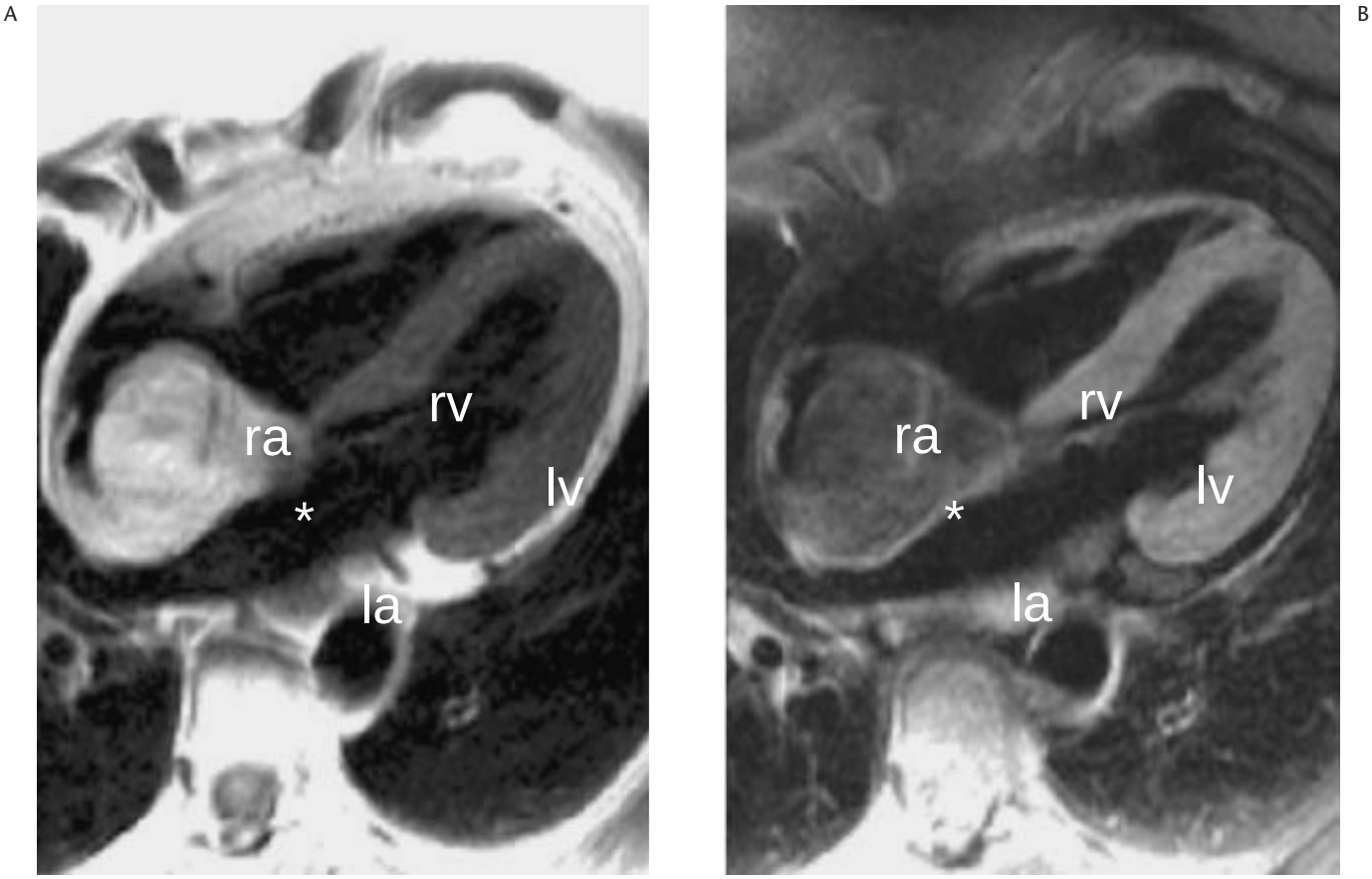

Figure 18.7 Lipomatous hypertrophy of the interatrial septum. Spin-echo images in the horizontal long axis of the left ventricle acquired without (A) and with (B) fat suppression. The lesion (*) and the pericardial/epicardial fat appear bright on (A) and dark (suppressed signal) on (B). la, left atrium; ra, right atrium; lv, left ventricle; rv, right ventricle.

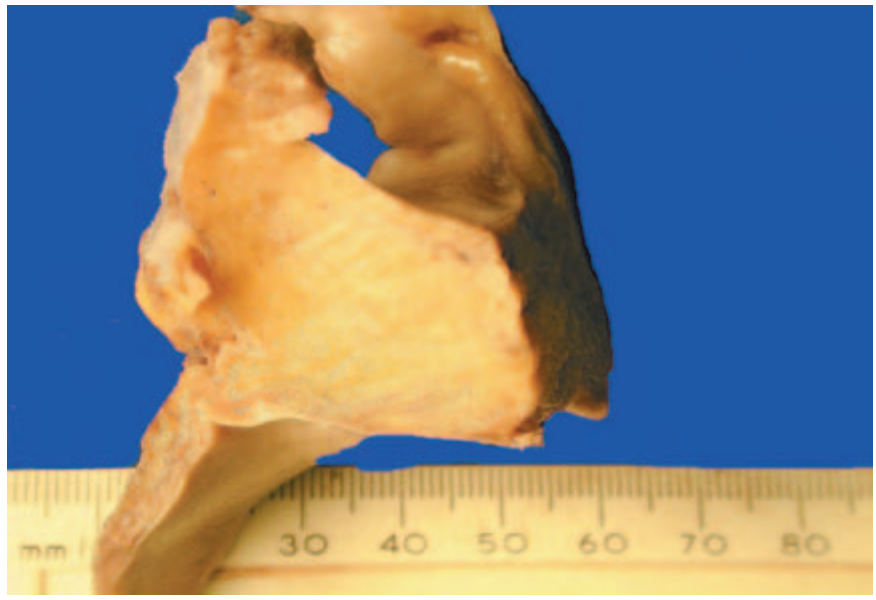

Figure 18.8 Lipomatous hypertrophy of interatrial septum.

especially associated with arrhythmias and can be a cause of sudden death in up to 30% of patients with such lesions.

Haemangioma

Haemangiomas consist of benign proliferations of endothelial cells usually forming channels containing blood. They are rare in the heart and may occur at any site in the ventricles, atria on the epicardial surface of the heart and in the pericardium. The age spread is wide, from 7 months to 80 years, and these tumours are often an incidental finding at necropsy. Symptoms are dependent on the location of the tumour. Characteristically, haemangiomas appear red and haemorrhagic. Capillary haemangiomas consist of haphazardly arranged closely packed capillary structures lined by flattened endothelial cells with minimal stroma. Cavernous haemangiomas consist of widely dilated vascular channels lined by flattened endothelial cells with focal abundant connective tissue between the channels. Only 42 cases in children have been published. In a review of six cases, three were intramuscular haemangiomas of the small-vessel type in older children, two congenital haemangiomas in infants, and one malignant polymorphous haemangioendothelioma. Intramuscular haemangiomas do not respond to corticosteroid therapy and are biologically distinct from congenital haemangiomas, which exhibit regression with pharmacotherapy. Age at diagnosis appears to predict histological type, tumour location, and clinical presentation [22].

Other rare tumours of the heart include leiomyomas and neurofibromas. Endodermal heterotopia of the atrioventricular node is one of the smallest tumours to cause sudden death by involvement of the conduction system. These are considered congenital rests of endodermal /mesodermal origin [23].

In infants less than 1 year, more than 75% of tumours and cysts of the heart are rhabdomyomas or teratomas. A teratoma by definition must contain elements derived from all three germ layers. They are often intrapericardial, attached to the root of the pulmonary artery or aorta. They affect young children with a predominance in girls. The tumours may be up to 15 cm in diameter and usually contain numerous multiloculated cysts with intervening solid areas.

Another rare lesion found in children is histiocytic cardiomyopathy, which can present with arrhythmias or sudden death. It is so called because the cell making up the lesion was considered to resemble a histiocyte but now the cell of origin is either a cardiac myocyte or a Purkinje cell. It is a rare condition with a predominance in girls. Cardiac defects associated with the condition include atrial and ventricular septal defects and hypoplastic left heart syndrome. Other abnormalities include central nervous system defects, ovarian cysts and generalized oncocytic change in endocrine glands. Macroscopically the lesions are multiple, yellow raised nodules usually less than 2 mm in diameter situated in the subendocardium at the base of the interventricular septum in the left ventricle but nodules can be found elsewhere. Microscopically the nodules consist of large foamy oncocytic cells with eccentric dark nuclei surrounded by collagen. No spider cells are seen. The cells are weakly positive for desmin, myoglobin and myosin while they are negative for histiocyte markers.

Malignant tumours of the heart

Twenty-five per cent of all tumours and cysts of the heart and pericardium are malignant. Angiosarcomas, rhabdomyosarcomas, mesotheliomas and fibrosarcomas are the most frequent.

Angiosarcoma

These are malignant tumours originating from vascular endothelium. They are rare tumours but are the most frequently occurring primary malignant cardiac tumour. Angiosarcomas are found more frequently in men than in women and are more often found in the right side of the heart. The majority have evidence of cardiac failure or pericardial disease. In many patients the tumour is large and infiltrating with increased vascularity on gadolinium injection (Fig. 18.9).

Microscopic appearance

Microscopically there is great variation in the appearance of angiosarcomas both between and within the same tumour. Basically angiosarcomas are composed of proliferations of malignant cell-forming vascular channels (Fig. 18.9). There may also be solid areas of spindle cells and sheets of anaplastic large cells. The vascular channels vary greatly in size and shape, frequently forming multiple anastomosing channels. These are lined by swollen multilayered endothelial cells. Nuclear pleomorphism and anaplasia are marked and mitoses are frequent.

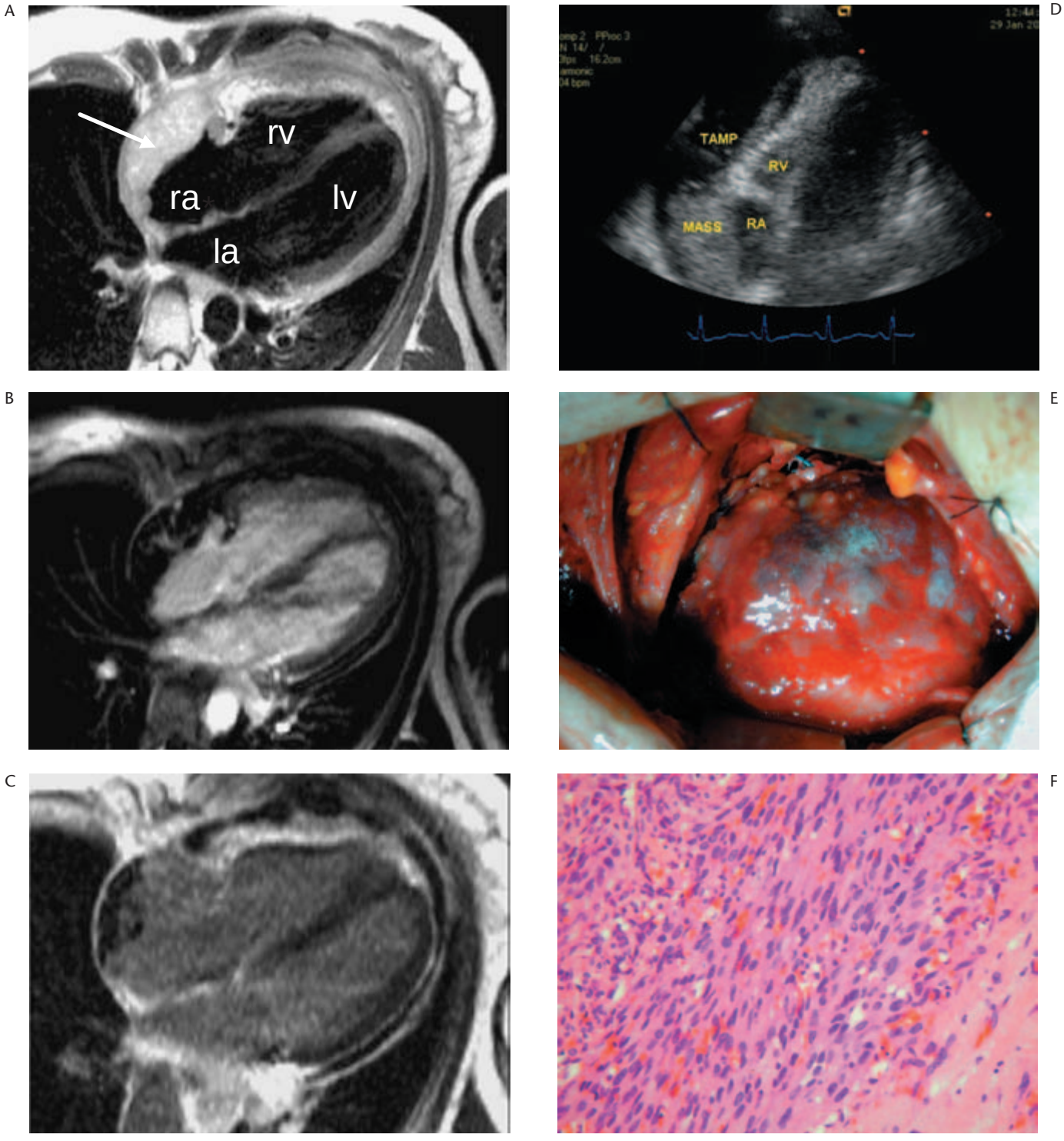

Figure 18.9 Angiosarcoma. (A) A spin-echo image in a four-chamber view and the corresponding inversion recovery gradient echo image acquired 2 minutes (B) and 15 minutes (C) after intravenous injection of gadolinium DTPA. The spin-echo image depicts the anatomical details of the right atrial mass (arrow) and its relation to surrounding structures. Early and late enhancement (B and C) indicate increased vascularity and necrosis/scarring respectively. (D) Initial echocardiogram apical four-chamber view demonstrating pericardial tamponade and a suspected right atrial mass. (E) Operative photograph showing tumour in the free wall of the right atrium. (F) High-power section showing a malignant spindle cell tumour with spaces filled with red blood cells typical of angiosarcoma. la, left atrium; ra, right atrium; lv, left ventricle; rv, right ventricle.

The tumours are usually unresectable because of extensive pericardial involvement. Radiotherapy and chemotherapy may offer temporary relief. Distant metastasis does occur, particularly to the central nervous system, and local spread is also extensive.

Rhabdomyosarcoma

This is a neoplasm of malignant cells with striated muscle features. It is the second most common primary sarcoma of the heart. The patients range in age from 3 months to 80 years. The majority of patients have non-specific symptoms. There appears to be no propensity of rhabdomyosarcomas to arise in any one of the cardiac chambers. The pericardium is usually involved by direct extension of the tumour from the myocardium. Diffuse pericardial involvement which can typically be seen in mesothelioma or angiosarcoma is not a feature of rhabdomyosarcomas. The tumours are usually nodular, soft and centrally necrotic. Microscopically embryonal or alveolar and adult forms occur, with the adult form being much more frequent. Diagnosis is made by finding a typical rhabdomyoblast. Myxoid areas, spindle cell areas and solid cellular areas are often found within the same tumour. Microscopic foci of necrosis and haemorrhage are often noted. The rhabdomyoblast on which the diagnosis rests includes strap-shaped cells with two or more nuclei, racket-shaped cells, rounded cells and spider-web cells with peripheral vacuoles. The cytoplasm is often eosinophilic and granular. Cross-striations may be seen as high magnifications, especially with phosphotungstic-acid–haematoxylin staining. However, cross-striations can be identified in only 20–30% of these tumours and electron microscopy may be more useful in delineating cross-striations in up to 90% of patients.

Sarcoma

These can be undifferentiated tumours or can produce osteoid and cartilage in a sarcomatous stroma. The tumours are similar to any other type of sarcoma macroscopically. Microscopically the tumours consist of spindle cells or pleomorphic cells with mitoses, necrosis and haemorrhage and can contain malignant osteoid or chondroid in association with sarcomatous multinucleated giant cells. Patients develop early metastases to the lungs, adjacent soft tissues or liver.

Malignant mesothelioma

Most mesotheliomas of the pericardium are diffuse and cover the visceral and parietal surfaces. The mesothelioma grows by direct extension to surrounding surfaces. The epicardial myocardium may be focally invaded but the tumour does not extend to the endocardial surface, which is an important differential diagnosis at autopsy because primary cardiac sarcomas within the cardiac chambers transverse the myocardium to diffusely involve the pericardium.

Histologically the tumours are indistinguishable from those in the lung; epithelial, biphasic and sarcomatous mesotheliomas are all histologically reported. Distant metastases are extremely unusual.

Lymphoma

Primary cardiac lymphoma is a very rare malignancy, which is typically of a non-Hodgkin type, and involves only the heart and pericardium with no or minimal evidence of extracardiac involvement. Primary cardiac lymphoma account for about 1% of the primary cardiac tumours and 0.5% of the extranodal lymphomas. On the other hand, disseminated lymphoma with cardiac involvement can occur in up to 20% of patients with lymphoma. There are many individual case reports of primary malignant lymphomas of the heart. The patients range in age from 18 to 77 years with equal numbers in men and women. The tumours can be multifocal (Fig. 18.10). Both B- and T-cell lymphomas have been reported. There has been an increase linked to AIDS, immunosuppression and cardiac transplantation. They can be difficult to diagnose as a recent case of ours illustrated which presented initially as an inflammatory 'pseudotumour' which, on further development of skin metastases, turned out to be an angiocentric T-cell lymphoma causing infarction and inflammation in the myocardium (Fig. 18.10) [24].

About 80% of cases of the primary cardiac lymphoma in immunocompetent hosts are of diffuse B-cell lymphoma, and in patients with immunodeficiency states, small non-cleaved or immunoblastic lymphomas are more frequent. The right atrium and right ventricle are the two most frequently involved sites. Clinical presentation is heterogeneous and is generally related to the site of involvement in the heart. The diagnosis is suspected when patients present with a cardiac mass or an unexplained refractory pericardial effusion. A thorough work-up should include transthoracic and transoesophageal echocardiography, CT and MRI. Diagnosis is confirmed by cytology of the serous fluid from pericardial or pleural effusion or biopsy of the pericardial mass or endomyocardial tissue. Chemotherapy has been used alone or combined with radiotherapy. Similarly, palliative cardiac surgery has been performed, mainly for tumour debulking. A combination of chemotherapy and radiation therapy is considered the treatment of choice. Survival is

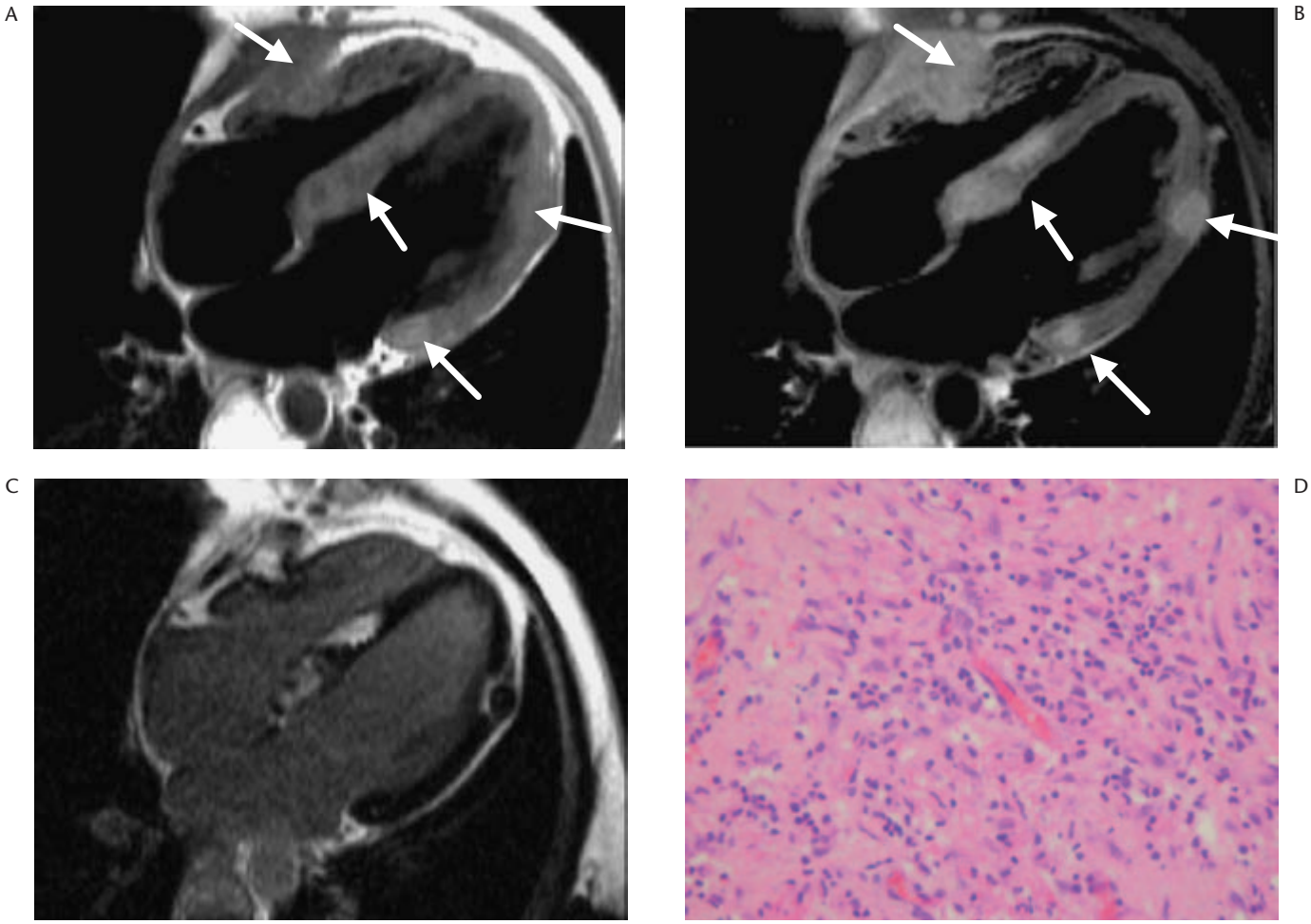

Figure 18.10 Cardiac lymphoma. T1-weighted (A), T2-weighted (B) and gadolinium-enhanced (C) images. Multiple regional myocardial hypertrophy with abnormal signal intensity on T2-weighted and the gadolinium-enhanced image. The hypertrophy is very localized (arrows) around the inferior interventricular groove, involving the right ventricle, septum and inferior wall of the left ventricle. The gadolinium pattern is also abnormal and indicates a myopathic process. Late gadolinium imaging demonstrates hyperenhancement from focal interstitial expansion likely to be fibrosis or oedema. (D) Haematoxylin and eosin stained section showing admixed histiocytes, blood vessels, lymphocytes and plasma cells. This tissue was infiltrating and destroying the myocardium and overlying pericardium. Magnification ×400.

generally less than a month without treatment but has been prolonged up to 5 years with palliative treatment [25].

Surgery in cardiac tumours

The results of surgical treatment of intracardiac benign tumours are good, regardless of their origins and multiplicity, both in the short term and in the long term. The prognosis for patients with primary cardiac sarcoma is poor. Median survival is less than 10 months, especially when complete surgical excision is not feasible. However, excision or resection had a beneficial effect on the haemodynamics in patients with congestive heart failure or cardiogenic shock [26].

Thirty-four patients with primary cardiac tumours were operated on between December 1989 and October 2001. They comprised 16 men and 18 women with a mean age of 40.05 ± 13.06 years (range 7–65 years). Echocardiography was confirmatory in the diagnosis of all the benign tumours, whereas the malignant tumours were incidentally found during surgery. All the patients survived the operation. Complete resection of the tumour was possible only in benign tumours; however, malignant

tumours were partly removed to relieve obstruction. All the excised benign tumours showed no recurrence on a mean follow-up of 54.78 ± 31.30 months (range 3–108 months). Both the patients with malignant tumours developed recurrence postoperatively, and succumbed to extensive distant metastases [27].

Patients with malignant sarcoma of the heart can show prolonged survival after radical resection without evidence of metastases for 29.6 ± 36.8 months. Precise preoperative localization of the tumour by means of imaging techniques is very important. If necessary, the right heart can be resected almost completely, and reconstructed in the form of a Fontan-type circulation. The results of radical resection are promising, but use of chemotherapy is also evolving [28].

In infants and children the most common primary tumours of the heart are the rhabdomyoma and fibroma. Spontaneous regression of these tumours has been well established so that surgical intervention is no longer indicated unless there are clinical indications from the heart [29].

With metastases, intracardiac extension of infradiaphragmatic tumours is uncommon but represents a significant surgical challenge. Renal cell carcinoma is the most common malignant tumour seen (Fig. 18.2), with Wilms' tumour, uterine tumours (both benign and malignant), adrenal tumours, hepatoma, and lymphoma less frequently encountered. Surgical resection requires involvement of a cardiothoracic surgeon, urologist, and/or gynaecologist. Cardiopulmonary bypass and deep hypothermic circulatory arrest provide the safest and most effective techniques for removing these tumours [30].

Transplantation

Removal of all cardiopulmonary structures involved by tumour followed by orthotopic allotransplantation has been proposed to improve long-term survival for malignant tumours. In one study, median survival after transplantation was 31 months (range 5–49 months). All patients had tumour recurrence. Combined heart and lung transplantation is a technically feasible treatment for highly selected patients with localized advanced primary cardiac sarcomas. The high incidence of metastatic disease limits its utility [31]. Generally heart transplantation is not justified because prognosis is not better and donor organs are too rare.

Personal perspective

Primary cardiac tumours are rare and experience with them in any one centre is limited. Presentation may range from cardiac arrhythmias, sudden death and cardiac failure to valve obstruction or embolization. Systemic effects may also predominate as in myxomas, resulting in a delay in diagnosis. Imaging has improved detection with echo being the mainstay of diagnosis. CT provides superior resolution for detecting calcification or fat, while MRI with its direct multiplanar ability more completely characterizes the heart, pericardium, mediastinum and lungs. MRI also helps elucidate the pathophysiological effects of these tumours on cardiac function through gated cine-loop sequences. Beyond tumour characterization, both modalities can help confirm diagnosis through the addition of contrast, which helps distinguish tumour from myocardium, thrombus and blood-flow artefact. Ultimately, MRI best facilitates surgical planning and post-treatment follow-up in large part because of its unparalleled ability to locate and delimit these tumours. Improvements in imaging are matched by histology where morphology combined with immunohistochemistry will result in specific diagnosis in most cases [32].

Most cardiac tumours are benign and, if resectable, the prognosis is excellent. However, even benign tumours such as fibromas can result in death if they are large and unresectable. Lymphomas respond to chemotherapy. Benign tumours are generally curable if surgically excised. The prognosis of malignant tumours is poor. However, aggressive surgery can palliate obstruction and allow time for adjuvant therapy to be carried out. The role of chemotherapy and radiotherapy remains to be established in cardiac sarcomas. Primary cardiac sarcomas have been uniformly associated with poor long-term survival. Individual case reports with extensive surgical excision followed by adjuvant radiation and chemotherapy can improve survival with a good quality of life. This approach of combined surgical, medical and radiation therapy may offer better long-term outcome [33].

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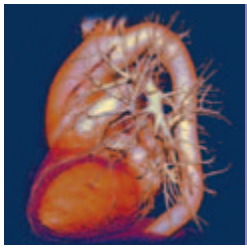

19 Congenital Heart Disease in Children and Adults

John E. Deanfield, Robert Yates and Vibeke E. Hjortdal

Summary

This chapter describes the enormous progress that has been made in the diagnosis, investigation and management of patients with congenital cardiac malformations. Nomenclature, aetiology and incidence are considered as well as common presenting features. Investigative strategies are reviewed as these have evolved rapidly in the last two decades, with a shift from invasive to non-invasive protocols involving echocardiography, magnetic resonance imaging (MRI) and computed tomography (CT). Modern treatment approaches have also developed considerably and now involve both surgery and interventional catheterization, often as part of a 'hybrid' lifetime strategy for management of a congenital malformation.

In the second half of the chapter the most important congenital cardiac malformations are described individually with discussion on morphology, pathophysiology, investigation, natural history and management. The spectrum in both childhood and adulthood is emphasized. Several conditions have been excluded, such as bicuspid aortic valve and mitral valve prolapse, as they are covered in other chapters.

More details on conditions that may complicate congenital cardiac malformations, such as arrhythmia and heart failure, can be found elsewhere in the text.

Introduction

A congenital cardiac malformation complicates 8 per 1000 live births [1]. In the last 60 years, advances in diagnosis as well as in medical and surgical treatment in the neonatal period have transformed the outlook for even the most complex of malformations. As a result, more than 80% of affected children survive to adulthood and there will soon be more adults than children with congenital cardiac malformations [2]. Accurate long-term survival data are still lacking, but in the UK it has been estimated that there is an annual increase of 1600 adults with congenital cardiac malformations and 800 patients annually require specialist follow-up [3]. Adult physicians are thus increasingly likely to encounter patients with a range of these complex conditions who will need ongoing surveillance and often further medical or surgical intervention. With improving outcome prospects, the goals of treatment have shifted from merely improving survival during childhood to 'lifetime management' aimed at optimizing life expectancy and quality of life.

There have been a number of important trends in the management of congenital cardiac malformations. Invasive diagnostic techniques, based on cardiac catheterization, have been replaced by the rapidly improving non-invasive modalities. In the 1980s, cross-sectional echocardiography revolutionized investigation, with enormous outcome benefits. Further evolution is continuing in the current era, with cross-sectional imaging by MRI and CT with three-dimensional reconstruction providing accurate definition of both anatomy and physiology. In parallel with a shift away from cardiac catheterization for diagnosis, there has been a spectacular increase in the range and number of therapeutic catheterization procedures. Paediatric cardiology has led the way in this area and progress shows no signs of

slowing. For example, the recent successful implantation of stent-mounted tissue valves in the pulmonary position should lead to new opportunities for treatment of other cardiac valves in children and adults with both congenital and acquired pathology [4]. Often a treatment plan that integrates surgery and interventional catheterization is required and this 'hybrid' approach can be tailored towards lifetime management. Reduced morbidity and mortality has also been achieved with treatment directed towards primary neonatal repair whenever possible, rather than the performance of staged repair with initial palliative procedures. This has occurred due to improvements in neonatal management as well as in cardiopulmonary bypass, together with increasing confidence instilled by the successful introduction of new corrective operations, such as the arterial switch operation for transposition of the great arteries (see below).

This chapter aims to cover the field of congenital cardiac malformations by describing the aetiology, presentation, principles of investigation and modern treatment approaches, as well as providing more detailed accounts of common individual malformations. We have excluded conditions such as bicuspid aortic valve and mitral valve prolapse, which are covered in other chapters. Furthermore, more information on conditions that may complicate congenital cardiac malformation, such as heart failure and arrhythmia, can be found in Chapters 23 and 24.

Nomenclature

The almost infinite number of complex cardiac congenital malformations requires the development of a consistent, easily comprehensible approach to nomenclature that is based on observation rather than assumptions about development. This has largely been achieved with the sequential segmental approach. Initially proposed by van Praagh and co-workers [5] in the 1960s and subsequently revised by Anderson and colleagues [1], this approach analyses malformed hearts on the basis of their atrial, ventricular and great arterial components as well as the connections between these segments and the abnormalities associated with them. It avoids the use of embryological terms such as 'endocardial cushion defect' to describe congenital cardiac malformations. The very rapid progress of molecular genetics and its application to cardiac development has dispelled many previously accepted embryological assumptions, often rendering such descriptive terms both incorrect and confusing.

The starting point for this system of nomenclature is the identification of atrial arrangement or situs. This is most accurately determined by examination of the atrial appendages as these are the most distinct morphological features of the atrium. Since all hearts have two atrial appendages, there are four possible combinations: usual (situs solitus), mirror image (situs inversus) and isomerism of the right or left appendages. Anatomical inspection of the appendages is rarely possible and therefore inference about atrial arrangement is usually based on echocardiographic findings. The most important of these is examination of the great vessels at the level of the diaphragm in the abdomen (Fig. 19.1).

The atria connect to the ventricles via the atrioventricular valves. The 'type' of connection describes what flows into what, being either concordant (right atrium to right ventricle and left atrium to left ventricle), discordant (right atrium to left ventricle and left atrium to right ventricle) or ambiguous when the atrial appendages are isomeric. The 'mode' of atrioventricular connection addresses the structural make-up of the connecting segments and includes a description about the nature of the valve or valves. Valves may be perforate, imperforate or absent. However, the atrioventricular junction could be guarded by a single atrioventricular valve as in absent right or left connection; equally, there may be two separate valves, or a common atrioventricular valve as in double-inlet left ventricle. It is the ventricles about which there is generally least consensus. There remains debate about the precise anatomical definition of a ventricle, but there is almost universal agreement that ventricles can be recognized as being either morphologically right or left on the basis of their individual characteristics. As there is no potential for ventricular isomerism, there are only two patterns of ventricular arrangement that can exist. The normal arrangement, with the right ventricle on the right and the left ventricle on the left, is described as 'right hand' topology and the inverse arrangement as 'left hand' topology. The 'type' of ventriculo-arterial connection can be concordant (right ventricle to pulmonary artery and left ventricle to aorta), discordant (right ventricle to aorta and left ventricle to pulmonary artery), double outlet (where usually right, but very occasionally left, ventricle gives rise to both great arteries) or solitary outlet from the heart, such as occurs in common arterial trunk or in many cases of tetralogy of Fallot with pulmonary atresia. Finally, it remains to catalogue precisely any additional malformations both within the heart itself as well as within the great vessels. Description of any isolated malformation is incomplete without first undertaking sequential segmental analysis of the heart in which it is contained [6].

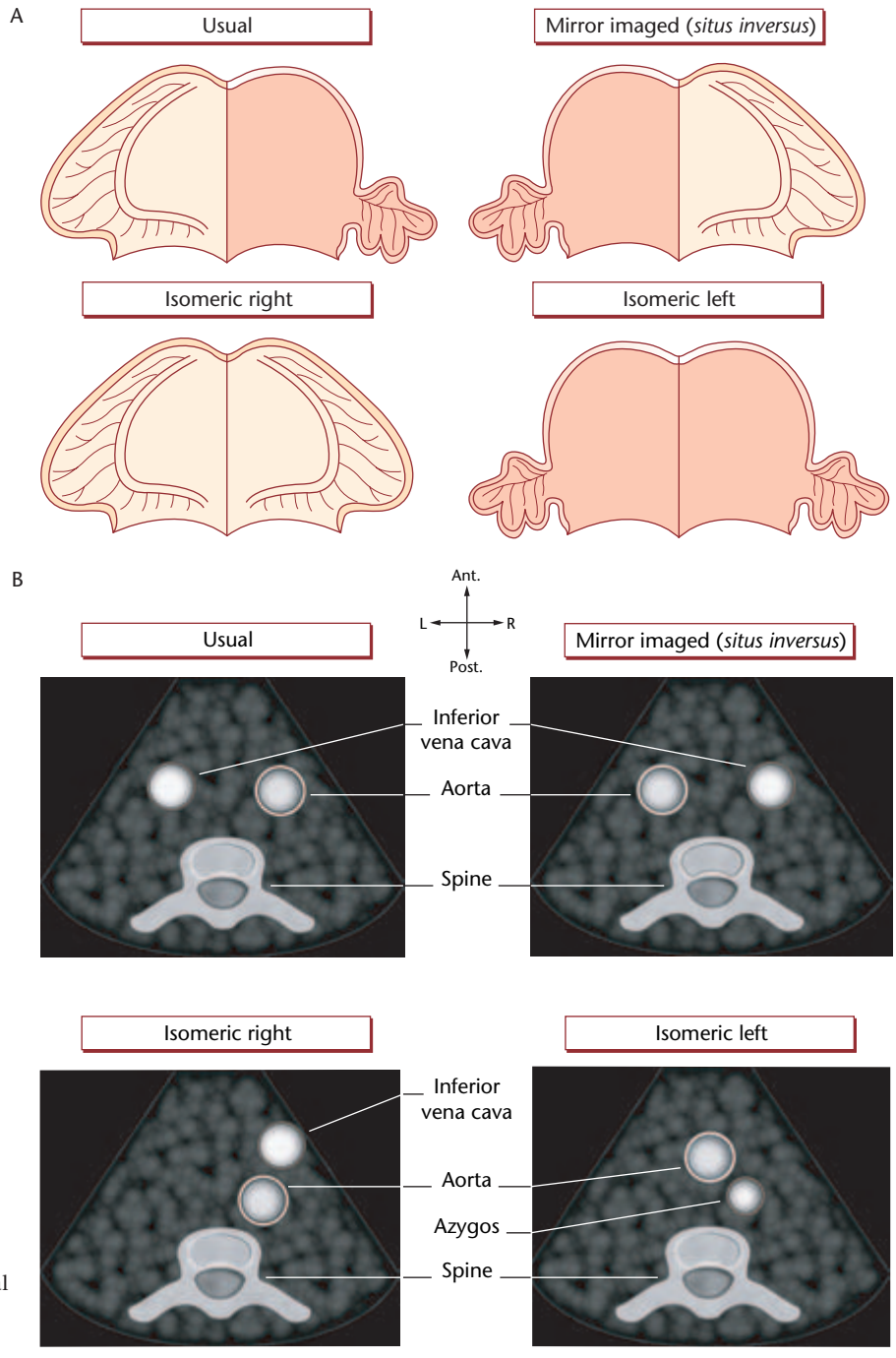

Figure 19.1 (A) Possible atrial arrangements. (B) Schematic representation of echocardiographic images of the great vessels at the level of the diaphragm associated with usual atrial arrangement, mirror-image arrangement as well as right and left atrial isomerism.

Epidemiology and incidence

A congenital cardiac malformation is usually described as 'the presence of a gross structural abnormality of the heart or great vessels which is of actual or potential functional significance' [7]. According to this definition, about 0.8% of live births are complicated by a cardiovascular malformation, but this fails to include a number of common abnormalities such as bicuspid non-stenotic aortic valve or mitral valve prolapse, which may significantly influence the true incidence. Furthermore, some less common abnormalities may remain undetected

	Median	25th–75th
Ventricular septal defect	32.0	27.1–42.3
Patent arterial duct	6.8	5.2–11.0
Atrial septal defect	7.5	6.2–10.8
Atrioventricular septal defect	3.8	2.8–5.2
Pulmonary stenosis	7.0	5.2–8.8
Aortic stenosis	3.9	2.7–5.8
Coarctation of the aorta	4.8	3.6–5.7
Transposition of the great arteries	4.4	3.5–5.4
Tetralogy of Fallot	5.2	3.8–7.6
Common arterial trunk	1.4	0.6–1.7
Hypoplastic left heart syndrome	2.8	1.6–3.4
Hypoplastic right heart syndrome	2.2	1.5–3.2
Double-inlet ventricle	1.5	0.8–1.9
Double-outlet right ventricle	1.8	1.0–3.0
Total anomalous pulmonary venous connection	1.0	0.6–1.9
Others	10.0	7.6–14.6

Adapted with permission from Hoffman J. Incidence, mortality and natural history. In: Anderson RH, Baker EJ, Macartney F, Rigby M, Shinebourne EA, Tynan M (eds). *Paediatric Cardiology*, 2002. London: Churchill Livingstone, pp. 111–139.

Table 19.1 Median and interquartile range (%) of congenital cardiac lesions in newborn infants obtained from 34 studies involving 26 904 patients

throughout life, such as a persistent left-sided superior caval vein draining to the coronary sinus. Ascertainment of the incidence of congenital heart disease may provide vital information on the aetiology of congenital cardiac malformations and can also be used in the planning of appropriate health-care resources (Table 19.1).

The incidence of congenital cardiac malformations is the number of children born with congenital cardiac malformations relative to the total number of births over a given period, usually a calendar year. Defining the denominator in such a rate has a significant influence as there are major differences between rates based on live births compared with those based on conception. For a measure of the true incidence of congenital cardiac malformations, it would be necessary to have accurate information about all children with congenital cardiac malformations, which is currently underestimated. In addition, calculations would need to include congenital cardiac malformations detected in stillbirths and aborted fetuses, in which cardiac abnormalities occur up to 10 times more frequently than in live-born babies. Accurate data on the incidence of individual congenital cardiac malformations are lacking. In many series, small ventricular septal defects (VSDs) were either not detected or were actively excluded and few studies include patent arterial ducts in preterm infants. Furthermore, selection of both the study population and the source of data will affect reported incidence. Table 19.1 is a compilation of a large number of series over many years and approximates the best estimate of the true incidence of specific congenital cardiovascular malformations. Congenital cardiac malformations often occur in association with extracardiac abnormalities, which may be multiple. The additional burden of such abnormalities may have an unexpectedly high adverse effect on mortality compared with that of the individual abnormalities in isolation. About 30% of children with both cardiac and extracardiac malformations have an identifiable syndrome. Further details of such syndromes can be obtained from a genetic database, such as the Oxford Medical Database for Dysmorphology.

Aetiology and prevention

The rapid progress of cytogenetics offers the prospect of improved understanding of the role of inherited and environmental factors and their interaction on the development of congenital cardiac malformations [8,9]. Environmental factors are rare, but important and potentially preventable. Congenital rubella is now less common in European populations and maternal diabetes, alcohol ingestion and possibly drugs are the most important external adverse influences on cardiac development [10,11]. Major chromosomal abnormalities can cause

syndromes, of which congenital cardiac malformations play an important part. Trisomy 21 (Down's syndrome) and Turner's syndrome (XO) are classic examples. Other important syndromes include Edwards' syndrome (trisomy 18) and Patau's syndrome (trisomy 13).

In several other syndromes associated with congenital cardiac malformations, such as Williams' syndrome, a specific microdeletion has been established, blurring the distinction with major chromosomal abnormalities. The most important example is the 22q11 deletion, which emerged as the basis of DiGeorge's syndrome in the late 1980s. A European study of almost 600 patients with 22q11 deletion showed that 75% had a ventricular outflow abnormality, emphasizing the importance for understanding of cardiac development as well as patient management. Alagille's syndrome is another example where a causative gene defect, loss of *jagged-1* on chromosome 20p12, is associated with peripheral pulmonary stenosis [12].

The traditional view that the majority of congenital cardiac malformations are not genetic but multifactorial is probably incorrect, and it appears likely that an increasing number of specific point mutations associated with cardiac malformations will be described (such as those already identified for Noonan's syndrome, Marfan's syndrome, Ellis–van Creveld syndrome and Holt–Oram syndrome and abnormalities of laterality). This will also lead to an improved understanding of the genetic regulation of cardiac development.

Understanding the aetiology and genetic basis for congenital cardiac malformations has practical implications for counselling. Risks of sibling recurrence have been difficult to define, often due to selection bias and limited phenotyping and only recently has the opportunity arisen to assess recurrence risk in offspring of mothers and fathers who themselves have congenital cardiac malformations. In a large UK multicentre study, the overall recurrence risk was 4.5%, which is significantly higher than the risk for siblings. Interestingly, the rate was higher in the offspring of affected females [13]. Preventative strategies for congenital cardiac malformations are still in their infancy. Physicians should always emphasize the importance of avoiding alcohol and drugs from the time pregnancy is planned. The increased availability of screening for major chromosomal abnormalities, which has become faster and more accurate, should permit the identification of affected fetuses at risk of congenital cardiac malformations. Fetal echocardiography, which can now reliably identify major malformations from as early as 14 weeks' gestation, does not provide true 'prevention opportunities' but does enable informed decisions to be made regarding continuation of pregnancy in the presence of cardiac malformations [14].

Fetal circulation

Much of the information about the fetal circulation has been derived from animal studies. Increasingly sophisticated, non-invasive, ultrasound assessment of the human fetal circulation has both confirmed these early data from animal studies and demonstrated important differences in the human fetus [15].

Fetal circulatory pathways

In contrast to the normal postnatal circulation, in the fetus the systemic and pulmonary circulations exist in parallel (Fig. 19.2). Prenatal survival is possible with even major structural cardiovascular malformations, provided that either the right or left ventricle is able to pump blood derived from the great veins into the fetal aorta. In the fetus, oxygenated blood returns from the placenta via the umbilical vein to the inferior caval vein, either through the portal system or through the venous duct. A proportion of inferior caval vein blood entering the right atrium is directed across the oral foramen to the left atrium. Superior caval vein blood enters the right atrium and the majority will enter the right ventricle via the tricuspid valve. Almost all of the right ventricular output will be directed through the arterial duct into the systemic circulation, bypassing the high resistance pulmonary circulation. The proportion of pulmonary blood flow changes with gestation, with an increase during the third trimester. Just as in postnatal hearts, the fetal pulmonary vascular bed is reactive. Fetal pulmonary blood flow can be increased by pulmonary vasodilator agents (such as oxygen) administered to the mother [16]. As pregnancy progresses, the effective cardiac output increases to a maximum of approximately 250 ml/kg/min by term, with the right ventricle contributing 55% and the left ventricle 45% of the fetal cardiac output. Of the combined output, 65% returns to the placenta and 35% to the fetal organs and tissues [17].

Function of the fetal heart

Compared with the adult heart, there are differences both within the fetal heart itself and between the physiological environment during fetal and postnatal life, which explain many of the observations of fetal cardiac function. The expression of contractile proteins in the fetus is different from the postnatal pattern [18]. In addition, the expression of different types of collagen within fetal heart muscle results in reduced compliance compared with the postnatal heart [19]. Therefore, the

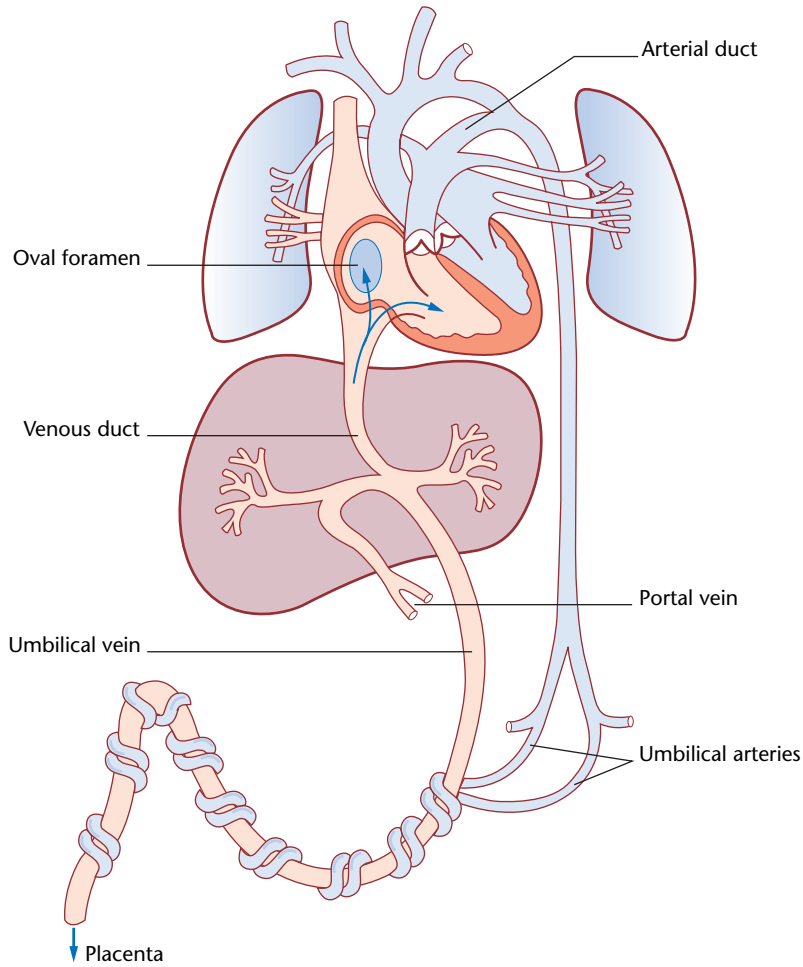

Figure 19.2 Schematic representation of the fetal circulation demonstrating sites of shunting, including venous duct, patent oval foramen and patent arterial duct. The venous duct acts as a regulator allowing variable amounts of blood to bypass the hepatic circulation according to the metabolic demands of the fetus.

immature fetal heart is both less compliant and less able to generate contractile force for the same degree of stretch [20]. Advancing gestation allows maturation of excitation–contraction coupling as well as increasing autonomic innervation [21]. Such findings have been used to account for a blunted Starling curve in the fetus. However, it has been shown that external constraints existing around the heart in the fetus, including the fluid-filled lungs and rigid chest wall, are equally important [22].

Circulation and changes at birth

With birth there is a shift from a circulation 'in parallel' to one 'in series', as well as a marked increase in cardiac output from both ventricles. At term, the cardiac output from each ventricle approximately equals the combined cardiac output from both ventricles in the immediately preterm fetus. With inspiration, there is a rapid fall in pulmonary vascular resistance, as lung expansion allows new vessels to open and existing vessels to enlarge. Reduced resistance and decreased pulmonary artery pressures increase pulmonary blood flow. Simultaneously, the lower-resistance placental circulation is removed from the systemic circulation as the cord is cut. The sudden increase in oxygen tension produced by breathing alters local prostaglandin synthesis, resulting in a constriction of both the arterial and venous ducts. For most neonates, functional closure of the arterial duct occurs within 24–72 h and anatomical closure is complete by 1–2 weeks [23]. The oval foramen and venous duct may remain patent for some time after birth, with the potential to allow shunting after birth. This can mask the signs of underlying structural congenital cardiovascular malformations, such as infracardiac total anomalous pulmonary venous drainage or, occasionally, transposition of the great arteries. The oval foramen is functionally closed in the majority of cases by the third month of life.

Table 19.2 Causes of common presenting manifestations of cardiac disease in early infancy

Heart failure
Hypoplastic left heart syndrome
Coarctation of the aorta
Critical aortic stenosis
Arteriovenous fistula
Patent arterial duct
Atrioventricular septal defect
Large ventricular septal defect
Unobstructed total anomalous pulmonary venous connection
Anomalous origin of left coronary artery from pulmonary artery
Cyanosis
Transposition of the great arteries with or without ventricular septal defect
Severe tetralogy of Fallot or pulmonary atresia with ventricular septal defect (pulmonary atresia with intact ventricular septum)
Critical pulmonary stenosis
Common arterial trunk
Functionally univentricular heart
Ebstein's anomaly
Total anomalous pulmonary venous connection
Abnormal heart rate
Supraventricular tachycardia
Complete heart block
Atrial or ventricular extrasystoles
Murmurs
Innocent, functional
Patent arterial duct
Pulmonary stenosis
Atrial septal defect
Ventricular septal defect
Atrioventricular septal defect
Atrioventricular valve regurgitation
Arteriovenous fistula

Pathophysiology

Without prompt recognition, accurate diagnosis and appropriate treatment, about one-third of all babies with congenital cardiac malformations will die within the first 2 months of life. Cardiac failure and cyanosis are the principal signs in infants (Table 19.2). There is a temporal progression in the presentation of congenital cardiac malformations. Whilst the majority of patients present in infancy, some will present in childhood or even in adolescence with a heart murmur, abnormal heart rate, absent pulses or hypertension, fits, faints and funny turns, chest pain, airway obstruction or abnormal chest radiograph.

Cardiac failure

While many of the mechanisms of cardiac failure are common to all ages (discussed in Chapter 23), the pathophysiology in children may be different and may vary with age. Fetal echocardiography has demonstrated prenatal cardiac failure due to structural abnormalities, myocardial dysfunction and arrhythmia [24]. In newborns, early heart failure usually results from left heart obstructive lesions, sustained tachyarrhythmias, primary myocardial dysfunction or large arteriovenous malformations. The major clinical manifestations are tachycardia, tachypnoea with recession, liver enlargement and cardiomegaly. These presentations should be considered medical emergencies. Beyond the newborn period, lesions causing a large left-to-right shunt are the most common cause of heart failure. They manifest when the pulmonary vascular resistance falls during the first few weeks of life. Combinations of lesions may hasten the presentation as well as increase the severity of clinical manifestations. The features are often subtly different from those in the newborn period, with poor feeding and failure to thrive in association with respiratory distress being most frequent. Additional findings include tachycardia with a gallop rhythm, cardiac murmurs, hepatomegaly, poor colour and excessive perspiration. As heart failure is most frequently caused by either unobstructed communication between the right and left sides of the heart or myocardial dysfunction involving both ventricles, a distinction between right and left heart failure is less meaningful than in adults. Cardiac failure rarely presents for the first time beyond infancy, except in association with primary myocardial dysfunction (see Common congenital cardiac malformations, below).

Cyanosis

Cyanosis is caused by the presence of reduced haemoglobin (> 5 g/dl) in the peripheral vasculature. Consequently, its detection depends not only on arterial oxygen saturation but also on haemoglobin concentration. For example, cyanosis may not be detectable despite significant desaturation in a child with moderate anaemia. Cyanosis in the presence of congenital cardiovascular malformations is produced by three principal mechanisms, which may coexist. The commonest is obstruction to pulmonary blood flow, with a right-to-left shunt. Cyanosis is also evident when there are discordant

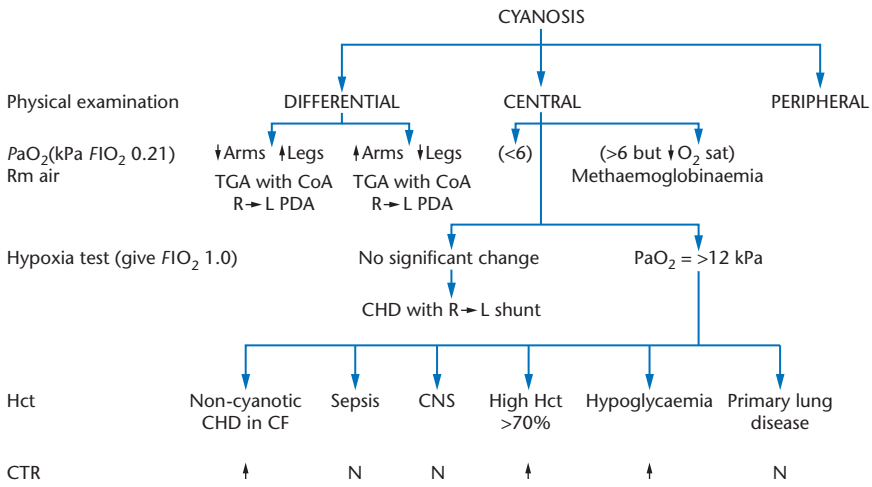

Figure 19.3 Algorithm for the evaluation of cyanotic infants.

ventriculo-arterial connections (as in complete transposition) with adverse streaming of blood through the heart. The third haemodynamic basis for cyanosis is common mixing of blood, which may occur at atrial, ventricular or great artery level. The mixed systemic and pulmonary venous returns are distributed to both pulmonary arteries and aorta. It should also be remembered that cyanosis presenting in the newborn period or in early infancy may have a primary respiratory cause. The algorithm in Fig. 19.3 provides assistance in decision-making. In patients with congenital cardiovascular malformations, a distinction should be made between those with cyanosis associated with reduced pulmonary blood flow and those with cyanosis associated with increased pulmonary blood flow. Reduced pulmonary blood flow may result from obstruction at tricuspid valve, right ventricular, pulmonary valve or pulmonary artery level. Associated with this is a communication within the heart that permits a right-to-left shunt. Examples include tetralogy of Fallot, pulmonary atresia (with or without VSD) and tricuspid atresia. Patients with cyanosis and normal or increased pulmonary blood flow most frequently have complete transposition or, less commonly, a complete mixing situation. Mixing at atrial level occurs in total anomalous pulmonary venous connection and at ventricular level in hearts with a functionally single ventricle. A common arterial trunk results in mixing at the level of the great arteries. Common mixing may occur with decreased or increased pulmonary blood flow, depending on the degree of pulmonary outflow obstruction. Cyanosis and cardiac failure may coexist where there is common mixing and unobstructed pulmonary blood flow. Long-term cyanosis is associated with a number of well-recognized sequelae, including impaired growth and delayed physical development, although mental development is rarely affected. Finger clubbing and polycythaemia are responses to chronic hypoxaemia and hypoxic spells may develop due to sudden reduction in pulmonary blood flow, as in tetralogy of Fallot. Such spells are potentially fatal. The incidence of cerebral abscess appears to be related to arterial saturation and occurs in older children. This should be considered in any patient with a cyanotic congenital cardiovascular malformation presenting with fever and neurological signs. Haemoptysis results from the enlargement of the bronchial collateral circulation in association with pulmonary vascular obstructive disease. A list of the complications of chronic cyanosis is given in Table 19.3.

Other presentations

Heart murmur

In later infancy and in older children, heart murmurs are the most common presenting manifestation of congenital cardiac malformations. Up to 0.6% of newborns will have a cardiac murmur in the first few days of life, but most innocent murmurs will have disappeared by the end of the first year of life [25]. Beyond infancy, a detectable murmur in a child warrants referral for specialist cardiac assessment. Persisting innocent murmurs are almost always systolic, very localized and occur in children who are otherwise well from a cardiovascular point of view.

Abnormal heart rate

Specific rhythm disturbances are detailed in Chapter 22 but, in brief, older children may present with paroxysmal tachycardia (as palpitations), most commonly due to supraventricular tachycardia or much less commonly ventricular tachycardia, or with persistent tachycardia.

Table 19.3 Medical complications of chronic cyanosis

Haematological
↑ Red cell mass
↑ Red cell turnover
↑ Viscosity

Haemostasis
↓ Platelet count
↓ Platelet function
Clotting factor deficiency

Metabolic
↑ Urate production
Calcium bilirubinate gallstones

Renal
↓ Glomerular filtration rate
↓ Creatinine
Proteinuria
↓ Urate clearance

Orthopaedic
Hypertrophic osteoarthropathy
Scoliosis

Skin
Clubbing
Acne

Infection
Cerebral abscess

Infrequently, children will present with sustained bradycardia secondary to congenital heart block. In both bradyarrhythmias and tachyarrhythmias, the rhythm disturbance may or may not be associated with an underlying structural cardiovascular malformation.

Absent pulses/hypertension

The identification of hypertension at routine examination should prompt a search for femoral pulses in all paediatric and young adult patients. Mild to moderate coarctation may not cause symptoms in infancy and symptoms may become evident only when the pace of somatic growth exceeds the growth of the narrowed segment.

Fits, faints and funny turns

Transient loss of consciousness may be associated with supraventricular tachycardias, atrial fibrillation or ventricular tachycardia, and are the most common presentation of the long QT syndrome. Loss of consciousness may occur in hypercyanotic spells, but also occurs during exercise when there is severe left heart obstruction at any level (e.g. in hypertrophic cardiomyopathy or severe aortic stenosis). Loss of consciousness may also occur as a primary cerebral event that results in transient asystole with a normal cardiac conduction system, as in 'anoxic seizures'.

Chest pain

This frequently encountered complaint is very rarely associated with an underlying structural cardiovascular malformation in childhood. Angina pectoris causing chest pain may occur in association with a coronary artery abnormality, including anomalous left coronary artery from the pulmonary artery, as well as in hypertrophic cardiomyopathy and other cases of severe outflow obstruction. Almost always there are baseline abnormalities of the ECG to suggest underlying disease.

Airway obstruction

This uncommon mode of presentation in infancy is usually associated with inspiratory stridor or difficulty in swallowing. When associated with a structural cardiac malformation, the manifestations are most frequently caused by a vascular ring, such as a double aortic arch or a pulmonary artery sling. In the newborn period, major airway obstruction can be an important manifestation of the absent pulmonary valve syndrome.

Abnormal chest radiograph

An abnormal cardiac contour is an unusual presentation for a haemodynamically significant congenital cardiac malformation, except when there is isolated cardiomegaly. Occasionally, a routine chest radiograph may reveal previously undetected abnormalities of cardiac position, which in turn may be associated with structural cardiac malformations.

Investigation

Strategies for investigation of anatomy and physiology in patients with congenital cardiac malformations are changing rapidly, with a shift away from invasive to non-invasive modalities. This is particularly true in neonates and small infants, where cross-sectional echocardiography has almost eliminated the need for diagnostic

cardiac catheterization. Newer imaging modalities such as MRI and CT are able to provide additional information, especially in the older patient.

Chest radiography

Chest radiography provides valuable information about the physiological consequences of congenital cardiac malformations. This includes pulmonary plethora associated with a large VSD or oligaemia associated with severe tetralogy of Fallot. Cardiac position and size, side of the aortic arch, associated bony abnormalities and visceral situs can also be assessed. Chest radiography is less valuable in newborns or during early infancy, as a normal appearance can still be associated with a severe congenital cardiac malformation. The chest radiograph is readily available and cheap, but its diagnostic role has diminished since cross-sectional echocardiography has become available.

Electrocardiography

The ECG is one of the earliest tests applied to the investigation of patients with suspected congenital cardiac malformations. Abnormal electrocardiographic findings are common, but are very rarely specific enough to provide a precise diagnosis. Exceptions in the newborn include the dominance of left ventricular forces seen in tricuspid atresia, the abnormally large P wave with prolonged PR interval and bundle branch block pattern associated with Ebstein's malformation, and the left-axis deviation with reversed septal depolarization characteristic of congenitally corrected transposition. However, the ECG remains a vital diagnostic tool in the evaluation of all paediatric arrhythmias and, like the chest radiograph, is readily available and inexpensive.

Blood gas analysis

In combination with other investigations, assessment of blood gases in the newborn and in infancy is one of the most commonly used means of distinguishing cardiac from non-cardiac causes of cyanosis. A hyperoxia test in the newborn assists in identifying patients who have a duct-dependent cardiovascular malformation and may be helpful when there is no immediate access to cross-sectional echocardiography.

Cross-sectional echocardiography

Cross-sectional echocardiography, together with Doppler studies, has revolutionized the practice of paediatric cardiology over the last two decades. Its non-invasive, immediate and portable nature make it ideally suited to the investigation of even the smallest children. It can define structure and function, which can also be quantified. Increasingly, echocardiography is also playing a role during cardiac catheterization and surgery. There are however some limitations. Whilst imaging windows are almost universally excellent in infants and small children, with growth and after multiple operations, transthoracic windows deteriorate significantly in older patients. A transoesophageal approach may therefore be required. Imaging of the intracardiac structures is usually excellent, but extracardiac structures such as the great vessels and abnormalities around the heart may be difficult to see. At present, most information is obtained in a two-dimensional format, and three-dimensional echocardiography has had a limited clinical role. There is continuing progress in this area, which will impact on the investigation of patients with congenital cardiac malformations. Additional functional information can now be obtained using techniques such as Doppler tissue imaging and its derivatives as well as colour kinesis [26]. The former may assist assessment of ventricular diastolic performance, which has been notoriously difficult to study. The use of contrast echocardiography and perfusion imaging may provide further functional information [27]. Stress echocardiography has had a limited role in the paediatric age group, but may be useful for assessment of myocardial perfusion in patients after operations such as the arterial switch [28]. Cross-sectional echocardiography is increasingly being complemented by additional imaging modalities, such as MRI and CT.

Cardiac catheterization and angiography

Diagnostic cardiac catheterization and angiography were for many years the principal means of evaluation of patients with congenital cardiovascular malformations. Measurement of oxygen saturation and pressures enables calculation of intracardiac shunts, gradients, flows and resistances. Anatomy and function with high resolution, particularly excellent edge detection, is obtained by angiography. Much of this diagnostic information can now be obtained less invasively. Cardiac catheterization in small children carries a small but definite risk, particularly when they are unwell, and almost inevitably requires general anaesthesia. This will influence cardiac physiology and the relevance of measurements obtained. Current diagnostic indications for catheterization and angiography include assessment of pulmonary vascular resistance in patients with suspected or established pulmonary vascular obstructive disease, imaging of the coronary arteries (although undertaken relatively infrequently in the paediatric age range), and evaluation of

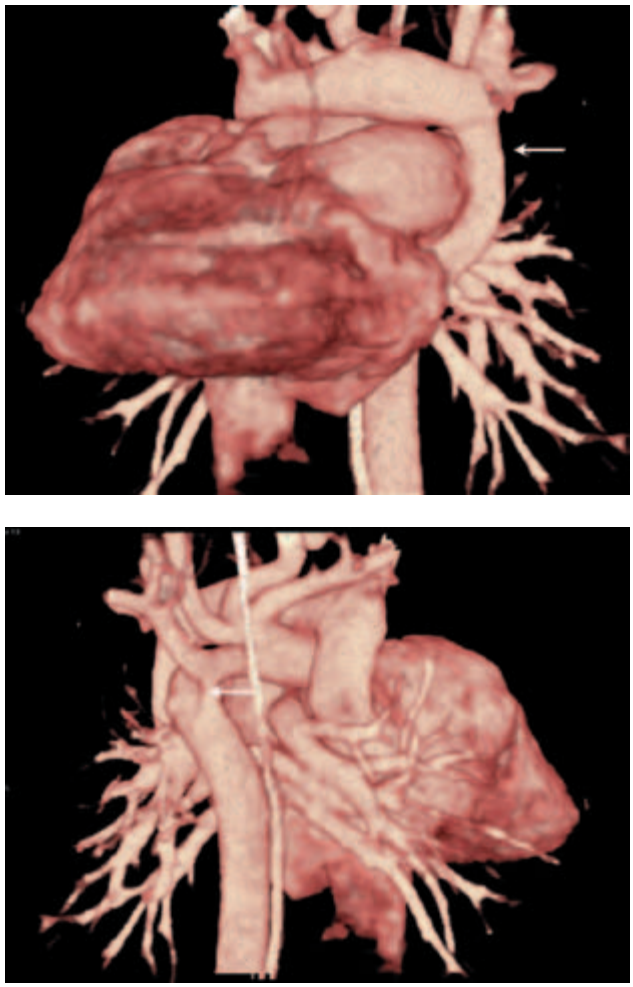

Figure 19.4 Multislice three-dimensional reconstruction of complex cardiac lesion with dextrocardia, functional univentricular heart, supracardiac total anomalous pulmonary venous drainage and anterior aorta with coarctation. (A) Arrow shows ascending vertical vein on the left side entering into dilated innominate vein. (B) From posterior aspect, arrow shows aortic coarctation just distal to the left subclavian artery. Entering into the superior aspect of the right atrium is a dilated superior caval vein.

extracardiac vessels such as aorto-pulmonary collateral arteries. Increasingly, invasive procedures are being performed for interventional purposes, with classical diagnostic information obtained during these procedures used to evaluate the success of treatment (see below).

MRI and CT (Figs 19.4 and 19.5)

MRI of the heart and great vessels is becoming commonplace in the assessment of adults with congenital cardiac malformations and is playing an increasing role in the evaluation of neonates, infants and younger children [29]. Multislice CT is also able to provide cross-sectional imaging. The indications for cardiovascular MRI include evaluation of right ventricular to pulmonary artery conduits, aortic pathology, anomalous coronary arteries and complex congenital cardiac malformations, where understanding of three-dimensional information is essential. MRI cannot measure pulmonary artery pressure or resistance, but measurement of central venous pressure at the time of MRI in patients with a bidirectional Glenn or Fontan circulation gives anatomical detail and sufficient assessment of pulmonary haemodynamics for clinical decision-making. Cardiovascular MRI in children less than 8 years of age is usually performed under general anaesthesia, but with the development of faster sequences, breath-holding may become less of a necessity and MRI data may be acquired more easily during sedation. Imaging sequences can be broadly divided into:

- 'black-blood' spin-echo images, where signal from blood is nulled and thus not seen (accurate anatomical imaging);
- 'white-blood' gradient echo or steady-state free precession (SSFP) images, where signal from blood is returned for anatomical and cine imaging;
- phase contrast imaging, where velocity information is encoded for quantification of vascular flow, and contrast-enhanced MR angiography, where non-ECG-gated three-dimensional data are acquired after gadolinium contrast has been administered for thoracic vascular imaging.

Multidetector CT enables acquisition of volumes of CT data that can be reformatted in any imaging plane. Multidetector CT images of the entire thorax can be acquired in 3–10 s depending on the size of the subject. Using iodinated contrast agents, CT angiography can now be rapidly performed and three-dimensional reconstruction aids considerably in the appreciation of complex cardiovascular anatomy. At present, ECG gating for cardiac CT is limited to subjects with slow heart rates (< 60 b.p.m.), excluding many patients with congenital cardiac malformations. Cardiac CT images of the intracardiac anatomy are often blurred and of limited value. The speed at which CT images can be acquired means that imaging in young children can be performed unsedated with 'feed and wrap', or with sedation, and general anaesthesia rarely required.

MRI is currently superior for acquisition of information on intracardiac anatomy, ventricular function and vascular flow quantification, whereas CT may be performed without general anaesthesia and may provide information on airways and lung parenchyma that is not obtained by MRI. CT may also be used to image subjects with permanent pacemakers, a contraindication to MRI. CT is currently used for evaluation of aortic pathology

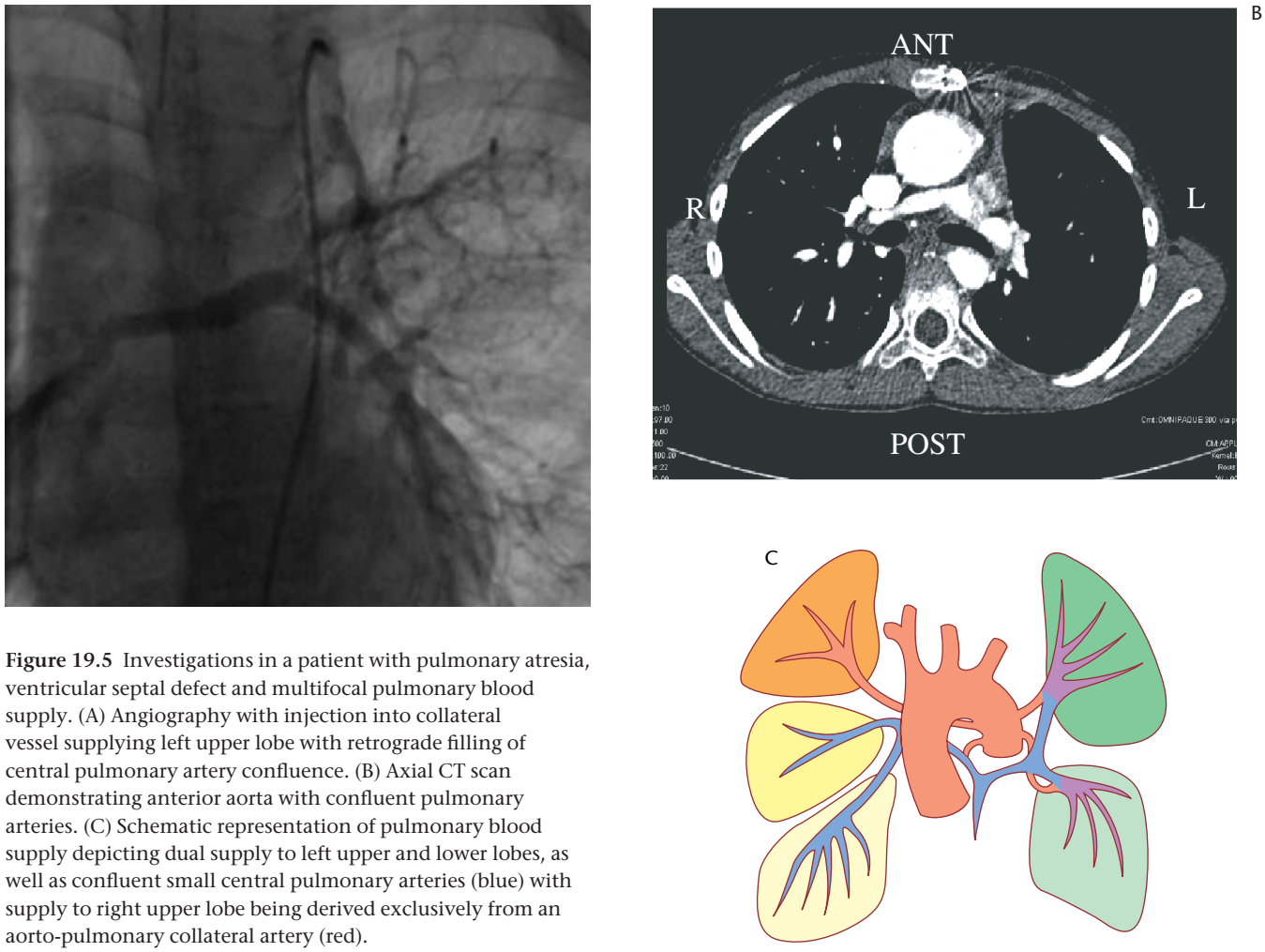

Figure 19.5 Investigations in a patient with pulmonary atresia, ventricular septal defect and multifocal pulmonary blood supply. (A) Angiography with injection into collateral vessel supplying left upper lobe with retrograde filling of central pulmonary artery confluence. (B) Axial CT scan demonstrating anterior aorta with confluent pulmonary arteries. (C) Schematic representation of pulmonary blood supply depicting dual supply to left upper and lower lobes, as well as confluent small central pulmonary arteries (blue) with supply to right upper lobe being derived exclusively from an aorto-pulmonary collateral artery (red).

(in particular the aortic arch and vascular rings, pulmonary artery and pulmonary venous anatomy), but this is a rapidly changing area and the indications are likely to increase considerably.

Management

Medical

With exceptions, medical management for congenital cardiac malformations is largely supportive (e.g. heart failure) and significant structural abnormalities usually require interventional treatment. The pathophysiology of cardiac and respiratory dysfunction is different from that of the failing adult circulation, so that extrapolation from the results of adult cardiac studies is not always easy, for example the use of angiotensin-converting enzyme (ACE) inhibitors in Fontan or Mustard/Senning circulations [30,31]. A few specific medical treatments do target the disease and its consequences more directly. For example, maintenance of ductal patency with prostaglandin infusion and use of nitric oxide and other experimental drugs for pulmonary hypertension have been important advances [32].

The electrophysiological consequences of congenital cardiac malformations are key issues for treatment, especially during long-term follow-up. The principles of arrhythmia diagnosis and management are the same as in normally formed hearts, but risk stratification, investigation and choice of treatment is often very different. The onset of arrhythmia may be the first sign of haemodynamic decompensation. Furthermore, the risk of arrhythmia may be much greater in the presence of the abnormal underlying circulation (e.g. atrial flutter

in a Mustard/Senning patient with right ventricular dysfunction and venous pathway narrowing) [33]. The complex anatomy and basis for arrhythmia makes interventional electrophysiology more challenging and the results are generally worse [34]. However, improved mapping and catheter design should make a difference in the next few years. Similarly, pacing is more demanding in patients with congenital cardiac malformations, due to the size and anatomy of the heart.

Surgical

Continuing improvement in surgical results for congenital cardiac malformations has been one of the triumphs of modern cardiology. Conditions which even 20 years ago were considered virtually untreatable, for example hypoplastic left heart syndrome (HLHS), now have very acceptable childhood mortality. This has been achieved through accurate diagnosis, better preoperative and postoperative management, improvements in anaesthesia and cardiopulmonary bypass, together with increasing surgical skill and confidence. Intraoperative transoesophageal echocardiography has also played a role in ensuring adequate repair. There has been a major shift from the early approach of palliation with later repair towards primary repair from the time of diagnosis. This has reduced anatomical distortion from palliative surgery (e.g. systemic to pulmonary artery shunt, pulmonary artery band), the decline in cardiac function before repair and the overall risk of treatment by a single intervention.

Improved surgical results even for patients with the most complex malformations have created a new population of adolescents and adults [35] (Tables 19.4 and 19.5). Evaluation of the cardiac and non-cardiac status of these survivors is now a major obligation for the specialty. There are, for example, important concerns about neurocognitive problems in HLHS survivors of the Norwood approach, which may influence future decision-making and treatment [36].

In the adolescent and adult, surgery may be required for (1) those who have not been diagnosed or considered severe enough in childhood, (2) those with prior palliation and (3) those with prior repair and residual or new haemodynamic complications (see Table 19.6). Surgical practice in this population is different from conventional adult cardiac surgery, providing a strong case for concentration of resources into specialist units for both treatment and training [2,35]. The majority (about 75%) of adolescents and adults will have had multiple previous operations, but still require further surgery. Reopening a sternal incision in such patients is a potentially hazardous undertaking, especially if the right ventricle or a conduit is in close proximity and establishing cardiopulmonary bypass by femoral cannulation may be required. There are often multiple collaterals in the cyanotic patient and abnormalities of myocardial function and the pulmonary bed together with comorbidity (e.g. kyphoscoliosis) are frequently present. Careful preoperative planning, by all the professionals involved in treatment, is vital for all stages of the intervention including myocardial protection, anaesthesia and blood salvage techniques. The risk–benefit ratio for these complex operations is often difficult to assess and to communicate with patients and their families.

Table 19.4 Common congenital heart defects compatible with survival to adult life without surgery or interventional catheterization

Mild pulmonary valve stenosis
Peripheral pulmonary stenosis
Bicuspid aortic valve
Mild subaortic stenosis
Mild supravalvar aortic stenosis
Small atrial septal defect
Small ventricular septal defect
Small patent ductus arteriosus
Mitral valve prolapse
Ostium primum atrial septal defect (atrioventricular septal defect)
Marfan's syndrome
Ebstein's anomaly
Corrected transposition (atrioventricular/ventriculo-arterial discordance)
Balanced complex lesions (e.g. double-inlet ventricle with pulmonary stenosis)
Defects with pulmonary vascular obstructive disease (Eisenmenger's syndrome)

Table 19.5 Common congenital heart defects surviving to adult life after surgery/interventional catheterization

Aortic valve disease, valvotomy or replacement
Pulmonary stenosis, valvotomy
Tetralogy of Fallot
Atrial septal defect
Ventricular septal defect
Atrioventricular septal defect
Transposition of the great arteries, atrial redirection
Complex transposition of the great arteries
Total anomalous pulmonary venous connection
Pulmonary atresia/ventricular septal defect
Fontan operation for complex congenital heart disease
Ebstein's anomaly
Coarctation of the aorta
Mitral valve disease

Table 19.6 Indications for reoperation in adults with congenital heart disease

Inevitable reoperation after definitive repair: prosthetic valves, extracardiac conduits placed at an early age that become of inadequate size because of body growth
Residual defects after definitive repair: ventricular septal defect after tetralogy of Fallot and left atrioventricular valve
New/recurrent defects after definitive repair: subaortic stenosis, restenosis of aortic valve, pulmonary regurgitation in tetralogy of Fallot
Staged repair of complex defects: pulmonary atresia with ventricular septal defect
Unexpected complications: infective endocarditis
Heart/heart–lung transplantation for uncorrectable congenital heart disease
Patient operated on for congenital heart disease with new acquired heart disease: coronary disease

Even relatively minor non-cardiac surgery may carry a high risk in patients with complex congenital cardiac malformations as a result of haemodynamic instability, hypotension, hypovolaemia and endocarditis. Careful preoperative planning and intraoperative monitoring is therefore vital if disasters are to be avoided. Despite the success of intervention for congenital cardiac malformations, in a number of children and adults cardiopulmonary function declines sufficiently for transplantation to be considered the only option. While this group is challenging because of previous surgery, comorbidity, pulmonary vascular problems and occasionally anatomical difficulties, results for paediatric and adult congenital transplantation have improved in specialist centres (Fig. 19.6) [37]. Despite this, the worsening donor situation means that many patients will never get a transplant unless viable alternatives such as long-term mechanical support or xenotransplantation become available [38].

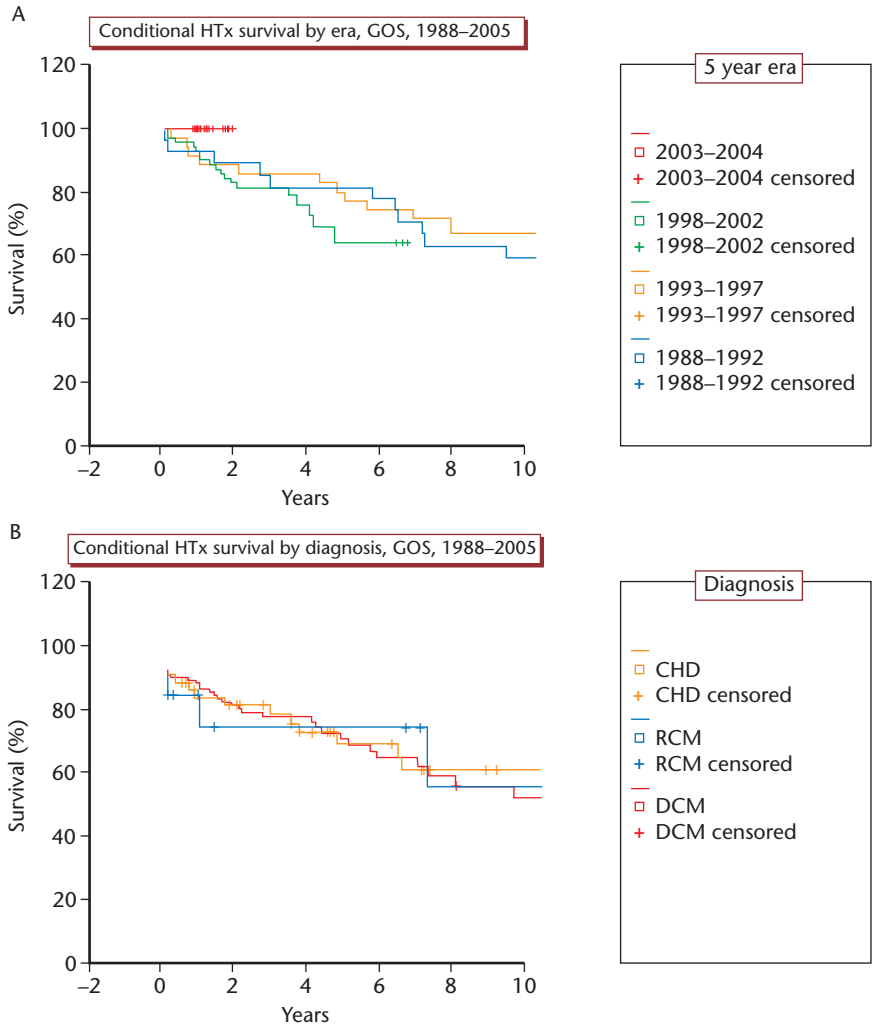

Figure 19.6 (A) Transplantation outcome by era. (B) Transplantation outcome by diagnosis.

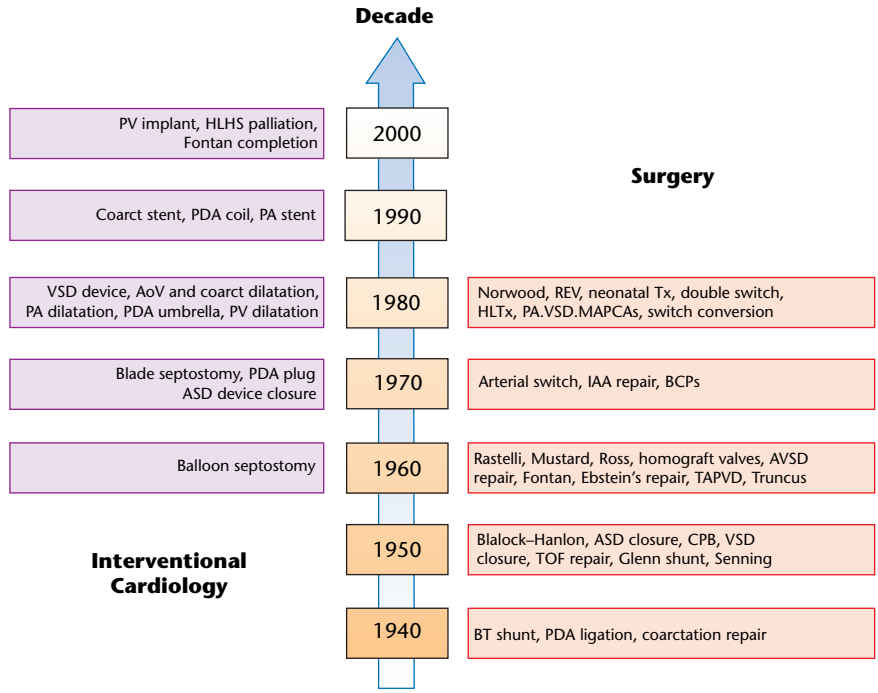

Figure 19.7 Advances in interventional cardiac catheterization according to era compared with surgical advances during the same periods. PV, percutaneous venous; HLH, hypoplastic left heart syndrome; PDA, patent ductus arteriosus; PA, pulmonary artery; VSD, ventricular septal defect; AoV, aortic valve; REV, reparation a l'étage ventriculaire; Tx, transplant; HLTx, heart and lung transplant; MAPCA's, major aortic pulmonary collateral arteries; IAA, interrupted aortic arch; BCPS, bidirectional cavopulmonary shunt; AVSD, atrioventricular septal defect; TAPVD, total anomalous pulmonary venous drainage; CPB, cardiopulmonary bypass; BT, blalock taussig. With kind permission of Phillip Moore MD, Clinical Professor of Paediatrics, Director, Congenital Cardiac Catheterization Program.

Interventional catheterization

There has been a spectacular increase in the number and range of interventional catheter techniques for congenital cardiac malformations, which has coincided with the decline in indications for diagnostic catheterization (Fig. 19.7). For many years, it has been possible to relieve obstructive lesions with balloon dilatation and more recently stenting. New opportunities have arisen to replace regurgitant cardiac valves without surgery (at present in a limited number of patients with pulmonary regurgitation) as well as to close not only patent arterial ducts and atrial septal defects (ASDs) but also VSDs [4,39–42]. The range of therapeutic procedures that can be performed without surgery is likely to increase, as even 'stitching' becomes possible using catheter techniques. In some situations, interventional catheterization has become the clear treatment of choice over surgery (e.g. pulmonary stenosis, closure of patent arterial duct). However, in the majority, no clear evidence of superiority has been demonstrated in clinical trials. The decision to perform an interventional catheter procedure should therefore undergo the same process of multidisciplinary peer review as for surgery. Treatment of congenital cardiac malformations can often best be achieved by a collaborative approach involving both interventional catheterization and surgery. The management of aorto-pulmonary collaterals in tetralogy of Fallot with pulmonary atresia is an example. Lesions accessible to the interventionalist are often challenging to the surgeon (e.g. peripheral pulmonary stenosis) and vice versa (e.g. non-valve outflow obstruction). In the near future, three-dimensional imaging by MRI during interventional catheterization should refine many of these procedures. Interventional catheterization is cheaper than surgery, less dependent on infrastructure and can be performed in a broader range of units. However, any specialized programme treating congenital cardiac malformations should have expertise in both approaches.

Grown-up congenital heart disease

Recognition of the needs of the increasing population of adults with congenital cardiac malformations has prompted the publication of several strategic documents, including the recent ESC Taskforce Report on grown-up congenital heart disease [2]. This set out principles for care delivery involving specialists and other practitioners as well as educational and training requirements. Implementation of a hierarchical system of care based on specialist units with appropriate transition from paediatrics will ensure continued excellence of care past childhood,

Table 19.7 Non-cardiac issues in grown-up congenital heart disease

Intellectual development
Psychosocial development
Employment
Insurance (medical)
Mortgage (life)
Contraception
Pregnancy
Exercise/sports
Air travel

provide feedback of late results to refine early treatment and drive forward progress in 'lifetime' management of congenital cardiac malformations. The key non-medical issues for adults, including education, employment, sports, contraception, pregnancy and insurance, are all discussed in this document (Table 19.7). Over the next few years, informed 'evidence-based' recommendations on all these issues should become possible. The Taskforce also provides consensus advice on the follow-up and management of the individual conditions that adult cardiologists will encounter with increasing frequency over the next few years.

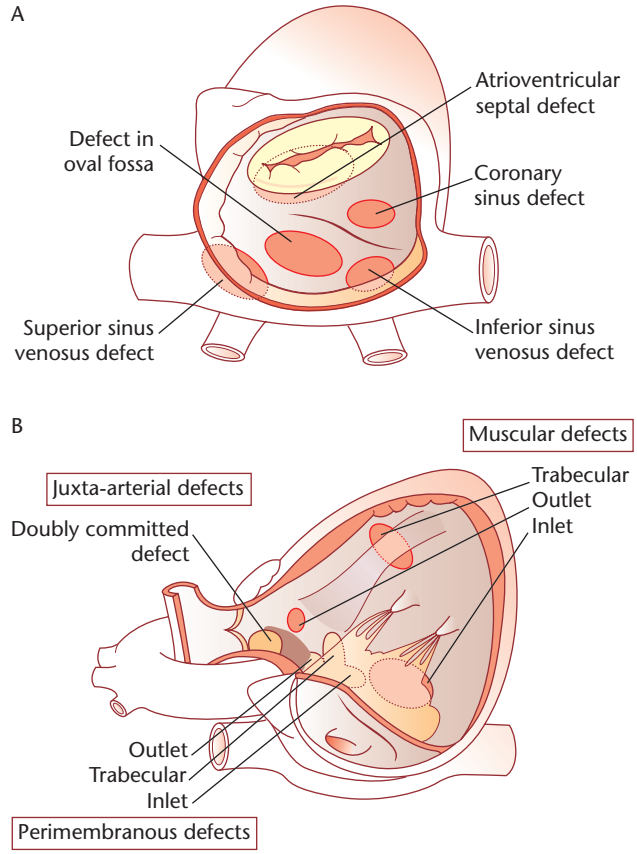

Figure 19.8 (A) Schematic representation of the various sites of atrial communication seen within the atrial septum. (B) Schematic representation of the various sites of ventricular communication seen within the ventricular septum.

Common congenital cardiac malformations

Ventricular septal defect

Excluding bicuspid aortic valves, VSD is the most common congenital cardiac malformation, occurring in 32% of patients either in isolation or with a range of other malformations.

Morphology

The ventricular septum is made up of four components: the membranous, inlet, trabecular and outlet or infundibular septum (Fig. 19.8). The most common defects are perimembranous, and these may be further classified according to their extension into adjacent areas (e.g. inlet or outlet). Outlet defects can be subdivided into those with anterior deviation of the outlet septum (as in tetralogy of Fallot, associated with aortic override) and those with posterior deviation (as seen associated with aortic arch interruption). VSDs with an entirely muscular margin are the next most common type. These may be situated in the inlet, trabecular, apical or anterior parts of the septum, and vary greatly in size, shape and number. Subarterial VSDs are a further important type, in which there is a deficiency of the infundibular septum resulting in an area of fibrous continuity between the semilunar valves.

Pathophysiology

This is determined by the size of the VSD and the pulmonary vascular resistance, which determines the magnitude and direction of flow through the defect. A small VSD with a high resistance to flow results in a small left-to-right shunt and minimal haemodynamic disturbance. A large defect results in a large left-to-right shunt if there is no pulmonary outflow tract obstruction and pulmonary vascular resistance is low. Typically, beyond infancy, as pulmonary vascular resistance starts to rise as a consequence of pulmonary vascular disease, the size of the shunt falls.

Table 19.8 Clinical findings in ventricular septal defect

Size	Very small	Small	Moderate	Large	With PVOD (Eisenmenger)
Thrill	No	Yes	Yes	No	No
Murmur and site	ESM at LSE	PSM loud LSE → apex	PSM, LSE → apex with mitral MDM	ESM at upper LSE and mitral MDM	None or soft ESM
Apex	Normal	Normal	LV+	LV+, RV+	RV++, palpable PA
S_2	Normal	Normal	Obscured by mitral	S_2 single with ↑P_2	Single loud palpable P_2
ECG	Normal	Normal	LV+, LA+, LAD	LV+, LA+, RV+	RV+, RA++, RAD
Chest X-ray	Normal	Normal	↑CTR, plethora	↑CTR, plethora, prominent PAs	↑CTR, large central PAs, no plethora

CTR, cardiothoracic ratio; ESM, ejection systolic murmur; LA, left atrium; LAD, left axis deviation; LSE, left sternal edge; LV, left ventricle; MDM, mid-diastolic edge; P_2, pulmonary component of second heart sound; PA, pulmonary artery; PSM, pan-systolic murmur; PVOD, pulmonary vascular obstructive disease; RAD, right axis deviation; RV, right ventricle; S_2, second heart sound.

Diagnosis

The clinical presentation, chest radiograph and ECG findings associated with VSDs of different sizes are shown in Table 19.8.

ECHOCARDIOGRAPHY

This provides an accurate and reliable method of interrogating the ventricular septum using a combination of imaging planes. The size of the defect and its relationship to adjacent structures within the heart can be documented. Doppler study yields useful haemodynamic data about the shunt and its direction. Colour flow techniques can demonstrate very small defects that are often not visible on two-dimensional imaging and occasionally not audible on auscultation. The search for additional abnormalities is important, especially atrioventricular valve straddling, aortic valve prolapse, right ventricular outflow tract obstruction and aortic coarctation.

CARDIAC CATHETERIZATION

The role of cardiac catheterization is now limited to evaluation of pulmonary vascular resistance in a small proportion of patients or transcatheter VSD closure.

Natural history

The majority of VSDs are small and do not require intervention. It is impossible to determine the proportion that close spontaneously but it may be as high as 80%, usually within the first few years of life. Even larger VSDs can become smaller, but complete closure is less common. Cardiac failure occurs in infants with a large VSD, often from the first few weeks of life, and early closure may be required to ensure survival. Unoperated patients are at risk of developing pulmonary vascular obstructive disease, which may be progressive and irreversible by 1 year of age and very occasionally earlier. These patients with Eisenmenger's syndrome usually survive into adult life but have a reduced life expectancy [43].

A small proportion of infants develop subpulmonary stenosis and become cyanosed (see Tetralogy of Fallot, below) and a further cohort (about 1% in the Western world) develop aortic regurgitation, most frequently associated with subarterial or perimembranous defects [44]. Usually, right coronary prolapse develops and this may actually close the VSD but cause aortic regurgitation that may progress rapidly [45]. Infective endocarditis is an important cause of morbidity and mortality in VSD (1–2 per 1000 patient-years or 10% incidence by 70 years) and is unrelated to the size of the defect [46].

Management

Medical management of heart failure is required in symptomatic neonates and surgical closure is usually performed within the first few months of life. Banding of the pulmonary trunk is now reserved for multiple VSDs, very large defects in small children or when significant contraindications to cardiopulmonary bypass are present. It is rare for VSD closure to be required over 1 year of age. Occasionally, older patients have a significant left-to-right shunt with left ventricular volume overload and normal or mild elevated right-sided pressures. Current evidence supports closure of such defects for best long-term results. Recently, closure of both muscular and perimembranous VSDs has been performed by interventional catheterization, obviating the need for surgery

[47]. This is clearly attractive for families, but a comparison of results between this approach and surgery is not yet available. Small restrictive VSDs, without left ventricular volume overload or increased right-sided pressures, appear benign into adult life and closure is only indicated if infective endocarditis or aortic regurgitation develop. Following closure of VSD, most patients have normal exercise capacity patterns and should be encouraged to lead normal lives. In the modern era, postoperative heart block is very uncommon, as are tachyarrhythmias. Unfortunately, patients with established pulmonary vascular obstructive disease and Eisenmenger's syndrome are still seen. They suffer the consequences of cyanosis and progressive exercise intolerance. Death usually occurs by 50 years, although life expectancy can be prolonged by careful medical management, especially avoidance of unnecessary, even minor, medical or surgical procedures [48]. Oral contraceptives and pregnancy in these patients are contraindicated as the latter carries an unacceptably high risk [48].

Atrial septal defect

Defects in the atrial septum are common and comprise 7% of all congenital cardiac malformations. They can occur at a variety of sites and this affects approach to management (Fig. 19.8):

- ostium secundum defect;
- sinus venosus defect (superior and inferior);
- ostium primum defect;
- coronary sinus defect.

Morphology

ASDs most frequently involve the oval fossa. Secundum defects occur as a result of a deficiency of the flap valve tissue of the oval foramen, so that the flap valve does not completely cover the oval fossa or there are fenestrations within the flap valve tissue. Secundum ASDs may be multiple. Sinus venosus defects occur either high up in the atrial septum, when they are described as superior sinus venosus defects, or more uncommonly low down in the atrium septum astride the entry of the inferior caval vein into the right atrium. Superior sinus venosus defects are very frequently associated with anomalous drainage of the right-sided pulmonary veins into the right atrium adjacent to the entrance of the superior caval vein. Ostium primum defects are more appropriately considered as a form of atrioventricular septal defect (AVSD) and are described below. The most uncommon form of intra-atrial communication occurs between the left and right atrium at the level of the coronary sinus. ASDs may occur in isolation but they are also often found as part of more complex congenital structural cardiac malformations.

Pathophysiology

Reversal of the direction of shunt across the atrial septum starts to occur following the transition from fetal to postnatal circulation. In the presence of persisting interatrial communication, the shunt from left to right increases as pulmonary vascular resistance falls, right ventricular compliance increases and left ventricular compliance decreases. Increased flow over the pulmonary and tricuspid valves causes audible murmurs. Pulmonary vascular resistance in infants and older children remains low in the presence of an ASD and the volume load is well tolerated despite a pulmonary to systemic flow ratio, which may be as high as 3 : 1. In late childhood and in adults, increasing right atrial and right ventricular dilatation predispose to the development of arrhythmias, which may not necessarily resolve with closure of the defect [49].

Diagnosis

CLINICAL

Most ASDs in childhood are identified during cross-sectional echocardiography following the detection of an asymptomatic cardiac murmur. Symptoms, if present, are usually minor and include an increase in frequency of chest infections, mild exercise intolerance and failure to thrive. Examination reveals:

- right ventricular heave;
- pulmonary ejection systolic flow murmur;
- fixed splitting of the second heart sound during all respiration phases;
- tricuspid diastolic flow murmur (with large defects).

Atrial arrhythmias, pulmonary hypertension and the development of pulmonary vascular disease are exceedingly uncommon in childhood. These features may however be part of the clinical presentation of an ASD during adult life.

CHEST RADIOGRAPH

This most frequently shows a normal or mildly increased cardiothoracic ratio with prominent pulmonary vascular markings and enlargement of the central pulmonary artery.

ECG

The most common findings include right axis deviation, right ventricular hypertrophy and an RSR′ pattern in the right precordial leads with a QRS duration < 120 ms (incomplete right bundle branch block). Left

axis deviation with right ventricular hypertrophy is found in ostium primum defects (see Atrioventricular septal defects, below).

CROSS-SECTIONAL ECHOCARDIOGRAPHY

The most important findings include right atrial and right ventricular dilatation, frequently occurring with pulmonary arterial dilatation and increased flow velocity across the pulmonary valve. Right heart volume loading may result in 'paradoxical' (anterior systolic) motion of the interventricular septum. The atrial defect should be visualized directly and is most obviously seen from a subcostal approach. Examination should include assessment of defect size, location within the septum, margin surrounding the defect, defect number and associated anomalies (e.g. anomalous pulmonary venous drainage). Diagnostic cardiac catheterization is almost never required, unless there is evidence of pulmonary hypertension.

Natural history

Secundum ASDs rarely cause symptoms in childhood but these increase in frequency from early adulthood with the appearance of atrial arrhythmias (flutter or fibrillation) and exercise limitation due to right heart failure. Pulmonary vascular disease may also develop in adults. Pulmonary and paradoxical embolism are occasional complications, but infective endocarditis is extremely rare in isolated secundum ASDs [50].

Management

Transcatheter occlusion usually with an Amplatzer device is currently the treatment of choice and is feasible in approximately 60% of cases [42] (Fig. 19.9). This is commonly undertaken electively at 3–5 years of age. Excellent results have been achieved with a very low incidence of embolization or perforation with damage

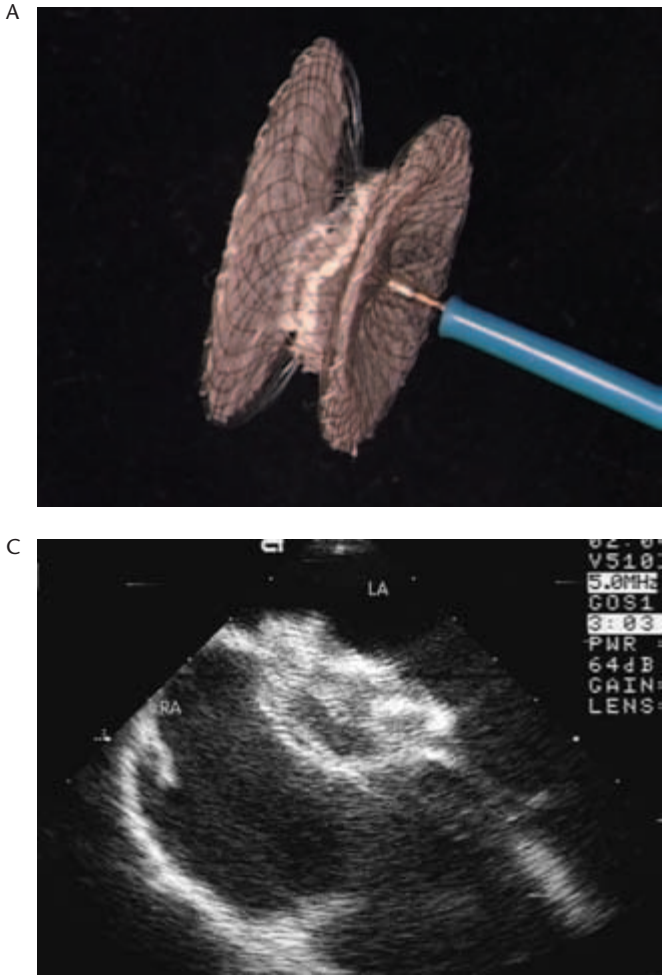

Figure 19.9 Transcatheter occlusion of atrial septal defect (ASD). (A) Amplatz ASD device attached to delivery wire and shown outside long delivery sheath. (B) Three-dimensional echocardiogram demonstrating ASD seen from right atrial aspect with clear superior and inferior margins. (C) Transoesophageal echocardiogram following delivery and release of Amplatz ASD device across defect. LA, left atrium; RA, right atrium.

to surrounding cardiac structures. Defects not suitable for transcatheter closure (including big defects, those with poorly developed margins or some multiple defects) should be closed by surgery. Closure should be undertaken during the preschool years or following later detection. Closure of ASDs in 'asymptomatic' adults used to be controversial but is now advocated by most, provided there is no evidence of pulmonary vascular obstructive disease or other risk factors. Exercise tolerance improves in the majority [51]. In patients with atrial flutter, a right-sided Maze operation at the time of surgery may restore and maintain sinus rhythm [49]. Operative risks in children are very low, with occasional morbidity from pericardial effusion or transient postoperative arrhythmia. Long-term prospects for normal life expectancy and functional capacity are excellent. Complications such as late arrhythmia are more likely to occur in patients who have undergone closure at an older age [49].

Atrioventricular septal defect

This group of abnormalities is characterized by a defect at the site of the atrioventricular septum, and accounts for approximately 3% of all congenital cardiovascular malformations. There is a strong association with trisomy 21 (Down's syndrome), which is present in more than 50% of children undergoing surgery for an AVSD.

Morphology (Fig. 19.10)

These defects are characterized by lack of continuity between atrial and ventricular septal structures. The atrioventricular valve, which is common to both ventricles, is fundamentally different from either a mitral or a tricuspid valve and is usually composed of five leaflets. The size of the atrial communication above the leaflets of the common atrioventricular valve and the ventricular defect below the leaflets can vary from non-existent to very large. When there is no ventricular defect, the common atrioventricular valve has separate orifices into each ventricle. It is more accurately described as a common atrioventricular valve with separate orifices but is also called a 'partial' AVSD or ostium primum ASD. Associated with the abnormal formation of the atrioventricular junction, there is displacement of the left ventricular outflow anterosuperiorly, causing elongation and predisposing to anatomical obstruction.

The morphology of the common atrioventricular valve leaflets is not consistent and may affect valve function. The various types of valve abnormalities have been described according to the Rastelli classification [52], but accurate description of the valvar leaflets is more useful, as this relates more closely to clinical outcomes. AVSDs are commonly associated with other abnormalities both within the heart itself and in the great vessels. Some of these may influence prognosis and operability (see below) and include ventricular disproportion, abnormalities of the outflow tracts including left ventricular outflow obstruction, tetralogy of Fallot and double outlet right ventricle. It should also be noted that AVSD is frequently seen with isomerism of the atrial appendages.

Pathophysiology

The haemodynamic consequences, and therefore the clinical presentation, depend on a number of different morphological features. Large atrial and ventricular components to the defect will cause clinical features similar to those of a large VSD (see above). If the defect is limited to a communication at atrial level, the clinical findings are similar to those of a secundum ASD provided there is no significant left atrioventricular valve regurgitation. This is a key determinant of presentation and outcome, which is also dependent on the presence of additional abnormalities.

Diagnosis

CLINICAL

The diagnosis of an AVSD may be made as part of a screening programme for babies with trisomy 21. If this is not the case, most children with complete AVSD will present before 1 year of age with features of a large left-to-right shunt, including increased frequency of respiratory infections and poor growth. In patients with an atrial communication alone, the physical signs are similar to those of an ASD but there may be an additional pansystolic murmur related to left atrioventricular valve regurgitation. For those with a defect with both atrial and ventricular components, the signs are similar to those found in large VSDs, with additional murmurs related to left atrioventricular valve regurgitation present at the cardiac apex.

CHEST RADIOGRAPH

An isolated AVSD is associated with laevocardia and cardiomegaly. Pulmonary plethora is evident and is partly a reflection of the size of the ventricular component of the defect.

In patients who have AVSD with atrial isomerism, there may be dextrocardia and/or pulmonary oligaemia if there is right ventricular outflow obstruction/pulmonary atresia.

ECG

The ECG almost invariably demonstrates a leftward or superior QRS axis, and an AVSD is one of the few

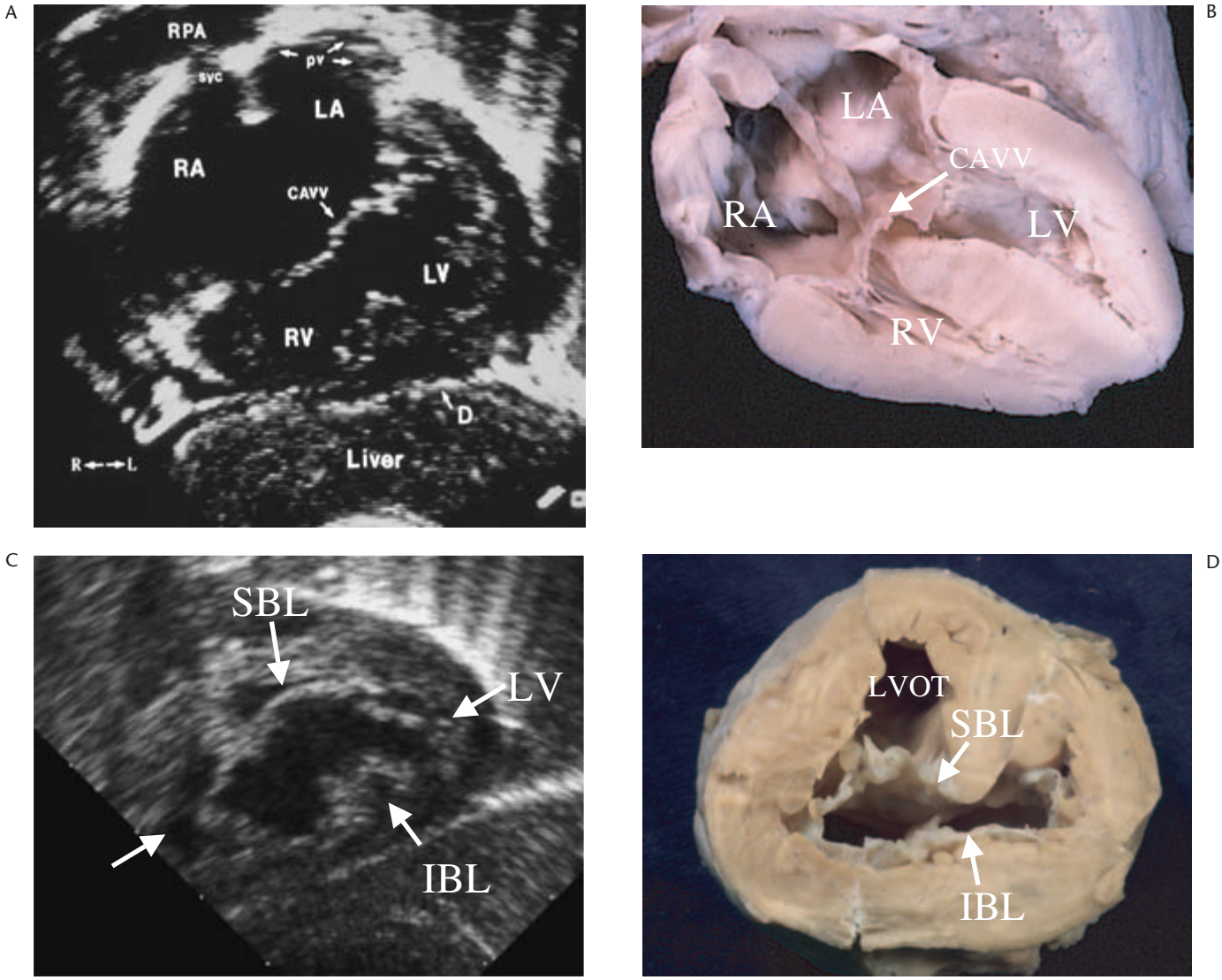

Figure 19.10 Echocardiographic and morphological correlates of atrioventricular septal defect (AVSD). (A) Subcostal four-chamber view of AVSD demonstrating large atrial and ventricular defects together with common atrioventricular valve. RPA, right pulmonary artery; SVC, superior caval vein; PV, pulmonary veins; LA, left atrium; RA, right atrium; CAVV, common atrioventricular valve; RV, right ventricle; LV, left ventricle; D, diaphragm. (B) Equivalent view of a morphological specimen (abbreviations as in A). (C) Subcostal short-axis view of AVSD demonstrating complete atrioventricular valve orifice. SBL, superior bridging leaflet; LV, left ventricle; IBL, inferior bridging leaflet. (D) Equivalent view of a morphological specimen demonstrating the same features (abbreviations as in C).

congenital cardiovascular malformations associated with a superior QRS axis in the neonatal period (others include a large VSD and tricuspid atresia). When present with left atrial isomerism, abnormalities of cardiac rhythm are frequent, including complete heart block.

ECHOCARDIOGRAPHY

The echocardiographic diagnosis of an AVSD is usually straightforward and requires recognition of some classic features, including:

- absence of normal atrioventricular valve offsetting;
- presence of a common atrioventricular valve with abnormal atrioventricular valve leaflets;
- abnormality in the normal inlet to outlet ratio of the ventricles.

Having established the diagnosis, important additional features include:

- atrioventricular function and the degree of regurgitation;
- ventricular and valvar disproportion, which may preclude surgical repair;

- additional abnormalities involving the outflow tracts and great arteries;
- in the presence of atrial isomerism, detailed echocardiographic examination of the points of entry of both the systemic and pulmonary veins should be undertaken.

CARDIAC CATHETERIZATION AND ANGIOGRAPHY

This is not required in infants with AVSD, unless there is concern about pulmonary vascular resistance, which may influence the chances of successful repair.

Natural history

Primum ASDs have a similar natural history to that of secundum defects, unless there is significant left atrioventricular valve regurgitation, apart from the risk of infective endocarditis. Significant left atrioventricular valve regurgitation results in cardiac failure, and requires early surgical intervention. Patients with complete AVSD present very differently, with heart failure from infancy and rapidly developing pulmonary vascular disease unless the defect is repaired early. Many have Down's syndrome and for many years surgical intervention was not performed. In these circumstances, pulmonary vascular obstructive disease results, with premature death and a slow downward course, usually from the second decade of life. The high surgical mortality for repair at some centres justified this approach in the early era of treatment, but as this has fallen substantially, a conservative strategy for children with Down's syndrome cannot be justified on medical grounds.

Management

With rare exceptions, all patients with AVSD will require surgical correction. The precise approach to repair depends on individual variation and anatomy, which is considerable. Key elements are closure of the atrial and ventricular communications and creation of a non-stenotic competent left atrioventricular valve. The success of left atrioventricular valve repair is the major determinant of long-term outcome and results have improved dramatically with better understanding of the trifoliate nature of the left atrioventricular valve [53]. Morphological factors determining postoperative atrioventricular valve regurgitation include quality of valve tissue, deficiency of the mural leaflet and important abnormalities of the subvalvar mechanism. There has been a gradual trend towards early repair for both complete and partial AVSD. Surgical results for complete AVSD appear best at around 3 months of age [54]. Traditionally, partial AVSDs have been managed like secundum ASDs, unless associated with significant atrioventricular valve regurgitation. Morphological evidence, however, suggests that early repair may be easier and a trial is awaited to assess this approach. AVSD repair may also be affected by valvar or ventricular disproportion. Occasionally, a 'small ventricle' can be enlarged at repair by judicious dissection of intraventricular muscle bundles to release the interventricular septum. The ability to deal with valvar disproportion depends largely on the chordal position and distribution. AVSDs can now be repaired successfully even when associated with other cardiac malformations, including tetralogy of Fallot. Long-term results of repair are excellent, provided the left atrioventricular valve is competent. Repeat surgery and valve replacement may be required in older patients. Early heart block is now rare and late arrhythmia uncommon. Late survival will be complicated by the non-cardiac complications of Down's syndrome, which is present in the majority of patients with complete AVSD.

Patent arterial duct

Persistent postnatal patency of the arterial duct has been estimated to be present in 7% of all congenital cardiac malformations, excluding premature infants.

Morphology

The arterial duct is derived from the sixth aortic arch and is almost always a unilateral left-sided structure, irrespective of the laterality of the aortic arch. Occasionally, when the arch is right-sided, a right-sided arterial duct arises from the ventrolateral aspect of the aortic arch, just distal to the right subclavian artery. With its function as a conduit between the pulmonary artery and the descending aorta, patency of the arterial duct is actively maintained *in utero* by local prostaglandin synthesis. At birth, the duct undergoes rapid constriction. A persistent arterial duct may therefore have a variable shape, depending on whether constriction has occurred circumferentially or longitudinally, or indeed if constriction has occurred at all. In cyanotic congenital heart disease with pulmonary atresia, the arterial duct tends to be smaller and more tortuous, as it only carries the relatively small amount of blood required to supply the fetal lungs during pregnancy. In contrast, when there is aortic atresia, the arterial duct tends to be shorter and may be larger than normal.

Pathophysiology

Distinction should be made between ductal patency in a preterm infant, whose mechanisms for ductal closure

are immature, and that in a term infant in whom patency is a true congenital malformation, possibly related to an abnormality of the elastic tissue within the wall of the duct. In the former, providing the infant does not succumb to the complications of prematurity or the duct itself, ductal closure would be expected as the infant matures.

In patients with congenital cardiac malformations, in whom continued ductal patency is required to maintain either the systemic or pulmonary circulation, spontaneous closure is associated with profound clinical deterioration. This can be reversed medically with the use of prostaglandin, given within the first few days of life, until either operative repair or a palliative procedure is undertaken.

In preterm infants:

- prolonged ductal patency is almost inevitable in infants weighing under 1500 g;
- in up to 30% of patients, this is associated with a significant left-to-right shunt at great artery level;
- increased aorto-pulmonary shunting will exacerbate existing lung disease of prematurity and prolong ventilator dependence.

Diagnosis

CLINICAL

Clinical findings in babies with significant arterial ducts usually include brisk peripheral pulses with a short systolic murmur audible at the left sternal edge. Most term infants and children with smaller ducts remain asymptomatic, with a cardiac murmur detected at routine medical examination. This is usually a soft continuous murmur beneath the left clavicle. A combination of patent arterial duct with an atrial communication may result in a disproportionately symptomatic patient because of left-to-right shunts at multiple sites. With larger ducts, pulses may be brisk, the left ventricle may be hyperdynamic and there is often a continuous machinery-type murmur that obscures the second heart sound.

CHEST RADIOGRAPH

The chest radiograph is unremarkable in patients with small ducts. In those with large ducts, the cardiothoracic ratio is increased and there is evidence of pulmonary plethora.

ECG

Normal in cases with a small patent arterial duct, but increased left ventricular forces are present when the duct is large.

ECHOCARDIOGRAPHY

The arterial duct can almost always be imaged adequately. Important features are the size of the duct, the direction and velocity of blood flow through the duct, as well as left atrial and left ventricular size. Echocardiography should exclude additional structural cardiac abnormalities, of which coarctation of the aorta is most important.

CARDIAC CATHETERIZATION AND ANGIOGRAPHY

This has become a therapeutic rather than a diagnostic procedure.

Natural history

The natural history is no longer seen, as closure should be undertaken once the diagnosis of persistent patency of the arterial duct is made, even if the shunt is small. A large duct may lead to heart failure and pulmonary vascular disease. Infective endocarditis may occur more commonly in large ducts and a persistent duct may calcify in adults. Closure of small ducts is more controversial, but is usually undertaken to reduce the risk of endocarditis [55]. In the era of high-resolution echocardiography, it is not uncommon to demonstrate trivial patency of the duct in the absence of a murmur ('silent duct') [56]. The natural history is unknown. Most cardiologists would ignore this finding, as endocarditis in these circumstances has not been described.

Management

In the premature baby, medical management includes fluid restriction and diuretics. Indometacin should be given to encourage duct closure and success depends on dosage, timing and, importantly, on gestational and postnatal age. Protocols and dosing vary. Indometacin treatment is not entirely benign and has been associated with increased bleeding, renal dysfunction and necrotizing enterocolitis [57,58].

In a small patient with a large duct, surgical closure is recommended (first performed in 1939) usually via a left thoracotomy. Complications are rare and complete closure is achieved in most [59]. Recently, thoracoscopic surgery, with a clip placed across the duct, has been undertaken even in very small babies (< 1 kg) with less morbidity and shorter hospital stay than with thoracotomy [60]. A patent arterial duct can be closed by interventional cardiac catheterization and this is now the treatment of choice for most older patients. Since Portsman's first procedures in 1971, a range of devices has been developed that can be applied to ducts of different morphologies [61]. Success rate is over 90% and late results are excellent. If closure has been achieved, patients can be discharged and endocarditis prophylaxis is no longer required.

Common arterial trunk

Persistent common arterial trunk (CAT) is a rare (1.6% of all congenital cardiovascular malformations) but serious abnormality in which a single vessel arises from the heart and supplies the systemic, pulmonary and coronary circulations.

Morphology

CAT results from failure of normal septation of the developing arterial trunk. There is always a VSD, overridden by the solitary arterial trunk that gives rise to the coronary, pulmonary and systemic arteries. Occasionally, CAT may arise predominantly or exclusively from one ventricle. The truncal valve frequently has an abnormal number of cusps and may be stenotic or regurgitant or both. In most cases, atrial situs is normal and there is laevocardia. The aortic arch may be right- or left-sided and on occasion there may be complete interruption of the aortic arch. A classification was devised by Collett and Edwards [62] according to the origin of the pulmonary arteries from the trunk, but description of the pulmonary artery pattern in each case is important. Occasionally, CAT may be the solitary outlet from a heart with a functionally single ventricle.

Pathophysiology

Pulmonary blood flow is governed by the size of the pulmonary arteries, the presence of pulmonary artery obstruction and the pulmonary vascular resistance. Once pulmonary vascular resistance has started to fall postnatally, patients with unobstructed pulmonary flow develop signs of early severe congestive cardiac failure. As this is a common mixing situation at great artery level, there is mild cyanosis. The clinical manifestations will be exacerbated if there is significant truncal regurgitation. Occasionally, there may be acute cardiovascular collapse in patients with CAT and aortic arch interruption.

Diagnosis

CLINICAL

The majority of patients present in the newborn period with mild cyanosis and increasing cardiac failure. Symptoms include poor feeding, poor weight gain and tachypnoea with an overactive precordium. The first heart sound is normal and there is a single second heart sound. There may be an associated ejection click. If there is significant truncal valve stenosis or regurgitation, there may be associated systolic ejection or early diastolic murmurs respectively. The association between this lesion and 22q11 deletion should be remembered and actively investigated.

CHEST RADIOGRAPH

- Usually laevocardia.
- Almost always cardiomegaly with pulmonary plethora.
- High 'take-off' of the pulmonary artery may be present.
- Approximately 25% of patients will have a right aortic arch.

ECG

The findings are non-specific, but include evidence of right ventricular hypertrophy, often associated with ST-segment and T-wave changes.

ECHOCARDIOGRAPHY

In the majority of cases, this provides all the necessary information to enable planning of neonatal surgical repair. Careful assessment of the VSD will normally confirm that this is a muscular defect. Occasionally there will be additional muscular VSDs. Detailed evaluation of the truncal valve function may be difficult in the face of the increased cardiac output passing through the single arterial valve. This may result in overestimation of the degree of stenosis. Regurgitation is usually easier to assess and is of great importance in relation to surgical repair. Careful evaluation of the aortic arch is important for ensuring that there is continuity and no interruption.

CARDIAC CATHETERIZATION AND ANGIOGRAPHY

Preoperative cardiac catheterization and angiography is now very rarely performed, but may occasionally be necessary in patients when there is suspicion that one of the pulmonary arteries arises from the descending aorta or from an arterial duct.

Natural history

The majority of children born with CAT would die during the first year without surgery, and many present as cardiac emergencies during the first weeks of life. The natural history is influenced by the associated malformations, especially abnormalities of the pulmonary arteries, aortic arch (including interruption) and function of the truncal valve. Survivors without pulmonary obstruction develop pulmonary obstructive disease. As a result, surgical intervention is indicated in all patients.

Management

Pulmonary artery banding no longer has a place in surgical management of CAT, and definitive neonatal repair is now performed. This consists of closure of the VSD to

commit the CAT to the left ventricle, disconnection of the pulmonary arteries from the trunk, and insertion of a conduit (usually a homograft) between the right ventricle and the pulmonary artery. Malfunction of the truncal valve may require intervention. Surgical results have improved dramatically over the last 20 years [63]. However, right ventricle to pulmonary artery conduit replacement will be required during childhood and adolescence, and long-term follow-up is mandatory for all. In the future, percutaneous pulmonary valve implantation may limit the lifetime number of reoperations required by such patients.

Aortic arch obstruction

Flow in the aorta can be compromised by coarctation (3% of congenital cardiac malformations) or interruption of the aortic arch.

Morphology

The most common site for aortic coarctation is between the left subclavian artery and the aorto-ductal junction. If the duct is open, there is infolding of the posterolateral wall of the aorta, causing a discrete ductal shelf. In neonates and small infants, there tends to be a variable degree of tubular hypoplasia. Frequently associated cardiac abnormalities include anomalous origin of the right subclavian artery, bicuspid aortic valve with or without aortic stenosis, VSD and varying degrees of mitral valve stenosis. Coarctation occurring beyond the duct in the neonatal period is one of the few remaining surgical emergencies, as clinical improvement does not occur despite prostaglandin infusion.

Pathophysiology

The manifestations of aortic coarctation depend on the severity of obstruction. In neonates, severe obstruction may develop rapidly following closure of the arterial duct, causing cardiac failure, systemic hypoperfusion and acidosis. In infants, aortic obstruction may develop more slowly if there is delayed ductal constriction. In the majority of cases, this occurs within the first few months of life and these infants present with cardiac failure including tachypnoea, poor feeding, excessive perspiration and absent femoral pulses. In neonates and infants, cardiac murmurs are usually due to associated cardiac lesions rather than to the coarctation itself. Coarctation may not present until childhood or adult life if it is not severe or if there is rapid development of a collateral circulation. The diagnosis is usually made at a routine medical examination, which reveals upper limb hypertension with absent femoral pulses or a cardiac murmur. On direct questioning, patients may complain of symptoms of claudication, cold feet and headaches. The typical continuous murmur of coarctation is audible, usually best heard over the back.

Diagnosis

CLINICAL

See Table 19.9.

CHEST RADIOGRAPH

Cardiomegaly with pulmonary plethora is present in infants. In older children (> 4 years), there is a normal cardiothoracic ratio with possible rib notching.

Table 19.9 Clinical features of aortic coarctation at different ages

	Neonate	Infant	Older child
Presenting feature	Circulatory collapse	Cardiac failure	Hypertension
Femoral pulses	Absent	Absent	Reduced or absent
Apex beat	Normal	Hyperdynamic	Displaced → apex, LV heave
Heart sounds	S_1, normal S_2, single	S_1, S_2 normal, often with S_3	S_1, S_2 normal
Murmurs	Absent	Short ESM at LSE	Continuous murmur at back, ESM at LSE
Hypertension	Absent	Usually	Invariably
Chest X-ray	↑CTR, plethora	↑CTR	CTR normal Rib notching
ECG	Right axis Right ventricular hypertrophy	Biventricular hypertrophy	Left axis Left ventricular hypertrophy

CTR, cardiothoracic ratio; ESM, ejection systolic murmur; LSE, left sternal edge; S_1, first heart sound; S_2, second heart sound.

ECG

It is not widely appreciated that neonates and infants with coarctation have right ventricular dominance with extreme rightward axis, and that left ventricular hypertrophy only develops later.

ECHOCARDIOGRAPHY

This is the investigation of choice in neonates and infants. Views from the suprasternal notch allow assessment of the severity of arch obstruction, the size of the transverse aortic arch and associated abnormalities of the head and neck vessels. Additional information about left ventricular contractility and a search for associated abnormalities, including persistent left superior caval vein, aortic stenosis, VSD and mitral stenosis, should be performed. In older children, assessment of left ventricular hypertrophy and the Doppler-derived coarctation gradient provide the most important information.

MRI AND CT

Both these forms of non-invasive imaging provide very detailed anatomical information about aortic arch anatomy, with the added advantage of being able to demonstrate the relations of the area of coarctation to adjacent structures. MRI can also quantify the functional severity of the coarctation.

CARDIAC CATHETERIZATION AND ANGIOGRAPHY

This is no longer required for preoperative assessment of aortic coarctation. However, there is increasing use of this technique as a therapeutic option (see below).

Natural history

Coarctation presenting in the neonatal period requires urgent surgical correction. In patients presenting in childhood or during adult life the natural history is poor, with systemic hypertension, as well as morbidity and premature death from coronary disease, heart failure and cerebrovascular complications. Occasionally, the first presentation may be a catastrophic cardiovascular event such as aortic dissection or rupture. There is also a risk of endocarditis. The average age of death of patients with coarctation who have survived childhood without intervention is 34 years [64].

Management

Symptomatic neonates presenting with coarctation may have a duct-dependent systemic circulation requiring urgent medical management with prostaglandin infusion and inotropic support for impaired left ventricular function. Prompt surgical correction is required, usually via a left thoracotomy. This can be achieved by a number of surgical techniques, including resection and end-to-end anastomosis and subclavian flap angioplasty [65,66]. Dacron patch angioplasty is no longer performed as the incidence of late aneurysm has been higher than with other techniques. A more extended arch reconstruction may be required if the aorta is hypoplastic, in addition to a discrete narrowing [67]. Operative results are excellent, although there is a small risk of paraplegia due to impairment of spinal cord blood supply [68]. The risk is higher in patients with anomalous origin of the right subclavian artery from the descending aorta. If additional cardiac lesions such as VSD are present, a 'complete repair' on cardiopulmonary bypass may be indicated [69]. Alternatively, coarctation repair and pulmonary artery banding may be performed, with later VSD closure and debanding. Re-coarctation in neonates occurs in up to 20% of cases [70].

Elective repair of coarctation is the treatment of choice for children when the diagnosis is made beyond infancy. Surgery is usually favoured, although balloon dilatation of native coarctation has been advocated. For both approaches, restenosis rates are higher in younger patients and late aneurysms are recognized [71].

In patients presenting in childhood or adult life, intervention is required in cases when there is a significant resting gradient (≥ 30 mmHg) together with rest- and/or exercise-induced hypertension. Balloon dilatation with stent implantation is an attractive option for native coarctation in the older patient and is increasingly the treatment of choice [72]. Long-term follow-up is required in all patients, even after successful relief of coarctation. This should include surveillance for re-coarctation or aneurysm formation as well as for the aortic valve. Hypertension may persist or develop despite excellent relief of arch obstruction, especially if this was performed at an older age [73]. Late outcome of balloon dilatation and stenting as well as the pathophysiology of late hypertension requires further research.

Aortic arch interruption

Morphology

Interruption of the aortic arch occurs with equal frequency distal to the left subclavian (type A) or distal to the left common carotid (type B). Infrequently, there will be interruption distal to the innominate artery (type C). Almost all cases have associated anomalies, most frequently a posterior malalignment VSD causing subaortic obstruction and associated patency of the arterial duct. Other forms of VSD may exist but are less common. There may be abnormal ventriculo-arterial

connections including discordance, and double outlet right ventricle (Taussig–Bing anomaly). The presence of 22q11 deletion should be considered in all cases of aortic arch interruption.

Pathophysiology

Most commonly, when interruption is associated with patency of the arterial duct, the infant will remain well until constriction of the duct precipitates a critical reduction in lower body perfusion. In the majority of cases, infants are admitted to specialist units within the first 2 weeks of life with acute onset of heart failure, often complicated by shock and acidosis. Rarely, the arterial duct remains open and excess pulmonary blood flow develops as pulmonary vascular resistance falls.

Diagnosis

CLINICAL

The most specific sign is differential upper body pulses with weakness of one or both arm pulses or one carotid pulse (these findings may change with pharmacological manipulation of the duct). Auscultation is usually unhelpful, with murmurs due to the presence of associated cardiac abnormalities.

CHEST RADIOGRAPH

- The heart is usually left-sided with evidence of cardiomegaly.
- Pulmonary vascular markings are usually increased.
- An absent thymic shadow may suggest 22q11 deletion.

ECG

There are no specific electrocardiographic features.

ECHOCARDIOGRAPHY

Echocardiography should enable a complete description of the aorta, the site of interruption as well as the origin of the head and neck vessels. Detailed evaluation of intracardiac anatomy for additional abnormalities is most important for planning of surgical strategy.

CARDIAC CATHETERIZATION

This is not normally required as a diagnostic investigation and has largely been superseded by echocardiography, sometimes with additional MRI or CT.

Management

Complete repair of the interrupted aortic arch together with closure of VSD is usually undertaken in the neonatal period. Operative results depend on the nature and severity of the aortic arch obstruction and the clinical condition of the child. Long-term surveillance of the arch is required because of the possibility of residual or recurrent arch obstruction, as in patients after coarctation repair.

Left ventricular outflow obstruction

Left ventricular outflow obstruction comprises 4% of all congenital cardiac malformations and may occur at subvalvar, valvar or supravalvar level. This excludes bicuspid aortic valve, which does not usually produce problems during childhood. Aortic valve stenosis may occur as an isolated lesion, but may also be associated with other left heart obstructive lesions at multiple levels (Shone's complex). In this condition, there is usually mitral valve stenosis with subaortic and/or aortic stenosis, as well as hypoplasia of the aortic arch and discrete coarctation.

Morphology

Valvar aortic stenosis is the commonest form of left ventricular outflow obstruction (75%). Valve morphology and severity are highly variable. In more severe cases, there may be a small left ventricle precluding consideration for a biventricular circulation. Furthermore, there may be associated endocardial fibroelastosis affecting left ventricular function.

When the obstruction is subvalvar, three different morphological types are identifiable. The commonest form is a discrete fibromuscular shelf, which is usually circumferential and may be adherent to the aortic valve leaflets and to the anterior mitral valve leaflets. In the 'tunnel' type of subaortic stenosis, there is usually narrowing of the aortic valve in addition to a small left ventricular outflow, which is often lined with fibrous tissue. Muscular outflow tract obstruction forms part of the spectrum of hypertrophic obstructive cardiomyopathy. Supravalvar aortic stenosis accounts for only 1–2% of left ventricular outflow tract obstruction in childhood. It may be sporadic or more commonly part of Williams–Beuren syndrome. Different morphological entities have been described, including discrete and diffuse narrowing, as well as association with abnormalities of the aortic arch, including coarctation. In Williams–Beuren syndrome, there are often coexisting multiple systemic and pulmonary arterial stenoses associated with deletion of the elastin gene on chromosome 7 [74].

Pathophysiology

Severe left ventricular outflow obstruction during the neonatal period is a medical emergency and most have

either critical aortic valve stenosis or outflow obstruction at multiple levels. When critical aortic stenosis is diagnosed in fetal life, the outlook is poor [75]. The evolution of worsening left heart hypoplasia in these patients has prompted the use of prenatal cardiac interventional catheterization in an attempt to encourage ventricular growth [76]. Postnatally, presentation of aortic valve stenosis depends on the severity of obstruction and left ventricular size and function. The degree of obstruction may be underestimated in the presence of poor left ventricular function and assessment requires evaluation of both the peak systolic pressure gradient (≥ 75 mmHg is severe) as well as the aortic valve area (≤ 0.5 cm^2/m^2 is severe).

Diagnosis

CLINICAL

Critical aortic stenosis in the neonate results in rapid development of cardiac failure, with a severe reduction in left ventricular function. Patients may be tachypnoeic with tachycardia and pallor and have decreased or absent peripheral pulses. The second heart sound is often single and there may be a gallop rhythm. An ejection systolic murmur may be present. These findings in the neonate contrast with the majority of patients who present later in childhood, usually with an asymptomatic murmur. In the more severe cases, this may be associated with exercise intolerance and occasionally with chest pain. Physical signs in such patients include normal or decreased peripheral pulses, a diminished aortic component to the second heart sound with a systolic ejection click and an ejection systolic murmur radiating to the neck. Supravalvar aortic stenosis is usually detected when Williams–Beuren syndrome is diagnosed and routine cardiac screen is undertaken. The findings of subaortic stenosis resemble those for aortic valve stenosis but patients do not have an ejection check.

CHEST RADIOGRAPH

Neonatal critical aortic valve stenosis is usually associated with laevocardia, cardiomegaly and pulmonary oedema. In older children, the chest radiograph findings are frequently normal.

ECG

There is usually left axis deviation and evidence of left ventricular hypertrophy. In more severe cases, there may be repolarization changes suggestive of ischaemia and strain in the lateral precordial leads.

ECHOCARDIOGRAPHY

Aortic stenosis can be diagnosed by cross-sectional echocardiography. In the neonatal period, it is crucial to evaluate:

- left ventricular size/volume;
- size of the mitral valve;
- evidence of mitral regurgitation;
- size of aortic outflow and aortic valve;
- severity of aortic valve stenosis using Doppler;
- presence or absence of endocardial fibroelastosis;
- left ventricular systolic function.

This enables appropriate decision-making regarding treatment.

In older children, assessment of the severity of valve stenosis by Doppler-derived gradients is the most widely accepted method for assessment of severity. Evaluation of left ventricular hypertrophy and function is also important in deciding on timing of intervention. The degree of aortic regurgitation, which may coexist, will influence suitability for interventional catheter treatment (see below). Echocardiography can usually define the nature and severity of the left ventricular outflow tract obstruction in patients with subaortic stenosis.

In supravalvar aortic stenosis, it is important to look for the extent and severity of aortic arch abnormalities as well as to assess the degree of left ventricular hypertrophy, which may be out of proportion to the degree of supravalvar aortic stenosis.

Recently, newer echocardiographic techniques using Doppler tissue imaging can be used to evaluate diastolic function and to relate this to the severity of the left ventricular outflow obstruction. This may help to define the optimal timing of intervention.

CARDIAC CATHETERIZATION AND ANGIOGRAPHY

This is not required for diagnosis but is increasingly used as a treatment of valvar aortic stenosis, both in neonates and older children (see below). It is not indicated in subaortic or supra-aortic stenosis and in the latter may be dangerous. MRI and CT have a role in the evaluation of all forms of left ventricular and aortic arch obstruction.

Management

In critical aortic valve stenosis, maintenance of patency of the arterial duct by prostaglandin may be life-saving, before relief of the obstruction can be attempted by either balloon dilatation or surgery. Infants and children with mild aortic stenosis may remain stable for many years, with slow progression, and intervention can be delayed until adulthood. Those with moderate or severe aortic stenosis progress more rapidly, and those with gradient greater than 75 mmHg and left ventricular hypertrophy have a risk of sudden death. Infective endocarditis is a serious complication at all ages.

Both balloon dilatation and surgery can be performed in the neonatal period. The results appear comparable in published series, although no randomized trial has

been undertaken [77]. Outcome after both approaches is determined by the severity of the valve deformity as well as by the left ventricular changes, which may include endocardial fibroelastosis, and infarction of the papillary muscles of the mitral valve. If the left ventricular cavity is small or if multiple obstructive lesions are present, an alternative Norwood approach may be preferable (see Hypoplastic left heart syndrome, below). Children who present beyond infancy should remain under careful cardiological follow-up, which should include regular ECG, echocardiography and exercise testing. Intervention is indicated if there are symptoms, progressive gradient increase, left ventricular hypertrophy, repolarization changes on resting or exercise ECG, or an abnormal exercise blood pressure response. Valve area should be calculated as gradients can be misleading if cardiac output is reduced. Balloon dilatation is usually the procedure of choice in the older child, unless there is significant aortic regurgitation. This can be undertaken by anterograde or retrograde approaches at all ages, and use of balloons one size below the valve diameter reduces the risk of important new aortic regurgitation [78]. Similar principles apply to surgery in the child. Aortic valvotomy, leaving a small gradient and little or no aortic regurgitation, is the preferred result. Risk of surgery or catheter intervention is high in neonates, but significantly lower in older patients [79]. Both treatments are palliative, however, and gradual restenosis is the rule. A second valvotomy in childhood can be attempted, unless the valve is calcified or significantly regurgitant, but aortic valve replacement is almost always eventually required. However, in the US Natural History Study of Congenital Heart Disease, only 27% of children who underwent aortic valvotomy at age > 2 years required a second intervention within 20 years [92].

In a small child, the Ross or 'autograft' operation is the approach of choice for valve replacement (implanting the pulmonary valve in the left ventricular outflow tract and a homograft in the right ventricular outflow tract) [80]. This permits growth of the neo-aortic valve and does not require anticoagulants. However, the homograft will require replacement and the long-term fate of the neo-aortic valve is still uncertain. In the older child, adolescent or adult, valve replacement with a mechanical or biological prosthesis is an alternative, but the Ross procedure is emerging as a favoured approach [81]. The choice of surgical approach depends on a number of factors including age, desirability and safety of anticoagulation and future pregnancy plans, as well as patient preference and local expertise. Occasionally more extensive surgery, such as a Konno procedure, is required when left ventricular outflow tract obstruction occurs at multiple levels, or if the aortic valve is small [82].

The severity of supravalvar aortic stenosis characteristically increases with time and patients may be at risk from sudden death [3]. The systemic arterial stenoses in key vessels such as the carotid and renal arteries may also progress. Indications for intervention are similar to those for aortic stenosis. Interventional catheterization, however, is not an option and surgery is required. This involves insertion of patches to enlarge the supravalvar area extending into the sinuses of Valsalva [83]. Induction of anaesthesia and onset of cardiopulmonary bypass may jeopardize coronary perfusion, and surgery may be difficult because a diffuse aortopathy is present in many cases.

Because of the progressive nature of subaortic stenosis, intervention is usually indicated at lower levels of severity than for aortic valve stenosis. This is controversial, as in some cases the malformation may be mild or stable for many years [84]. Most would recommend intervention if aortic regurgitation develops, as it can progress rapidly [85]. Interventional catheterization is not appropriate and surgical resection is required. The immediate and early results are excellent, but recurrence is common [86]. Complete removal of the obstruction at surgery is essential and recurrence risk appears lower when a myotomy or myectomy is also performed [87].

Lifelong follow-up is required for all types of left ventricular outflow tract obstruction. Advice about physical activity and sport is not based on secure evidence. Vigorous activities are probably contraindicated in the presence of left ventricular hypertrophy or residual obstruction (> 30 mmHg), but social exercise should be permitted in most cases.

Hypoplastic left heart syndrome

This term is used to describe a group of closely associated abnormalities whose common morphological feature is severe hypoplasia of the left heart structures. It accounts for 2–3% of all congenital cardiovascular malformations.

Morphology

The pathogenesis of this group of abnormalities is not well understood. Hypoplasia of left heart structures occurs if inflow to the left side of the heart is restricted in animal models, but the increased recurrence risk in siblings and relatives [88] would suggest that there is more likely to be a genetic basis for this condition. The heart is usually left-sided and enlarged, with the apex formed by the right ventricle. The left atrium is small with or without a narrowed or occluded atrial foramen. There is either severe mitral stenosis or mitral atresia. The left ventricle is usually small and frequently there is a diminutive ascending aorta with aortic atresia. The tricuspid valve is usually normal and there is right ventricular hypertrophy. The main pulmonary arteries

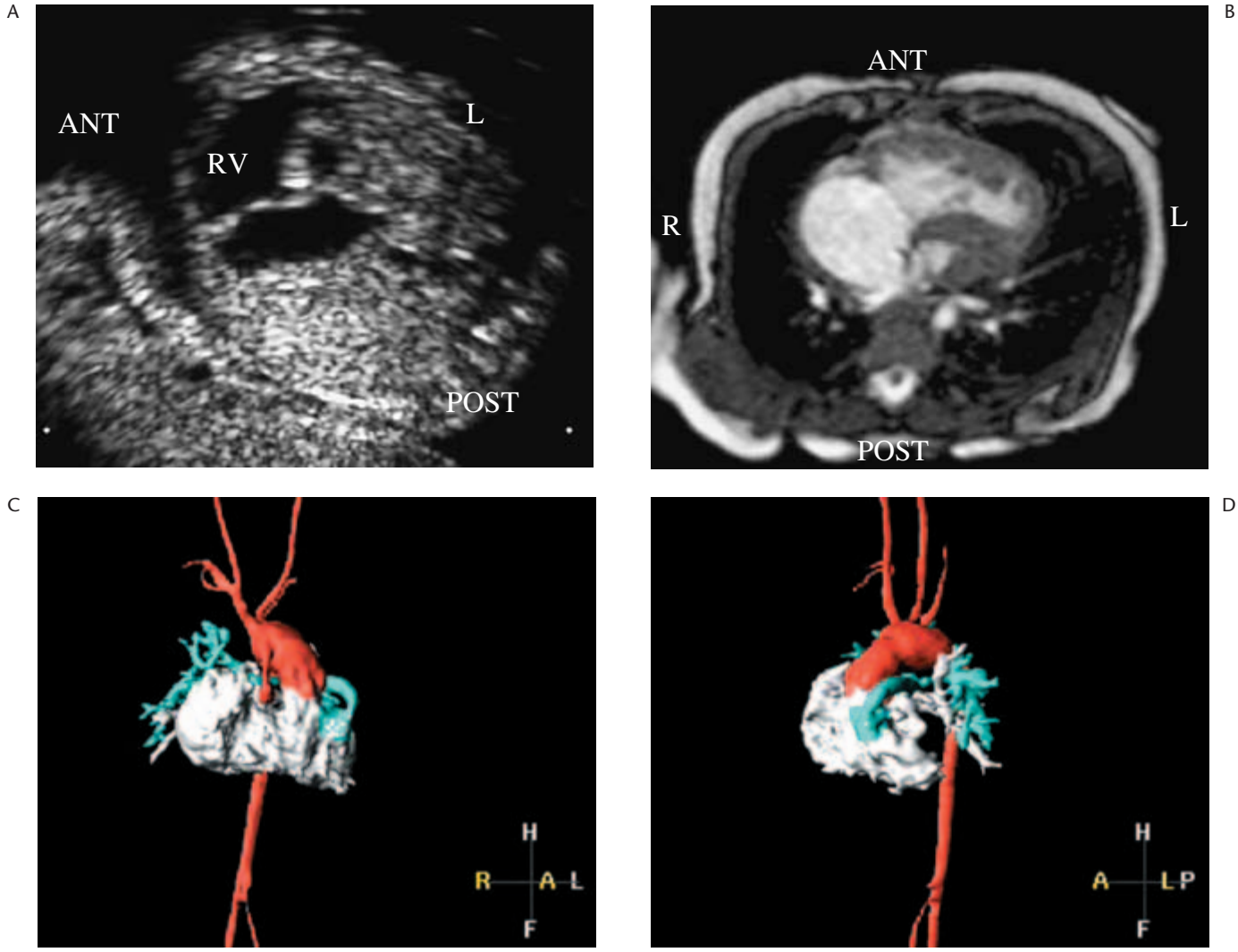

Figure 19.11 Images of hypoplastic left heart. (A) Four-chamber view through the fetal thorax demonstrating hypoplastic left heart. The left ventricle is seen as a small echogenic area adjacent to dilated right ventricle. ANT, anterior; RV, right ventricle; L, left; R, right; POST, posterior. (B) Axial MRI in postnatal scan of infant with hypoplastic left heart. The small hypertrophied left ventricle can be seen posterior to the dilated and apex-forming right ventricle (abbreviations as in A). (C, D) Three-dimensional MRI reconstructions of patient with hypoplastic left heart following Norwood stage I reconstruction with Sano modification. Images are colour coded, with white depicting the right ventricle, green the right ventricle to pulmonary artery conduit and branch pulmonary arteries, and red the aortic arch reconstruction and descending aorta. (C) View from the left side; note diminutive ascending aorta adjacent to much larger pulmonary valve incorporated into aortic arch reconstruction. (D) View from the left side; note anteriorly placed right ventricle to pulmonary artery conduit supplying branch pulmonary arteries. H, head; A, anterior; L, left; F, foot; P, posterior.

are dilated with enlargement of the arterial duct. The pulmonary venous return is usually to the left atrium, but in association with an intact atrial septum (in about 10% of cases) there may be anomalous pulmonary venous return. The aortic valve is small and either atretic or severely stenotic. There is almost invariably aortic coarctation.

Pathophysiology (Fig. 19.11)

HLHS is a good example of the remarkable extent of adaptability in the fetal circulation. Cerebral and coronary circulation is maintained retrogradely round the aortic arch via the arterial duct. There are reports of congenital structural abnormalities in the brain in about

30% of patients [89]. Postnatally, the systemic circulation remains dependent on continued patency of the arterial duct. The pulmonary venous return must enter the right ventricle (usually through the atrial septum) in order to maintain the systemic circulation. An imperforate or restrictive atrial septum results in early pulmonary congestion. The proportion of flow to the pulmonary and systemic circulations is dependent on the balance between the systemic and pulmonary vascular resistances. Assuming the duct remains patent, as pulmonary vascular resistance falls postnatally, there will be progressive pulmonary over-circulation and decreased systemic perfusion with acidosis.

Diagnosis

CLINICAL

A significant number of infants with this condition will have had the diagnosis made prenatally following fetal echocardiography. This provides the opportunity to optimize postnatal management and limit complications. Therefore, the clinical presentation described below reflects the situation when the diagnosis has not been anticipated prenatally. Immediately postnatally, most babies with this condition are well and relatively asymptomatic, unless there is an intact or very restrictive atrial septum. Symptoms start following closure of the arterial duct. Signs of cardiac failure develop rapidly, with increasing cyanosis, acidaemia and respiratory distress. Prompt respiratory support and use of prostaglandin is needed to re-establish ductal patency on which such infants depend. Physical signs in the newborn infant include:

- tachypnoea with dyspnoea;
- cyanosis with absent lower limb pulses and pallor;
- hyperdynamic precordium;
- normal first heart sound, single second heart sound and a gallop rhythm;
- ejection systolic murmur (usually soft);
- hepatomegaly.

CHEST RADIOGRAPH

- Laevocardia with cardiomegaly.
- Large right atrial shadow.
- Pulmonary venous congestion/pulmonary oedema.

ECG

- Rightward QRS axis with conspicuous right ventricular hypertrophy.
- Frequently evidence of myocardial ischaemia.

ECHOCARDIOGRAPHY

The echocardiographic examination should document the marked variability of this condition, from a left ventricle that is virtually non-existent in some cases to one associated with a reasonable cavity size, with or without severe endocardial fibroelastosis. Having confirmed HLHS, the echocardiographic examination should be tailored systematically towards identification of those features that will impact on the likelihood of surgical survival:

- pulmonary venous return;
- assessment of the size and flow characteristics of any atrial communication;
- evaluation of tricuspid valve function and incompetence;
- interrogation of the pulmonary valve, excluding significant stenosis or incompetence;
- careful measurement of the dimensions of the ascending aorta and aortic arch;
- flow characteristics through the arterial duct;
- establishing whether aortic coarctation is present;
- assessment of ventricular function.

CARDIAC CATHETERIZATION AND ANGIOGRAPHY

Catheterization has little or no diagnostic role in the initial management of such infants who are often critically unwell. On occasion, interventional catheterization has been used as therapeutic modality for stage I palliation of this condition.

Natural history

Despite theoretical advantages, improved survival after prenatal diagnosis has been difficult to demonstrate. Without intervention, neonates die when the arterial duct usually closes, within the first week of life. The advent of prostaglandin infusion and the subsequent development of staged palliative procedures for surgical management has dramatically improved the outlook. Prenatal diagnosis offers the opportunity for parents to opt for termination of pregnancy.

Management

Management of HLHS can involve staged surgery (Norwood approach) or transplantation or, alternatively, compassionate care if no active intervention is agreed. A few centres consider transplantation as first-line treatment, but lack of donors in this age group (particularly in Europe) limits this approach. Surgical palliation was pioneered by Norwood and colleagues and has subsequently been adopted widely with improving survival in many centres [90]. Initial surgery is performed in the neonatal period and requires transection of the pulmonary trunk, which is anastomosed to the hypoplastic aorta, which in turn may be augmented with a homograft patch. Supply to the detached pulmonary arteries is

achieved through a modified right-sided Blalock–Taussig shunt or more recently by placement of a restrictive right ventricle to pulmonary artery conduit (Fig. 19.12) [91]. This first stage is followed by a superior cavopulmonary anastomosis at 4–6 months and completion of the cavopulmonary circulation with an inferior cavopulmonary connection at around 2–3 years of age. Survival for stage I is now 80–90% in most specialist centres and is usually higher for the second and third stages. There is continuing attrition of patients between stages and following the third stage. Furthermore, evidence would suggest that neurological outcome in the majority of patients treated with the Norwood protocol is not normal [36]. It is possible that transplantation as a treatment modality for HLHS may have less associated neurological disability, but there is concern about the emergence of long-term complications, especially early coronary artery disease.

Pulmonary valve stenosis

This is a common isolated cardiac abnormality representing almost 10% of all congenital cardiovascular malformations. However, it may also occur in association with a range of other complex defects.

Morphology

The most typical finding is fusion of the commissures of a trileaflet valve, associated with a small valve orifice, which may be central or eccentric. The degree of commissural fusion varies from severe, with presentation in the neonatal period or early infancy, to mild, which may result in minimal clinical sequelae other than an asymptomatic cardiac murmur. Right ventricular hypertrophy and frequently tricuspid incompetence are the consequences of severe obstruction. In Noonan's syndrome there is a characteristic pulmonary valve abnormality with little commissural fusion but thickened dysplastic valve cusps. Isolated supravalvar pulmonary stenosis and branch pulmonary artery stenoses may occur. Frequently, this is associated with an identifiable genetic syndrome such as Noonan's syndrome, Williams' syndrome, Alagille's syndrome and 22q11 deletion.

Pathophysiology

The haemodynamic and clinical consequences of pulmonary stenosis depend mainly on the severity of the obstruction. When severe and presenting in the neonatal period, there is severe right ventricular hypertrophy with cavity obliteration. The oval foramen remains patent and decreased right ventricular compliance with increased right ventricular systolic pressures results in a significant right-to-left shunt at atrial level. In very severe stenosis, the pulmonary circulation may be duct dependent postnatally. When the valve is only moderately narrowed, there is usually continued valve growth through childhood and early infancy with a degree of narrowing remaining constant or even improving with age.

Diagnosis

CLINICAL

In its most severe form, cyanosis will be evident in the immediate postnatal period, with profound cyanosis developing following ductal closure. Such infants require urgent evaluation and treatment. Physical examination will confirm cyanosis and there may be associated respiratory distress. The first heart sound is normal and there is a single second heart sound. Frequently, there is a pansystolic murmur due to associated tricuspid regurgitation.

In the older child with less severe stenosis, the predominant finding is a systolic ejection murmur loudest at the upper left sternal edge. First and second heart sounds are normal and there may be an associated ejection click. Occasionally, a thrill may be evident at the upper left sternal edge or in the suprasternal notch.

CHEST RADIOGRAPH

In severe neonatal pulmonary stenosis, there may be marked cardiac enlargement with a very prominent right atrial shadow. There is usually associated pulmonary oligaemia. In infants and children, the chest radiograph is usually normal but it may be possible to identify prominent pulmonary artery shadow due to dilatation of the main pulmonary artery.

ECG

The right ventricular forces in the anterior precordial leads tend to correlate well with a degree of obstruction. In severe stenosis, there is associated right axis deviation and right atrial hypertrophy.

ECHOCARDIOGRAPHY

Accurate delineation of the severity of the lesion is performed with echocardiography. Doppler studies are used in assessment of the severity of stenosis but can be misleading in the presence of very severe stenosis and continued ductal patency. Echocardiography should assess the atrial septum for the presence of an atrial communication as well as evaluate the size of the tricuspid valve annulus, the presence of tricuspid valve regurgitation and the size of the right ventricular cavity. In less severe cases, the Doppler-derived pulmonary valve gradient is used to monitor severity in those patients for whom

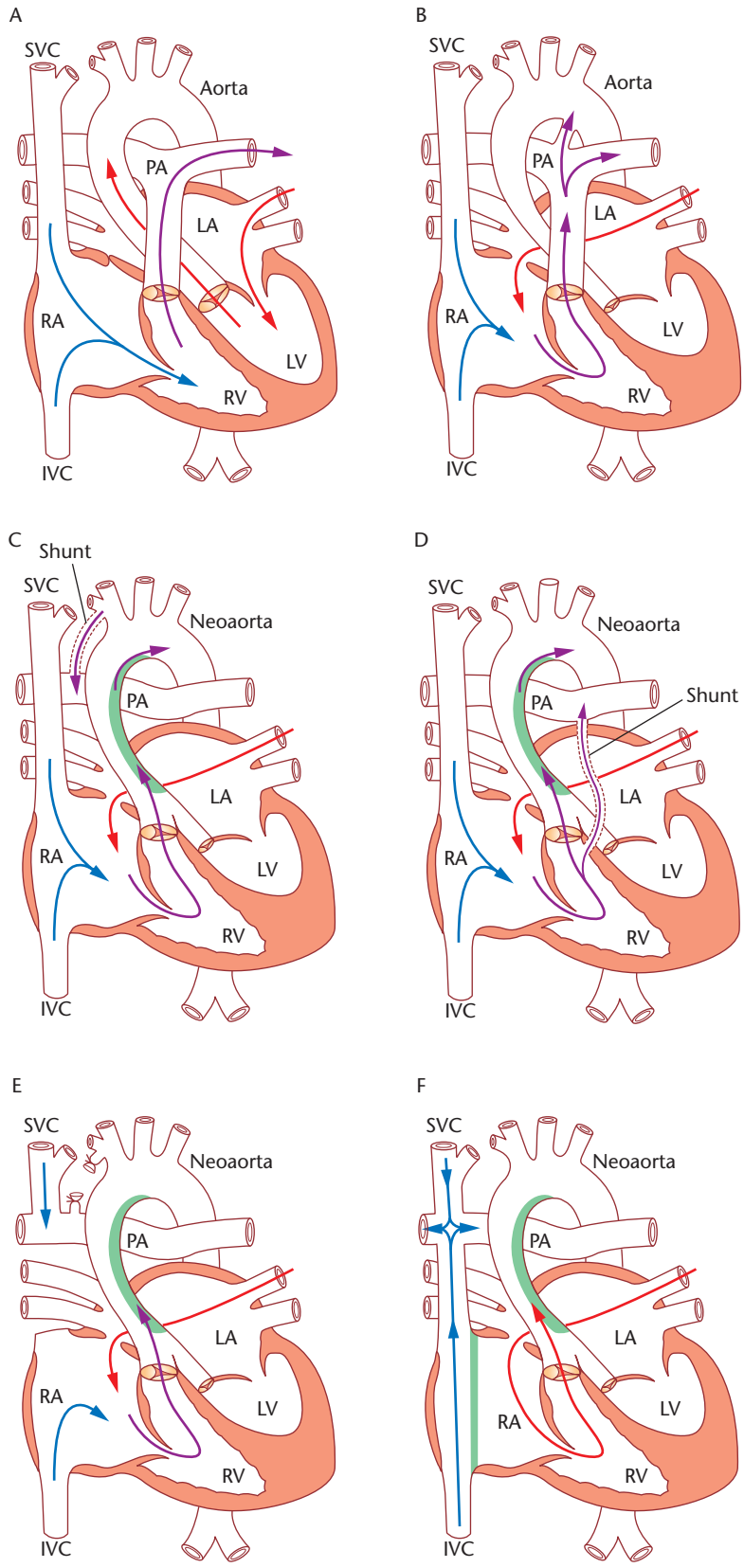

Figure 19.12 Norwood staged approach for hypoplastic left heart syndrome: (A) normal cardiac anatomy; (B) hypoplastic left heart syndrome; (C) Norwood with modified Blalock–Taussig shunt; (D) Norwood with right ventricle to pulmonary artery shunt; (E) stage II procedure; (F) Fontan procedure. SVC, superior vena cava; IVC, inferior vena cava; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; PA, pulmonary artery.

medical surveillance rather than active intervention is indicated.

CARDIAC CATHETERIZATION AND ANGIOGRAPHY

This technique is no longer a diagnostic test in this condition but plays a major therapeutic role (see below).

Natural history

Neonates or infants may present with critical pulmonary stenosis and require urgent intervention. Outcome depends on the size and function of the right ventricle. The natural history of patients with mild and moderate pulmonary stenosis is much better and most are asymptomatic. Progression during childhood is rare and 25-year survival approached the normal population in the collaborative US study [92]. Obstruction may progress at valvar level and subvalvar narrowing with right ventricular hypertrophy may also develop.

There are few data for prognosis of pulmonary artery stenosis. Interestingly, in Williams' syndrome, pulmonary artery narrowing tends to improve with time, in contrast to supravalvar aortic stenosis which may also be present.

Management

This has been revolutionized by balloon dilatation, which is now clearly the treatment of choice and which obviates the need for surgery in the majority of patients. In neonates with critical stenosis, patency of the arterial duct should be maintained with prostaglandin infusion prior to intervention. There is some debate about measures of right ventricular outflow tract gradient (assessed by echo Doppler) that require intervention. In general, most cardiologists would undertake an interventional catheter if the gradient is in excess of 40 mmHg. The results are excellent unless the valve is very dysplastic (as in some cases of Noonan's syndrome). Repeat valvotomy may be required in some cases. Subvalvar obstruction will often regress over months after valvar pulmonary stenosis has been relieved.

Surgery is limited to patients who have failed to respond adequately to interventional catheterization and consists of pulmonary valvotomy or valve excision. In adults, surgery is occasionally required if the valve is calcified or if multiple levels of obstruction are present. Long-term results are excellent, although follow-up is required for pulmonary regurgitation. Infective endocarditis prophylaxis is necessary.

Peripheral pulmonary stenosis may also be amenable to balloon dilatation. Results may be disappointing due to recoil/restenosis and multiple sites of obstruction are often present. In the older patient, stent implantation can produce dramatic improvement even in arteries that would be inaccessible to the surgeon.

Pulmonary atresia with intact ventricular septum

This severe condition accounts for 2–3% of all congenital malformations. There is right ventricular outflow obstruction, and a spectrum of morphological abnormalities of the right ventricle is an intrinsic part of the defect.

Morphology

There is usually cardiac enlargement that varies from mild to massive, with huge enlargement of the right atrium, which may occupy much of the chest, as in hearts with Ebstein's malformation. There is almost always an interatrial communication. The tricuspid valve is frequently small and may be dysplastic. The right ventricular cavity varies in size from diminutive to almost normal due to a variable degree of hypertrophy of its component parts. The extent of atresia of the pulmonary outflow tract varies from valvar alone to more severe forms where the atresia extends into the right ventricular infundibulum. Abnormalities of the coronary arteries, involving fistulae between the right ventricular cavity and the coronary circulation, are common and occasionally may influence management. These abnormal connections may result in myocardial ischaemia, leading to a 'right ventricular coronary dependent circulation' [93]. The pulmonary arteries themselves are usually confluent and supply all the pulmonary segments (unlike those in tetralogy of Fallot with pulmonary atresia).

Pathophysiology

As the right ventricular outflow valve is imperforate, systemic venous return will enter the left atrium through the oval foramen. The maintenance of postnatal pulmonary blood flow therefore relies on continued patency of the arterial duct. Duct closure results in extreme hypoxia, cyanosis, acidosis and rapid demise without early intervention.

Diagnosis

CLINICAL

Clinical cyanosis is evident in the immediate newborn period and becomes severe as the duct closes. Cardiac findings largely depend on tricuspid valve size and function, which relate to right ventricular morphology. When there is significant tricuspid regurgitation with massive cardiomegaly, the precordium will be hyperactive. In contrast, if tricuspid regurgitation is mild, cardiovascular

examination may be remarkably normal. Physical signs include:

- cyanosis;
- mild to severe respiratory distress, depending on the extent of cardiac enlargement;
- normal first heart sound, single second heart sound;
- pansystolic murmur when there is severe tricuspid regurgitation;
- hepatomegaly.

CHEST RADIOGRAPH

There is laevocardia with variable degrees of cardiac enlargement, depending on the severity of tricuspid regurgitation. With severe cardiomegaly, there may be pulmonary hypoplasia and pulmonary oligaemia is evident.

ECG

There is a leftward QRS axis and decreased right ventricular forces. Evidence of right atrial enlargement, with very large P waves, is common.

ECHOCARDIOGRAM

Cross-sectional echocardiography is able to identify this condition and a systematic approach should include assessment of:

- size of the atrial communication;
- size of the tricuspid valve;
- severity of tricuspid regurgitation and right ventricle to right atrial pressure drop (by Doppler);
- individual components of the right ventricle including inlet, trabecular and outlet portions and their size and function;
- size of pulmonary valve annulus, main pulmonary artery and branches;
- patency of the arterial duct.

However, echocardiography is poor for assessment of right ventricular to coronary artery communications.

Natural history

Surgery is always required in the neonatal period to establish a secure source of pulmonary blood flow.

Management

Patients should be treated with prostaglandin infusion to maintain patency of the arterial duct. The surgical approach depends on the morphology of the right ventricle, as well as on associated abnormalities of the coronary circulation. The ventricle can be considered a tripartite structure (inlet, trabecular portion, outlet) for decision-making purposes. In patients with an inlet only and hypoplastic tricuspid valve, there is no hope of creating a biventricular circulation. These patients are managed by insertion of a systemic to pulmonary shunt and balloon atrial septostomy, if the interatrial communication is restrictive. In those with a tripartite right ventricle and an adequate tricuspid valve dimension, an interventional catheter (radiofrequency perforation) or operation should be performed to open the right ventricular outflow tract. In patients with a moderately small two-portion right ventricle, the prospects of an eventual biventricular circulation depend on the growth of the right ventricle. Evidence suggests that opening the right ventricular outflow tract encourages right ventricular and tricuspid valve growth, with reduction in right ventricular hypertrophy. However, the small right ventricle is often not able to support the pulmonary circulation early after surgery and a systemic to pulmonary shunt may also be required. The long-term outcome of all approaches has been disappointing and difficult to predict. Definitive treatment ranges from a Fontan for those with persistent right ventricular cavity hypoplasia to a biventricular repair if the right ventricle is adequate (often after multiple catheter/surgical interventions to relieve right ventricular outflow tract obstruction, close the ASD and insert a competent pulmonary valve). If the right ventricle grows but remains too small to support the entire systemic venous return, a hybrid $1^1/_2$ ventricle repair can be considered. Optimal management of abnormalities of the coronary circulation is also unclear [92].

Tetralogy of Fallot

Morphology

Tetralogy of Fallot (TOF) constitutes 7% of all congenital cardiac malformations and consists of right ventricular outflow obstruction, a subaortic VSD with overriding aorta, and right ventricular hypertrophy. These morphological features arise from anterior and cephalad deviation of the infundibular septum, which results in muscular outflow tract obstruction. This may be aggravated by a small pulmonary valve ring and valvar pulmonary stenosis. Right ventricular hypertrophy reflects the myocardial response to right ventricular hypertension. The VSD is typically large and perimembranous but may be a muscular outlet defect. The degree of aortic override varies, and in some cases the majority of the aorta is committed to the right ventricle (double outlet right ventricle). Associated abnormalities of the origin and calibre of the pulmonary arteries are common, and the right or left pulmonary artery may originate from the arterial duct or from the aorta. Abnormal coronary artery distribution (such as origin of the left anterior artery from

the right coronary system in approximately 5%) may influence the timing and approach of surgical repair. In its most severe form, TOF is associated with atresia of the right ventricular outflow tract, and these patients have marked variations in the arterial blood supply to the lungs. In the most favourable situation, the pulmonary arteries are central and confluent, and supply is derived from the arterial duct. At the other end of the spectrum, the pulmonary arterial supply is derived entirely from aorto-pulmonary collateral arteries, with no discernible central pulmonary arteries. In a significant proportion of cases, the pulmonary blood supply is mixed, with some lung segments being supplied by aorto-pulmonary collateral arteries whilst others are supplied by pulmonary arteries, which may or may not communicate with the aorto-pulmonary collateral arteries (see below).

Pathophysiology

Right ventricular ejection in the presence of right ventricular outflow obstruction results in shunting of blood into the ascending aorta, causing systemic arterial desaturation. Right and left ventricular pressures are equal. The degree of arterial desaturation will depend on the severity of the outflow tract obstruction, which tends to increase with time. The pulmonary blood flow may be augmented by persistent patency of the arterial duct or by coexisting aorto-pulmonary collateral arteries.

Diagnosis

CLINICAL

This depends mainly on the severity of the right ventricular outflow obstruction. A haemodynamically 'well-balanced' situation may be present and these patients may merely have an asymptomatic murmur. However, cyanosis usually becomes detectable as the right ventricular outflow obstruction gradually increases. TOF with cyanosis from birth or in early infancy may require early intervention. Hypercyanotic spells, resulting from the dynamic nature of the infundibular obstruction, may be triggered by crying or feeding and may result in syncope, convulsions and occasionally death. In contrast, some patients with minimal or mild right ventricular outflow obstruction may have a significant left-to-right shunt with no cyanosis and occasionally develop cardiac failure in infancy.

Physical signs include:

- cyanosis, polycythaemia and clubbing;
- parasternal heave due to right ventricular hypertrophy;
- ejection systolic murmur at upper left sternal edge, due to right ventricular obstruction;
- single second heart sound.

CHEST RADIOGRAPH

This typically shows:

- left-sided heart (boot-shaped);
- concave pulmonary artery segment (hollow pulmonary bay);
- pulmonary oligaemia (with cyanosis);
- right-sided aortic arch (in 25% of cases).

ECG

This is not diagnostic but shows sinus rhythm, rightward QRS axis and right ventricular hypertrophy.

ECHOCARDIOGRAPHY

This is the most important single investigation. Patients are often referred for surgery, when primary repair is planned or following systemic to pulmonary shunt, without preoperative cardiac catheterization. The important features to establish include:

- size and position of the VSD;
- severity and nature of right ventricular outflow obstruction;
- size of the main pulmonary artery, pulmonary artery branches and their confluence;
- side of the aortic arch;
- coronary artery distribution;
- identification of additional abnormalities (including ASD, additional VSD, arterial duct, aorto-pulmonary collateral arteries and persistence of the left superior caval vein).

CARDIAC CATHETERIZATION AND ANGIOGRAPHY

This is rarely required for preoperative diagnosis. The use of MRI or CT, with contrast angiography and three-dimensional reconstruction, has further reduced the need for diagnostic cardiac catheterization, even after initial palliation by a systemic to pulmonary artery shunt. Haemodynamic evaluation may occasionally be required when there is concern about pulmonary hypertension, in cases with non-confluent branch pulmonary arteries and also in patients in whom aorto-pulmonary collateral arteries have been detected. In such patients, the demonstration of central pulmonary arteries, even if small, has a major impact on management and angiography, and pulmonary venous wedge injection should be considered early in infancy. A further indication for cardiac catheterization is the evaluation of the coronary artery distribution, when this cannot be adequately detected by echocardiography.

Natural history

Treatment for TOF is surgical and it is rare to encounter the natural history in developed countries. Right ventric-

ular outflow obstruction is progressive and results in increasing cyanosis. There may also be increasingly frequent cyanotic spells, which may be fatal. Without surgery, only 10% of patients are alive by 25 years, although prolonged survival is possible. The natural history is further complicated by the risk of infective endocarditis and cerebral abscess as well as the systemic complications of cyanosis with polycythaemia (see above).

Management

Hypercyanotic spells should be treated by placing the child in the knee–elbow position, establishing intravenous access and administering oxygen. Morphine sulphate (0.1 mg/kg) can be helpful but the main treatment is intravenous beta-blocker (propranolol 0.1 mg/kg). Acidosis should be corrected with sodium bicarbonate. Propranolol may be given as prophylaxis against further spells, prior to surgery. Palliation, by creation of a surgical systemic to pulmonary shunt, ushered in the era of surgical treatment of congenital cardiac malformations. TOF has been corrected since the 1950s (closure of VSD and relief of right ventricular outflow obstruction) [94]. The important decision for each case is whether a prior palliative shunt is required. As the results of neonatal and infant cardiac surgery have improved, the trend has been towards earlier primary repair, reserving palliation for cases with complicating features. These include hypoplastic pulmonary arteries, anomalous coronary arteries and other associated lesions. Units differ in their approach [95]. Many routinely perform primary repair in infants presenting at > 3 months of age. Operative mortality is now very low and long-term survival is excellent, approaching that of the general population in favourable subgroups [96]. The most important issue in long-term care is now recognized to be the impact of pulmonary regurgitation. This is very common and is well tolerated in most patients for decades. In others, however, it leads to progressive right ventricular dilatation, right heart failure, tricuspid regurgitation and supraventricular arrhythmia [97]. Pulmonary valve replacement is required in these circumstances and produces significant clinical benefits in most patients [98]. However, right ventricular function does not appear to improve in all patients and hence optimal timing of pulmonary valve implantation to preserve cardiac function is a key issue for ongoing research [99]. Evidence is accumulating that earlier treatment will be more beneficial and the exciting new option of percutaneous pulmonary valve implantation may influence management (Fig. 19.13).

Sudden unexpected death is a rare event during long-term follow-up [100]. Non-sustained ventricular arrhythmia is very common but not an indicator of risk, so that routine antiarrhythmic therapy is not indicated for asymptomatic patients [101]. Recent work linking pulmonary regurgitation, cardiomegaly and late ventricular arrhythmia with QRS duration > 180 ms on the surface ECG may aid risk stratification [101,102] (Fig. 19.14). Symptomatic individuals with syncope or sustained arrhythmia require prompt management, which may include electrophysiological testing, correction of residual haemodynamic lesion and an implantable defibrillator. Supraventricular arrhythmia (atrial flutter or fibrillation) is often a marker of cardiac decompensation and these patients require full haemodynamic and electrophysiological review. With increasing follow-up, late aortic regurgitation is observed [103].

Management of patients with TOF and pulmonary atresia is one of the biggest challenges in congenital heart disease. Their pulmonary blood supply is highly variable and this determines the presentation, natural history, management and outcomes (see Fig. 19.5). Neonates with pulmonary atresia and duct-dependent pulmonary blood supply require prostaglandin infusion, followed by urgent surgery to survive. Others may have increased pulmonary blood supply as a result of multiple major aortic pulmonary collateral arteries (MAPCAs) and present with heart failure. A third group with a 'balanced' pulmonary supply can remain well without any treatment for many years [104]. They develop pulmonary vascular obstructive disease in the unprotected pulmonary segments supplied by vessels arising from the aorta.

Management strategies differ greatly between institutions and have evolved rapidly in the last few years. Generalizations are therefore difficult. If there is a single source of pulmonary blood flow supplying adequate pulmonary arteries to the majority of bronchopulmonary segments, a complete repair as a single stage can be contemplated. The timing will depend on whether a right ventricle to pulmonary artery conduit is required to establish anterograde flow to the pulmonary artery (usually the case). If central pulmonary arteries are diminutive or absent, many consider such patients as uncorrectable and treatment concentrates on optimizing the pulmonary circulation by surgery or interventional catheterization as the clinical condition dictates. Other patients have a small central pulmonary artery, supplying a variable proportion of pulmonary segments, supplemented by an almost infinite variety of MAPCAs. Prospects for repair depend on establishing a single source of pulmonary blood flow ('unifocalization') which can then be connected to the right ventricle, together with closure of the VSD. Multiple-stage palliative procedures may be required to achieve this result and some patients may never become candidates for repair. Long-term results for these surgical protocols are only beginning to appear

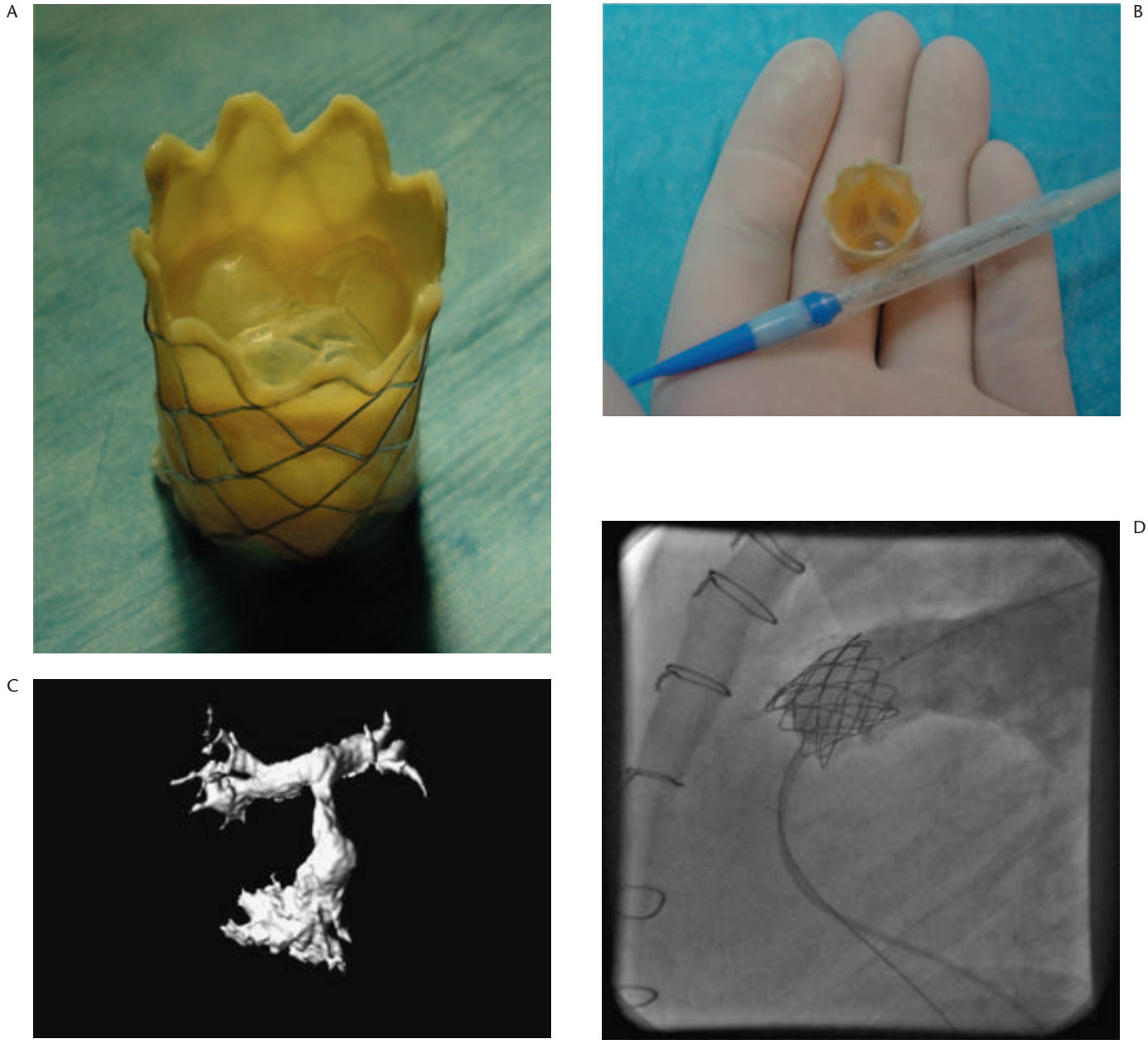

Figure 19.13 (A) Stent-mounted tissue valve used for percutaneous pulmonary valve insertion. (B) Delivery catheter with covered balloon developed for percutaneous pulmonary valve insertion. (C) Three-dimensional MRI reconstruction of right ventricular outflow tract and branch pulmonary arteries for improved visualization of ideal placement of stent-mounted valve. (D) Lateral angiogram following placement of stent-mounted valve confirming good relief of obstruction and valve competency.

[105]. Although encouraging, patients may be left with right ventricular hypertension that is likely to limit life expectancy and quality of life. Right ventricle to pulmonary artery conduits will deteriorate with time and require further surgical replacement or percutaneous pulmonary valve insertion.

Ebstein's malformation

This is characterized by downward displacement of the tricuspid valve into the right ventricle. It is an uncommon disorder, accounting for 0.5% of all congenital cardiovascular malformations in live-born infants, but is

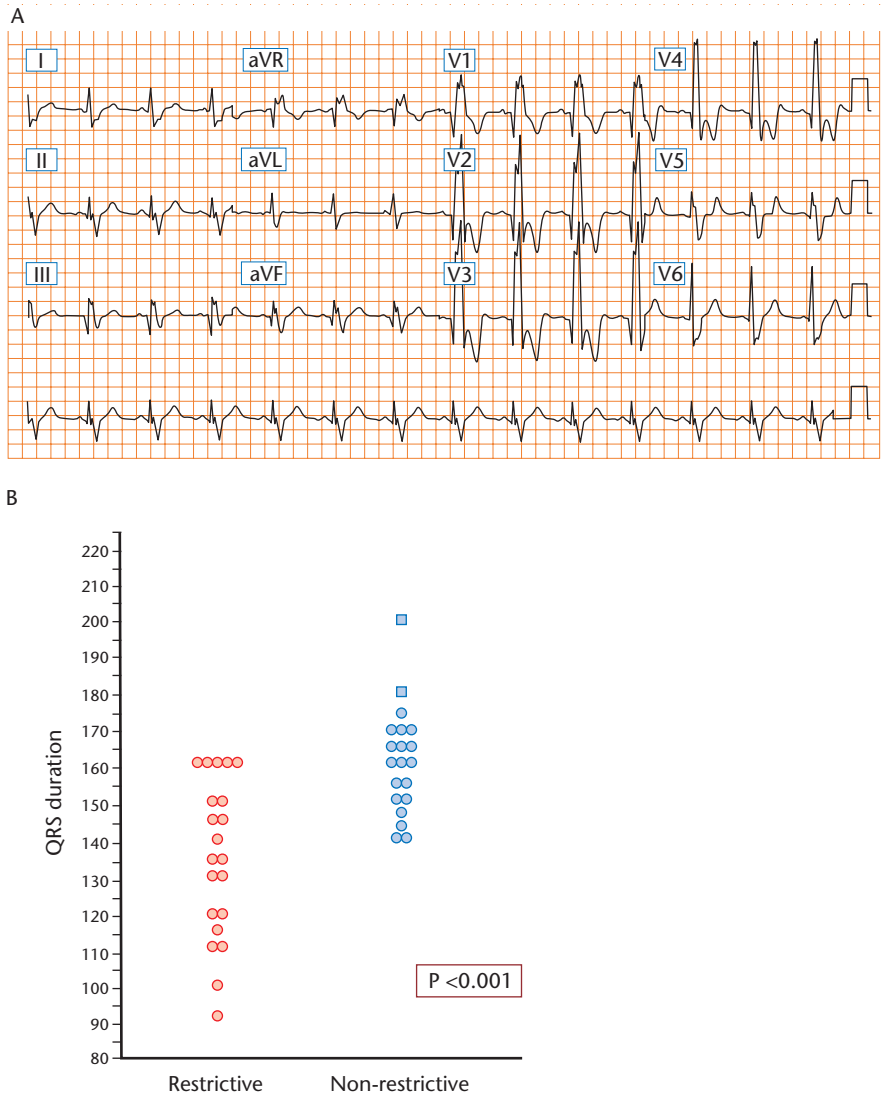

Figure 19.14 (A) 12-lead ECG in adult patient following surgical repair of tetralogy of Fallot demonstrating right bundle branch block pattern together with prolonged QRS duration measuring > 180 ms. (B) Comparison of QRS duration in patients in whom there was restrictive and non-restrictive physiology following surgical repair of tetralogy of Fallot. QRS duration > 180 ms predicted a greater risk of sudden-onset ventricular tachycardia. Reproduced with permission from Gatzoulis *et al*. [102].

disproportionately represented in adults. The reported association between Ebstein's malformation and maternal lithium ingestion is not borne out in most studies [10].

Morphology

Most hearts with typical Ebstein's malformation will have laevocardia and concordant atrioventricular and ventriculo-arterial connections. Ebstein's malformation of the tricuspid valve has also been described in association with congenitally corrected transposition of the great arteries (TGA). The degree of displacement of the tricuspid valve into the right ventricular cavity varies from minimal to very severe. The findings are further complicated by dysplasia of the valve and abnormal attachments of the leaflets. Because of the abnormally situated tricuspid valve orifice, a portion of the right ventricle lies between the true atrioventricular valve ring and the origin of the valve, in continuity with the right atrium. This proximal portion of the right ventricle is described as 'atrialized' and leaves a small distal functional right ventricle. The most commonly associated cardiac abnormalities include varying degrees of right ventricular outflow obstruction, ASD and less commonly VSD.

Pathophysiology

Ebstein's malformation has an extremely variable course depending on the degree of abnormality of the tricuspid valve apparatus and the associated cardiac abnormalities [106] (Fig. 19.15). If the deformity of the tricuspid valve is severe, intrauterine death may result or neonates may present with profound congestive cardiac failure and cyanosis. The cardiac malformation may be compounded

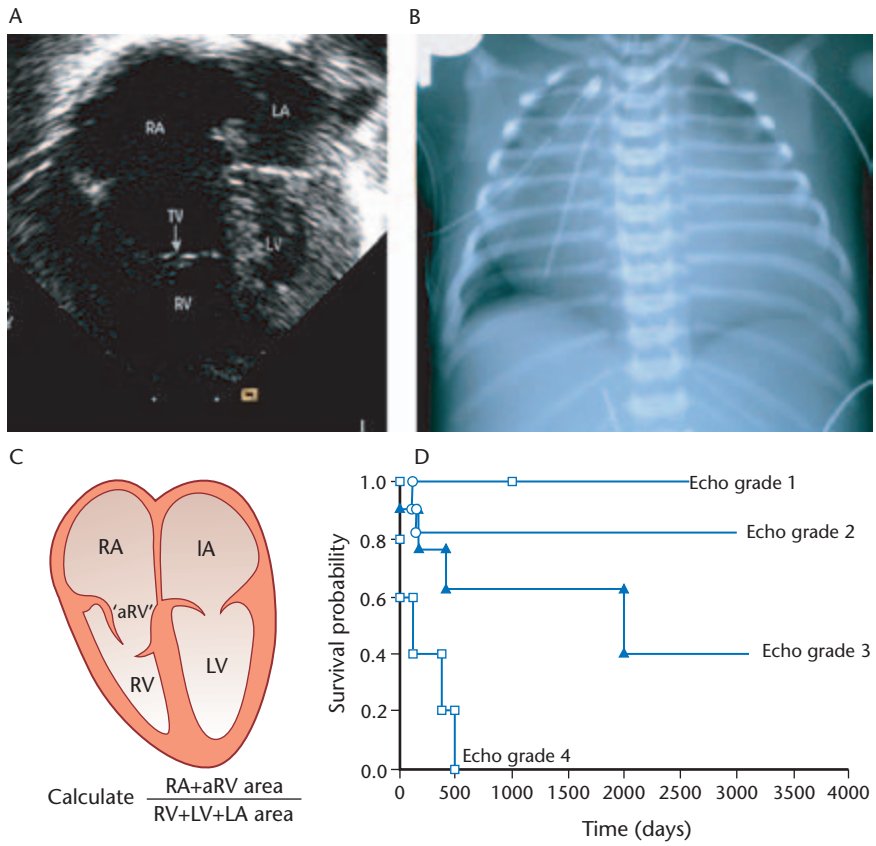

Figure 19.15 Features of Ebstein's malformation. (A) Apical view from transthoracic echocardiogram demonstrating apical displacement of tricuspid valve with large right atrium and atrialized component of right ventricle. Functional right ventricular size is small. There is moderate right heart dilatation. (B) Severe Ebstein's anomaly in the newborn period demonstrating massive cardiomegaly in a ventilated patient due to severe tricuspid regurgitation and massive right atrial enlargement. This is associated with severe pulmonary hypoplasia. (C) Grading of the severity of Ebstein's anomaly as a measure of prognosis using a ratio of right atrial size to the size of the other cardiac chambers at end diastole. Grading used to define increasing severity: grade I, < 0.5; grade II, 0.5–0.99; grade III, 1–1.49; grade IV, > 1.5. (D) Survival probability of patients with Ebstein's anomaly according to previous grading system. Reproduced with permission from Celemajer *et al*. Outcome in neonates with Ebstein's anomaly. *J Am Coll Cardiol* 1992; **19**: 1041–1046.

by respiratory problems as a result of pulmonary hypoplasia due to massive cardiomegaly. Survival is particularly poor in the presence of pulmonary stenosis or atresia. Presentation in childhood with palpitation, a murmur or cyanosis is associated with a better outcome, with an actuarial survival of 85% at 10 years. Patients presenting in adolescence or adult life generally have mild symptoms, are acyanotic and have a good prognosis. Arrhythmia (atrial flutter or fibrillation) is the most common presenting feature and is often, but not always, associated with pre-excitation. This may be difficult to treat medically or by ablation and may occasionally precipitate heart failure in a previously well patient. The true natural history is difficult to assess because of selection bias in series collected before the introduction of echocardiography, which can now pick up the problem much earlier. It may also be difficult sometimes to separate Ebstein's malformation from other forms of tricuspid valve dysplasia.

Diagnosis

CLINICAL

In severe disease, neonatal heart failure, often with severe cyanosis, occurs. Physical signs include:

- cyanosis with tachycardia and tachypnoea;
- an overactive precordium;
- first and second heart sounds are usually normal, but there is frequently an audible third and fourth heart sound;
- pansystolic murmur loudest at the lower left sternal edge is present, due to tricuspid regurgitation;
- there may be an ejection murmur due to right ventricular outflow obstruction.

In milder cases, there may be few manifestations other than variable exertional dyspnoea, fatigue and cyanosis during childhood. In such cases, physical findings may include widely split first and second heart sounds with prominent third and fourth sounds, so that auscultation has an almost rhythmical quality. There is frequently a pansystolic murmur at the lower left sternal edge.

CHEST RADIOGRAPH

- Babies presenting in the newborn period will almost always have cardiomegaly, which may be massive.
- Pulmonary hypoplasia with pulmonary oligaemia.
- In milder forms, the only finding may be mild to moderate cardiomegaly.

ECG

Most frequently, there is a low-voltage QRS complex pattern with a right bundle branch block morphology and prolonged PR interval. Right atrial enlargement

is suggested by tall peaked T waves. Supraventricular arrhythmias may occur in the neonatal period but are more common in older patients. There may be evidence of ventricular pre-excitation.

ECHOCARDIOGRAPHY

This clearly defines the abnormality, but there are specific features that need detailed assessment. These include:

- accurate evaluation of the tricuspid valve leaflets, their attachments and the severity of regurgitation;
- the integrity of the atrial septum;
- the integrity of the ventricular septum;
- estimation of the size of the right ventricle;
- patency and size of the right ventricular outflow and pulmonary artery branches;
- patency of the arterial duct;
- exclusion of associated left-sided lesions.

CARDIAC CATHETERIZATION AND ANGIOGRAPHY

There is no indication for diagnostic cardiac catheterization in patients with Ebstein's malformation.

Management

Treatment of the critically ill neonate involves prostaglandin infusion to maintain patency of the arterial duct and the use of pulmonary vasodilators, including prostacyclin and nitric oxide. Many babies improve spontaneously as the pulmonary vascular resistance falls, but intensive support may be required for the first few days. Most older children, adolescents and adults are asymptomatic and can be managed conservatively. Arrhythmias are notoriously difficult to manage by antiarrhythmic drugs or radiofrequency ablation, as patients have distorted tricuspid valve anatomy, a dilated right atrium and often multiple accessory pathways. Heart failure may be treated with diuretics or afterload reducers, if there is left ventricular dysfunction [107].

In the newborn period, a systemic to pulmonary shunt is indicated for cyanosis and right ventricular outflow obstruction and permits consideration of more definitive surgery at a later date. In the older child and adult, surgery should be considered if there is progressive functional decline, increasing cyanosis, right heart failure or paradoxical emboli. Selection of cases remains difficult, however. Results are poor in 'end-stage' patients and there is no evidence that surgery reduces the risk of late sudden death. As a result, most units reserve surgery for symptomatic cases.

A superior cavopulmonary anastomosis and Fontan operation has been performed in cases where the right ventricle is not considered adequate to sustain the cardiac output. Occasionally, an ASD with left-to-right shunt can be closed as an isolated procedure. In most cases, surgery has been directed at reconstruction or replacement of the tricuspid valve apparatus, often with plication/resection of the right atrial wall. Tricuspid valve reconstruction has been performed by a variety of approaches and results have been good in selected patients at expert centres [108]. Most patients have improved functional status and a competent tricuspid valve, although late tachyarrhythmias may remain a problem [109]. However, the long-term fate of survivors is still unknown and lifelong follow-up is required for both operated and unoperated cases.

Total anomalous pulmonary venous connection

Total anomalous pulmonary venous connection (TAPVC) accounts for approximately 2% of all congenital cardiac malformations in live births.

Morphology (Fig. 19.16)

Most commonly, the pulmonary veins draining from the lungs join a confluence or chamber behind the left atrium. Arising from this confluence, one or more primitive vessels persist and drain pulmonary venous blood into a systemic vein or directly into the atrium. Persistence of the left cardinal vein drains blood to the innominate vein. Drainage to the right cardinal vein is to the superior caval vein, azygos vein or directly to the right atrium. This type of anomalous pulmonary venous drainage is described as 'supracardiac' and may not be

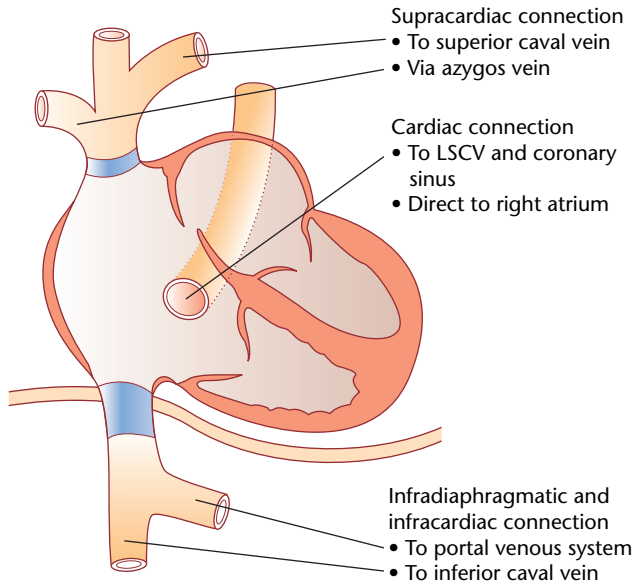

Figure 19.16 Schematic representation of the potential sites of anomalous pulmonary venous drainage in the heart.

obstructed. Flow may also be directed from the confluence into the coronary sinus, producing 'cardiac' TAPVC. Finally, there may be persistence of a descending channel that passes beneath the diaphragm and enters the portal system ('infradiaphragmatic' TAPVC), and this type is almost always obstructed. There is always an atrial communication present, which may rarely become restrictive postnatally. Anomalous pulmonary venous drainage may occur in association with right atrial isomerism, in the context of complex cardiac abnormalities and the pattern of pulmonary venous drainage is different.

Pathophysiology

In TAPVC, both systemic and pulmonary venous return enter the right atrium and some of the mixed blood passes across the atrial foramen into the left side of the heart. In obstructed TAPVC, the increased pulmonary blood flow postnatally causes marked pulmonary venous congestion and increased pulmonary vascular resistance. In the absence of ductal patency, right ventricular systolic pressure becomes suprasystemic and the right ventricle fails. If the duct remains patent, there is profound cyanosis with right-to-left flow across the arterial duct. If there is no obstruction to pulmonary venous return, there is a large left-to-right shunt with features similar to a large ASD associated with mild to moderate cyanosis.

Diagnosis

CLINICAL

Obstructed TAPVD presents in the neonatal period as a medical emergency with profound respiratory distress, often requiring support associated with severe hypoxaemia. Cardiovascular findings are unimpressive, with a normal first heart sound, a single loud second heart sound, and there are frequently no murmurs.

When unobstructed, the features are suggestive of a large ASD associated with cyanosis. Patients are tachypnoeic with a normal first heart sound, a widely split second heart sound and a pulmonary systolic murmur loudest at the upper left sternal edge. There is usually an associated right ventricular heave.

CHEST RADIOGRAPH

In obstructed TAPVC, the heart is of normal size or small, with diffuse shadowing through both lung fields due to pulmonary venous congestion. This may be confused with lung disease.

In unobstructed TAPVC, there is cardiomegaly with pulmonary plethora. In supracardiac TAPVC there may be a left-sided vertical vein shadow and a prominent superior caval vein, producing the 'snowman' appearance.

ECG

There are no specific findings but right ventricular hypertrophy with right axis deviation is almost universal.

ECHOCARDIOGRAPHY

TAPVC as an isolated abnormality can be accurately diagnosed on cross-sectional echocardiography and, with patience and multiple views, it is possible to confirm the site of drainage for all four pulmonary veins in almost all cases. A clinical index of suspicion needs to be maintained to ensure that this diagnosis is not overlooked in the critically ill neonate. Obstructed infracardiac TAPVC can be diagnosed by the presence of prominent and dilated veins within the hepatic system, as well as by a descending channel flowing from the heart and traversing the diaphragm to enter the portal system (often adjacent to the inferior caval vein). In the supracardiac type, demonstration of an ascending channel to join the innominate or superior caval vein is associated with dilatation of the superior caval vein and prominent venous return into the right atrium from the superior caval vein. Flow at atrial level is exclusively right to left. In most cases, it is also possible to identify the presence of a pulmonary venous confluence, into which the pulmonary veins drain, with clear separation from the left atrium. There is almost always marked right to left ventricular disproportion. However, the left ventricle is usually apex forming, and despite its appearance is able to support the systemic circulation. Obstructed types may be associated with features of severe pulmonary hypertension. Careful evaluation to exclude additional abnormalities is mandatory.

CARDIAC CATHETERIZATION

Echocardiography has superseded cardiac catheterization as the diagnostic technique for this condition, but cardiac catheterization may still be used for delineation of anomalous pulmonary venous drainage of mixed type, when some veins may drain to the superior caval vein and others to the innominate vein via an ascending vertical vein. The advent of MRI and CT is likely to eliminate the need for preoperative catheterization (see Fig. 19.4).

Natural history

The natural history depends on the degree of obstruction to pulmonary venous return, which is influenced by the pattern of anomalous pulmonary venous connection. Obstructed TAPVC, presenting as a cardiac emergency in the neonate, is fatal without surgery. Patients with unobstructed TAPVC also require repair within the first few months of life.

Management

The only place for medical management is for resuscitation of the critically sick neonate and balloon atrial septostomy has no role. Surgery involves cardiopulmonary bypass and creation of a wide communication between the pulmonary veins and left atrium, closure of anomalous pulmonary vein connections to the systemic circulation and usually closure of the atrial communication. Mixed forms of pulmonary venous return may be particularly challenging operations. Early results of surgery have improved dramatically, with a low incidence of recurrent pulmonary venous obstruction (unless there are intrinsic abnormalities extending into the pulmonary veins themselves). Reoperation in these circumstances carries a high risk but interventional catheterization has also not been very successful. The late results are excellent, with a very low incidence of pulmonary venous obstruction, arrhythmia and essentially normal quality of life [110].

Complete transposition of the great arteries

In complete TGA (4.4% of congenital cardiac malformations), the aorta arises from the right ventricle and the pulmonary artery from the left ventricle (ventriculoarterial discordance).

Morphology

TGA may be complicated by associated malformations (VSD or left ventricular outflow tract obstruction or both). TGA may exist in the setting of either usual or mirror-image atrial arrangement. Subtle abnormalities of the relationship between the atrioventricular valves and the shape of the ventricular septum exist in hearts with TGA, compared with normal hearts. However, the most obvious external abnormality is the relationship between the aorta and the pulmonary trunk. In the majority of cases of TGA with intact ventricular septum, the aortic root lies anterior and to the right of the pulmonary artery. However, uncommon variations do exist and become relevant when considering the arterial switch operation.

Defects in the ventricular septum in TGA have the same spectrum as those in the normal heart. Left ventricular outflow obstruction, seen most frequently in association with a VSD, is due to caudal displacement of the infundibular septum, causing subpulmonary and pulmonary stenosis. With an intact ventricular septum, left ventricular outflow obstruction may be caused by an abnormal pulmonary valve, dynamic subpulmonary outflow tract obstruction or, occasionally, abnormal mitral valve attachments. The anatomy of the coronary arteries has assumed major importance since the introduction of the arterial switch operation. The coronary arteries usually originate from the facing or posterior sinuses of the aortic valve. The most noteworthy abnormality is the presence of an intramural segment of either right or left proximal coronary artery, making coronary artery transfer during the arterial switch operation significantly more difficult [111].

Pathophysiology

In TGA, the two circulations operate in parallel, with desaturated systemic blood flow routed back to the body and saturated pulmonary venous return routed back to the lungs. With closure of the normal fetal shunts, there is no mixing within the circulation, and without early intervention profound hypoxaemia with acidosis develops rapidly. Providing the foramen remains open, mixing of blood at atrial level can achieve sufficient 'effective' pulmonary blood flow.

In patients with TGA and intact ventricular septum, cyanosis usually becomes evident soon after birth and may progress rapidly. Differential cyanosis may be evident, with lower extremities that are pinker than upper extremities due to flow from pulmonary artery to aorta through the arterial duct.

Diagnosis

CLINICAL

Physical signs include cyanosis, prominent right ventricular impulse, soft mid-systolic murmur and single second heart sound. In those with an associated VSD or large patent arterial duct, the onset of cyanosis is usually slower and less severe.

CHEST RADIOGRAPH

The classical appearances are laevocardia (but dextrocardia is recognized) with a normal or slightly increased cardiothoracic ratio, but with an 'egg on side' appearance due to the anteroposterior relationship of great arteries. Pulmonary vascular markings are usually mildly increased.

ECG

This is not helpful in diagnosis but shows sinus rhythm, rightward QRS axis and right ventricular hypertrophy.

ECHOCARDIOGRAPHY

Cross-sectional echocardiography has made the identification of TGA straightforward. Multiple views and serial images have meant that there is now little or no role for

angiography in the initial evaluation. The important echocardiographic features include:

- confirmation of atrioventricular concordance and ventriculo-arterial discordance;
- assessment of adequacy of the interatrial communication;
- assessment of any VSDs;
- exclusion of left ventricular outflow obstruction;
- confirmation of morphologically normal semilunar valves;
- evaluation of the spatial relationships of the great arteries;
- assessment of the patency of the arterial duct;
- exclusion of coarctation of the aorta;
- detailed assessment of coronary artery anatomy.

Natural history

Unless treated properly, TGA is a lethal condition and 90% of patients die within the first year of life [1]. The associated malformations affect presentation and management.

Management

Early treatment is directed towards improving mixing between the two parallel circulations to increase systemic arterial saturation. This can be achieved by maintaining patency of the arterial duct using prostaglandin infusion and/or by enlarging the intra-atrial communication by balloon atrial septostomy. This can be performed under echo guidance, which will also permit assessment of the adequacy of the resulting ASD. Definitive surgery has been performed for many years using either the Mustard or Senning operation. Both involve creation of an intra-atrial baffle to re-route the systemic and pulmonary systemic venous return to the pulmonary artery and aorta respectively [112]. Both procedures produce excellent results through childhood and adolescence and there are many adult survivors [113]. With long-term follow-up, however, a number of important late complications have emerged. These include venous pathway narrowing, loss of sinus rhythm with tachycardia and bradycardia and failure of the systemic right ventricle, together with tricuspid regurgitation [113]. The combination of atrial tachyarrhythmias, venous pathway narrowing and right ventricular dysfunction places the patient at risk of sudden death [33]. Nevertheless, risk stratification remains challenging, as is treatment for right ventricular failure with tricuspid regurgitation. ACE inhibitors have been used with questionable rationale and beta-blockers may be preferable [114]. Some patients are considered for transplantation or conversion to an arterial switch. However, this is not straightforward and the left ventricle needs to be 'retrained' by pulmonary artery banding to deal with the higher afterload of the systemic circulation. The increasing evidence of late problems after atrial redirection operations has led to the widespread adoption of the neonatal arterial switch procedure (anatomical repair) [115]. In patients with an intact ventricular septum, this should be performed within the first few weeks (ideally < 4 weeks) of life before left ventricular pressure falls and 'detraining' occurs. The early mortality is now very low and medium-term data suggest excellent survival with a much lower incidence of arrhythmia and preserved ventricular function [116]. Potential long-term problems, especially related to 'neo-aortic' regurgitation and coronary artery patency, will need careful evaluation [117,118]. For infants with TGA and a large VSD or a large arterial duct, an arterial switch operation with closure of the VSD/patent arterial duct should be performed ideally within the first 2 months of life. If there is a VSD and pulmonary stenosis, a palliative systemic to pulmonary shunt in infancy may be required followed by later repair, which often involves insertion of a right ventricle to pulmonary artery conduit (Rastelli operation) [119].

Congenitally corrected transposition of the great arteries

Congenitally corrected transposition of the great arteries (ccTGA) or atrioventricular and ventriculo-arterial discordance is uncommon, accounting for less than 1% of all congenital cardiovascular malformations.

Morphology

The abnormal connections in 'double' discordance may be present in hearts with usual or mirror-image atrial arrangement. The heart itself may be left-sided, right-sided or in the midline. The ventricles are inverted when compared with the normal situation, with the aorta arising anteriorly from the right ventricle and the pulmonary artery arising posteriorly from the left ventricle. The aorta arises from a free-standing infundibulum, which separates the aortic valve from the tricuspid valve. In contrast, the pulmonary valve is in fibrous continuity with the mitral valve. Associated lesions are common (80–90%). Usually a VSD is present (75% of cases), often in a perimembranous subpulmonary position, but VSDs may occur anywhere and are frequently multiple. The left-sided tricuspid valve may have features of Ebstein's malformation and straddling of either atrioventricular valve is well recognized. Pulmonary stenosis or atresia occurs in almost half of cases (usually with VSD).

Pathophysiology

Isolated ccTGA may have no haemodynamic consequences in childhood. The pathophysiology is determined by the associated lesions.

Diagnosis

CLINICAL

Fetal diagnosis may be triggered by detection of a prenatal arrhythmia. Patients with isolated ccTGA are often asymptomatic through childhood and into middle age. They may be detected because of an abnormal chest radiograph or ECG (often at routine medical examination). The physical signs depend on the nature of the associated malformations. In patients with a large VSD, congestive cardiac failure may develop in infancy. When there is a VSD and pulmonary stenosis, increasing cyanosis may develop or the patient may deteriorate acutely when the duct closes, if pulmonary atresia is present.

CHEST RADIOGRAPH

In isolated ccTGA with laevocardia, there is a normal cardiothoracic ratio with an abnormally straight left heart border due to the left and anterior position of the ascending aorta. The cardiothoracic ratio may be increased with pulmonary plethora when there is an associated VSD or atrioventricular valve regurgitation.

ECG

This shows variable degrees of atrioventricular block, abnormal P-wave axis and abnormal QRS activation with reversal of the Q-wave pattern in precordial leads.

CROSS-SECTIONAL ECHOCARDIOGRAPHY

This is able to identify the morphological characteristics of ccTGA. The abnormal position of the ventricular septum frequently means that subcostal imaging provides the most useful windows in the infant or small child, whilst transoesophageal echocardiography may be required for older children and adults. It is particularly important to identify associated anomalies, particularly atrioventricular valve straddling, VSD, left ventricular outflow obstruction and atrioventricular valve regurgitation. It is usually possible to plan appropriate management strategies without invasive testing.

CARDIAC CATHETERIZATION AND ANGIOGRAPHY

This is rarely indicated as a diagnostic procedure.

Natural history

The natural history and management are usually determined by the associated cardiac malformations. Late right (systemic) ventricular failure with tricuspid regurgitation (especially with an Ebstein-like tricuspid valve) may result during the fourth and fifth decades [120] and there is a progressive tendency to develop atrioventricular conduction problems (reported as 2% per year incidence of complete heart block) [120]. Tachyarrhythmia associated with ventricular pre-excitation may also develop.

Management

In patients with VSD and/or left ventricular outflow obstruction, surgery is complicated because of the location of the conduction tissue and resultant operative risk of complete heart block. Relief of pulmonary stenosis often requires insertion of a left ventricle to pulmonary artery conduit. A 'double-switch' approach (atrial redirection by Mustard or Senning operation with an arterial switch or connection of the left ventricle to aorta via a VSD if present) is a novel approach that restores the left ventricle to the systemic circulation [121]. However, the results remain uncertain. Intervention is not required for the asymptomatic patient with isolated ccTGA, apart from the insertion of a pacemaker if complete heart block develops. Patients with significant tricuspid regurgitation require surgery as regurgitation is progressive and associated with 'right ventricular' failure. Valve replacement has been the most common procedure and results have been better when undertaken before ventricular function is severely compromised [122]. Recently, banding of the pulmonary artery has been performed and can markedly improve tricuspid regurgitation by inducing a shift in the interventricular septum (Fig. 19.17). A double switch can be considered after such 'left ventricular' retraining. Too few patients have reached adult life after the various surgical approaches for comparison of outcome. Long-term surveillance of all operated and unoperated patients with ccTGA is required for arrhythmia as well as valve and ventricular function.

Univentricular atrioventricular connection (single ventricle)

Hearts with a univentricular atrioventricular connection (including tricuspid atresia, mitral atresia and double-inlet ventricle) are characterized by the output from both atria being directed into a single ventricular chamber. This heterogeneous group of abnormalities accounts for 1.5–2% of all congenital cardiac malformations.

Morphology

Description of the morphological abnormalities in this group has long been an area of contention because of

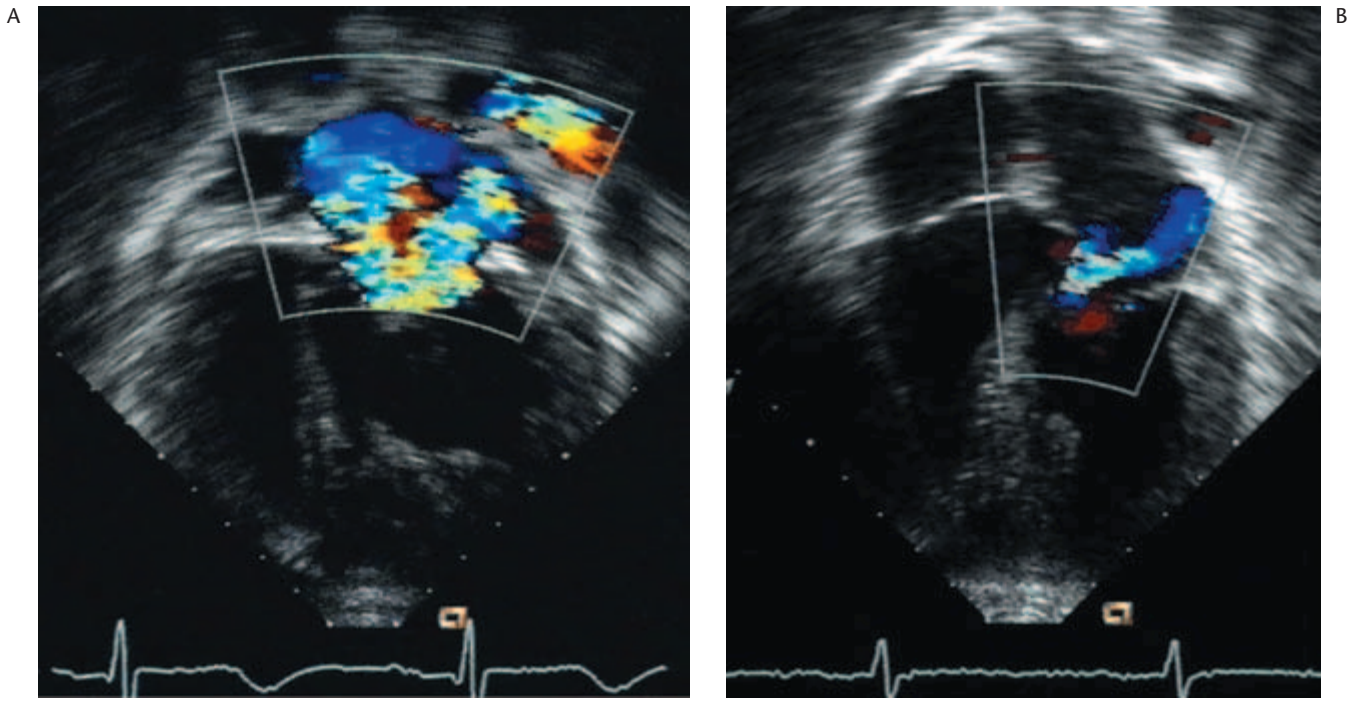

Figure 19.17 Transthoracic apical echocardiographic images of patient with congenitally corrected transposition and ventricular septal defect. (A) Severe tricuspid regurgitation associated with morphological right ventricular dilatation. (B) Following pulmonary artery banding, there is marked reduction in the degree of tricuspid regurgitation as well as significant reduction in the morphological right ventricular dilatation.

a lack of consensus about the definition of a ventricle. Most commonly, there is a dominant right or left ventricle and an additional second ventricular chamber, which is rudimentary. The 'mode' of connection (see Nomenclature, above) may include absent atrioventricular connection (right or left) or double-inlet ventricle with two separate or a common atrioventricular valve. The arterial connections can be concordant, discordant, double outlet or solitary outlet with atresia of the pulmonary artery or of the aorta. In practice, there are usually two arterial trunks with stenosis of one or other artery. The sequential segmental approach, together with description of associated abnormalities, facilitates classification of these complex hearts.

Pathophysiology

Pathophysiology depends mainly on the pulmonary and systemic blood flows and the associated malformations. In all cases, there is a degree of cyanosis, as a result of mixing at ventricular level.

Diagnosis

CLINICAL

Most patients present in the neonatal period with a varied clinical picture, unless prenatal diagnosis has already been made. If they have pulmonary stenosis, there is cyanosis, a ventricular heave, a normal first heart sound and a single second heart sound. There is usually an ejection systolic murmur caused by pulmonary outflow obstruction. In contrast, those with unobstructed pulmonary blood flow have much less severe cyanosis and may have features of cardiac failure. Physical signs include an overactive precordium with a normal first heart sound and a variable second heart sound with a loud pulmonary component. There is usually a soft systolic murmur. Other patients may present in critical condition with obstructed systemic flow (caused by subaortic stenosis, coarctation or interrupted aortic arch) or the consequences of coexisting abnormalities (e.g. TAPVC with atrial isomerism).

CHEST RADIOGRAPH

Abnormalities of cardiac position are common and there may be discordance between the side of the stomach and the heart, in association with atrial isomerism. There is almost always cardiomegaly. In cases with pulmonary outflow obstruction, there will be pulmonary oligaemia, whereas pulmonary plethora is usually seen in those with unobstructed pulmonary blood flow.

ECG

The ECG findings are diverse. Attention should be paid to rhythm abnormalities, particularly in patients with suspected atrial isomerism. A superior P-wave axis is a strong clue for the presence of left isomerism, with interruption of the inferior caval vein.

ECHOCARDIOGRAPHY

Demonstration of the cardiac connections as well as the intracardiac and extracardiac malformations is usually possible, but is time-consuming and requires a cooperative or sedated patient in order to obtain complete information. In particular, definition of the systemic and pulmonary venous connections of the heart has important immediate and long-term management implications. Atrioventricular valve function must also be assessed.

CARDIAC CATHETERIZATION AND ANGIOGRAPHY

There may still be a role for diagnostic cardiac catheterization and angiography in the evaluation of some of these complex patients, who have abnormalities of systemic and pulmonary venous connection that may not be defined completely by echocardiography. However, it is probable that MRI and/or CT will increasingly be able to provide this important information less invasively.

Natural history

The natural history is highly variable and depends particularly on the degree of obstruction in the systemic and pulmonary outlets and, to a lesser extent, on the ventricular morphology and atrioventricular connection. Most patients who present as neonates require urgent or early palliative surgery to ensure survival. If the circulation is 'well balanced', survival into adult life with relatively few symptoms is possible. Predicted survival curves can be created for combinations of malformations (patients with double-inlet left ventricle, two atrioventricular valves with ventriculo-arterial discordance and pulmonary stenosis do best) [123]. An adequate arterial saturation in these complete mixing situations requires a high pulmonary blood flow and consequently greatly increased load on the ventricle. As a result, progressive deterioration with ventricular failure usually begins from the second or third decade of life.

Management

In the neonate or infant, palliative surgery is often required, for example systemic to pulmonary shunt, pulmonary artery band, complex surgery for subaortic stenosis together with treatment of any associated malformations such as TAPVC or coarctation. Since its introduction in 1971, the Fontan operation has become the definitive procedure of choice for suitable patients [124]. Surgery involves separation of the systemic and pulmonary venous returns without a subpulmonary ventricle. A number of modifications have been made since the original surgical description, aimed largely at streamlining the systemic venous return to the pulmonary arteries. The atriopulmonary connection has been abandoned in favour of a total cavopulmonary connection (TCPC), either intracardiac or with an extracardiac conduit between the inferior caval vein and the pulmonary artery, together with a superior caval vein to pulmonary artery connection (bidirectional Glenn) [125]. Frequently, the cavopulmonary circulation is established in two stages, with an initial bidirectional Glenn anastomosis. The TCPC completion is often fenestrated, creating a small communication between the cavopulmonary connection and atrium to allow controlled right-to-left shunting [126].

It is now appreciated that both operative mortality and postoperative outcome after TCPC depend on suitability of the circulation and adherence to defined criteria dealing with pulmonary artery size and anatomy, pulmonary vascular resistance, atrioventricular valve and ventricular function. In the best cases, operative risk is now less than 5% [127]. A number of important problems have emerged during long-term follow-up and premature decline in function, with reduced survival, is 'built in' to the Fontan circulation [128]. Key issues contributing to the 'failing Fontan' include the function of the systemic ventricle (which is 'preload deprived'), a rise in pulmonary vascular resistance, atrioventricular valve regurgitation, the development of pulmonary atrioventricular communications and the consequences of chronic venous hypertension [129]. These include massive right atrial dilatation, pulmonary venous obstruction, protein-losing enteropathy and, particularly, supraventricular arrhythmia. Approximately 20% of patients have clinically important arrhythmia (including intraatrial re-entry tachycardias and atrial flutter) by 10 years after Fontan and this incidence is likely to increase further

with longer follow-up [130]. Surgical modifications such as TCPC, which excludes the hypertensive right atrium from the subpulmonary circulation, may result in a lower incidence of long-term arrhythmia but this is not yet proven [130]. Protein-losing enteropathy results in peripheral oedema, pleural effusions and ascites. It can be diagnosed by gastrointestinal clearance of α_1-antitrypsin and has an ominous prognostic significance, with a 5-year survival rate of less than 50% [131]. Comprehensive investigation is mandatory for patients with any of these manifestations of the failing Fontan complex. In particular, it is crucial to exclude obstruction to the systemic venous return, as even a minor degree may have major clinical consequences. Appropriate investigations include transoesophageal echocardiography, MRI and/or cardiac catheterization. Intervention by stent implantation or surgery may be required. Right atrial blood stasis, coagulation abnormalities, development of right atrial thrombus and in particular the potential for recurrent subclinical pulmonary emboli have led many to advise lifelong anticoagulant therapy, although this is not yet supported by rigorous long-term data [132]. Arrhythmia must be treated actively, as loss of sinus rhythm itself leads to accelerated haemodynamic decline. Antiarrhythmic drugs, apart from amiodarone, have been disappointing. Results of radiofrequency ablation of the often multiple atrial re-entry circuits has improved, but these procedures remain challenging. Treatment of protein-losing enteropathy includes sodium restriction, high protein diet, diuretics, ACE inhibitors, steroids, albumin infusions, chronic subcutaneous heparin and creation of a fenestration (by interventional catheter) [133]. Patients with a failing Fontan should be considered for surgical conversion or for transplantation. Conversion of an atriopulmonary connection to a more energy-efficient TCPC, together with arrhythmia surgery, has produced good results in selected patients, but has a surgical mortality and ongoing postoperative morbidity [134]. The Fontan operation should thus be considered the 'best' palliation for patients with these complex cardiac malformations and lifelong specialist follow-up is required for the many unresolved treatment issues.

Personal perspective

The management of congenital cardiac malformations has been one of the biggest success stories of modern medicine. As a result of improvements in medical and surgical management, more than 80% of children born with congenital cardiac malformations now survive to adulthood and adults will soon outnumber children with congenital cardiac malformations. Increasingly, therefore, adult cardiologists need to become involved in the lifetime management of this new population of patients and are likely to encounter patients with a range of complex malformations in their practice.

A number of important trends have emerged. Investigation has shifted away from invasive cardiac catheterization towards non-invasive modalities as echocardiography, and more recently MRI and CT, have become able to define anatomy and physiology accurately. In parallel with the reduction of diagnostic cardiac catheterization has been the spectacular rise in the range and number of therapeutic cardiac catheterization procedures. These are now often integrated into a long-term management strategy together with surgery and will in some cases obviate the need for surgery completely.

Improvements in diagnosis, neonatal intensive care, cardiopulmonary bypass and surgical skill and confidence has resulted in a clear shift away from palliation towards primary definitive repair wherever possible. This has contributed to a dramatic reduction in surgical morbidity and mortality and improved haemodynamic results. With better outcome prospects, the goals of treatment have shifted from merely early survival towards 'lifetime' management aimed at optimizing life expectancy and quality of life. Paediatric cardiology and adult cardiology will need to reintegrate in order to provide the best care for the increasing number of survivors of treatment for congenital cardiac malformations, and this will be a major challenge for the profession in the next few years.

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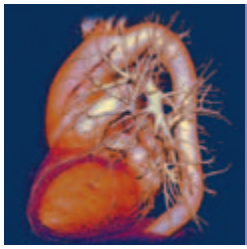

20 Pregnancy and Heart Disease

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Summary

Heart disease, though rare, can be present or discovered during pregnancy because of haemodynamic overload of the heart particulary during the third trimester when cardiac output doubles.

Most of the knowledge in recognition and treatment of cardiac disease during pregnancy is not based on evidence from randomized trials, but is derived from clinical experience, few case reports and small consecutive series. These are summarized in the guidelines on "Management of Cardiovascular Diseases During Pregnancy" from the European Society of Cardiology, the basis for this chapter. The physiological changes that occur during pregnancy have a different impact depending on the type and severity of cardiac anomalies. Differential diagnosis with normal pregnancy related physiological changes is also discussed.

Particular emphasis is placed on early and accurate diagnosis of congenital or acquired cardiac anomalies because often early intervention is essential for a safe pregnancy and delivery.

Women at low risk are those in NYHA class I or II with good ventricular function, without severe left ventricular inflow or outflow obstruction or pulmonary hypertension and who do not need to take anticoagulants. Women at high risk are those showing symptoms, of severe mitral or aortic stenosis or unoperated coarctation, with cyanotic congenital heart disease with or without pulmonary hypertension, with impaired left ventricular function and/or life-threatening arrhythmias. The same conditions that endanger the mother also affect fetal survival.

Multiple therapeutic options including percutaneous or surgical intervention are now available to allow for a safe completion of the pregnancy. Management of these patients requires teamwork from cardiologists, obstetricians, anaesthetists, neonatologists and, sometimes cardiac surgeons.

Cardiovascular adaptations during normal pregnancy

Pregnancy physiology is characterized by significant haemodynamic changes that allow the uterus and developing fetus to receive an adequate blood supply. These adaptations are well tolerated by the normal heart but may result in haemodynamic problems for the diseased heart. This implies that pregnancy may unmask previously silent heart disease.

Heart disease is present in 0.5–1% [1,2] of all pregnant women and accounts for about 10–15% of all maternal mortality [3]. Although the incidence of acquired disease has fallen (to below 0.2%) in Western countries due to the reduction in the incidence of rheumatic fever following the introduction of penicillin [1,2], rheumatic heart disease is still the prevalent cause. Congenital heart disease is becoming an increasing problem during pregnancy as a result of the success of neonatal corrective or palliative cardiac surgery. Because of the increased delay to first pregnancy, maternal older age and the increase in women's smoking habits, symptomatic coronary disease, although rare, can occur and is likely to increase.

Haemodynamic changes during pregnancy

The evaluation and management of heart disease in pregnant women require knowledge of the normal physiological changes associated with gestation, labour, delivery and the early postpartum period (Fig. 20.1).

Blood volume and cardiac output

The most remarkable change related to pregnancy is the increase in blood volume, which almost doubles by the end of pregnancy. It starts to increase from the sixth week, rising rapidly in the second trimester and becoming stable in the last 8 weeks [4]. Red cell mass increases later in pregnancy but to a lesser extent than the plasma volume, leading to slight haemodilution and the physiological anaemia of pregnancy, with haematocrit at about 33–34% and haemoglobin around 11–12 g/dl [5]. These changes are more marked in twin or multiple pregnancies. In the last trimester, peripheral arterial vasodilatation may reduce arterial vascular filling and thereby induce sodium and water retention mediated by aldosterone. In an average pregnancy, there is a gradual accumulation of 500–900 mEq of sodium and total body water increases by 6–8 litres, mostly extracellular. All these haemodynamic changes, which evolved to protect the mother from blood loss at delivery, could play a role in the pathogenesis of heart failure.

Cardiac output also increases to about 40% above the non-pregnant value. Most of this increment is achieved early in pregnancy, with peak values at 20–24 weeks [6]. This is achieved by an increase in stroke volume and heart rate. In late pregnancy the increase in venous return is sensitive to posture: a sharp drop in preload due to inferior vena cava compression by the gravid uterus in the supine position may cause hypotension, with weakness and light-headedness or syncope and even (short) fetal distress. These symptoms are easily resolved by turning the woman from the supine to the lateral decubitus position.

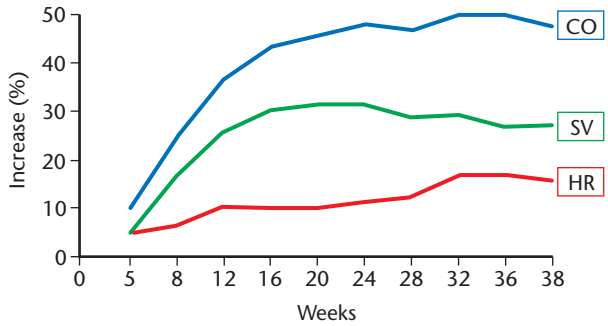


Figure 20.1 Increase in cardiac output (CO), stroke volume (SV) and heart rate (HR) during pregnancy.

Heart rate

Heart rate starts to increase in the first weeks of pregnancy and peaks in the first half of the third trimester. The increase in resting heart rate averages 10–20 b.p.m. Atrial tachyarrhythmias can be present in normal pregnancy due to increased plasma catecholamine concentrations and/or adrenoreceptor sensitivity, and to the stretched atrial wall because of increased heart volumes [7].

Peripheral vascular resistance

Maternal peripheral and pulmonary vascular resistance fall as a result of the low-resistance uteroplacental circulation, decreased mean aortic pressure and endogenous hormones. Recently, there has been a focus on the role of nitric oxide in the pathogenesis of vasodilatation [8]. Venous return increases, with a consequent rise in left ventricular end-diastolic volume, although the filling pressure does not rise because of ventricular structural changes (increased compliance). In the first two trimesters, the fall in systemic vascular resistance, which exceeds the increase in cardiac output, leads to a drop in both systolic and, especially, diastolic blood pressure, resulting in a wide pulse pressure.

Labour, delivery and early postpartum period

The most dramatic swings in haemodynamic parameters occur during labour, delivery and the immediate postpartum period. Uterine contractions significantly increase venous return, and during a contraction cardiac output may rise by a further 25%. Pain and anxiety cause an increase in sympathetic tone during the second stage of labour, which in turn enhances cardiac output and blood pressure. These changes may be influenced by the type of anaesthesia and analgesia used in labour and by the mode of delivery [9]. Reduction of pain and apprehension can be achieved by local and caudal anaesthesia. The patient should be lying in the left lateral position during labour.

During the early postpartum period, cardiac output increases as a result of a blood shift from the contracting uterus to the systemic circulation and because of inferior vena cava decompression (autotransfusion) [10]. There are no haemodynamic differences between lactating and non-lactating mothers. The cardiovascular adaptations associated with pregnancy regress by approximately 6 weeks after delivery.

Cardiac evaluation in normal pregnancy

During pregnancy, cardiovascular disease or worsening of a previous cardiac disease is difficult to detect: cardiopulmonary signs and symptoms typically reported during normal pregnancy may mimic heart disease. Fatigue and decreased exercise capacity are common, along with chest pain at rest that may be caused by oesophageal reflux. As many as 75% of women may complain of mild dyspnoea, whereas progressive orthopnoea or paroxysmal nocturnal dyspnoea are rare. Palpitations are very common and are due to either a physiological increase in the resting heart rate or atrial or ventricular ectopic beats [11] (Table 20.1).

Physical examination

The physical examination of a healthy pregnant woman shows a slightly fast resting heart, a bounding pulse, a widened pulse pressure and warm flushed peripheries. In addition, a slight elevation of venous pressure, the presence of 'tense' soft tissues and peripheral oedema (pedal oedema) are common.

The precordial impulse is hyperkinetic and the first heart sound (S_1) is increased, with prominent splitting that may be misinterpreted as a fourth heart sound (S_4) or as a systolic click. During the later stages of pregnancy, the physiological splitting of the second heart sound (S_2) may seem fixed. Third sound gallop (S_3) is frequently present by week 20 of gestation, whereas S_4 is uncommon and requires further evaluation.

Murmurs develop in nearly all women during pregnancy. They are usually soft, mid-systolic and heard at the mid to upper left sternal border, and are secondary to increased pulmonary blood flow. Benign murmurs include the continuous bruit resulting from increased blood flow to the breasts, the 'mammary soufflé', and the suprasternal venous hums, which can be obliterated through ipsilateral jugular digital compression or by firm pressure of the stethoscope. Diastolic murmurs are unusual and therefore call for further evaluation. The murmurs of stenotic heart valves (aortic stenosis, pulmonary stenosis, mitral stenosis) may increase in intensity because of the physiological increase in cardiac output and fall in systemic vascular resistance. On the other hand, the murmurs of incompetent heart valves (aortic insufficiency, mitral insufficiency) may decrease. Detection of murmurs as diastolic murmurs, continuous murmurs and loud systolic murmurs equal or greater than grade III in intensity cannot be considered physiological and hence need further careful examination, starting with transthoracic echocardiography (Table 20.1) [12].

Additional diagnostic tools

Electrocardiogram

In normal pregnancy, there are non-characteristic electrocardiographic changes except for a slight leftward shift of the electrical axis, which can give rise to a small Q wave in lead III [13]. Severe left-axis deviation is not a normal pregnancy variant and needs further evaluation.

Doppler echocardiography

Because of its safety and diagnostic power, Doppler echocardiography is the first advisable diagnostic tool. In a normal pregnancy, serial echocardiography usually shows a significant increase in cardiac output, cardiac index, left ventricular end-diastolic volume and left ventricular wall thickness. An increase in left (up to 6%)

Table 20.1 Symptoms and signs during pregnancy

	Normal pregnancy	Indicators of heart disease
Symptoms	Mild dyspnoea	Severe or progressive dyspnoea
	Fatiguability	Paroxysmal nocturnal dyspnoea
	Decreased exercise tolerance	Syncope with exertion
	Rest chest pain	Effort or emotion chest pain
	Palpitations	
Signs	Pedal oedema	Severe peripheral oedema
	Warm extremities	Clubbing and cyanosis
	Full, sharp and collapsing pulse	Persistent neck vein distension
	Prominent left ventricular impulse	Cardiomegaly
	Third heart sound (S_3)	Fourth heart sound (S_4)
	Grade 1–2 systolic ejection murmurs	Grade ≥ 3 systolic ejection murmurs
	Premature beats	Sustained arrhythmias
	Continuous murmurs	Diastolic murmurs

and right (up to 12%) ventricular diastolic dimensions is present [14]. A mild increase in right atrial size (up to 20%) and transvalvular flow velocities and the presence of mild atrioventricular valve regurgitation are normal echocardiographic findings during pregnancy [15].

Chest radiography

Exposure to ionizing radiation should be avoided whenever possible, especially during early pregnancy since malignancies and congenital abnormalities in offspring have been described. Routine chest radiography (1.5 mGy) exposes the uterus to a minimal (0.05 mGy) radiation dose. Chest radiography should therefore be used only if clinically indicated and performed with the minimum amount of radiation, shielding the pelvic area. In addition, whenever possible it should be delayed until at least the completion of the first trimester. In normal pregnancy, the heart may appear enlarged due to the horizontal position, and increased lung markings and small pleural effusions can be detected [16].

Assessment of heart disease in pregnancy

The assessment of women with heart disease should take place before conception in order to counsel them adequately and to minimize maternal and fetal morbidity and mortality. The type and severity of cardiac disease, general conditions, previous cardiovascular and cerebral events, NYHA class, medications and obstetric and family history should be taken into account in evaluating the risks and possibility of successful pregnancy. For example, aortic insufficiency is normally well tolerated during pregnancy because of the low peripheral resistance; however, if systemic hypertension, NYHA class III–IV, an ejection fraction around 40% or ventricular arrhythmias are present, it becomes a high-risk condition. Counselling, surveillance and treatment of women with cardiac disease should be a collaborative effort including obstetric, cardiological and anaesthesiological services.

The risk of recurrence in the offspring should be discussed. All patients with congenital heart diseases should have informed genetic counselling before conception (Table 20.2). An exercise test before pregnancy is very important for evaluating functional capacity. The physiological changes of pregnancy are similar to the ones that occur during exercise but over an extended period, so a good exercise test will predict a well-tolerated pregnancy. Echocardiography is required to assess cardiac haemodynamics, particularly pulmonary pressure, left ventricular systolic function and severity of valve obstructions. When the heart disease is severe (e.g. severe mitral stenosis), balloon valvuloplasty or mitral valve surgery should be considered before pregnancy. If a woman with heart disease presents already pregnant, her cardiac status and medication should be evaluated and should be treated by a specialized team of cardiologist, obstetricians and anaesthesiologist. A detailed plan for her pregnancy and delivery should be made early in pregnancy and changed if cardiac deterioration occurs.

Table 20.2 Recurrence risks of congenital heart disease in offspring*

Type of heart disease	Total risk (%)	Mother affected (%)	Father affected (%)
Acyanotic congenital heart disease			
Atrial septal defect	3–5	4.5–6	1.5
Ventricular septal defect	4–8	6–9.5	2–2.5
Atrioventricular septal defect	10–15	7.5–15	1–7
Patent ductus arteriosus	3–4	4	2
Pulmonary stenosis	4	6.5	2
Left ventricular obstruction	11–15	10–11	3
Coarctation of aorta	6	4	2.5
Cyanotic congenital heart disease			
Tetralogy of Fallot	2.2–3.1	2.5	1.5
Transposition of great vessels	0.5		
Mendelian disorders			
Holt–Oram syndrome	50	50	50
Noonan's syndrome	50	50	50
Marfan's syndrome	50	50	50

*Based on multiple studies [36–40].

Maternal low-risk conditions

All the conditions which benefit from the decrease in systemic vascular resistance that occurs during pregnancy are very well tolerated regardless of their severity, provided that left and right ventricular function is not impaired. These conditions include mild and moderate valve regurgitation [16,17] and small–moderate left-to-right shunts without pulmonary hypertension.

Mild, moderate and moderately severe right ventricular outflow tract obstruction are very well tolerated during pregnancy, as shown by previous series in which no deaths and a low incidence of complications have been reported [18]. However, the severe form of pulmonary valve stenosis and moderate stenosis with impaired right ventricular function should be treated before conception. Percutaneous pulmonary balloon valvuloplasty during pregnancy may be indicated in very severe (gradient suprasystemic) and/or symptomatic cases. A few successful cases have been reported [16] (Fig. 20.2). Stenting of pulmonary arteries can also be performed successfully during pregnancy. Mild left ventricular outflow tract obstruction is well tolerated during pregnancy even if pressure gradient doubles due to the increased cardiac output (Fig. 20.3) [18], whereas the moderate form must be followed carefully due to the possibility of rapid clinical deterioration. Aortic coarctation carries a small risk of dissection [19] and should be corrected before pregnancy. During pregnancy women with mild coarctation should undergo close monitoring of blood pressure and treatment with a beta-blocking agent will be indicated if hypertension develops [20]. Percutaneous balloon angioplasty should be avoided in coarctation during pregnancy because of the risk of aortic dissection or rupture [21]. Because of the risk of restenosis after repair of coarctation in childhood, all women with a history of operated coarctation who consider pregnancy should be assessed.

In patients who have undergone previous successful surgical repair without mechanical heart valve implantation (tetralogy of Fallot, atrial repair for transposition of the great arteries [22], atrial and ventricular defects, aortic coarctation [19,20]), pregnancy is well tolerated if normal exercise tolerance, good functional status and normal ventricular function are present. Close follow-up is recommended (cardiac assessment every trimester).

Although women with some conditions are at low risk during pregnancy, other conditions can worsen after delivery, including intra-atrial repair of transposition of the great arteries [22,23], Ebstein's anomaly [24], mild valve stenosis and mild cardiomyopathies (ejection fraction 45–55%). For example, 25% of women with intra-atrial repair of transposition experience deterioration of their right ventricular function during pregnancy and most of them do not recover to the baseline level [25].

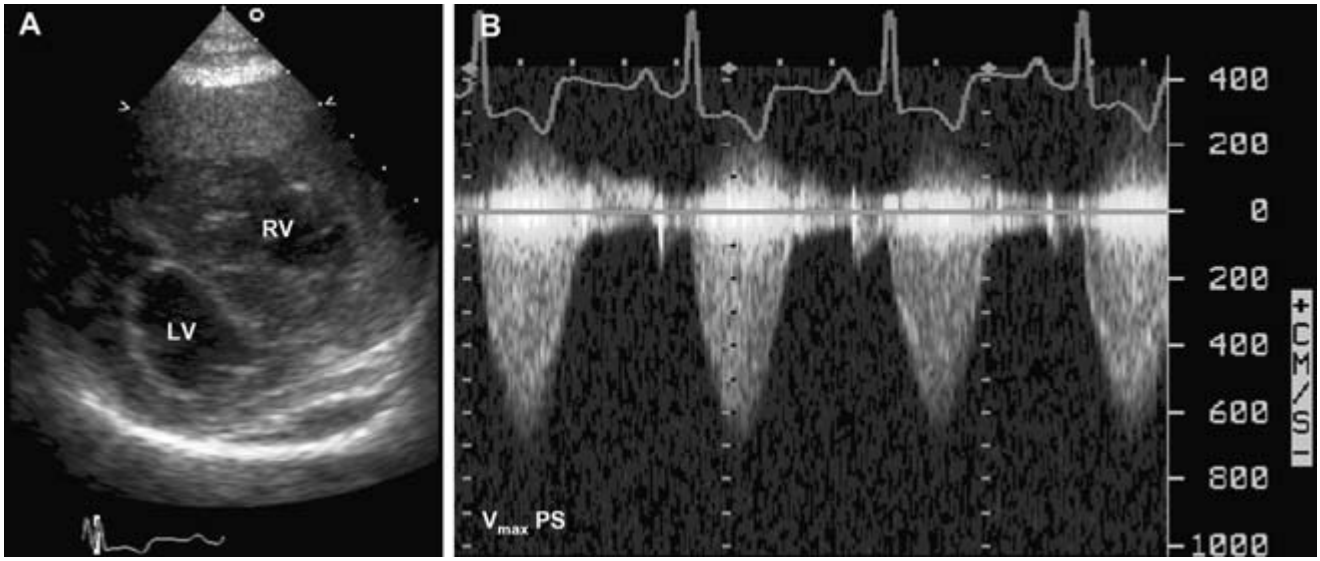
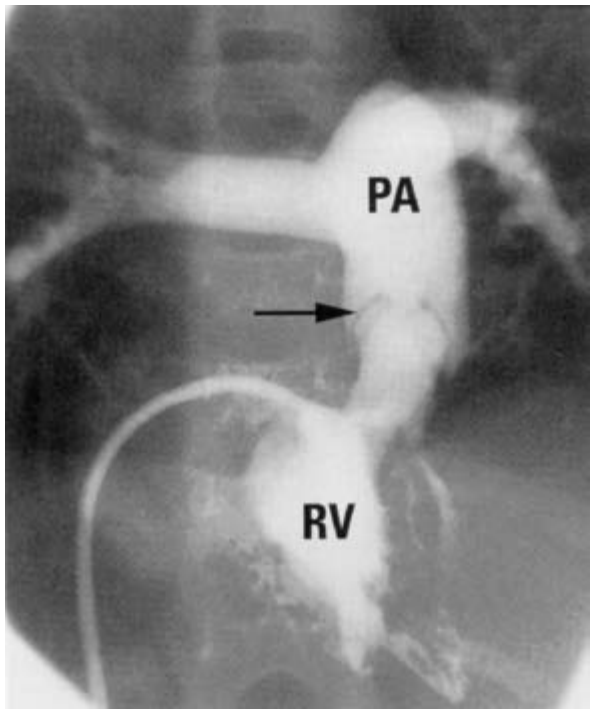


Figure 20.2 (A,B) Echocardiographic (A, parasternal short-axis view; B, continous-wave Doppler) and (C) angiographic image of a pregnant woman with severe pulmonic stenosis. Peak gradient was 144 mmHg. She was treated with balloon dilatation during pregnancy (D), the peak gradient decreasing to 40 mmHg after dilatation (E). RV, right ventricle; LV, left ventricle; PA, pulmonary artery; V_{max}, maximal velocity (m/s) measured over the pulmonic valve. (*Continued p. 612*)

C



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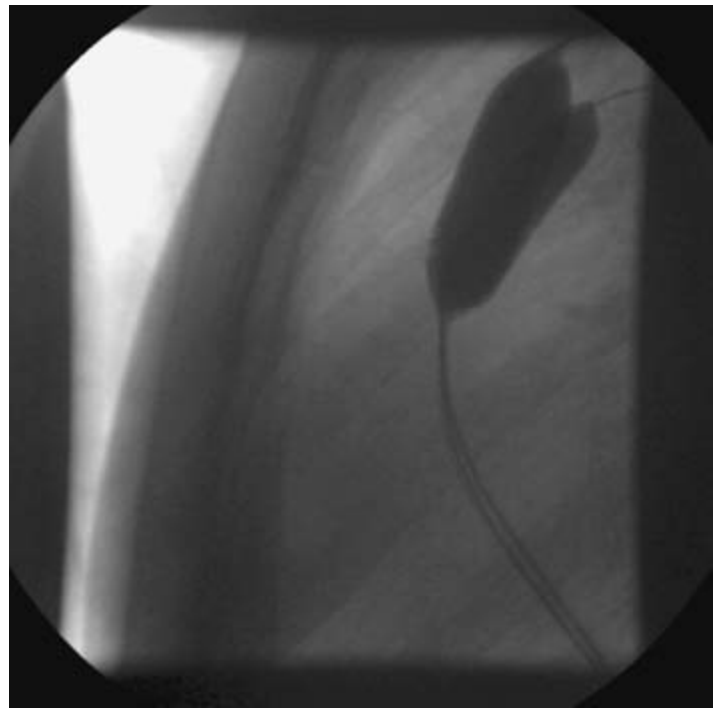

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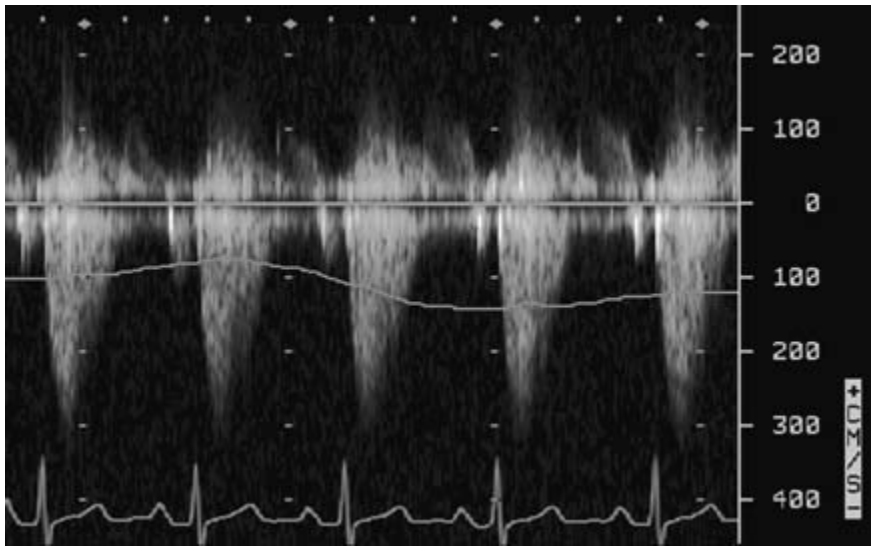

Figure 20.2 (*cont'd*).

Maternal high-risk conditions

Previous studies have recognized that prior cardiac events or arrhythmias, poor functional class, cyanosis, left heart obstruction and left ventricular systolic dysfunction independently predict maternal cardiac complications [26,27]. There are some specific conditions at particular risk during pregnancy.

Pulmonary hypertension

A 30–50% maternal mortality risk is still reported in patients with severe pulmonary vascular disease, either with septal defects (Eisenmenger's syndrome) or without [28,29], and fetal loss is of a similar magnitude. Systemic vasodilatation increases the right-to-left shunt and decreases pulmonary output, leading to a low-output status. Death occurs in the last months of pregnancy or in the first few days after delivery because of pulmon-

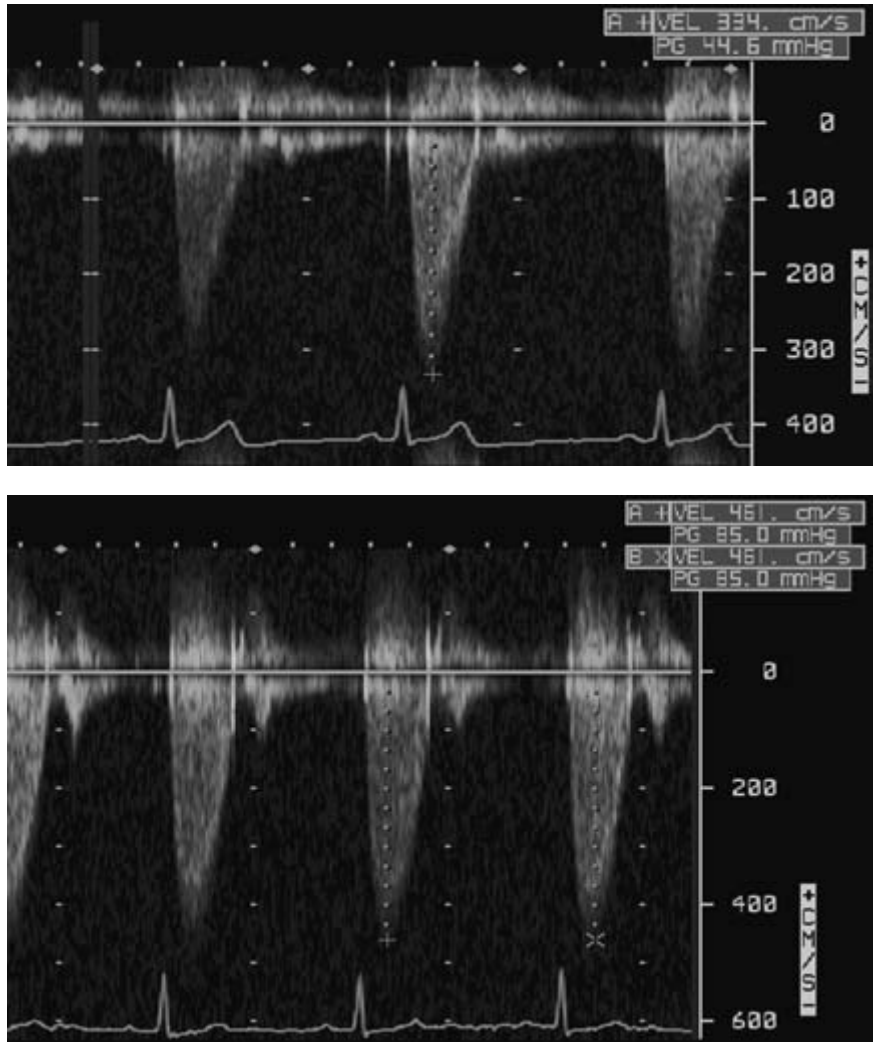

Figure 20.3 Echocardiographic continous-wave Doppler images of a severe aortic stenosis in a pregnant woman. The peak gradient changed from 45 mmHg before pregnancy (A) to 85 mmHg after 18 weeks of pregnancy (B).

ary hypertensive crises, mostly due to fibrinoid necrosis, rarely to pulmonary thrombosis. It can happen even in patients with little or no disability before or during pregnancy. The level of pulmonary hypertension that should be considered at risk is around 70 mmHg systolic or > 30 mmHg mean pulmonary pressure. Even moderate forms of pulmonary vascular disease can worsen during pregnancy as a result of the decrease in systemic resistance and of overload of the right ventricle. Termination of pregnancy is advisable. If pregnancy continues, patients should restrict their physical activity, avoid the supine position and take subcutaneous heparin as prophylaxis against thromboembolism [17,30]. Intravenous or pulmonary infusion of prostacyclin (epoprostenol) has been occasionally used to decrease pulmonary pressure during delivery and postpartum in order to manage pulmonary hypertensive crises [31,32]. Further evaluation is needed before using new drugs such as the oral phosphodiesterase inhibitor sildenafil and the endothelin receptor antagonist bosentan during pregnancy [33,34]. Invasive monitoring during labour and delivery is recommended.

Severe left ventricular tract obstruction

Congenital, most often bicuspid, aortic valve stenosis is rare during pregnancy because patients have usually had percutaneous or surgical valvuloplasty in childhood or before conception. Women with an aortic valve area < 1.0 cm^2 should be discouraged from conceiving before treatment especially when they are symptomatic. In severe aortic stenosis, the fixed resistance may not be able to accommodate the increased cardiac output that occurs during pregnancy. An increase in both gradient and left ventricular end-diastolic pressure is induced and can cause heart failure, low output and reduction in uteroplacental perfusion. Important ECG changes of left ventricular overload in a previously normal ECG, signs of

A

PREGNANCY IN CYANOTIC CHD

Logistic regression analysis of risk factors determinant for fetal survival

RISK FACTORS	PREDICTIVE POWER	*P*-VALUE
Maternal disease	+	0.002
Hb	+	<0.0001
O_2 saturation	+	0.0001
Age	–	0.74
Aortic insufficiency	–	0.02
Previous shunt	+	0.16

B

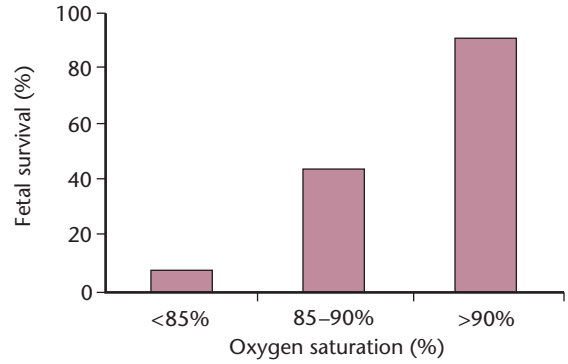

Figure 20.4 Risk factors affecting fetal survival: (A) multiple regression analysis shows that maternal disease, haemoglobin and oxygen saturation are significantly related to fetal survival; (B) fetal survival declines with the decrease in maternal oxygen saturation.

heart failure and low systemic blood pressure can appear. The clinical symptoms occur at 20–24 weeks of gestation. Previous series which reported high mortality in aortic stenosis [35] were probably due to the underestimation of these signs during pregnancy as well as the lack of immediate intervention. If the fetus is viable (> 34 weeks) delivery is advised, thus restoring the pre-pregnancy haemodynamic status. If the valve is not heavily calcified and no regurgitation is present, percutaneous balloon valvotomy can be successfully performed. Five cases have been reported, with significant reduction of valve gradient, enabling the pregnancy to continue [21,36]. Surgery can be an alternative [37]. Most recent series [38] of pregnancy in aortic stenosis reported no deaths but some complications, such as pulmonary oedema and further valve deterioration requiring surgery.

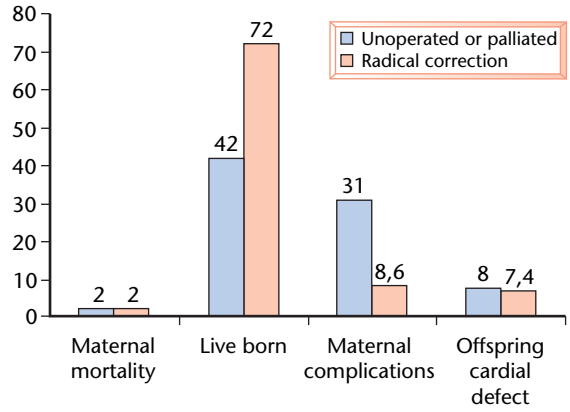

Figure 20.5 Maternal and fetal complications in cyanotic patients (mostly tetralogy of Fallot) selected to receive either no operation/palliation or radical correction. Maternal complications decreased and live births increased substantially with radical correction.

Cyanotic heart disease without pulmonary hypertension

Cyanotic congenital heart diseases are usually corrected before pregnancy, but some inoperable or palliated cases can reach child-bearing age. The degree of maternal hypoxaemia is the most important predictor of maternal and fetal outcome (Fig. 20.4). With resting maternal blood saturation below 85%, maternal mortality is 2–5%, fetal loss is 85% and premature delivery or a low-birth-weight neonate is around 50%; pregnancy should therefore be discouraged [39]. Maternal complications (heart failure, pulmonary or systemic thrombosis, supraventricular arrhythmias) occur in 30% of cases. Low-dose heparin prophylaxis is widely used and recommended, although its value has not been proved. If oxygen saturation is 85–92%, it is advisable to measure it during exercise. If there is a sudden and important drop in oxygen saturation during exercise, the pregnancy has a poor prognosis and should be discouraged.

Tetralogy of Fallot is the most common cyanotic congenital heart defect. Comparing fetal and maternal outcome in uncorrected (i.e. cyanotic) and corrected tetralogy of Fallot, it is evident that persistent cyanosis is the most important determinant of maternal and fetal outcome (Fig. 20.5). Offspring of mothers with tetralogy of Fallot regardless of correction carry a risk of having congenital heart disease (3–10%) (see Table 20.2).

Impaired left ventricular function

Besides basic cardiac disease, left ventricular function is one of the main determinants of maternal and neonatal outcome. No reviews are available that indicate a cut-off value for left ventricular ejection fraction below which pregnancy is contraindicated. An echocardiographic ejection fraction > 40% with a good rise in systemic arterial pressure on exercise testing allows the continuation of pregnancy, although complications can still occur. Pregnancy termination should be advised if ejection fraction is below 40% with increased left ventricular dimensions [17].

During pregnancy, restriction of physical activity and serial echocardiogram evaluation should be performed. Particular attention should be focused on the recognition of ventricular arrhythmias during pregnancy and after delivery, in which case 24-h Holter registration should be indicated. Particular attention should be paid when valvular disease with impaired ventricular function is present because the prognosis can be worse.

Fetal high-risk conditions

The fetal risks are as follows.

1 The recurrence risk of congenital malformations in the offspring of patients with major heart defects (see Table 20.2) ranges from 2 to 50% depending on the type of parental disease, with an excess in the offspring of affected women [17,40–44]. Fetal echocardiography can detect the presence of congenital heart disease and should be performed if the mother or father has congenital heart disease.
2 Abortion.
3 Intrauterine growth retardation.
4 Prematurity (Fig. 20.6).

The last three complications depend on type and severity of maternal disease and poor maternal functional class (NYHA > II) [25]. Additional risk factors for adverse fetal/neonatal events, besides the conventional obstetric ones (history of premature delivery or rupture of membranes, incompetent cervix, or caesarean section; intrauterine growth retardation, antepartum bleeding > 12 weeks' gestation, febrile illness, or uterine/placental abnormalities during present pregnancy), include maternal age > 35, multiple gestation, smoking during pregnancy and anticoagulation therapy [45]. Besides cyanotic heart disease, another condition that carries an adverse fetal outcome (45% fetal survival) is the Fontan repair for tricuspid atresia or single ventricle. In this condition the venous congestion that occurs during pregnancy leads to congestion of the intrauterine veins, with a very high incidence of spontaneous abortion. Nowadays conversion from classic Fontan to total cavopulmonary connection should be considered before pregnancy. We have to emphasize that the prematurity associated with poor maternal condition carries a high risk of newborn disabilities: 30% when the fetus is delivered at 27 weeks, 60% at 24 weeks [43].

Specific conditions

Mitral valve stenosis

Although its incidence is decreasing in Europe, rheumatic heart disease is still responsible for most of the cardiac complications during pregnancy. Mitral valve stenosis, nearly always of rheumatic origin, is the most common (90%) and important cardiac valvular problem during pregnancy. Mortality among pregnant women with minimal symptoms is less than 1% but in severe disease can reach 5%. Labour, delivery and the immediate puerperium appear to be the periods most at risk [17,46–48].

The pressure gradient across the narrowed mitral valve may increase greatly during pregnancy because of

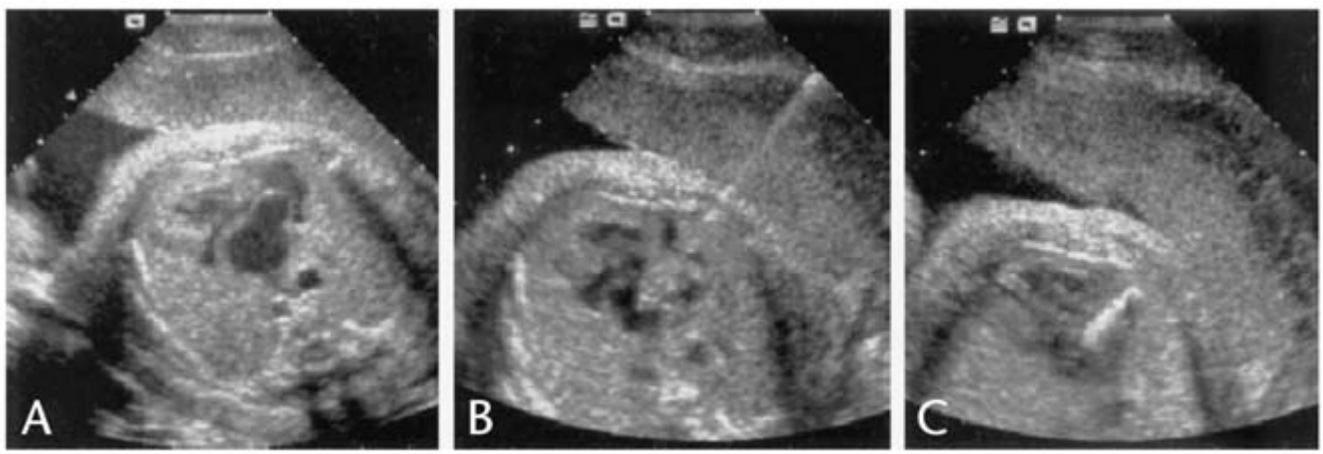

Figure 20.6 Creation of an atrial septal defect *in utero* for fetus with hypoplastic left heart syndrome and intact atrial septum. Transabdominal ultrasound image of the heart in a fetus with dilated left atrium and thin bulging atrial septum before atrial septal puncture (A), during septal puncture with Chuba needle (B) and during dilatation with 3-mm coronary angloplasty balloon (C). With permission of James E. Lock *Circulation* (2004) 110: 253–258.

the physiological increase in heart rate (decreasing left ventricular diastolic filling time) and cardiac output. This can lead to a rise in left atrial and pulmonary wedge pressures and inability of cardiac output to increase appropriately with exercise. The onset of clinical symptoms (excessive fatigue, breathlessness on exertion, orthopnoea and nocturnal dyspnoea) may occur even in women with moderate valve stenosis or who were previously symptom-free, usually in the middle trimester. Development of atrial fibrillation could further aggravate the clinical status, leading to acute pulmonary oedema.

Predictors of adverse maternal outcomes include degree of mitral valve stenosis (valve area < 1.5 cm^2), NYHA functional class II or more before pregnancy and history of cardiac events [25,45]. Patients with mild valve stenosis (valve area > 1.5 cm^2) who are either asymptomatic or have minor symptoms can almost always be managed with behavioural advice (restriction of salt intake, reduction of physical activity up to complete bed rest) and judicious medical therapy (diuretics to reduce pulmonary and venous congestion; beta-blockers to reduce heart rate and increase diastolic filling period). The onset of tachyarrhythmias such as atrial fibrillation or supraventricular tachycardia requires immediate treatment with cardioversion. Anticoagulation therapy is indicated in patients with atrial fibrillation. In patients with moderate mitral valve stenosis (valve area 1.1–1.5 cm^2), the different therapeutic strategies depend on the severity of symptoms before and during pregnancy and the rise in pulmonary pressure: patients who are either asymptomatic or mildly symptomatic (NYHA I–II) should undergo close follow-up with serial echocardiographic assessment (measurement of mean transmitral gradient and pulmonary artery pressure) and clinical evaluation; percutaneous balloon valvuloplasty or valve repair/replacement during pregnancy should be considered in cases with persistent symptoms despite optimal medical therapy. In patients with severe mitral valve stenosis (valve area < 1 cm^2), percutaneous balloon valvuloplasty or surgical intervention before conception is indicated. In pregnant women, careful monitoring and performance of these procedures at the right time have to be planned.

Percutaneous balloon valvuloplasty has been shown to be a successful and safe procedure during pregnancy in experienced centres, and has become the first-choice interventional treatment in anatomically suitable valves (young patients with non-calcified pliable valves without too much subvalvular thickening or significant mitral regurgitation) are present as a result of the significant reduction in fetal and neonatal mortality [21,49].

Labour and delivery should be planned carefully. Effective anaesthesia to minimize pain and anxiety, in addition to shortening of the second stage of labour, will decrease the haemodynamic demand on the maternal heart. Bedside ECG monitoring should be used to document rhythm disturbances. Swan–Ganz catheters are frequently used in moderate and severe mitral stenosis to monitor fluid balance. The safety of breast-feeding depends on the mother's medication in the postpartum period.

Hypertrophic cardiomyopathy

Although symptoms, particularly chest pain, may increase, pregnancy is generally well tolerated and absolute maternal mortality is very low and mostly limited to high-risk patients [50,51]. Management of hypertrophic cardiomyopathy during pregnancy should not differ from that outside pregnancy. No treatment other than reassurance should be indicated in asymptomatic or mild symptomatic women, whereas in symptomatic patients beta-blockers and low-dose diuretic therapy may be indicated. Because of the negative impact of tachycardia, if supraventricular arrhythmias develop, rate-control therapy and prompt electrical cardioversion are needed. Normal vaginal delivery is safe but careful monitoring of blood loss is needed [50].

Prosthetic heart valves

In women of child-bearing age, surgical valve repair is always preferable to replacement and must be performed whenever possible. If valve replacement is needed, the decision about the best type of valve prosthesis to use should take into account the woman's age (in very young women rapid tissue valve degeneration is common), the presence of other conditions such as atrial fibrillation requiring anticoagulant therapy, and the risk of reoperation (complex anatomy, re-repeat). Bioprosthetic valve appears to be the best choice provided that the woman is informed about the structural valve deterioration associated with pregnancy and the inevitability and risk of reoperation. Previous studies have shown that pregnancy is associated with an accelerated rate of structural valve deterioration (12–60%) [49,54,55]. The incidence of prosthetic valve reoperation is 60–80% at 5–10 years follow-up, and the mortality of reoperation is 2–3.8% [54]. The management of women with bioprosthetic valves should include serial clinical evaluation and two-dimensional echocardiography for early detection of valve structural deterioration, and antibiotic prophylaxis at delivery.

In women with mechanical valves, pregnancy is associated with a 10% risk of prosthetic valve thrombosis and/or systemic embolization, necessitating the use of some form of anticoagulation during pregnancy throughout pregnancy. On the other hand, the use of warfarin, particularly between weeks 6 and 12 of pregnancy, is

Table 20.3 Risks of anticoagulant treatment during pregnancy reported in the literature series

	Warfarin	Heparin (in first trimester)	Heparin throughout pregnancy	Low molecular weight heparinH
Fetal risk				
Death	30%	24%	–	?
Embryopathy	4–10%	2%	–	?
Maternal risk				
Death	1.8%	4.2%	7%	?
Thromboembolism	3.9%	9–24%	25%	?

associated with fetal embryopathy (nasal hypoplasia, bone stippling and optic atrophy) that occurs in approximately 6% of cases and an increased risk of miscarriage or stillbirth (cerebral fetal haemorrhage). Because of this maternal and fetal 'double jeopardy', women with mechanical valves should be informed about the risks of pregnancy and the necessity for immediate pregnancy testing if menstrual periods are missed.

The most appropriate anticoagulation regimen will be based on several factors: type of valve prosthesis (e.g. old generation caged-ball prosthesis vs. new bileaflet tilting disc), valve position (mitral vs. aortic), warfarin dose and the desires of prospective parents. Low-risk patients are those with an aortic new-generation valve prosthesis or those who need low doses of warfarin (≤ 5 mg) to maintain an adequate international normalized ratio (INR). The risks of anticoagulant treatment (Table 20.3) always have to be discussed with the mother.

As a result of the controversial recommendations of the cardiology societies about the use of low-molecular-weight heparin (LMWH), there is no consensus of opinion [47,52–57]. The management options, which await confirmation, include the following.

1 Heparin and warfarin combination: stop warfarin treatment as soon as the pregnancy test is positive. Unfractioned heparin in the first 13 weeks of pregnancy, switching to warfarin in the second trimester, continuing it until week 36 of gestation or 2 days before the planned delivery and then changing again to heparin until 4–5 days after delivery. Heparin should be terminated at the onset of labour and re-instituted shortly (12–24 h) after delivery. During pregnancy heparin should be given subcutaneously two or three times daily and the dose adjusted to maintain the partial thromboplastin time at greater than twice control levels at all times; the monitoring should be performed at least twice weekly. In clinical practice this option is rarely chosen.
2 LMWH and warfarin combination: stop warfarin treatment as soon as the pregnancy test is positive. LMWH (nadroparin calcium or enoxaparin) in the first 13 weeks of pregnancy, switching to warfarin in the second trimester, continuing it until week 36 of gestation or 2 days before the planned delivery and then changing to heparin. LMWH should be given subcutaneously twice daily and the dose adjusted to body weight to maintain anti-Xa between 0.5 and 1.0 U/ml 4–6 h after injection. LMWH does not cross the placenta. Meticulous attention should be paid when shifting from one regimen to the other because most of the complications reported occur during these periods. These therapy changes are best followed with a hospitalized regimen. This option is probably best in high risk patients.
3 Warfarin throughout the whole of pregnancy if low doses are needed to maintain appropriate INR, with patients' consensus.
4 LMWH throughout the whole of pregnancy, administered twice daily with dose adjusted to body weight. (This option awaits confirmation and should therefore be considered only in low-risk patients.)

Marfan's syndrome

With a population incidence of 1 in 5000, Marfan's syndrome is the most frequently encountered fibrillin-1 deficiency disorder. It is transmitted as an autosomal dominant trait and is characterized by multiorgan dysfunction, predominantly affecting the eyes, skeleton and cardiovascular system. There are two main problems in a woman with Marfan's syndrome who is contemplating pregnancy: (1) the risk of serious maternal complications during or shortly after pregnancy and (2) the risk of recurrence in offspring.

Whenever possible before starting pregnancy, any woman with Marfan's syndrome should undergo a full clinical assessment (family history, ultrasound examination of the entire aorta, echocardiography, magnetic resonance imaging) and a careful counselling of maternal and fetal risk. The risk of aortic dissection or other serious cardiovascular complication (endocarditis or congestive heart failure) during pregnancy is 1% even in the absence of aortic root dilatation, and may further increase, reaching 10%, in the presence of poor family history, aortic root diameter > 45 mm and significant mitral or aortic valve regurgitation [25,58]. The recommendations are as follows.

1 Patients with aortic root enlargement > 4.5–5 cm and aortic or mitral severe regurgitation should undergo elective surgery before pregnancy; if they refuse, they will be advised against pregnancy.
2 In patients with aortic root enlargement of 4–4.5 cm, aortic root dimension assessment with serial echocardiography (each trimester until 6 months after delivery) should be recommended. During pregnancy, physical activity should be limited and the use of beta-blocker therapy is recommended.
3 Even in patients without cardiovascular involvement, the relatively 'small' risk of complications should be discussed, as these can occur outside pregnancy. Clinical and echocardiographic monitoring should be performed during pregnancy and normal vaginal delivery should be conducted.

Besides the risk of cardiovascular involvement, women with Marfan's syndrome must know and accept that there is a 50% risk of their offspring having Marfan's and that the degree of severity of the disease could be worse than that of the parent.

Coronary heart disease

Acute myocardial infarction rarely occurs in women of child-bearing age and has been estimated to occur in only 1 in 10 000 women during pregnancy [59]. However, with the current trend of child-bearing at an older age and the ongoing effects of cigarette smoking, diabetes and stress, the occurrence of acute myocardial infarction during pregnancy can be expected to increase. Myocardial infarction occurs mostly in multiple pregnancies and most commonly in the anterior wall. The reported maternal mortality rate, before the current practice of primary percutaneous coronary angioplasty, varies from 21 to 48%, either at the time of infarction (mostly in the third trimester) or within 2 weeks of the infarction [59,60]. The differential diagnosis of ischaemic chest pain includes haemorrhage, sickle crises, pre-eclampsia, acute pulmonary embolism and aortic dissection [61]. It is confirmed by ECG changes and increase in enzyme levels. Management includes coronary angiography with abdominal shielding. Spontaneous coronary dissection of the proximal left anterior coronary artery is the most common cause of myocardial infarction, especially in the postpartum period. Successful treatment includes coronary stenting, emergency coronary artery bypass grafting or administration of tissue plasminogen activator, as described in case reports [62].

The delivery should be postponed for at least 2 or 3 weeks after the myocardial infarction to allow adequate healing. The mode of delivery should be determined by obstetric reasons and the clinical status of the mother.

Cardiac transplantation

If ventricular function is normal and there are no signs of rejection, pregnancy is usually successful. The absence of rejection should be established before conception and needs to be assessed during pregnancy. Preconceptional genetic counselling is necessary depending on the indication for transplantation, such as mitochondrial myopathy or familial dilated cardiomyopathy. Management during pregnancy includes monitoring left ventricular function and preventing complications such as hypertension, infection, preterm labour, intrauterine growth restriction and pre-eclampsia [61,63,64]. The choice of delivery mode is based on obstetric indications.

Cardiovascular treatment during pregnancy

Treatment in pregnancy is not based on randomized trials but on limited data from case reports (successes tend to be reported), observational studies and clinical individual experience. The safety of both mother and fetus has to be taken into account because treatment for one can have adverse effects on the other. Pregnant patients with heart disease and their close relatives should receive general advice such as limitation of physical activity, with complete bed rest in severe cases, and salt and fluid restriction. Self-weighing should be encouraged and in the case of sudden unexpected weight gain the physician should be contacted. Other general advice includes stopping smoking and avoiding excessive alcohol intake and all unnecessary medications.

Pharmacological therapy

The use of any medication in pregnancy and during lactation has to consider the safety and tolerability for the fetus and infant, the physiological maternal changes and the risk–benefit ratio. In patients who are already taking cardiovascular medications, discontinuation or the switch to a 'safer' drug should be discussed before conception. Because of the lack of randomized trials and the fear of tragedies such as the thalidomide disaster, there is an extreme reluctance to introduce any new drugs in pregnancy. Drugs with the longest record of safety should be used as the first-choice therapy [65,66]. However, the fear of 'unpredictable' complications must not overcome the correct use of drug treatment in pregnancy, because most of the drugs used to treat heart disease can be prescribed safely during pregnancy.

The effective plasma concentration of drugs varies during pregnancy. For example, the progesterone-induced reduction in gastrointestinal motility and the estrogen-induced increase in gastric secretion may result in altered drug absorption. Intravascular volume is increased during pregnancy, resulting in enhanced volume distribution and lower serum concentrations that may require an increase in the loading dose. Serum protein concentration falls during pregnancy, causing a reduction in protein binding and an increase in the non-protein-bound fraction. Increases in renal blood flow and glomerular filtration rate may augment drug clearance. The transplacental transfer of drugs depends on liposolubility or hydrosolubility and molecular weight of the drug, the pH of maternal and fetal fluids, the link with carrier protein and the gradient between maternal and fetal concentration [67,68].

Table 20.4 categorizes drugs according to the reliability of evidence of fetal risk and the potential risk–benefit ratio [65–81].

Therapy of heart failure

Diuretics are the first drugs to be employed in order to reduce hypervolaemia in patients with severe symptomatic congestive heart failure not responding to water and salt restriction. Diuretics are not recommended for management of pedal oedema or prophylaxis of eclampsia. In patients already receiving diuretics, the therapy should be continued during pregnancy and the peripartum period independently of the presence of mild hypotension. Although furosemide crosses the placental barrier, it is the drug of choice because no teratogenic or cardiovascular fetal effects have been described. Collateral effects to be controlled are hypovolaemia and hypokalaemia. Particular caution should be taken in cyanotic patients because haemoconcentration can cause thrombosis. No adverse events have been reported in patients treated with spironolactone, particularly indicated in cases of hypokalaemia. Thiazides are not recommended due to the reported neonatal thrombocytopenia, jaundice, hyponatraemia and bradycardia [67,68].

Angiotensin-converting enzyme (ACE) inhibitors should be withdrawn during pregnancy because of teratogenic effects. Reported complications include fetal and neonatal renal failure, oligohydramnios, intrauterine growth retardation and hypoplasia of skull bones especially in the second and third trimester [69]. There are no data available about angiotensin II receptor antagonists in pregnancy, but because their actions are similar to those of ACE inhibitors their use is contraindicated.

Specific information on the safety of nitrates and sodium nitroprusside is lacking. Intravenous as well as oral nitrates have been used in a few patients for the treatment of hypertension, myocardial ischaemia and heart failure, although case reports of fetal heart decelerations have been reported.

Dopamine and dobutamine can be used in low-output congestive heart failure. A few cases have been reported with no adverse effect [67–69]. However, during pregnancy with a viable fetus, fetal monitoring is advisable.

The experience with digoxin is extensive and there are no reports of teratogenicity associated with its use. It is considered a preferred choice for treatment of congestive heart failure, especially when supraventricular arrhythmias and systolic dysfunction are present. Furthermore, digoxin is the first-line drug for maternal and fetal rate control in atrial fibrillation/flutter and for the treatment of fetal supraventricular tachycardias [70,71]. Because of increased renal clearance, the serum digoxin concentration may be lower and so maternal dose should be increased. In the presence of decreased renal function or concomitant administration of amiodarone, maintenance doses may require reduction. Even if higher doses are required during pregnancy, caution in changing the amount of digitalis is advised because digitalis toxicity has been associated with miscarriage and fetal death. In the third trimester, serum digoxin levels may appear falsely elevated because of the presence of digoxin-like substances interfering with radioimmunoassays. Hence, the monitoring of digoxin levels would not be helpful in guiding treatment [71].

Management of arrhythmias

Pregnancy may increase the incidence of arrhythmias. Knowledge of the underlying heart disease is important for the correct treatment. Most of the antiarrhythmic drugs can be prescribed safely in pregnancy but an attempt to recognize a correctable cause should be undertaken before starting therapy. All antiarrhythmic drugs cross the placental barrier and their potentially toxic effect on the fetus should be taken into consideration, particularly during the first weeks of pregnancy [71].

MATERNAL TACHYARRHYTHMIAS

Ectopic beats are present in one-third of pregnant women but are generally benign and well tolerated. No treatment other than reassurance and correction/elimination of potential stimulants are indicated. An increased risk of new-onset, and exacerbation of, supraventricular tachycardia during pregnancy has been reported (3%), while ventricular tachycardia is rare. When dysrhythmias such as atrial fibrillation or flutter are present during pregnancy, an underlying cause should be considered.

Electrical cardioversion is the treatment of choice for all drug-refractory maternal arrhythmias or those

Table 20.4 Cardiovascular drugs during pregnancy*

Drug	Use during pregnancy	Adverse fetal or neonatal effects	Breast-feeding
Antiarrhythmic agents			
Adenosine	First-line treatment: paroxysmal supraventricular tachycardia	No teratogenicity or other adverse effects	Short half-life makes a problem unlikely
Amiodarone	Refractory maternal and fetal arrhythmias Maternal arrhythmias in presence of impaired left ventricular function	Intrauterine growth retardation, premature birth, fetal hypothyroidism	Secreted in maternal milk so not recommended
Beta-blockers (atenolol, propranolol, metoprolol)	Control ventricular rate in atrial fibrillation Second-line treatment of maternal supraventricular arrhythmias Prophylactic therapy for supraventricular and ventricular tachycardias	No teratogenicity Fetal bradycardia, hypoglycaemia, premature labour and metabolic abnormalities Intrauterine growth retardation?	Compatible
Digoxin (see heart failure)			
Flecainide	Second-line therapy for maternal and fetal supraventricular arrhythmias	No reports of teratogenicity	Limited data
Lidocaine	Maternal ventricular arrhythmias Local anaesthesia	Fetal bradycardia, central nervous system toxicity	Limited data
Propafenone	Second-line therapy for maternal supraventricular arrhythmias		Limited data
Sotalol	Second-line therapy for maternal supraventricular arrhythmias Fetal tachycardia	Fetal bradycardia, intrauterine growth retardation	Limited data
Verapamil	Second-line therapy for maternal supraventricular arrhythmias	Maternal hypotension and subsequent fetal hypoperfusion	Limited data
Heart failure therapy			
ACE inhibitors	Not recommended	Teratogenic effects	Compatible
Angiotensin II receptor antagonists	Not recommended	Limited data	Limited data
Digoxin	Prophylactic therapy for supraventricular tachycardias Control of ventricular rate in atrial fibrillation Fetal tachycardia Heart failure	No reports of teratogenicity	Compatible
Loop diuretics (furosemide)	Severe symptomatic congestive heart failure	No teratogenic or cardiovascular fetal effects	Compatible
Sparing diuretics (spironolactone)	Congestive heart failure and hypokalaemia	No teratogenic effects	Compatible
Nitrates	Myocardial ischaemia Heart failure Hypertension	Fetal heart deceleration, maternal hypotension and subsequent fetal hypoperfusion	Limited data
Hypertensive disease therapy			
Prophylactic treatment in women with historical risk factors			
Aspirin	Reduces the risk of perinatal death and pre-eclampsia	Haemorrhage, prolongation of labour	
Calcium supplementation	Positive impact on maternal and fetal morbidity needs to be confirmed		Limited data
Magnesium sulphate	Reduces the risk of eclampsia in women with severe pre-eclampsia		Limited data
Severe hypertension			
Hydralazine	Second-line therapy	Neonatal bradycardia	Compatible
Labetalol	First-line therapy	Neonatal bradycardia	Limited data
Nifedipine	First-line therapy	Fetal distress	Limited data
Nitroprusside	Second-line therapy	Thiocyanate poisoning	Limited data

*Based on multiple studies [57–73].

causing haemodynamic compromise and can be performed safely at any time during pregnancy. Paroxysmal supraventricular tachycardias are usually well tolerated and require active therapy only if very frequent or long-lasting or with haemodynamic instability. Vagal manoeuvre should be tried first and, if ineffective, intravenous adenosine would be the first-choice drug. Maternal effects may include facial flushing, headache, dyspnoea and nausea. Adenosine crosses the placenta but no adverse fetal effects have been described. Second-line drugs include beta-blocking agents or propafenone. Intravenous verapamil can be used but maternal hypotension, heart failure and inhibition of labour have been reported. If prophylactic drug therapy is needed, then β_1 receptor blockers or digoxin are the first choice [69,70].

Atrial fibrillation and flutter are rare in pregnancy and often secondary to congenital or valvular heart disease. Therapy includes ventricular rate control using digoxin or beta-blocking agents and conversion to sinus rhythm using propafenone or amiodarone (termination of atrial episodes should be attempted in order to avoid anticoagulation therapy). Ventricular tachycardia during pregnancy is rare in healthy women without organic disease but it can occur when ventricular scars are present (e.g. tetralogy of Fallot). Beta-blockers are the first-line therapy when ventricular function is preserved. Some forms of non-sustained ventricular tachycardia in normal hearts respond well to verapamil. If ventricular function is impaired, amiodarone is the only option. Chronic administration of amiodarone can have adverse effects on the mother in 3–5% of cases, including thyroid malfunction, photosensitivity and corneal deposition. In the fetus, long-term treatment with amiodarone can cause neonatal hypothyroidism [71,72], which is however reversible.

Although catheter ablation has been performed in a pregnant patient, it should be recommended only in patients with drug-refractory, poorly tolerated or life-threatening arrhythmias [68]. The presence of an implantable cardioverter–defibrillator should not be considered a contraindication to pregnancy [73], but implantation during pregnancy has never been reported in the literature.

MATERNAL BRADYARRHYTHMIAS

Compared with the tachyarrhythmias, bradyarrhythmias are uncommon, but when they occur are usually well tolerated. Management should not be influenced by pregnancy. Temporary or permanent pacemaker, if required, can be implanted at any stage of pregnancy, although treatment is generally not indicated unless the conduction abnormality causes symptoms. Women with congenital complete heart block, as previously reported, can accomplish an uneventful and successful pregnancy [74] with or without a pacemaker.

FETAL ARRHYTHMIAS

Fetal tachycardia, defined as a heart rate greater than 180 b.p.m., is a condition that occurs in approximately 0.4–0.6% of all pregnancies, and may cause non-immune fetal hydrops and lead to fetal morbidity and mortality. Maternal full-dose digoxin is the first-line antiarrhythmic agent in non-hydropic fetuses, while verapamil and beta-blocking agents are second-line therapy. In drug-refractory fetal tachycardia, particularly if accompanied by hydrops fetalis or ventricular dysfunction, amiodarone represents a safe and effective option [75]. Sotalol should be considered a valuable treatment option for fetal atrial fibrillation, which is extremely rare [76].

Prophylaxis of endocarditis

As in the non-pregnant state, antibiotic prophylaxis is indicated before undergoing a procedure likely to cause bacteraemia. Since the incidence of bacteraemia following vaginal delivery has been reported to be low (0–5%), routine antibiotic prophylaxis for uncomplicated vaginal delivery or primary (or planned) caesarean section in women with heart disease is not recommended [17,46,77]. However, the high morbidity and mortality associated with cardiac infection, the risk of unpredictable complications and the relatively safety of antibiotic prophylaxis in patients who are already receiving it should lead to consideration of antibiotic prophylaxis in all high-risk cardiac conditions. Antibiotic therapy should be administered 30 min before caesarean section or at the beginning of spontaneous delivery.

Percutaneous therapy

Over the last 20 years, interventional cardiology has emerged as a new therapeutic tool and as an effective alternative to surgical therapy in several cardiac diseases, such as valve stenosis and coronary artery disease [21]. Cardiac catheterization in the pregnant patient carries the risk of fetal radiation exposure. The effects of radiation on the fetus depend on the radiation dose and the gestational age at which exposure occurs. As previously reported, the maximum permissible dose of radiation to the pregnant woman has been set at 5 mGy. During cardiac catheterization the mean radiation exposure to the unshielded abdomen is 1.5 mGy, and less than 20% of this reaches the fetus because of tissue attenuation. Shielding the gravid uterus from direct radiation, shortening fluoroscopic time and delaying the procedure until at least the completion of the period of major organogenesis (> 12 weeks after menses) will minimize radiation exposure. With these provisions, cardiac catheterization and interventional procedures during

pregnancy are safe for the fetus but should be considered only in patients not manageable with medical therapy (see Fig. 20.2).

Cardiac surgery

Open heart surgery can be performed during pregnancy, with the same risk to the mother as outside pregnancy but with a high incidence of fetal death (20–33%). The best period to perform surgery is early in the second trimester because in the first trimester it may cause abortion and later in the third trimester premature labour. The poor fetal outcome is due to non-pulsatile blood flow and hypotension associated with cardiopulmonary bypass that can adversely affect placental blood flow. Cardiopulmonary bypass in pregnancy must be performed at high flow and high pressure, in normothermia, with the shortest possible cross-clamping time.

Personal perspective

Pregnancy is a part of a woman's life and not a disease and most of the time is surprisingly well tolerated in patients with mild or moderate heart disease. The important rise in cardiac output that occurs particularly in the second and third trimesters of pregnancy is well balanced by the decrease in peripheral vascular resistance. Pregnancy continuation should be encouraged in the majority of cases, although patients with a severe degree of mitral or aortic valve stenosis remain particularly at risk. Pregnancy must be followed by an experienced team, particularly in the third trimester and during and after delivery.

The panorama of heart disease in women of child-bearing age has changed and will change further. The profile of the cases at risk has become different: pulmonary hypertension and cyanotic heart disease have become rare because of early correction during infancy; palliated or corrected forms of congenital heart disease with residual defects, valvular heart disease in immigrants and cardiomyopathies with or without coronary artery disease in older women have become more frequent.

Multiple other factors can increase the risk during pregnancy in women with heart disease. Older age at pregnancy, smoking habits and twin or triple pregnancy secondary to frequent *in vitro* fertilization are much more common and have to be taken into consideration when assessing the risk. Heart failure secondary to impaired left or right ventricular function has become a common complication in this setting and its early recognition and treatment is mandatory. Correction of residual defects or aortic or mitral valve disease, particularly stenotic valves even with moderate degrees of stenosis, should be considered before pregnancy. Percutaneous procedures or minimally invasive surgical repair can today be performed in these young women with low rates of complications, making it easier to accomplish pregnancy without problems.

Rest is the first step in all patients at risk. Heart failure should be managed according to conventional guidelines, except for the use of ACE inhibitors because of their known fetal toxicity. Particular attention should be paid to fluid retention in the immediate postpartum period. Interventional procedures or heart surgery, particularly during the second and third trimesters, can be done with acceptable risks for mother and fetus. From the surgical standpoint, short pump runs with high flow rates are essential criteria, ensuring low levels of fetal loss.

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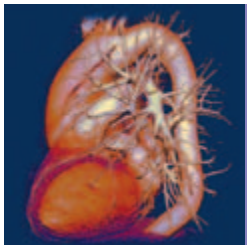

21 Valvular Heart Disease

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Summary

Valvular heart disease (VHD), although not as common as coronary disease, heart failure or hypertension, is an important, and challenging, clinical entity. It is of interest for the following reasons: substantial advances have been made in the understanding of its pathophysiology; important changes in patient characteristics and aetiologies have occurred over recent years; diagnosis is now largely dominated by echocardiography, which has become the standard to evaluate valve structure and function; and, finally, treatment has not only developed through the continuing progress in prosthetic valve technology, but also has been re-orientated by the development of conservative surgical techniques and the introduction of interventional cardiology.

This chapter will review the main aspects of acquired valve disease in adults, including the important subgroup of patients who have previously undergone valve replacement. Useful complements to this chapter can be found in Chapters 2, 19, 20 and 34.

Introduction

Epidemiology

During recent decades, important changes have occurred in the geographical distribution of the aetiologies of VHD in Western countries. The continuous decline of acute rheumatic fever explains the decrease in the incidence of rheumatic valve disease, while increased life expectancy partially accounts for the increase in the incidence of degenerative valvular diseases. The incidence of endocarditis remains stable and other aetiologies, such as congenital, inflammatory or carcinoid valve diseases, remain rare [1]. Emerging aetiologies that have been identified more recently, in particular drug- or radiation-related valve lesions, may also be an occasional cause [2].

Because of the predominance of degenerative valve disease, the two most frequent valve diseases are currently calcified aortic stenosis (AS) and mitral regurgitation (MR), whereas aortic regurgitation (AR) and mitral stenosis (MS) have become less frequent (Table 21.1) [3]. The prevalence of AS increases after the age of 70 years and the number of cases will also increase with population ageing [4]. Another particularity of contemporary heart valve disease is the growing proportion of previously operated patients, who accounted for 28% of patients in the Euro Heart Survey [3].

Nevertheless, rheumatic valve disease still remains a major public health problem in developing countries, where it predominantly affects young adults. A recent survey performed in Pakistan estimated the prevalence of rheumatic valve disease at 5.7 per 1000, without any decrease over time [5]. Most patients were not aware of the diagnosis and prophylaxis was under-used.

Despite the decrease in the prevalence of rheumatic heart disease in Western countries, the number of valve procedures did not decrease in surgical registries [6,7]. Surgical series analysing temporal trends over the two last decades consistently show that changes in aetiologies have important implications in patient presentation and management as degenerative valve disease predominantly affects the elderly [8,9]. The mean age was 65 years in the Euro Heart Survey, 38% being aged over 70 [3]. Increased age is associated with a higher frequency of comorbidity, which contributes to increased operative risk and renders decision-making for intervention more complex.

Table 21.1 Distribution of the aetiologies of native single-valve diseases in the Euro Heart Survey on valvular heart disease

	Aortic stenosis ($n = 1197$)	Aortic regurgitation ($n = 369$)	Mitral stenosis ($n = 336$)	Mitral regurgitation ($n = 877$)
Degenerative (%)	82	50	12	61
Rheumatic (%)	11	15	85	14
Endocarditis (%)	1	8	1	4
Inflammatory (%)	0	4	0	1
Congenital (%)	5	15	1	5
Ischaemic (%)	0	0	0	7
Other (%)	1	8	1	8

Adapted from Iung *et al.* [3].

Aortic stenosis

AS is the most common valve disease in Western countries [3,4], which explains the interest in its management.

Aetiology

The most frequent aetiologies are degenerative (accounting for 80% of the cases in Western countries), followed by rheumatic and congenital [3]. Degenerative AS occurs on tri-leaflet valves. Calcification begins at the base of the cusps and progresses towards the edges, while the commissures remain open (Fig. 21.1). Rheumatic disease is characterized by commissural fusion and fibrosis, with retraction and stiffening of the cusps. Bicuspid valves are of unequal size and tend to progressively thicken and calcify. Other rare causes are: familial hypercholesterolaemia, hyperuricaemia, hyperparathyroidism, Paget disease, ochronosis, Fabry disease, lupus erythematosus, and drug-induced diseases.

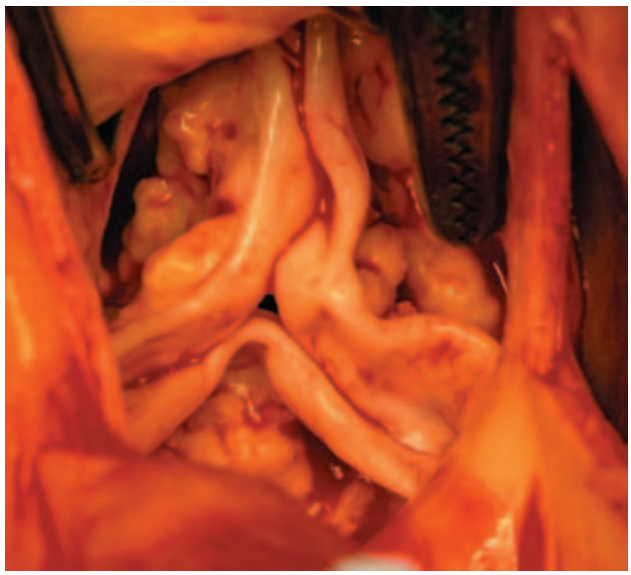

Figure 21.1 Perioperative view of severe calcified aortic stenosis. Severe calcification is located in the aortic cusps. There is no commissural fusion. (Courtesy of Dr P. Nataf.)

Pathophysiology

The evolution from degenerative aortic sclerosis to AS does not simply result from a 'wear and tear mechanism' and ageing, but probably from an active inflammatory process similar to that of atherosclerosis. This assertion is supported by the findings of epidemiological studies, which suggest that risk factors are common to both coronary disease and degenerative AS [10–12], as well as histological studies that document the presence of lipid particles and inflammatory infiltrates in the valves [13]. Furthermore, experiments suggest that valve calcification is an active regulated process in which cholesterol contributes to the early valve injury [14] and is associated with an osteoblast-like phenotype leading to bone formation in the end stages of the disease. Potential genetic factors have also been identified. These findings indicate that 'degenerative' may not be the most accurate term for this process, however, it remains in common usage.

Normal aortic valve area is 2–4 cm^2. A gradient between left ventricle (LV) and aorta appears if valve area is < 1.5 cm^2 and AS is considered severe when the area is < 1 cm^2 or, more accurately, 0.6 cm^2/m^2 body surface area (BSA). The obstruction develops gradually and imposes a pressure overload on the LV, which subsequently causes the development of concentric hypertrophy at rates that vary according to the individual. Ventricular hypertrophy is a key adaptive mechanism to counter pressure overload as it normalizes wall stress

[15]. However, it also has adverse consequences: increase in the total collagen volume of the myocardium; reduction of LV compliance leading to a limited preload reserve; and myocardial ischaemia, which may be present even when coronary disease is not, and is caused by the combination of increased myocardial oxygen demand and limited coronary flow [16]. LV systolic performance may be impaired (even if contractility is normal) due to afterload mismatch, leftwards shift of the ventricular preload on the Starling curve, or asynchrony of the temporal sequence of contraction. Late in the course of the disease, the cardiac output, and therefore the transvalvular gradient, declines, whereas the pressures in the left atrium and pulmonary artery rise, leading to dyspnoea. Syncope on exertion occurs when elevated LV pressures stimulate baroreceptors located in the LV, inducing arterial hypotension, decreased venous return and bradycardia.

Diagnosis

The following procedures are used to assist diagnosis.

HISTORY

Frequently, the diagnosis is made when a systolic murmur is detected during a routine physical examination. AS is gradually progressive and symptoms usually appear between the second and fourth decade in rheumatic AS, the fifth and sixth decade in patients with bicuspid valves, and the seventh or eighth decade in degenerative aetiology.

The most common initial symptom is exertional dyspnoea or fatigue. Angina is a poor indicator of coronary disease, as coronary disease may be present in 25% of patients without angina and in 40–80% of those with angina [17]. Syncope, or light-headedness, also occurs on exertion. Later, dyspnoea may progress to overt heart failure. In practice, AS may be discovered during attempted diagnosis of unexplained congestive heart failure.

PHYSICAL EXAMINATION

In severe AS the carotid pulse is typically slow rising and of small amplitude. The murmur is crescendo–decrescendo and mid-systolic, with a late peaking sound indicating severe stenosis. It is harsh and rasping at the base and is transmitted to the carotids. It often radiates towards the apex as a high-pitched murmur mimicking MR. When it is of high intensity, a thrill may be palpated; conversely, it may be soft if cardiac output is low. In severe AS, the second heart sound may be single or, paradoxically, split. An ejection click may be heard at the base in patients with mobile valves. Finally, a fourth sound is frequent at the apex.

CHEST RADIOGRAPH

Overall cardiac silhouette and pulmonary vascularization are normal unless cardiac decompensation is present. Post-stenotic dilatation of the ascending aorta is frequent. Calcification of the valve is found in almost all adults with severe AS; however, fluoroscopy may be necessary to detect it.

ELECTROCARDIOGRAM

LV hypertrophy, with or without repolarization abnormalities, is seen in approximately 80% of patients with severe AS. Other non-specific signs include left atrial enlargement, left axis deviation and left bundle branch block. First-degree atrioventricular block is rare. Atrial fibrillation can be seen at a late stage and otherwise suggests coexisting mitral valve disease or coronary disease.

ECHOCARDIOGRAPHY

Echocardiography has emerged as the principal method to define the valve anatomy, determine the severity of stenosis, assess LV function and identify other coexisting abnormalities. It often reveals thickened valves with reduced motion. Sometimes the aortic annulus and surrounding aortic walls are calcified. Echocardiography reports should include a comprehensive evaluation of stenosis severity, including maximal and mean gradient, peak aortic jet velocity, and, most importantly, calculation of valve area using the continuity equation, which is essential for clinical decision-making and follow-up [18] (Fig. 21.2).

The ratio of peak LV outflow tract velocity to peak aortic valve velocity and valve resistance are also useful but have no clear additional advantages when used with calculation of valve area.

Two-dimensional echocardiography enables calculation of LV volumes, ejection fraction, wall thickness and mass. Doppler echocardiography is useful to assess diastolic function.

Evaluation of the changes in valve area with changes in flow rate in response to low-dose dobutamine is helpful in patients with severe LV dysfunction, when valve area remains unchanged while pressure gradient increases if severe obstruction is present [19]. Exercise echocardiography can be performed safely in asymptomatic patients but its predictive value is not well established.

Transoesophageal imaging is rarely needed; however, planimetry of the valve may provide useful information when ultrasound tissue penetration is poor and the leaflets are only moderately calcified.

Common coexisting valvular lesions include mitral annular calcification in degenerative disease and MR or MS in rheumatic disease. An asymmetric subvalvular LV obstruction may be present, especially in elderly women.

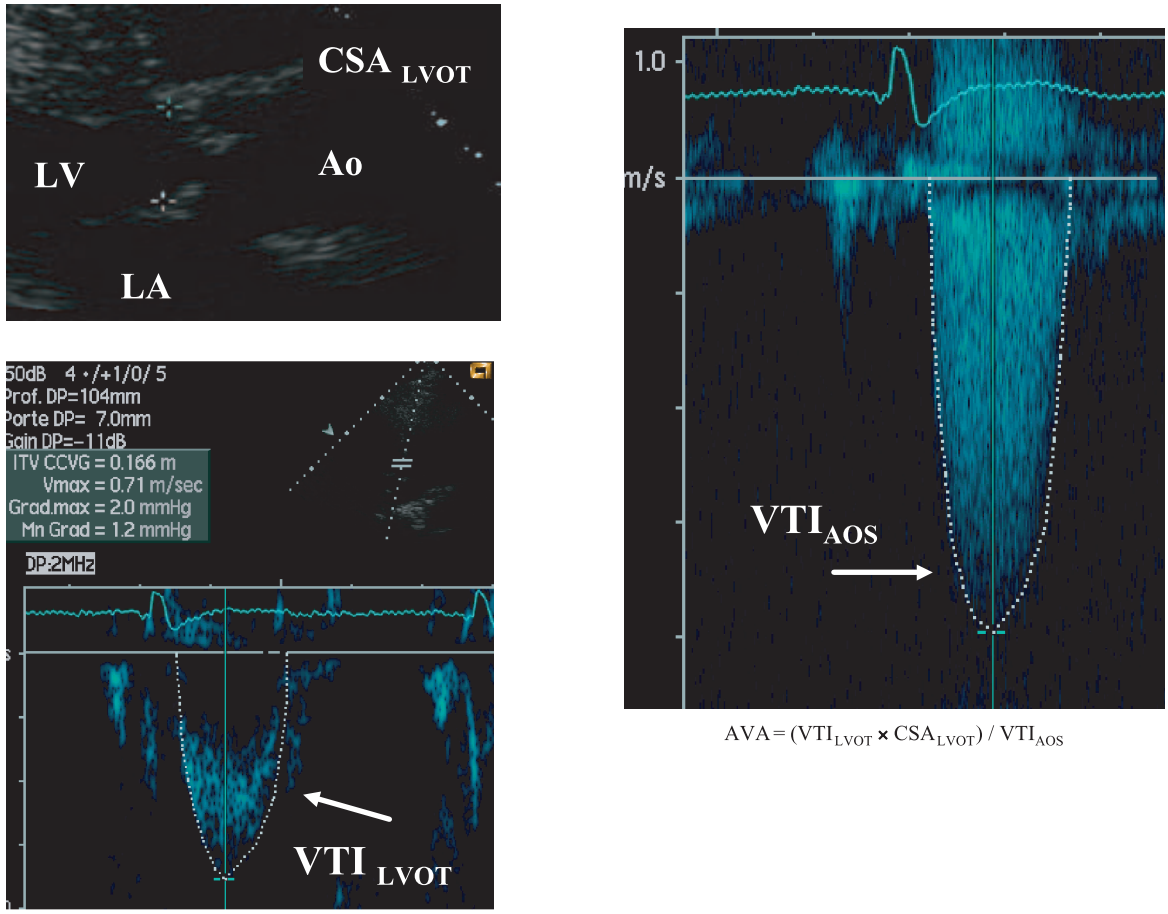

Figure 21.2 Calculation of the aortic valve area using the continuity equation. The continuity equation is based on the conservation of energy. Flow through an orifice is equal to the area of this orifice × velocity time integral. AOS, aorta; AVA, aortic valve area (cm^2); CSA, cross-sectional area; LA, left atrium; LV, left ventricle; LVOT, left ventricular outflow tract; VTI, velocity time integral. (Courtesy of Dr E. Brochet.)

EXERCISE TESTING

Exercise testing is contraindicated in symptomatic patients, but is safe and useful for unmasking symptoms in, and the risk stratification of, asymptomatic patients. Exercise-induced hypotension, or inadequate rise in blood pressure, is a good predictor of poor outcome [20,21]. Non-invasive stress testing, including myocardial perfusion imaging, is generally not helpful in detecting coronary disease as specificity is low and sensitivity is not 100%.

CARDIAC CATHETERIZATION

Because echocardiography is so effective at evaluating the severity of AS, invasive measurements are only needed in the rare cases when echocardiographic data are non-diagnostic or discordant with clinical data. Furthermore, catheterization should be used with caution, as it is not without risk [22].

Coronary angiography remains the gold standard to detect coronary artery disease (present in 30–60% of cases depending on population characteristics). In AS, as in other VHDs, it should be performed preoperatively in men over 40, in post-menopausal women over 50 or in patients with coronary risk factors [23,24].

OTHER NON-INVASIVE TECHNIQUES

Multislice computerized tomography (CT) provides high sensitivity and specificity in the detection of high-grade coronary artery stenosis but is not always available or feasible.

As most patients with severe AS are elderly and have comorbidities, the preoperative assessment should also include a comprehensive search for extracardiac abnormalities and other localizations of atherosclerosis.

Natural history

The natural history of AS has been evaluated in several recent prospective studies. The average decrease in valve

area is approximately 0.1 cm^2/year, the increase in gradient is 7 mmHg/year, and the increase in peak aortic jet velocity is 0.25 m/s. In general the rate of progression is linear, although it varies markedly among individuals. More rapid progression is associated with a higher event rate; however, the specific degree of valve narrowing associated with clinical symptoms shows considerable individual variability. The main predictors of rapid progression are old age, smoking, the presence of coronary disease, hypertension or dyslipidaemia [10–12].

Large population-based studies have shown that even AS has an important impact on prognosis as it was associated with a 50% increased risk of cardiovascular mortality and morbidity [10]. Recent studies have also shown that mild to moderate AS is not a benign disease as it is associated with a substantial mortality rate [25]. Progression to severe stenosis may be quicker than previously assumed; however, this only partially accounts for the high mortality rate as over 50% of the deaths were not cardiac. The mechanism of this association is not clear and is most likely linked to the presence of atherosclerosis in the entire cardiovascular system.

In asymptomatic patients with AS, the incidence of sudden death is low (less than 1%). The occurrence of symptoms is highly variable and ranges from 5% to 23% per year (Table 21.2). The main predictors of outcome derived from echocardiography are peak aortic jet velocity (Fig. 21.3), rapid increase in peak velocity and moderate to severe calcification [20,26]. In the study by Rosenhek and colleagues [26], the combination of moderate to severe calcification and rapid increase in peak velocity identified 79% of patients who either underwent surgery or became symptomatic within 2 years. An abnormal exercise capacity is also a strong predictor of poor outcome: in the study by Amato and colleagues [21] the probability of a patient with a positive stress test surviving event free after 24 months was only 19% compared with 85% in those with a negative test.

Table 21.2 Natural history of asymptomatic patients with aortic stenosis

Study	*n*	Severity of AS	Follow-up (years)	Event-free survival (%)
Otto *et al.* [20]	123	PV < 3 m/s	2.5	84
		PV 3–4 m/s	2	66
		> 4 m/s	2	21
Rosenhek *et al.* [25]	176	PV 2.5–3.9 m/s overall	3	75
		PV < 3 m/s	3	89
		PV < 3–4 m/s	3	70
		No or moderate Ca^{2+}	3	82
		Moderate to severe Ca^{2+}	3	61
Rosenhek *et al.* [26]	128	PV > 4 m/s	4	
		No or moderate Ca^{2+}	4	75
		Moderate to severe Ca^{2+}	4	20

AS = aortic stenosis; Ca^{2+} = valve calcification; PV = peak aortic velocity jet.

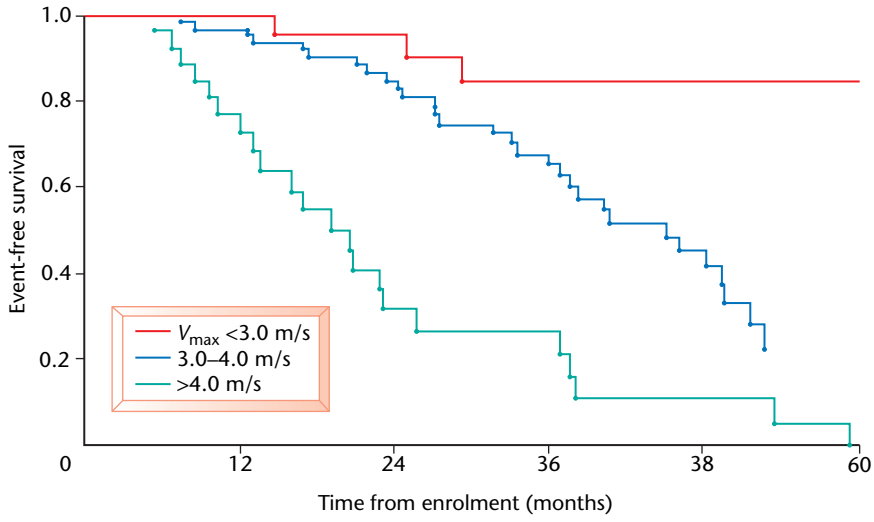

Figure 21.3 Natural history of asymptomatic patients with aortic stenosis according to peak aortic jet velocity. V_{Max} = peak aortic jet velocity at entry. Adapted from [20]. Reproduced, with permission, from Otto CM, Burwash IG, Legget ME *et al. Circulation* 1997; 95: 2262–2270.

Outcome is poor when any symptoms are present, with survival rates of only 15–50% at 5 years [27].

Medical treatment

The wide variability of the progression of AS heightens the need for physicians to be further educated regarding expected symptoms and follow-up. Stress test findings should determine the recommended level of physical activity [24].

No medical treatment for AS is able to delay the inevitability of surgery. Inotropes and diuretics may transiently improve heart failure.

Risk factors for atherosclerosis must be controlled even though further studies are needed to assess the preventive value of aggressive lipid lowering therapy on clinical outcome [28].

All patients should receive antibiotic prophylaxis to prevent endocarditis [29].

Percutaneous aortic valvuloplasty

Percutaneous aortic valvuloplasty (PAV) was first described by Cribier and colleagues in 1986 [30]. Its efficacy is limited as final valve area is only between 0.7 and 1.1 cm^2. Mortality and morbidity of the procedure are high. It is now recognized that PAV alone does not change the natural course of the disease.

The first cases of percutaneous aortic valve replacement have recently been performed under compassionate indications [31].

Surgery

Aortic valve replacement is the definitive therapy for severe AS. It uses either a mechanical or a bioprosthesis (Table 21.3).

In contemporary series, operative mortality of isolated aortic valve replacement is around 3–5% in patients below 70 years and 5–15% in older adults (Table 21.4). The following factors all increase the risk of operative mortality: older age, associated comorbidities, female gender, higher functional class, emergency operation, LV dysfunction, pulmonary hypertension, coexisting coronary disease and previous bypass or valve surgery. In patients with severe coronary disease the performance of concomitant bypass surgery approximately doubles operative mortality; however, these figures compare favourably with mortality in patients with coronary disease who did not undergo combined bypass surgery [3,7,17,32]. After successful valve replacement long-term survival rates are close to those expected, symptoms are less marked and

Table 21.3 Types of intervention performed for native single-valve diseases in the Euro Heart Survey on valvular heart disease (among a total of 1269 patients operated on during the study period)

	Aortic stenosis (*n* = 512)	Aortic regurgitation (*n* = 119)	Mitral stenosis (*n* = 112)	Mitral regurgitation (*n* = 155)
Mechanical prosthesis (%)	49	76	58	43
Bioprosthesis (%)	50	18	4.5	10
Valve repair (%)	0	1.7	3.5	47
Homograft (%)	0.6	2.6	0	0
Autograft (%)	0.4	1.7	0	0
Percutaneous intervention (%)	0	0	34	0

Adapted from Iung *et al.* [3].

Table 21.4 Operative mortality after surgery for valvular heart disease

	STS (2001)	UKCSR (1999–2000)	EHS (2001)
Aortic valve replacement no CABG (%)	3.7	3.1	2.7
Aortic valve replacement + CABG (%)	6.3	7	4.3
Mitral valve repair no CABG (%)	2.2	2.8	0
Mitral valve replacement no CABG (%)	5.8	6.2	1.7
Mitral valve repair or replacement + CABG (%)	10.1	8.6	8.2

STS = Society of Thoracic Surgeons (USA). Mortality for STS includes first and re-do interventions [7].
UKCSR = United Kingdom Cardiac Surgical Register. Mortality for UKCSR corresponds to first interventions only [6].
EHS = Euro Heart Survey [3].
CABG = coronary artery bypass grafting.

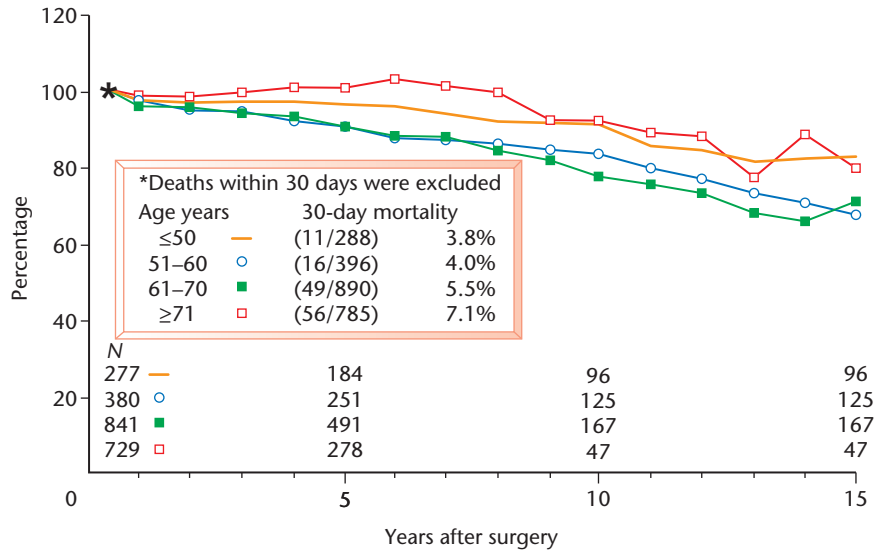

Figure 21.4 Long-term outcome after aortic valve replacement in aortic stenosis. Relative survival after aortic valve replacement in operative survivors by age. Adapted from [34]. Reproduced, with permission, from Kvidal P, Bergstrom R, Horte LG, Stahle E. *J Am Coll Cardiol* 2000; 35: 747–756.

quality of life is greatly improved [33,34] (Fig. 21.4). Risk factors for late death include age, comorbidities, severe functional condition, irreversible myocardial damage (which could also be due to myocardial scarring after infarction or ischaemic cardiomyopathy), ventricular arrhythmias and untreated coexisting coronary artery disease. In addition, poor postoperative outcome may result from prosthesis-related complications or sub-optimal prosthetic valve haemodynamic performance.

Treatment strategy

In patients with severe symptomatic AS, surgery must be performed soon after symptom onset. Most groups have abandoned PAV, whereas for others it would appear that there is a limited role in the following cases: cardiogenic shock and multivisceral failure; severe and poorly tolerated AS coupled with the need for major emergency non-cardiac surgery; absolute, but non-life-threatening, short-term contraindications to surgery; and refusal of surgery [23].

The decision to intervene in asymptomatic patients with severe AS is controversial and must be taken on an individual basis. Surgery can be recommended in the following circumstances: abnormal response to exercise, peak aortic jet velocity > 4 m/s and rate of progression of peak aortic jet velocity > 0.3 m/s/year, moderate to severe calcification, LV dysfunction (ejection fraction < 50%), severe LV hypertrophy (> 15-mm wall thickness) not due to hypertension or severe ventricular arrhythmias [23,24].

Asymptomatic patients who do not meet the criteria for intervention should be followed up at individualized intervals. In cases of moderate to severe calcification of the valve and peak jet velocity > 4 m/s at initial evaluation, patients should be re-evaluated every 6 months for the occurrence of symptoms or changes in exercise tolerance/echo parameters. If any evidence of progression is present, surgery should be considered. If no changes have occurred, 6-monthly clinical and 6- to 12-monthly clinical and echocardiographic re-evaluation is recommended. In patients who do not meet these criteria, a yearly follow-up visit is sufficient, follow-up being sooner in those with borderline values [24].

Whatever their functional status, patients with severe AS who undergo bypass surgery, aortic surgery or other valve surgery should also undergo aortic valve replacement. Patients with severe AS and significant coronary disease should undergo combined bypass grafting [23].

Special populations

Non-cardiac surgery

If stenosis is severe and leads to symptoms valve surgery is the first treatment to be considered. Asymptomatic patients can successfully undergo non-cardiac surgery if procedures are planned to optimize its management [35].

Elderly

Octogenarians, or even nonagenarians, experience higher morbidity and operative mortality; however, surgery can prolong and improve the quality of life [36]. Decisions should be made on an individual basis, taking into account cardiac and non-cardiac factors. Unfortunately, a large proportion of potentially suitable candidates are not referred for surgery at present [3], even although

valve replacement is the procedure of choice in this population.

Moderate aortic stenosis and significant coronary artery disease

Percutaneous revascularization should be considered whenever possible. The decision necessitates an individual assessment taking into account life expectancy, surgical risk, prosthetic-related complications, and factors determining the progression of AS. In practice, combined surgery should be considered if the valve area is between 1 and 1.5 cm^2, and in cases when rapid haemodynamic progression is more likely [17,37].

Aortic stenosis with low-gradient, low ejection fraction

This small group of patients is characterized by high operative risk and a dismal spontaneous prognosis [38]. Recent studies have shown that dobutamine echocardiography is useful in clarifying the pathophysiology and in predicting which patients will benefit most from surgery [19]. In patients with a contractile reserve, surgery carries an acceptable risk and improves long-term outcome in most cases. The outcome of patients without a contractile reserve is compromised by high operative mortality; however, there is a trend towards better survival after surgery. Decision-making in these patients should take into account clinical status, extent of coronary artery disease and degree of calcification as well as contractile reserve.

Aortic regurgitation

AR may be the consequence of diverse aetiologies, the distribution of which has changed over time. Aetiology influences patient management, in particular when the ascending thoracic aorta is involved. The severity of AR, its consequences on LV, and the morphology of the ascending aorta should be assessed at an early stage to allow for timely and appropriate intervention.

Aetiology

Degenerative AR is the most common aetiology in Western countries, accounting for approximately one-half of the cases of AR in the Euro Heart Survey on VHD (Table 21.1). It is a heterogeneous entity involving leaflet lesions, which are thin and subject to prolapse, and an aneurysmal dilatation of the ascending aorta predominating at the sinuses of Valsalva. Aortic aneurysm alone may cause AR, even with normal leaflets, because changes in the geometry of the aortic root create abnormal stress on the leaflet implantation [39].

Aortic root aneurysm is encountered in Marfan syndrome and in rare degenerative diseases, such as Ehlers–Danlos disease or osteogenesis imperfecta, as well as in patients who do not have generalized tissue disease (known as annulo-aortic ectasia) [40,41].

Rheumatic fever accounts for less than 15% of AR in Europe [3] but remains common in developing countries. Central regurgitation is the consequence of thickening and retraction of aortic leaflets.

Bicuspid valve disease represents 10–15% of the causes of AR. Abnormal stress on the leaflets progressively modifies valve structure and may cause AR, mainly by valve prolapse. An aneurysm that predominates above the sinuses of Valsalva is often associated [42].

Endocarditis still represents approximately 10% of the aetiologies of AR [3]. Regurgitation is related to leaflet tearing or perforation and, in certain cases, to a perivalvular abscess communicating with the aorta and the LV.

Aortitis is a heterogeneous group representing less than 5% of the aetiologies of AR [1]. Aortitis may be encountered in inflammatory diseases, such as ankylosing spondylitis, Takayasu arteritis, rheumatoid arthritis, lupus erythematosus, Behçet disease, giant cell arteritis, relapsing polychondritis or syphilis, now a very unusual cause.

Dissection of the ascending aorta compromises commissural support and causes acute AR, which is usually well tolerated, while tamponade is the major complication.

Besides bicuspid aortic valve, AR can be associated with ventricular septal defect or subvalvular AS in which regurgitation is caused by jet lesions.

The other rare causes are traumatism, radiation therapy and drug-induced AR.

Pathophysiology

Acute severe AR in a non-dilated LV causes a large increase in end-diastolic pressure, whereas cardiac output decreases as there is no compensatory increase in stroke volume, accounting for poor haemodynamic tolerance.

In chronic AR, progressive LV enlargement limits the increase in LV end-diastolic pressure and enables total stroke volume to increase, thereby compensating for the regurgitant volume and helping preserve normal cardiac output. Increased afterload is compensated by eccentric

LV hypertrophy. This compensation of volume and pressure overload explains the length of time that patients with chronic severe AR may remain asymptomatic [43]. LV dysfunction is potentially reversible if related to afterload mismatch but may persist after the correction of AR if related to structural myocardial injury.

Diagnosis

History

Dyspnoea is the most common symptom of AR; however, it only occurs at a late stage of the disease. Impaired coronary perfusion may cause angina. Conversely, acute AR rapidly leads to disabling dyspnoea or pulmonary oedema.

Physical examination

Exaggerated arterial pulsations are related to the increased stroke volume and diastolic flow reversal and represent the main clinical sign for quantifying AR. LV apical impulse is enlarged and displaced leftwards. The holodiastolic murmur is at its maximum at the left sternal border and is frequently associated with a mesosystolic murmur caused by the increased stroke volume. Other signs are an apical diastolic rumble (Austin Flint) and a mesosystolic sound ('pistol shot'). The second aortic sound may be louder in the case of aortic root aneurysm. In acute AR, diastolic murmur and peripheral signs are attenuated.

Electrocardiography

LV hypertrophy is the main feature of AR.

Chest radiograph

Cardiomegaly is the main abnormality in chronic AR. Signs of left heart failure are only observed at an advanced stage, except in acute AR.

Echocardiography

A number of indices have been proposed to quantify AR; the most frequently used with colour Doppler are the width of regurgitant jet at its origin and its extension into the LV (Fig. 21.5). Measurements using continuous-wave Doppler are the rate of decline of aortic regurgitant flow and diastolic flow reversal in the descending aorta. All these indices are influenced by loading conditions and the compliance of the ascending aorta and LV. Quantitative Doppler echocardiography should be favoured, using the continuity equation or analysis of proximal isovelocity surface area, which is less sensitive to loading conditions. The criteria for defining severe AR are an effective regurgitant orifice area of > 0.30 cm^2, regurgitant volume > 60 ml or a regurgitant fraction of > 50% [44].

The reference measurement of LV diameters is time–motion echocardiography as it was used in the prognostic studies. The accuracy of echocardiographic evaluation of LV ejection fraction is debated and it may usefully be completed with radionuclide ventriculography.

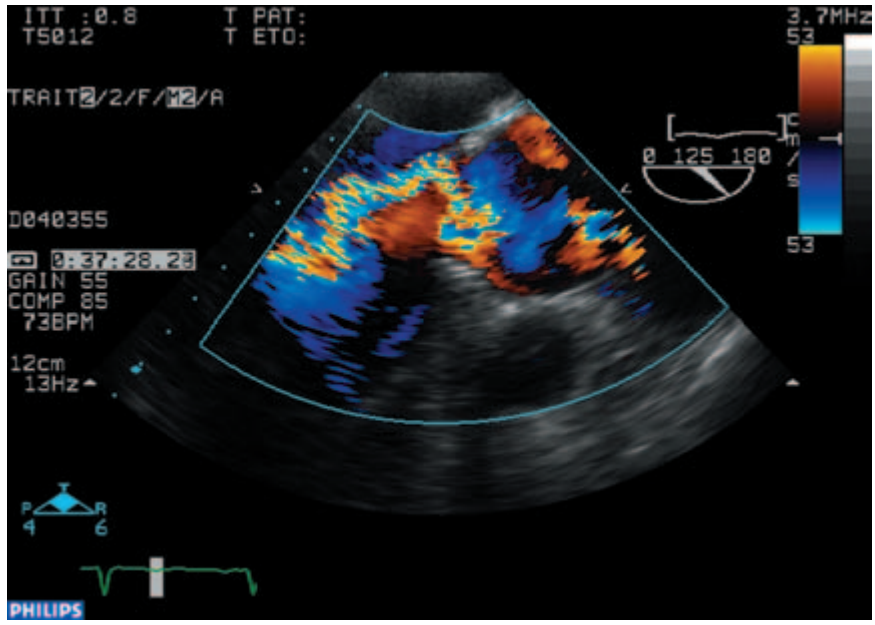

Figure 21.5 Severe aortic regurgitation. Transoesophageal echocardiography. Eccentric jet caused by valve prolapse in degenerative aortic regurgitation. (Courtesy of Dr D. Messika-Zeitoun.)

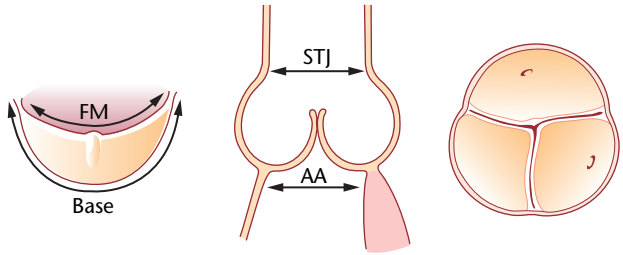

Figure 21.6 Geometric relationships of the aortic root. AA, aortic annulus; STJ, sinotubular junction; FM, free margin. From [58]. Reproduced, with permission, from David T, In: *Cardiac Surgery in the Adult*, 2nd edn, 2003, McGraw-Hill, Philadelphia PA, 811–823.

Transthoracic and/or transoesophageal echocardiography enable the anatomy of aortic leaflets and the aortic root to be accurately assessed, thereby contributing to the identification of the aetiology of AR.

Morphological analysis of the ascending aorta is of particular importance in the case of degenerative AR or bicuspid aortic valve. Diameters should be measured at four levels: aortic annulus, sinuses of Valsalva, sinotubular junction and ascending aorta [40] (Fig. 21.6).

Other valves should be examined since mitral valve disease may be associated in particular with Marfan syndrome or rheumatic AR.

Exercise testing

The main interest of exercise testing is to objectively evaluate exercise capacity. The studies of the prognostic value of exercise testing combined with electrocardiogram, echocardiography or radionuclide ventriculography led to conflicting results, which explains why these methods are not taken into account in current guidelines [23,24].

Imaging of ascending aorta

Morphology of the ascending aorta can be analysed and accurately quantified using computerized tomography or magnetic resonance imaging.

Cardiac catheterization

Quantification of AR, LV volumes and ejection fraction is generally obtained non-invasively using echocardiography.

Coronary angiography is required in preoperative evaluation [23]. Coronary angiography may not be performed in certain cases of acute AR, in particular in aortic dissection or acute endocarditis with large vegetations.

Natural history

The severity of AR increases more rapidly for moderate than mild regurgitation and in patients with bicuspid valve or degenerative disease than in those with pure rheumatic AR [45,46].

In asymptomatic patients with chronic severe AR and initially normal LV function, prospective studies have estimated the incidence of cardiac events, i.e. symptoms, LV dysfunction, or sudden death, at between 3% and 6% per year (Table 21.5) [47–51]. The strongest predictor of event is initial LV end-systolic dimension [48]. In addition to the initial measurements, the temporal changes of LV function should also be taken into account when making decisions about surgery. Symptom onset carries a poor prognosis and is frequently preceded by LV enlargement.

Progressive enlargement of the aortic root in Marfan syndrome increases the risk of complications, the main one being aortic dissection [40,52]. Most complications occur in patients whose aortic root diameter is > 50 mm, although this should be interpreted according to age and body surface area. Aortic complications are particularly rare when the ratio between observed and predicted aortic root

Table 21.5 Natural history of asymptomatic patients with chronic aortic regurgitation

	n	Mean follow-up (years)	Incidence of symptoms, death or LV dysfunction for 100 patients/year	Incidence of asymptomatic LV dysfunction for 100 patients/year
Siemienczuk *et al.* [47]	50	3.7	4.0	0.5
Bonow *et al.* [48]	104	8.0	3.8	0.5
Scognamiglio *et al.* [49]	74	6.0	5.7	3.4
Tornos *et al.* [50]	101	4.6	3.0	1.3
Borer *et al.* [51]*	104	7.3	6.2	0.9

LV = left ventricle.
*20% of patients in New York Heart Association class II.

Table 21.6 Predicted diameter of aortic root, measured at the level of the sinuses of Valsalva, according to age and body surface area [53]

Age (years)	Predicted diameter of the aortic root (cm)
< 18	1.02 + (0.98 × BSA)
18–40	0.97 + (1.12 × BSA)
> 40	1.92 + (0.74 × BSA)

BSA = body surface area (m^2).

diameter is < 1.3 [53] (Table 21.6). Aortic complications also occur in the case of annulo-aortic ectasia or aneurysm associated with bicuspid aortic valve, although there is less information on this than with Marfan syndrome.

Medical treatment

Randomized studies have shown favourable effects of vasodilators on the LV [54]. The body of evidence favours the use of the dihydropyridin class of calcium-channel blockers; the sole randomized study demonstrating a clinical benefit of vasodilators, enabling valve replacement to be postponed, used nifedipine [49].

In patients with Marfan syndrome, beta-blockers slow the dilatation of the aortic root and decrease the risk of aortic complications [55]. Beta-blockers should be avoided if AR is severe, as lengthening the diastole increases the regurgitant volume. Medical treatment of AR includes endocarditis prophylaxis [29].

Surgical treatment

Technique

Surgical treatment of AR is aortic valve replacement when there is no associated aortic aneurysm. When an aneurysm of the aortic root is associated with severe AR, the reference technique is the replacement of the ascending aorta using a composite graft comprising an aortic prosthesis, associated with a re-implantation of coronary arteries, according to the Bentall technique [52]. Replacing only the supracoronary section of ascending aorta is technically easier, but certain teams favour the Bentall technique because of the intrinsic abnormalities of the aortic wall.

In pulmonary autograft, also known as Ross intervention, the aortic valve is replaced with the patient's pulmonary valve, which is replaced by a homograft. Durability of the valve substitute is excellent in the aortic position [56]. Besides technical complexity, the main drawbacks are long cross-clamping times and the risk of pulmonary stenosis. This is the technique of choice in infants but it is seldom used in adults in current practice [3].

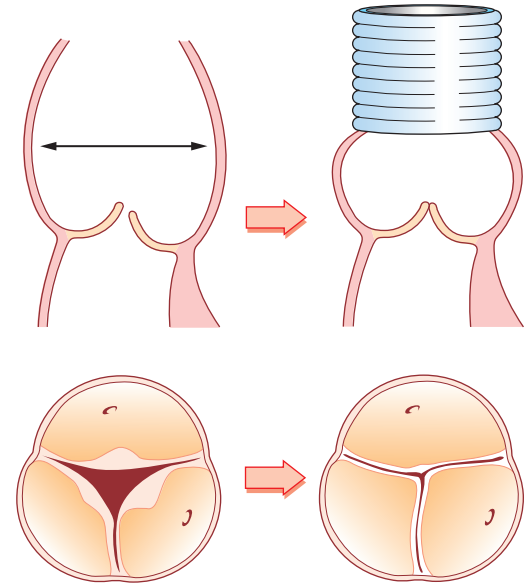

Figure 21.7 Correction of aortic regurgitation by replacement of the ascending aorta and adjustment of sinotubular junction. (Courtesy of Dr T. David.)

Approximately 15% of the regurgitant aortic valves can be repaired, the majority of them being associated with an aortic root pathology. The quality of the cusps is essential for repair; they should be pliable and the length of the free margin should be 1.5 times shorter than the base of implantation. The other structures, such as the annulus and sinotubular junction, can be re-adapted to the cusps (Fig. 21.6). The surgical procedure is adapted to the mechanism of AR.

- In the case of dilatation of the sinotubular junction, AR can be simply treated by adjustment of sinotubular junction to the annulus using a short Dacron graft (Fig. 21.7).
- In aortic root aneurysm, two techniques have been proposed: first, remodelling of the aortic root with replacement of the Valsalva sinuses with or without annuloplasty [57] (Fig. 21.8), the diameter of the graft being equal to that of the ideal sinotubular junction, and second, re-implantation of the aortic valve inside a Dacron conduit [58] (Fig. 21.9).
- When valve pathology is isolated, central plication with potential reinforcement of the free margin with Gore-Tex thread can be performed to treat the prolapse of only one cusp on a tricuspid valve. A patch repair can be used to treat perforation. A bicuspid valve can be treated by resectioning the raphe of the common prolapsing cusp and by bilateral commissuroplasty to ensure sufficient coaptation [59].

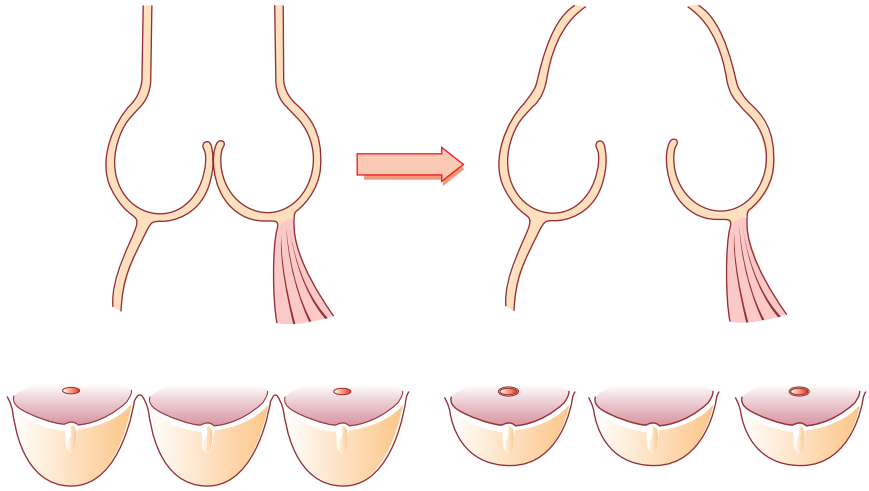

Figure 21.8 Aortic root aneurysm with annulo-aortic ectasia. Left, normal aortic annulus. (Courtesy of Dr T. David.)

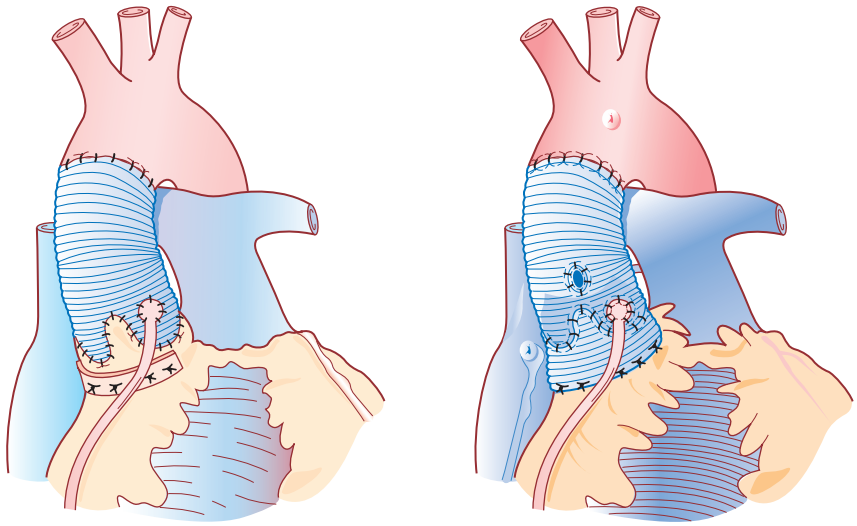

Figure 21.9 Conservative surgery techniques for aortic root aneurysm. Left, remodelling of the aortic root with aortic annuloplasty; right, re-implantation of the aortic valve inside a Dacron graft (from [58]). Reproduced, with permission, from David T, In: *Cardiac Surgery in the Adult*, 2nd edn, 2003, McGraw-Hill, Philadelphia PA, 811–823.

In current practice, prosthetic valve replacement remains the standard and the other procedures are performed in only a small percentage of patients (Table 21.3).

Results

Operative mortality in AR is globally low (Table 21.4). Operative risk is strongly determined by age, degree of LV dysfunction and comorbidity.

Late results of valve surgery for AR are related to preoperative LV function [60]. Prospective series have identified thresholds of LV dimensions, mostly end-systolic dimension or ejection fraction, which were related to outcome [61,62]. Thresholds should take into account patient stature [63]; preoperative end-systolic LV diameter < 25 mm/m^2 BSA was associated with a good late outcome after valve replacement [64].

The aim of surgery is also to avoid aortic complications in patients who present with aortic aneurysm. Isolated aortic valve replacement does not preclude further aortic dilatation in patients who had preoperative dilatation of the ascending aorta [41,52,65,66]. Immediate and late results of the replacement of the ascending aorta using a composite graft are excellent in Marfan syndrome when performed by experienced teams on an elective basis [67]. This technique should also be favoured in annulo-aortic ectasia.

Data on conservative surgery are more limited and come from expert centres. Yacoub and colleagues [57] reported a 10-year freedom from valve replacement of 89% in 158 consecutive patients. David [58], in a series of 120 patients, has reported an operative mortality of 1.6%, 10-year survival of 88%, freedom from aortic valve replacement of 99% and freedom from at least moderate AR of 83%.

Treatment strategy

Asymptomatic patients with chronic aortic regurgitation and normal left ventricular function

There is an over-mortality in patients who have severe AR as soon as they become symptomatic or when LV function begins to deteriorate [64]. These findings, combined with good results of surgery, are the rationale behind advising early surgery in asymptomatic patients with chronic AR. In ACC/AHA guidelines, surgery is advised in asymptomatic AR when LV ejection fraction is < 50% or LV dimensions are > 75 mm in end-diastole or > 55 mm in end-systole [23]. In the recommendations from the ESC working group on VHD, the threshold for ejection fraction is the same, but surgery is considered for less severe LV enlargement: > 70 mm in end-diastole or > 50 mm in end-systole, where the value of 25 mm/m^2 BSA is preferred [24]. Indication for surgery should also take into account temporal changes.

In asymptomatic patients with aortic aneurysm, intervention is advised when maximal aortic diameter is > 55 mm, regardless of the degree of AR, with a current trend to intervene when diameter is > 50 mm in Marfan syndrome. When valve replacement is required because of the severity of AR, replacement of ascending aorta is advised for aortic diameters of > 50 mm [23,24].

The decision should be adapted according to patient age and body size, although no accurate thresholds can be advised in this regard [53]. Measurements should be based on different imaging techniques and take into account the rate of change.

Vasodilators are indicated only in severe AR with LV enlargement, which does not reach the thresholds for surgery. Beta-blockers are advised in patients with ascending aortic aneurysm and should be used systematically for Marfan syndrome.

Patients with chronic aortic regurgitation and symptoms or left ventricular dysfunction

Symptom onset is an indication for surgery, even if there is a transient improvement under medical therapy. Surgery should not be denied in patients with LV dysfunction, at least when LV ejection fraction is > 25%. Below this threshold, the choice between valve replacement, heart transplantation or medical therapy is made on an individual basis [23].

Acute aortic regurgitation

Urgent intervention is indicated in most cases of acute AR because of poor haemodynamic tolerance.

Particular situations

Infective endocarditis

Severe AR is a particularly serious complication of infective endocarditis and urgent intervention should be considered, without waiting for poor haemodynamic tolerance, which increases operative mortality [29].

AR associated with hypertension

Trivial or mild AR is common in hypertensive patients. It may be difficult to determine the respective contributions of hypertension and AR to LV enlargement and dysfunction, which requires a careful quantification and analysis of the mechanisms of AR.

Mitral stenosis

Although the prevalence of rheumatic fever has greatly decreased in Western countries, MS still results in significant morbidity and mortality world-wide [1,5].

Aetiology

Rheumatic heart disease is almost the unique cause of MS. The anatomic lesions combine to varying degrees: fusion of one or both commissures; thickening, fibrosis, and calcification of the valves; and shortening, thickening, and fusion of the subvalvular apparatus. Other valves are also involved in over one-third of cases, the most frequent associated lesions being tricuspid disease and AR [68]. Degenerative and congenital MS are very seldom seen [3]. Other rare aetiologies are carcinoid disease, Fabry disease, mucopolysaccharidosis, Whipple disease, gout, rheumatoid arthritis, lupus erythematosus, methysergide therapy, or obstruction of the valve by an atrial tumour or a large vegetation.

Pathophysiology

After rheumatic attack, the alterations of the valve slowly progress, mostly driven by the abnormal flow dynamics caused by the initial and eventually repeated rheumatic insults.

Normal mitral valve area is 4–6 cm^2. A diastolic transvalvular gradient between left atrium and LV appears if valve area is less than 2 cm^2. MS is significant if valve area is < 1.5 cm^2, or 1 cm^2/m^2 BSA in large individuals.

Valve obstruction progressively limits cardiac output and increases pressure in the left atrium, which, in turn, raises pulmonary circulation pressure. Pulmonary oedema, related to transudation from the pulmonary capillaries, occurs when mean capillary pressure is > 25 mmHg [69]. Transvalvular gradient and its consequences are highly dependent on heart rate and transvalvular flow. Exercise limitation is multifactorial and heterogeneous, and may not be simply related to valve area or either resting or exercise left atrial pressure [70]. The degree of pulmonary hypertension is variable and often greater than the passive increase caused by elevated left atrial pressures. This could be due to initially reversible morphological changes in pulmonary vasculature, reactive pulmonary vasoconstriction or reduced lung compliance [71]. Chronic pulmonary hypertension causes right ventricular hypertrophy, which, possibly exacerbated by tricuspid regurgitation (TR), causes failure of the right ventricle.

Intrinsic LV contractility is usually preserved; however, chronic afterload elevation and preload reduction, related to MS and ventricular interactions, cause decreased ejection fraction in 25% of cases.

Atrial fibrillation, which is not strictly linked to the severity of MS, is a consequence of left atrial dilatation and hypertrophy, as well as rheumatic insult to the atria, internodal tracts and sino-atrial node. Atrial fibrillation causes haemodynamic compromise through decreased cardiac output due to the loss of atrial contraction and shortening of diastole. It also increases thromboembolic risk as a result of left atrial enlargement, blood stagnation and increased concentrations of prothrombotic markers.

Diagnosis

History

Usually, symptoms appear gradually over years, with patients first reporting dyspnoea on exertion. Pregnancy, emotional stress, sexual intercourse, infection or the onset of atrial fibrillation may all be precipitating factors of marked dyspnoea or pulmonary oedema. Haemoptysis, as well as chest discomfort, is infrequent.

Atrial fibrillation often begins in paroxysms and eventually becomes established. Embolic events, which may be the initial event in 20% of cases, are most often cerebral and leave sequelae in one-third of cases.

At a more advanced stage, patients may complain of discomfort due to hepatomegaly, fatigue, weakness and occasionally hoarseness.

Physical examination

The main signs of auscultation are perceived at the apex. The diastolic low-pitched murmur (typically decrescendo with a presystolic accentuation in sinus rhythm) can be palpated when it is of high intensity. It may be of low intensity or even inaudible in patients with low output, emphysema or obesity. The opening snap occurs 0.013–0.03 seconds after the second heart sound—the more severe the stenosis the shorter the interval. The accentuated first heart sound (a high-pitched snap related to valve closure) may be blunted in patients with severe calcification.

Pulmonary hypertension causes both a murmur of tricuspid regurgitation and a louder second heart sound at the base. In patients with right ventricular failure, the dilated ventricle can be palpated at the xiphoid, as can a systolic impulse of the pulmonary artery at the third left intercostal space.

At an advanced stage, mitral facies with intermittent malar flushes, jugular distension and peripheral cyanosis may be seen. Respiratory failure, cachexia and findings of severe pulmonary hypertension dominate examination.

Electrocardiography

Patients who are in sinus rhythm demonstrate signs of left atrial enlargement with a prolonged P wave and a negative deflection in lead V1 and left axial deviation. Atrial fibrillation is frequent. Signs of right ventricular hypertrophy are usually present in cases with severe pulmonary hypertension.

Chest radiograph

Cardiac silhouette is only mildly enlarged during the early stages with left atrial enlargement, straightening of the left heart border and double density, followed by right ventricular enlargement as the disease develops. Redistribution of pulmonary vascular flow towards the upper lung fields, a progressively enlarged pulmonary trunk, and signs of interstitial pulmonary and alveolar oedema are all indicative of the elevation of pulmonary pressures. Usually, fluoroscopy is necessary to visualize valve calcification.

Echocardiography

Echocardiography is the main method to assess the severity, and consequences of MS, as well as the extent of anatomic lesions. Measurements of the mean transvalvular gradient from Doppler velocities are highly rate and flow dependent; however, they provide useful information for patients in sinus rhythm. Severity of MS should ideally be quantified using two-dimensional planimetry (the most accurate way of assessing valve area after percutaneous mitral commissurotomy, PMC) and the pressure half-time method, which are complementary.

Table 21.7a Anatomical scores predicting outcome after percutaneous mitral commissurotomy: Wilkins' mitral valve morphology score [72]

Grade	Mobility	Subvalvular thickening	Thickening	Calcification
1	Highly mobile valve with only leaflet tips restricted	Minimal thickening just below the mitral leaflets	Leaflets near normal in thickness (4–5 mm)	A single area of increased echo brightness
2	Leaflet mid and base portions have normal mobility	Thickening of chordal structures extending to one chordal length	Mid-leaflets normal, considerable thickening of margins (5–8 mm)	Scattered areas of brightness confined to leaflet margins
3	Valve continues to move forward in diastole, mainly from the base	Thickening extended to distal third of the chords	Thickening extending through the entire leaflet (5–8 mm)	Brightness extending into the mid-portions of the leaflets
4	No or minimal forward movement of the leaflets in diastole	Extensive thickening and shortening of all chordal structures extending down to the papillary muscles	Considerable thickening of all leaflet tissue (> 8–10 mm)	Extensive brightness throughout much of the leaflet tissue

Table 21.7b Anatomic scores predicting outcome after percutaneous mitral commissurotomy: Cormier's grading of mitral valve anatomy [73]

Echocardiographic group	Mitral valve anatomy
Group 1	Pliable non-calcified anterior mitral leaflet and mild subvalvular disease (i.e. thin chordae ≥ 10 mm long)
Group 2	Pliable non-calcified anterior mitral leaflet and severe subvalvular disease (i.e. thickened chordae < 10 mm long)
Group 3	Calcification of mitral valve of any extent, as assessed by fluoroscopy, whatever the state of subvalvular apparatus

Continuity equation is less frequently used to calculate valve area. The assessment of valve morphology is increasingly important for the selection of candidates for PMC. Scores have been developed that take into account valve thickening, mobility, calcification, subvalvular deformity and, more recently, commissural areas [72,73] (Table 21.7).

Echocardiography also evaluates pulmonary circulation, the presence of associated MR, concomitant valve disease and the consequences of MS on the left atrium [74].

A transthoracic approach provides sufficient information for routine management and decision-making; however, transoesophageal examination should also be performed to exclude left atrial thrombosis, in particular in the appendage, before PMC or in case of suspicion.

Dobutamine or, better, exercise echocardiography, by assessing the evolution of mitral gradient and pulmonary pressure, may aid decision-making in patients with doubtful symptoms [75] (Fig. 21.10).

Cardiac catheterization

The accuracy of echocardiography has virtually eliminated its use in assessing the severity of valve obstruction or associated valve lesions. There remain occasional indications for catheterization when clinical and echocardiographic data are discordant. Coronary angiography is required prior to surgery [23].

Natural history

The rate of progression of stenosis is variable: ranging from 0.1 to 0.3 cm^2/year, the higher rates being observed in patients with severe anatomic deformity and high transmitral gradient. Studies on natural history are old and non-controlled. In asymptomatic patients, survival was 84% at 10 years; among patients with few symptoms, survival was 42% at 10 years and the incidence of heart failure was approximately 60% [76]. Symptomatic patients had a poor prognosis with a 5-year survival of only 44% [77]. Here again the progression was highly variable with gradual deterioration in one-half of the patients, and sudden deterioration, precipitated by a complication, in the rest. Atrial fibrillation can occur in asymptomatic patients and is often preceded by supraventricular arrhythmias. The occurrence of atrial fibrillation increases with age and left atrial enlargement [78], and the incidence of thromboembolism with age, atrial fibrillation, larger left atrium, smaller valve area, and,

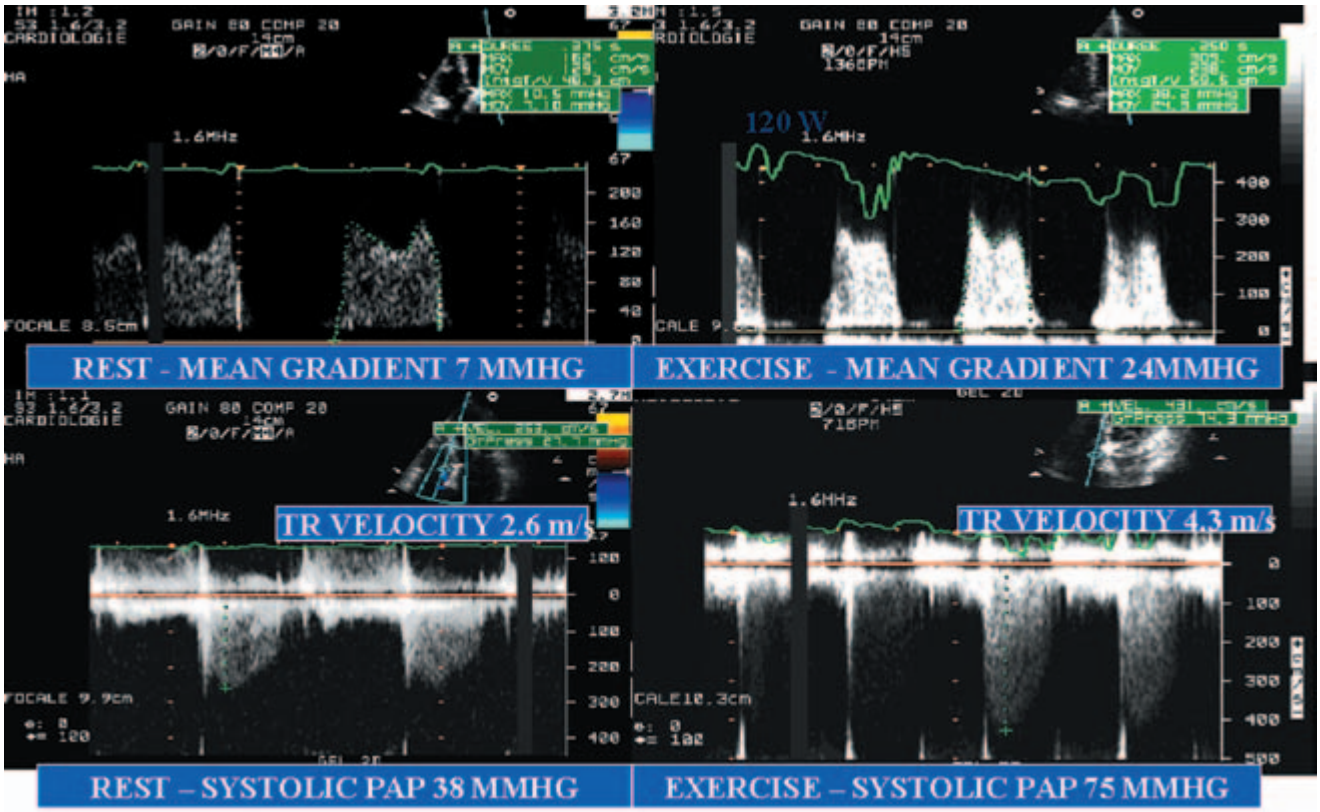

Figure 21.10 Exercise echocardiography in mitral stenosis. During exercise there is an increase in mean gradient of tricuspid regurgitation (TR) from 7 to 24 mmHg and in systolic pulmonary artery pressure (PAP) from 38 to 75 mmHg. (Courtesy of Dr E. Brochet.)

most significantly, the presence of left atrial spontaneous echo contrast [79].

In developing countries, severe MS is commonly observed in infants or young adults, whereas in industrialized countries symptoms are usually delayed until the fifth decade [80].

Medical treatment

Diuretics or long-acting nitrates transiently ameliorate dyspnoea. Beta-blockers or calcium channel blockers are useful to slow the heart rate.

Anticoagulant therapy with a target international normalized ratio (INR) of between 2.5 and 3.5 is indicated in patients with atrial fibrillation. In patients with sinus rhythm, anticoagulation is mandatory when there has been prior embolism or a thrombus is present in the left atrium, and it is recommended in patients who have an enlarged left atrium (> 50 or 55 mm in diameter) or a dense spontaneous echo contrast [24,81].

Cardioversion is not indicated before intervention in patients with severe MS, as it does not durably restore sinus rhythm. If atrial fibrillation is of recent onset and the left atrium only moderately enlarged, cardioversion should be performed soon after successful intervention.

Infective endocarditis prophylaxis is always indicated [29]. In countries with a high prevalence of rheumatic disease, rheumatic fever prophylaxis should be given to young patients and be continued after conservative intervention.

Percutaneous intervention

Since its introduction in the early 1980s, PMC has had a significant impact on the treatment of MS and its successful results have led to increasing use world-wide.

Trans-septal catheterization is one of the most crucial steps of the procedure and the Inoue balloon technique has become the most popular technique world-wide (Fig. 21.11). In developing countries, economic constraints lead to a residual use of the double-balloon technique and the re-usable metallic commissurotome [82].

PMC, which results in commissural splitting (Fig. 21.12), usually provides over a 100% increase in valve area,

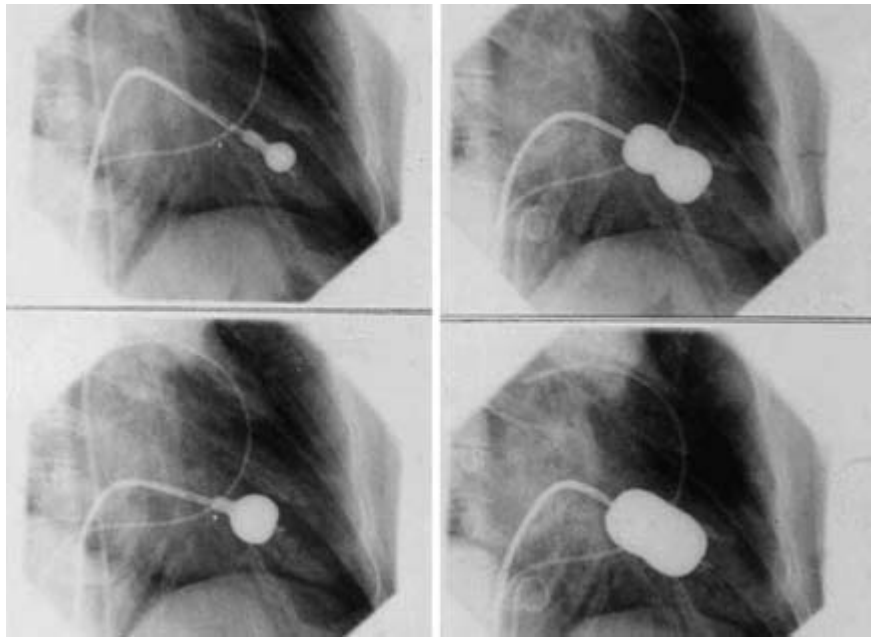

Figure 21.11 Percutaneous mitral commissurotomy using the Inoue balloon technique. Right anterior oblique view. Upper left, the distal part of the balloon is inflated with contrast in the centre of the mitral valve; lower left, the distal part is further inflated and the balloon is pulled back into the mitral orifice; upper right, inflation occurs in the central portion; lower right, at full inflation the waist on the balloon disappears.

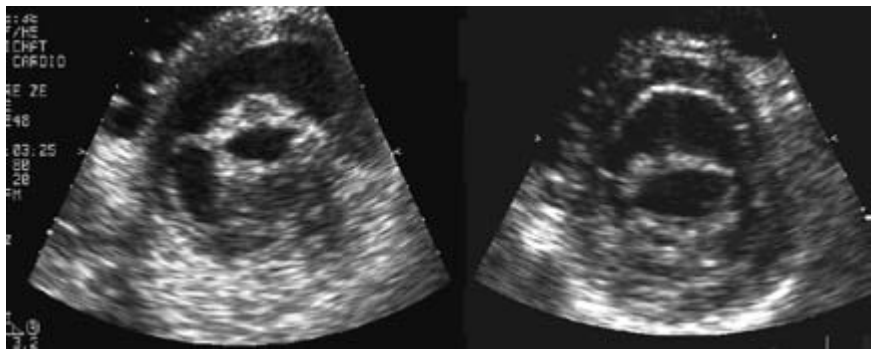

Figure 21.12 Opening of the mitral valve after percutaneous mitral commissurotomy. Mitral orifice in short axis view before (left) and after (right) percutaneous mitral commissurotomy. After commissurotomy there is bilateral commissural splitting. (Courtesy of Dr E. Brochet.)

with a final valve area of approximately 2 cm^2. The improvement in valve function results in an immediate decrease in pulmonary pressures, both at rest and during exercise.

Failure rates range from 1% to 15%. Procedural mortality ranges from 0% to 3%, incidence of haemopericardium varies from 0.5% to 12%. Embolism is encountered in 0.5% to 5% of cases. Severe MR, which occurs in 2 to 10% of patients, is a result of non-commissural leaflet tearing. Urgent surgery is seldom needed for complications (< 1%). Immediately after PMC, in 40% to 80% of patients, colour Doppler echo shows small intra-atrial shunts, which are likely to close later in the majority of cases. The complication rate of the procedure is related to the experience of the team [82–84].

Clinical follow-up data confirm the late efficacy of PMC since event-free survival ranges from 35% to 70% after 10–12 years [85,86]. When the immediate results are unsatisfactory, surgery is usually required in the following months. Conversely, after successful PMC, long-term results are good in the majority of cases. When functional deterioration occurs, it is late and mainly related to re-stenosis (around 40% after 7 years). Repeat PMC can be proposed in selected patients with favourable characteristics if re-stenosis leads to symptoms, occurs several years after an initially successful procedure, and the predominant mechanism is commissural re-fusion [82]. Successful PMC has been shown to reduce embolic risk [79].

The prediction of the results of PMC is multifactorial; besides morphological factors, preoperative variables such as age, history of commissurotomy, functional class, small mitral valve area and presence of TR are all independent predictors of poor results. The prediction of the long-term results is also closely related to the immediate results [85,86].

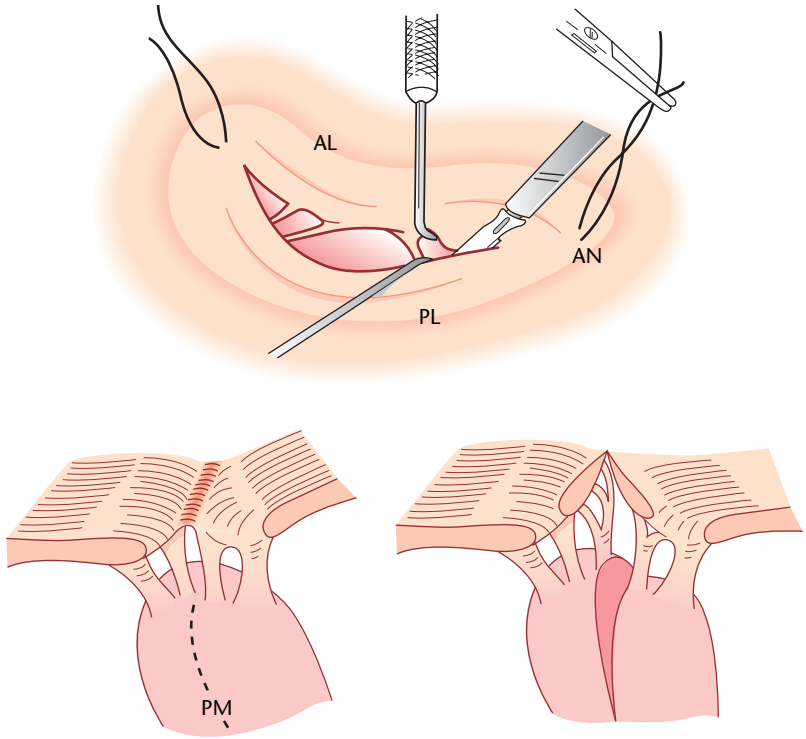

Figure 21.13 Surgical commissurotomy. AL = anterior leaflet, AN = annulus, PL = posterior leaflet. Upper panel: incision of the fused commissure with a scalpel blade, commencing in the central orifice and progressing towards the annulus in a gentle upwards curve. Lower panel: incision of the papillary muscle (PM) at commissural level permitting the opening of the lateral portions of the mitral orifice. Reproduced, with permission, from Antunes MJ, *Mitral Valve Repair*, 1989, Verlag R.S. Schulz.

Surgery

Conservative surgery

The first operation performed more than 50 years ago was closed mitral valve commissurotomy [87]. This operation was effective and easily accessible, which explains its large use until very recently in developing countries. Today it has been replaced by open-heart mitral commissurotomy using cardiopulmonary bypass, which enables surgeons to see the valve and not only corrects commissural fusion, but also acts on chordal and papillary fusion (Fig. 21.13), and may even improve leaflet mobility and pliability by enlarging the posterior valve using pericardial patches. The use of prosthetic rings is controversial in these cases. In young patients and with experienced operators, long-term results are good, with survival of 96% and freedom from valve-related complications of 92% at 15 years [88].

Valve replacement

Valve replacement uses mostly mechanical valves because of their better durability in the mitral position and because most patients require long-term anticoagulation for atrial fibrillation.

Operative mortality ranges between 3% and 10% and correlates with age, functional class, pulmonary hypertension and presence of coronary artery disease [3,89–91] (Table 21.4). Long-term survival is related to age, functional class, atrial fibrillation, pulmonary hypertension, preoperative LV function, and complications of the prosthetic valve, especially thromboembolism and haemorrhage [89].

The recent Euro Heart Survey [3] reveals that, in current practice, percutaneous intervention has almost replaced open-heart commissurotomy and valve replacement mostly uses mechanical prosthesis (Table 21.3).

Treatment strategy

Intervention should be performed only in patients with significant MS.

Surgery is the only alternative when PMC is contraindicated, the most important contraindication being left atrial thrombosis. A contraindication is self evident if the thrombus is localized in the cavity. No consensus has been reached in cases with thrombosis localized in the left atrial appendage. Other contraindications for PMC are MR > 2/4, severe calcification, absence of commissural fusion, combined severe aortic or tricuspid valve disease, or coronary disease requiring bypass surgery. In such patients, valve replacement is preferred in most cases, whereas open commissurotomy may be performed by experienced teams in young patients who are in sinus rhythm, with no or mild calcification and mild to moderate MR.

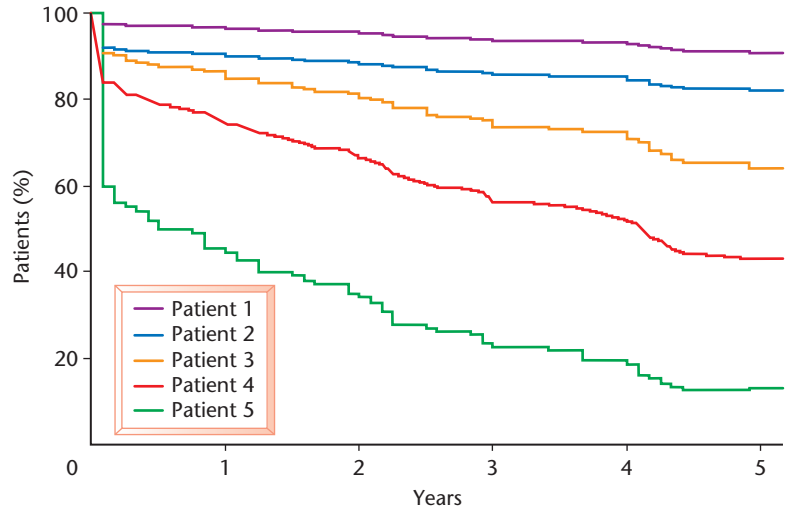

Figure 21.14 Prediction of the long-term event-free survival of percutaneous mitral commissurotomy in calcified mitral stenosis. Patient 1: < 50 years, NYHA class 2, sinus rhythm, mild calcification, valve area 1.2 cm^2; patient 2: < 50 years, NYHA class 2, sinus rhythm, moderate calcification, valve area 1 cm^2; patient 3: 50–70 years, NYHA class 3, sinus rhythm, moderate calcification, valve area 1.25 cm^2; patient 4: 50–70 years, NYHA class 3, atrial fibrillation, moderate calcification, valve area 1.2 cm^2; patient 5: < 70 years, NYHA class 4, atrial fibrillation, severe calcification, valve area 0.75 cm^2. Adapted from [93]. Reproduced, with permission, from Iung B, Garbarz E, Doutrelant L *et al., Am J Cardiol* 2000; **85**: 1308–1314.

On the other hand, PMC is the procedure of choice when surgery is contraindicated or for patients with favourable characteristics, i.e. young patients with sinus rhythm and favourable anatomy [23,24,92].

Much remains to be done in refining indications for the patients with unfavourable anatomy. Because of the less satisfying results of PMC, some favour immediate surgery, whereas others prefer PMC as initial treatment for selected patients, resorting to surgery in the event of failure. Such a decision must take into account the multifactorial nature of result prediction. PMC can achieve good long-term results and may be useful to defer surgery in selected patients with mild to moderate calcification or severe impairment of the subvalvular apparatus, who have otherwise favourable characteristics [93] (Fig. 21.14).

The alternatives for asymptomatic patients are medical treatment or PMC. Because of the small but definite risk inherent in PMC, truly asymptomatic patients are not usually candidates for the procedure, except in the following cases: increased risk of thromboembolism (previous history of embolism, dense spontaneous contrast in the left atrium, or, to a lesser extent, recent or paroxysmal atrial fibrillation); risk of haemodynamic decompensation (systolic pulmonary pressure > 50 mmHg at rest or > 60 mmHg during exercise); need for major extracardiac surgery; or finally, to allow pregnancy. In such patients, if they have favourable characteristics [24], PMC should only be performed by experienced operators.

Special populations

After surgical commissurotomy, re-operation almost always requires valve replacement at somewhat higher risk. Here, PMC can delay re-operation in patients with favourable characteristics and if the predominant mechanism of re-stenosis is commissural re-fusion [94].

For information on MS during pregnancy, see Chapter 18.

In the elderly, surgery is high risk, especially if comorbidity is present. PMC is a valid treatment, if only palliative, because it results in moderate but significant improvement in valve function at an acceptable risk, although secondary deterioration is frequent [95].

Mitral regurgitation

Current interest in MR is fuelled by the complexity of the mitral valve apparatus, the various aetiologies leading to different anatomical lesions and functional mechanisms of MR, the diversity of clinical presentations and the reorientation of the treatment resulting from the good results of valve repair [96,97].

Aetiology

Reduced prevalence of rheumatic fever and increased lifespan in Western countries have progressively changed the distribution of aetiologies (Table 21.1).

Degenerative MR is the most common aetiology in Europe [3]. The most frequent condition within this disorder is myxomatous degeneration, which produces increased thickness and redundancy of leaflets, chordal elongation and rupture, and abnormal leaflet systolic displacement billowing across the mitral annulus [98]. Histology shows leaflet infiltration by mucopolysaccharides.

Chordal rupture can subsequently occur. The Marfan and Ehlers–Danlos syndromes can also be classified as degenerative MR.

In rheumatic heart disease, MR is frequently associated with various degrees of MS. Regurgitation is essentially due to valvular and subvalvular retraction, rather than thickening. Other causes leading to similar lesions are: rheumatoid arthritis, lupus erythematosus, antiphospholipid syndrome, carcinoid disease, and diseases induced by drugs such as methysergide, fenfluramine, dexfenfluramine or pergolide [99–101].

Endocarditis, which results in leaflet perforation and chordal rupture, as well as vegetations and possible perivalvular abscesses, remains common.

Ischaemic MR, although an increasingly common cause of MR, is frequently unrecognized. The rupture of a papillary muscle (most frequently a head of the posteromedial muscle) is a rare and dramatic complication of acute myocardial infarction. Functional MR, frequent in patients with heart failure, occurs despite a structurally normal valve, and is due to annular dilatation, papillary muscle displacement tethering the leaflets, and LV dysfunction decreasing the mitral valve closing force [102]. Acute or chronic papillary muscle ischaemia or dysfunction in isolation does not result in MR.

Pathophysiology

MR consists in abnormal systolic regurgitation of blood from the LV to the left atrium and results from incomplete mitral valve closure and a pressure gradient between LV and left atrium. MR can result from dysfunction of one or more of the following components: the annulus, the leaflets, the chordae tendineae, the papillary muscles and the LV. The Carpentier classification [103] is very useful to assess the valve function: type I, normal leaflet motion, annulus dilatation; type II, excess leaflet motion, prolapse; and type III, restricted leaflet motion in diastole (rheumatic disease) or in systole (ischaemic and/or heart failure). The mechanisms of regurgitation can be valve prolapse due to redundant leaflets and elongation or rupture of chordae, loss of valvular tissue by retraction, perforation or tethering on the leaflets (usually the posterior valve by chordal retraction), or by LV remodelling causing valvular deformation.

The regurgitant volume is determined by the area of, and systolic pressure gradient across, the MR orifice and systolic duration. Systolic ventriculo-atrial pressure gradient is present throughout isovolumic contraction, ejection and isovolumic relaxation. When the regurgitant orifice area is small, MR predominates in early systole [104]. The regurgitant orifice increases during systole in valve prolapse. In ischaemic MR it peaks in early and late systole [105] and increases parallel with LV enlargement or rise in afterload.

Acute mitral regurgitation

Acute MR, resulting from papillary muscle or chordal rupture, induces an immediate decrease in afterload, LV emptying increases, and left atrial pressure rises acutely, which can be transmitted back to the pulmonary circulation. LV function is normal and ejection fraction is increased. Forward stroke volume is reduced resulting in tachycardia to maintain cardiac output.

Chronic mitral regurgitation

In chronic MR, eccentric LV hypertrophy develops by lengthening of the myocytes, leading to LV end-diastolic dilatation and increased total and forward stroke volumes according to the Frank–Starling mechanism. Both LV and atrial compliance increase [106]. Regurgitant volume is progressively handled without a large increase in left atrial pressure and pulmonary congestion. This haemodynamic state may remain compensated for many years. However, as concentric hypertrophy does not develop, the increased volume is not compensated by increased thickness: the radius–thickness ratio remains high, which maintains increased systolic and diastolic stress.

Neurohormonal mechanisms are therefore activated [107], leading to progressive contractile dysfunction by loss of contractile elements and abnormal calcium handling [108].

Diagnosis

History

Acute severe MR usually results in severe dyspnoea, acute pulmonary oedema or congestive heart failure.

Patients with chronic severe MR may remain asymptomatic for years [109,110]. Symptoms, such as fatigue or dyspnoea, occur late when contractile dysfunction develops or at the onset of atrial fibrillation. Ischaemic MR is a dynamic condition and its severity may vary over time in relation to arrhythmias, ischaemia, hypertension or exercise. The degree of ischaemic MR at rest is not related to exercise-induced changes [111]. Acute pulmonary oedema is associated with a large exercise-induced increase in ischaemic MR [112].

Physical examination

The main sign of auscultation is a systolic murmur [113].

If MR is at least moderate, the murmur is holosystolic, beginning at the onset of the first heart sound and continuing after the second heart sound. Its peak intensity is usually heard in early systole in ischaemic MR and late systole in valve prolapse. If prolapse is not holosystolic, the typical features are a mid-systolic click followed by a late systolic murmur, both varying in intensity and timing with manoeuvres that induce changes in LV volume. In ischaemic MR, the murmur is of low intensity. In acute MR, the murmur is shortened by the rapid reduction in the pressure gradient between LV and left atrium; it may even be inaudible in cases of papillary muscle rupture with low output. In chronic severe MR, the apical impulse is displaced to the left, the murmur is intense, and a third heart sound and a short diastolic rumble reflect the rapid and voluminous LV filling.

Electrocardiography

Patients in sinus rhythm may present LV and left atrial hypertrophy. Atrial fibrillation is common. In ischaemic MR, Q waves may be seen, most frequently in the inferior and/or lateral leads; and a left bundle branch block may be present.

Chest radiograph

Chronic severe MR leads to cardiomegaly due to LV and left atrial enlargement, and radiological signs of left heart failure when cardiac dysfunction is present. In acute MR, heart volume may be normal, with evidence of interstitial or alveolar pulmonary oedema.

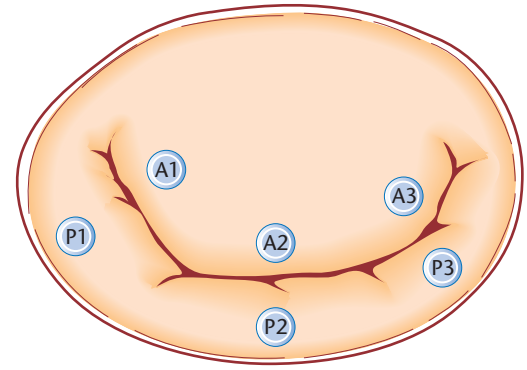

Figure 21.15 Carpentier classification. The posterior leaflets segments are designated as P1, P2 and P3. P1 is adjacent to the anterolateral commissure, P2 is the middle scallop and P3 is adjacent to the posteromedial commissure. The anterior leaflet has less clearly defined segments, designated as A1, A2 and A3, corresponding to the adjacent posterior leaflet segments. (Courtesy of Dr D. Koolbergen.)

Echocardiography

Echocardiography is the cornerstone for diagnosing MR and more specifically for establishing its aetiology and mechanisms, for quantifying its severity, progression and consequences, and for assessing the possibility of valve repair.

Transthoracic echocardiography provides precise anatomical definition of the different possible lesions (type II and III lesions must be related to the segmental anatomy) (Fig. 21.15) and of the mechanisms according to the Carpentier classification [96,103] (Figs 21.16 and 21.17).

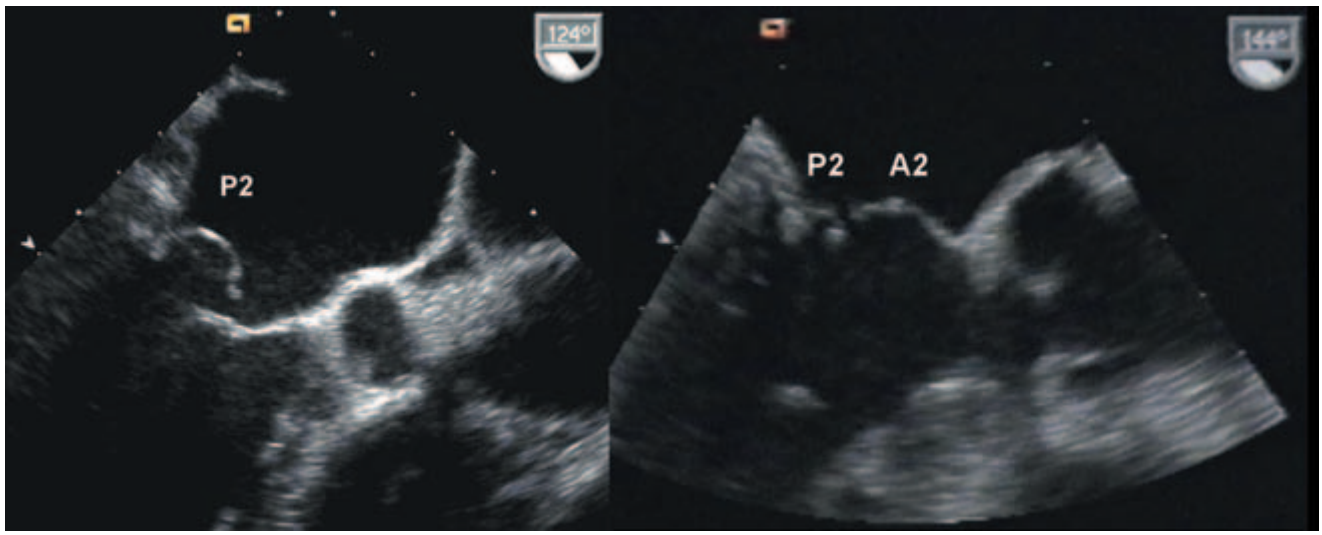

Figure 21.16 Prolapse of the mitral leaflets. Transoesophageal view. Left, prolapse of the posterior leaflet (P2); right, prolapse of the anterior leaflet (A2). (Courtesy of Dr E. Brochet.)

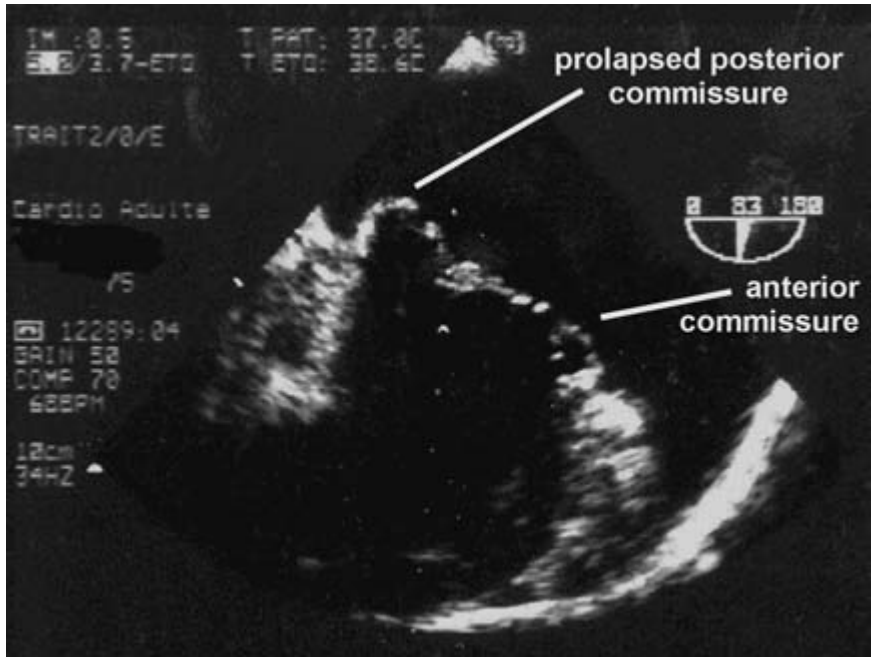

Figure 21.17 Prolapse of the posterior commissure. Transoesophageal echocardiography. (Courtesy of Dr B. Cormier.)

Several methods can be used to determine the severity of MR. Colour-flow mapping of the regurgitant jet appears to be the easiest method but its accuracy is limited by physical and technical factors; it largely overestimates the severity of ischaemic MR and underestimates it when the jet is eccentric and lateral [114] (Fig. 21.18). The width of the vena contracta—the narrowest part of the jet—correlates with quantitative measurements of MR; a > 6-mm-width jet corresponds to severe MR [115]. The moderate lateral resolution is, however, a limitation. The following two quantitative methods are reliable and clinically applicable but require experience. The Doppler method is based on the calculation of mitral and aortic stroke volumes, and how the difference between them corresponds to the regurgitant volume [116]. The second is the flow-convergence method, based on the principle

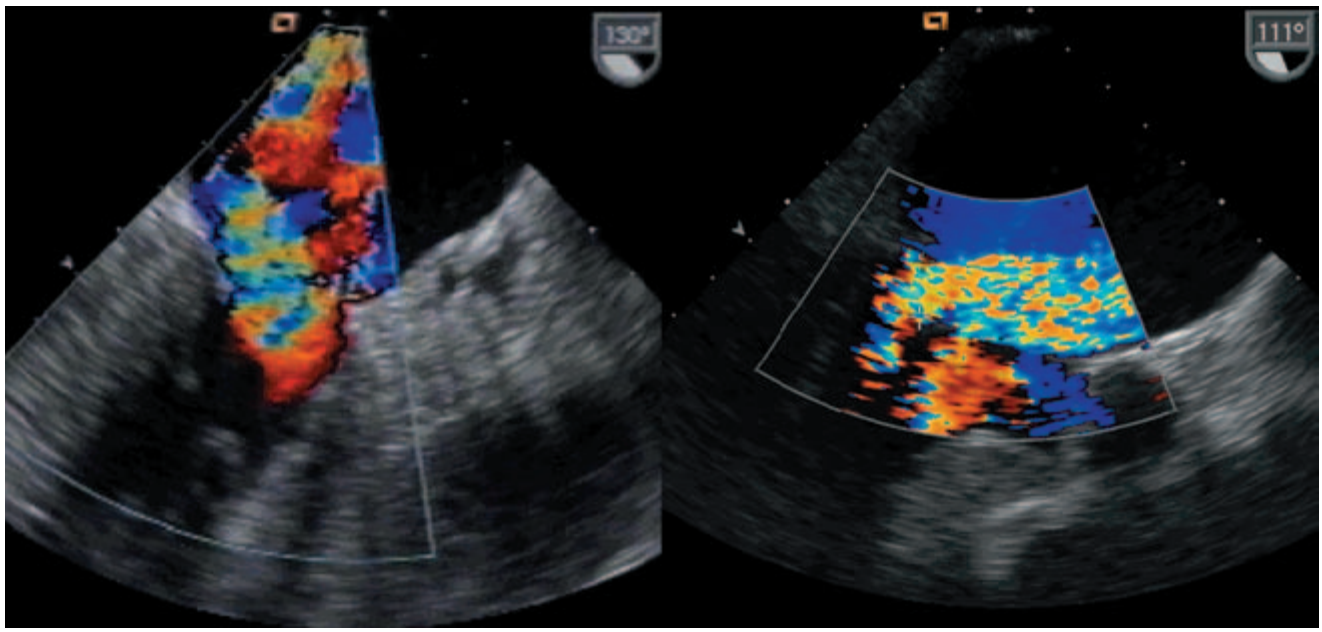

Figure 21.18 Colour Doppler echocardiography in mitral regurgitation. Transoesophageal view. Left, prolapse of the posterior leaflet; right, prolapse of the anterior leaflet. (Courtesy of Dr E. Brochet.)

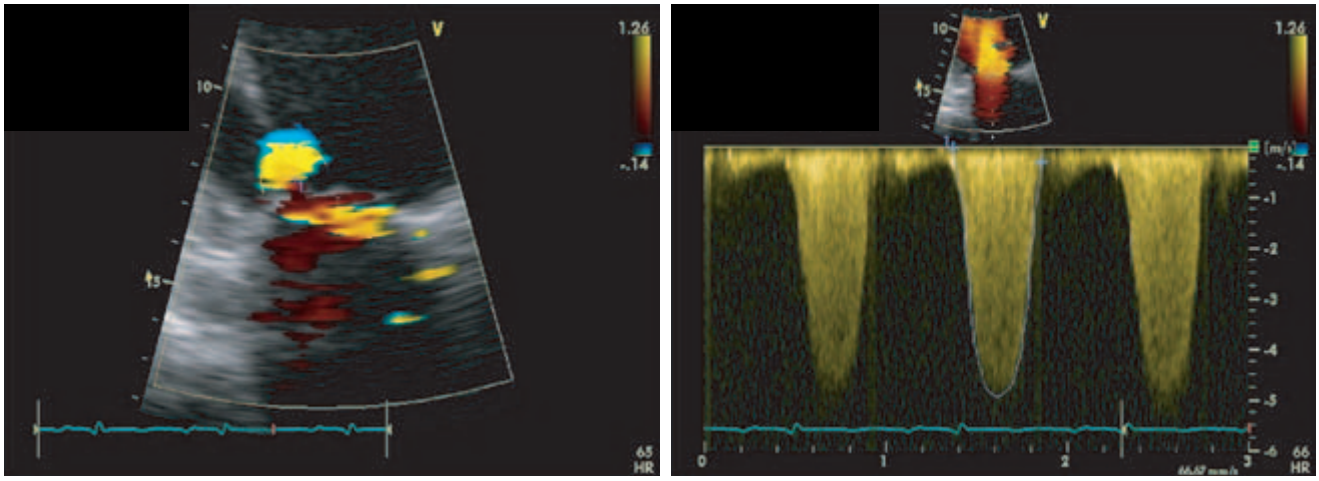

Figure 21.19 Estimation of MR severity using the PISA method. This method is based on the conservation of energy and assumes that blood flow converging towards a flat orifice forms an hemispheric isovelocity shells. ERO, effective regurgitant orifice; R, radius of the flow convergence; RVOL, regurgitant volume; TVI, time velocity integral; VA, velocity of the isovelocity shell, which is arbitrarily selected by shifting the colour-flow scale baseline; V max, velocity at the level of the regurgitant orifice measured in continuous wave Doppler. (Courtesy of Dr E. Brochet.)

of conservation of momentum using the measurements of the proximal isovelocity surface area, maximum velocity and time velocity integral to regurgitant flow [117] (Fig. 21.19). Organic MR is considered severe if regurgitant orifice area is ≥ 40 mm^2 and regurgitation volume is ≥ 60 ml [44]. In ischaemic MR, the corresponding thresholds of severity are 20 mm^2 and 30 ml respectively [44,118].

The consequences of MR are assessed by measuring left atrial diameter, LV diameter and volume, and by calculating LV ejection fraction (which, however, overestimates systolic function due to the changes in loading conditions) and systolic pulmonary arterial pressure.

In ischaemic MR, quantification of MR during exercise is feasible, provides a good appreciation of dynamic characteristics [119] and has prognostic importance [120] (Fig. 21.20).

Transoesophageal examination is necessary preoperatively only if the transthoracic approach is not adequate, but is of utmost importance perioperatively to assess the results of valve repair.

Cardiac catheterization

Invasive quantification of MR is no longer mandatory. Cardiac catheterization is only useful when clinical and echocardiographic features are discordant. Coronary angiography is necessary prior to surgery as in other valve disease [23].

Natural history

Acute MR secondary to papillary muscle rupture has a dismal short-term spontaneous prognosis. After chordal rupture, following an initial symptomatic period, clinical condition may stabilize. However, it carries a poor spontaneous prognosis owing to subsequent development of pulmonary hypertension.

Our knowledge of the natural history of chronic MR has greatly improved due to recent observational studies evaluating the bearing clinical and echocardiographic variables have on outcome [109,110]. In a recent analysis of the natural history of degenerative MR, including 71% of patients in NYHA class I or II, there was a yearly mortality rate of 6.3%, associated with a high morbidity at 10 years since the incidence of heart failure and atrial fibrillations were 63% and 30% respectively [109]. Moreover, a linear rate of sudden death of 1.8% per year has recently been reported in patients with MR due to flail leaflets not operated on, the figure being 0.8% per year in patients with no or minimal symptoms [121]. In addition to symptoms, age, atrial fibrillation, degree of MR, left atrial dilatation, LV dilatation and low LV ejection fraction are all predictors of poor outcome [109,110,122].

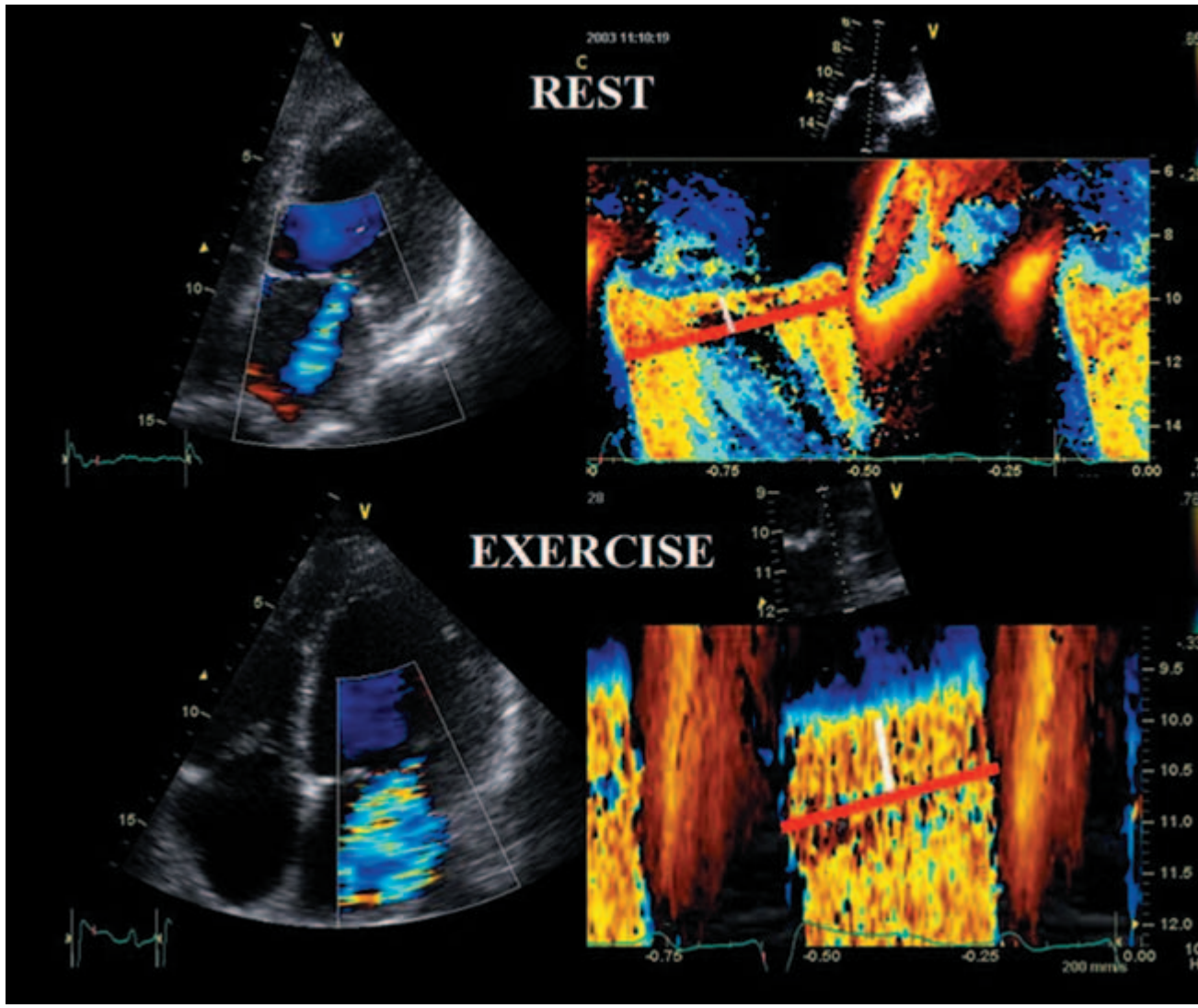

Figure 21.20 Exercise echocardiography in ischaemic mitral regurgitation. Apical four-chamber view showing colour-flow Doppler and colour M-mode of the proximal flow-convergence region at rest and during exercise in a patient with dynamic mitral regurgitation. A large exercise-induced increase in PISA radius mitral regurgitation is observed.

Patients with ischaemic MR have a poor prognosis. Although coronary artery disease and LV dysfunction have prognostic importance, the presence and severity of MR are independently associated with increased mortality [118].

Medical treatment

In acute MR, reduction of filling pressures can be obtained using diuretics and nitrates. Vasodilators, such as nitroprusside, are useful for lowering afterload and regurgitant fraction. In the presence of systemic hypotension, intra-aortic balloon pumping may help to stabilize the patient before surgery.

In chronic MR, the use of vasodilator therapy remains controversial in asymptomatic patients with organic MR since long-term therapy has not been shown to prevent or delay LV dysfunction and it should not be used if surgery is indicated [23,24,123]. In functional MR associated with systolic dysfunction, medical therapy is the front-line treatment. Angiotensin-converting enzyme inhibitors and beta-blockers, which reduce MR by progressive inverse remodelling, are indicated [124]. Sublingual nitrates are useful for treating acute dyspnoea secondary to the dynamic component.

Patients with persistent or paroxysmal atrial fibrillation should receive anticoagulant therapy with an INR of 2.5–3.5 [81] and drugs for controlling heart rate. In

severe MR, maintenance of sinus rhythm after cardioversion is illusory in the absence of surgery.

Endocarditis prophylaxis is required in classic conditions [29].

Percutaneous intervention

Percutaneous techniques using either rings, introduced via the coronary sinus, or stitches mimicking the Alfieri operation, introduced trans-septally, have shown a reduction in the degree of MR in experiments [125]. The first in-man implantations have been performed successfully very recently.

Surgery

Technique

VALVE REPLACEMENT

It is now admitted that valve replacement in MR should include preservation of as much as possible of the subvalvular apparatus in order to better preserve postoperative LV function.

CONSERVATIVE SURGERY

Valve repair may combine different techniques according to aetiology.

In degenerative MR, annuloplasty is almost always used. Its principle is to reduce—or remodel—the posterior annulus in order to restore an optimal surface of coaptation. It mostly uses rings, usually sized according to the area of the anterior leaflet, which can be complete or incomplete, rigid or pliable [96].

Posterior leaflet prolapse could be treated using a combination of quadrangular resection (Fig. 21.21), sliding plasty (Fig. 21.22), transfer of normal chord to the free margin of the prolapsed segment, replacement of elongated or ruptured chords using Gore-Tex neo-chordae [126] or, finally, the Alfieri stitch, when the prolapsed segment is sutured to the opposite normal segment, creating a double-orifice valve [127].

Anterior leaflet prolapse can be treated by transferring of a normal chord, or a normal segment of posterior leaflet with normal chords, to the free margin of the prolapsed segment, or through chordal replacement, papillary muscle repositioning [128] or the Alfieri stitch.

The treatment of commissural prolapse is more difficult and less standardized. It could include resection plus sliding plasty, neo-chordae and papillary muscle repositioning.

In endocarditis the first step is to resect all infected tissues and then assess for repair.

Leaflet perforation requires pericardial patch plasty (Fig. 21.23). Commissural destruction can be treated using sliding plasty or neo-chordae chordal replacement,

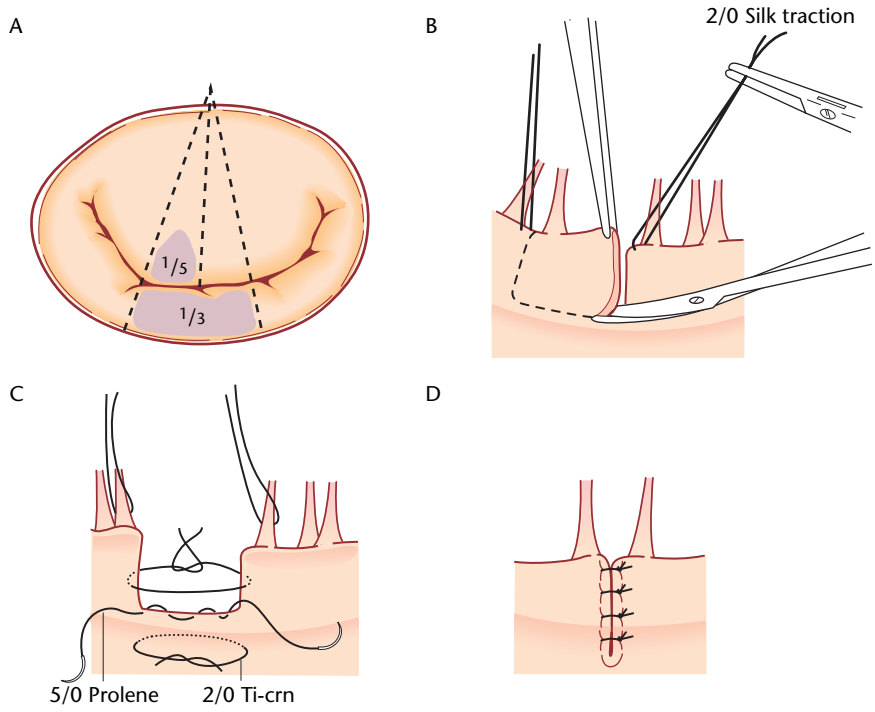

Figure 21.21 Mitral valve repair in degenerative mitral regurgitation. Quadrangular resection. AL = anterior leaflet; AN = annulus; PL = posterior leaflet. (A) Leaflet resection. Identification of a rectangular segment of up to one-third of the total length of the posterior leaflet that can be resected. (B) The segment of the posterior leaflet is resected close to the annulus. (C) The annulus is plicated and the continuity of the leaflet is re-established with sutures. (D) Completed repair. Reproduced, with permission, from Antunes MJ, *Mitral Valve Repair*, 1989, Verlag.

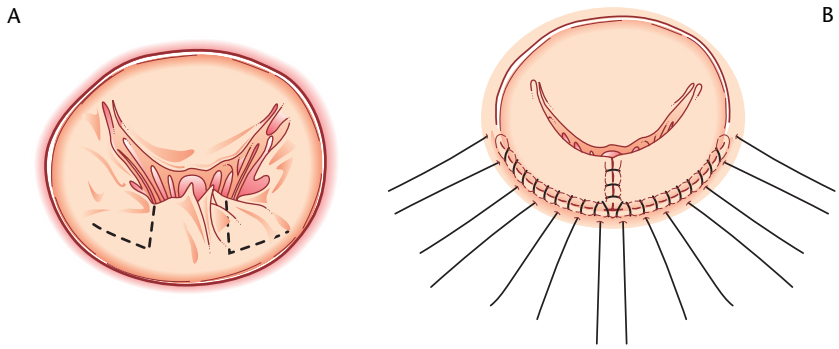

Figure 21.22 Mitral valve repair in degenerative mitral regurgitation. Sliding plasty technique. (A) resection of excessive tissue in prolapsed segment of the posterior leaflet; (B) repair is completed. (Courtesy of Dr V. Jebara.)

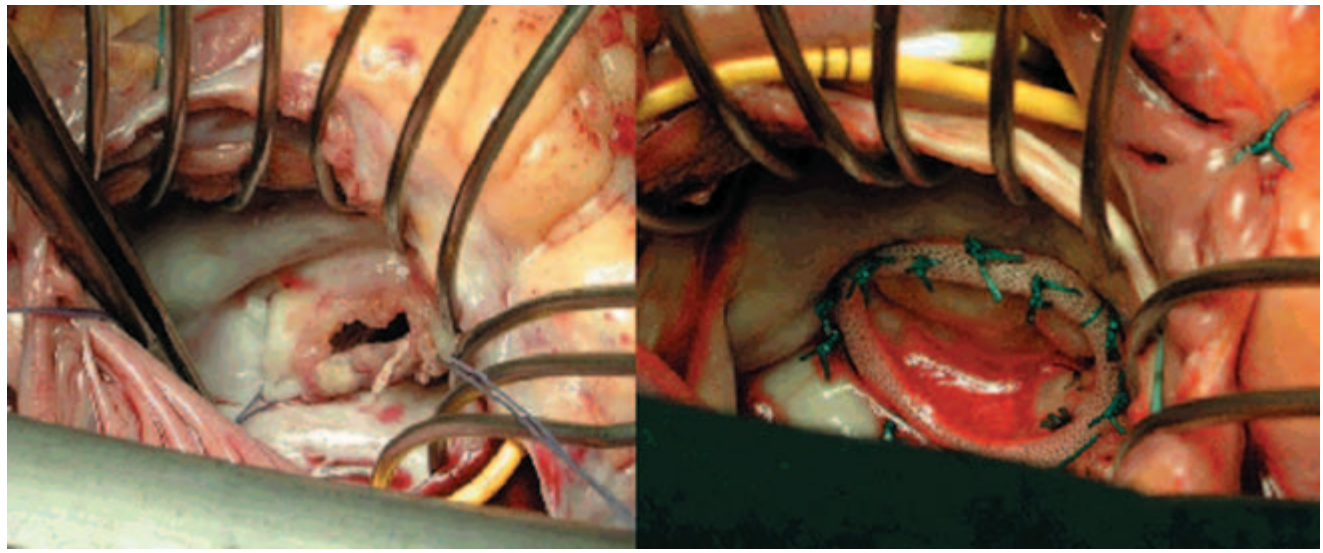

Figure 21.23 Mitral valve repair in mitral valve endocarditis. (A) abscess and perforation of the anterior leaflet, respecting the free margin of the leaflet; (B) final result after pericardial patch plasty.

or by transferring the posterior leaflet tricuspid valve. Annular abscesses require de-insertion, of the leaflet, debridement, reconstruction using pericardium, and re-insertion of leaflet.

In functional MR, the main technique is restrictive annuloplasty (two sizes under) in order to obtain a coaptation length of at least 8 mm [129,130]. Finally other techniques aim at LV reverse remodelling, surgical ventricular restoration [131] and repositioning of papillary muscle.

In rheumatic MR, repair uses all the artifices described for MS and cure of prolapse as described for degenerative disease. Specific techniques for rheumatic disease combine: shaving of the free margin of anterior leaflet and repositioning of the marginal chords; leaflet augmentation, usually of the posterior leaflet using pericardial patches [132,133]; and, in extreme cases, resection of subvalvular apparatus and re-suspension by means of neochordae; and finally 'oversized' annuloplasty, merely for remodelling.

Antiarrhythmic surgery Recently additional antiarrhythmic procedures have been proposed in patients with preoperative atrial fibrillation [134]. The limited amount of data available suggests that the results vary according to patient variables (characteristics, atrial fibrillation, LV function, atrial size) and techniques (Maze or Cox techniques, cryoablation, radiofrequency ablation). Currently, these procedures are still rarely used and their definitive role remains to be determined.

In current practice, valve repair is increasingly performed and is used in 30–40% of cases in the most recent registries (Table 21.3) and in up to 90% of patients in experienced centres [135].

Results of surgery

Despite the absence of randomized comparison between the results of valve replacement and repair, and the possible inherent biases resulting from this, it is widely accepted that valve repair is the optimal surgical treat-

ment in patients with severe MR. When compared with replacement, repair has lower perioperative mortality (Table 21.4), improved survival, better preservation of postoperative LV function, and lower long-term morbidity (thromboembolism, endocarditis and need for re-operation) [136–138].

Besides symptoms, the most important predictors of postoperative outcome after surgery for MR are age, atrial fibrillation, preoperative LV function and the reparability of the valve. The best results of surgery are observed in the group with a preoperative LV ejection fraction > 60%. A preoperative end-systolic diameter of < 45 mm is also closely correlated with a good postoperative prognosis. However, a value over which postoperative LV dysfunction will not occur has not been demonstrated, rendering the prediction of the postoperative dysfunction difficult in the individual patient. Progressive development of pulmonary hypertension is also a marker for poor prognosis.

The probability of a successful outcome for valve repair is of crucial importance. Degenerative MR due to valve prolapse can usually be successfully repaired (10-year survival of 90% for valve repair compared with 74% for valve replacement [137] and cardiac event-free survival of 74% at 20 years [138]) (Fig. 21.24). The re-operation rate is higher after replacement [23%] than after repair [16%] [137]. However, extensive annular calcification represents a surgical challenge for valve repair, and probably even more so for valve replacement. In the other aetiologies experience with valve repair is much more limited and results are not as consistent, even in experienced hands [135]. In rheumatic lesions, good long-term results, with survival rates of up to 82% at 20 years, were reported in selected patients [132,133]. A higher re-operation rate is expected, however, in young patients when there is a risk of further episodes of rheumatic fever [133]. The limitations of repair are the absence of pliable anterior leaflet and of at least one commissure free from calcification. In endocarditis, Iung and colleagues [139] recently reported 78 cases, of which 63 benefited from mitral valve repair, even in acute endocarditis. Operative mortality was 3.2% and the 7-year event-free survival was 78%. Here the limitation for repair is extensive destruction of the leaflets and subvalvular apparatus. The exact timing of surgery is also debated. In functional MR the data are more limited. Depending on the degree of emergency, operative mortality has been reported at between 5% and 18%. In patients with an ejection fraction of < 30%, 2- and 5-year survivals of 70% [129] and 61% [131], respectively, have been reported, with good functional results.

Finally, the results of valve repair are also highly dependent on the experience of the surgeon; this holds to be even more true as the lesions get more complex [135,137].

Treatment strategy

Acute mitral regurgitation

Urgent surgery is required.

Patients with chronic organic mitral regurgitation

The indications for surgery depend on risk stratification and on the possibility of valve repair; surgery is recommended earlier when repair is more feasible.

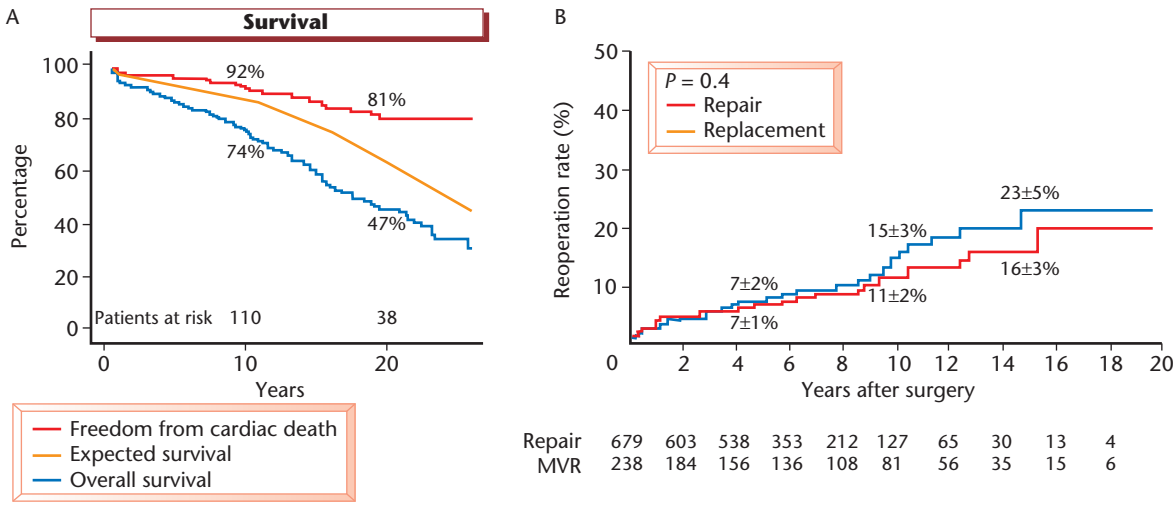

Figure 21.24 Long-term results after mitral valve repair. (A) Survival 30 years after conservative surgery (adapted from [138]). (B) Comparative freedom from re-operation between mitral valve repair and mitral valve replacement (adapted from [137]).

Asymptomatic patients

Indications for surgery are:

- Presence of LV dysfunction (ejection fraction < 60%, end-systolic diameter > 45 mm) [23,24]. In addition to the initial measurements, the temporal changes in LV function should also be taken into account. Surgery in this group should be considered, even in patients with a high likelihood of valve replacement.
- Normal LV function but atrial fibrillation and/or pulmonary hypertension (systolic pulmonary arterial pressure > 50 mmHg or > 60 mmHg on effort) with a high likelihood of repair.
- Finally, even if this indication is still debated, normal LV function when valve repair is highly possible, MR is severe, and operative risk is low. Conversely, careful follow-up is recommended for patients with relatively high operative risk (e.g. patients 75 years or older) or when the feasibility of valve repair is doubtful.

Asymptomatic patients with severe MR and preserved LV function, who are not operated on, should be seen every 6 months and echocardiography performed every 12 months, the follow-up being closer in patients with borderline values. Asymptomatic patients with moderate MR and preserved LV function can be clinically followed up on a yearly basis and echocardiography should be performed every 2 years [24]. The role of exercise echocardiography in serial testing of asymptomatic patients with moderate MR and preserved function requires further evaluation.

Symptomatic patients with severe MR and normal LV function or moderate dysfunction require surgery. In the presence of severe dysfunction, surgery can still be recommended if the ejection fraction is ≥ 30%. When ejection fraction is < 30%, surgery can still improve function in patients in whom valve repair is highly likely.

Specific situations

Mitral regurgitation associated with Marfan syndrome

The lesions of the mitral valve are frequently complex and extensive. The association of severe annular calcification reduces the feasibility of valve repair, even in experienced hands. As MR can be associated with lesions of the aorta, choice of treatment is also influenced by the dimensions of the ascending aorta.

Ischaemic mitral regurgitation

The data on the treatment of ischaemic MR are far more limited than in the other aetiologies and this results in a less evidence-based management [118]. Severe MR should be corrected at the time of bypass surgery [140,141]. However, there is a continuing debate on the management of moderate MR in these patients. In such cases the decision must be made preoperatively and valve repair is preferable [141]. If intervention is indicated, the preferred surgical procedure remains controversial. There is a trend favouring valve repair even if it carries a higher risk of mortality and of recurrence than in the other aetiologies [135].

In patients with increased QRS duration and intraventricular asynchrony, cardiac resynchronization therapy may increase the mitral valve closing force and reduce MR severity [142].

Tricuspid valve disease

Tricuspid stenosis

Tricuspid stenosis (TS), although still present in developing countries, is rarely observed in the West. Detection requires careful attention, as it is almost always associated with left-sided valve lesions that dominate the presentation.

Aetiology

TS is often combined with TR, most frequently of rheumatic origin, and almost always associated with left-sided valve disease, particularly MS. The anatomical changes of rheumatic TS resemble those of MS.

Metastatic carcinoid disease may cause TS and TR, which are frequently associated with pulmonic stenosis [99]. Carcinoid disease leads to deposits of fibrous tissue on the endocardium of the cusps and cardiac cavities.

Other aetiologies are rare: congenital, therapy with ergot-like drugs, Whipple's disease, endocarditis or large right atrial tumour.

Pathophysiology

TS usually induces a small diastolic pressure gradient between right atrium and ventricle, which increases during inspiration, and which tends to be limited by systemic venous compliance and reduced cardiac output. Normal valve area is around 7–8 cm^2, a pressure gradient occurs if < 2 cm^2, and valve area < 1.5 cm^2 is associated with symptoms.

Diagnosis

HISTORY

The main symptoms are those of the other valvular lesions. Right subcostal pain, corresponding to hepatalgia, on exercise or after meals, may be more directly a consequence of TS. Low cardiac output causes fatigue.

PHYSICAL EXAMINATION

Clinical signs are often masked by those of the combined valvular lesions, especially MS. The diastolic murmur is of low intensity and increases with inspiration, and is preceded by a subtle opening snap. Presystolic jugular distension, Harzer's sign, systemic venous congestion, oedema, or even anasarca may be seen in the most severe cases.

ELECTROCARDIOGRAPHY

In patients in sinus rhythm, the most frequent abnormality is right atrial hypertrophy with a peaked P wave or, more frequently, biatrial hypertrophy. Atrial fibrillation is present in one-half of the cases.

CHEST RADIOGRAPH

Cardiac silhouette is enlarged with right atrial dilatation. Coexistent MS results in left atrial enlargement, but the degree of pulmonary congestion is less than usual.

ECHOCARDIOGRAPHY

Echocardiography provides the most useful information. TS is often overlooked and requires careful evaluation. In rheumatic disease the leaflets are thickened with reduced motion, the chordae are shortened and thickened, and diastolic doming is seen. In carcinoid syndrome, retraction of leaflets and/or subvalvular apparatus towards the apex persists during systole [99]. The pressure half-time method can be used; however, the continuity equation can rarely be obtained because of frequent associated regurgitation. Planimetry of the valve area is difficult [143].

CARDIAC CATHETERIZATION

Catheterization has been replaced by echocardiography for evaluating severity.

Medical treatment

In the presence of congestive heart failure, diuretics are useful but are of limited efficacy.

Percutaneous intervention

Percutaneous balloon tricuspid dilatation has been performed in a limited number of cases, either alone or alongside PMC, but frequently induces significant regurgitation [82].

Surgery

The lack of pliable leaflet tissue is the main limitation for conservative techniques. Open valvotomy usually combines commissurotomy, leaflet augmentation using a pericardial patch, annuloplasty and papillary muscle split [144].

For valve replacement, biological prostheses are preferred to mechanical ones because of the higher risk of thrombosis carried by the latter and the satisfactory long-term durability of the former in the tricuspid position [145].

Treatment strategy

Intervention is usually carried out at the time of intervention on the other valves. Conservative surgery, or more often valve replacement, according to anatomy and surgical expertise in valve repair, are preferred to balloon commissurotomy, which can only be considered in the rare cases of pure TS.

Tricuspid regurgitation

The trivial form of TR is frequently detected by echocardiography in normal subjects. Pathological TR is more often functional than primary.

Aetiology

FUNCTIONAL TRICUSPID REGURGITATION

Functional TR is due to annular dilatation and secondary to right ventricular pressure and/or volume overload [146]. Pressure overload is most often caused by pulmonary hypertension resulting from left-sided heart disease or, more rarely, cor pulmonale, primary pulmonary hypertension and ventricular volume overload, possibly relating to atrial septal defects or intrinsic disease of the right ventricle (ischaemic or cardiomyopathy).

PRIMARY TRICUSPID REGURGITATION

Possible causes are infective endocarditis (especially in intravenous drug addicts) [147], rheumatic heart disease, carcinoid syndrome, myxomatous disease, endomyocardial fibrosis, Ebstein's anomaly, ergot-like drugs, thoracic trauma and iatrogenic diseases.

Pathophysiology

TR induces right ventricular and atrial dilatation, both

of which tend to increase annular dilatation, which is the key finding in functional TR. If TR is severe and right atrial compliance is low, the increase in right atrial pressure is transmitted upstream to the systemic veins. Severe TR can also induce ventricular interdependency and reduction in both right-sided stroke volume and LV preload. Haemodynamic abnormalities increase during inspiration.

Diagnosis

HISTORY

Predominant symptoms are those of associated diseases and even severe TR may be well tolerated for a long period of time. Dyspnoea and fatigue are common. Symptoms more specifically related to TR are right-sided congestion and discomfort due to hepatomegaly. Anorexia and weight loss may occur at a later stage.

PHYSICAL EXAMINATION

Three signs are typical: first, a soft holosystolic murmur, best heard along the left sternal border and in the xiphoid region (increasing with inspiration, this murmur could be mild, or even absent, in severe TR when turbulent flow disappears); second, systolic jugular vein, or exceptionally varices expansion; and, finally, pulsatile enlarged liver with hepatojugular reflux. Peripheral cyanosis, leg oedema or even ascites may be observed.

ELECTROCARDIOGRAPHY

Atrial fibrillation and incomplete right bundle branch block are frequent.

CHEST RADIOGRAPH

Marked cardiomegaly is usually present due to enlargement of the right cavities.

ECHOCARDIOGRAPHY

Echocardiography is the ideal technique to quantify TR and distinguish between its functional and primary forms (Fig. 21.25). In the latter form, the aetiology can usually be identified from specific abnormalities: vegetations in endocarditis, leaflet retraction in rheumatic, flail leaflet in myxomatous or post-traumatic disease. TR is identified using colour flow mapping of the systolic regurgitant jet in the right atrium, inferior vena cava and hepatic veins. The severity of TR is estimated from the extent of the jet or better by vena contracta width [44,148]. Measurement of systolic velocity of the regurgitant jet permits one to quantify trans-tricuspid pressure gradient using the simplified Bernoulli equation and to estimate systolic pulmonary arterial pressure. This may be inaccurate in the presence of voluminous TR, which leads to less- or non-turbulent flow and equalization of right ventricular and atrial pressures. Severe TR is defined by a regurgitant volume > 45 ml and an effective regurgitant orifice area superior to 40 mm^2. Finally, echocardiography will carefully evaluate the right ventricle, despite the existing limitations, and the degree of the combined lesions.

CARDIAC CATHETERIZATION

Today, catheterization is not needed to diagnose TR or to estimate its severity.

Natural history

Functional TR may diminish or disappear as RV failure

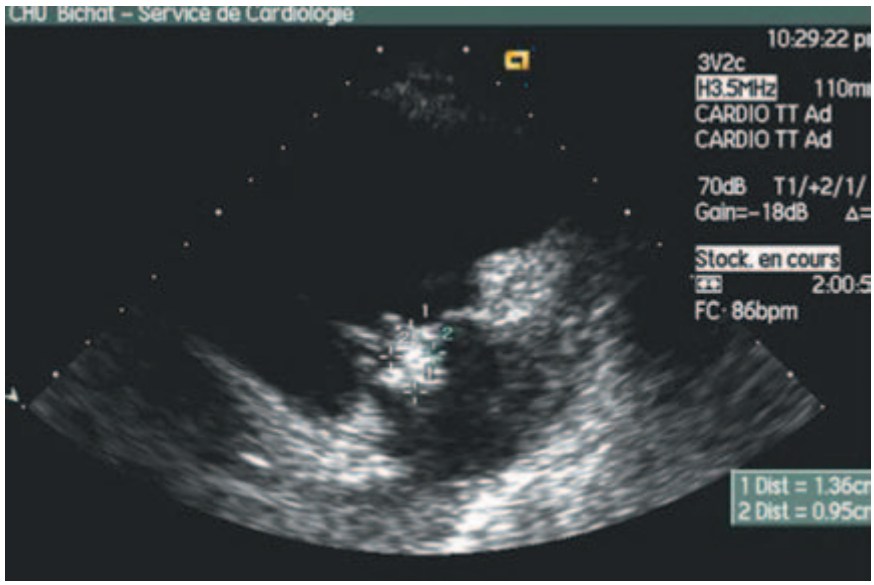

Figure 21.25 Tricuspid endocarditis: vegetation on the tricuspid valve. Transthoracic echocardiography. (Courtesy of Dr E. Brochet.)

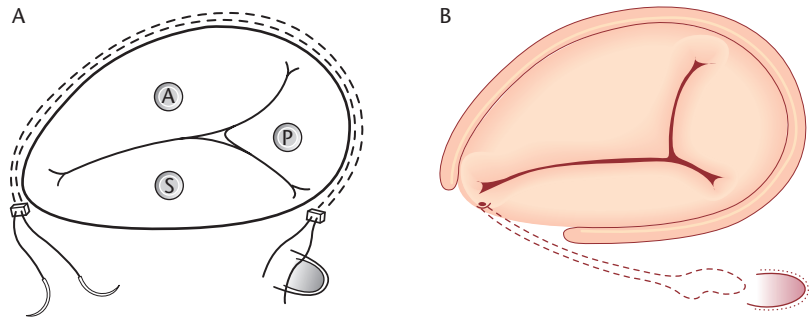

Figure 21.26 Conservative surgery for tricuspid regurgitation. (A) Tricuspid annuloplasty using stitches (De Vega). A = Anterior leaflet; P = Posterior leaflet; S = Septal leaflet. (B) Tricuspid annuloplasty using ring (Carpentier, Cosgrove, Duran). (Courtesy of Dr D. Koolbergen.)

improves following the treatment of its cause. Predicting the evolution of functional TR before intervention on the mitral valve disease remains difficult. Pulmonary hypertension, increased right ventricular pressure and dimension, reduced right ventricular function and the diameter of tricuspid annulus are important risk factors for persistence or late worsening of TR [149]. However, TR may persist even after successful correction of left-sided lesions [150,151]. The limited data on the natural history of primary TR suggest that severe TR has a poor prognosis even if it may be well tolerated for years.

Medical treatment

Diuretics improve signs of congestion. Specific therapy of the underlying disease is warranted.

Surgery

Valve replacement carries a risk of operative mortality ranging from 7% to 40%. Ten-year survival ranges from 30% to 50%, the predictors being preoperative functional class, LV and right ventricular function, and prosthetic complications [145]. The current experience favours the use of large bioprostheses over mechanical valves. Experience with mitral homografts in cases of TR caused by rheumatic disease or endocarditis is limited.

Annuloplasty, which restricts the annulus corresponding to the anterior and posterior leaflets but should respect the membranous septum at the apex of the triangle of Koch (bundle of His), is key to conservative surgery. Annuloplasty may be performed using a stitch or either flexible or rigid rings (Fig. 21.26) [144,152,153]. Additional techniques are used according to aetiology: resection, repositioning, sliding plasty or neo-chordae in prolapse, and pericardial patch in localized perforation.

Better long-term results are observed with the ring technique than with the stitch technique. In particular the incidence of residual TR is lower with rings: 10% vs 20–35% at 5 years [144,152–154].

Treatment strategy

The timing of surgical intervention and the appropriate technique remain controversial. The indication is usually discussed at the time of surgical correction of left-sided valvular lesions.

In these circumstances, severe TR should be corrected. On the other hand mild TR does not warrant intervention. In the other cases, surgical correction can be recommended when there is pulmonary hypertension, important dilatation of the annulus (diameter > 21 mm/m^2 [153]), or even more so if TR is of organic origin; however, this is debated. If technically possible, conservative surgery is preferable to valve replacement.

Surgery limited to the tricuspid valve can be required in symptomatic patients with severe TR resulting from trauma or endocarditis, or for persistent or recurrent TR after mitral valve surgery in the absence of left-sided myocardial-, valve- or severe right ventricular dysfunction.

Prosthetic valve surgery

Preoperative evaluation

Preoperative evaluation is a key issue as it enables spontaneous prognosis, operative risk and long-term outcome after surgery to be evaluated. Patient evaluation should assess the severity of the valve disease and its consequences. Consequences are, in particular, symptoms associated with valve stenosis and LV dilatation and/or dysfunction associated with valve regurgitations. Symptom assessment should be carefully conducted and completed through exercise testing when symptoms are unclear [23,24]. When LV dimensions or function are borderline for advising surgery, the repetition of examination is useful to analyse trends and to compensate for the variability of measurements. In such cases, it is also

advised to compare different techniques. The evaluation of comorbidity is another important step in decision-making, especially given the increasing age of patients in Western countries. The most common comorbidities that influence operative risk are coronary and carotid atherosclerosis, renal insufficiency and chronic obstructive pulmonary disease. Finally, the analysis of local resources and patient environment also plays a role in decision-making. This is particularly relevant as regards availability of techniques such as valve repair or percutaneous intervention, as well as the possibility for patients to follow lifelong anticoagulant therapy.

Estimation of operative risk is paramount to the therapeutic decision and depends on a number of factors related to heart disease, comorbidity and modalities of surgery. Multivariate scores have been derived from large registries, thereby enabling the risk of an individual patient to be easily assessed. The Euroscore is widely used in cardiac surgery and one of its strengths is to have been validated in a number of diverse populations, including patients with heart valve disease [155] (Table 21.8). Specific models have been elaborated according to the type of valve disease [156]. The aim of this approach is to allow for timely intervention and

Table 21.8 Detail of the calculation of the additive Euroscore

Risk factor	Euroscore definition	Points
Age	< 60 years	0
	60–64	1
	65–69	2
	70–74	3
	75–79	4
	80–84	5
	85–89	6
	90–94	7
	95–99	8
Sex	Female	1
Chronic pulmonary disease	Long-term use of bronchodilators or steroids for lung disease	1
Extracardiac arteriopathy	Any one or more of the following: claudication, carotid occlusion or > 50% stenosis, previous or planned intervention on the abdominal aorta, limb arteries or carotids	2
Neurological dysfunction	Severely affecting ambulation or day-to-day functioning	2
Previous cardiac surgery	Requiring opening of the pericardium	3
Serum creatinine	> 200 μmol/l preoperatively	2
Active endocarditis	Patient still under antibiotic treatment for endocarditis at the time of surgery	3
Critical preoperative state	Any one of more of the following: ventricular tachycardia or fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the anaesthetic room, preoperative inotropic support, intra-aortic balloon counterpulsation or preoperative acute renal failure (anuria or oliguria, 10 ml/h)	3
Unstable angina	Rest angina requiring intravenous nitrates until arrival in the anaesthetic room	2
Left ventricular dysfunction	Moderate or left ventricular ejection fraction 30–50%	1
	Poor or left ventricular ejection fraction < 30%	3
Recent myocardial infarction	< 90 days	2
Pulmonary hypertension	Systolic pulmonary artery pressure > 60 mmHg	2
Emergency	Carried out on referral before the beginning of the next working day	2
Other than isolated CABG	Major cardiac procedure other than or in addition to CABG	2
Surgery on thoracic aorta	For disorder of ascending, arch or descending aorta	3
Post-infarct septal rupture	—	4

The logistic Euroscore enables the operative mortality to be predicted for any given patient, using the same factors, and can be computed on the website http://www.euroscore.org/calc.html [195].

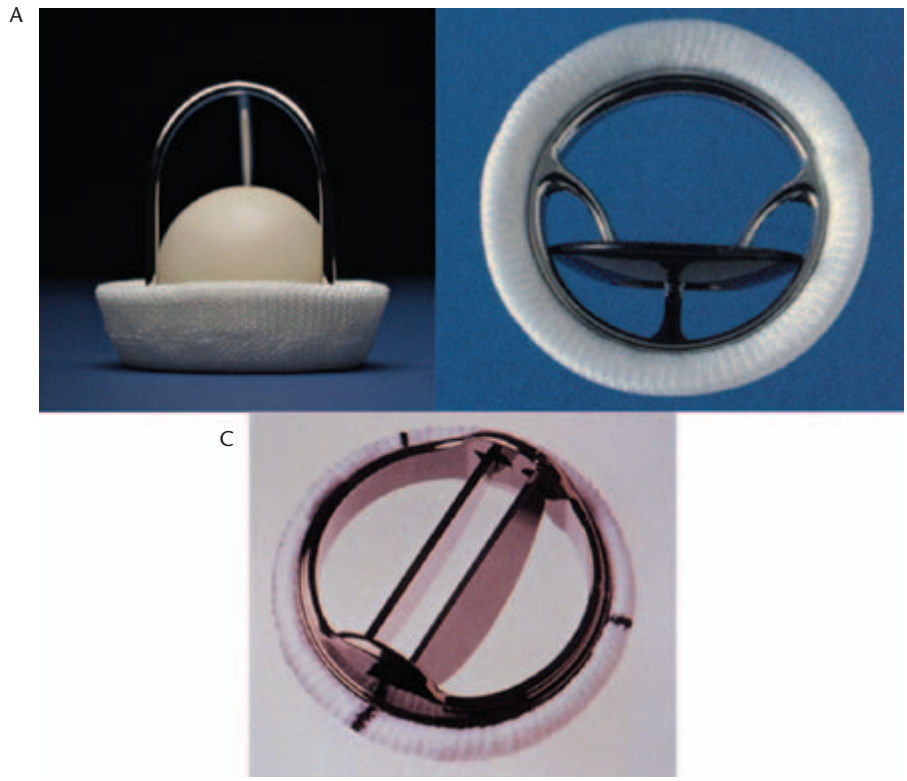

Figure 21.27 The three main designs of mechanical valve: (A) ball and cage; (B) single disk; (C) bileaflet.

to reduce the subjective component in the estimation of the risk–benefit ratio.

Surgical techniques and valve substitutes

Prostheses

The ideal valve substitute would mimic the haemodynamic properties of native valves, be durable and chemically inert. In addition, it would be silent, carry no risk of thromboembolism and require no valve-specific medication. Despite the fact that over 100 different types of valve have been produced for human use in the last 40 years, this goal still remains elusive.

The design of mechanical valves can be catalogued into three types (Fig. 21.27). The design of biological valves (Fig. 21.28) can be divided into true biological valves, such as the homograft or autograft, and valves constructed from xenogeneic biological material, rendered immunologically quiescent by treatment with glutaraldehyde. Porcine valve or bovine pericardium is sewn onto an artificial stent to produce a bioprosthetic valve.

The design of the stentless porcine valve was intended to reduce residual obstruction to transaortic flow by maximizing the available flow area. Better haemodynamics and a greater resolution of LV hypertrophy have been reported, but no superiority regarding long-term durability has been demonstrated so far [157].

The realization of the importance of achieving as low a transvalvular gradient as possible has led manufacturers to develop 'supra-annular' designs.

Homografts

In the early 1960s, Ross and Barratt-Boyes separately introduced the aortic homograft, but only a few skilled surgeons were able to obtain predictable results with a free-sewn valve. Changes in the technique have resulted from different methods of preservation, such as cryopreservation or storage in antibiotics, and of implantation: full root or subcoronary.

One of the largest and most complete series comes from O'Brien and colleagues [158]. With cryopreserved valves, the re-operation rate at 15 years for structural valve degeneration (SVD) was 53% for age 1–20 years; 15% for 2–40; 19% for 41–60, and 16% for those aged over 60 years. In this study, valve preservation techniques and implantation technique had no effect on the overall actuarial 20-year incidence of endocarditis, thromboembolism, SVD or late survival. One limitation of the technique is the shortage of high-quality homografts. Aortic homografts are now the substitute of choice for infective

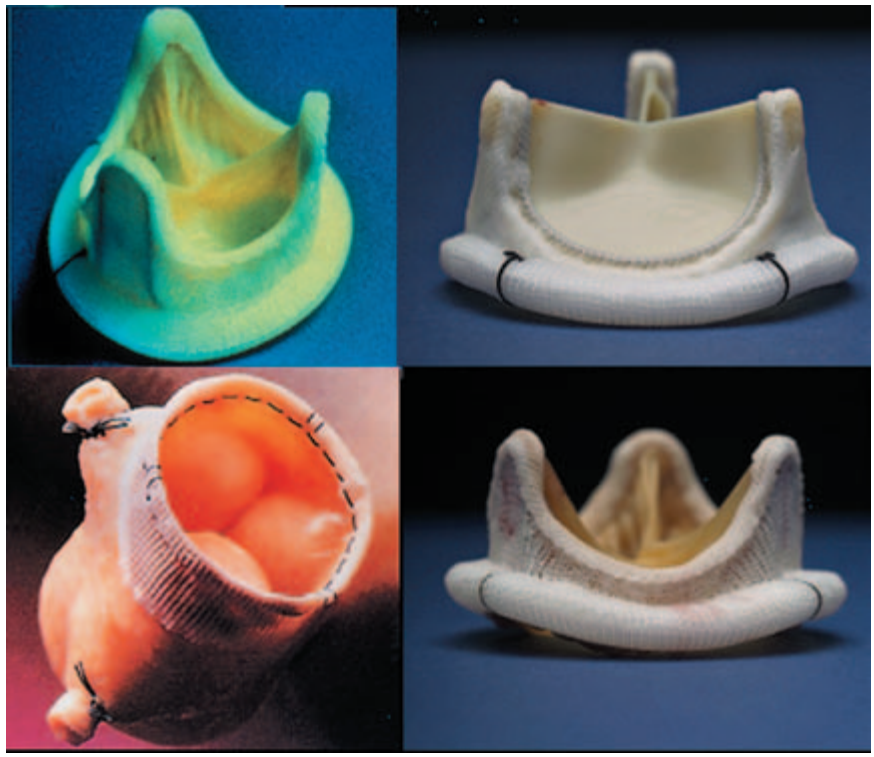

Figure 21.28 The four main designs of bioprosthetic valve: (A) porcine intra-annular valve; (B) pericardial intra-annular valve; (C) stentless porcine valve; (D) supra-annular porcine valve.

endocarditis with perivalvular lesions. However, concerns remain regarding their superiority to bioprostheses in terms of durability. Experience with mitral homografts is still limited [159].

The pulmonary autograft

In 1967, Ross introduced the pulmonary autograft as a possible long-term biological solution to replace diseased aortic valves. Although it is a more complex and difficult procedure, it has the advantage in children that the valve is able to grow as the child grows. The autograft remains viable and grows in proportion with somatic growth and the annulus and sinotubular junction increase in size to the normal range. Elkins and colleagues [160] reported that freedom from re-operation at 7 years was 96.5% for autografts in the aortic position and homograft reconstruction of the right ventricular outflow tract. The incidence of thromboembolism is very low, as is that of infective endocarditis. Those with rheumatic heart disease may develop rheumatic valvulitis in the autograft. The exact role of the pulmonary autograft remains controversial, and it is only performed for children or young adults by a few surgeons in specialist centres.

Given their availability, the experience of their use and the standardization of surgical techniques, mechanical and biological prostheses are by far the most widely used valve substitutes (Table 21.3).

Minimal invasive valve surgery

A number of centres have promoted the minimal invasive approach [161] but it has not been widely adopted. More recently, an endoscopic, video-assisted approach via the right chest has been reported [162], in which 306 patients underwent endoscopic mitral valve surgery (226 repairs and 80 replacements). Hospital mortality was 1%. Freedom from mitral valve re-operation at 4 years was 91%, 94% of the patients reported no pain or mild postoperative pain and 46% were back at work within 4 weeks.

Long-term results of valve substitutes

Late outcome after valve surgery depends on a number of patient-related factors, the type of intervention, and the prosthesis. The clinical performance of valvular substitutes is judged according to the 'Guidelines for Reporting Morbidity and Mortality After Cardiac Valvular Operations' [163].

The specific complications associated with cardiac valve prostheses are structural valve degeneration (SVD), non-structural dysfunction, thromboembolism and thrombosis, anticoagulant-related haemorrhage and prosthetic valve endocarditis.

Randomized studies

Two large randomized trials have compared long-term

Table 21.9 Actuarial rates (%) of events 15 years after valve replacement in the Veterans Affairs randomized trial [89]

	Aortic prostheses			Mitral prostheses		
	Mechanical ($n = 198$)	Bioprosthesis ($n = 196$)	*P*	Mechanical ($n = 88$)	Bioprosthesis ($n = 93$)	*P*
Death	66 ± 3	79 ± 3	0.02	81 ± 4	79 ± 4	0.30
Re-operation	10 ± 3	29 ± 5	0.004	25 ± 6	50 ± 8	0.15
Embolism	18 ± 4	18 ± 4	0.66	18 ± 5	22 ± 5	0.96
Prosthetic thrombosis	2 ± 1	1 ± 1	0.33	1 ± 1	1 ± 1	0.95
Bleeding	51 ± 4	30 ± 4	0.0001	53 ± 7	31 ± 6	0.01
Endocarditis	7 ± 2	15 ± 5	0.45	11 ± 4	17 ± 5	0.37

Table 21.10 Actuarial rates (%) of events 20 years after valve replacement in the Edinburgh Heart Valve randomized trial [163]

	Aortic prostheses			Mitral prostheses		
	Mechanical ($n = 109$)	Bioprosthesis ($n = 102$)	*P*	Mechanical ($n = 129$)	Bioprosthesis ($n = 132$)	*P*
Survival	28 ± 4	31 ± 5	0.57	22 ± 4	18 ± 4	0.41
Re-operation	7 ± 3	56 ± 8	< 0.0001	13 ± 4	78 ± 7	< 0.0001
Embolism	24 ± 6	39 ± 9	0.13	53 ± 7	32 ± 6	0.32
Bleeding	61 ± 8	42 ± 12	0.001	53 ± 8	37 ± 11	0.39
Endocarditis	8 ± 4	9 ± 6	0.71	4 ± 3	7 ± 3	0.38

The 61 patients who had double valve replacement are not represented.

results of valve replacement using a mechanical or a biological prosthesis.

The Veterans Affairs trial reported a mean 15-year follow-up of 575 randomized men, between 1987 and 1992 (Table 21.9) [89]. Mortality was lower in patients who had undergone aortic valve replacement using a mechanical prosthesis, but the difference only appeared after 10 years. Primary SVD of bioprostheses begins to occur 5 years after mitral valve replacement and 7 years after aortic valve replacement. Bioprosthesis SVD seldom occurred in patients aged over 65.

In the Edinburgh Heart Valve trial, 541 men and women were randomized between 1975 and 1979 and followed up for 20 years (Table 21.10) [164]. Major event-free survival was significantly higher in patients with a mechanical prosthesis than those with a bioprosthesis (14 ± 2% vs. 5 ± 1%, $P = 0.0007$), but there was no difference in survival.

In both studies, the incidence of thromboembolism and endocarditis were not significantly different, whereas bleeding rate was higher with mechanical valves.

Non-randomized studies

Overall, late mortality rates in large series of valve replacements are high, in the order of 15–20% at 10–15 years [165–168]. There are wide variations in prognosis, even for a given type of prosthesis, which shows the importance of patient characteristics in late outcome after valve surgery, in particular: age, LV dysfunction, the presence of heart failure, NYHA functional class, signs of congestive heart failure, arrhythmias, pulmonary hypertension, and comorbidity, such as coronary artery disease, diabetes, renal insufficiency and lung disease. The modalities of intervention also play a role, late survival being consistently lower in the case of associated coronary bypass grafting. Thus, comparison of different series should be cautious as differences in outcome are more likely to be the consequence of differences in patient characteristics rather than the type of prosthesis used.

Does improved valve design result in improved clinical outcome?

Series based on the first generation of mechanical prostheses reported 10- and 20-year survival rates of 60% and 35%, respectively, after aortic valve replacement using the Starr–Edwards prosthesis model 1260, with an incidence of thromboembolic events of 1.4% per year [169]. The 5-year data from a prospective randomized trial reported by Murday and colleagues [170] showed no statistically significant difference in patient outcomes between the St Jude and Starr–Edwards valves in either the aortic or mitral position.

The mortality and complication rates in patients with the use of various prosthetic devices followed up

Table 21.11 Linearized rates (per 100 patients-year) of thromboembolism and bleeding in randomized controlled trials on anticoagulant therapy in patients with mechanical heart valve prosthesis

	n	INR	Symptomatic TE	Major bleeding	All bleeding
Saour *et al.* [172]	122	2.65	4	0.9	5.2
	125	9	3.7	2.1	10.1
Altman *et al.* [173]	51	2–3	1.92	—	3.8
	48	3–4.5	4.94	—	24.7
AREVA study [174]	188	2–3	1.9	4.0	7.1
	192	3–4.5	1.7	5.6	15.0

INR, international normalized ratio; TE, thromboembolic events.

for longer than 10 years indicate that there are no major differences in patient outcomes among the different valve substitutes. However, there may be differences in quality of life, which is more difficult to measure.

Complications of valve substitutes

A review of 95 series of mechanical prosthesis and 70 series of bioprosthesis has shown that the incidence of thromboembolic events is not significantly different according to type of mechanical prosthesis or, for that matter, among the bioprostheses [171]. Similarly, the incidence of thrombosis, bleeding, endocarditis and paraprosthetic regurgitation does not significantly differ between the diverse models of mechanical prosthesis and bioprosthesis.

Thromboembolism and anticoagulation-related haemorrhage

Thromboembolic risk is higher after mitral than after aortic valve replacement and with mechanical prosthesis than with bioprosthesis. The analysis of the incidence of thromboembolism and bleeding in retrospective series should be cautious because of the frequent underestimation of event rates. For an evaluation to be accurate, it must be prospectively defined and repeated for the duration of follow-up. Furthermore, comparison between series may be influenced by differences in treatment, as well as patient- and prosthesis-related characteristics. Therefore, optimizing antithrombotic therapy requires randomized controlled trials.

The incidence of thromboembolism and bleeding in randomized trials is detailed in Table 21.11 [172–174]. There was no significant increase in the thromboembolic risk of patients receiving a moderate compared with a standard anticoagulation, whereas there was a 30–50% decrease in the incidence of bleeding. This was confirmed by the GELIA trial, although the interpretation may be difficult because of overlapping INR target ranges [175,176].

There may be a further decrease in the thromboembolic risk by associating antiplatelet drugs, which should be balanced with the increase in bleeding risk [177]. A randomized study demonstrated a decrease in the incidence of thromboembolism when low-dose aspirin was added to warfarin and the benefit remained significant when taking into account severe bleeding [178]. In the aspirin group, the main benefit was related to the decrease in sudden death and heart failure. As 30% of the population had associated coronary artery disease, the benefit of aspirin may have been due more to the prevention of atherosclerotic- rather than prosthetic-related events.

Endocarditis

The management of prosthetic endocarditis is detailed in Chapter 22.

Structural valve disease

The risk of SVD is considered 'negligible' with current models of mechanical prosthesis.

Bioprosthesis failure occurs via several mechanisms: regurgitation via leaflet tears, stenosis due to leaflet calcification or perforations unrelated to calcification. The two main predictive factors of the risk of bioprosthesis SVD are the site of the prosthesis and patient age [166,171]. SVD occurs earlier after mitral than after aortic valve replacement because of a higher closing pressure. The older the patient at the time of surgery, the lower the rate of SVD: less than 15% 15 years after aortic valve replacement in patients aged over 70, whereas the corresponding 10-year rate is approximately 60% under the age of 40.

Non-structural dysfunction

The conditions referred to under this heading are paraprosthetic leaks, pannus and haemolysis. Pannus refers to a membrane of material, which encroaches on the surface of the valve usually on the inflow side in either

the mitral or aortic position. A retrospective study of mechanical valves in the mitral position [179] revealed a constant but low risk of valve obstruction due to pannus over a 14-year period.

Paraprosthetic regurgitation has been reported in 6% of patients after aortic valve replacement and in 32% after mitral valve replacement when using systematic transoesophageal echocardiography [180]. Even mild paraprosthetic regurgitation may cause haemolysis, requiring re-operation if there is severe and recurrent anaemia. Subclinical haemolysis is frequently observed in patients with a normally functioning mechanical prosthesis.

Out of 2680 patients with mechanical prosthesis, 250 required re-operation between 1970 and 1997: 133 for paravalvular leaks, 48 for obstructive pannus and 29 for thrombotic obstruction [181].

Valve prosthesis–patient mismatch

Depending on its severity, valve prosthesis–patient mismatch may result in higher gradients at rest and on exercise, persistence of LV hypertrophy, impaired functional capacity or even an increase in late morbidity and mortality [182]. The severity of valve prosthesis–patient mismatch is evaluated by the effective prosthetic valve area 6–12 months after surgery, indexed to BSA [166].

Choice of prosthesis for the individual patient

The choice of the type of prosthesis for any given patient should include a risk–benefit analysis of the drawbacks of the main types of valve substitutes, i.e. bleeding with mechanical prostheses and the risk of re-operation with bioprostheses. Results from randomized and non-randomized series enable these respective risks to be evaluated according to patient characteristics. Age is a key issue, as bleeding risk tends to increase with age, whereas the presumed durability of a bioprosthesis exceeds life expectancy in the elderly. Thus, in the ACC/AHA guidelines, the use of bioprostheses is advised after the age of 65 in the aortic position and 70 in the mitral position [23]. However, the choice of the type of valve substitute should not over-stress patient age and should also take into account patient characteristics, which influence life expectancy as well as the risk of bleeding, bioprosthesis deterioration and re-operation [166,167]. Furthermore, it is of utmost importance to inform the patient and to take into account her/his feeling on the prospect of re-operation versus the constraint and risks of anticoagulant therapy as well as specific wishes related to lifestyle or, for example, the desire of pregnancy. In the final analysis, the decision on which valve to use is an individual one between the patient, cardiologist and cardiac surgeon.

Patient management after valve surgery

Modalities of follow-up

Clinical evaluation is the cornerstone of follow-up after valve surgery. During the postoperative period, repeated clinical examination is the best means to diagnose early complications, in particular concerning tamponade or septic complications. Functional deterioration or change in auscultation during late follow-up raises the question of valve dysfunction and requires prompt echocardiographic examination. If there is suspicion of a neurological event, transoesophageal echocardiography and CT of the brain must be carried out.

There is no consensus regarding the usefulness of systematic echocardiographic follow-up, except 5–7 years after valve replacement using a bioprosthesis [23]. Interpretation of follow-up echocardiography should take into account a baseline evaluation performed 3–6 months after surgery, as the relevance of gradients is questionable during the early postoperative period. The diagnosis of prosthetic dysfunction relies more on the analysis of trends in measurements than on the comparison with predicted values for a given prosthesis, which supports the case for annual echocardiographic examination after any valve surgery.

The main usefulness of blood tests is to detect silent bleeding in patients under anticoagulant therapy or in those suffering from pathological haemolysis or infection according to the clinical context.

Anticoagulant therapy

GUIDELINES

A moderate anticoagulation, with a target INR of between 2 and 3, is now advised in selected patients with an aortic prosthesis (Table 21.12). Higher levels of anticoagulation are recommended in patients who have mitral prosthesis or older types of aortic prosthesis, but there is no consensus concerning the target INR [23,183–185].

In European guidelines, the combination of aspirin with vitamin K antagonists is restricted to patients with associated atherosclerosis or who experience recurrent embolism despite correct anticoagulation, whereas in USA guidelines it is considered more widely.

ANTICOAGULATION MONITORING

In a retrospective study, INR variability was a strong predictive factor of late survival after valve replacement [186]. Besides patient education, there are two main approaches for improving effective INR stability: anticoagulation clinics and self-monitoring. Randomized studies have

Table 21.12 Target INR according to guidelines on oral anticoagulant therapy in patients with mechanical prosthetic heart valves

Prosthesis	ACCP 2001	ACC/AHA 1998	SFC 1998	ESC 1995
Aortic prosthesis at low risk*	2.0–3.0	2.0–3.0	2.0–3.0	2.5–3.0
Other aortic prostheses	2.5–3.5 or 2.0–3.0 + ASA	2.5–3.5 or 2.0–3.0 + ASA	3.0–4.5	3.0–4.5
Mitral prosthesis	2.5–3.5	2.5–3.5	3.0–4.5	3.0–3.5

ACC, American College of Cardiology [23]; ACCP, American College of Chest Physicians [185]; AHA, American Heart Association [23]; ASA, aspirin (low-dose: 80–100 mg); ESC, European Society of Cardiology [183]; INR, international normalized ratio; SFC, Société Française de Cardiologie (French Society of Cardiology) [185].
*Low risk for thromboembolism is defined as: Bileaflet or Medtronic Hall prosthesis; sinus rhythm without left atrial enlargement; normal left ventricular function; no previous thromboembolism.

shown that self-monitoring improves INR stability and decreases the incidence of thromboembolism and bleeding compared with conventional monitoring [187].

SPECIFIC SITUATIONS

Bioprosthesis Guidelines advise a moderate anticoagulation with a target INR of between 2 and 3 during the first 3 months following valve replacement using a bioprosthesis [23].

Postoperative Period The incidence of thromboembolism is higher during the first month following valve replacement using a mechanical prosthesis. There is a wide heterogeneity in the practice of postoperative anticoagulant therapy. Because of the lack of series, there are no specific guidelines in this field. The only randomized trial conducted during the postoperative period evaluated the association of low-dose aspirin with conventional oral anticoagulation [188]. It showed a decrease in the incidence of thromboembolism but an increase in bleeding with an adverse trend on 1-year survival in patients who received aspirin in addition to vitamin K blockers.

Pregnancy The specificity of anticoagulant therapy during pregnancy is described in Chapter 20.

Management of Anticoagulant Therapy During Non-cardiac Interventions Bleeding risk during non-cardiac interventions under anticoagulant therapy is mainly related to the type of procedure. Minor surgery or vascular catheterization can be performed under moderate anticoagulation, but major surgery requires an INR < 1.5 and, therefore, temporary withdrawal of oral anticoagulation (Table 21.13) [189]. It has been suggested that the thromboembolic risk can be low enough (approximately 0.1%) for a 3-day interruption [23]. However, this was the result of debatable extrapolations, and thromboembolic risk during non-cardiac interventions was estimated at 1.6% in a recent review [190]. Management of anticoagulation during non-cardiac interventions should be adapted to the type of procedure and patient risk for thromboembolism [189]:

- Minor intervention can be performed under moderate oral anticoagulant therapy alone in low-risk patients.
- Major surgery requires withdrawal of oral anticoagulation, which should be replaced by heparin when INR is < 2 in low-risk patients or < 2.5 in high-risk patients. Heparin is stopped 6 h before surgery

Table 21.13 Maximum INR according to different types of procedures under oral anticoagulant therapy [189]

Procedure	INR
Heart catheterization (without angioplasty)	< 2.5
Dental care	< 2.5
Minor surgery	< 2.0
Major surgery	< 1.5

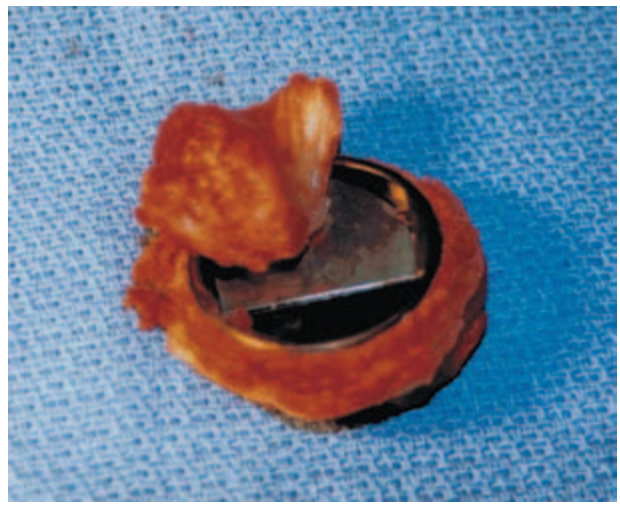

Figure 21.29 Occlusive thrombosis on a bileaflet mechanical prosthesis in the mitral position. (Courtesy of Dr I. Philip.)

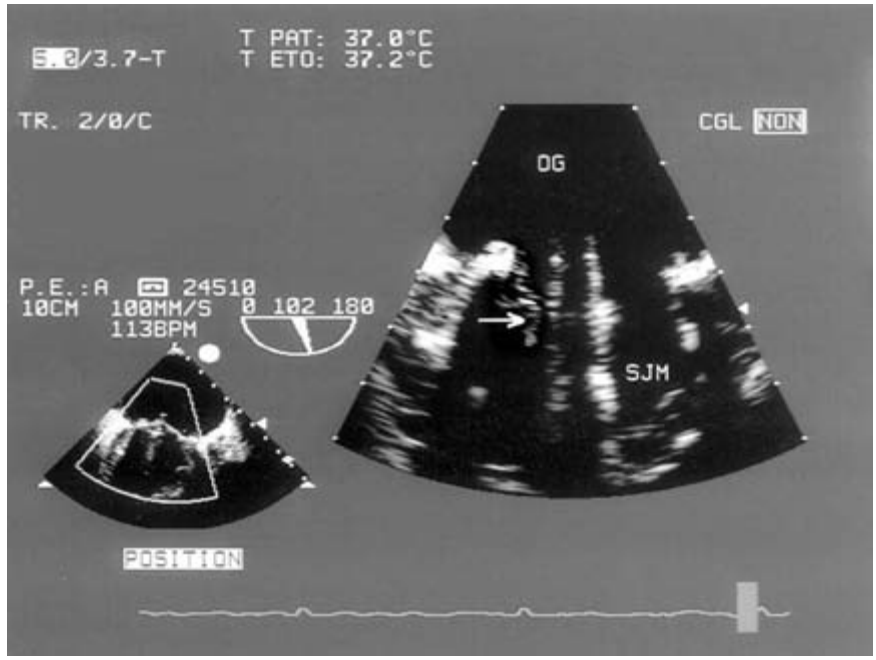

Figure 21.30 Non-occlusive prosthetic thrombosis (arrow) on the ring of a bileaflet prosthesis in mitral position. Transoesophageal echocardiography. (Courtesy of Dr B. Cormier.)

and resumed 6–12 h after. Unfractionated intravenous heparin should be favoured. Low-molecular-weight heparins are an interesting alternative but their use has not been approved so far in patients with valve prosthesis [191].

Endocarditis prophylaxis

Infective endocarditis prophylaxis is of particular importance in patients with heart valve prosthesis, who are considered at high-risk for endocarditis in all guidelines [29]. Principles are described in Chapter 22.

Treatment of specific complications

PROSTHETIC THROMBOSIS

Occlusive prosthetic thrombosis is characterized by impaired motion of the mobile part of the prosthesis and is usually treated by redo surgery, which carries a relatively high risk, particularly when patients are in poor haemodynamic condition [192] (Fig. 21.29). Thrombolysis is an alternative but it is associated with high mortality rates due to failure or embolic events [193]. It is only advised if surgery is contraindicated or not available in urgent situations. However, thrombolysis is the first-line treatment for thrombosis of a tricuspid prosthesis.

Non-occlusive prosthetic thrombosis is mainly diagnosed on transoesophageal echocardiography in as many as 10–15% of patients after mitral valve replacement using a mechanical prosthesis [194] (Fig. 21.30). First-line treatment is intensification of anticoagulation under close echocardiographic monitoring.

BIOPROSTHESIS FAILURE

Re-operation is indicated in symptomatic patients in whom there is an increase in transprosthetic gradient or new regurgitation. Surgery should be considered early, as its risk rapidly increases in patients in NYHA class III or IV. There is no consensus in asymptomatic patients with SVD and the decision should take into account the magnitude of the gradient or regurgitation as well as its evolution, consequences and risk of re-operation.

ENDOCARDITIS

Prosthetic valve endocarditis frequently requires surgery, which should not be delayed to avoid intervening in a patient in poor haemodynamic condition. The management of prosthetic endocarditis is detailed in Chapter 22.

Conclusion

Although the mortality for elective valve replacement is low, the long-term survival is far from satisfactory. This highlights the need to optimize the choice of valve substitute as well as improve education and follow-up after surgery.

Personal perspective

Valve disease will remain a public health problem: AS will assert its presence due to population ageing and may become the first indication for open-heart surgery. MR is also an emerging disease with growing emphasis on functional MR, either due to congestive heart failure or ischaemia, and patients with previous valve intervention will increase.

Basic science collaboration will elucidate the molecular mechanisms of 'degenerative' valve disease and LV response to overload, and support identification of new prognostic factors and novel therapies.

Non-invasive techniques will be improved for the evaluation of VHD, most importantly three-dimensional echocardiography, intracardiac echocardiography, computerized tomography and magnetic resonance imaging. Earlier evaluation of VHD will necessitate greater use of echo-based stress testing, and biomarkers such as BNP.

A great challenge will be to prevent or delay degenerative AS, as was done with rheumatic disease. Coming studies may confirm current hypotheses concerning statins, ACE inhibitors, a combination of these agents and anti-metalloproteases. There are great expectations for the use of new antithrombotic agents, easier to use and safer than the current vitamin K antagonists, in patients with mechanical prosthesis.

Education of patients is key for the prevention of endocarditis and thromboembolism, as well as rheumatic fever (still a major public health problem in many parts of the world).

The search for the 'perfect valvular substitute' will continue. Tissue-engineered valves may emerge. Conservative techniques will gain wider acceptance in MR (and later AR) through their dissemination and further evaluation.

The role of interventional cardiology will increase. PMC will remain a useful complement to valve replacement in the treatment of MS. The first human applications of percutaneous valve replacement and repair opens a new era for research and potential clinical applications for AS and MR. These current trends hold promise, with interaction between less invasive surgery (using endoscopic approaches or robotics) and percutaneous interventions.

Finally, in order to improve patient care in the field of VHD, well-designed trials are required to create more evidence-based guidelines, which need to be implemented and scrutinized by surveys.

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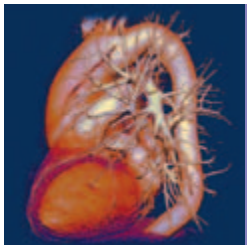

22 Infective Endocarditis

Werner G. Daniel and Frank A. Flachskampf

Summary

This protean disease, whose salient features have been known for centuries, continues to pose major diagnostic and therapeutic challenges. Infective endocarditis predominantly affects cardiac valves and leads to local destruction with subsequent regurgitation. Embolism, especially to the brain, is the most feared extracardiac complication. Diagnosis rests on positive blood cultures and demonstration of vegetations by echocardiography. The rise of aggressive pathogens and the frequency of unfavourable clinical circumstances, such as presence of prosthetic valves or compromised immunocompetence, have resulted in more frequent and earlier surgical therapy. Although endocarditis is no longer uniformly fatal, outcomes are still characterized by high morbidity and mortality.

Definition

Infection of valvular tissue or cardiovascular endothelium by a variety of pathogens constitutes infective endocarditis. Although endocarditis mostly involves the cardiac valves, it may also manifest as endarteritis (e.g. in aortic coarctation) or develop on foreign bodies such as intravenous lines, pacemaker leads, conduits, etc. Former classifications of endocarditis as subacute, acute or chronic have been discarded. A newer classification based on ESC task force recommendations [1] is provided in Table 22.1.

Table 22.1 ESC recommendations on classification and terminology of infective endocarditis [1]

Infective endocarditis may be classified by
Activity: active/healed
Recurrence: recurrent, if a relapse occurs within 1 year of eradication/operation; persistent, if no eradication has occurred
Confidence of diagnosis: definite, if vegetations are demonstrated in the presence of systemic infection; suspected, if clinically strongly suggested, and possible if clinical suspicion is less strong (e.g. differential diagnosis of fever)
Special circumstances: prosthetic endocarditis (early if within 1 year of valve replacement, otherwise late), pacemaker endocarditis, and endocarditis in a patient with intravenous drug abuse
According to the site of involvement: aortic, mitral, tricuspid, pulmonary, right heart, left heart
According to the causative agent: e.g. staphylococcal endocarditis

Epidemiology

The incidence of infective endocarditis in the general population is estimated at 14–31 per million persons and year [2–5]. Subgroups such as immunocompromised persons and addicts of intravenous drugs have a much higher

incidence of endocarditis. The incidence increases with age and is higher in men than in women.

Pathology and pathophysiology

The initial necessary condition for the development of infective endocarditis is endocardial or endothelial damage. Such damage may be induced by regurgitant, stenotic or shunt lesions creating high-velocity blood jets, (micro-) trauma, surgery, foreign bodies, etc. Adherence of platelets to the injured endothelium leads to a small local, initially sterile fibrin–platelet aggregate, the so-called non-bacterial thrombotic endocarditis, which then becomes infected by pathogens circulating in the blood. Conversely, intact endothelium is very resistant to bacterial colonization. Bacteraemia most often originates from the skin and oropharynx. The ability of microorganisms to adhere to the initial thrombus, to colonize it, and to grow differs widely and depends, among other factors, on their ability to bind to fibronectin, a surface glycoprotein found on many cells, including endothelial cells. If the initial microthrombus is colonized and to the degree in which cellular and humoral host defences are overcome, rapid growth ensues and within days a macroscopically detectable vegetation is formed, which contains staggering amounts of bacteria (in the order of 10^{10}/g), thrombus and leucocytes, together with tissue debris. The vegetation is the hallmark of infective endocarditis (Fig. 22.1). It may grow from nearly invisible to several centimetres in length and is most often (although not exclusively) attached on the low-pressure side of the underlying structure, i.e. the atrial side of atrioventricular valves and the low-pressure side of shunt lesions, owing to the endothelial damage secondary to high-velocity jets at these sites.

Vegetations may lead to valve incompetence or, rarely, obstruction. Bacterial invasion may also lead to direct damage of valve structures, such as leaflet defects or tears, chordal rupture, to the development of fistulae between heart cavities or to perivalvular abscess formation. A rare form of an endocarditic abscess is the so-called pseudoaneurysm of the mitral aortic intervalvular fibrosa [6], which is a ring abscess located in the section of the aortic and mitral valve circumference which is contiguous. These outpouchings may communicate with the left ventricle or left ventricular outflow tract and, after rupture, create a fistula to the left atrium. Tissue invasion may lead to conduction abnormalities, such as complete atrioventricular block, and to pericardial effusion. Prosthetic

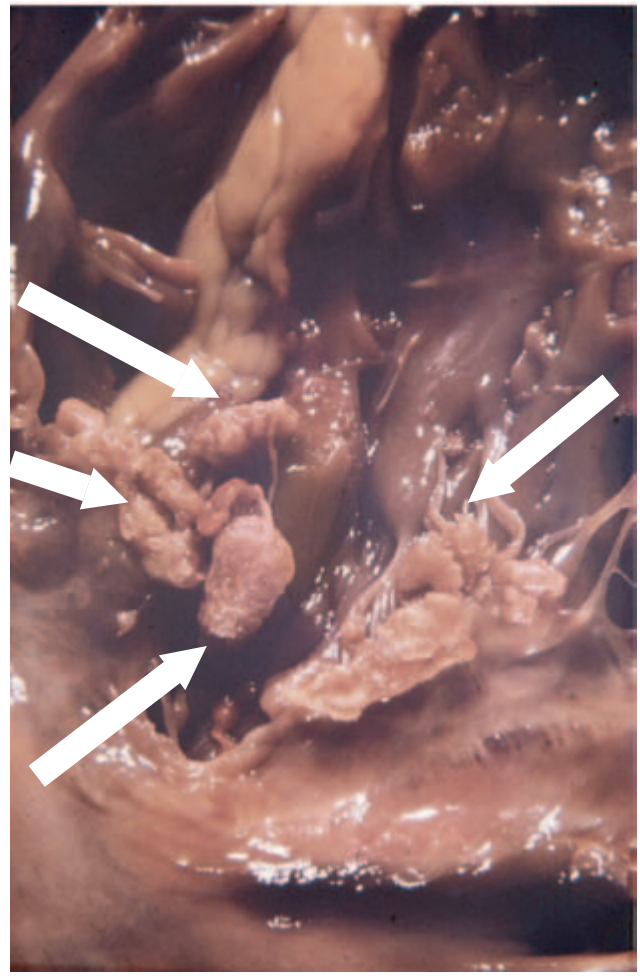

Figure 22.1 Large vegetations (arrows) on the tricuspid valve in candida endocarditis.

valves are high-risk lesions for endocarditis. In mechanical valves, usually the sewing ring is affected, with a high incidence of periprosthetic leaks and abscesses. In bioprostheses, both the ring and the leaflets themselves can be affected. Intravenous lines and pacemaker leads may develop adherent vegetations and infection may spread to contiguous tissue.

Vegetations are prone to embolization, in particular if they are large and mobile. Clinically, embolism is found in one-third to one-half of cases but the true incidence is much higher due to often silent embolism. Left heart endocarditis embolizes predominantly to the brain, the spleen and the kidneys, as well as the limbs. Metastatic abscesses may ensue. Right heart endocarditis embolizes to the lung with subsequent lung abscess or pneumonia. Aortic vegetations prolapsing into the left ventricle may create secondary infection of the anterior mitral leaflet by direct contact during diastole ('kissing lesions').

Renal involvement in infective endocarditis includes septic renal embolism, immune complex-mediated glomerulonephritis and interstitial nephritis due to antimicrobial therapy [7].

Infective endocarditis leads to a constant, often low-grade, bacteraemia. Frank sepsis often ensues, especially with aggressive organisms such as staphylococci. Infective endocarditis is believed to be uniformly fatal if not treated.

Infective endocarditis may also arise in extracardiac locations, mostly the cerebral and thoracic large arteries, and create so-called mycotic aneurysms, which may rupture.

Risk factors

Congenital and acquired valvular heart disease is a strong risk factor for infective endocarditis. It is estimated that approximately one-half of patients with endocarditis have some form of underlying heart disease, most often bicuspid aortic valve, mitral valve prolapse, other degenerative valvular disease, ventricular septal defect, hypertrophic obstructive cardiomyopathy, aortic coarctation and others. Prosthetic heart valves, both of the mechanical and biological type, are prone to infection, as are other foreign bodies such as central venous lines, pacemaker leads, intravenous ports, ventriculo-atrial shunts, Dacron patches or conduits. Of note, while ventricular septal defects carry a high risk of endocarditis, atrial septal defect of secundum type or patent foramen ovale do not entail an elevated risk. All patients with risk lesions should receive endocarditis prophylaxis (see Tables 22.2 and 22.3) whenever they undergo procedures inducive of bacteraemia, such as oropharyngeal procedures or surgery, dental procedures, lower digestive tract procedures (in particular with biopsy) and others. Furthermore, immunosuppression, dialysis, intravenous drug abuse, HIV infection and long-term intensive care treatment all increase the risk of acquiring infective endocarditis, in particular in the presence of a pre-existent cardiovascular lesion.

Causative pathogens

Almost all known pathogenic bacteria have been implied in cases of infective endocarditis. In practice, however, a

Table 22.2 Interventions and procedures predisposing to infective endocarditis and necessitating antibiotic prophylaxis in patients at risk (modified from [28])

Dental procedures that cause oral bleeding (e.g. dental extraction, removal of tartar)
Oropharyngeal surgery, including tonsillectomy
Oesophageal dilatation, sclerotherapy of oesophageal varices and endoscopic retrograde cholangiography with biliary obstruction
Gall bladder surgery, appendectomy, colectomy
Genitourinary procedures, including catheterization and cystoscopy in the presence of urinary tract infection, transurethral prostate resection
Abscess surgery
Lesions conferring elevated risk of infective endocarditis
Acquired or congenital valvular heart disease, including bicuspid aortic valve and mitral valve prolapse
Presence of a valvular prosthesis or surgically created conduit
Previous endocarditis
Immunosuppression (e.g. after organ transplantation)
Hypertrophic obstructive cardiomyopathy
Ventricular septal defect
Complex, especially cyanotic congenital heart disease
Shunt lesions (congenital or surgically constructed) except atrial septal defects of secundum type
Aortic coarctation
Prophylaxis NOT recommended
Endotracheal intubation
Cardiac catheterization
Flexible bronchoscopy (prophylaxis for biopsy is debated)
Transoesophageal echocardiography
Gastrointestinal endoscopy (prophylaxis for biopsy is debated)
Pacemaker implantation
Vaginal delivery

Table 22.3 Currently recommended prophylactic antibiotic regimens [1]

Upper respiratory and oesophageal procedures
Oral amoxicillin, 2 g, 1 h before procedure (or i.v. 30–60 min before procedure)
Genitourinary or gastrointestinal procedures
Oral ampicillin, 2 g, 1 h before procedure or i.v. ampicillin or amoxicillin 2 g 30–60 min before procedure
In high-risk patients plus 1.5 mg/kg gentamicin before procedure plus oral ampicillin or amoxicillin, 1 g, 6 h after procedure
The Task Force of the European Society classified patients with prosthetic valves or surgical conduits, previous endocarditis or cyanotic congenital lesions as 'high risk'.

limited variety of organisms are significant. Only the most frequent pathogens will therefore be discussed. Remarkably, infective endocarditis is most often a disease produced by Gram-positive bacteria, especially cocci.

Streptococcal disease

These bacteria are still the most frequent cause of infective endocarditis and typically produce the classic protracted, 'subacute' course of endocarditis. The origin of streptococci is most often the oropharynx. They are mostly, but not always, susceptible to penicillin G. *Streptococcus bovis* endocarditis has been found to be associated with adenoma and adenocarcinoma of the colon, making colonoscopy advisable if *Streptococcus bovis* bacteraemia is documented [8,9].

Staphylococci

Staphylococcal endocarditis has increased substantially in frequency and is now the second most common aetiological agent in native valve endocarditis. *Staphylococcus aureus*, an extremely aggressive and destructive organism, causes 90% of all cases of staphylococcal endocarditis. *Staphylococcus epidermidis* is the most frequent cause of early prosthetic valve endocarditis. Staphylococci often produce beta-lactamase and are therefore resistant to many, if not all, beta-lactam antibiotics, i.e. penicillins and cephalosporins. Vancomycin and teicoplanin remain effective. The origin of staphylococci is most frequently the skin. Hospital-acquired staphylococcal infections via catheters and intravenous lines are also frequent.

Q fever endocarditis

Q fever, a zoonosis caused by the intracellular rickettsia *Coxiella burnetii*, is endemic worldwide, but particularly frequent in France. Its natural sources are cattle, sheep, goats and others. An estimated 10% of cases affect the heart. *Coxiella burnetii* does not grow on culture media. Diagnosis is by serology or polymerase chain reaction. Doxycycline in combination with rifampicin is the recommended antibiotic therapy.

Enterococci

Enterococcus faecalis is the most frequent pathogen of this group, typically originating in the gastrointestinal tract. Antibiotic resistance in these organisms is variable, although they are usually susceptible to the combination of a beta-lactam antibiotic and an aminoglycoside such as gentamicin.

Fungi

Fungal infections are typical for immunocompromised patients or following long-term intravenous therapy. Treatment usually requires surgery.

Symptoms and signs

The clinical and laboratory signs are detailed as follows.

Clinical signs

Fever, chills, malaise, night sweats, arthralgias and weight loss are unspecific systemic symptoms of infectious endocarditis, in particular the more protracted forms formerly designated as 'subacute'. It should be noted that in the elderly these symptoms, including temperature elevation, may be mitigated or absent. In immunosuppressed patients, clinical signs of generalized infection may also be unapparent. Haemofiltration may suppress temperature elevation. However, endocarditis without at least a minor degree of temperature elevation is very rare. A warm dry skin, tachycardia and spleen enlargement (in particular in protracted endocarditis) are additional physical signs of systemic inflammation.

The classical specific physical signs of endocarditis are largely signs of destructive (valvular regurgitation murmurs and heart failure) or embolic (although in part immunologically mediated) complications of endocarditis and thus signal advanced disease.

Cardiac signs include:

- *in mitral endocarditis*, the new or greatly increased typical holosystolic murmur of mitral regurgitation, best heard over the apex and radiating to the left axilla, associated with dyspnoea, pulmonary congestion or oedema and other signs of left heart backward failure;
- *in aortic endocarditis*, the new typical diastolic murmur of aortic regurgitation, best heard over the left sternal border, associated with dyspnoea, pulmonary congestion or oedema and other signs of left heart backward failure;
- *in tricuspid endocarditis*, the typical soft parasternal systolic murmur of tricuspid regurgitation increasing with inspiration, together with jugular vein distension, a prominent systolic jugular vein pulse and liver enlargement.

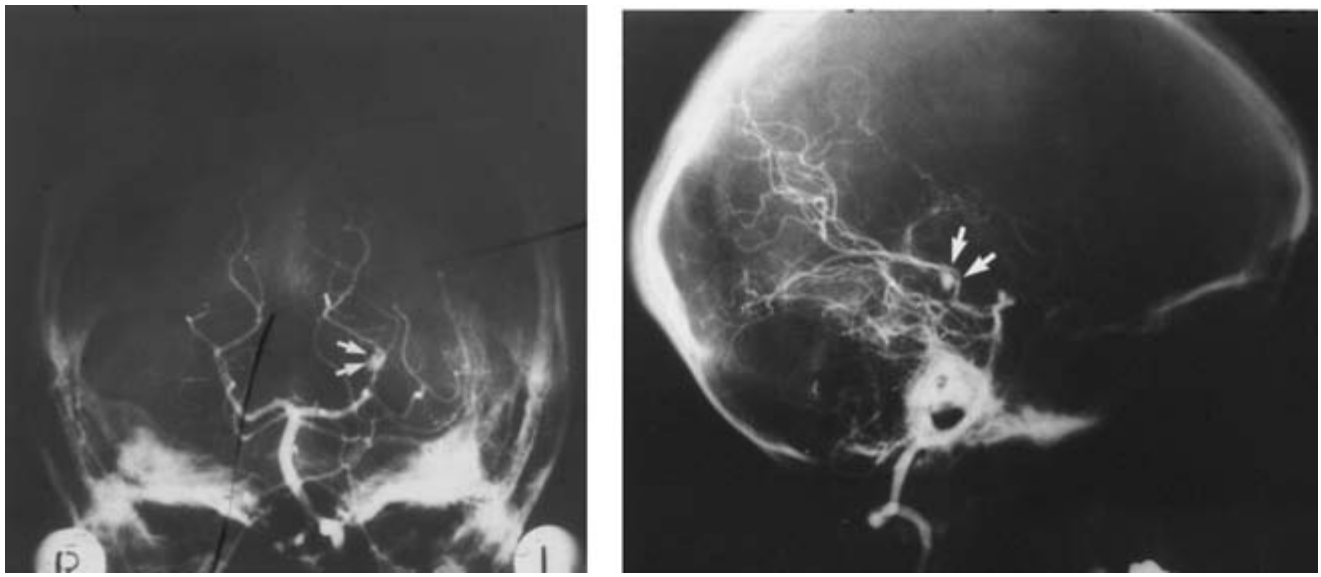

Figure 22.2 Mycotic aneurysm (arrows) of the left posterior cerebral artery.

Systemic embolism from left heart (or arterial) endocarditis is often the first clinically apparent sign of endocarditis, and may manifest as:

- neurological impairment, ranging from transient symptoms to fatal massive stroke;
  - intracranial haemorrhage in infective endocarditis occurs in 5% of patients and may be due to secondary bleeding into an infarcted zone or to rupture of a mycotic aneurysm of a cerebral artery (Fig. 22.2);
  - meningitis may develop due to a septic cerebral abscess;
  - neurological complications in infective endocarditis are ominous and predict dramatically increased mortality;
- limb, abdominal (kidney, spleen) or even coronary ischaemia (rare).

All of these sites may develop septic abscesses. Right heart endocarditis in the majority of cases leads to—sometimes silent—septic pulmonary embolism and may present with signs of pneumonia and pleuritis. For typical cutaneous signs of endocarditis see Table 22.4 and Figs 22.3 and 22.4. Fundoscopy may reveal retinal haemorrhage with a pale centre (Roth's spots, see Fig. 22.5). It cannot be overemphasized that, despite the wealth of time-honoured clinical signs and symptoms of infective endocarditis, this is a notoriously difficult disease to diagnose. This holds particularly true for the early stages, before destructive or embolic events have occurred. In a large multicentre registry [10], average time from onset of symptoms to hospital admission was 29 days!

Table 22.4 Cutaneous signs of infective endocarditis (mediated by microembolism, haemorrhage or immunological responses)

Petechiae (extremities, conjunctivae, buccal mucosa) (see Fig. 22.3)
Splinter haemorrhages (subungual)
Osler nodes (small, tender, purple, subcutaneous nodules on the palmar side of the digits)
Janeway lesions (erythematous non-tender macular lesions on palms and soles)

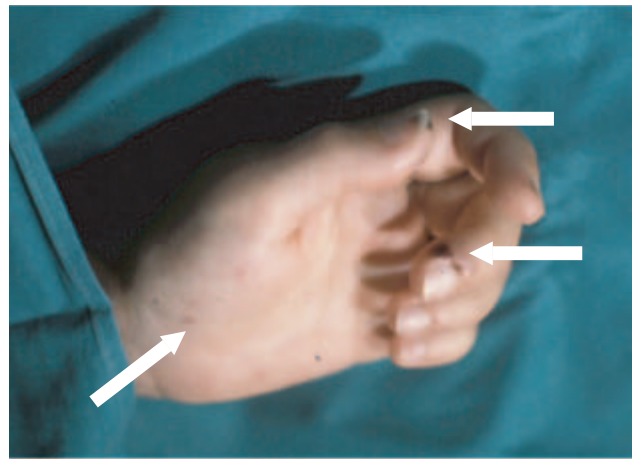

Figure 22.3 Macular petechial and embolic skin lesions (arrows) in infective staphylococcal endocarditis.

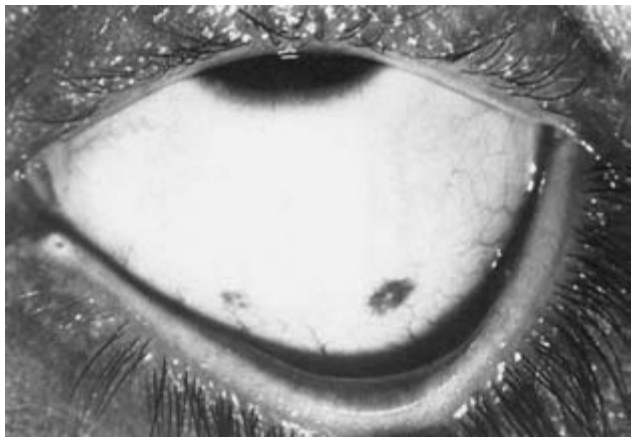

Figure 22.4 Bulbar conjunctival petechial haemorrhage. Reproduced, with permission, from Gahl K, (ed.), *Infektiöse Endokarditis*, Steinkopff Darmstadt, 2nd edn, 1994.

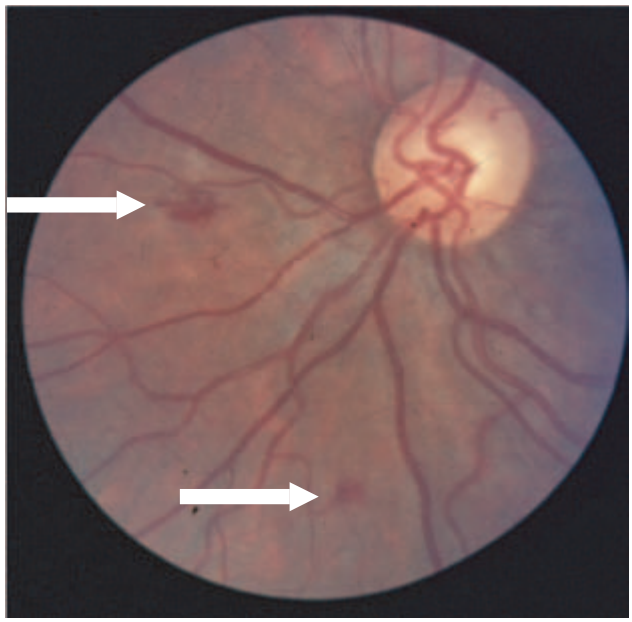

Figure 22.5 Roth's spots (arrows) in streptococcal endocarditis. Fundoscopy of the left eye. Reproduced, with permission, from Gahl K, ed., *Infektiöse Endokarditis*, Steinkopff Darmstadt, 2nd edn, 1994.

Laboratory signs

There is no specific laboratory marker of infective endocarditis. Laboratory abnormalities include leucocytosis with granulocytosis with a left shift (or leucopenia, especially in overt sepsis), elevated sedimentation rate, elevated C-reactive protein and gamma globulin levels. Anaemia of infection with low serum iron levels is a cardinal sign of endocarditis. Circulating immune complexes and occasionally a positive rheuma factor are detectable. Importantly, urinalysis is very frequently pathological, even without manifest septic embolism to the kidney. Haematuria (often only microscopic) and proteinuria, and sometimes red blood cell casts, are present. However, the most important laboratory test is unquestionably the blood culture. Infective endocarditis usually leads to a continuous bacteraemia, such that (in the absence of pretreatment with antibiotics) blood cultures are very sensitive to detect the disease and may be drawn at any time independent from the time course of fever. It has been reported that one of the first two separate blood cultures was positive in 98% of patients with infective bacterial endocarditis in patients not receiving antibiotics [11]. For proper technique, see Table 22.5. However, if the patient is already being treated with antibiotics the diagnostic yield decreases drastically. Furthermore, some pathogens are fastidious or do not grow at all on usual culture media. Table 22.6 provides a list of difficult-to-identify pathogens and techniques to identify them.

Pathogens can, and should, also be cultured or identified by polymerase chain reaction from excised material, for example valves or emboli, especially if blood cultures

Table 22.5 Properly obtaining blood cultures in suspected endocarditis

Three separate sets from three different venepunctures over 24 h, at least 1 h apart
If possible before antibiotic therapy or after cessation of antibiotic therapy (3–7 days, depending on previous therapy duration)
Each set contains one aerobic and one anaerobic flask, to each of which 5–(preferably) 10 ml blood are added
Rapid processing or storage at appropriate temperature (check with laboratory); notify laboratory of the clinical suspicion of infective endocarditis

Table 22.6 Culture-negative endocarditis: difficult-to-identify pathogens and tests to detect them

Coxiella burnetii (Q fever): serology or polymerase chain reaction (PCR)
Bartonella spp.: acridine orange staining of blood cultures, extended subculturing, serology, PCR
Brucella spp.: serology, PCR
Legionella spp.: serology, PCR
Fungi other than *Candida* spp.: lysis-centrifugation and culturing on special fungal media
'HACEK' pathogens: (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella* spp.): prolonged culturing

remain negative, to guide appropriate antibiotic therapy, in particular after surgery. This technique may also identify specific pathogenic strains and thus elucidate their source.

Diagnosis

The definitive diagnosis of endocarditis rests on two pillars: the positive blood culture and evidence of vegetations, usually by echocardiography. Table 22.7 lays out the accepted criteria for the diagnosis of infective endocarditis, the so-called Duke criteria [12]. Echocardiography is therefore the imaging technique of choice and its findings are pivotal for patient management. Transoesophageal echocardiography has a well-documented superior sensitivity to transthoracic echo to diagnose endocarditic vegetations, destructive complications and abscesses [13–17]. Whenever there is a strong clinical suspicion of endocarditis and the transthoracic echo is inconclusive or negative, transoesophageal echocardiography should be performed. Conversely, a negative transoesophageal echo argues strongly against infective endocarditis. However, if the clinical suspicion is substantial (e.g. positive blood cultures of a typical pathogen), transoesophageal echocardiography should be repeated after a few days, in particular in the presence of underlying heart disease, for example a prosthetic heart valve. It has been shown that repeat negative transoesophageal echocardiography carries a very high negative predictive value for infective endocarditis and may be the clinical 'gold standard' for excluding infective endocarditis [18]. Because of the increasing frequency of (1) antibiotic pretreatment, leading to false-negative blood cultures and (2) prosthetic valve endocarditis, with its attendant difficulty of visualization of vegetations, it has been proposed to modify the Duke criteria to include patients with clear vegetations on echo and systemic inflammatory signs but negative blood cultures if they have had antibiotic pretreatment, and to require a repeat negative transoesophageal echo study to exclude endocarditis in patients with prosthetic valves. Furthermore, Q fever endocarditis should be routinely ruled out serologically, as blood cultures remain negative in this disease [19].

Table 22.7 The 'Duke criteria' [12] for the diagnosis of infective endocarditis

'Definite' diagnosis
Established by pathology (histological evidence of active endocarditis in an endocarditic lesion or identification of microorganisms in a vegetation or abscess) or clinically: two major *or* one major plus three minor *or* five minor criteria
major criteria: positive blood culture (> 1) of typical pathogens; vegetation, abscess or prosthesis dehiscence on echo; new valvular regurgitation;
minor criteria: predisposition (predisposing heart disease or intravenous drug use), fever ≥ 38°C, embolic events, immunological/embolic signs (conjunctival haemorrhages, Janeway lesions, Osler nodes, Roth's spots, glomerulonephritis, rheumatoid factor), serology consistent with endocarditis, positive blood culture that is not typical for infective endocarditis

Possible diagnosis
Neither definite nor rejected

Rejected diagnosis
Firm alternative diagnosis for symptoms suggestive of endocarditis, resolution of symptoms after < 4 days of antibiotic treatment, no pathological evidence of endocarditis during surgery or autopsy

Echocardiographic signs of infective endocarditis

Conceptually, these can be divided into additional structures due to the disease (vegetation, abscess, pseudoaneurysm) and defects (regurgitant lesions, perforations, fistulae). The hallmark of endocarditis on echo is the identification of a vegetation, appearing as a mobile, irregular mass with jagged edges attached to a valvular structure (Figs 22.6 and 22.7). Size may vary from a few millimetres to several centimetres. Vegetations typically arise from the low-pressure side of a valve leaflet (e.g. the atrial side of the mitral valve) and are highly mobile. They may prolapse through the valve with the blood flow. Their echodensity is relatively low (similar to myocardium) in the early stages and increases over time. Highly echogenic, 'fibrous' or 'calcified' vegetations usually indicate that the vegetation is old, with lower embolic risk. If vegetations are large, obstruction may occur. Typically, endocarditis causes valvular regurgitation by several mechanisms: defects in the valvular tissue (Fig. 22.8), rupture of chordae, and interposition of vegetations between the leaflet tips. Valvular regurgitation due to endocarditis is very frequent and often severe and dramatic. All typical echocardiographic signs of acute severe mitral or aortic regurgitation may be present. Endocarditis may progress to invasion of the tissue with central necrotization, i.e. abscess formation. This is typical of aortic

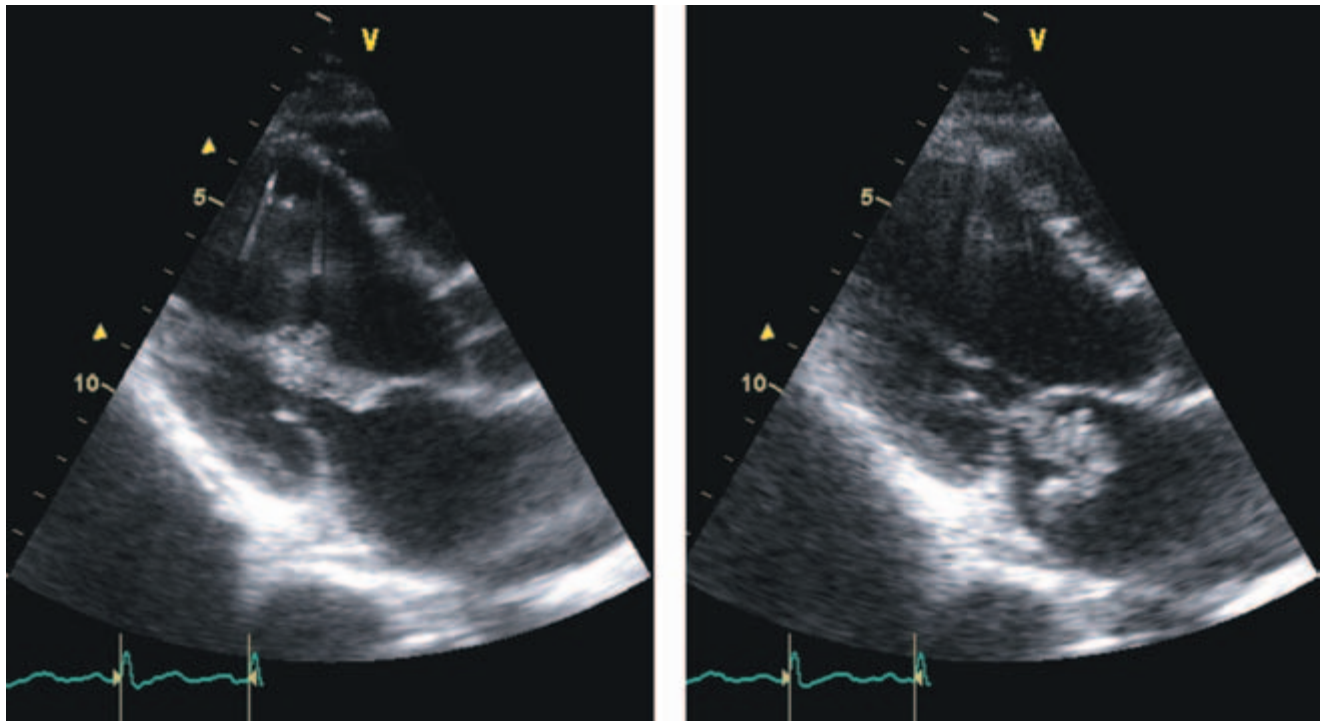

Figure 22.6 Large, mobile vegetation on the mitral valve. The vegetation is in the left ventricle during diastole (A) and prolapses into the left atrium in systole (B). There was also severe mitral regurgitation.

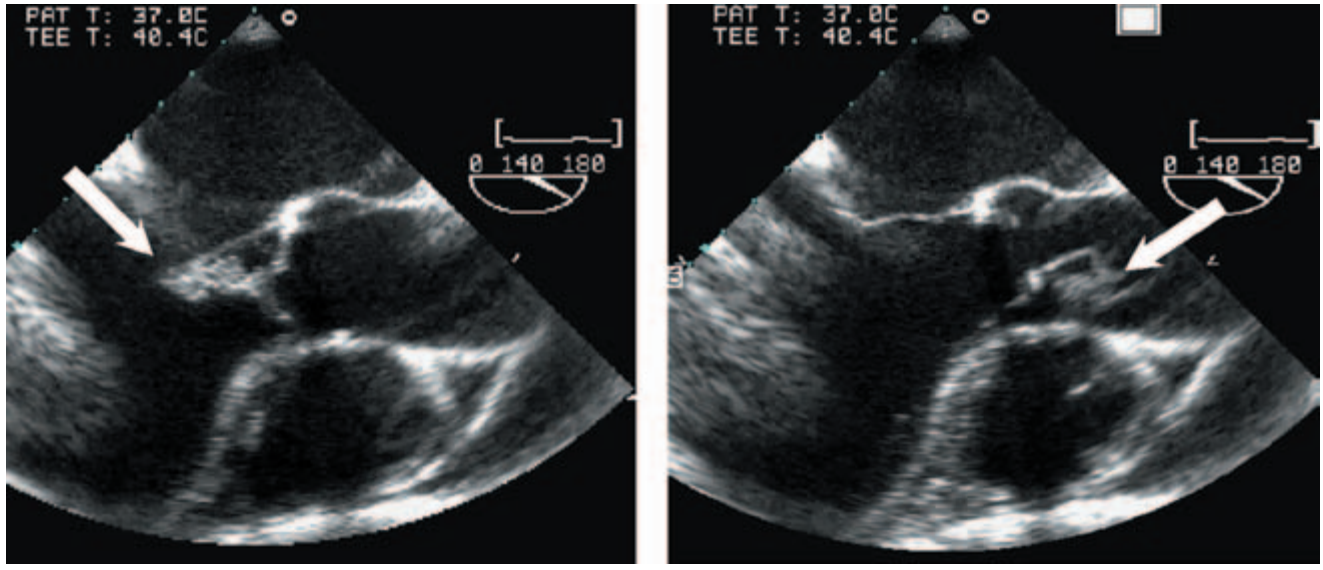

Figure 22.7 Long, mobile vegetation (arrows) attached to the right coronary cusp of the aortic valve. Transoesophageal long-axis views of the aortic valve in diastole (A), with the vegetation prolapsing into the left ventricular outflow tract, and in systole (B), with the vegetation in the aortic root.

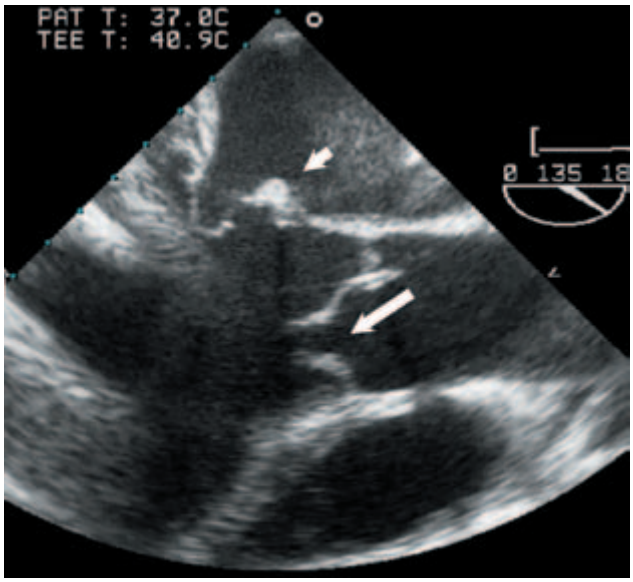

Figure 22.8 Streptococcal endocarditis with destruction of the aortic valve, which shows severe prolapse and a defect (arrow). There is also an endocarditic lesion on the anterior mitral leaflet (small arrow) – compare with Fig. 22.11. Transoesophageal long-axis view. The patient had severe acute aortic regurgitation.

and prosthetic endocarditis and aggressive pathogens such as staphylococci. On echocardiography, abscesses are perivalvular zones of abnormal tissue thickening, sometimes with central echolucency and possible flow in and out of an abscess cavity (Figs 22.9 and 22.10). They are recognized better and much more frequently by transoesophageal echocardiography [15]; recognition is important because formation of an abscess not infrequently predicts failure of conservative antibiotic treatment. A special form of abscess is the mitral valve pseudoaneurysm (Fig. 22.11), a localized outpouching of a mitral leaflet or the intervalvular fibrous tissue between aortic and mitral valve, often with a perforation and regurgitation [6].

Other imaging modalities, such as magnetic resonance imaging or scintigraphy with radioactively labelled leucocytes, have been disappointing.

Problems in the diagnosis of infective endocarditis

The widespread use of antibiotics in the presence of signs of systemic inflammation, for example fever, often without a clear diagnosis of the type of infection, greatly impairs the sensitivity of blood cultures. In one large registry [10], at least 23% of patients were treated with antibiotics before blood cultures were obtained, without recognizing endocarditis as the underlying disease. Thus, one is often left with a clinical picture compatible with

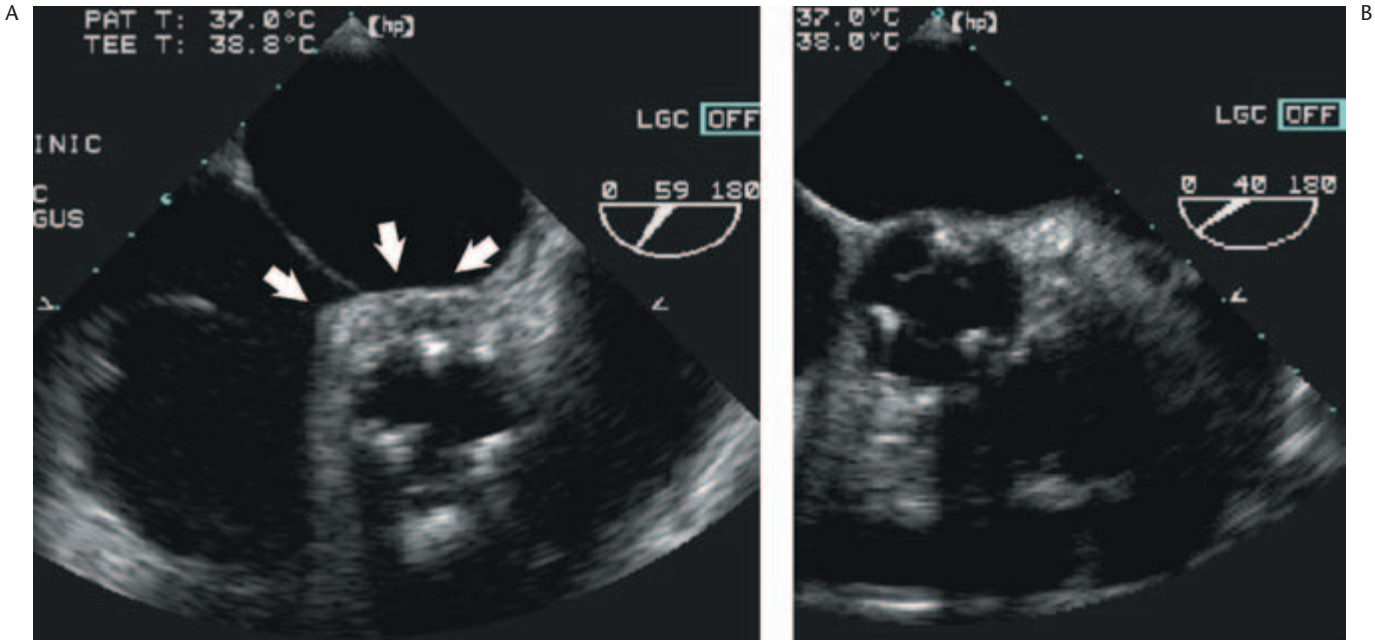

Figure 22.9 (A) Carpentier–Edwards bioprosthesis in the aortic position (transoesophageal short-axis view). Perivalvular aortic wall thickening is visible (arrows), indicating endocarditic tissue invasion. For comparison: (B), normal aspect of an aortic Carpentier–Edwards bioprosthesis.

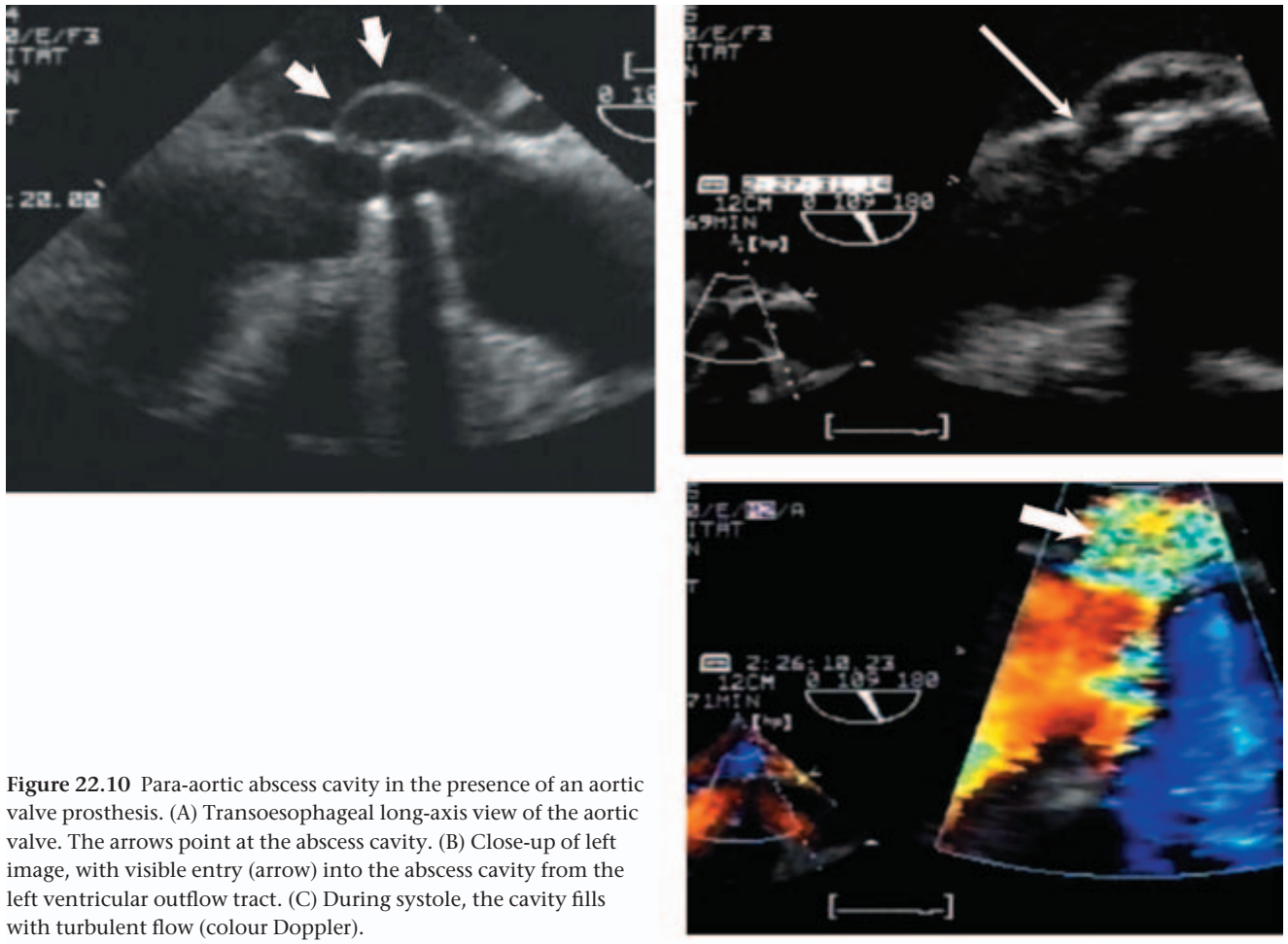

Figure 22.10 Para-aortic abscess cavity in the presence of an aortic valve prosthesis. (A) Transoesophageal long-axis view of the aortic valve. The arrows point at the abscess cavity. (B) Close-up of left image, with visible entry (arrow) into the abscess cavity from the left ventricular outflow tract. (C) During systole, the cavity fills with turbulent flow (colour Doppler).

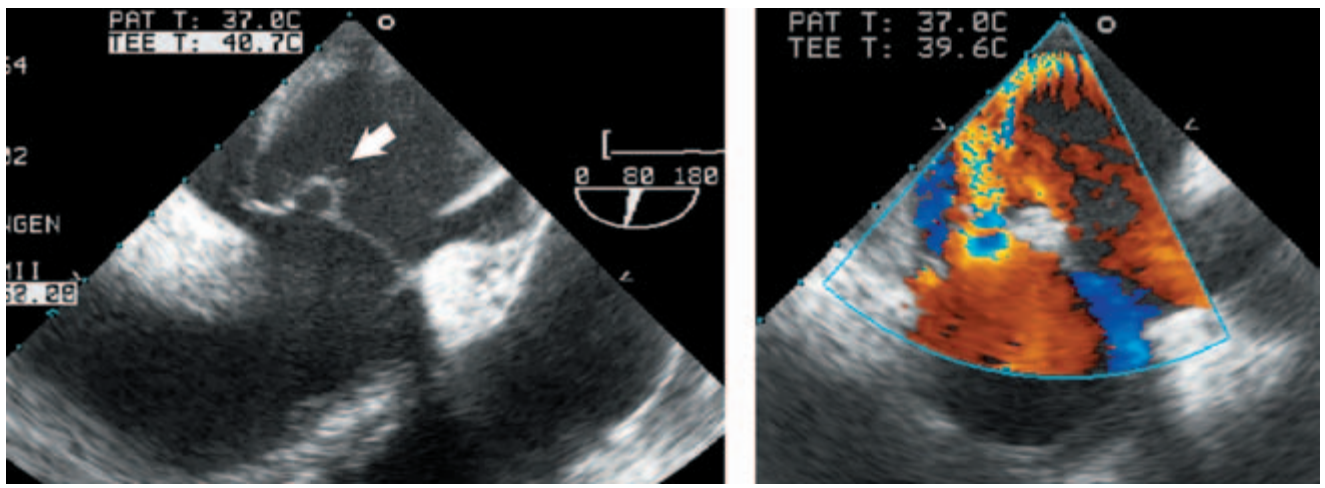

Figure 22.11 (A) Streptococcal endocarditis with pseudoaneurysm of the anterior mitral leaflet, with two small attached vegetations (arrow). The patient (same patient as in Fig. 22.8) also had severe mitral regurgitation, as evidenced by colour Doppler (B).

infective endocarditis, but negative blood cultures. This situation would not qualify as 'definite endocarditis' applying the Duke criteria strictly, and a corresponding modification of the Duke criteria has been advocated, as outlined above [19]. There is now consensus that if in the presence of systemic inflammatory signs clear-cut echocardiographic evidence of fresh vegetations or abscess can be obtained, these patients should be managed as having acute infective endocarditis. However, the situation remains problematic if morphological evidence is less clear, for example in the presence of degenerative valvular changes, in prosthetic valves or pacemaker leads without unequivocal vegetations, or if old endocarditic changes are present. In these cases, it is often essential that the course of the disease and changes in valve appearance over time are awaited to make a clear diagnostic decision.

Prosthetic valve endocarditis

Infective endocarditis in a patient with a prosthetic valve is conceptually classified into early endocarditis, which is perceived as nosocomial disease originating in the surgical valve replacement, occurring up to 1 year after surgery, and late (usually community acquired) prosthetic valve endocarditis. The risk is highest in the first weeks and months after surgery, and mortality in early prosthetic endocarditis has been reported to be extremely high. Although the absolute number of patients with prosthetic valves is increasing, the relative incidence of prosthetic endocarditis has declined in recent years and is now well under 0.5% per year for late prosthetic endocarditis [20]. Early prosthetic endocarditis is characterized by a preponderance of *Staphylococcus epidermidis* as a causative agent, whereas the pathogens of late endocarditis are similar to native valve endocarditis. Prosthetic endocarditis tends to be more severe than native valve endocarditis, is difficult to diagnose due to echocardiographic imaging problems with prostheses, and almost always necessitates repeat surgery. In staphylococcal prosthetic valve endocarditis, mortality has been reported to be 75%(!) with medical treatment and still 25% with surgical treatment [21]. In mechanical prostheses, the disease is almost exclusively located along the sewing ring of the prosthesis, creating paravalvular leaks, fistulae and abscesses, whereas in bioprostheses both the ring and the leaflets may be colonized by bacteria. Transoesophageal examination is extremely useful and should always be performed.

Infective endocarditis in addicts of intravenous drugs

Several features set this type of infective endocarditis apart from the general picture. Infections are often mixed, involving in more than 50% *Staphylococcus aureus* and predominantly affect the tricuspid valve (because of the venous entry site of the infection). The majority of patients are HIV infected or otherwise immunocompromised, but mostly have no underlying heart disease. The prognosis of tricuspid endocarditis of intravenous drug addicts is relatively good under conservative treatment, but recurrence is common due to patients' lifestyles.

Therapy

Antibiotic treatment is mandatory and should be instituted immediately by intravenous route after a sufficient number of blood cultures have been taken (see Table 22.5) and the diagnosis is clear or probable. Susceptibility testing should always be obtained if a pathogen is identified. Vancomycin and aminoglycoside therapy may be optimized by drug serum level determinations. Table 22.8 lists typical antibiotic regimens for different clinical situations and causative agents. Duration of therapy is somewhat arbitrary and should be guided by the course of the disease, but 4 weeks of intravenous therapy is usually considered the minimum. Response to treatment is best monitored by clinical status (in particular course of fever) and by C-reactive protein. C-reactive protein and leucocyte count should fall rapidly and may remain slightly but not markedly elevated if the patient responds to therapy [1]. Echo follow-up examinations are important for later comparisons and detection of complications.

Indications, timing and type of surgery

Traditionally, infective endocarditis has been seen as a disease amenable to antibiotic therapy, which in case of complications necessitated surgery. The typical complications were heart failure due to severe acute regurgitation or sepsis, and systemic embolism. This view was supported by the frequency of streptococcal endocarditis

Table 22.8 Antibiotic therapy of infective endocarditis (modified from the European Society of Cardiology Recommendations [1], where further regimens for special clinical situations may be looked up)

Native valve endocarditis due to penicillin-sensitive streptococci
Penicillin G i.v. 3–6 million units every 6 h for 4 weeks plus gentamicin i.v. 1 mg/kg every 8 h over 2 weeks

Empirical therapy of culture-negative native valve endocarditis
Vancomycin i.v.15 mg/kg every 12 h over 4–6 weeks plus gentamicin i.v. 1 mg/kg every 8 h over 2 weeks; some recommendations add i.v. ampicillin or amoxicillin to this regimen
(Empirical therapy of culture-negative prosthetic valve endocarditis: as above plus rifampicin p.o. 300–450 mg every 8 h 4–6 weeks)

Staphylococcal native valve endocarditis
If methicillin-susceptible: oxacillin i.v. 2–3 g every 6 h over 4 weeks plus gentamicin i.v. 1 mg/kg every 8 h over 3–5 days
If methicillin-resistant: vancomycin i.v. 15 mg/kg every 12 h over 6 weeks

Staphylococcal prosthetic valve endocarditis
If methicillin susceptible: oxacillin i.v. 2–3 g every 6 h over 6 weeks plus gentamicin i.v. 1 mg/kg every 8 h over 2 weeks plus rifampicin i.v. 300 mg every 8 h, over 6 weeks
If methicillin resistant: vancomycin i.v. 15 mg/kg every 12 h over 6 weeks plus gentamicin i.v. 1 mg/kg every 8 h over 6 weeks plus rifampicin i.v. 300 mg every 8 h over 6 weeks

Note that in prosthetic valve endocarditis, surgery is recommended. Vancomycin may be replaced by teicoplanin.

of native valves with its relatively protracted, subacute course; indeed, this led to the term 'endocarditis lenta', or slow endocarditis. This type of endocarditis responds relatively well to penicillin therapy. Unfortunately, today the physician often confronts more aggressive infections, in particular staphylococcal endocarditis, and often the disease arises in immunocompromised patients or patients with implanted devices, such as prosthetic valves, pacemaker electrodes, central venous lines, port access lines, etc. Moreover, the focus of attention has shifted to prevent, rather than treat, catastrophic complications such as embolism and valvular destruction. Thus, in referral centres nowadays surgery is used much more frequently than previously. Table 22.9 lists accepted indications for surgery in infective endocarditis. Although the decision must always be individualized, indications for surgery include heart failure from valvular dysfunction, presence of a device such as a valvular prosthesis, a high risk of embolism (large mobile vegetations), presence of an abscess and treatment-resistant sepsis. The most difficult problem in the decision to proceed to surgery revolves around preventing embolism or recurrence of embolism.

Table 22.9 Indications for surgery in infective endocarditis

Congestive heart failure due to valvular regurgitation
Untreatable sepsis, ineffective antibiotic therapy (e.g. in fungi)
Large (> 10 mm maximal diameter) mobile vegetation or recurrent embolism
Endocarditic abscess or other evidence of local tissue invasion, e.g. fistula
Involvement of a valve prosthesis or other foreign body

Although it is generally accepted that large (usually defined as > 10 mm) mobile vegetations pose a grave embolic threat and should therefore be removed surgically as soon as possible [22,23], there are conflicting data on how to treat smaller vegetations. Particularly difficult clinical decisions have to be made after a cerebral embolic event. Several retrospective analyses have suggested that immediate operation on cardiopulmonary bypass with its profound anticoagulation entails a substantial risk of haemorrhagic transformation of an embolic insult and subsequent aggravation of neurological damage [24]. Traditionally, therefore, an interval of 2–3 weeks after a cerebral embolism has been recommended before surgery. However, recently there has been some support for early operation (within 72 h) after an embolic insult if no haemorrhage is detectable on cerebral CT [1,25]. Because of the critical importance of cerebral embolism in the decision for surgery, it is advisable to obtain a preoperative cerebral CT in all patients undergoing surgery for endocarditis. If concomitant coronary artery disease is suspected, coronary angiography may be performed but should not delay surgery for endocarditis; in the presence of mobile aortic vegetations, coronary angiography should be withheld. Surgically, it is usually necessary to replace the valve if disease is extensive or destruction has occurred. Operation may become even more extensive if surrounding tissue is affected, for example in the case of aortic abscess. In rare cases, valve repair or vegectomy (removal of vegetations leaving the valve intact) suffices. Valve replacement may be done with any kind of prosthetic valves, although some authors have found homografts to be particularly successful [26].

Anticoagulation

It has been hypothesized that anticoagulatory or antiaggregatory drugs might be beneficial in reducing the growth of vegetations [27]. However, there is no clinical

evidence for such measures and anticoagulation may even be hazardous in view of the potential for haemorrhagic complications after cerebral embolization. Thus, anticoagulation or aspirin in the setting of infective endocarditis is not recommended unless there is a compelling independent reason for anticoagulation (e.g. a mechanical prosthetic valve).

Prognosis

Despite antibiotic and surgical therapy, infective endocarditis is not an easily treated disease. Mortality in large series ranges between 15% and 20% [5,10]. Mortality is highest in staphylococcal and fungal endocarditis, and in (especially early) prosthetic endocarditis. The disease also entails a tremendous morbidity from neurological events and from valvular damage. It is estimated that approximately 30–50% of patients with endocarditis undergo early heart surgery [5,10] and many sustain a permanent neurological damage.

Prophylaxis and prevention

Antibiotic prophylaxis of endocarditis, although not rigorously proven in its value, should be heeded carefully. The concept is to abolish or mitigate bacteraemia arising predictably from certain procedures in patients who are considered at risk for infective endocarditis, by administering one or two properly timed doses of antibiotics. Risk lesions and prophylactic regimens are outlined in Tables 22.2 and 22.3. Although no clear data exist, oral hygiene is considered very important.

Personal perspective

Despite the substantial advances made in the past in diagnosis (e.g. transoesophageal echocardiography, polymerase chain reaction) and treatment (early surgery, new and better antibiotics) of infective endocarditis, its toll remains depressingly high. The wide spectrum of presenting symptoms, from fever of unexplained origin to stroke to congestive heart failure, implies that very often the physician first confronting the patient is not a cardiologist, and therefore the entire medical community must be better prepared to recognize the disease. In unclear cases of serious infection, much would be gained if antibiotic therapy were not instituted before blood cultures are drawn. Although improvements in diagnostic imaging and in therapy are likely to be rather incremental in the near future (e.g. intracardiac imaging for better assessment of prostheses), the ability to rapidly detect and type pathogens may improve dramatically by the use of molecular methods (e.g. polymerase chain reaction) in the near future.

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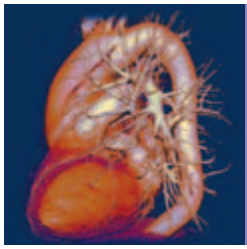

23 Heart Failure: Epidemiology, Pathophysiology and Diagnosis

John McMurray, Michel Komajda, Stefan Anker and Roy Gardner

Summary

The term 'heart failure' describes the common clinical syndrome arising when delivery of oxygen to the metabolizing tissues is impaired because of defective function of the heart as a pump (or, rarely, by extracardiac disorders). The syndrome is characterized by breathlessness, exercise intolerance and sodium and water retention, often manifest as oedema. There are numerous causes of heart failure, the most common of which are myocardial disease and valvular disease. Left ventricular myocardial damage is commonly caused by hypertension, coronary artery disease (usually myocardial infarction) or both. Those disease processes can cause left ventricular systolic dysfunction, diastolic dysfunction or both. The aim of investigation is to establish the underlying cardiac cause of heart failure, quantify ventricular and valvular function, estimate the severity of symptoms and the degree of functional limitation and identify relevant comorbidities. These determine which treatments should and can or cannot be used. A resting 12-lead ECG, transthoracic Doppler echocardiogram, blood chemistry and haematological measurements are essential basic investigations. Investigations also provide information on prognosis which is, to a large extent, determined by left ventricular systolic function and comorbidity, as well as age. The pathophysiology of one type of heart failure, that caused by left ventricular systolic dysfunction, is partially understood. Two key elements are neurohumoral activity and left ventricular remodelling. Untreated, patients with that type of heart failure demonstrate chronic, sustained, neurohumoral activation and show progressive enlargement of the left ventricle with an associated decline in systolic function. The most successful treatments, to date, alter these processes.

Introduction

Heart failure is the term used to describe a common clinical syndrome arising, in ways that are incompletely understood, as a consequence of reduced cardiac pump function. The term 'syndrome' merely describes a constellation of symptoms and signs and, therefore, heart failure is not a diagnosis as such. Unfortunately, the typical symptoms (breathlessness and fatigue) and signs (e.g. oedema) of heart failure are relatively non-specific, making clinical confirmation of the syndrome difficult. The syndrome of heart failure itself can arise as a result of almost any abnormality of the structure, mechanical function, or electrical activity of the heart, each of which may require quite different treatments, emphasizing the importance of appropriate investigation of patients with suspected heart failure. Many of the typical clinical symptoms and signs of heart failure do not arise directly as a result of the cardiac abnormality but rather from secondary dysfunction of other organs and tissues, e.g. the kidneys and muscles. These secondary consequences of pump failure are myriad and their causes are not fully elucidated. Dysfunction of tissues and organs remote from the heart cannot, however, be explained solely by reduced perfusion and it is generally believed that other systemic processes (e.g. neurohumoral activation) are involved. In other words, the pathophysiology of heart failure is complex and incompletely understood and, consequently, so is the pathophysiological basis of treatment. It has even proved difficult to agree a simple definition of heart failure (Table 23.1) [1]. The terms used to describe different types of heart failure can also

Table 23.1 Definitions of heart failure

1933	A condition in which the heart fails to discharge its contents adequately. (Lewis)
1950	A state in which the heart fails to maintain an adequate circulation for the needs of the body despite a satisfactory filling pressure. (Wood)
1980	A pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues. (Braunwald)
1985	A clinical syndrome caused by an abnormality of the heart and recognized by a characteristic pattern of haemodynamic, renal, neural and hormonal responses. (Poole-Wilson)
1987	. . . syndrome . . . which arises when the heart is chronically unable to maintain an appropriately high blood pressure without support. (Harris)
1988	A syndrome in which cardiac dysfunction is associated with reduced exercise tolerance, a high incidence of ventricular arrhythmias and shortened life expectancy. (Cohn)
1989	. . . ventricular dysfunction with symptoms . . . (Anonymous)
1993	Heart failure is the state of any heart disease in which, despite adequate ventricular filling, the heart's output is decreased or in which the heart is unable to pump blood at a rate adequate for satisfying the requirements of the tissues with function parameters remaining within normal limits. (Denolin *et al*.)
1994	The principal functions of the heart are to accept blood from the venous system, deliver it to the lungs where it is oxygenated (aerated), and pump the oxygenated blood to all body tissues. Heart failure occurs when these functions are disturbed substantially. (Lenfant)
1996	Abnormal ventricular function, symptoms or signs of heart failure (past or current), and on treatment (? with a favourable response to treatment). (Poole-Wilson)
2001	(1) Symptoms of heart failure (at rest or during exercise) and (2) objective evidence (preferably by echocardiography) of cardiac dysfunction (systolic and/or diastolic) at rest (both criteria 1 and 2 must be fulfilled) and (3) in cases where the diagnosis is in doubt, response to treatment directed towards heart failure. (ESC Task Force)

Adapted from Purcell and Poole-Wilson [1].

be confusing. Generally the term 'heart failure' is used to describe the symptomatic syndrome, although a patient can be rendered asymptomatic with treatment. A patient who has never exhibited the typical signs or symptoms of heart failure is better described as having asymptomatic left ventricular systolic dysfunction (or whatever the underlying cardiac abnormality is). Patients who have had heart failure for some time are often said to have 'chronic heart failure'. If chronic heart failure deteriorates the patient may be described as 'decompensated' and this may happen suddenly, i.e. 'acutely', usually leading to hospital admission. New heart failure may also present acutely, for example as a consequence of acute myocardial infarction (or in a subacute or acute on chronic fashion, for example in a patient who has had asymptomatic cardiac dysfunction for an often indeterminate period) and may resolve (the patient may become 'compensated') or persist. 'Congestive heart failure' is a term still used commonly in the United States and may describe acute or chronic heart failure with evidence of congestion, i.e. sodium and water retention. Congestion, though not some symptoms of heart failure (e.g. fatigue), may resolve with diuretic treatment. Many or all of these terms may be accurately applied to the same patient at different times, depending on what stage of their illness they are in.

Epidemiology

The epidemiology of symptomatic heart failure in developed countries is well understood, especially in Europe (Fig. 23.1) [2–10]. Approximately 2% of the adult population has heart failure, although the syndrome mainly afflicts the elderly, affecting 6–10% of people over the age of 65 years [2–11]. In Europe and North America, the lifetime risk of developing heart failure is approximately one in five for a 40-year-old [12,13]. The age-adjusted incidence of heart failure appears to have remained stable over the past 20 years [14,15]. Prevalence is thought to be increasing, partly because survival is increasing [16]. Approximately two in a thousand of the adult population are discharged from hospital with heart failure each year and heart failure accounts for about 5% of

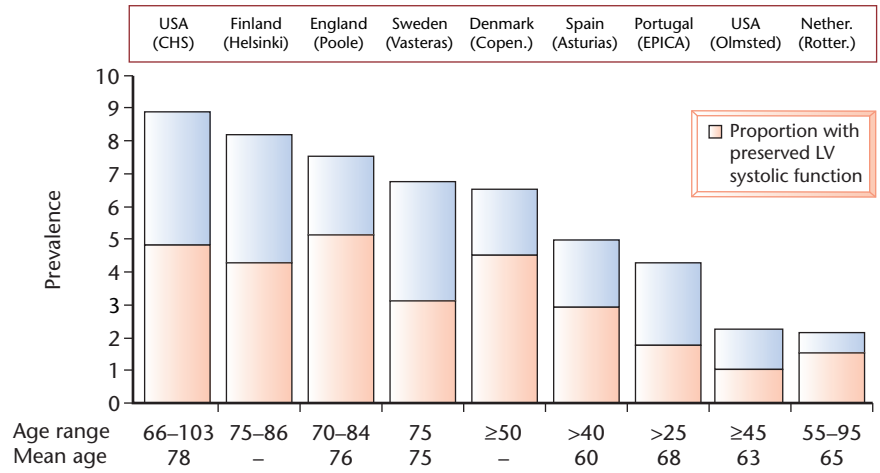

Figure 23.1 Prevalence of heart failure in cross-sectional population echocardiographic studies: proportion of subjects with preserved left ventricular systolic function. Adapted from McMurray and Pfeffer [173].

all medical and geriatric admissions and is the single most common cause of such admissions in those over 65 years [17–23]. Age at admission (and at death) seems to be increasing, suggesting that preventive treatments, such as antihypertensives, and secondary prevention after myocardial infarction are delaying the development of heart failure [17–23]. Hospital discharges include patients developing heart failure suddenly, *de novo*, as a consequence of another cardiac event (usually myocardial infarction), patients presenting for the first time with decompensation of previously unrecognized cardiac dysfunction and patients with established, chronic, heart failure who have suffered worsening sufficiently severe to lead to hospital admission (though it is recognized that the 'threshold' for admission to hospital may vary substantially between countries). Some of these admissions are unavoidable, reflecting the progressive natural history of heart failure (see below) whereas others may be avoidable (e.g. as a result of non-adherence to treatment, failure of prompt recognition and treatment of early decompensation) [24]. After years of steady increase, age-adjusted rates of admission for heart failure seem to have reached a plateau, or even decreased, in Europe and North America (Fig. 23.2) though absolute numbers of admissions continue to increase and heart failure is still an enormous burden on health services and a cost to society, accounting for approximately 2% of all health-care spending [17–23,25]. Hospital admissions account for the main part of this expenditure, typically about 70%. Even in primary care, heart failure accounts for more consultations than angina (Fig. 23.3), reflecting the limiting symptoms and reduction in well-being experienced by patients with heart failure [26]. Indeed, quality of life has, consistently, been shown to be reduced more by heart failure than by other chronic illnesses (Fig. 23.4) [27].

Heart failure is deadly as well as disabling. Community-based surveys indicate that 30–40% of patients die within 1 year of diagnosis and 60–70% die within 5 years, mainly from worsening heart failure or suddenly (probably because of a ventricular arrhythmia) [11,13,15,28]. Thus an adult living to age 40 has a one in five risk of developing heart failure and, once apparent, a one in three chance of dying within a year of diagnosis. Mortality is even higher in patients requiring hospital admission, exceeding that of most cancers (Fig. 23.5), though a number of recent studies indicate that prognosis may be improving (Fig. 23.6) [18–23,29,30].

Left ventricular function has also been measured in a number of population-based echocardiographic studies, notably in Europe, enabling estimation of the prevalence of heart failure with reduced and preserved systolic function, as well as the prevalence of asymptomatic left ventricular systolic and diastolic dysfunction (Fig. 23.6) [31–39]. Synthesis of these epidemiological surveys suggests that approximately half of patients with symptomatic heart failure in the community have reduced systolic function (and half have preserved function) [31]. The epidemiology of symptomatic heart failure with reduced systolic function differs from that of heart failure with preserved systolic function in that patients with preserved function are, on average, older, are more often women, have more comorbidity and have a better age-adjusted survival (Fig. 23.7) [31–39]. The causes of heart failure in patients with preserved systolic function also differ from those with reduced systolic function (see below) [31–39].

Because about half of cases of left ventricular systolic dysfunction are asymptomatic the argument has been made for screening for symptomless cases although no consensus has been reached on this point [40]. Recent studies have reported very disparate prevalence rates of diastolic dysfunction and proportions of symptomatic

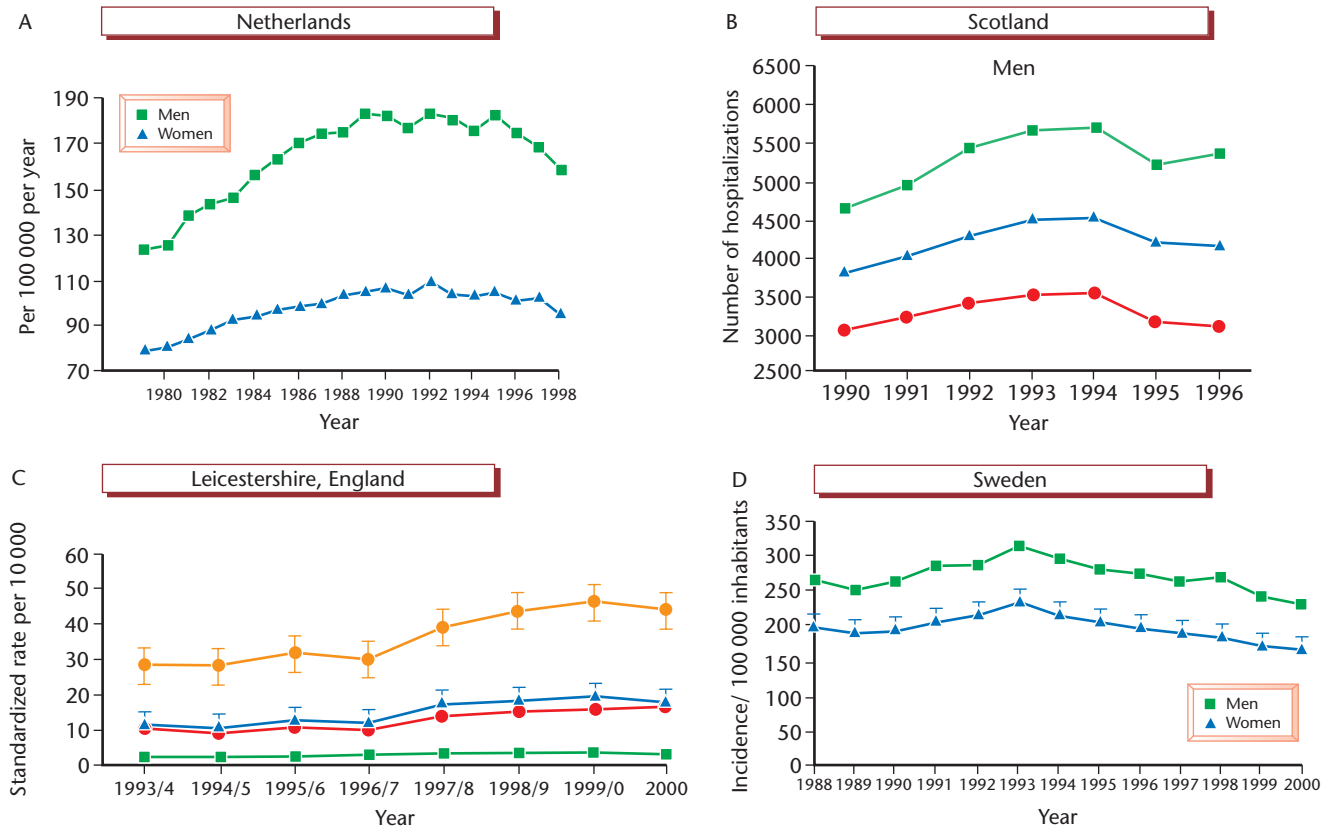

Figure 23.2 Trends in hospital admissions for heart failure demonstrating recent plateau or decline. (A) Age-adjusted discharge rate for heart failure in men and women. (B) Gender-specific trends in hospitalizations (principal diagnosis) for heart failure in men. Squares, total episodes; triangles, number of individuals; circles, first-ever hospitalization. (C) Gender- and age-specific trends in first-ever heart failure hospitalization rates (principal diagnosis) in individuals ≥ 40 years. Orange circles, men and women ≥ 65 years; blue triangles, all men; red circles, all women; green squares, men and women < 65. (D) Age-adjusted annual incidence of first-ever hospitalization for heart failure as the principal diagnosis. Reprinted with permission [174].

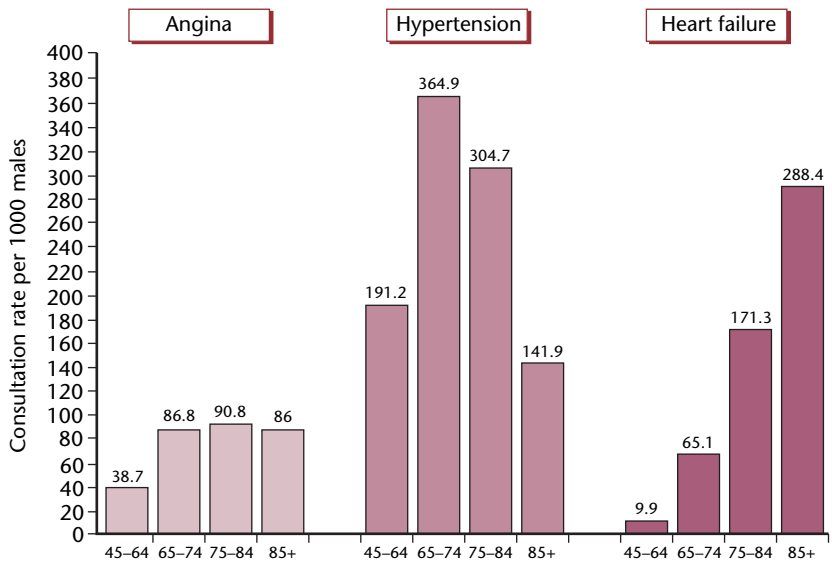

Figure 23.3 Age-stratified primary-care consultation rates per 1000 population for heart failure, angina and hypertension in men. Reprinted with permission [26].

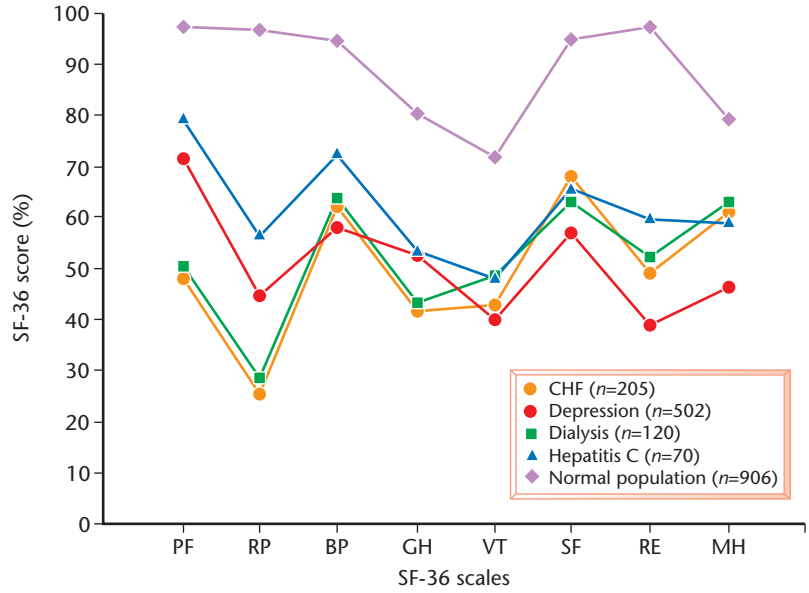

Figure 23.4 Quality of life in patients with congestive heart failure compared to other chronic illnesses and the normal population. The eight scales of the SF-36 short-form health survey instrument are physical functioning (PF), role limitations due to physical limitations (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations caused by emotional problems (RE), and mental health (MH). Reprinted with permission [175].

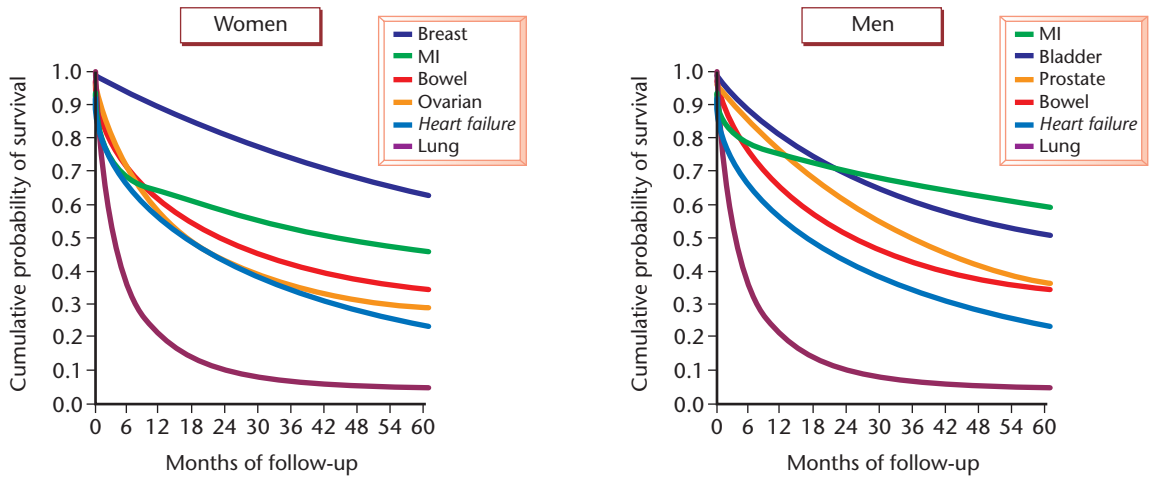

Figure 23.5 Five-year survival following a first admission to any Scottish hospital in 1991 for heart failure, myocardial infarction, and the four most common sites of cancer specific to men and women. Reprinted with permission [30].

and asymptomatic individuals and no conclusions can yet be drawn about the epidemiology of asymptomatic diastolic dysfunction [31–39,41].

Aetiology: causes of heart failure

As already mentioned, any structural, mechanical or electrical abnormality of the heart can cause it to fail (Table 23.2). Similarly, heart failure can be caused by ischaemic, metabolic, endocrine, immune, inflammatory, infective, endocrine, genetic and neoplastic processes, by failure of the heart to develop properly and even by pregnancy. The potential causes of heart failure are, therefore, legion, vary geographically and have changed over time. Rheumatic valvular disease remains a common cause in many developing countries whereas this diagnosis is now uncommon in developed countries; in the latter, degenerative valvular disease in the elderly is now more common [42–45]. Valve disease may lead to volume and pressure overload of the heart, as described in more detail below. Endocardial disease is very rare in Europe but much less so in parts of Africa, where it can

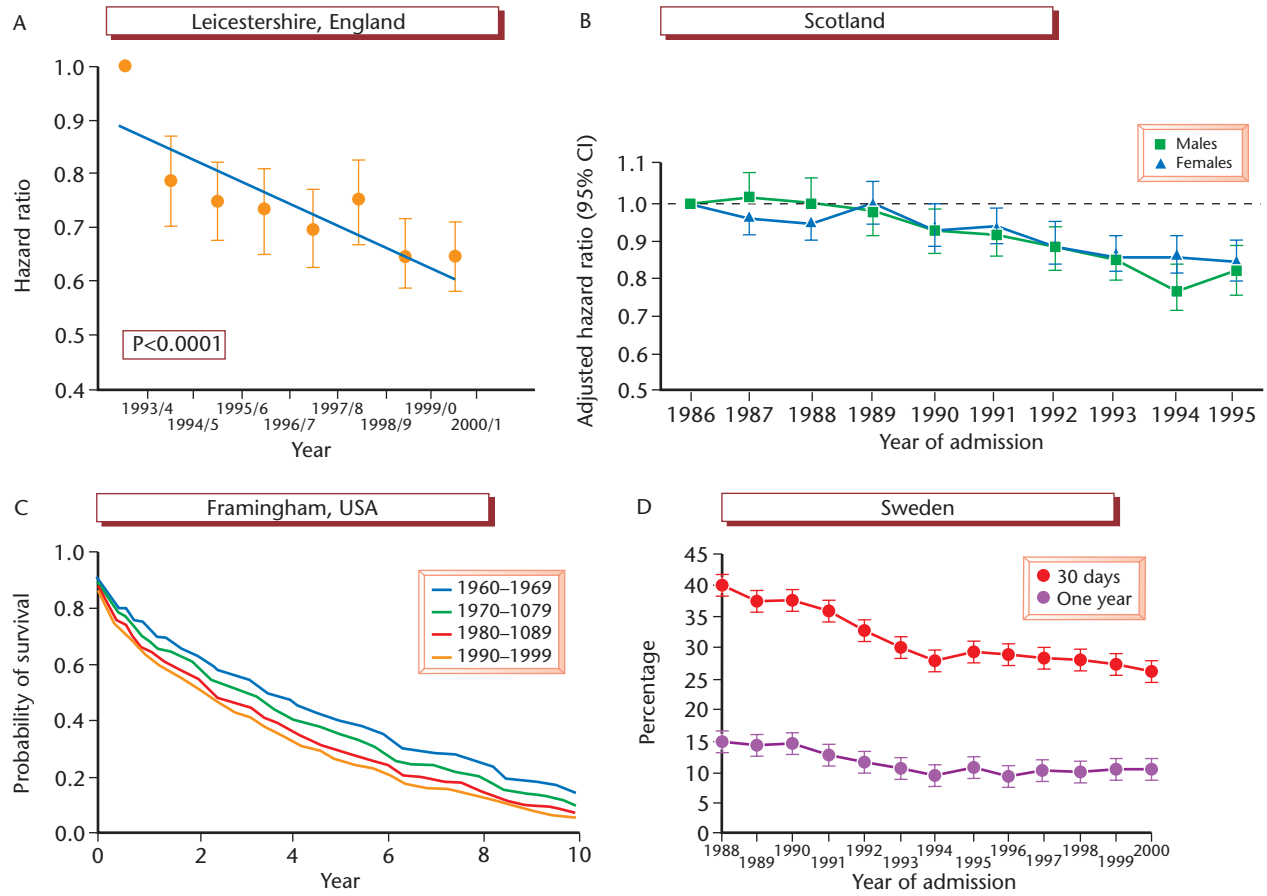

Figure 23.6 Evidence of improving survival from heart failure in the general population. (A) Hazard ratio and 95% confidence intervals for all-cause mortality in patients having a first admission for heart failure, according to year of admission (adjusted for age, gender, comorbidity, and social deprivation). Hazard ratio for first year of study (1993/1994) set at 1. (B) Odds ratios and 95% confidence intervals for all-cause mortality (≥ 30 days after a first heart failure admission), according to year of admission (adjusted for age, gender, comorbidity, and social deprivation). Odds ratio for first year of period of study (1986) set at 1. (C) Standardized 30-day and 1-year case fatality rates (%) for women with a first admission to hospital for heart failure. (D) Age-adjusted survival after the onset of heart failure in men. Values were adjusted for age (< 55, 55 to 64, 65 to 74, 75 to 84, and ≥ 85 years). Estimates are shown for men who were 65 to 74 years of age. Similar trends were observed in women. Reprinted with permission [174].

cause what is referred to as a restrictive cardiomyopathy, as described further below [42–45].

In the developed world, ventricular dysfunction is the commonest underlying problem and is caused, mainly, by myocardial infarction (leading to systolic ventricular dysfunction, i.e. failure of normal contraction and emptying of the heart), hypertension (causing systolic dysfunction, diastolic dysfunction, i.e. failure of normal relaxation and filling of the heart or both) or, often, both infarction and hypertension. Whether persisting systolic dysfunction is caused by coronary artery disease in the absence of infarction is uncertain. The converse, i.e. whether treatment of ischaemia and a state known as 'hibernation' (where chronic poor perfusion results in non-contracting but viable myocardium) improves systolic function, is also a question of great current interest, addressed by ongoing studies of coronary 'revascularization' [46].

In Europe, North America and Australasia, hypertension was once the principal cause of heart failure whereas now that position is filled by coronary heart disease (or more exactly, myocardial infarction); this is also increasingly the case in many developing countries [47].

While myocardial infarction is a much more important individual risk factor than hypertension, the population-attributable risk due to hypertension is probably still more important [48]. Both causal factors also interact to augment the risk of heart failure. By the time heart failure presents, prior hypertension may no longer be present. Both of these factors probably result in underestimation

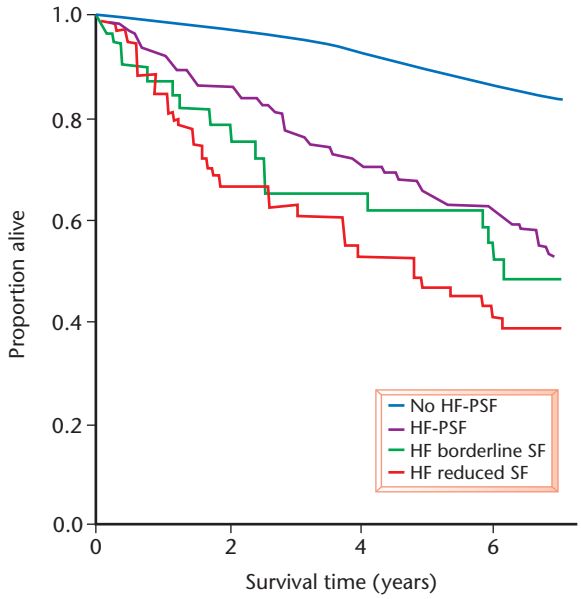

Figure 23.7 Unadjusted Kaplan–Meier survival curves for participants with heart failure (HF) based on left ventricular function from The Cardiovascular Health Study. Preserved systolic function (PSF), Systolic function (SF). Reprinted with permission [35].

of the role of hypertension in causing heart failure. Hypertension is a more common aetiology in women than men.

'Idiopathic' dilated cardiomyopathy remains the only other cause of systolic dysfunction commonly encountered, perhaps accounting for 15–20% of cases of heart failure with reduced systolic function. These cases probably have multiple causes and an increasing number of genetic causes are being identified [49]. Prior viral infection and current or previous excessive alcohol consumption may also cause a dilated cardiomyopathy, as can exposure to other toxins, including chemotherapeutic agents used in cancer treatment. These must always be considered when a patient presents with an unexplained dilated cardiomyopathy. If angiography is not carried out to exclude coronary disease, it may also be wrongly concluded that the patient has an 'idiopathic' dilated cardiomyopathy. Chagas' disease caused by the protozoan parasite *Trypanosoma cruzi* can also cause systolic dysfunction. Though rarely encountered in Europe it is a relatively common cause of heart failure in South America and is now recognized in Central and North America [42–45].

The contribution of diabetes to systolic and diastolic dysfunction is not well understood, as is the relationship between atrial fibrillation and both types of heart failure [50,51]. Diabetics have a higher prevalence of heart failure. Diabetes accelerates the development of coronary atherosclerosis and is often associated with hypertension

Table 23.2 Aetiology of heart failure

There is no agreed or satisfactory classification for the causes of heart failure with much overlap between potential categories, e.g. dilated cardiomyopathy may be variously regarded as idiopathic, genetic, caused by a remote virus infection or the result of current or previous excessive alcohol consumption.

Myocardial disease
- coronary artery disease
- hypertension
- immune/inflammatory
  - viral myocarditis
  - Chagas' disease
- metabolic/infiltrative
  - thiamine deficiency
  - haemochromatosis
  - amyloidosis
  - sarcoidosis
- endocrine
  - thyrotoxicosis
- toxic
  - alcohol
  - cytotoxics
  - negatively inotropic drugs (e.g. calcium-channel blockers)
- idiopathic
  - cardiomyopathy (dilated, hypertrophic, restrictive, peri-partum)

Valvular disease
- mitral stenosis/regurgitation
- aortic stenosis/regurgitation
- pulmonary stenosis/regurgitation
- tricuspid stenosis/regurgitation

Pericardial disease
- effusion
- constriction

Endocardial/endomyocardial disease
- Loeffler endocarditis
- endomyocardial fibrosis

Congenital heart disease
- e.g. atrial or ventricular septal defect

Genetic
- e.g. familial dilated cardiomyopathy

Arrhythmias (brady- or tachy-)
- atrial
- ventricular

Conduction disorders
- sinus node dysfunction
- second-degree atrioventricular block
- third-degree atrioventricular block

High output states
- anaemia
- sepsis
- thyrotoxicosis
- Paget's disease
- arteriovenous fistula

Volume overload
- renal failure
- iatrogenic

[50,52]. Whether it directly causes a specific cardiomyopathy is, however, uncertain [50]. Diabetes also increases the risk of developing heart failure in patients with other causes, e.g. acute myocardial infarction. It is believed that diabetes promotes the development of myocardial fibrosis and diastolic dysfunction [53]. Diabetes is also associated with more autonomic dysfunction and worse renal, pulmonary and endothelial function, as well as worse functional status and a worse prognosis. Conversely, heart failure increases the risk of developing diabetes [54].

Atrial fibrillation can cause heart failure directly as a consequence of the loss of the atrial contribution to cardiac output and reduced diastolic filling as a result of tachycardia [51]. Patients with underlying structural or functional cardiac disease are more likely to develop failure as a consequence of these effects with the onset of atrial fibrillation. There is, however, a growing belief that atrial fibrillation can cause a dilated cardiomyopathy the exact mechanism of which is uncertain, though persistent tachycardia may play a role (i.e. atrial fibrillation may cause a 'rate-related cardiomyopathy') [55,56]. Heart failure also increases the risk of developing atrial fibrillation and this risk increases with the severity of heart failure. Consequently, when a patient presents with left ventricular dilatation systolic dysfunction and atrial fibrillation it can be difficult to determine which came first.

Comorbidity

It is important to appreciate that heart failure does not occur in isolation. It is caused by an underlying cardiac defect in, usually, elderly individuals frequently treated for other medical problems with multiple medications. Consequently, the patient with heart failure often has comorbidity related to the underlying cardiac problem or its cause (e.g. angina, hypertension, diabetes, smoking-related lung disease) and age (e.g. osteoarthritis), as well as a consequence of heart failure (e.g. arrhythmias) and its treatment (e.g. gout from diuretics) [57]. Some common comorbidities have multiple causes (e.g. renal dysfunction – see below), whereas others are not fully explained (e.g. anaemia, depression, disorders of breathing and cachexia) [57–61]. The existence of multiple comorbidities creates the potential for drug intolerance [e.g. angiotensin-converting enzyme (ACE) inhibitor and renal dysfunction], drug interactions [e.g. non-steroidal anti-inflammatory drugs (NSAIDs) and ACE inhibitors] and makes the management of heart failure very complex [57,62–65]. This is especially true of renal dysfunction, the importance of which is increasingly recognized by a growing use of the term 'cardiorenal syndrome' [66,67] to describe concurrent heart and renal failure.

Cardiorenal syndrome

This syndrome arises from multiple interactions between the age-related decline in glomerular filtration, the effects of treatment for heart failure (diuretics, ACE inhibitors, angiotensin receptor blockers and aldosterone antagonists) and other conditions (e.g. NSAIDs for arthritis), comorbidity (e.g. hypertension, diabetes, atherosclerosis), reduced renal blood flow and the actions on the kidneys of the array of neurohumoral pathways activated in heart failure [66,67]. The prevalence of severe renal dysfunction in heart failure is often underestimated because serum creatinine concentration may not be greatly elevated because of the reduction in skeletal muscle mass in advanced heart failure. Renal dysfunction may contribute to the high prevalence of anaemia in patients with heart failure.

Anaemia

Anaemia is another important comorbidity and can be both the cause and, it seems, consequence of heart failure [68–71]. Anaemia is common (especially in more severe heart failure) and is associated with worse symptoms, increased risk of hospital admission and reduced survival. The causes are unknown but may include renal dysfunction, poor nutrition, inflammation (see below), blood loss related to medication and reduced production of (or response to) erythropoietin.

Catabolic/anabolic imbalance and cachexia

Patients with heart failure often exhibit some degree of muscle wasting which is restricted to the lower limbs (disuse atrophy) [72,73]. This loss of tissue may become more extensive in some patients, usually when their heart failure is more advanced, and may affect all body compartments (muscle, fat and bone tissue). This general wasting is referred to as cardiac cachexia. The underlying metabolic causes are complex and differ from patient to patient. Three important contributors are, probably, dietary deficiency (exacerbated by anorexia) and loss of nutrients through the urinary or digestive tracts (malabsorption) and metabolic dysfunction (including an imbalance of anabolic and catabolic factors and inflammation). The development of cachexia is an ominous sign.

It is important to appreciate that it is comorbidity, along with the key pathophysiological processes in heart

failure, i.e. left ventricular remodelling and activation of systemic pathways (and age), that are the principal determinants of prognosis.

Pathophysiology

We have only limited knowledge of the pathophysiology of heart failure, and that of left ventricular systolic dysfunction is best understood. Much of our understanding comes from studies of myocardial infarction (Fig. 23.8) [74–77]. Following an initial injury to the myocytes and cytoskeleton, heart failure may develop immediately, in the short term (over days or weeks), over a longer time period (months to years), or not at all. The factors leading to the development of heart failure acutely after myocardial infarction (e.g. size of infarction), the important pathophysiological mechanisms operating (e.g. cardiac remodelling) and the time-course of this complication of infarction are fairly well established. On the other hand, the natural history of asymptomatic left ventricular systolic dysfunction is less well understood, as are the pathophysiological mechanisms causing progression from the asymptomatic to the symptomatic state. Once symptomatic heart failure has developed we believe that the pathophysiology is again better understood, at least in patients with systolic dysfunction. One thing is certain: the syndrome is characterized by progressive worsening of the patient's symptoms, of cardiac function and of the function of other tissues (e.g. skeletal muscle) and organs (e.g. the kidneys).

The progression of left ventricular systolic dysfunction (and the heart failure syndrome), because of 'remodelling' of the left (and right) ventricle (as a result of the loss of myocytes and maladaptive changes in the surviving myocytes and extracellular matrix), probably occurs in two main ways [76–79]. One is because of intercurrent cardiac events (e.g. myocardial infarction) and the other is as a consequence of the local processes (e.g. the autocrine pathway and molecular adaptations, including, perhaps, apoptosis) and systemic processes (e.g. neurohumoral pathways) that are activated as a result of reduced systolic function (Fig. 23.9) [80–82]. These systemic processes, which are discussed in detail below, also have detrimental effects on the functioning of the lungs, blood vessels, kidneys, muscles and probably other organs (e.g. the liver) and contribute to a pathophysiological vicious cycle (Fig. 23.10). The molecular, structural and functional changes in the heart and these systemic processes, coupled with electrolyte imbalances,

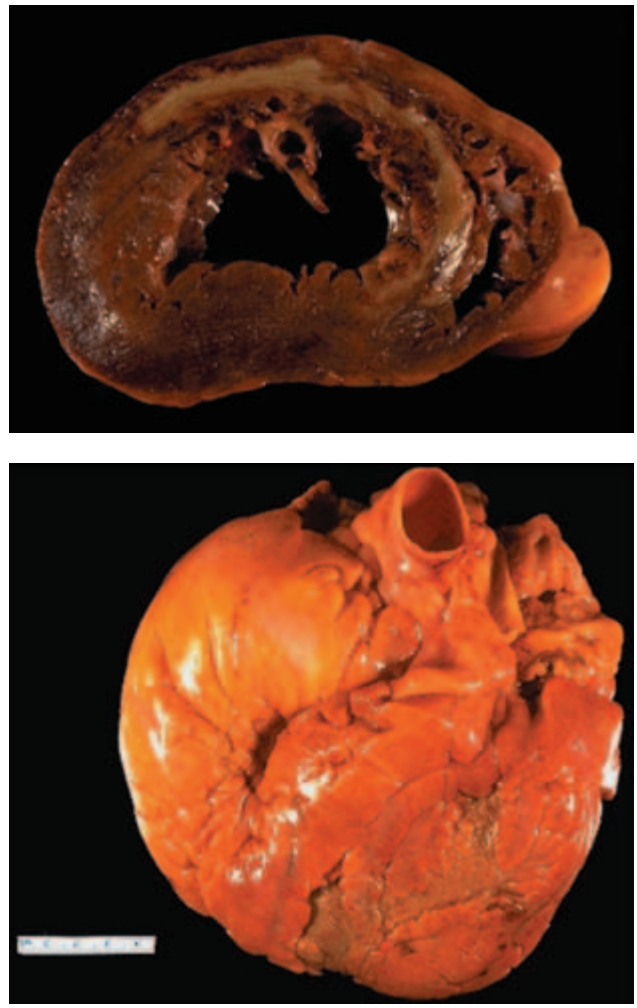

Figure 23.8 Gross pathological appearance of (A) an anteroseptal myocardial infarction, with wall thinning and endocardial fibrosis, in a patient with a background of left ventricular hypertrophy due to hypertension, and (B) a heart in idiopathic dilated cardiomyopathy characterized by four chamber enlargement.

result in electrical as well as mechanical dysfunction of the heart.

It is important to remember that atrial function (see above), synchronized contraction of the left ventricle and normal interaction between the right and left ventricles are also important in preserving stroke volume [83]. Loss of these key mechanical interactions are often secondary to disturbances of conduction arising as a consequence of cardiac fibrosis.

Dilated and ischaemic cardiomyopathy

Myocyte necrosis whether caused by infarction or by other injury has a common consequence. Whether

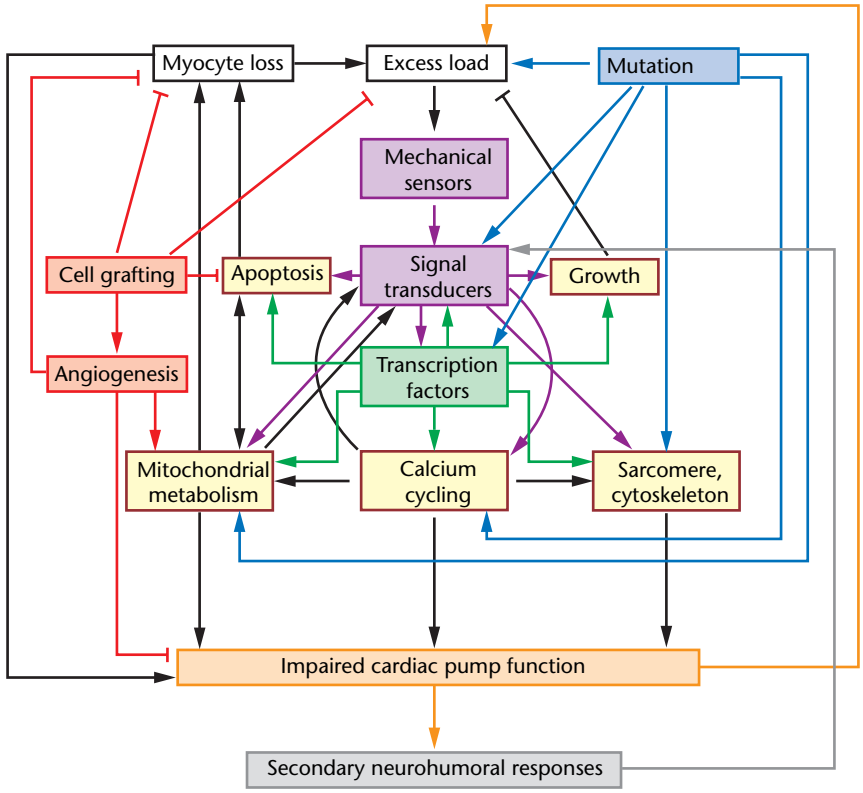

Figure 23.9 A partial wiring diagram of biological circuits for heart failure. Impaired pump function after myocyte death from myocardial infarction or abnormal loading conditions such as found in hypertension (white) activate a biomechanical stress-dependent signalling cascade (purple). The responsible targets of altered signal transduction cascades in heart failure include transcription factors, coactivators and co-repressors for cardiac gene expression (green) as well as the effector mechanisms like calcium cycling, metabolism, growth and apoptosis (yellow) that culminate in ventricular dysfunction (orange) and secondary neurohumoral responses (grey) such as adrenergic drive and intramyocardial growth factors. Inherited mutations for cardiomyopathy (blue) affect proteins at many of these points and are thought to engage a similar cascade of events to elicit the full myopathic phenotype. Cell-based therapies (red), although often envisioned working chiefly or wholly by replacing dead myocytes, probably improve ventricular performance through a combination of mechanisms, including angiogenesis, paracrine signals for myocyte protection, and conceivably augmenting host self-repair. Reprinted with permission [176].

diffuse or focal, myocyte loss leads to replacement fibrosis, hypertrophy of the remaining myocytes and dilatation of the affected cardiac chamber [84–89]. How these molecular and cellular changes affect the left ventricle macroscopically (by causing remodelling) is discussed in more detail below [76]. The resulting anatomical and pathophysiological picture is, however, identified by clinicians as a dilated cardiomyopathy (Fig. 23.8; see also Chapter 16). Patients with a dilated poorly contracting left ventricle as a result of prior myocardial infarction are sometimes referred to as having an 'ischaemic cardiomyopathy'. Poor contraction and emptying of the ventricle are usually referred to as systolic dysfunction.

Systolic vs. diastolic dysfunction

Systolic and diastolic dysfunction are terms used to describe whether the principal abnormality of the myocardium is an inability of the ventricle to contract and expel blood or to relax and fill normally, respectively (though in reality these two abnormalities frequently coexist). Systolic dysfunction is the result of reduced shortening of sarcomeres, which is a consequence of a global or regional reduction of contractility or greatly increased impedance to left ventricular ejection. An increase in preload can provide short-term compensation (via the Frank–Starling mechanism – see below) for a reduction in contractility or increases in impedance. However, long-term compensation usually involves myocardial hypertrophy, which is the result of laying down new sarcomeres that increase the width (concentric) or the length (eccentric) of myocytes [76,90]. Remodelling also contributes to reduced sarcomere shortening. All these factors causing reduced fibre shortening also lead to a decrease in the left ventricular ejection fraction (LVEF). Hence, end-systolic volume increases.

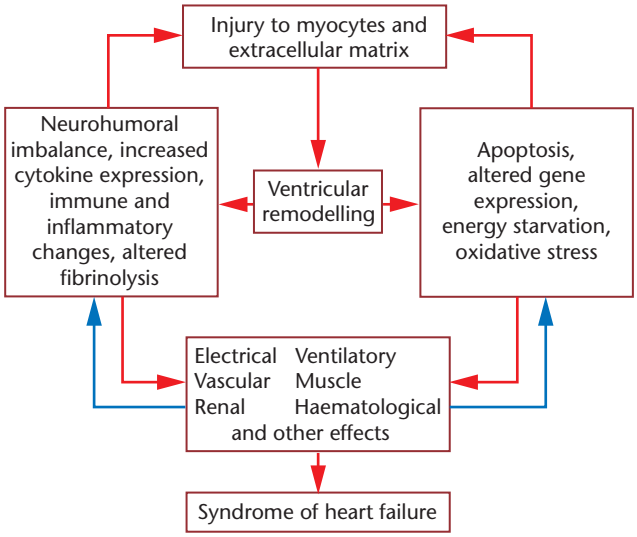

Figure 23.10 Pathophysiology of heart failure as a result of left-ventricular systolic dysfunction. Damage to the myocytes and extracellular matrix leads to changes in the size, shape, and function of the left ventricle and heart more generally ('remodelling'). These changes, in turn, lead to electrical instability, systemic processes resulting in many effects on other organs and tissues, and further damage to the heart. These vicious cycles, along with intercurrent events, such as myocardial infarction, are believed to cause progressive worsening of the heart-failure syndrome over time. Adapted from McMurray JJ and Pfeffer MA [173].

Rapid filling during systole is assisted by active, energy-dependent, relaxation of the ventricle [85,91]. Primary myocardial diseases may affect this process. Ventricular relaxation also depends on myocardial mass, collagen content and extrinsic forces (e.g. the pericardium) [91]. The hallmark of diastolic dysfunction is elevation in left ventricular end-diastolic pressure or left arterial pressure in the absence of systolic dysfunction [92–97].

Restrictive cardiomyopathy and pericardial constriction

Infiltrative processes in the myocardium or pericardium may cause a restrictive cardiomyopathy [98]. The principal consequence of these processes is impaired ventricular filling with normal or decreased diastolic volume of either or both ventricles, akin to the diastolic dysfunction described above. Systolic function is typically maintained during the early stages of the disease and wall thickness is normal or increased. The main problem is that increased stiffness of the myocardium causes pressure within the ventricle to rise precipitously with only small increases in volume. Restrictive cardiomyopathy may affect either or both ventricles. Elevated jugular venous pressure, peripheral oedema and ascites are often prominent features (see below).

Valve disease: pressure and volume overload

Arterial hypertension and aortic stenosis cause a sustained increase in systolic wall stress during left ventricular ejection leading to concentric hypertrophy of the left ventricle because of myocyte hypertrophy and extracellular matrix overgrowth [99].

Conversely, mitral and aortic regurgitation result in an increased volume load on the ventricle. The resultant ventricular remodelling is characterized by dilatation, representing, at least in part, lengthening of the cardiac myocytes [100,101].

Other terms sometimes used when describing heart failure

Right and left heart failure

These terms are not useful and are reminiscent of the now discarded terminology of 'backwards and forwards heart failure'. The term right heart failure is often used to describe patients in whom there are prominent signs of 'congestion', e.g. a raised jugular venous pressure (Fig. 23.11), hepatomegaly and peripheral oedema (Fig. 23.11), on the basis that these findings reflect right ventricular failure; in fact all of these signs are also found in patients with predominantly left ventricular involvement. The description pulmonary heart disease is used to depict patients who do have isolated right heart failure as a result of primary lung disease and has generally replaced the term 'cor pulmonale'.

High- and low-output heart failure

A more useful pathophysiological classification is to distinguish between high- and low-output heart failure, although the former is uncommonly encountered in Western clinical practice. Cardiac index is normally 2.2–3.5 l/min/m^2. Low-output cardiac failure implies that cardiac output fails to rise adequately during exercise or that it is inadequate even at rest. This prototypical form of heart failure is seen in cases of heart failure as a result of left ventricular systolic dysfunction. High-output cardiac failure, on the other hand, implies that although the pumping action of the heart is intact other factors make it difficult for the heart to deliver oxygen commensurate with the needs of the metabolizing tissues, either because of increased tissue demand (e.g. as a result of anaemia, hyperthyroidism or pregnancy) or reduced oxygen carrying content of the blood (e.g.

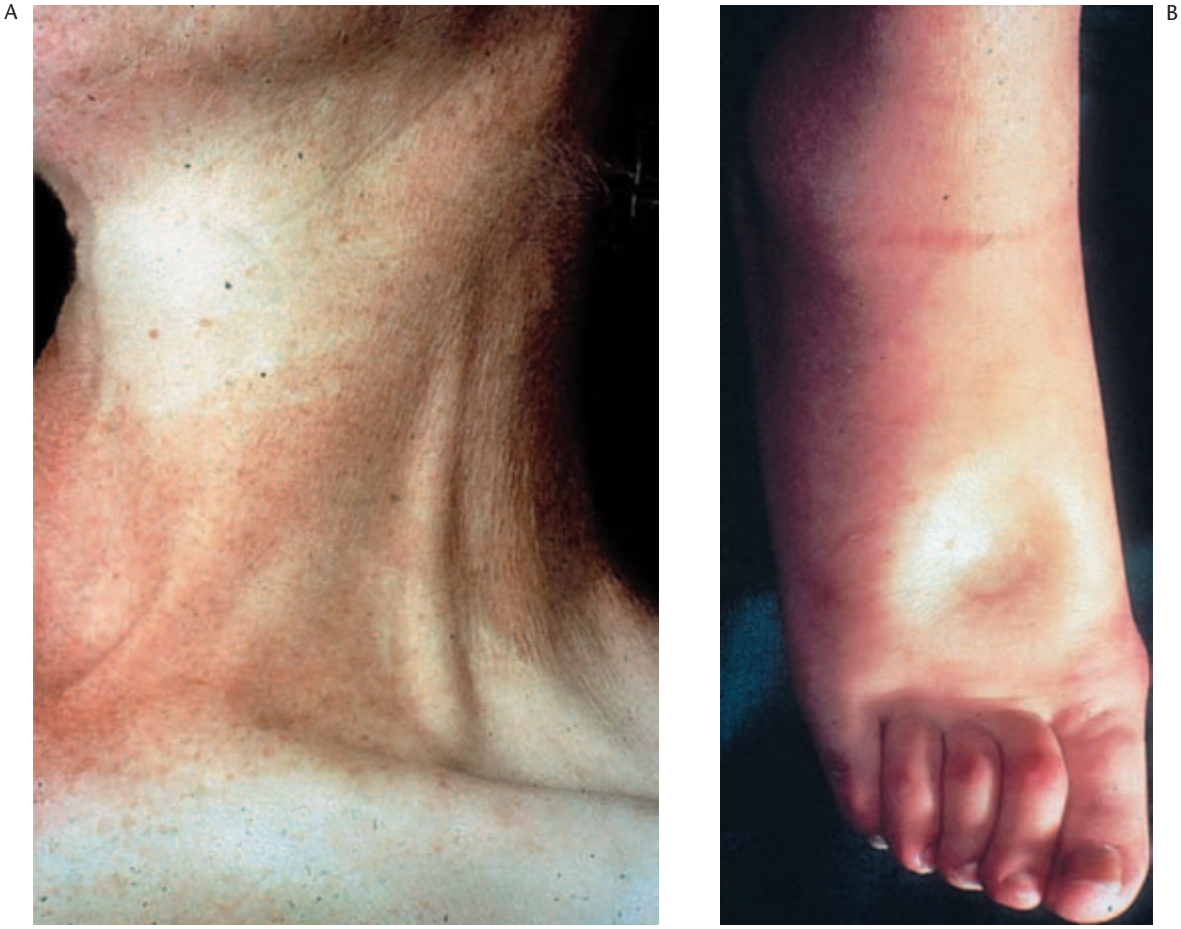

Figure 23.11 (A) A raised jugular venous pressure (JVP) reflects an elevation in right atrial pressure as occurs in heart failure. However this can also be seen in pericardial disease, tricuspid stenosis, superior vena cava obstruction, reduced compliance of the right ventricle, and hypervolaemia. (B) Pitting pedal oedema as seen in a patient with heart failure. This can also be seen in hypoalbuminaemia, nephrotic syndrome, chronic venous insufficiency and myxoedema.

anaemia). This type of heart failure can also be caused by arteriovenous shunting.

Cardiac responses to ventricular injury and reduced stroke volume

Frank–Starling mechanism

The Frank–Starling law describes an intrinsic mechanism that helps maintain stroke volume when the heart is acutely injured and may also play a compensatory role in chronic heart failure, though this is less certain [103]. Together with neurohumoral activation (an extrinsic mechanism), the Frank–Starling law is an adaptive phenomenon that comes into play within minutes of cardiac injury. The resultant acute fall in the volume of blood ejected by the ventricle (the stroke volume) leads to a rise in left ventricular end-diastolic volume (and pressure). Through the Frank–Starling mechanism this rise in preload increases the force of contraction, thereby helping restore stroke volume. The mechanism whereby increased stretch of the myocyte causes increased force of contraction is also referred to as the law of heterometric autoregualtion. In the chronic setting, sodium retention, water retention and venoconstriction may represent continuing attempts by the body to use the Frank–Starling mechanism by increasing left ventricular filling pressure and preload.

These adaptations may, however, lead to abnormally high pulmonary capillary and artery pressures, probably contributing to the shortness of breath experienced by patients with heart failure. Furthermore arterial constric-

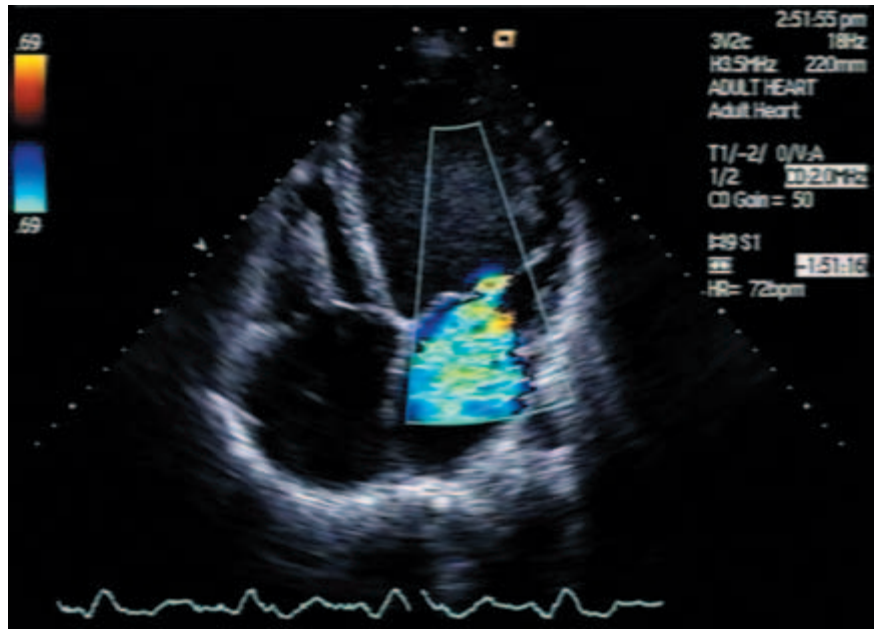

Figure 23.12 Colour-flow Doppler study of a patient with mitral regurgitation as a result of left ventricular dilatation seen in the apical four-chamber view.

tion and stiffening (as a result of sodium and water retention in the vascular wall) increase afterload and will eventually cause the injured left ventricle to fail further because it is especially sensitive to increases in afterload (law of homeometric regulation).

Ventricular remodelling

The heart attempts to compensate for increased preload (e.g. because of increased extracellular fluid volume and venous return) and afterload (e.g. because of systemic arterial constriction) in several ways. One is the development of ventricular hypertrophy in an attempt to maintain systolic wall stress within normal limits [76,90,103]. Pressure overload tends to lead to concentric hypertrophy, whereas volume overload tends to lead to ventricular dilatation [76,85,90,103]. Both entities are distinct at the molecular level. Pressure overload is associated with parallel replication of myofibrils and thickening of individual myocytes. Volume overload, on the other hand, leads to replication of sarcomeres in series and elongation of myocytes. The two types of haemodynamic overload are presumed to activate distinct signalling pathways.

Compensated remodelling results in relatively little change in ventricular dimensions, shape, function and wall thickness. However, these compensatory adaptations only seem to be capable of maintaining pump function over a limited period of time and a ventricle subjected to an elevated load for a prolonged period will ultimately fail [76]. Ventricular dilatation may lead to stretching of the mitral valve ring and cause valvular incompetence (Fig. 23.12). This may further increase the load on the failing ventricle; this is an example of another 'vicious cycle' that develops and which may drive progression of heart failure.

An initial stress-induced increase in sarcomere length yields an optimal overlap between myofilaments [85,86,90,103,104]. Severe haemodynamic overload eventually yields depression of myocardial contractility [85,86,90,103,104]. In patients with mild disease, this depression is manifested by reduced velocity of shortening of the myocardium or by a reduction in the rate of force development during isometric contraction. More severe stages are accompanied by a decline in isometric force development and shortening as well. Ejection fraction and cardiac output during exercise decline [105].

Our understanding of the molecular mechanisms behind these changes is still limited and can only be touched upon briefly (Fig. 23.9). They comprise myocyte loss by necrosis and apoptosis, alterations in excitation–contraction coupling, and alterations in composition of the extracellular matrix [76,84,87–89]. Myocyte loss as a result of necrosis is a well-understood process which is localized after myocardial infarction but more diffuse in patients with dilated cardiomyopathy or myocarditis. Apoptosis, or programmed cell death, on the other hand, results from the induction of a genetic programme that leads to degradation of nuclear DNA (Fig. 23.9) [79,87,88]. Several recent reports have described apoptotic cells in the failing myocardium. It may be relevant that several substances, such as angiotensin II, reactive oxygen species, nitric oxide (NO), and pro-inflammatory

cytokines may induce apoptosis experimentally in cardiac myocytes. However, the precise frequency of occurrence and role of apoptosis in the failing myocardium remains unclear. Changes in the extracellular matrix are usually manifested by an increase in collagen content though both degradation and synthesis (and the activity of the enzymes controlling these processes) may be increased [78,79,89,90]. While this change in collagen content may contribute to impaired systolic contraction it may be even more important in reducing ventricular compliance and impaired ventricular filling.

Systemic responses

Neurohumoral responses

The human body responds to the haemodynamic changes in patients with heart failure in a highly complex way. Many neurohumoral systems appear to be involved to varying degrees and at different stages. It has been suggested that these are initially activated in a manner appropriate to haemorrhage or some other crisis threatening vital organ perfusion [80,82,105,106]. Their sustained activation in heart failure, however, is not only inappropriate but probably detrimental (Fig. 23.10). Moreover, at some stage during the progression of heart failure, haemodynamic abnormalities may cease to be the main trigger of neurohumoral activation. Instead, a number of other self-sustaining pathophysiological vicious cycles may develop.

The predominant effects of the neurohumoral systems activated in heart failure are to cause vasoconstriction, sodium and water retention and abnormal cell growth. Two exceptions are the natriuretic peptides [107] (secreted mainly by the failing heart, Fig. 23.13) and adrenomedullin (secreted mainly from blood vessels) [108].

The neurohumoral pathways activated in heart failure are thought to be particularly important because they appear to explain how many of the successful pharmacological treatments for heart failure work (and offer the potential for more such therapeutic interventions).

Sympathetic nervous system It has long been recognized that an increased activity of the sympathetic nervous system and parasympathetic withdrawal are prototypical characteristics of heart failure [109,110]. Elevated levels of plasma noradrenaline are a common finding in patients with heart failure. Increased sympathetic nerve traffic and enhanced spill-over of noradrenaline from the synaptic cleft account for this. Raised plasma noradrenaline concentrations predict higher mortality rates [111]. Heart failure is also characterized by reductions in myocardial noradrenaline stores and in myocardial beta-receptor density. These again reflect generalized adrenergic activation.

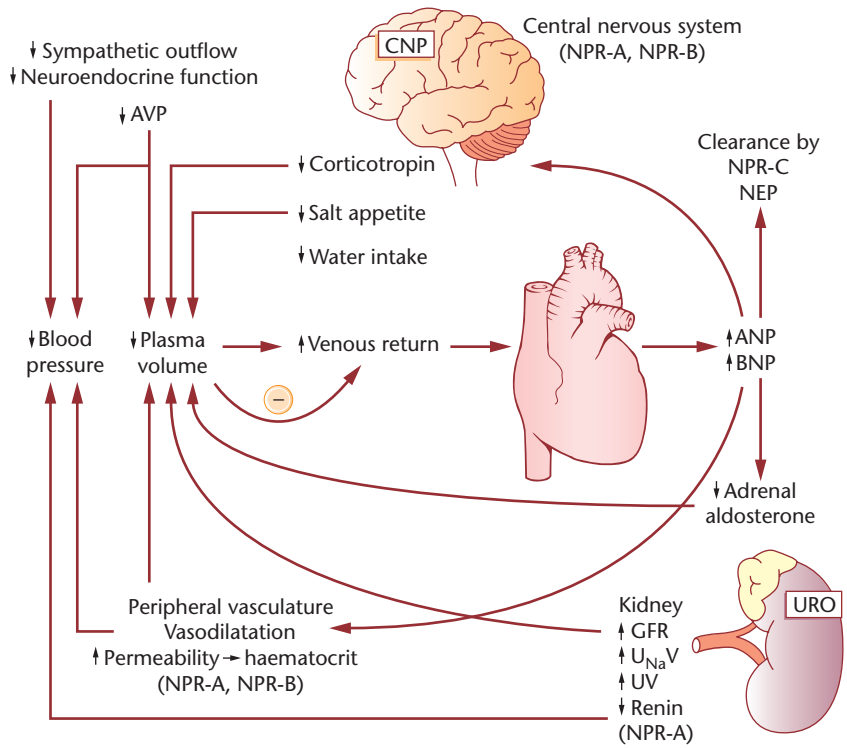

Figure 23.13 Physiological effects of the natriuretic peptides in heart failure. Increased secretion of the natriuretic peptides reduces blood pressure and plasma volume through coordinated actions in the brain, adrenal gland, kidney, and vasculature. Urodilatin (URO); neutral endopeptidase (NEP); C-type natriuretic peptide (CNP); natriuretic peptide receptors A, B and C (NPR-A, NPR-B, and NPR-C respectively); arginine vasopressin (AVP); atrial and brain natriuretic peptides (ANP and BNP); glomerular filtration rate (GFR); urinary sodium excretion ($U_{Na}V$); urinary volume (UV); blood pressure (BP). Reprinted with permission [177].

It is believed that enhanced sympathetic activity initially increases myocardial contractility and heart rate (leading to an increase in cardiac output). Sympathetic activation also promotes renin release, sodium retention and vasoconstriction thereby increasing preload and activating the Frank–Starling mechanism (see above). These responses are capable of maintaining ventricular performance and cardiac output for a limited period of time. In part this may be because the increase in afterload caused by arterial constriction (to which the failing ventricle is particularly sensitive) leads to a further fall in stroke volume (see above). Sympathetic overdrive probably alters myocardial metabolism and catecholamines may also even be directly toxic to cardiomyocytes. Excessive adrenergic activity (and reduced vagal activity) also increases the electrical instability of the heart. As well as having complex and changing effects on myocardial contractility and structure, activation of the sympathetic nervous system leads to redistribution of regional blood flow and even to changes in the structure of the vasculature [110].

The precise cause of sympathetic activation in heart failure is unknown. Reduced stimulation of stretch-activated baroreceptors in the carotid arteries and the aorta from decreased arterial pressure and stroke volume may contribute (in an analogous way to haemorrhage). Another factor suggested is structural and functional abnormalities of afferent receptors. Other neurohumoral systems may also activate the sympathetic nervous system and augment its actions, i.e. many neurohumoral systems act in concert, synergistically reinforcing each other.

Renin–angiotensin–aldosterone system Increased activity of the renin–angiotensin–aldosterone system (RAAS) also produces deleterious effects on the cardiovascular system (and other organs and tissues) and contributes to the poor prognosis in heart failure [80,82,112]. The plasma components of this system are usually increased in patients with heart failure and a low serum sodium concentration is a marker for particularly excessive activation of the RAAS [113]. The increase in renin release is mediated by decreased stretch of the glomerular afferent arteriole and reduced delivery of chloride to the macula densa. Although the sympathetic nervous system also stimulates renin release, the two systems are independently regulated. One puzzle about heart failure is why the sodium and volume overload that characterizes the syndrome does not suppress renin release, as would normally occur.

The increased secretion of renin leads to an augmented production of angiotensin II, which, it is believed, has mostly deleterious effects in heart failure (although its efferent glomerular arteriolar action may help maintain glomerular filtration). The deleterious effects of angiotensin II are mediated via the angiotensin type I receptor. Angiotensin II not only induces vasoconstriction, but also salt and water retention directly and via aldosterone [114]. Moreover, it mediates myocardial cell hypertrophy and fibrosis and these effects may contribute to the progressive loss of myocardial function in heart failure.

Plasma aldosterone levels are also increased in heart failure, and release of this hormone is influenced by angiotensin and other stimuli such as potassium and corticotropin. Aldosterone is now recognized as an independent and harmful component of the RAAS [115]. It causes sodium and water retention, potassium wastage and may contribute to myocardial and vascular fibrosis, autonomic dysfunction and other abnormalities in heart failure.

Vasopressin Vasopressin (also known as antidiuretic hormone) is a neurohypophysial peptide involved in the regulation of free water reabsorption, body fluid osmolality, blood volume, blood pressure, cell contraction, cell proliferation and adrenocorticotropin secretion [116,117]. Vasopressin binds to three different specific G protein-coupled receptors. These are currently classified as V1-vascular, V2-renal, and V3-pituitary subtypes. All subtypes have distinct pharmacological profiles and intracellular second messengers. As well as reducing renal water excretion, vasopressin is one of the most powerful vasoconstricting substances known. It also stimulates blood platelet aggregation, coagulation factor release and cellular proliferation. This profile of action is clearly unattractive in heart failure.

Elevated circulating levels of vasopressin are often, but not invariably, found in patients with chronic heart failure. It appears that vasopressin release from the posterior pituitary in heart failure is largely non-osmotic, although, normally, increased serum osmolality is the major physiological stimulus for its secretion.

Natriuretic peptides A-type (atrial) natriuretic peptide (ANP) and B-type (brain) natriuretic peptide (BNP) are released in response to atrial and ventricular wall stretch and, as their names suggest, serve to maintain sodium homeostasis by enhancing renal sodium and water excretion (Fig. 23.13) [118,119]. These peptides also have haemodynamic effects, dilating arteries and, especially, veins. They also suppress the RAAS and, possibly, the sympathetic nervous system. There is some evidence that natriuretic peptides inhibit arginine vasopressin and endothelin-1 release and the biological actions of these peptides. Consequently, the natriuretic peptides are thought to play an important protective role in heart

failure, countering the actions of the other vasoconstricting and anti-natriuretic neurohumoral systems which are activated in heart failure.

Circulating levels of both ANP and BNP are greatly increased in heart failure. This is the consequence of an increased synthesis and release of these hormones. In humans, BNP is mostly secreted from the ventricles in both healthy individuals and patients with heart failure. ANP secretion, on the other hand, is mainly from the atria in healthy individuals but from both the atria and the ventricles in patients with heart failure. Therefore, it appears that BNP is the only natriuretic peptide that is specific to the ventricles. Pro-BNP, the precursor of BNP, is stored in granules in myocytes. Pro-BNP is activated by a protease to form its biologically active form, BNP, and N-terminal (NT)-proBNP.

BNP levels vary according to sex and age in healthy subjects [120]. Female patients display higher plasma concentrations than male patients with heart failure. Advancing age and declining renal function are associated with increases in BNP levels (Fig. 23.14).

C-type natriuretic peptide (CNP), which was originally believed to be of endothelial origin, may also be produced by the failing heart. A D-type (Dendroaspis) natriuretic peptide has also been described recently though its origins and actions in humans are not yet well defined [121].

As well as having important physiological effects, the various A-type and B-type natriuretic peptides and related fragments can be used to aid the diagnosis of heart failure and to provide prognostic information (see below).

The endothelium, nitric oxide and endothelin-1 The principal product of the endothelium, NO, plays a central role in vascular homeostasis. Endothelial dysfunction, which is characterized by reduced production and action of NO, occurs as a result of ageing, as well as in a number of chronic conditions related to heart failure, such as hypercholesterolaemia, atherosclerosis, as well as in heart failure itself [122]. Endothelium-dependent dilatation of coronary and peripheral resistance vessels is blunted in patients with heart failure. This probably contributes to the impaired reactive hyperaemia in various vascular beds, an impairment in tissue perfusion and, perhaps, reduced muscular function [123]. There has even been speculation that NO might be a key regulator of lung function and that exercise-induced dyspnoea may be related to impaired pulmonary vasodilatation resulting from reduced NO production compared to healthy subjects. Endothelial dysfunction in heart failure may be partly the result of increased oxidative stress (see below).

Although lack of NO is associated with the development of endothelial dysfunction, its overproduction by the inducible isoform of NO synthase (iNOS) may also be detrimental [124]. Increased iNOS activity is thought to lead to increased free radical formation and to depression of myocardial activity. Increased iNOS expression may result from the actions of inflammatory cytokines (see below).

The endothelins are another important product of the endothelium and endothelin-1 is one of the most powerful vasoconstrictor peptides known [125]. It is also a mitogen and generally shares the potentially detrimental properties of angiotensin II and vasopressin in heart failure. Plasma concentrations of endothelin-1 are increased in heart failure, probably because of increased secretion, both by blood vessels and the failing myocardium. The importance of this is, however, uncertain because specific antagonists have not improved outcome in heart failure.

Oxidative stress, xanthine oxidase and uric acid Oxygen free radicals have a number of potentially detrimental actions in heart failure [126,127]. They inactivate NO, depress myocardial contractility and may induce apoptosis [128]. One source of the superoxide anion radical is NADPH oxidase which is activated by angio-tensisn II and aldosterone [129]. Xanthine oxidase may be another source of

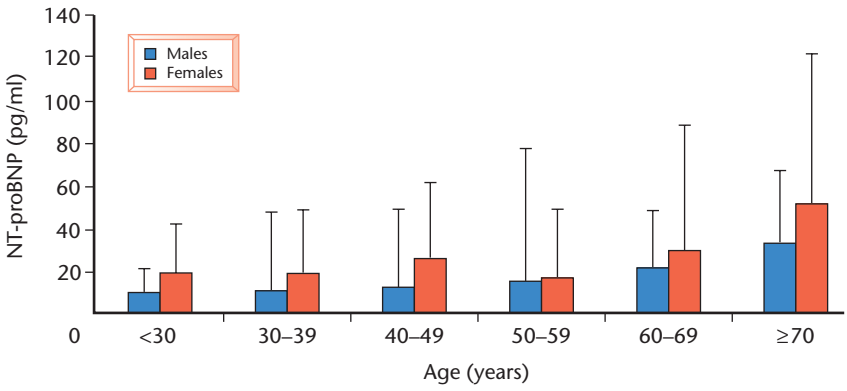

Figure 23.14 NT-proBNP concentrations in normal subjects, according to age and sex. The concentrations are in medians, the bars represent the 95th centile values. Reprinted with permission [178].

increased free oxygen radical load in heart failure and is normally involved in the last step of purine breakdown which yields uric acid. Hyperuricaemia is a consistent finding in patients with heart failure, may reflect impairment of oxidative metabolism and is a predictor of worse outcome [130]. Oxidative stress may be part of the generalized inflammatory state that characterizes at least some patients with heart failure.

Inflammatory responses Inflammation may also be a factor contributing to the progression of heart failure although its role has not been 'confirmed' in the same way as neurohumoral activation, i.e. by the demonstration of improved outcomes with blocking agents [131]. Several cytokines have been studied in detail. Different cell types secrete cytokines for the purpose of altering either their own function (autocrine) or that of adjacent cells (paracrine). Some cytokines also act as circulating hormones (i.e. have an endocrine action). Tumour necrosis factor-α (TNF-α), interleukin-1 and interleukin-6 are thought to be the most important pro-inflammatory cytokines that may be implicated in heart failure progression. Among those, TNF-α has been studied in the greatest detail. It exerts its effects via TNF-α receptors (TNFR), which are expressed by almost all nucleated cells. The origin of cytokine activation in heart failure remains unclear. Pro-inflammatory cytokines may be secreted by mononuclear cells, hypoxic peripheral tissue or even by the myocardium itself. Catecholamines may augment myocardial cytokine production, one of several possible links between neurohumoral activity and inflammation. It has also been hypothesized that increased bowel wall oedema may lead to translocation of bacterial endotoxin or lipopolysaccharide from the gut which may cause pro-inflammatory cytokine production from blood monocytes and possibly other tissues [132].

Plasma TNF-α and TNFR concentrations are increased in some patients with heart failure, especially in those whose disease is severe, and they are independent predictors of poor prognosis. Although TNF-α has several potentially untoward effects that could contribute to the progression of heart failure, studies of TNF antagonists to date have not shown benefit in this syndrome.

Diagnosis: symptoms, signs and investigations

It is symptoms and signs that usually alert the patient (and physician) to the presence of a cardiac disorder. However, neither the symptoms nor signs commonly recognized as suggesting the presence of heart failure are specific for this syndrome. Therefore confirmation of heart failure requires objective tests to confirm that the patient's symptoms and the physical findings are the result of abnormal cardiac function and not of another cause (see below) [133].

Symptoms

Fatigue is a key symptom reported by patients with heart failure. Its origins are not clearly understood but probably include low cardiac output and skeletal muscle abnormalities (see Pathophysiology). Fatigue is very non-specific and is found in the population at large, as well as in many non-cardiovascular disorders.

Dyspnoea or breathlessness is another cardinal symptom of heart failure. Dyspnoea is usually first manifested on exertion and the level of exertion which causes breathlessness is useful in gauging heart failure severity and monitoring the patient's progress. Though it is more specific than fatigue, dyspnoea is still caused by many other disorders such as pulmonary disease, obesity and anaemia which are common in the elderly population and may coexist with heart failure. Even ageing is associated with dyspnoea on exercise. The origin of dyspnoea in heart failure is also probably multifactorial. It may be related to elevated pulmonary pressures, abnormalities in pulmonary compliance, respiratory dysfunction, accentuated respiratory drive, increased airway resistance and even low haemoglobin [134]. It is notable that there is a poor correlation between dyspnoea and left ventricular function at rest [135].

Orthopnoea is defined as dyspnoea which occurs in the recumbent position and is usually relieved by sitting upright or by the addition of pillows. In extreme cases, the patient is unable to lie down and may spend the night in the sitting position. Orthopnoea results from the return of venous blood which has pooled in the lower extremities while the patient is ambulatory. The failing heart may be unable to cope with return of this blood from the legs on adoption of the recumbent position and pulmonary oedema may occur.

Paroxysmal noctural dyspnoea (PND) is characterized by acute episodes of suffocation usually occurring while recumbent at night. It has the same pathogenesis as orthopnoea. PND may manifest as cough or wheezing, possibly because increased pressure in the bronchial arteries (and resultant increase in their diameter), along with interstitial pulmonary oedema, leads to increased airways resistance. Sometimes these patients are described as having 'cardiac asthma', which must be differentiated from primary asthma and pulmonary causes of wheezing.

Both orthopnoea and PND are relatively specific for heart failure but are usually only encountered in untreated or advanced heart failure and are uncommon in most patients with mild to moderate heart failure taking diuretics [136]. Treated patients developing either symptom should be advised to report this to their physician/nurse as soon as possible. PND requires urgent treatment.

Cerebral symptoms such as confusion, disorientation, sleep or mood disturbances may be observed in advanced heart failure, particularly in the presence of hyponatraemia. These symptoms can be the first manifestation of heart failure in elderly patients. Sometimes sleep disturbances can be associated with ventilatory abnormalities (obstructive sleep apnoea and Cheyne–Stokes respiration) which occur in advanced heart failure and may be reported by the patient's spouse or partner [137,138].

Nausea and abdominal discomfort may occur when there is marked congestion of the liver and gastrointestinal tract. Congestion of the liver and stretching of its capsule may cause pain in the right upper quadrant of the abdomen.

Oliguria is usually present in advanced heart failure as the result of reduced renal perfusion and avid sodium and water retention.

Functional classification

The New York Heart Association (NYHA) functional classification is the most commonly used means of describing the degree to which a patient is restricted in ordinary activities by the typical symptoms of heart failure [139]. Although it is subjective and has a large interobserver variation, the NYHA classification is used world-wide and has been employed as an entry criterion in almost all important clinical trials in heart failure.

- **Class I:** no limitation—ordinary physical activity does not cause undue fatigue, dyspnoea or palpitations.
- **Class II:** slight limitation of physical activity—patient is comfortable at rest but ordinary activity results in fatigue, palpitations, or dyspnoea. These patients are sometimes described as having mild heart failure (nomenclature referring to their symptoms and not cardiac function or prognosis).
- **Class III:** marked limitation of physical activity—patient comfortable at rest but less than ordinary activity results in symptoms. These patients are sometimes described as having moderate heart failure.
- **Class IV:** inability to carry out any physical activity without discomfort—symptoms of heart failure are present even at rest with increased discomfort with any physical activity. These patients are sometimes described as having severe heart failure.

At the individual patient level it is useful to measure functional limitation (and monitor progress) by way of the distance the patient can walk on the level, the number of steps that can be climbed and ordinary activities that can (or cannot) be carried out, e.g. washing, bed-making, vacuum-cleaning, sweeping, shopping, etc. Because there is a poor correlation between symptoms and cardiac dysfunction, it must be emphasized that mild symptoms do not imply minor cardiac dysfunction or a good prognosis. Patients with very different ejection fractions can experience quite similar degrees of functional limitation and treatment with a diuretic may lead to a marked improvement in symptoms without having any effect on cardiac function [140].

The Killip classification may be used to assess the severity of heart failure in the acute context, e.g. in myocardial infarction [141].

Quality of life

'Quality of life' assessments have been used to assess the impact of heart failure on patient well-being in a more complete way than just measuring specific symptoms or functional limitations. Various dimensions of quality of life including those reflecting physical, social, sexual and professional activities can be measured, along with indices of mood, emotions and mental health. Various questionnaires or visual scales have been proposed but none has been universally accepted. One of the most widely used is the Minnesota Living with Heart Failure questionnaire which includes a list of 21 questions, each answered on a scale of 0 to –5 [142]. These measures are more often used in clinical trials than in clinical practice.

Signs

Clinical examination, including observation of the patient and palpation and auscultation of the heart, is essential in the assessment of an individual with suspected heart failure. Percussion of the heart is seldom performed although it can provide an accurate assessment of cardiac size; percussion of the lung fields is valuable [136].

General examination

Patients with advanced heart failure are sometimes severely dyspnoeic even when speaking and have peripheral oedema (see below), cachexia or cyanosis. Conversely, the general appearance of a patient presenting with mild to moderate heart failure is often normal.

Systolic blood pressure is usually reduced in heart failure because of left ventricular systolic dysfunction,

especially if severe or treated. Sometimes blood pressure may be elevated, especially if hypertension is the cause of heart failure and particularly if systolic function is preserved. Blood pressure can be markedly increased during an episode of acute pulmonary oedema. It is important to distinguish between low blood pressure (hypotension) which may be unimportant per se and hypoperfusion of the vital organs, i.e. where there are symptoms such as dizziness or confusion, renal dysfunction or myocardial ischaemia, which is always important and requires treatment.

Sinus tachycardia is a non-specific sign which is caused by increased sympathetic activity and can be absent in the presence of conduction disturbances (or if the patient is taking β-adrenergic blocker therapy). Some patients may also have tachycardia because of atrial fibrillation (or another supraventricular arrhythmia) or, rarely, ventricular tachycardia.

Peripheral vasoconstriction with coldness, cyanosis and pallor of extremities is also caused by increased sympathetic activity.

Peripheral oedema is a key manifestation of heart failure but is non-specific and usually absent in patients already treated with diuretics (Fig. 23.11). It is related to extracellular volume expansion, is accompanied (and even preceded) by weight gain and is progressive. It is usually bilateral and symmetrical, painless, pitting and occurs first in the lower extremities in ambulatory patients, namely the feet and the ankles. In bedridden patients, oedema may instead be found over the sacrum and scrotum. Even oedema to mid-calf may reflect an increase of two or more litres in extracellular fluid volume. Long-standing leg oedema may be associated with indurated and pigmented skin. If untreated, oedema may become generalized (anasarca), with the development of hepatic congestion, ascites and hydrothorax (pleural effusions—see below). At this stage there is usually clear jugular venous distension (Fig. 23.11—see below). Generalized oedema is often accompanied by resistance to oral diuretic treatment. Patients should be warned to be observant for progressive increases in weight, accompanied by ankle swelling and, especially, increasing dyspnoea. Daily weight monitoring is important to identify sodium and water retention episodes and initiate early therapy. A prompt (and often temporary) increase in diuretic therapy may resolve worsening congestion in this situation.

Hepatomegaly is an important but uncommon sign in patients with heart failure. The liver is usually tender except in long-standing heart failure and can pulsate during systole in the presence of tricuspid regurgitation. Firm and continuous compression of the right upper abdominal quadrant for 30 seconds to 1 minute may exhibit hepato-jugular reflux, i.e. an increase in jugular distension that is sustained during and after compression (see Jugular venous distension, below). Examination should be made on a patient lying comfortably with their head resting on a pillow.

Cardiac signs

Jugular venous distension, detected by inspection of the internal jugular veins, may identify an elevated right atrial pressure and by inference (and in the absence of tricuspid and pulmonary valve disease) left atrial pressure (Fig. 23.11). However, estimates of jugular venous pressure by physical examination correlate poorly with invasive measurement of right atrial pressure and interobserver reproducibility is low among non-specialists [143–145]. Giant 'V waves' indicate the presence of tricuspid incompetence.

A third heart sound is usually only heard when there is left ventricular dilatation and systolic dysfunction, but interobserver agreement on this sign is low. A third heart sound is more common in severe heart failure and is associated with poor prognosis [146].

A systolic murmur as because of mitral or tricuspid regurgitation can be present, even in the absence of primary valve disease, when the left or right ventricle is markedly enlarged, leading to a dilatation of the mitral or the tricuspid annulus. In the latter case, the tricuspid murmur is selectively increased in loudness following inspiration (Carvallo's sign). The degree of mitral regurgitation can be dynamic and increase on exertion.

Lung examination

Pulmonary crackles (crepitations or rales) result from the transudation of fluid from the intravascular space into the alveoli. The presence of crackles at the lung bases is suggestive of pulmonary congestion but the positive predictive value of this sign is low and the interobserver variability is high [143]. Moreover, the origin of crackles can be difficult to assess in smokers who may also have chronic pulmonary disease (or in patients at risk of pulmonary disease for some other reason). In acute pulmonary oedema, bubbling crackles may be accompanied by expectoration of frothy sputum which is blood stained. Patients with long-standing heart failure may become resistant to developing pulmonary oedema and only do so at very high left atrial pressures. Pleural effusions can

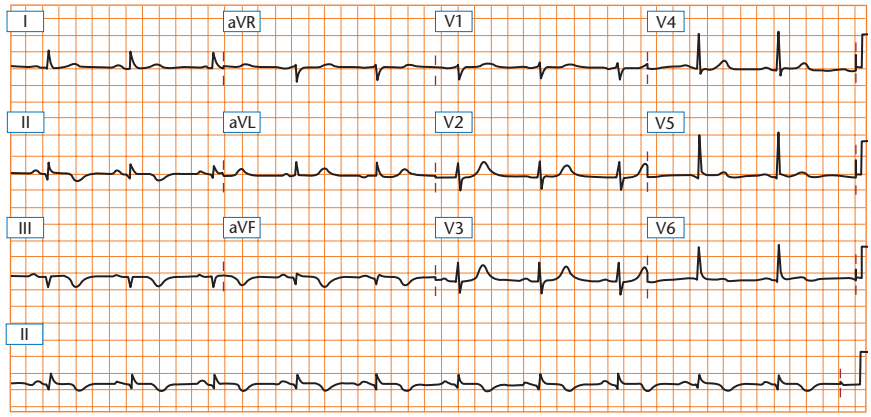

Figure 23.15 Twelve-lead ECG depicting an established transmural inferior myocardial infarction—there are Q-waves and T-wave inversion seen in leads II, III, and aVF.

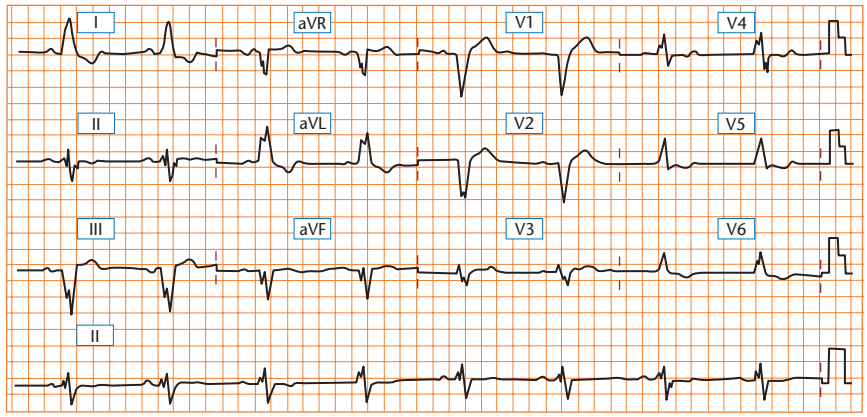

Figure 23.16 Twelve-lead electrocardiogram depicting left bundle branch block (LBBB).

also be detected in patients with heart failure; they are normally bilateral and usually associated with marked dyspnoea and generalized congestion.

Overall, the presence of several of the aforementioned symptoms and signs, particularly in the context of a history of previous cardiac disease, is suggestive of heart failure, if not its precise cause. The declining skill of physicians in clinical examination, the lack of sensitivity and specificity of most signs (and the large inter-observer variability in their detection) and the subjective nature of clinical assessment highlight the need for objective assessment of cardiac function. This objective assessment is also essential for diagnosis of the cause of heart failure and, therefore, treatment tailored to aetiology.

Simple investigations

Electrocardiogram

A resting 12-lead ECG is one of the most useful investigations in a patient with suspected heart failure and is recommended as a first-line diagnostic test in the European Society of Cardiology (ESC) Guidelines [133]. The ECG provides diagnostic and prognostic information and helps in choosing treatment. ECG changes are frequent in heart failure and a normal ECG virtually excludes left ventricular systolic dysfunction [147]. Various abnormalities may be present, such as abnormal Q waves (Fig. 23.15), left bundle branch block (Fig. 23.16) and other conduction disturbances, left atrial or left ventricular hypertrophy (Fig. 23.17), atrial or ventricular arrhythmias may suggest a specific aetiology or precipitating factor. Some abnormalities provide prognostic information and help in choosing treatment, e.g. bundle branch block is predictive of a worse prognosis in patients with left ventricular systolic dysfunction and may also identify patients who benefit from a specific treatment (cardiac resynchronization therapy). The same is true of atrial fibrillation where there may be an indication for warfarin.

Chest X-ray

The chest X-ray (or radiograph) is also recommended as a first-line investigation. It may identify a non-cardiac

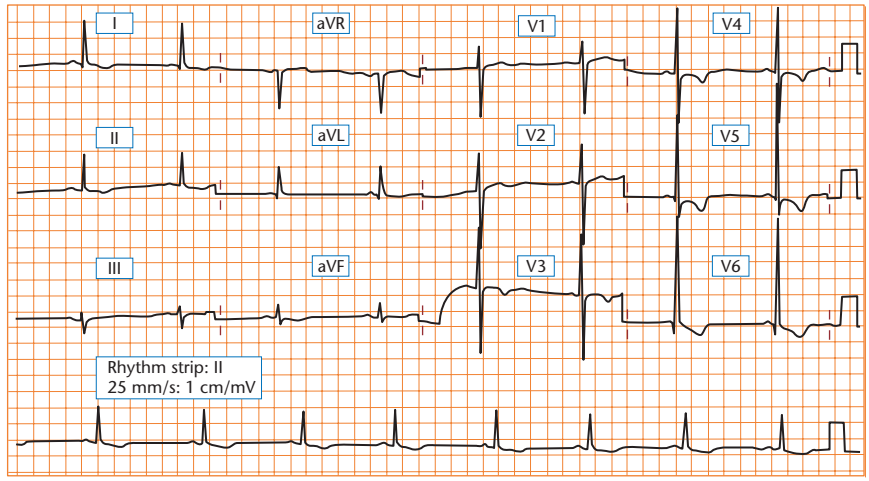

Figure 23.17 Twelve-lead electrocardiogram depicting left ventricular hypertrophy.

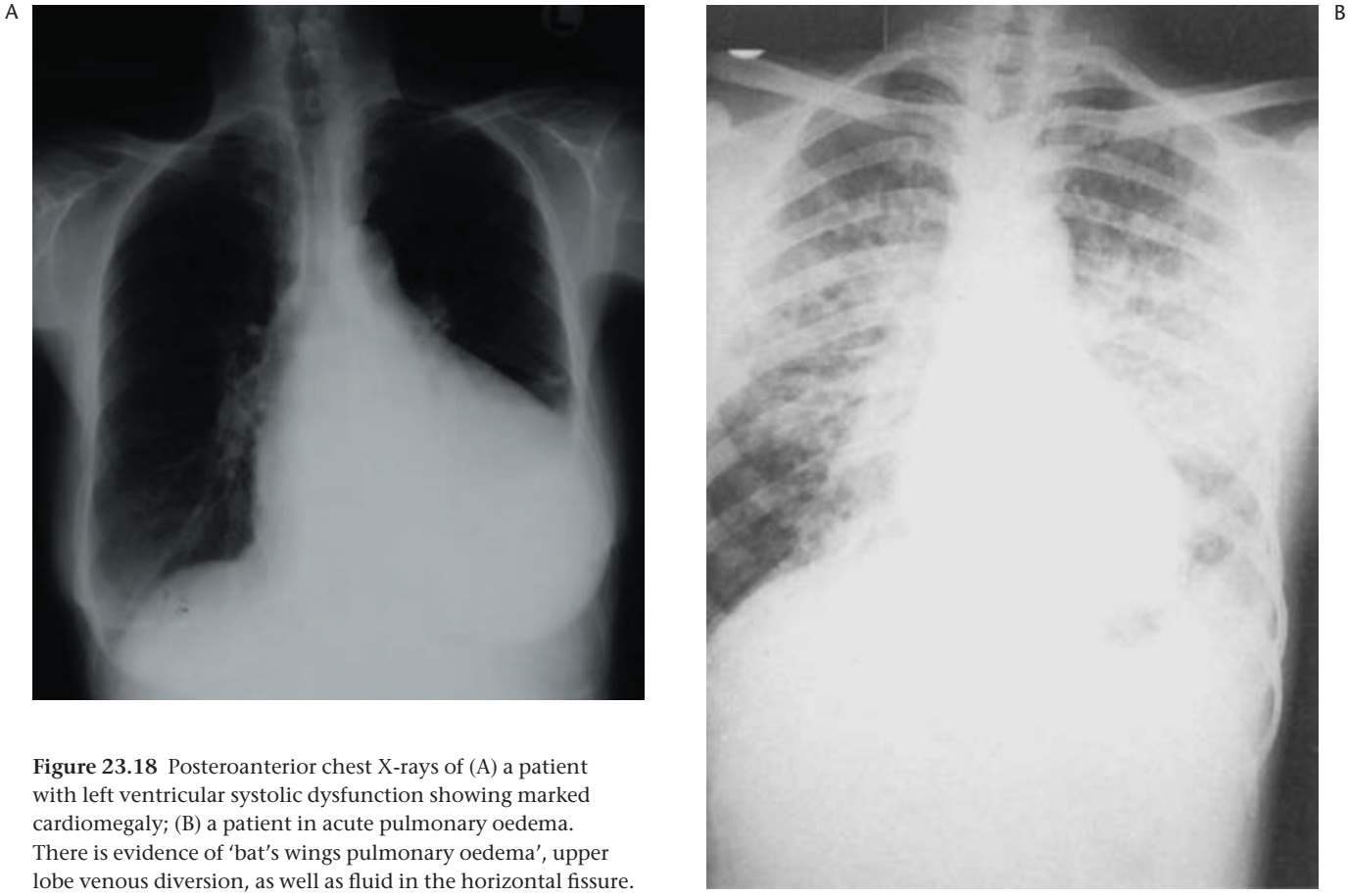

Figure 23.18 Posteroanterior chest X-rays of (A) a patient with left ventricular systolic dysfunction showing marked cardiomegaly; (B) a patient in acute pulmonary oedema. There is evidence of 'bat's wings pulmonary oedema', upper lobe venous diversion, as well as fluid in the horizontal fissure.

cause for the patient's symptoms. It also provides information on the size and shape of the cardiac silhouette and the state of the pulmonary vasculature [148]. This information is, however, of limited value [149]. The absence of cardiomegaly (Fig. 23.18) does not exclude valve disease or left ventricular systolic dysfunction (heart size is more often normal in patients with left ventricular diastolic dysfunction and in acute compared to chronic heart failure). Even if cardiomegaly is present (Fig. 23.18), the chest X-ray does not identify the cause

of cardiac enlargement. The relationship between central haemodynamic and pulmonary vascular radiological abnormalities is also variable and some patients with long-standing severe heart failure may not show pulmonary venous congestion or oedema (Fig. 23.18) despite a very high pulmonary capillary pressure [150].

Haematology and biochemistry

Several laboratory investigations are recommended in the ESC guidelines as part of the routine diagnostic evaluation of patients with suspected heart failure: complete blood count, electrolytes, glucose, urea, creatinine, hepatic enzymes and urinalysis. Myocardial biomarkers such as troponin T or I are important during an acute episode to rule out myocardial infarction. Other tests including serum uric acid, C-reactive protein and thyroid stimulating hormone are optional. It is important to repeat some of these tests during follow-up and after the initiation of certain treatments (or dose changes), e.g. urea, creatinine and potassium.

Electrolyte disturbances are uncommon in untreated mild to moderate heart failure.

Hyponatraemia is sometimes found in severe heart failure and its cause is complex and probably multifactorial. Impaired free water excretion, sodium restriction and diuretic therapy (especially thiazide diuretic treatment or excessive use of loop diuretics) are thought to be important. Hyponatraemia may identify patients with a particularly activated RAAS [113].

Potassium concentration is usually normal but may be reduced by the use of kaliuretic agents such as loop diuretics, or increased in patients with end-stage heart failure with markedly reduced glomerular filtration rate, particularly in the presence of concomitant renal disease, treatment with an inhibitor of the RAAS (e.g. some combination of an ACE inhibitor, angiotensin II receptor blocker or spironolactone) [151]. Nephrotoxic drugs such as NSAIDs may also precipitate hyperkalaemia.

Elevation of creatinine and urea is common in treated heart failure, especially if severe. A significant reduction in glomerular filtration rate may be present despite a normal urea and creatinine, especially in patients with reduced muscle mass. Several causes are recognized: (1) primary renal disease particularly renal artery stenosis, (2) reduced glomerular filtration rate in advanced heart failure, (3) excessive treatment with diuretics alone or in combination with inhibitors of the RAAS (e.g. some combination of an ACE inhibitor, angiotensin II receptor blocker or spironolactone), and (4) ageing.

Impaired renal function and worsening renal function are associated with a poor outcome in chronic heart failure though, paradoxically, drugs which improve prognosis, particularly inhibitors of the RAAS, may cause some deterioration in renal function (although this is usually mild).

Elevation of liver enzymes, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and of serum bilirubin, is often observed in heart failure. These changes may be caused by reduced hepatic blood flow as much as by liver congestion [152].

Anaemia may be the cause or consequence of heart failure. It is common, especially in advanced heart failure, and is associated with a worse prognosis.

Urinalysis is important for the detection of proteinuria or glycosuria, indications of underlying renal disease and diabetes mellitus, respectively.

Thyroid function tests are indicated if either hyper- or hypothyroidism is suspected.

Natriuretic peptides

The use of plasma natriuretic peptides as a tool for the diagnosis of heart failure has developed in recent years, particularly in primary care and emergency units (Fig. 23.19) [153]. Both BNP and N-terminal pro-BNP are available as commercial assays. In clinical practice, both

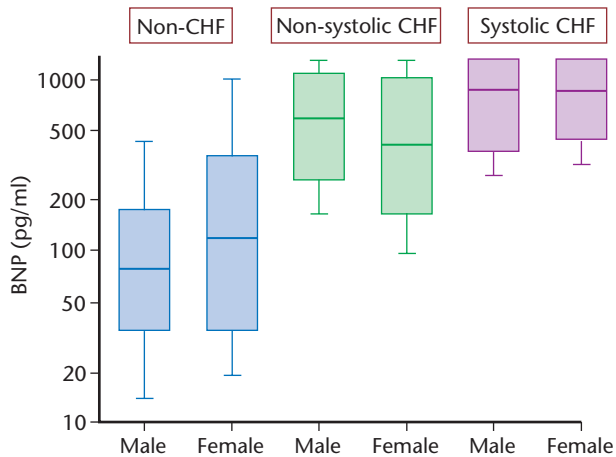

Figure 23.19 Box plots showing median levels of B-type natriuretic peptide (BNP) measured in men and women over 70 years of age with dyspnoea not caused by heart failure, and those with an adjudicated final diagnosis of heart failure, subdivided into those with systolic and those with non-systolic congestive heart failure. Reprinted with permission [156].

are used as 'rule out' tests, i.e. a normal concentration of either peptide in an untreated patient means that it is very unlikely that heart failure is present [154]. Conversely, an elevated concentration identifies a patient who merits comprehensive cardiac examination including echocardiography. Natriuretic peptides may, therefore, offer a cost-effective means of ensuring the efficient use of echocardiography. One important caveat is that prior treatment may reduce natriuretic peptide concentrations to within the normal range.

Age and female gender both influence the plasma concentration of natriuretic peptides and must be considered when defining 'normal' cut-off values which are also assay-specific (Fig. 23.14) [155]. Plasma levels are also increased in other conditions including renal dysfunction, pulmonary embolism, left ventricular hypertrophy, acute ischaemia and hypertension. Because these various cardiac and non-cardiac disorders lead to a moderate increase in plasma concentrations of natriuretic peptides, a 'grey zone' exists and is the reason why natriuretic peptides are used as a 'rule out' (rather than a 'rule in') test.

In heart failure with preserved ejection fraction, plasma levels of BNP, although higher than in patients without heart failure, are significantly lower than in patients with left ventricular systolic dysfunction (Fig. 23.19) [156]. In a general population, the ability of plasma natriuretic peptides to detect left ventricular hypertrophy appears limited [157]. Patients with relaxation abnormalities and mild symptoms or who are asymptomatic may have normal levels of natriuretic peptides. Thus low levels cannot be used to rule out diagnosis of diastolic dysfunction [158]. Among patients with heart failure and preserved ejection fraction, those with definite diastolic dysfunction seem to have higher natriuretic peptide concentrations [159].

Doppler echocardiography

Transthoracic Doppler echocardiography (or ultrasound) is recognized by the ESC guidelines as the most important investigation for the patient with suspected heart failure. Echocardiography is a widely available, rapid, non-invasive and safe technique which provides extensive information on chamber dimensions, wall thickness and measures of systolic and diastolic function.

Determination of the LVEF is a key measure of left ventricular systolic function. Systolic function is usually considered to be reduced when the LVEF is < 0.40 and 'preserved' if > 0.50. This clearly leaves a 'grey area' in the range 0.40–0.50. Furthermore, LVEF is a crude method for the evaluation of systolic function and is dependent not only on the intrinsic inotropic state of the myocardium, but also on the loading conditions of the heart.

The most widely recommended approach to the accurate measurement of LVEF is the modified Simpson's method, using apical biplane summation of discs (Fig. 23.20) [160]. It is, however, dependent on reliable endocardial detection. Other methods are less accurate, particularly in the presence of regional hypokinesia or akinesia. Other measures are, however, used including fractional shortening, sphericity index and left ventricular wall motion index.

Identification of diastolic dysfunction is even more difficult and requires evidence of abnormal left ventricular

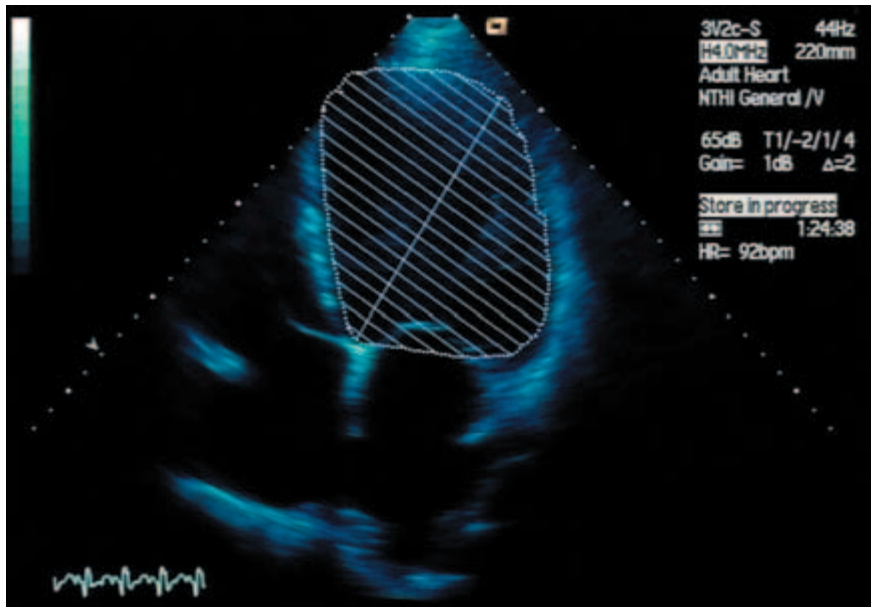

Figure 23.20 Measurement of ejection fraction using Simpson's biplane method. Only the apical four-chamber view at end-diastole is shown here. This young man has a dilated cardiomyopathy, with a left ventricular end-diastolic diameter of 9.7 cm.

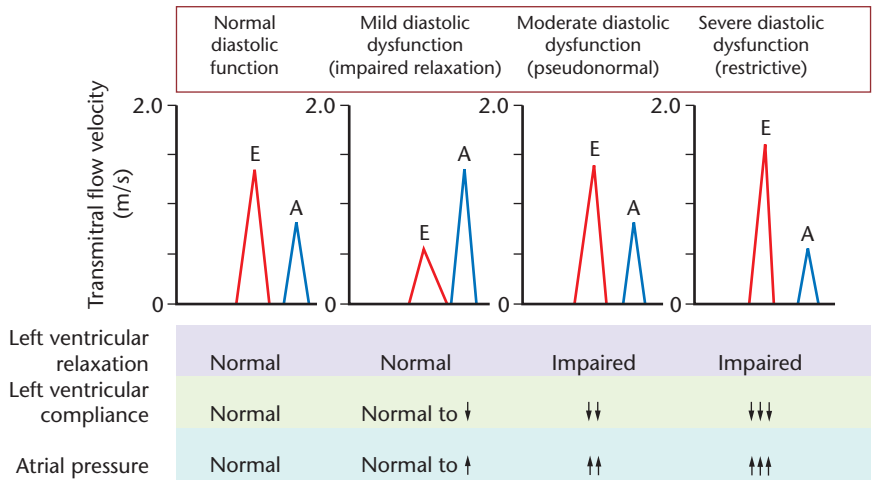

Figure 23.21 Patterns of left ventricular diastolic filling as shown by standard Doppler echocardiography. The abnormal relaxation pattern (mild diastolic dysfunction) is brought on by abnormally slow left ventricular relaxation, a reduced velocity of early filling (E wave), an increase in the velocity associated with atrial contraction (A wave), and a ratio of E to A that is lower than normal. In more advanced heart disease, when left atrial pressure has risen, the E-wave velocity and E : A ratio is similar to that in normal subjects (the pseudonormal pattern). In advanced disease, abnormalities in left ventricular compliance may supervene (called the restrictive pattern because it was originally described in patients with restrictive cardiomyopathy). Reprinted with permission [165].

relaxation or diastolic distensibility or diastolic stiffness, all of which are difficult to assess in daily practice [161–165].

The presence of morphological changes such as left atrial dilatation or left ventricular hypertrophy, together with measures of left ventricular diastolic filling (including transmitral and pulmonary venous flow velocities with pulsed Doppler echocardiography or mitral annulus velocities with tissue Doppler imaging), frequently help demonstrate diastolic dysfunction.

Three abnormal left ventricular filling patterns have been described (Fig. 23.21) [166]:

- Impaired relaxation with a reduction in peak transmitral E-wave velocity, coupled with an increase in A-wave velocity, resulting in a decrease in the E : A ratio to < 1.
- A restrictive filling pattern, with a short isovolumetric relaxation time, an increased E velocity and increased E : A ratio, considered the hallmark of severe diastolic dysfunction.
- Pseudonormal filling pattern, when atrial pressure rises in more advanced heart failure, the E-wave velocity and E : A ratio may be similar to those in normal subjects.

These patterns are however influenced by intrinsic cardiac properties, loading conditions and are age dependent. However, they also have some prognostic importance: the restrictive pattern in particular, with a short transmitral E-deceleration time and increased E : A flow velocity ratio, is associated with poor outcome. It is important to appreciate that the terms heart failure with preserved ejection fraction and heart failure as a result of diastolic dysfunction ('diastolic heart failure') describe overlapping but not identical syndromes (Fig. 23.22).

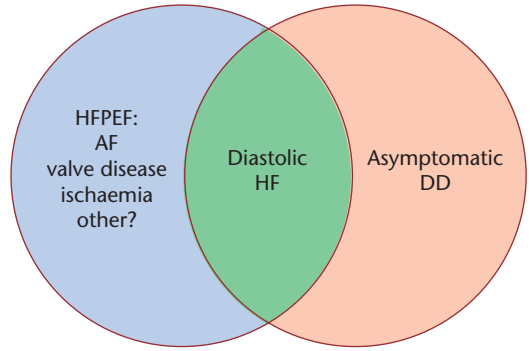

Figure 23.22 The overlapping syndromes of heart failure with preserved election fraction (HFPEF) and heart failure due to diastolic dysfunction (DD). Atrial fibrillation (AF); heart failure (HF).

Valve function can also be assessed by Doppler echocardiography, e.g. semi-quantitative evaluation of mitral regurgitation is possible (Fig. 23.12), as is calculation of pulmonary artery systolic pressure (based on the velocity of tricuspid regurgitation).

Doppler echocardiography may also be repeated during the follow-up of patients receiving treatment, to assess changes in cardiac structure and function.

Despite the value of Doppler echocardiography, surveys in Europe commonly show that cardiac function is only evaluated in approximately 50% of such patients [167]. The recent development of portable echocardiography machines, together with the potential of remote analysis of echocardiograms, may help improve this situation.

Other new ultrasound techniques, such as three-dimensional echocardiography, are still being evaluated clinically.

Stress echocardiography

Dobutamine (or exercise) stress echocardiography may be used to detect ischaemia as a cause of cardiac dysfunction and to assess myocardial viability in the presence of marked hypokinesia or akinesia. It may be useful in identifying myocardial stunning and hibernating myocardium.

Other imaging techniques

Radionuclide angiography

This technique provides information on left and right ventricular volumes and ejection fraction but is not widely available. It does not provide information on valve function but is generally more accurate than echocardiography for measuring right ventricular function. The reproducibility of this technique is also better than that of echocardiography.

Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) allows comprehensive and reproducible analysis of cardiac anatomy and function, including cardiac volumes and mass, global and regional function and wall thickening [168]. When combined with contrast agents such as gadolinium, CMR also provides information on myocardial perfusion at rest (Fig. 23.23) or following pharmacological intervention. CMR is now the gold standard for the assessment of mass volumes and wall motion but it is expensive and is not as widely available as echocardiography.

Other functional tests

Exercise testing

Treadmill or bicycle testing can be used to determine the maximum level of exercise which can be achieved. Recommendations on testing have been published by the ESC [169]. Small increments in workload are recommended. As well as exercise duration, gas exchange is often measured. Peak oxygen uptake ($V\text{O}_2$) and the anaerobic threshold are useful indicators of the patient's capacity to exercise. There is a poor correlation between exercise capacity and ejection fraction. Peak $V\text{O}_2$ has been used also for prognostication and selection of patients for heart transplantation (see below). A peak $V\text{O}_2$ > 14 ml/kg/min is associated with a relatively good prognosis unlikely to be improved by heart transplantation. Patients with a $V\text{O}_2$ max of less than 14 ml/kg/min have been shown to have a better survival if transplanted than if treated medically. This latter threshold is part of the criteria used for listing patients for heart transplanta-

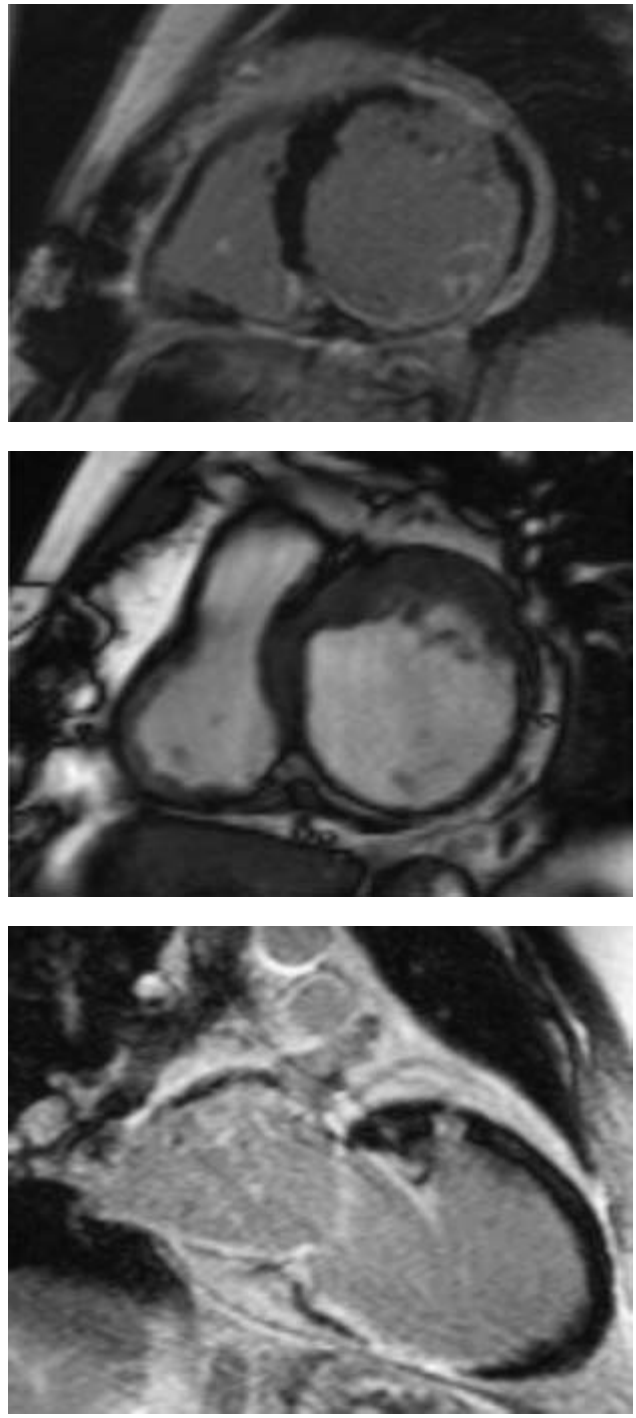

Figure 23.23 (A) Short-axis contrast-enhanced CMR demonstrating extensive inferior myocardial infarction indicated by late gadolinium enhancement. There is also a smaller anterior infarct. (B) Non-contrast still end-diastolic cine image showing marked wall thinning in the inferior wall corresponding with the area of infarction. There is marked ventricular dilatation and systolic dysfunction. (C) Vertical long-axis view of the same patient demonstrating both a large inferior infarct and a much smaller apical anterior infarct. (Courtesy of Dr Patrick Mark, Western Infirmary, Glasgow.)

tion. It should be noted that the survival studies on which this threshold is based were carried out before the advent of modern treatments for heart failure such as beta-blockers and cardiac resynchronization therapy.

Pulmonary function testing

Pulmonary function testing is indicated in patients in whom the origin of dyspnoea is unclear, to determine whether it is of cardiac or pulmonary origin or both. Heart failure itself is associated with abnormalities of pulmonary function. These include reductions in vital capacity, pulmonary diffusion at rest (and on exercise) and pulmonary compliance. Conversely, airway resistance is usually increased.

Invasive investigations

Pulmonary arterial catheterization is usually only used in acute or emergency situations, especially in patients not responding to appropriate medical therapy. This procedure allows close monitoring of haemodynamic changes following medical intervention. It is also indicated in patients with valvular heart disease who are candidates for valve replacement or repair and in the assessment of patients for transplantation.

Coronary angiography is indicated in patients with heart failure and angina or evidence of myocardial ischaemia, if revascularization is being considered. However, the role of revascularization in the treatment of heart failure, including in patients with hibernating myocardium, remains to be determined [170].

Coronary angiography may also be indicated in acute heart failure with shock that is not responding to initial therapy.

Many also believe that coronary angiography is indicated as a diagnostic test in patients with heart failure or left ventricular systolic dysfunction of unknown origin.

Endomyocardial biopsy of the left or the right ventricle is only indicated when a specific myocarditis or a specific myocardial disease is suspected and during the follow-up of patients after cardiac transplantation to detect graft rejection.

Overall, the indication for invasive procedures in heart failure has declined. They are not necessary to establish the presence of heart failure but may be helpful on an individual basis to determine the aetiology and for the monitoring of patients in acute or difficult situations.

Ambulatory ECG monitoring

Ambulatory monitoring is valuable in the assessment of patients with symptoms suggestive of an arrhythmia (e.g. palpitations and syncope) and in monitoring ventricular rate control in patients with atrial fibrillation.

Asymptomatic ventricular premature beats and non-sustained ventricular tachycardia are frequent in heart failure but do not appear to be predictive of sudden death or of selecting treatment to reduce sudden death.

An approach to the diagnosis of a patient with suspected heart failure

The following describes a stepwise approach to the diagnosis of the patient with suspected heart failure (Table 23.3).

Table 23.3 Stepwise approach to the diagnosis of heart failure

Step 1: Diagnosis
Signs and symptoms of heart failure
History of cardiac disease
First-line tests: ECG, X-ray, BNP or NT-proBNP
Documentation of cardiac dysfunction: Doppler echocardiography
Nuclear angiography/Nuclear magnetic resonance

Step 2: Clinical profile
Clinical presentation: acute *de novo*/decompensated/chronic heart failure
Left/right side heart failure
Comorbidities
Age and severity

Step 3: Aetiology
Consider other diagnostic tests (coronary angiography, central haemodynamics, etc.)

Step 4: Precipitating factors
Anaemia
Infection (pulmonary infection)
Tachycardia (atrial fibrillation)
Bradycardia
Pulmonary embolism
Hypertensive crisis
Acute myocardial ischaemia
Poor compliance (diet and/or drugs)
Thyroid disorders
Medications (NSAIDs, cyclooxygenase-2 inhibitors [coxibs], glitazones, class I antiarrhythmics, corticosteroids, tricyclic antidepressants)

Step 5: Prognostic evaluation
Clinical factors
Biological factors
Neurohumoral factors and cytokines
Electrical variables
Imaging variables
Exercise testing
Central hemodynamic indices
Genetic factors

Step 6: Treatment and follow-up

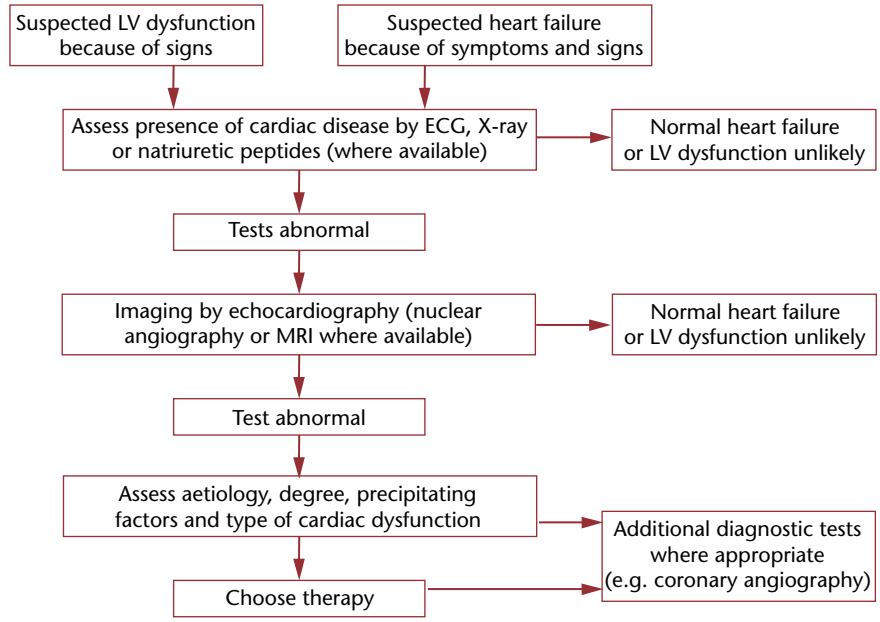

Figure 23.24 Algorithm for the diagnosis of heart failure: task force for the diagnosis and treatment of chronic heart failure of the European Society of Cardiology. Reprinted with permission [133].

Step 1: Establish the presence of heart failure

This requires the presence of signs and symptoms suggestive of heart failure at rest or on exercise and also objective evidence of a cardiac abnormality, preferably by Doppler echocardiography. Doppler echocardiography may not be necessary in previously untreated patients with a normal plasma natriuretic peptide concentration and those patients should be investigated for another cause of their symptoms or signs. Other essential first-line diagnostic tests should be performed, including an ECG, chest X-ray and blood tests. Pulmonary function and exercise testing may help when the diagnosis remains doubtful. The guidelines of the ESC usefully illustrate how these investigations are combined in the patient presenting with suspected heart failure (Fig. 23.24).

Step 2: Evaluation of the patient's clinical status

This step includes:

- The assessment of clinical profile: patients may present with acute new-onset heart failure, e.g. after acute myocardial infarction, acute or subacute decompensation of chronic heart failure or acute or subacute onset of heart failure in a patient with previously asymptomatic cardiac dysfunction. The clinical presentation may be in primary care or to hospital. The patient may have breathlessness, fatigue or both with few clinical signs. Alternatively, the patient may have these symptoms and peripheral oedema or may present as an emergency with frank pulmonary oedema. The clinical profile of patients with preserved systolic function may be different from that of patients with systolic dysfunction: on average, the former patients are older and are more likely to be women. They are also more likely to have hypertension but are less likely to have a third heart sound (Fig. 23.25) [171]. It is important to assess the severity of symptoms, with the Killip and NYHA classifications being the most widely used in the acute and chronic setting, respectively. In acute new-onset heart failure, the patient may be hypotensive if there has been a haemodynamic catastrophe, e.g. rupture of a mitral valve papillary muscle or interventricular septum (Fig. 23.26).
- In advanced heart failure, another system of classification may be useful. This is based on the presence/absence of signs of congestion and adequate/inadequate perfusion. Four categories have been proposed: dry–warm, wet–warm, dry–cold and wet–cold [172]. Wet patients with or without hypoperfusion are at higher risk than dry patients.
- It is also important to identify comorbid factors such as stroke, chronic pulmonary obstructive disease, asthma, diabetes mellitus and renal failure, which can complicate patient management and modify outcome. The proportion of patients presenting with multiple comorbidities increases with age. In the Euro Heart Failure Survey, 9% had had a previous stroke, 10% a previous transient ischaemic attack, 27% were reported to have diabetes mellitus, 12% had dementia, 17% a renal dysfunction and 32% a pulmonary disease [167].

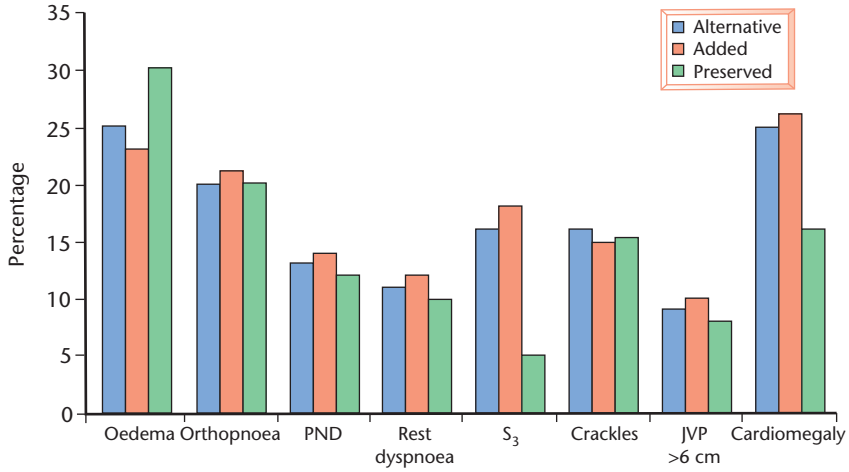

Figure 23.25 Signs, symptoms and radiographic findings in patients with reduced and preserved left ventricular ejection fraction in the CHARM studies (CHARM-alternative, -added, and -preserved). Paroxysmal nocturnal dyspnoea (PND); third heart sound (S3). Reprinted with permission [179].

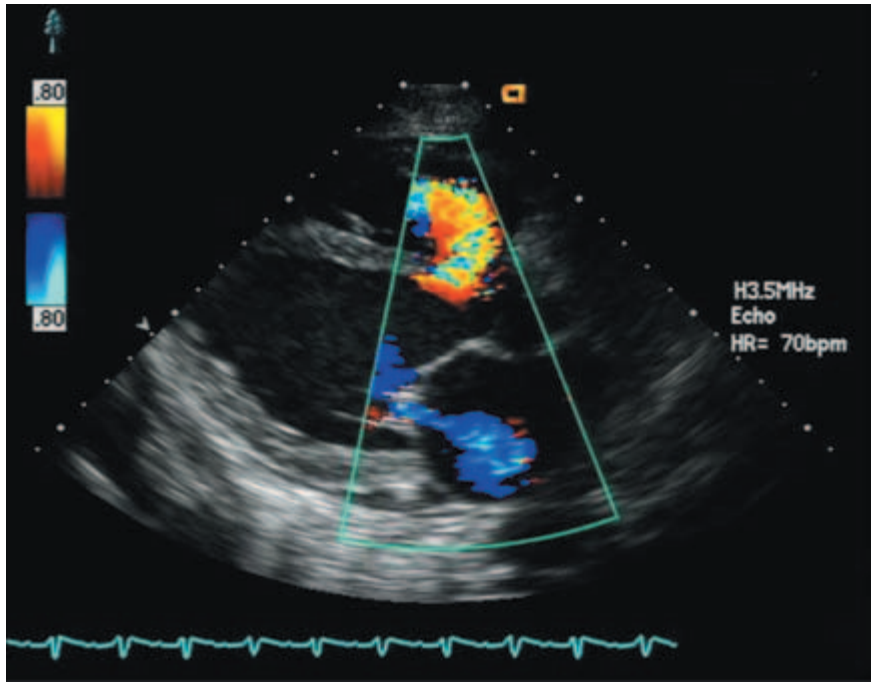

Figure 23.26 Colour flow Doppler of mitral regurgitation and a ventricular septal rupture post-myocardial infarction in the parasternal long-axis view.

Step 3: Identify underlying aetiology

Ischaemic heart disease and hypertension are the commonest causes of heart failure in Western countries and their contribution to heart failure is also rapidly expanding in the developing countries. In the Euro Heart Failure Survey, ischaemic heart disease was the commonest cause of heart failure, 40% of patients having myocardial infarction and 51% a history of angina; 53% of the patients also had hypertension [167]. The extent of investigation to identify the underlying cardiac disease should be decided on an individual basis taking into consideration the patient profile (age, severity of heart failure and comorbidities) and the potential reversibility of cardiac dysfunction (such as valvular heart disease, reversible ischaemia).

Step 4: Identify precipitating factors

It is also important to identify precipitating factors: decompensation of heart failure is frequently associated with comorbid factors which: (1) increase body metabolic requirements such as fever, infection or hyperthyroidism, (2) decrease cardiac output such as rapid tachycardia or marked bradycardia, (3) reduce the oxygen transport capacity (anaemia) or oxygen exchange (pulmonary infection), (4) induce a sudden haemodynamic overload (pulmonary embolism or hypertension crisis) or water

and sodium overload (excessive sodium intake, poor compliance with diet and heart failure medications) or (5) ischaemic episodes (Table 23.3).

Among arrhythmias, a new episode of atrial fibrillation can be particularly harmful because it combines both an increase in ventricular rate (with a risk of myocardial ischaemia and reduced time for diastolic filling) and loss of atrial contraction.

Step 5: Prognostic evaluation

Prognostic assessment in heart failure remains difficult. Indeed the number of clinical, aetiological, comorbid, biological, haemodynamic, structural, functional, electrical and neurohumoral variables independently associated with poor outcome is high and suggests that there is no simple method to assess the risk of death or re-hospitalization in patients with this syndrome (Table 23.4). Most studies have been performed in populations of patients with systolic dysfunction and little is known about prognostic evaluation in patients with preserved systolic function.

The assessment of prognosis has also been conducted differently in acute and in chronic heart failure: in acute heart failure, in-hospital and short-term (3–6 months) mortality or readmission have usually been evaluated whereas in chronic heart failure, long-term (> 1 year) prognosis and re-hospitalization rates have normally been considered.

Furthermore, factors which predispose to overall mortality or pump failure mortality do not necessarily apply to sudden death.

An additional problem is that extrapolation of risk assessment based on a small series of selected patients exposed to conventional therapy (including low rate of prescription of ACE inhibitors and beta-blockers) to the overall current heart failure population is difficult. The changing background therapy of heart failure also makes it difficult to provide simple prognostic algorithms. For instance, beta-blockers have more influence on the remodelling process than exercise capacity, so that the relative role of these two independent predictors of mortality may be different in patients treated with a beta-blocker and those not so treated.

The temporal role of the various prognostic factors can be variable: the time course of the activation of the neurohumoral systems after myocardial injury is different. Therefore, the relative weight of elevated plasma levels of neurohumoral factors may be different in the short term compared to the longer term. Moreover, little is known about the relation between the change in plasma concentrations of biochemical markers as a result of treatment and long-term prognosis.

Table 23.4 Prognostic factors

Clinical factors
Age, ethnicity, NYHA class
Signs of congestion, jugular vein pressure, third heart sound, low systolic blood pressure
Diabetes mellitus, renal dysfunction, depression
Ischaemic aetiology
Biochemical factors
Serum sodium
Serum creatinine/creatinine clearance
Haemoglobin
Neurohormones and cytokines
Plasma renin activity
Angiotensin II
Aldosterone
Noradrenaline
Endothelin-1
Adrenomedullin
B type natriuretic peptide/N-terminal pro-BNP
Tumour necrosis factor-α
Vasopressin
Electrical variables
QRS width
Left ventricular hypertrophy
Atrial fibrillation
Complex ventricular arrhythmia
Heart rate variability
Imaging variables
Left ventricular internal dimensions and fractional shortening
Cardiothoracic ration X-ray (normal < 0.55)
Wall motion index (various*)
Ejection fraction (normal > 0.40)
Restrictive filling pattern/short deceleration time (various*)
Right ventricular function (various*)
Exercise test/haemodynamic variables (rest/exercise)
Vo_2 max/peak (normal > 20 ml/kg/min†)
6-minute walk distance (normal > 600 m†)
Cardiac index (normal > 2.5 l/min/m^2)
Left ventricular end-diastolic pressure/pulmonary artery wedge pressure (normal < 12 mmHg)

*Various measures/classifications can be used and no single threshold for normal/abnormal can be given; †functional capacity varies greatly according to prior fitness, age and sex; values given are a guideline for older (> 65 years) adults.

The multivariable analyses reported so far usually include only a limited number of parameters and these may lose their predictive power in more comprehensive analyses.

Finally, some factors can provide prognostic information in advanced heart failure but not in mild to moderate heart failure: severely reduced functional capacity,

measured by Vo_2, is a recognized index for the selection of patients who might benefit from heart transplantation whereas elevated, non-reversible, pulmonary resistance is an index of poor outcome after heart transplantation or implantation of a ventricular assist device.

Step 6: Treatment and management

Full diagnosis is a prerequisite for optimal treatment [133]. Often, however, a diuretic may be required before a full diagnostic work-up is completed. The further treatment of heart failure depends on the underlying aetiology (e.g. valve replacement for aortic stenosis), functional status (e.g. spironolactone is severely symptomatic patients), co-morbidity (e.g. warfarin if atrial fibrillation) and the results of investigations (e.g. cardiac resynchronization therapy if a broad QRS on the ECG). Each of these may contraindicate treatments as well as indicate them (e.g. caution with ACE inhibitors in aortic stenosis, beta-blockers if atrioventricular block, spironolactone if renal dysfunction etc). The treatment of heart failure is discussed in detail in the next chapter.

Personal perspective

Though we have learnt much about heart failure there is a lot we still do not know. The epidemiology of heart failure outside Europe and North America has not been studied to any great extent. We know much less about the natural history of heart failure with preserved ejection fraction than that with reduced ejection fraction. Similarly, we know very little about the pathophysiology of the former compared to the latter. Understanding of the entity of heart failure with preserved ejection fraction is greatly hampered by the lack of simple, agreed and universally applicable diagnostic criteria. Surprisingly, although coronary artery disease is probably the commonest cause of heart failure in most developed countries, the role of myocardial ischaemia and other manifestations of coronary artery stenosis and occlusion in the pathophysiology, natural history and treatment of heart failure is remarkably poorly understood. The role of new investigative approaches such as cardiac magnetic resonance imaging may provide valuable, additional, diagnostic and prognostic information and this should be clarified over the next few years.

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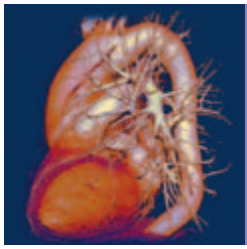

24 Management of Chronic Heart Failure

Karl Swedberg, Bert Andersson, Christophe Leclercq and Marko Turina

Summary

Chronic heart failure (CHF) is common, disabling, dangerous and costly. However, during the last 10–15 years, management of CHF has improved dramatically, with evidence-based therapy being able to reduce both morbidity and mortality, improving symptoms as well as cost-effectiveness. The introduction of neurohormonal blockers has resulted in a marked reduction in morbidity and mortality together with improved quality of life. In this chapter we have outlined the rationale for managing patients with CHF or left ventricular dysfunction after a recent myocardial infarction including recommendations on non-pharmacological therapies such as pacemakers and surgery.

- ACE inhibitor use is discussed both as preventive medication as well as the reason for, and the initiation of, ACE inhibitors in CHF patients.
- Angiotensin receptor blockers (ARBs) have emerged as valuable options based on recent studies. Treatment with an ARB has now been documented to be effective in patients intolerant to an ACE inhibitor beta-blocker and also to have additive effects on top of these agents.
- Beta-blockers are important in addition to renin–angiotensin system inhibitors in order to counteract the increased adrenergic activity in CHF. The importance of initiating beta-blocker therapy with a low dose is emphasized.
- The next neurohormonal blocker to consider is an aldosterone antagonist. These agents have demonstrated beneficial effects on mortality both in severe CHF and in left ventricular dysfunction after a recent myocardial infarction.
- The rationale for the use of a device for CRT is outlined in detail. ICD use is only briefly discussed as these devices are discussed elsewhere in this textbook.
- Surgical options are presented including indications for revascularization, correction of mitral incompetence, surgical remodelling and heart transplantation. Emerging technologies (e.g. cell transplantation) are also discussed.
- In order to accomplish optimal effects of therapeutic options, nurse-monitored out-patient clinics are recommended.

Management in addition to pharmacological or device therapy

All cardiac disorders may eventually lead to chronic heart failure (CHF). Further, CHF is a condition with profound effects on the human body, and as such has consequences on most aspects of the patient's daily life and other concomitant diseases. The outstanding benefits of drug therapy in CHF cannot be accomplished without a more holistic approach to the care of patients. It is well known that better overall treatment is obtained if a multidisciplinary approach is applied, such as non-pharmacological management and consultation with specialists in different fields as described below [1,2].

Education

In order to obtain an adequate treatment effect, it is mandatory to achieve patient cooperation. It has been shown that therapeutic failures, such as readmittance to hospital,

are often caused by poor patient compliance [3]. To enable the introduction and maintenance of CHF regimens, the patient has to be motivated and must also understand the benefits and the expected adverse effects of medication. When the patient is diagnosed with heart failure, it should be anticipated that he or she may not be fully capable of comprehending all aspects of this serious disease at once. Therefore, information and counselling should be given on several occasions, and by different health personnel including nurses. When the patient returns to the out-patient clinic, sufficient time should be set aside to inform, and to allow questions from, the patient. The presence of spouses should be encouraged, especially when treating elderly patients. Besides information about medical therapy, other aspects of daily life and self-treatment should be covered, as detailed below.

Nurse-monitored out-patient clinics

In order to accomplish titration of heart failure medication, it is now generally agreed that a nurse-monitored facility is necessary for the care of patients discharged from hospital [4,5]. Nurses trained in the treatment of heart failure patients can manage titration of different drug combinations with a high degree of efficiency and safety. The benefits of nurse-monitored clinics have been described in several publications, including reports of improvements in survival. Using accepted titration schemes with prespecified limits concerning symptoms, signs and laboratory values, which determine when up-titration should be allowed or withheld, it is possible to achieve the target dose of angiotensin-converting enzyme (ACE) inhibitor or beta-blocker in the majority of patients. Besides the management of drug titration, an important task for the nurse is to inform and educate patients and relatives about the nature of heart failure and its treatment [6]. Telephone counselling is another important facility that should be available at these clinics. Nurses at heart failure clinics should also give advice on other therapies, such as temporary diuretic adjustments, exercise and cessation of smoking. When needed, patients should be referred to other professionals for dietary counselling, physiotherapy, diabetes care or psychological therapy.

Dietary advice

Water is the most obvious problem for the patient with heart failure. Pathophysiological mechanisms favour salt and water retention via renal effects and by centrally mediated thirst-driven neurohormonal pathways. Weight gain and oedema formation are often the first signs of disease, and are also obvious to the patient during periods of exasperation. Therefore, patients are usually advised to monitor their ingestion of water and salt. In severe heart failure, the maximum amount of water allowed is often set at 1.5–2.0 l/day. Although the benefit of a low-salt diet has not been proven in heart failure, patients should be advised to avoid salty food and not to add additional salt to meals. It is not uncommon for patients with severe heart failure to suffer from significant thirst and for a type of addiction to water to develop. In such cases, the patient may be unconscious of his or her drinking habits and can therefore be inaccurate when reporting amounts drunk.

Apart from salt and water, there is no general dietary advice to patients with heart failure. The underlying aetiology, however, may very well be influenced by the diet, especially in cases of coronary artery disease or diabetes. In such cases the dietary advice should not differ from that given to other patients with these diseases. It is anticipated that underlying obesity and diabetes will be more common among patients with heart failure in the future, necessitating appropriate dietary advice.

Another important aspect of energy consumption is that patients with more severe heart failure often suffer from cachexia. The underlying reason for this has not been established, but the degree of heart failure often correlates with the degree of cachexia [7,8]. Wasting of body components can be quite severe and can be life-threatening. If untoward weight loss is discovered, the diet should incorporate high-energy food components. Furthermore, the development of cachexia is a sign of severe heart failure and, if possible, other measures should be taken to improve cardiac function and to explore other reasons for deterioration of the condition.

Alcohol and smoking

Smoking is a well-known risk factor for several disorders, and coronary artery disease in particular. As this condition is the main aetiology of CHF, it is important to discuss cessation of smoking with many patients treated for heart failure. Although there are few data concerning the effects of smoking on myocardial function, the detrimental effects on vascular function and blood oxygenation require that all patients with CHF be encouraged to stop smoking. Conversely, alcohol may have preventive effects on atherosclerosis, and moderate drinking is probably beneficial for patients with coronary artery disease. Larger doses of alcohol cause depression of myocardial function, and an alcoholic cardiomyopathy might result following heavy drinking. Patients with CHF should be advised to use alcohol with care and avoid heavy bouts of drinking. One to two drinks per day is probably not harmful in heart failure, but conclusive data are lacking.

Drug abuse (e.g. cocaine, amphetamine, anabolic steroids) may be responsible for the development of myocardial dysfunction and cardiomyopathy.

Work

The likelihood of maintaining occupational work differs markedly among patients with heart failure. Although the majority of patients with this disorder have reached retirement age, a large proportion is in age groups where work is a natural part of life. Heavy physical work or conditions with high psychological stress are usually not compatible with CHF. Depending on the degree of restoration of cardiac function, the working conditions of the individual patient have to be considered when discussing future working capacity. Full- or part-time retirement is often required, although some patients may regain full working capacity.

Exercise

Previously, exercise training was thought to be harmful in CHF. Today, several studies have shown that programmes of different forms of exercise induce improved exercise capacity and quality of life [9]. Improvement in survival has not been proven, but there are no reports of adverse effects of training. As reduction in exercise capacity is one of the most important restrictions in patients with CHF, it is advisable that all patients (except those in severe NYHA class IV heart failure) should be encouraged to start regular physical training. Such training should be individualized, ranging from short periods of walking to peripheral muscle training and endurance training. Preferably, maximal exercise capacity should be determined before starting an exercise programme. Related to estimated or measured maximal oxygen consumption, patients should mostly be started on light intensity training, increasing to moderate intensity under the supervision of a physiotherapist (Table 24.1). Hard endurance training or competitive sports are not advised in patients with heart failure. Programmes using peripheral muscle training have used 35–80% of one repetition maximum (1 RM) two to seven times per week, during 15–60 min of exercise. Endurance training programmes have been performed at 40–80% of maximal Vo_2 two to seven times per week, during 10–45 min of exercise. Peripheral muscle training and endurance training could be combined to facilitate increase in muscle strength as well as improvement in general capacity.

Table 24.1 Classification of physical activity intensity

	Relative intensity		
Intensity	**Vo_2max (%)**	**Heart rate (%)**	**RPE***
Very light	< 20	< 35	< 10
Light	20–39	35–54	10–11
Moderate	40–59	55–69	12–13
Hard	60–84	70–89	14–16
Maximum	100	100	20

*Relative perceived exertion, Borg rating on scale of 6–20.

Sexual activity

For patients with heart failure, it is often possible to continue with sexual activity. However, several factors might negatively influence this ability. The underlying condition, in combination with decreased cardiovascular function, could per se be of such magnitude that the urge or capacity for sexual activity is severely reduced. There is often also a psychological fear of intercourse associated with a severe disease. This is partly a prudent response, since cardiovascular disorders are associated with an increased risk of events during sexual activity. The risk increases with the severity of the disease [10]. Last, the most common drugs used for heart failure may have effects on sexual function and libido. As these drugs prolong life expectancy and also improve quality of life, they are usually not withdrawn. Drugs like sildenafil may be used to improve sexual function but must not be combined with nitroglycerine.

Factors to avoid

There are several factors that may increase the risk of cardiac dysfunction and which patients with heart failure should avoid. Several medical therapies can interact with heart failure treatment and may, at worst, induce heart failure [11]. Non-steroidal anti-inflammatory drugs (NSAIDs) are a common reason for deterioration of heart failure, and these drugs should be prohibited in such patients. This is also true for the newer cyclo-oxygenase (COX)-2 inhibitors. Several antitumour agents can be harmful to the heart, anthracyclines in particular. Further, irradiation to the chest can damage the myocardium and the endothelium of the coronary vessels. Both heart failure and cancer are diseases with high mortality and, if both conditions prevail simultaneously, the treatment opportunities should be considered and discussed with the specialist in charge of the respective disease. In daily life, patients should if possible avoid factors that might induce an excessive burden on the cardiovascular system, such as heavy exercise, psychological stress, heavy meals and long flights.

Concomitant disorders

All cases of heart failure have an underlying cause. In order to optimize treatment of heart failure, the background disorder should be properly treated together with heart failure maintenance. Coronary artery disease and hypertension are the most common aetiologies, and they fit well into the treatment tradition of CHF. In other cases treatment may be more difficult, for example in patients with renal dysfunction, valvular diseases and malignancies. Organ function and concomitant treatments might then interfere with the management of heart failure. In each case it has to be decided how to prioritize different therapeutic measures.

Psychological/pain

Patients suffering from a potentially lethal disease often suffer from anguish and sleeping disorders. Such reactions are usually appropriate in view of the nature of the disease, but may be severely handicapping to the individual patient. Psychotherapy may be helpful. Sedatives and sleeping drugs are indicated, especially in cases with terminal disease. Although chronic pain may be present, drugs are usually not specifically requested by the patients. In cases with chronic angina pectoris not amenable to revascularization, chest pain could be a dominating factor in daily life. Treatment with opioids and long-lasting benzodiazepines could be helpful in such cases.

Pharmacological therapy of patients with systolic dysfunction (reduced left ventricular ejection fraction)

Angiotensin-converting enzyme inhibitors

ACE inhibitors were introduced for the treatment of heart failure initially because of their vasodilating properties. However, more recent understanding of the pathophysiology of CHF has demonstrated that the beneficial effects of these agents are associated with the neurohormonal blockade they produce [12,13]. The compensatory activation of neurohormonal systems was previously considered essential for maintaining the cardiovascular system during deteriorating cardiac output. However, the degree of activation is directly related to adverse prognosis. The reason is probably due to harmful effects on tissues from chronic exposure to hormones such as noradrenaline (norepinephrine) and angiotensin II.

There are also studies demonstrating beneficial effects

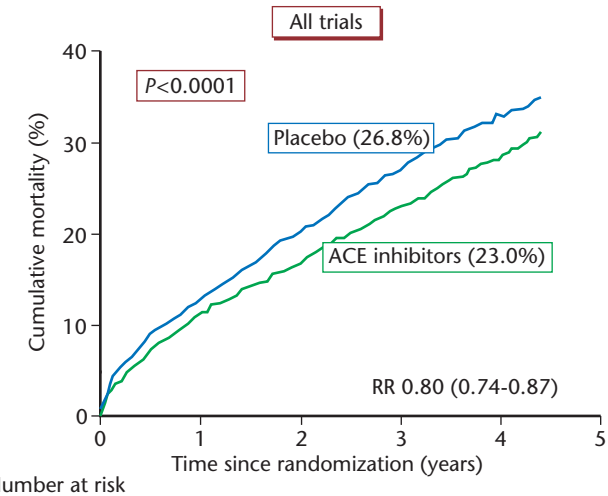

Figure 24.1 Meta-analysis of long-term (> 1-year duration) placebo-controlled trials (> 1000 patients) of angiotensin-converting enzyme (ACE) inhibitors in chronic heart failure or left ventricular dysfunction after a recent myocardial infarction. RR, relative risk. Reproduced with permission from Flather *et al*. [20].

on remodelling, including attenuated ventricular dilatation [14,15]. Their potential value was suggested by studies showing improved symptomatology [16], haemodynamics [17,18] and survival (Fig. 24.1) [19,20]. Several studies have reported results on the effects of ACE inhibitors on survival in patients with clinical heart failure, following acute myocardial infarction generally and following myocardial infarction with left ventricular dysfunction or heart failure [20].

In CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study), 253 patients in NYHA class IV were randomized to placebo or enalapril. After a follow-up of 6 months (primary objective), the overall mortality was reduced by 50% ($P = 0.003$) and during total study duration (average 183 days) by 26% ($P = 0.002$). Number of days for hospital care was reduced and NYHA classification significantly improved with enalapril [19]. In the largest study, the SOLVD (Studies of Left Ventricular Treatment) trial, 2569 patients with symptomatic heart failure (NYHA class II–III) received placebo or enalapril besides conventional heart failure therapy [21]. The average follow-up was 41.4 months. Mortality was significantly reduced from 40 to 35% ($P = 0.0036$). Hospitalizations for heart failure were also reduced. The largest reduction in mortality occurred among deaths attributed to progressive heart failure. Symptoms and quality of life assessed by questionnaire were improved [22].

Benefits in patients with left ventricular systolic dysfunction and/or heart failure after an acute myocardial

infarction have been documented in three major trials. In the SAVE (Survival and Ventricular Enlargement) trial, 2231 patients with a recent myocardial infarction and left ventricular ejection fraction (LVEF) of 40% or less, but without overt heart failure or symptoms of myocardial ischaemia, were randomly assigned treatment with captopril or placebo. Mortality was reduced by 19% ($P = 0.019$) [23]. In the TRACE study, 1749 patients with left ventricular dysfunction after a myocardial infarction were randomly assigned treatment with placebo or trandolapril. Treatment was initiated 3–7 days from the onset of myocardial infarction. All-cause mortality was reduced by 22% ($P = 0.0007$) [24]. In the AIRE study, 2006 patients with clinical evidence of heart failure any time after the index infarction were randomly allocated to treatment with ramipril or placebo on days 3–10 after the onset of infarction [25]. Clinical evidence of heart failure was defined as at least one of the following: signs of left ventricular failure on chest radiography, bilateral auscultatory crackles extending at least one-third of the way up the lung fields in the absence of chronic pulmonary disease, or auscultatory evidence of a third heart sound with persistent tachycardia. The average follow-up was 15 months with a minimum of 6 months. Mortality from all causes was decreased 27% ($P = 0.002$).

Improved blockade of the renin–angiotensin system by high doses of the ACE inhibitor lisinopril was tested in the ATLAS trial. Patients with CHF ($n = 3164$) and LVEF < 30% were randomized to a low dose (2.5–5.0 mg daily) or a high dose (32.5–35 mg daily) of lisinopril for a median of 45.7 months [26]. Effects on survival showed a hazard ratio of 0.92 ($P = 0.128$) for the high dose. The combined end-point of all-cause mortality or hospitalization for any reason showed a hazard ratio of 0.88 ($P = 0.002$). The adverse effects and tolerability were similar in the two groups. These findings indicate that patients with heart failure should generally not be maintained on very low doses of an ACE inhibitor and suggest that the difference in efficacy between intermediate and high doses of ACE inhibitor is likely to be very small. Thus, patients should be titrated to dose levels observed in clinical trials (Table 24.2). The value of additional dose levels, i.e. > 20 mg lisinopril daily, is uncertain but supported by the results of the ATLAS trial.

A meta-analysis of individual patients from five large randomized studies with ACE inhibitors was presented by Flather *et al.* [20]. Three of these studies were post-infarction trials, enrolling 5966 patients, of a total of 12 763 cases. The risk of death was significantly lower in the ACE inhibitor-treated group (23% vs. 27%; odds ratio 0.80; 95% CI 0.74–0.87), as was the risk of re-infarction (8.9% vs. 11%; odds ratio 0.79; 95% CI 0.70–0.89). The treatment benefits were independent of age, sex and baseline treatment.

Table 24.2 ACE inhibitors approved in Europe for the treatment of heart failure

Drug	Initiating dose	Maintenance dose
Documented effects on mortality/hospitalization		
Captopril	6.25 mg t.i.d.	25–50 mg t.i.d.
Enalapril	2.5 mg daily	10 mg b.i.d.
Lisinopril	2.5 mg daily	5–20 mg daily
Ramipril	1.25–2.5 mg daily	2.5–5 mg b.i.d.
Trandolapril	0.5 mg daily	4 mg daily
Also approved for heart failure in some countries		
Benazepril	2.5 mg	5–10 mg b.i.d.
Cilazapril	0.5 mg daily	1–2.5 mg daily
Fosinopril	10 mg daily	20 mg daily
Perindopril	2 mg daily	20 mg daily
Quinapril	2.5–5 mg daily	5–10 mg daily

Important adverse effects associated with ACE inhibitors are cough, hypotension, syncope, renal insufficiency, hyperkalaemia and angio-oedema. Although cough may often be due to heart failure or concomitant diseases (e.g. respiratory disease), dry cough is an adverse effect of ACE inhibitors. Severe cough may lead to discontinuation of ACE inhibitor therapy. Some patients may tolerate re-institution of the ACE inhibitor after a drug-free period.

Prevention

A reduced incidence of heart failure with use of ACE inhibitors has been demonstrated in several trials. In the prevention arm of the SOLVD study, the incidence of heart failure and the number of hospitalizations were reduced [27]. Similar findings were reported in SAVE [23]. In an overview of ACE inhibitor trials the preventive potential of ACE inhibitors was demonstrated [28]. In the HOPE trial, where high-risk patients without CHF were included, a significant reduction in new diagnosis of heart failure was demonstrated by ramipril compared with placebo [29]. The primary composite end-point of myocardial infarction, stroke or death from cardiovascular causes was significantly reduced in the treatment group by 22% ($P < 0.001$). Ramipril also reduced the risk of heart failure by 23% ($P < 0.0001$). Thus, even though this was not a study on CHF patients, ramipril appeared to protect high-risk atherosclerotic and diabetic patients from future development of CHF and other cardiovascular complications.

Cost-effectiveness

In the SOLVD study, enalapril therapy for patients with heart failure was cost-effective and justified by added benefits compared with other vasodilator therapy [30]. In

asymptomatic patients with left ventricular dysfunction after an acute myocardial infarction (SAVE), captopril was cost-effective in patients 50–80 years of age compared with other interventions [31]. Ramipril therapy for patients with clinical heart failure after acute myocardial infarction appears highly cost-effective when assessed using data from the AIRE study [32]. ACE inhibitor treatment was considered cost-effective in an evaluation of five independent studies regarding economic analysis [33].

Adverse effects

Reducing the effects of angiotensin II can lower blood pressure and intra-glomerular filtration pressure, both of potential critical importance in CHF. Accordingly, patients with low systolic blood pressure (e.g. < 90–100 mmHg) need careful monitoring during initiation. The same is important in patients with reduced renal function, particularly if they have increased renin production because of renal artery stenosis. Impaired renal function can sometimes be reflected by increased serum creatinine. It is thus important to monitor serum creatinine and serum potassium during initiation of these agents.

Clinical perspective

All patients with documented left ventricular systolic dysfunction (LVEF < 35–40%) should be considered for treatment with an ACE inhibitor. In symptomatic patients this should be considered first-line therapy in addition to a diuretic agent. Treatment should be continued long term. Changes in systolic and diastolic blood pressure and increases in serum creatinine are usually small in normotensive patients. Moderate renal insufficiency and a relatively low blood pressure (serum creatinine up to 250 μmol/l and systolic blood pressure as low as 90 mmHg) are not contraindications to ACE inhibitor treatment. Serum creatinine might increase by 10–15% in patients with severe heart failure, irrespective of baseline serum creatinine [34]. In most of these patients creatinine levels either remain stable or decrease towards pretreatment values during continued treatment. It should be stressed that mortality is higher among patients with elevated creatinine levels and that these patients in particular benefit from treatment with ACE inhibitors. The risk of hypotension and renal dysfunction increases in patients with severe heart failure, those treated with high doses of diuretics, elderly patients and patients with renal dysfunction or hyponatraemia. Changes in serum potassium are usually small (< 0.2 mmol/l). Although mild hyperkalaemia is not a contraindication to use of ACE inhibitors, serum potassium levels above 5.5 mmol/l are. If potassium-sparing diuretics have been prescribed to correct serum potassium levels, they should be discontinued during initiation of ACE inhibitor therapy. Absolute contraindications for initiation of ACE inhibitor treatment are bilateral renal artery stenosis and angio-oedema during previous ACE inhibitor therapy.

The dosage to be used should be titrated from a low dose to the moderately high levels employed in clinical trials. If no hypotension or renal dysfunction develops, the most effective titration comprises the following: enalapril up to 10 mg b.i.d., captopril up to 50 mg b.i.d., ramipril up to 10 mg daily (5 mg b.i.d.), trandolapril up to 4 mg q.d. and quinapril up to 10 mg b.i.d.

Angiotensin II receptor blockers

ACE inhibition does not provide complete blockade of the synthesis of angiotensin II and escape from ACE inhibition has been demonstrated [35]. Briefly, angiotensin II may be produced by enzymes other than ACE, which means that ACE inhibitors might be less effective at blocking the deleterious effects of angiotensin II than an angiotensin II receptor blocker (ARB) [36]. Because ACE is also a kininase II, ACE inhibitors, unlike ARBs, inhibit bradykinin breakdown. The resultant augmentation of bradykinin may have potentially advantageous actions, which may contribute to the clinical benefits of ACE inhibitors. Conversely, bradykinin accumulation may cause some of the adverse effects of ACE inhibitors that lead to treatment discontinuation, such as cough, rash and angio-oedema.

Evaluation of the clinical effects of ARBs in CHF and acute myocardial infarction has therefore been challenging because of the incontrovertible role of ACE inhibitors in these conditions, raising major questions about trial design, dose selection, statistics and even ethics. A particular issue has been the need for direct comparisons, including formally conducted tests for 'non-inferiority', with all the implications this has for patient selection, choice of ACE inhibitor and dose, sample size and end-points. In addition, the question of whether an ARB can provide benefits above those obtained with an ACE inhibitor is of particular importance. It is therefore worth discussing the evidence based on the design of the clinical trials.

ARBs vs. placebo

In the Val-HeFT study, 5010 patients in NYHA class II–IV and LVEF < 40% were randomized to placebo or valsartan [37]. Dose levels were increased to 160 mg twice daily. Background therapy with an ACE inhibitor was present in 93% of patients. There was no effect on all-cause mortality. In the other primary end-point, mortality or hospitalizations, there was a significant reduction (risk ratio 0.87; $P = 0.009$). In a retrospective subgroup

analysis, patients on background therapy with a beta-blocker and ACE inhibitor were found to have an increased risk when given valsartan. Valsartan significantly improved the combined end-point of mortality and morbidity and mortality alone in the small subgroup (7%) of patients not receiving an ACE inhibitor [38].

The CHARM programme was designed to study the effects of candesartan in a broad spectrum of patients with CHF. Three component trials included patients with reduced systolic left ventricular function (LVEF ≤ 40%) in two studies (CHARM Alternative and CHARM Added) and patients with preserved left ventricular function (LVEF > 40%) in the CHARM Preserved study. Primary outcome in each component trial was cardiovascular death or hospital admission for heart failure. In CHARM Overall the trials were combined and the effects on all-cause mortality were assessed.

Symptomatic patients with CHF intolerant of ACE inhibitors because of cough, symptomatic hypotension or renal dysfunction were included in CHARM Alternative ($n = 2028$). Candesartan significantly reduced cardiovascular death or hospital admission for heart failure by 23% ($P = 0.0004$), whereas the rate of discontinuation of the study drug was similar to placebo [39]. In CHARM Added ($n = 2548$), candesartan in addition to ACE inhibitors significantly reduced the primary outcome of cardiovascular death or hospital admission for heart failure by 15% ($P = 0.011$). Hospitalizations for heart failure were also reduced significantly ($P = 0.014$) [40]. In CHARM Preserved ($n = 3023$), there was a non-significant effect on mortality. Hospitalizations for heart failure as reported by the investigators were reduced by 15% ($P = 0.017$) [41].

In all patients with symptomatic heart failure ($n = 7599$), irrespective of background ACE inhibitor or beta-blocker therapy, candesartan reduced all-cause mortality by 9% ($P = 0.055$), particularly among those with left ventricular systolic dysfunction (hazard ratio 0.88; $P = 0.018$) (Fig. 24.2) [42,43]. Among these patients, the effects on mortality were seen early and the hazard ratio was 0.67 and 0.82 (both $P < 0.001$) at 1 and 2 years respectively. Further, hospital admissions for heart failure were reduced significantly by 21% ($P < 0.001$) [37].

ARBs vs. ACE inhibitors

In a dose-finding study between enalapril, candesartan and the combination, there were no differences between candesartan and enalapril in exercise tolerance, ventricular function or symptomatic status over 43 weeks [44]. However, combined therapy with candesartan plus enalapril markedly reduced ventricular volumes and improved LVEF over 43 weeks compared with either candesartan or enalapril alone. There was greater inhibition

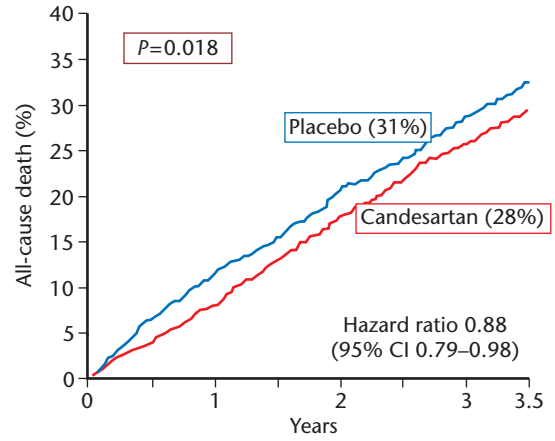

Figure 24.2 Mortality curve from the pooling of CHARM (Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity) Alternative and CHARM Added trials [43].

of aldosterone levels with the combination at 20 weeks but this difference narrowed at 43 weeks. The study was too small to examine the impact of clinical outcomes.

In the ELITE study, 3152 NYHA class II–IV patients with LVEF < 40% were randomized to losartan 50 mg once daily or captopril 50 mg three times daily [45]. There was no significant difference in all-cause mortality or sudden death. Significantly fewer patients in the losartan group discontinued study treatment because of adverse effects.

Together with smaller trials, meta-analyses show similar efficacy of ACE inhibitors and ARBs on mortality and morbidity [46,47]. Two trials evaluated ARBs and ACE inhibition in patients recovering after myocardial infarction with left ventricular dysfunction or signs of heart failure. The direct comparison of losartan with captopril indicated that losartan was not as effective as captopril on all-cause mortality [48], whereas valsartan, although not superior, was demonstrated to be as effective as captopril on the same outcome in the second trial [49].

ARBs and beta-blockers

Early studies, including ELITE II and Val-HeFT, suggest a trend towards a negative effect of the combinations losartan/beta-blocker or valsartan/ACE inhibitor/beta-blocker. However, such an interaction has been excluded in the OPTIMAAL trial for the combination losartan/beta-blocker after myocardial infarction, in the CHARM Added trial for the combination candesartan/ACE inhibitor/beta-blocker in CHF, and in the Valiant trial for the combination valsartan/captopril/beta-blocker. Therefore,there is no evidence that the combination ARB/beta-blocker or ARB/ACE inhibitor/beta-blocker has a deleterious effect either in CHF or after myocardial infarction.

Adverse effects

Blocking of the effects of angiotensin II by an ARB can cause the same adverse reactions as during initiation of ACE inhibitor therapy. The same monitoring and precautions should therefore be applied (see above).

Clinical perspective

The fact that the doses of losartan used in ELITE II and OPTIMAAL (target dose 50 mg) were not as effective as the ACE inhibitor captopril whereas high doses of candesartan (target dose 32 mg once daily) or valsartan (up to 160 mg twice daily) were associated with significant improvement in cardiovascular morbidity and mortality (CHARM Added and CHARM Alternative) or heart failure morbidity (Val-HeFT) in addition to ACE inhibition raises the hypothesis that high target doses of ARBs are required to result in a beneficial effect in CHF or to be as effective as ACE inhibition in this setting. Importantly, these findings demonstrate the incremental effects of a high-dose ARB above and beyond those achieved with an ACE inhibitor alone.

Aldosterone receptor blockers

Aldosterone plays an important role in the pathophysiology of heart failure, facilitating sodium retention and potassium loss. Further, it activates the sympathetic nervous system and stimulates myocardial and vascular fibrosis, and is a component of the circulating renin–angiotensin–aldosterone system [50].

Although aldosterone antagonists have diuretic effects, they differ from other diuretic agents in that they are neuroendocrine antagonists and thereby have a potential to be effective in the long-term treatment of patients with congestive CHF. Spironolactone is an old drug that has been used for decades as a potassium-sparing agent. However, the long-term clinical effects in the treatment of CHF have not been tested until recently. The concept of aldosterone antagonism was evaluated in the RALES study, where 1663 patients in NYHA class III or IV were randomized to spironolactone or placebo [51]. Spironolactone was initiated with 25 mg daily, with adjustments to 12.5 or 50 mg depending on serum potassium; 95% of the patients were on ACE inhibitors while only 11% had a background therapy of beta-blockers. The trial was discontinued early after a mean follow-up period of 24 months because of beneficial effect of spironolactone (Fig. 24.3). Mortality was reduced by 30% ($P < 0.001$). The lower risk was attributed to both a lower risk from progressive heart failure and sudden death from cardiac causes. The RALES trial demonstrated that improved antagonism of the renin–angiotensin system by spironolactone reduces the risk of both morbidity and mortality in CHF.

The EPHESUS study randomized patients with left ventricular systolic dysfunction after a recent myocardial infarction to the selective aldosterone antagonist

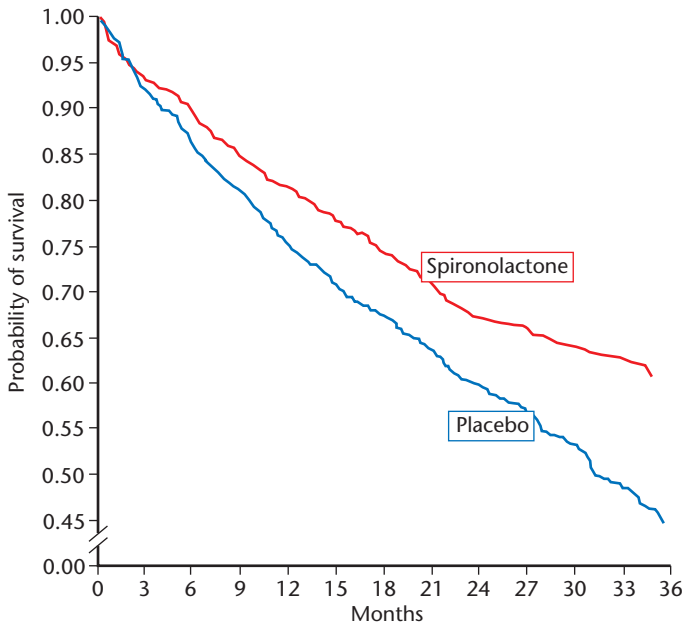

Figure 24.3 Effect of spironolactone in severe chronic heart failure: findings from RALES (Randomized Aldactone Evaluation Study). Risk reduction 0.70; 95% CI 0.62–0.80; $P < 0.001$. Reproduced with permission from Pitt *et al.* [51].

eplerenone or placebo. These heart failure patients were taking ACE inhibitors or ARBs (87%), beta-blockers (75%), diuretics (61%) and statins (47%) at baseline. The primary outcome of death from any cause was reduced by 15% ($P = 0.008$). The most significant reduction (21%) was in sudden death from cardiac causes [52].

Adverse effects

If painful gynaecomastia develops (10% in RALES), spironolactone may need to be stopped. Both spironolactone and eplerenone increase the risk of severe hyperkalaemia but reduce the risk of hypokalaemia, which emphasizes the need for monitoring. Therefore, the outcome trials with spironolactone and eplerenone excluded patients with serum creatinine > 221 μmol/l (2.5 mg/dl) and serum potassium > 5 mmol/l. When spironolactone was more widely used, an increased risk of hyperkalaemia was reported.

Clinical perspective

In symptomatic patients with systolic dysfunction who deteriorate despite treatment with an ACE inhibitor or beta-blocker, addition of spironolactone 25–50 mg should be considered. Careful monitoring of serum creatinine and potassium is recommended. In patients with signs of heart failure and/or reduced LVEF shortly after an acute myocardial infarction, the addition of eplerenone should be considered in addition to ongoing ACE inhibitor or ARB therapy as well as a beta-blocker. The treatment should be initiated with 25 mg daily and increased after 1 month to 50 mg. Significant renal dysfunction with estimated glomerular filtration rate below 30 ml/min per 1.73 m^2 is a contraindication.

Beta-blockers

After the development of the first β-adrenergic blocker, the first indications for therapy were soon discovered. Although there was much evidence in the 1960s of the detrimental effects of an activated sympathetic nervous system, only few considered the possibility of using beta-blockers as therapy in CHF. Following the first reports by Waagstein *et al*. in 1975, 25 years lapsed until it was finally proven that chronic beta-blockade is an excellent therapy for patients with CHF [1,3].

Mechanisms of action

A plausible reason for the delay in acceptance of beta-blockers as therapy for CHF is that the mechanism of action is not easily understood. Further, short-term effects are often negative and could possibly also increase signs of heart failure. In the short term, beta-blockers positively affect heart rate, myocardial metabolism and energy expenditure, while inducing negative effects on inotropy and cardiac output [53,54]. During careful titration of therapy the positive effects dominate, causing restoration of myocardial function and an increase in resting and exercise-induced myocardial performance [55,56]. Simultaneously, there is stabilization of cardiac rhythm and a reduced risk of lethal arrhythmias and sudden death. During established heart failure, the cardiovascular system becomes dependent on an elevated tonus of sympathetic stimulation [57]. Therefore, if this stimulation is interrupted, such as when a high dose of beta-blocker is administered, there is an imminent risk of increased cardiac failure. The key is to give small incremental doses of the beta-blocker in order to obtain positive effects on myocardial metabolism, without jeopardizing systemic circulation. Although there are several subtypes of adrenergic receptor (β_1, β_2, β_3, α_1, α_2), the dominating receptor in the heart is the β_1 receptor. The common denominator of the action of the four documented beta-blockers (bisoprolol, metoprolol, carvedilol, nebivolol) is that they block the β_1 receptor to various degrees [58–61] (Fig. 24.4). The non-selective beta-blocker carvedilol also has alpha-blocking properties. Because the non-selective beta-blocker bucindolol is not effective [62] and because the effect of carvedilol is superior to metoprolol tartrate [63], it is important to use one of the documented beta-blockers and to administer it in documented doses.

Clinical perspective

All patients with chronic systolic heart failure should be considered for beta-blocker treatment. Beta-blockers are considered first-line treatment besides ACE inhibitors (Fig. 24.5). Common underlying disorders, such as hypertension, diabetes and after myocardial infarction, are all amendable to treatment [60,64]. Further, the most frequent cardiomyopathies, i.e. dilated cardiomyopathy and hypertrophic cardiomyopathy [65], should be treated with beta-blockers. Diastolic heart failure (or heart failure with preserved systolic ejection fraction) has been poorly studied with regard to effects of drug treatment. There has been a general consensus that patients with compromised diastolic function would be candidates for beta-blocker treatment, in view of the mechanisms of these agents. Prolongation of diastole promotes diastolic filling and improves myocardial perfusion. There are no mortality data with beta-blockers in diastolic heart failure, although a recent study with carvedilol showed improvement in diastolic function, particularly in patients with higher heart rates [66] (Fig. 24.6).

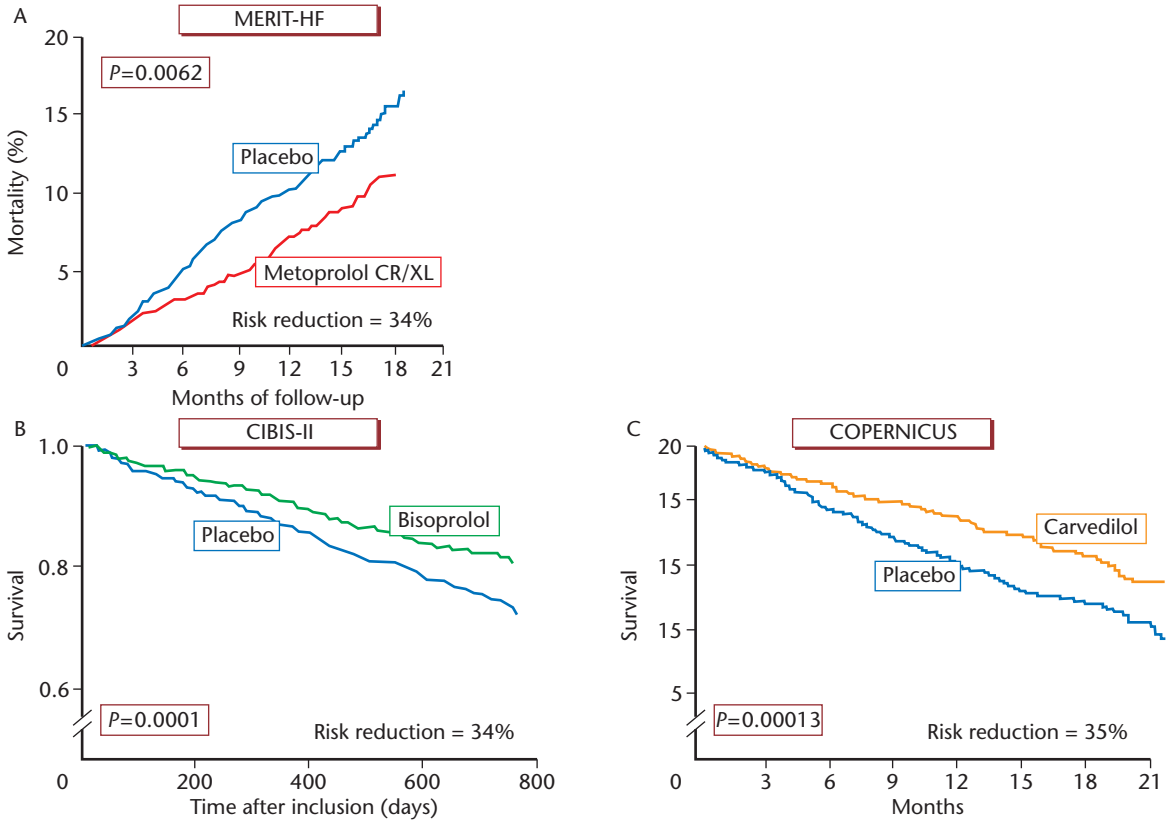

Figure 24.4 Kaplan–Meier curves of the three major survival studies with beta-blocker therapy: (A) Metoprolol CR/XL Randomized Intervention Trial (MERIT-HF); (B) Cardiac Insufficiency Bisoprolol Study II (CIBIS-II); (C) Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study. Reproduced with permission from MERIT-HF Study Group [58], CIBIS-II Investigators and Committees [59] and Packer *et al*. [60].

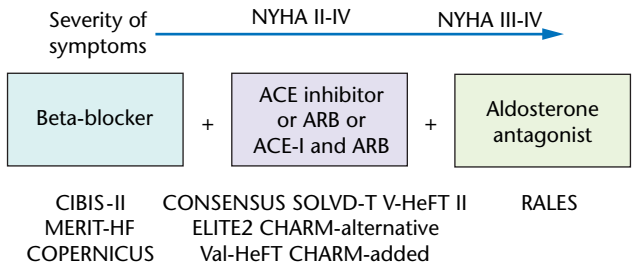

Figure 24.5 Pharmacological treatment of patients with chronic heart failure and left ventricular systolic dysfunction by severity of symptoms. Reproduced with permission from McMurray J *et al*. *Circulation* 2004; **110**: 3281–3288.

CONTRAINDICATIONS

If beta-blockers are given correctly, they are well tolerated and not inferior to the tolerability of ACE inhibitors [67,68]. There are few definite contraindications, but the following require special attention:

- bradycardia;
- hypotension;
- atrioventricular (AV) block;
- significant obstructive airway disease;
- acute or decompensated heart failure;
- ongoing treatment with drugs that affect contractility (e.g. calcium channel blockers).

BEGINNING BETA-BLOCKER TREATMENT

Patients with untreated or acute heart failure should not be considered for treatment. Circulatory function should be stabilized with diuretics and ACE inhibitors (or vasodilators if needed) and, in general, fluid overload should be removed before beta-blockers are started. However, it is not necessary to fully titrate an ACE inhibitor before beta-blockers are introduced. The two types of drug are complementary in action, and it is desirable that the antiarrhythmic effect of beta-blockers be achieved early during treatment. Especially in patients with arrhythmias (including atrial fibrillation), high heart rate or hypertension, ACE inhibitors and beta-blockers could be titrated simultaneously. Treatment is started with low doses, with increments every 1–2 weeks (Table 24.3). The target doses used in the controlled trials should be aimed for, although lower doses probably have

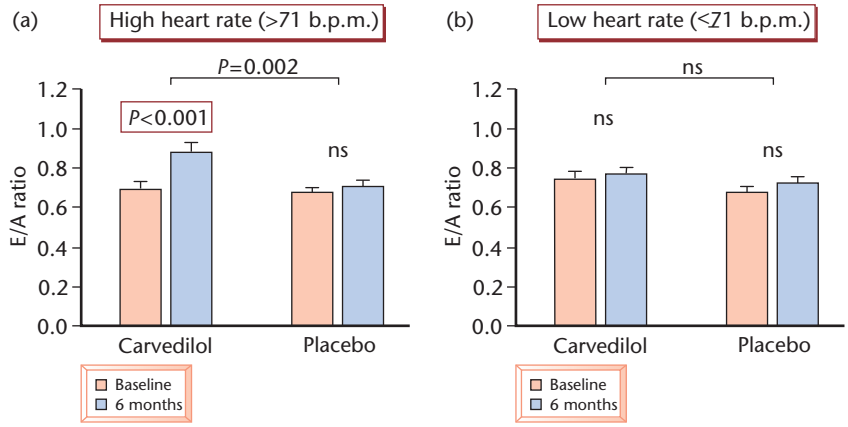

Figure 24.6 Changes in transmitral E/A ratio in relation to baseline heart rate in 113 patients with diastolic heart failure treated with carvedilol or placebo. Patients with heart rate above 71 b.p.m. had a significant increase in E/A ratio and E-wave velocity and a decrease in A-wave velocity when treated with carvedilol, whereas no effect was observed in patients with lower heart rates. Reproduced with permission from Bergström *et al*. [66].

Table 24.3 Beta-blockers used in large controlled trials for heart failure treatment

Drug	Initiating dose (mg)	Maintenance dose (mg/day)
Bisoprolol	1.25	10
Metoprolol succinate CR	12.5/25	200
Carvedilol*	3.125	50/100
Nebivolol	1.25	10

*Carvedilol is dosed two times daily, other beta-blockers once daily.

positive effects. It is important to inform patients that symptomatic improvement may be slow and possibly first noted after several months of treatment (Table 24.4).

MANAGEMENT OF ADVERSE EFFECTS

If problems do arise during beta-blocker titration, the most common adverse effect is an excessively profound blockade of inotropic action, resulting in low cardiac output with consequent fatigue or tiredness. If these signs occur, the duration of the ongoing dose should be prolonged, before attempts are made to increase the dose. If problems are more severe, the dose may be reduced, although it is rare that complete discontinuation is necessary. Fluid retention as a sign of increased heart failure is less common but can be treated with a temporary increase in diuretics. Bradycardia and hypotension may be asymptomatic and if so do not require any action. If these symptoms are accompanied by signs of poor circulation, dose adjustments should be made, in line with the advice given above. Psychological effects and nightmares could be a reason for discontinuation of beta-blocker therapy. A more selective β_1-receptor blocker (bisoprolol) may be tried or alternatively a water-soluble drug (atenolol), although the latter has no documentation with regard to heart failure treatment. It is also important that other drugs that might interact with beta-blockers are discontinued if problems arise during titration. This is particularly important if such drugs have poor documentation in the treatment of heart failure. Examples of such treatments are nitrates, digitalis, calcium channel blockers and antiarrhythmic drugs that affect contractility. Owing to superior documentation, beta-blockers should be preferred over other treatments.

Table 24.4 Temporal effects of beta-blocker treatment

Period	Effect
Days to weeks	Negative inotropy, reduced heart rate, improved myocardial substrate utilization, possibly increased signs of reduced cardiac output with or without symptoms. Symptomatic relief in some patients (dyspnoea, chest oppression)
Weeks to months	Improvement in invasive and non-invasive measurements of cardiac function. Stabilization of clinical symptoms
Months to 1 year	Improvement in clinical symptoms and possibly physical capacity. Reduced risk of hospitalization and death

Long-term treatment

As with other chronic treatments, it has not been established whether it is possible to discontinue beta-blockers if cardiac function has normalized. The major survival studies have followed patients for a maximum of 4 years. However, the general opinion is that ACE inhibitors and beta-blockers should be maintained lifelong after an episode of heart failure. There are examples in the scientific literature where removal of beta-blocker therapy has had deleterious consequences, with signs of increased heart failure and cases of sudden death [69]. When beta-blockers are removed suddenly, there is a rebound phenomenon with increased sympathetic drive and increased

receptor sensitivity. Therefore, if beta-blockers should for some reason be removed, they should be down-titrated over a period of time, closely observing possible signs of deterioration. If a patient already treated with a full dose of beta-blocker experiences an episode of deterioration that causes admission to hospital, the question of what to do about the beta-blocker dose often arises. Generally, it is advised that the dose is maintained while other measures are taken to control signs of increased heart failure. If inotropic therapy is chosen, phosphodiesterase inhibitors or calcium sensitizers could be combined with a beta-blocker. However, β-adrenergic agonists are less suitable as the action of these drugs is antagonized by beta-blockers. In very severe cases of heart failure, the dose of beta-blocker can be reduced in order to obtain a short-term increase in inotropic function or blood pressure. However, such measures often only provide temporary relief. This action could be compared with cases given beta-stimulating inotropic support without a beta-blocker. While rendering a temporary improvement in circulatory function, inotropic therapy is associated with increased mortality.

Diuretics

Diuretics were among the first therapies to be used for treatment of heart failure. Conditions with significant oedema formation were recognized long before the exact nature of the disease in question was known. Fluid retention could not be handled effectively until the thiazides were introduced [70], although the first thiazide agents had weak effects. However, after introduction of loop diuretics, the medical profession was in possession of a powerful tool [71].

Mechanisms of action

Different diuretics have their pharmacological action in diffferent parts of the renal tubular system. Thiazides cause diuresis by blocking the sodium/chloride transporter in proximal and distal parts of the tubuli. Potassium, magnesium and bicarbonate secretion increases, while calcium secretion decreases. The diuretic effect of thiazides is relatively weak, whereas they are effective as antihypertensive therapy. The site of action of loop diuretics is in the ascending thick limb of the loop of Henle [72]. By blocking the sodium/potassium/chloride transporter, chloride uptake is diminished with ensuing secretion of sodium, potassium, magnesium and calcium ions. The diuretic effect is short and the hypotensive effect is modest. In contrast to thiazides and loop diuretics that both increase urinary output of potassium, potassium-sparing diuretics decrease sodium reabsorption and potassium excretion and can thus increase plasma levels of potassium. Aldosterone antagonists are also potassium sparing, and these drugs are described elsewhere in this chapter. Acetazolamide is a carbonic anhydrase inhibitor that acts on the proximal tubule cells, resulting in a decrease in bicarbonate and sodium reabsorption. This produces hyperchloraemic metabolic acidosis, which might be of use in patients suffering hypochloraemic alkalosis following high doses of loop diuretics.

Clinical implications

Following intravenous administration of a loop diuretic (e.g. furosemide, the most widely used drug), congestive symptoms may be rapidly relieved. A reduction in left ventricular filling pressure has been noted before initiation of natriuresis, implying that venodilatation could be an early effect of the drug [73]. In the short term, arterial vasoconstriction has been observed [74,75] and the vascular effect has been thought to be mediated by an increased secretion of renin. However, the effect of renin and ensuing angiotensin II might be less when patients are treated with ACE inhibitors. Vascular effects are followed by a profound increase in diuresis and further reduction in plasma volume and filling pressures. Most loop diuretics are short-acting, while torasemide and slow-release preparations of furosemide have longer duration [76]. Diuretics relieve clinical symptoms of fluid overload, decrease oedema and dyspnoea, and increase exercise capacity as shown in short-term studies [77–79]. Effects of long-term treatment have not been studied in controlled trials.

ADVERSE EFFECTS

The increased diuresis caused by these agents is accompanied by increased urinary loss of electrolytes. Hyponatraemia, hypokalaemia and hypomagnesaemia are commonly found during long-term treatment. Hypokalaemia in particular may increase the risk of arrhythmias, including life-threatening ventricular tachyarrhythmias. Other metabolic effects are hypochloraemia, metabolic alkalosis, hyperuricaemia and hypocalcaemia. Thiazides in particular may increase blood glucose and lipids that can be of importance in patients at risk of diabetes or hyperlipidaemia. Loop diuretics are associated with an increased risk of vasculitis and ototoxicity. Imperative diuresis is often a problem for elderly patients with impaired bladder function or for those with a tendency to incontinence. Other common adverse effects are related to dry skin, eczema and function of the otic salpinx. Adverse effects often mandate additional treatment, such as potassium supplementation or potassium-sparing diuretics. Because of better documentation, an aldosterone antagonist is preferred over other therapy for increasing plasma levels of potassium. Spironolactone

therapy is described elsewhere. If potassium supplements or potassium-sparing diuretics are introduced or the dose adjusted, the plasma concentration of potassium should be monitored until stabilized; it is recommended that a first test be obtained 5–7 days after dose adjustments. Thereafter, electrolytes and creatinine should be monitored at regular intervals as needed.

Loss of urinary potassium is usually accompanied by magnesium depletion. Hypomagnesaemia has the same consequences as hypokalaemia, particularly an increased risk of arrhythmias. Homeostasis of magnesium is not easily monitored, as serum concentration is poorly correlated with intracellular concentrations. As with potassium, magnesium supplementation can be given. Patients with severe CHF managed with high doses of diuretics often suffer from hyponatraemia that can be profound [80]. This is often difficult to manage, as both total body free water and total content of sodium are increased. Mild hyponatraemia (120–135 mmol/l) may respond to moderate fluid and sodium restriction. Severe hyponatraemia (< 120 mmol/l) can be treated with isotonic saline intravenously during haemodynamic monitoring. The use of hypertonic saline is controversial and potentially harmful. It is believed that concomitant treatment with an ACE inhibitor impedes the degree of hyponatraemia. Another consequence of heavy diuretic therapy is acid–base disturbances, especially hypochloraemic metabolic alkalosis. This can be treated with saline intravenously or with small doses of acetazolamide (250 mg twice daily). Combinations of different diuretics increase the risk of adverse effects, particularly electrolyte disturbances, and there is an increased risk of renal insufficiency. Hyperuricaemia is a common complication of long-term diuretic therapy. Actual gout is rare but, if it occurs or if high concentration of uric acid is noted, treatment with allopurinol is indicated.

INTERACTIONS

Apart from potassium-sparing diuretics, a combination of different diuretic agents will invariably increase the risk of electrolyte disturbances and possibly renal dysfunction. When potassium supplementation is given, especially in combination with renin–angiotensin–aldosterone antagonists, there is risk of hyperkalaemia and increase in serum creatinine. The NSAIDs, including the more recently introduced COX-2 inhibitors, impede the natriuretic effect of diuretics and may reduce glomerular filtration [81]. Therefore, treatment with NSAIDs is a very common cause of acute or increased heart failure, especially in the elderly. In patients with CHF, regardless of treatment with diuretics or renin–angiotensin antagonists, NSAIDs should be avoided. Only short-term use can be justified in selected cases, and then under close observation for increased signs of heart failure.

DOSING (Table 24.5)

The amount of oral furosemide absorbed is usually 50% (range 10–100%). Individual differences in absorption

Table 24.5 Dosage and effects of different diuretics

Diuretic	Usual dosage	Effect on electrolytes	Half-life (h)		Peak effect (h)
			Normal	CHF	
Thiazides					
Chlorothiazide	500–1000 mg/day	$Na^+ \downarrow$, $K^+ \downarrow$, $Mg^{2+} \downarrow$, $Cl^- \downarrow$,	1.5	–	4
Hydrochlorothiazide	25–100 mg/day	$HCO_3^- \uparrow$, uric acid $\uparrow$, $Ca^{2+} \uparrow$	2.5	–	4
Bendroflumethiazide	2.5–30 mg/day	Mild metabolic alkalosis	2–5	–	4
Metolazone	2.5–10 mg/day		14	–	2
Carbonic anhydrase inhibitors					
Acetazolamide	250–500 mg/day	Metabolic acidosis	10–15	–	8–12*
Loop diuretics					
Furosemide	20–1000 mg/day	$Na^+ \downarrow$, $K^+ \downarrow$, $Mg^{2+} \downarrow$, $Cl^- \downarrow$,	1.5–2	2.7	1–2
Bumetanide	0.5–6.0 mg/day	$HCO_3^- \uparrow$, uric acid $\uparrow$	1.0	1.3	1–2
Ethacrynic acid	50–200 mg i.v.	Hypochloraemic alkalosis			
Torasemide	2.5–20 mg/day		3–4	6	1–2
Potassium-sparing diuretics					
Triamterene	100–300 mg/day	$K^+ \uparrow$, $Mg^{2+} \uparrow$	2–5	–	2–4
Amiloride	5–10 mg/day	Metabolic acidosis	17–26	–	3–4

*Data for extended-release formulations.
CHF, chronic heart failure.

may be of importance to the clinical effect. Decompensated patients have a similar rate of absorption but slower than normal. Bumetanide and torasemide are more completely absorbed (80–100%). The action of diuretics is dependent on their presence in the tubuli, and patients with reduced renal function require higher doses. The large variation in the individual clinical response to a single dose of diuretic could therefore be attributable to differences in absorption and renal function. The smallest effective dose of the diuretic should be determined in each patient. Besides giving larger doses, more frequent dosing may be effective in increasing diuresis. Similarly, continuous infusion of furosemide is more effective than equal doses given intermittently [82]. Additional diuretic effect is also obtained if a loop diuretic is combined with a thiazide, because of the different sites of action in the nephron. Combination of diuretics tends to increase electrolyte loss and resulting adverse effects. Patients not previously treated with a diuretic usually respond to a low–moderate dose with increased diuresis. Patients already on long-term treatment or with impaired renal function require higher doses. Cases with severe oedema or fluid retention (e.g. pulmonary oedema) should be treated with a loop diuretic administered intravenously; 40 mg of furosemide is a standard dose, but can be adjusted according to the individual response. Injections are usually repeated two or three times daily to maintain adequate diuresis. If adequate diuresis cannot be obtained by injections of loop diuretics, a continuous intravenous infusion can be used. Further, loop diuretics can be combined with other types of diuretic to increase the effect. Inotropic therapy (e.g. levosimendan) can improve diuresis by vasodilatation and by increasing cardiac output. Ultrafiltration and dialysis may be necessary in selected patients with refractory heart failure [83].

Long-term management

Following removal of excess volume and oedema, maintenance diuretic therapy should be considered. Diuretic therapy should not be used as monotherapy but only in conjunction with ACE inhibitors and beta-blockers. The need for diuretics is thereby reduced, and many patients do not require maintenance therapy [84]. The long-term dosage of diuretics should be as low as possible in order to achieve a state free of oedema and with adequate filling pressures. Patients should be advised to monitor weight on a regular basis and be allowed to use diuretics temporarily if signs of water retention occur. An increased number of patients with CHF are now treated with a combination of renin–angiotensin and aldosterone blockers. If an aldosterone antagonist is included in the regimen, the diuretic action of the drug is included [85]. Generally, spironolactone is preferred as first-line choice if a diuretic is needed for long-term use, thereby also achieving a potassium-sparing effect.

DIURETIC RESISTANCE

Long-term treatment with high doses of loop diuretics is often associated with decreased effect of the drug, referred to as diuretic resistance. The cause is hypertrophy of tubule cells in the loop of Henle. Sodium will then escape from the loop and be absorbed at more distal sites, with a concomitant decrease in diuresis [86]. As thiazides block the nephron at the site of hypertrophy, a synergistic diuretic effect can be achieved by adding a thiazide. Metolazone is a potent thiazide commonly combined with loop diuretics. The effects on electrolytes and renal function may be profound, and temporary use is advised. A shift from furosemide to another type of loop diuretic, or a long-acting preparation, can sometimes be more effective. Further, decreased intestinal absorption and decreased renal blood flow may be involved in diuretic resistance [87].

Clinical perspective

During the progression from an asymptomatic state of ventricular dysfunction to a symptomatic state, fluid retention is almost invariably present. Sodium and water retention is responsible for the typical signs of heart failure, including elevated filling pressures, peripheral oedema, pulmonary congestion, hepatomegaly and ascites [88]. Thus, patients seeking medical help for heart failure mostly have symptoms and signs consistent with various degrees of plasma volume overload. Also, when stabilized on chronic treatment, an exacerbation is often followed by increased weight gain due to water retention. Under such circumstances diuretics are the obvious drugs of choice, in conjunction with other long-term treatment strategies [89,90]. However, there are serious concerns regarding the long-term effects of diuretics. Although all large controlled trials of these agents in patients with CHF have been done with background therapy, there has been no controlled study on the long-term effects of diuretics. Smaller studies have suggested that diuretics might increase neurohormonal activation [91,92]. Further, there are data suggesting that high-volume urine output per se is not a sign of adequate renal function [93]. Taking these data together, it would be wise to use diuretics in as small a dose as possible. A temporary increase in the dose can be used for symptomatic relief, followed by a return to a lower maintenance dose.

Cardiac glycosides

Digoxin and digitoxin are the most frequently used

cardiac glycosides. They have identical pharmacodynamic effects but different pharmacokinetic profiles. Elimination of digoxin is renal. In contrast, digitoxin is metabolized in the liver and is less dependent on renal function, potentially useful in renal dysfunction and in elderly patients.

In the DIG trial of 6800 patients with ischaemic and non-ischaemic cardiomyopathy and mild to moderate heart failure, long-term digoxin did not improve survival. Furthermore, a small decrease in the risk of death from heart failure was offset by an increase in the risk of death from other causes. However, there was a significant reduction in hospitalizations for worsening heart failure as well as all-cause hospitalizations and total number of hospitalizations per patient [94]. A later report from this trial suggests an increased risk of death in women but not in men with digoxin [95]. Thus, the primary benefit of, and indication for, digoxin in heart failure is the reduction of symptoms and improvement in the clinical status, and thereby reduction in the risk of hospitalization for heart failure without an impact on survival.

Clinical perspective

Digoxin is indicated in all patients with symptomatic heart failure and atrial fibrillation irrespective of myocardial function. In these patients, combination with a beta-blocker can even be additive [96]. There is limited evidence that digoxin provides additive benefits in patients in sinus rhythm already taking ACE inhibitors, beta-blockers, ARBs and spironolactone.

Contraindications to the use of cardiac glycosides include bradycardia, second- and third-degree AV block, sick sinus syndrome, carotid sinus syndrome, Wolff–Parkinson–White syndrome, hypertrophic obstructive cardiomyopathy, hypokalaemia and hyperkalaemia.

Digoxin

The usual daily dose of oral digoxin is 0.25–0.375 mg if serum creatinine is in the normal range (in the elderly 0.0625–0.125 mg, occasionally 0.25 mg). No loading dose is needed when treating chronic conditions. The treatment can be initiated with 0.25 mg b.i.d. for 2 days. Renal function and plasma potassium should always be measured before starting treatment. In renal failure the daily doses should be reduced accordingly. As digoxin clearance closely approximates creatinine clearance, the latter should be estimated according to the Cockroft-Gault or MDRD formula (see reference 141).

Vasodilators

Reduction of afterload and preload in CHF improves left ventricular performance according to the Frank–Starling relation, with decreased myocardial oxygen demand and increased cardiac output [97]. Further, vasodilation may reduce valvular regurgitation by means of afterload reduction. Vasodilation may improve organ dysfunction by acting directly on selected vascular beds, such as the coronary and renal vasculature.

Acute vasodilator therapy

Nitroglycerine and nitroprusside are the drugs most commonly used for acute short-term vasodilation in heart failure.

NITROGLYCERINE

Nitroglycerine causes smooth muscle cell relaxation and vasodilation of arterial and venous vessels by affecting guanylate cyclase and the generation of cyclic guanosine monophosphate (cGMP). Nitrates can be used as sublingual tablet, lingual/buccal spray or intravenous infusion. Administration causes reduction in left ventricular filling pressures within 3–5 min, mainly by venodilation and lowering of preload [98]. Further, nitroglycerine reduces systemic vascular resistance and afterload, with consequent improvement in cardiac output. Acute nitrate administration appears to be especially useful in patients with elevated filling pressures and ischaemic conditions, such as ischaemic cardiomyopathy and myocardial infarction.

Nitrates may be used for the treatment of concomitant angina or relief of acute dyspnoea. Early development of haemodynamic tolerance (tachyphylaxis) to nitrates may occur with regular dosing (every 4–6 h) but this is less frequent when intervals of 8–12 h are used [99] or when nitrates are given in conjunction with ACE inhibitors or hydralazine [100].

NITROPRUSSIDE

Nitroprusside generates nitric oxide and nitrosothiols, which stimulate guanylate cyclase to increase intracellular cGMP. Smooth muscle cell relaxation is rapidly induced after administration. Sodium nitroprusside is converted to cyanide, which is metabolized to thiocyanate. Thiocyanate may accumulate and lead to thiocyanate toxicity during prolonged nitroprusside therapy. Compared with nitroglycerine, nitroprusside is far more potent and causes more pronounced arterial vasodilation [101]. The most prominent effect of nitroprusside is arterial vasodilation with afterload reduction. Nitroprusside is best employed in cases of acute heart failure after cardiac surgery or myocardial infarction, or when the patient is waiting for a more definitive intervention (e.g. valvular surgery). Because it is a potent vasodilator, nitroprusside may cause

adverse hypotension, especially in patients with inadequate filling pressures. Thiocyanate and cyanide toxicity are rare during short-term administration (≤ 3 μg/kg/min for less than 72 h).

Haemodynamic effects of long-term vasodilator therapy

NITRATES AND HYDRALAZINE

Oral nitroglycerine and hydralazine have been studied either alone or in combination therapy. The effects on left ventricular function and haemodynamics are similar to the acute effects of vasodilators described above [102,103].

Hydralazine acts as a dominant arterial vasodilator, but probably also has mild inotropic properties, which may be due to reflex activation of sympathetic activity. Relatively high doses of hydralazine (up to 300 mg) in combination with high-dose isosorbide dinitrate (up to 160 mg) without ACE inhibition may have some beneficial effects on mortality [104]. In African-American patients, the administration of one to two tablets t.i.d. of the fixed-dose combination of isosorbide dinitrate (20 mg) and hydralazine (37.5 mg) reduced mortality and morbidity and improved quality of life [105]. At these doses, the combination increased exercise performance more as compared with enalapril [106]. There is no evidence of proven benefit when either nitrates or hydralazine are used alone in addition to current therapy.

CALCIUM CHANNEL BLOCKERS

Besides its vasodilatory effect, the first-generation calcium channel blocker nifedipine possesses negative inotropic effects. Deleterious effects with regard to haemodynamics, neurohormonal activation and disease progression have been demonstrated in several trials [107]. The second-generation calcium channel blocker felodipine caused vasodilation and an increase in cardiac output during 8 weeks of treatment in a placebo-controlled trial [108].

Effects on survival

HYDRALAZINE AND ISOSORBIDE DINITRATE

The initial V-HeFT study was the first placebo-controlled clinical trial to study the effect of a vasodilator on survival in patients with CHF. The study recruited 642 patients with mild to moderate heart failure and randomized them to receive placebo, prazosin hydrochloride or the combination of hydralazine hydrochloride and isosorbide dinitrate. Two years after randomization, survival in the group treated with hydralazine and isosorbide dinitrate was significantly better than that in the placebo group ($P < 0.028$). For the entire follow-up, the difference was not significant ($P = 0.093$). The mortality rate in the prazosin group was no different from that in the placebo group [104].

The second V-HeFT study examined the efficacy of hydralazine and isosorbide dinitrate with that of enalapril; 804 patients were randomized to the two treatment strategies. Two years after randomization, all-cause mortality was 18% in the group treated with enalapril compared with 25% in the group treated with hydralazine and isosorbide dinitrate ($P = 0.016$). For the total follow-up, the difference was not significant ($P = 0.08$) [106].

There is no evidence of proven benefit when either nitrates or hydralazine are used alone in addition to current therapy.

CALCIUM CHANNEL BLOCKERS

Felodipine was studied in the third V-HeFT study, in which the effect on survival was neutral [109]. Amlodipine, a third-generation calcium channel blocker, was investigated in the PRAISE trial [110]. A total of 1153 patients in NYHA class III–IV were randomized, including 421 patients with non-ischaemic dilated cardiomyopathy. The overall effect on mortality, as well as on the combined end-point of mortality and hospitalization, was neutral. Although mortality was unchanged in the subgroup with ischaemic heart failure, there were significantly fewer end-points in the non-ischaemic group treated with amlodipine as compared with patients on placebo (22% vs. 35%, $P < 0.001$). However, this was not expected prior to conducting the study and the hypothesis was assessed in the PRAISE-2 trial among patients with non-ischaemic CHF [111]. Patients with non-ischaemic aetiology of CHF in NYHA class IIIb or IV ($n = 1652$) were randomized to placebo or amlodipine 10 mg daily. There was no significant difference in all-cause or cardiac mortality and cardiac event rates between the two groups. Combining the data of PRAISE-1 and PRAISE-2 suggests a complete prognostic neutrality. However, based on these trials, amlodipine and felodipine may be safely used to treat angina or hypertension in patients with CHF, if other proven drugs such as ACE inhibitors and beta-blockers are ineffective or not tolerated.

NON-DIGITALIS INOTROPIC DRUGS

In CHF it is often apparent that the heart suffers from inotropic failure. It is therefore not surprising that vast efforts have been invested in order to develop drugs that might increase contractility or the state of inotropy. Although several drugs with inotropic activity are available today, it has become increasingly evident that these drugs are associated with important negative effects.

Inotropic agents are classified according to their mode of action. Cardiac glycosides affect sarcolemmal ions through their effects on ion channels or ion pumps. These drugs are discussed on p. 734. Other drugs increase the intracellular level of cyclic adenosine monophosphate (cAMP), either by receptor stimulation (β-adrenergic

agonists) or by decreasing cAMP breakdown (phosphodiesterase inhibitors). Another class of agents affects intracellular calcium mechanisms by release of sarcoplasmic reticulum calcium or by increasing the sensitivity of contractile proteins to calcium. Finally, there are inotropic drugs with multiple mechanisms of action.

BETA-AGONIST DRUGS

Dobutamine Drugs with β-adrenergic agonist properties induce an increase in intracellular cAMP activity by stimulation of cellular receptors. During the 1960s patients with cardiogenic shock were treated with the beta-agonists isoprenaline and noradrenaline. It was realized that both drugs had potential negative effects, such as an increased risk of arrhythmias or, in the case of noradrenaline, untoward vasoconstriction. The development of dobutamine, a drug that is a modification of the isoprenaline molecule, resulted in an agent with β_1-, β_2- and α_1-adrenergic activity. Dobutamine induces vasodilation in combination with an increase in contractility, leading to an increase in stroke volume and cardiac output [112]. Enhancement of contractility is usually associated with an increase in myocardial oxygen consumption [113]. Adverse effects, such as arrhythmias or an unfavourable blood pressure response, are usually modest. Dobutamine can only be administered intravenously in doses from 2 up to 20–25 μg/kg/min. However, prolonged infusion over 96 h has been associated with a decrease in the haemodynamic effect by as much as 50% [114].

Beneficial short-term action encouraged investigators to use the drug in patients with CHF on an out-patient basis. Intermittent therapy was found to increase quality of life and haemodynamics [115]. However, a clinical trial had to be stopped prematurely because of an increase in mortality in the dobutamine-treated group [116].

Newer inotropic agents have been developed where increased myocardial efficiency is obtained by 'increased calcium sensitivity' in the contractile proteins. Early reports on levosimendan indicates beneficial effects on symptoms and end-organ function by limited infusions over 24 h [117].

Because of these limitations, repeated or prolonged treatment with oral inotropic agents increases mortality and is not recommended in CHF. Intravenous administration of inotropic agents is commonly used in patients with severe heart failure in order to limit severe episodes of heart failure or as a bridge to heart transplantation in end-stage heart failure. However, treatment-related complications may occur and their effect on prognosis is uncertain.

Dopamine Dopamine is an adrenergic agonist with predominantly β_1-receptor activity. This drug increases contractility with minor effects on heart rate or blood pressure. At low doses (0.5–2.0 μg/kg/min) dopamine acts on dopamine receptors, while at doses above 5.0 μg/kg/min it has effects through β_1 receptors, and at higher doses also through α receptors. Infusion at low doses causes dilation of smooth muscles in renal, mesenteric and coronary arteries, leading to an increase in diuresis [118].

Ibopamine Ibopamine is an orally active dopaminergic agonist, with the active metabolite epinine *N*-methyldopamine acting on DA_1 and DA_2 receptors. To evaluate the long-term effects of ibopamine, a study (PRIME-II) was initiated in 1906 patients with NYHA class III–IV heart failure. However, the study was terminated prematurely due to an increase in mortality in the ibopamine group: 232 of 953 (25%) in the ibopamine group died compared with 193 of 953 (20%) in the placebo group (relative risk 1.26; 95% CI 1.04–1.53; $P = 0.017$) [119].

Xamoterol Xamoterol is a drug with β-adrenergic blocking effects and high partial agonist activity, and long-term effects are similar to other inotropic agents. A multicentre trial had to be discontinued because of an increase in mortality in the active treatment group: 32 of 352 (9.1%) patients in the xamoterol group compared with 6 of 164 (3.7%) patients in the placebo group died ($P = 0.02$) [120].

PHOSPHODIESTERASE INHIBITORS

By inhibiting cAMP breakdown, the phosphodiesterase inhibitors bypass the β-receptor pathway. The first phosphodiesterase inhibitor was amrinone, a drug with inotropic and vasodilatory effects. During infusion, amrinone induced afterload reduction, a decrease in filling pressures, increase in cardiac index, and also an increased rate of contractility and relaxation [121]. As phosphodiesterase inhibitors elicit intracellular effects via pathways different from those mediated by β-adrenergic drugs, it has been hypothesized that the combination of these two classes of drugs would enhance myocardial performance. Results from clinical trials have supported this concept [122].

Although short-term administration may improve myocardial performance and clinical condition in congestive heart failure, the long-term effects of phosphodiesterase inhibitors have been discouraging. Oral phosphodiesterase administration has been tested in several trials with CHF, all of which have demonstrated no beneficial effect or a substantial increase in mortality in patients receiving the investigated drug. In the PROMISE trial, 1088 NYHA class III–IV patients were given milrinone or placebo. There was a 28% increase in mortality in patients treated with milrinone (relative risk 1.28; 95% CI 1.01–1.61; $P = 0.038$) [123].

CALCIUM-SENSITIZING DRUGS

Pimobendan is the most thoroughly studied drug in this class of inotropics. The effect is mediated by an increase in the affinity of troponin C for intracellular calcium [124]. Pimobendan inhibits phosphodiesterase and thereby has effects similar to milrinone [125]. Furthermore, treatment effects did not show congruity among different doses, and there was also a tendency toward increased mortality in a large 24-week trial [126].

Vesnarinone seems to have effects on contractility without increasing heart rate, which made it an interesting candidate for long-term therapy in heart failure. Furthermore, it was demonstrated that vesnarinone might inhibit the production of cytokines, including tumour necrosis factor-α. After initial promising dose-finding trials, a larger placebo-controlled trial (VEST) was initiated with 3833 patients. However, the study was stopped early because of a 26% increase in mortality in patients treated with 60 mg of vesnarinone [127].

Levosimendan is a new calcium-sensitizing agent with properties similar to pimobendan. In a comparison with dobutamine, levosimendan was tested in 151 patients. A 10-min bolus was followed by a 24-h infusion of 0.05–0.6 μg/kg/min. Dobutamine was given as an open-label infusion (6 μg/kg/min). The primary efficacy variable was an increase in stroke volume, a decrease in pulmonary capillary wedge pressure or an increase in cardiac output. The response rate to levosimendan ranged from 50% at the lowest dose to 88% at the highest dose (compared with placebo 14%, dobutamine 70%) [128]. Short-term infusion (up to 24 h) of levosimendan (0.05–0.2 μg/kg/min) is well tolerated and leads to favourable haemodynamic effects [117].

The clinical effects appear to be similar to those of phosphodiesterase inhibitors, although experimental data suggest that no adverse effects on myocardial metabolism occur with levosimendan. No comparable studies have been conducted between levosimendan and a phosphodiesterase inhibitor and long-term data are still pending, which are required before the clinical value can be established.

Antiarrhythmic agents

Although progressive pump dysfunction is a common cause of death in heart failure, sudden death is probably the most common reason and has been considered responsible for 25–50% of all deaths [129,130]. Besides a few cases of primary asystole, the majority of sudden deaths are due to ventricular arrhythmias. The issue of antiarrhythmic therapy in heart failure patients has therefore been of major interest. Implantable cardioverter-defibrillators (ICDs) are now used for prevention of sudden death due to ventricular arrhythmias and the use of these therapeutic devices is discussed later in the chapter.

Most antiarrhythmic agents cause depression of left ventricular function. Although frequent and complex ventricular arrhythmias may be predictive of sudden death, left ventricular dysfunction is a more powerful predictor [131]. Furthermore, these drugs may have a pro-arrhythmic effect, especially in cases of left ventricular dysfunction. In the CAST study, the efficacy of antiarrhythmic drugs in patients with left ventricular dysfunction after myocardial infarction and with complex ventricular arrhythmias was evaluated. Patients who responded with attenuation of arrhythmias after drug testing were randomized to encainide, flecainide or moricizine. The results showed an increase in mortality in patients treated with these agents [132]. Amiodarone is a class III antiarrhythmic drug with little or no negative inotropic effect. Previous promising smaller trials encouraged larger trials, such as the GESICA study. In this study, 516 patients with heart failure on conventional treatment were randomized to open-label amiodarone treatment (n = 260) or conventional treatment (n = 256). Both sudden deaths and deaths due to heart failure were reduced, comprising in total 87 deaths in patients on amiodarone and 106 in the placebo group (P = 0.02) [133]. However, these results were not reproduced in another study in patients with congestive heart failure and asymptomatic ventricular arrhythmias [134]. In this study, 674 patients were investigated but amiodarone treatment was not associated with reduction of overall mortality or mortality due to sudden death. As well, two other parallel studies have evaluated amiodarone in patients with recent myocardial infarction and left ventricular dysfunction [135,136]. In addition, patients in the CAMIAT study had complex ventricular arrhythmias. Although all-cause mortality was not significantly lower in the treatment groups, both studies showed a reduction in arrhythmic deaths. A meta-analysis of 13 amiodarone trials demonstrated a significant reduction in total mortality of 13% (10.9% vs. 12.3% per year, P = 0.03) and in arrhythymic deaths of 29% (P = 0.0003) [137,138]. Recently, important results from the SCD-HeFT trial were published. In this trial, 2521 patients with CHF and LVEF ≤ 35% were randomized to placebo, amiodarone or single-lead ICD. After a median follow-up of 45.5 months, there was no difference in mortality (primary outcome) between placebo and amiodarone [139]. The most impressive effects on sudden death have been found in the large survival studies with beta-blockers. Consistent effects were found with all three agents, i.e. bisoprolol, metoprolol and carvedilol [58–60].

Clinical perspective

Amiodarone is effective against most supraventricular and ventricular arrhythmias. It may restore and maintain sinus rhythm in patients with heart failure and atrial fibrillation or improve the success of electrical cardioversion. Amiodarone is the preferred treatment in this condition [140]. Amiodarone is the only antiarrhythmic drug without clinically relevant negative inotropic effects. The risk of adverse effects, such as hyperthyroidism, hypothyroidism, hepatitis, pulmonary fibrosis and neuropathy, although shown to be relatively low in recent large placebo-controlled trials, must be weighed against the potential benefits of amiodarone. Lower doses (100–200 mg/day) may reduce the risk. However, routine administration of amiodarone in patients with heart failure is not justified [139].

Pharmacological therapy of patients with preserved left ventricular ejection fraction

Although recent epidemiological studies suggest that in the elderly the percentage of patients hospitalized with heart failure-like symptoms and preserved LVEF may be as high as 35–45%, there is uncertainty about the prevalence of diastolic dysfunction in patients with heart failure symptoms and normal systolic function in the community. Further, much debate prevails about the prevalence of heart failure due to pure diastolic dysfunction. Heart failure with preserved LVEF and heart failure due to diastolic dysfunction are not synonymous. The former diagnosis implies evidence of preserved LVEF and not the demonstration of left ventricular diastolic dysfunction. The diagnosis of isolated diastolic heart failure also requires evidence of abnormal diastolic function, which may be difficult to assess in atrial fibrillation.

Causes of heart failure due to diastolic dysfunction include myocardial ischaemia, hypertension, myocardial hypertrophy and myocardial/pericardial constriction. These causes should be identified and treated appropriately. Precipitating factors should be identified and corrected, in particular tachyarrhythmias should be prevented and sinus rhythm restored whenever possible. Rate control is important. The treatment approach is similar to patients without heart failure.

There is still little evidence from clinical trials or observational studies on how to treat patients with preserved LVEF. The reason for the sparsity of data is that patients are excluded from nearly all large controlled trials in heart failure. Presently, we do not have clear evidence that patients with primary diastolic heart failure benefit from any specific drug regimen. Some evidence is available from the DIG study indicating that patients with heart failure and preserved LVEF benefit from digoxin with regard to death or hospitalizations for heart failure [94]. Inhibition of the renin–angiotensin system with candesartan in the CHARM Preserved study reduced cardiovascular mortality or hospitalizations for heart failure slightly and heart failure hospitalizations significantly; mortality, on the other hand, was not influenced [41]. However, these studies did not include an objective measurement of diastolic function and consequently do not permit any conclusion about treatment of diastolic function in general. Because heart failure is most often due to coronary artery disease and/or hypertension, it is logical to search for these conditions using appropriate tests and then to treat the patients according to the general principles for managing these disorders.

Clinical implications

An approach to the management of these patients as recommended by the recent ESC guidelines on the treatment of CHF is listed below [141].

- ACE inhibitors may improve relaxation and cardiac distensibility directly and may have long-term activity via their antihypertensive action and regression of hypertrophy and fibrosis.
- Diuretics may be necessary when episodes with fluid overload are present, but should be used cautiously so as not to lower preload excessively and thereby reduce stroke volume and cardiac output.
- Beta-blockade could be instituted to lower heart rate and increase the diastolic period.
- Verapamil-type calcium antagonists may be used for the same reason. Some studies with verapamil have shown functional improvement in patients with hypertrophic cardiomyopathy.
- A high dose of an ARB may reduce hospitalizations.

In general, the treatment of patients with preserved LVEF/diastolic dysfunction remains difficult and often unsatisfactory. One of the main problems is that isolated diastolic dysfunction may be rare, the condition often occurring in conjunction with some degree of systolic dysfunction. As the conditions that lead to preserved LVEF/diastolic dysfunction vary between patients and no controlled data from studies exist, straightforward therapeutic algorithms for each individual are not easy to provide.

Summary of pharmacological therapy

The pharmacological management of CHF has achieved major successes over the last 10–15 years, with significant benefits on survival, morbidity and symptoms. These results require the combination of several neurohormonal antagonists, diuretics and vasodilators as appropriate. These treatment combinations are sometimes complicated and best managed in a setting where patients can also be offered structured care.

Device therapy

Despite major and continuing advances in pharmacological treatment, many heart failure patients are lapsing into advanced heart failure in a very poor condition in terms of quality of life and prognosis [142]. Among the non-pharmacological approaches, electrical therapies, including cardiac pacing and/or ICDs, have been widely developed and evaluated over the last 10 years in order to treat this severe, rapidly growing and ageing population. After an initial but disappointing attempt with conventional dual-chamber pacing [143], a new treatment, so-called cardiac resynchronization therapy (CRT) (mainly using atrio-biventricular pacing), was developed 10 years ago with very encouraging results [144]. Moreover, we know that a large proportion of heart failure patients die from sudden cardiac death, with a high prevalence of fatal ventricular arrhythmias, which can be effectively treated with ICD. Recently, the combination of CRT and ICD yielded very interesting results for improving morbidity and mortality in selected patients with advanced heart failure [145].

Conventional dual-chamber pacing

In 1990, Hochleitner *et al*. [143] reported a significant short-term improvement in symptoms and left ventricular systolic function in 17 patients with severe symptoms following the implantation of a conventional dual-chamber pacemaker with a single right apical ventricular lead and short AV delay (100 ms) programming [143]. Nishimura *et al*. [146] showed that DDD pacing with individually optimized AV delay could improve cardiac performance only in the subgroup of patients with a long PR interval (> 200 ms) and signs of major AV mechanical asynchrony in the left heart on echocardiography. In contrast, pacing therapy was not effective in patients without significant PR interval prolongation.

Cardiac resynchronization therapy

CRT began in 1994 when Cazeau *et al*. [147] in France and Bakker *et al*. [148] in the Netherlands described the first cases of atrio-biventricular pacemaker implantation in patients with severe drug-refractory heart failure without conventional pacemaker indications. This concept was mainly based on the fact that in CHF patients with left ventricular systolic dysfunction, high-grade intraventricular conduction delays are frequently observed: 25–50% of patients have QRS duration > 120 ms and 15–27% of patients have left bundle branch block (LBBB). Moreover, in such patients, AV dyssynchrony is also often present, with prolonged PR interval on surface ECG in up to 35% of cases [149,150] (Fig. 24.7).

Rationale

Both AV and intraventricular conduction delays further impair left ventricular function in patients with underlying cardiomyopathies. Notably, LBBB changes left ventricular contraction patterns, leading to regions of early and late contraction, generating myocardial blood flow redistribution, regional non-uniform myocardial metabolism and regional molecular changes such as calcium handling and stress kinase proteins [149,150]. In addition to intraventricular conduction, AV time delay also influences net chamber mechanics, with linkage between optimal timing of atrial systole and improvement in cardiac output and diastolic filling time and a role in presystolic mitral regurgitation [149,150]. Thus, it is likely that dyssynchrony per se represents a pathophysiological process that directly depresses ventricular function and ultimately leads to left ventricular remodelling and heart failure and so represents an independent risk factor for mortality [149,150]. Recent new imaging technologies, especially echocardiographic techniques such as tissue Doppler imaging, were developed to evaluate the extent of global cardiac dyssynchrony, i.e. AV, interventricular and intraventricular asynchrony [151,152]. One of the major findings is that there is not a direct correlation between the magnitude of electrical and mechanical asynchrony and that some patients with 'narrow' QRS duration on surface ECG (< 120 ms) may exhibit criteria of intraventricular and interventricular asynchrony [153]. However, these new technologies have to be validated by controlled studies before being routinely used for the diagnosis and correction of cardiac dyssynchrony.

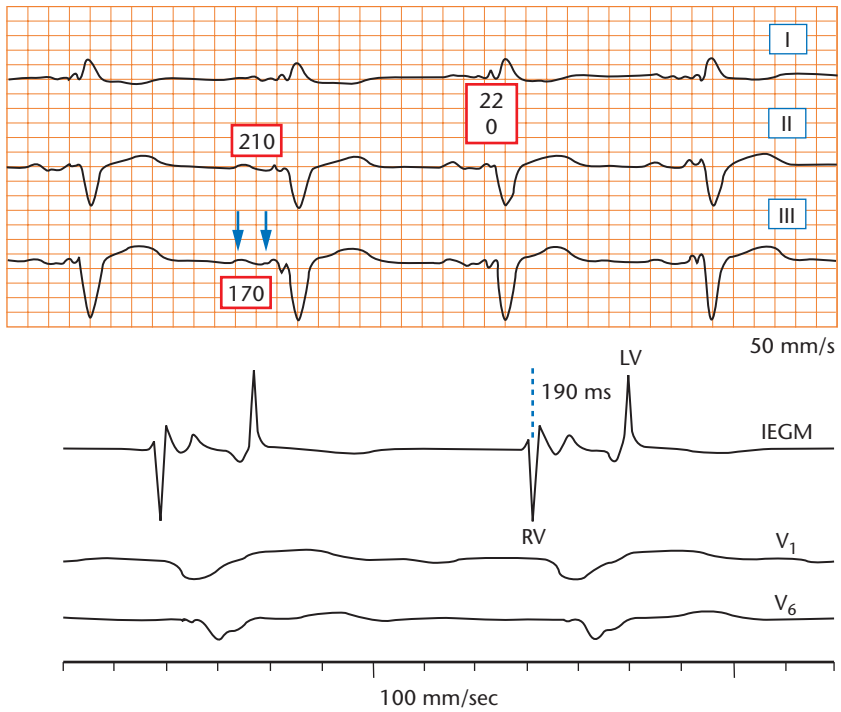

Figure 24.7 Atrioventricular conduction delay (PR interval 210 ms) and intraventricular conduction delay (QRS width on surface ECG, 220 ms; intracardiac interventricular conduction delay, 190 ms) in a patient with severe dilated cardiomyopathy.

Haemodynamic studies

Biventricular or left ventricular pacing improves haemodynamics in patients with CHF and LBBB, increasing cardiac output and reducing ventricular filling pressures. The haemodynamic improvements due to CRT may begin almost immediately after pacing is initiated (Fig. 24.8). In addition, CRT is associated with reductions in sympathetic nervous activity as well as brain natriuretic peptide release, suggesting potentially beneficial neurohormonal effects [149]. Importantly, CRT improves systolic function without increasing cardiac oxygen consumption, unlike inotropic drugs, which increase it for a given rise in contractile performance [149,150]. Thus, CRT contri-

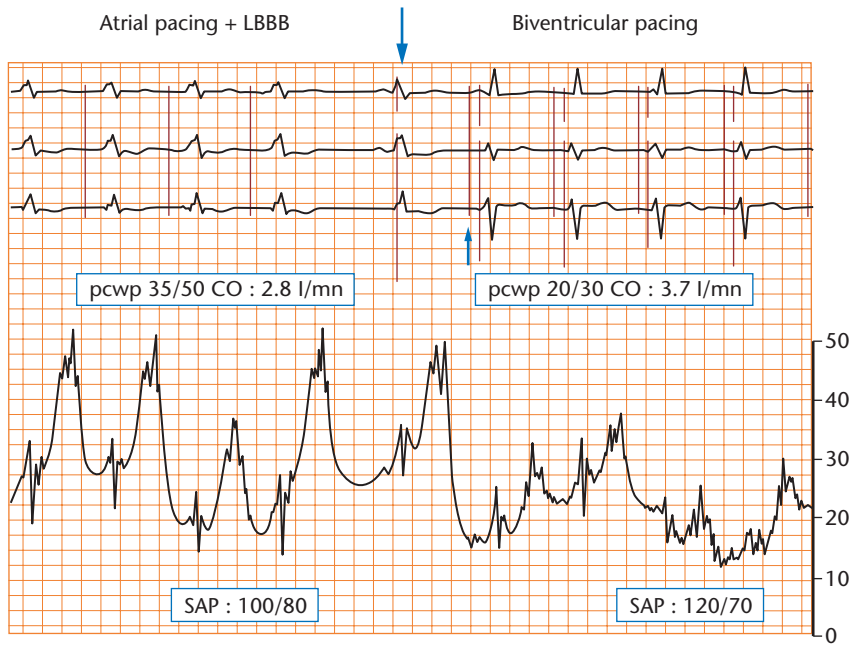

Figure 24.8 Acute haemodynamic benefit of biventricular pacing. LBBB, left bundle branch block; pcwp, pulmonary capillary wedge pressure; CO, cardiac output; SAP, systemic arterial pressure.

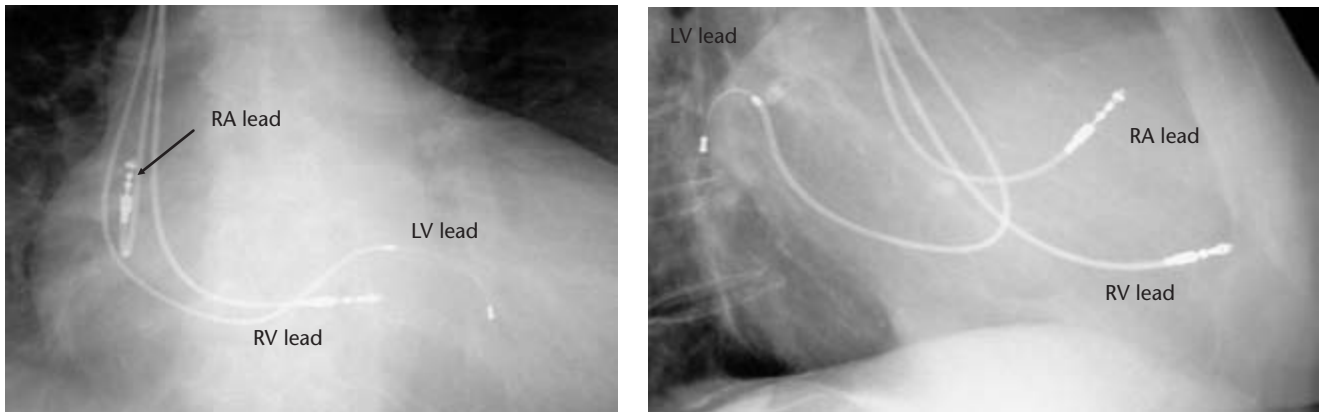

Figure 24.9 Chest radiograph (anteroposterior and sagittal views) showing the location of the three pacing leads. RA, right atrial; RV, right ventricular; LV, left ventricular lead implanted in a coronary sinus lateral vein.

butes to reversing mechano-energetic uncoupling associated with CHF.

Technical issues

So far, in most of the patients included in the different trials, CRT has been provided by biventricular pacing with a lead inserted transvenously in a tributary vein of the coronary sinus for epicardial pacing of the left ventricle as described by Daubert *et al.* [154] (Figs 24.9 and 24.10). The technology of CRT is still evolving. With improving specific catheter and left ventricular leads, implantation success is now greater than 90%. However, the procedure is invasive with the associated risk of complications. As reported in the MIRACLE study of 453 patients, the major complications of left ventricular lead implantation were death (2), complete AV block (2), coronary sinus dissection (23) or perforation (12). The pacing leads had to be repositioned in 20 patients, replaced in 10 patients and removed in seven patients [155].

Clinical effects

Initial reports from open non-randomized trials on the clinical effects of CRT demonstrated a significant benefit in patients implanted with a biventricular pacemaker. Later, controlled, randomized and prospective trials with a cross-over or parallel design have been completed and have demonstrated the clinical benefit of CRT in patients

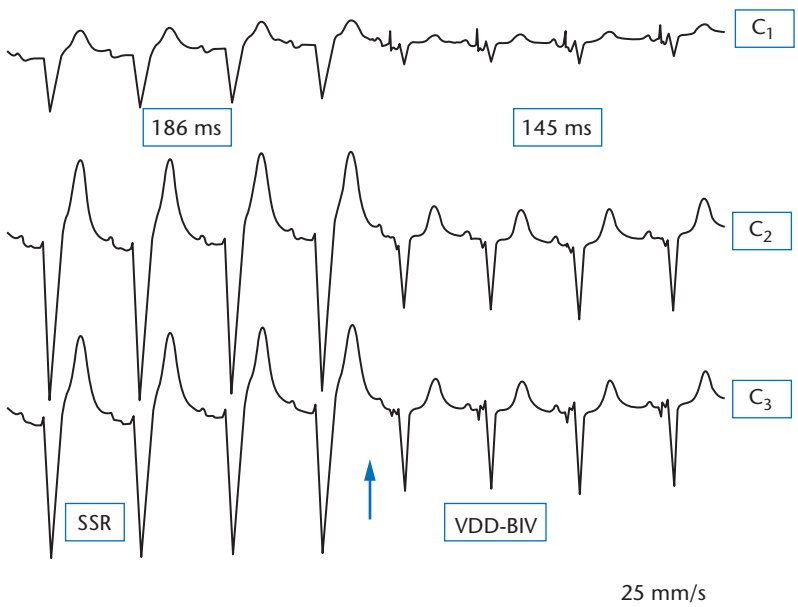

Figure 24.10 Surface ECG (25 mm/s) in sinus rhythm (SSR) and with atrio-biventricular pacing (VDD-BIV) showing the reduction in QRS width from 186 to 145 ms.

Table 24.5 Randomized trials with cardiac resynchronization therapy

	Duration	*N*	Design	Control group	Primary end-point	Follow-up months	NYHA class	SR/AF	ICD	Results with multisite pacing
PATH-CHF	1995–1998	42	Yes	No		3	III/IV	SR	No	+22% 6MWT; +43% QOL; 20% Vo_2max
MUSTIC SR	1998–1999	67	Crossover	No pacing		3/3	III	SR	No	+23% 6MWT; +32% QOL; 8% Vo_2max; mortality (7.5 months) 7.5%
MUSTIC AF	1998–1999	43	Crossover	RV pacing		3/3	III	AF	No	+9.3% 6MWT; 13% Vo_2max
MIRACLE	1998–2000	266	Parallel	No pacing		6	III/IV	SR	No	+13% 6MWT; +13% QOL
MIRACLE-ICD	1999–2001	369	Parallel	No pacing		6	III/IV	SR	Yes	+8% Vo_2max; +30% QOL
CONTAK CD	1998–2000	490	Crossover/ parallel	No pacing		4.5	II-IV	SR	Yes	Class III-IV: +15% 6MWT; +15% Vo_2max; +29% QOL Class II: no change
COMPANION	2000–2002	1520	Parallel, three arms	No pacing	All-cause death or all-cause hospitalizations	12	III-IV	SR	No	Primary outcome: 0.81 (95% CI 0.69–0.96; $P = 0.014$) Mortality (1 year) HR 0.75 (95% CI 0.63–0.90; $P = 0.002$)
CARE HF	2001–2004	813	Parallel	No pacing	All-cause death or cardiovascular hospitalization	18	III-IV	SR	No	Primary outcome: HR 0.63 (95% CI 0.51–0.77; $P < 0.001$) Mortality: HR 0.64 (95% CI 0.48–0.85; $P < 0.002$)

AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; 6MWT, six-minute walk test; QOL, quality of life; RV, right ventricular; SR, sinus rhythm.

with advanced heart failure, e.g. MUSTIC, MIRACLE, PATH CHF, MIRACLE-ICD, CONTAK-CD and COMPANION [145,156]. All trials except CONTAK-CD and MIRACLE-ICD included patients with severe heart failure (NYHA class III or IV) despite optimal drug therapy with left ventricular systolic dysfunction, dilated left ventricle and wide QRS (> 120–150 ms).

IMPACT ON SYMPTOMS AND EXERCISE TOLERANCE

All prospective, randomized and controlled studies have yielded concordant results, with significant benefit of CRT on symptoms and exercise tolerance. All these trials except two included patients with severe heart failure (NYHA class III and IV) despite optimal drug treatment, low LVEF (< 35%), end-diastolic diameter > 55–60 mm and intraventricular conduction delay (QRS duration > 120–150 ms) [155–160] (Table 24.5). CRT produced a significant reduction in NYHA class (on average by one class), an increase of 20–30% in the six-minute walking distance and an increase in Vo_2max by 10–15%. Quality of life, assessed with the Minnesota Living with Heart Failure questionnaire, was significantly improved by CRT in all trials. The follow-up duration of these studies was rather short (3–6 months) and thus questions the long-term effect of CRT. However, results at 1- and 2-year follow-up demonstrated that the clinical benefit observed after the 3-month cross-over phases remained stable over time [161]. Finally, in trials which included patients in NYHA class II–IV, CRT showed significant improvement in class III and IV patients but not in class II patients [155–160].

IMPACT ON HEART FAILURE HOSPITALIZATION

Improvement in major outcomes such as reduction in hospitalizations has also been reported. In the MUSTIC trial, the monthly rate of heart failure hospitalizations was reduced from 0.14 with no pacing to 0.02 with biventricular pacing [158] and in the MIRACLE trialheart failure hospitalization days were reduced by 80% in the CRT arm [155]. These findings were confirmed in a recent meta-analysis including 1634 patients [157]. The COMPANION trial included 1520 patients randomized to three different arms (in a 1 : 2 : 2 ratio): optimal drug treatment (OPT), OPT plus CRT, and OPT plus CRT plus ICD. Inclusion criteria were moderate to severe heart failure (NYHA class III and IV) despite pharmacological therapy, LVEF < 35%, left ventricular end-diastolic diameter > 60 mm and QRS width > 120 ms [145]. No patient had a conventional indication for cardiac pacing and/or ICD. The results of the COMPANION trial showed that CRT with or without ICD significantly reduced the combined end-point of all-cause mortality and hospitalizations by 20% [145].

IMPACT ON LEFT VENTRICULAR REMODELLING

Left ventricular remodelling is a potentially valuable surrogate marker of therapeutic response to some heart failure therapy. Reverse remodelling and prevention of disease progression could be associated with a reduction in morbidity and mortality [162]. Several non-controlled studies have demonstrated reverse left ventricular remodelling due to CRT, with a decrease in left ventricular end-systolic and end-diastolic volumes and an increase in LVEF [149,150]. These benefits have been shown to be pacing dependent, because discontinuation of pacing resulted in loss of cardiac improvement [162]. Improved left ventricular structure and function were also observed in the 6-month MIRACLE follow-up and in the 1-year MUSTIC follow-up [161,163], with a more pronounced effect in patients with non-ischaemic cardiomyopathy [163].

IMPACT ON MORTALITY

The results of the first non-controlled and controlled trials on mortality were encouraging, but they have to be interpreted very carefully because the primary outcome was not mortality [149,150]. For instance, in the MUSTIC trial [158] the 1-year mortality rate was 12%, whereas in the MIRACLE trial [155] the 6-month mortality rate was 5%. For patients in advanced heart failure these events rates are relatively low [142]. Two prospective randomized trials with morbidity/mortality as primary outcome have been initiated: the CARE-HF trial and the COMPANION trial. In the COMPANION trial, both CRT arms (CRT + OPT and CRT + OPT + ICD) demonstrated a significant reduction in the primary outcome (all-cause mortality and hospitalization) ($P = 0.01$) and in the two secondary end-points: death and cardiovascular hospitalizations, death and heart failure hospitalizations [145]. However, only CRT plus ICD therapy was associated with a significant 36% reduction in total mortality ($P = 0.003$) at 1 year, the 24% reduction in mortality observed in the CRT arm being not statistically significant ($P = 0.059$). Unfortunately, this trial was not designed to compare CRT and CRT plus ICD.

The CARE-HF trial randomized 813 patients with echocardiographic evidence of cardiac dyssynchrony and QRS duration of 120–150 ms or ≥ 150 ms to CRT or optimal pharmacological therapy alone. The results demonstrated a significant 37% relative (16% absolute) reduction in the composite of death or hospitalization for major cardiovascular event ($P < 0.001$) by CRT and a 36% relative (10% absolute) reduction in all-cause deaths ($P < 0.002$) [164].

IMPACT ON HEALTH-CARE UTILIZATION

The cost-effectiveness of CRT has not yet been evaluated [150]. Recently, a virtual estimation demonstrated that compared with drug therapy, CRT cost about $90 000 more per quality-adjusted life-year it saved [165]. However, the estimates of cost-effectiveness were sensitive to modifications in the assumptions for several key factors, including estimates of the effect of CRT on hospitalization and death [165].

Unsolved issues with CRT

NON-RESPONDER PATIENTS

A major problem with CRT is the non-responding population, estimated to comprise 20–30% of all patients implanted with a CRT device [155–160]. A possible explanation for this could be that, until now, patients were selected only if they fulfilled certain criteria, i.e. electrical dyssynchrony with QRS duration > 120–150 ms. Recent studies using Doppler echocardiography to assess mechanical ventricular dyssynchrony demonstrated that 20–25% of patients with a broad QRS did not exhibit mechanical dyssynchrony criteria [153]. Previous studies suggested that the magnitude of improvement with CRT was related to the magnitude of mechanical left ventricular dyssynchrony and not related to the QRS duration on surface ECG [166,167]. Another reason for non-response could be position of the leads in the right and left ventricles. Finally, non-optimal tuning of the device could be the cause of CRT failure: the AV delay has to be individually optimized by the echocardiographic Doppler technique [151]. Modalities and clinical benefits of the VV timing optimization remain to be clarified [166].

PATIENTS WITH PERMANENT ATRIAL FIBRILLATION

The prevalence of atrial fibrillation in the heart failure population is directly related to the severity of CHF. In clinical trials atrial fibrillation is present in 25–30% of patients. In the different published trials of CRT, only 2% of patients were in permanent atrial fibrillation and there are no consistent data to assess the clinical impact of CRT in this population [168]. Further specifically designed and powered studies are needed.

BIVENTRICULAR PACEMAKER AND/OR DEFIBRILLATOR?

Sudden cardiac death is common in CHF and is negatively correlated with NYHA class: 64% in class II and 33% in class IV [58]. ICD may be helpful in reducing this outcome. In patients with a secondary indication for ICD, i.e. after cardiac arrest due to ventricular tachycardia (VT) or ventricular fibrillation, or poorly clinically tolerated VT and with CRT criteria, a CRT-D should be implanted. The benefit of ICD in secondary prevention of sudden cardiac death was clearly demonstrated in CASH (Cardiac

Arrests Study Hamburg), AVID (Antiarrhythmics Versus Implantable Defibrillators) and CIDS (Canadian Implantable Defibrillator Study) [169]. ICD therapy yielded a significant decrease in total mortality by 20–31% and in arrhythmic mortality by 33–56%. Interestingly, the benefit was significant only in patients with LVEF < 35%. Two controlled studies, MIRACLE-ICD and CONTAK-CD, have demonstrated the safety and clinical efficacy of combining ICD and CRT in NYHA class III–IV patients with evidence of cardiac dyssynchrony [156,160].

In primary prevention, indications for combined therapy are more questionable. In patients with ischaemic cardiomyopathy, primary prevention trials did show a significant improvement in survival rate. MADIT (Multicenter Automatic Defibrillator Implantation Trial) and MUSTT (Multicenter Unsustained Tachycardia Trial) included 900 patients, mean age 65 years, with previous myocardial infarction, low LVEF (< 35 or 40%), spontaneous non-sustained VT and inducible VT during electrophysiological testing [170,171]. Compared with antiarrhythmic drug, ICD significantly reduced total mortality by 55% and arrhythmic mortality by 75% during a follow-up of 23 and 39 months respectively. Still more impressive are the results of the MADIT II trial, which included 1232 patients with prior myocardial infarction (> 3 weeks) and LVEF < 30% without arrhythmic inclusion criteria [172]. The trial was stopped prematurely by the safety committee when pre-specified boundaries were crossed. At 20 months follow-up, total mortality rate decreased significantly by 31% and arrhythmic death by 61% in the ICD arm compared with the control arm. Subgroup analysis showed that the benefit was higher in patients with broad QRS (> 120 ms). In patients with a CRT indication and ischaemic cardiomyopathy, the choice would be CRT-D rather than CRT alone.

In the case of non-ischaemic cardiomyopathy, the DEFINITE (Defibrillators in Non-ischaemic Cardiomyopathy Treatment Evaluation) trial included 458 patients (NYHA class II and III) with non-ischaemic cardiomyopathy (LVEF < 35%) and non-sustained VT or premature ventricular complexes [173]. Prophylactic implantation of an ICD reduced all-cause mortality by 35% ($P = 0.06$). The SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) compared the effects of ICD or amiodarone on overall mortality in patients with mild to moderate heart failure with LVEF < 35%. The results of SCD-HeFT showed that ICD was associated with a significant 23% reduction in total mortality at 5 years compared with control [139]. Interestingly, no difference was observed between the placebo and amiodarone arms. Finally, as previously discussed, the results of the COMPANION trial showed that the 1-year mortality rate was significantly decreased only in the ICD plus CRT arm, with a mean reduction of 36% and the same benefit whatever the origin of the cardiomyopathy [145].

Finally, two recent meta-analyses have estimated the effect of ICD implantation on all-cause mortality in symptomatic patients with reduced LVEF [174,175]. Nanthakumar *et al*. [174] found a significant 25% reduction in mortality with ICD implantation based on 1623 deaths ($P = 0.003$). Unfortunately, no subgroup analysis including age was described. Desai *et al*. [175] focused their analysis on studies including heart failure of non-ischaemic aetiology, including 1854 patients in trials on primary prevention. ICD treatment was effective in reducing all-cause mortality by 31% ($P = 0.002$).

POTENTIAL NEW INDICATIONS FOR CRT

Current ESC guidelines recommend CRT (with class I strength and evidence level A) in patients with medically refractory, symptomatic NYHA class III or IV heart failure with idiopathic or ischaemic cardiomyopathy, prolonged QRS interval (≥ 120 ms), left ventricular end-diastolic diameter ≥ 55 mm and LVEF ≤ 35% [141]. However, we may expect that in the near future new indications will be validated as in the following examples.

Previously right ventricular paced patients Right ventricular apical pacing induces ventricular dyssynchrony and causes deterioration of cardiac performance and clinical outcome. The results of the controlled and cross-over designed RD-CHF trial suggest that in previously right ventricular paced patients with advanced heart failure and intraventricular conduction delay, up-grading from uni-right ventricular pacing to biventricular pacing significantly improved clinical outcome [176].

Patients with conventional pacemaker indications The DAVID trial clearly showed that in an ICD population without pacemaker indication, right ventricular apical pacing increased morbidity and mortality compared with no pacing [177]. In order to avoid the left ventricular dyssynchrony induced by right ventricular apical pacing in patients with conventional pacemaker indications requiring permanent ventricular pacing, the question of pacing both ventricles simultaneously was raised.

CRT in asymptomatic patients or those with mild heart failure Previous studies have shown that CRT is not effective in improving symptoms and exercise tolerance in NYHA class II patients [156,178]. In contrast, CRT significantly decreased left ventricular end-systolic and end-diastolic volumes and mitral regurgitation and increased LVEF and thus might be beneficial in class II patients with a left ventricular reverse remodelling target.

Summary of device therapies

Electrical therapy by CRT alone or combined with ICD should be considered in the treatment strategy of CHF. Before considering implantation of a CRT device, the physician must optimize pharmacological treatment. At present, CRT is indicated in patients with refractory and severe heart failure, left ventricular systolic dysfunction with a dilated ventricle and intraventricular conduction delay in order to improve symptoms, exercise tolerance, quality of life and morbidity. ICD therapy is indicated for secondary prevention of sudden cardiac death related to ventricular arrhythmias. For primary prevention, ICD implantation is reasonable in selected patients with LVEF < 30–35% in order to improve survival from sudden cardiac death. The combination of CRT and ICD can be considered in patients who remain symptomatic with severe heart failure (NYHA class III or IV), LVEF ≤ 35% and QRS duration > 120 ms in order to improve morbidity or mortality in ischaemic and non-ischaemic heart failure.

Surgical treatment

Surgical treatment is presently offered to a small proportion of patients with CHF. Nevertheless, some patient subgroups can profit from surgery, and this field is undergoing rapid development. Surgical techniques available to patients with CHF can be grouped into three categories (Table 24.6). Substantial evidence has been gathered in the last decade about the validity of these methods, and firm recommendations can be made for the established group of techniques. The situation is much less clear for the emerging technologies, which must be considered as less well proven, remaining the domain of centres with experience in the particular technology.

Table 24.6 Surgical techniques available for patients with chronic heart failure

Established treatments
Correction of mitral incompetence
Surgical remodelling of the left ventricle
High-risk coronary revascularization
Heart transplantation
Bridge to transplant with assist devices
Emerging technologies
Circulatory assist devices in destination therapy
Cellular transplantation
Ventricular constraint devices
Debatable techniques
Cardiomyoplasty
Ventricular volume reduction

Correction of mitral incompetence

Mitral regurgitation in CHF results from alterations in the annular–ventricular apparatus and from changes in ventricular geometry, resulting in incomplete leaflet coaptation. Depending on volume load, it has a deleterious effect on long-term survival [179,180], which warrants surgical efforts in this group of patients. Replacement of the mitral valve, although preventing mitral regurgitation, can have deleterious effects on left ventricular performance [181] and has not been routinely recommended for this condition. Mitral valve repair, with careful preservation of the chordal suspension and papillary muscle apparatus, has a positive effect on left ventricular performance and results in improved cardiac output, reduction in NYHA class and increase in LVEF [181,182]. It can be performed with a reasonable operative risk of less than 4% [183]. This procedure also has a positive effect in ischaemic cardiomyopathy. The mechanism of ischaemic mitral regurgitation is related to local left ventricular remodelling, with papillary displacement producing apical tethering or tenting of the leaflets, resulting in restricted systolic leaflet motion [184]. When global left ventricular dilation occurs, both papillary muscles are displaced posteriorly, laterally and apically. As a consequence, the tethering forces on both leaflets increase, reducing their movement. Although improved survival has been stipulated, mitral valve surgery in ischaemic cardiomyopathy exhibits a substantial operative mortality, even in very experienced institutions [184], and a sobering long-term survival of 55% at 5 years. The advantages of mitral repair versus replacement have been questioned in some recent reports, especially in the highest risk groups [183,185,186].

What type of patient can be expected to profit from correction of mitral incompetence? The procedure should be reserved for patients with substantial (grade 3 and 4) mitral regurgitation, especially when the procedure can be combined with coronary revascularization [184]. Patients with enlarged left ventricles with increased sphericity, reduced LVEF and pulmonary hypertension are good candidates. Recent success with various surgical ablation procedures for treatment and prevention of atrial fibrillation, common in this condition [187], can be expected to improve the long-term results of mitral surgery and should be applied in conjunction with mitral repair in CHF [188].

Surgical remodelling of the left ventricle

In ischaemic CHF, a dyskinetic area of the left ventricle can be resected, with considerable improvement in LVEF, reduction in left ventricular end-systolic and end-diastolic dimensions, improvement in NYHA class and increase in work capacity [189,190]. This operation, variously described as Cooley's [191], Jatene's [192] or Dor's procedure [193], presently carries a low operative risk of less than 3% [190] and long-term survival is satisfactory, with more than 80% of patients surviving 2 years after repair of akinetic and 98% after repair of a dyskinetic segment of the left ventricle. Best results are achieved in patients with marked dyskinesia, especially when the operation is combined with coronary revascularization [190].

High-risk coronary revascularization

Previously, patients with reduced left ventricular systolic function and absence of angina have been considered poor candidates for coronary bypass grafting, with a high operative mortality exceeding 15% and poor late survival. The new diagnostic techniques allow more reliable assessment of hibernating myocardium and can predict patients who might profit from revascularization. Three techniques are commonly used to identify viable myocardium in patients with post-ischaemic left ventricular dysfunction: dobutamine echocardiography, thallium scintigraphy and positron emission tomography [194]. In recent years, the operative risk associated with coronary bypass grafting in patients with heart failure seems to have decreased, from 11% to 16% to less than 6% [195]. However, it remains consistently higher in patients with heart failure than in patients with less severe left ventricular impairment, and the decision to revascularize these patients must balance the risk of perioperative death against all the potential benefits of revascularizing hibernating myocardium [194]. Off-pump coronary revascularization may lower the surgical risk of both cardiac and cerebral complications for patients with heart failure undergoing surgical revascularization, although randomized clinical trials have questioned the results of observational data. The ongoing STITCH and HEART trials [196] are addressing the issue of usefulness of revascularization in impaired left ventricular function. At present, it is safe to assume that carefully selected patients, presenting with reduced left ventricular function, signs of heart failure and evidence of viable myocardium, can derive benefits from coronary bypass grafting with regard to symptoms and, potentially, morbidity and survival [141,197,198]. Indeed, there is some evidence that this treatment can offer better survival than heart transplantation [198].

Heart transplantation

This method has now been in widespread use for more than three decades, and firm guidelines for the conduct of the operation, indication for transplantation and long-term management of these patients have been established [195]. According to the large data bank of Collaborative Transplant Study [199], a 5-year survival of about 70% can be expected in the representative sample of almost 60 000 patients collected by this organization (Fig. 24.11). The 8-year survival still shows some attrition, with 55% of patients living after heart transplantation. Shortage of adequate organ donors leads to high mortality on the waiting lists and necessitates the use of assist devices as a 'bridge to transplant' [200]. Recent data from the United Network for Organ Sharing in the USA show that in 2004 there were only 2096 heart donors, and at present there are 3144 patients on the waiting list. Average waiting time for heart transplant for a status 2 patient (elective transplant) is now a median of 393 days [201]. Given the annual incidence of 400 000 new cases of CHF in the USA, it is obvious that only a small (<1 %) selected

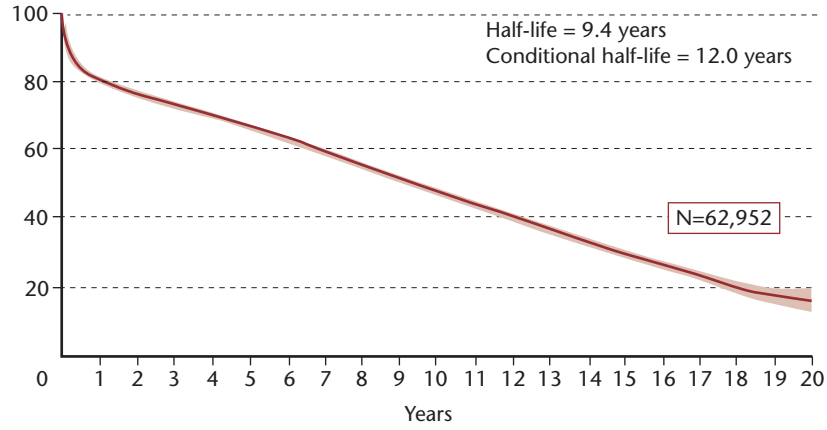

Figure 24.11 Actuarial survival after heart transplantation as reported to the International Registry (January 1982 to June 2001). Reproduced with permission from Hertz *et al*. [199].

proportion of patients with CHF will qualify and have access to heart transplantation.

Bridge to transplant with assist devices

Rapidly progressing heart failure in a transplant candidate can only be corrected by a circulatory assist device. It has been estimated that in the USA up to one-fifth of all transplant candidates need some circulatory assistance prior to transplantation [202]. Presently, there are various devices available, ranging from 'simple' extracorporeal assist systems intended for shorter postoperative use to the pulsatile and non-pulsatile devices used for 'destination therapy' and which are not meant to be removed, the patient not being considered a candidate for transplantation. Despite great expectations, the orthotopically implanted total artificial heart has not gained popular acceptance due to the high incidence of thromboembolism and infection, and this method is rarely used as bridge to transplant [203]. Most popular are implantable left ventricular assist devices with an external controller and energy supply, either as pulsatile or continuous-flow devices [204–206]. Success rates of 70–80% from assist implantation to transplant survival can be achieved [207], especially if the assist device is implanted before onset of renal or hepatic failure. Because of their substantial cost, necessity for precise anticoagulation in continuous-flow devices and heavy demands on hospital infrastructure, the use of assist devices remains limited. With the device functioning in optimal fashion, patients can leave the hospital and return only for periodic check-ups, with transplantation becoming an elective procedure.

Circulatory assist devices in destination therapy

In recent years, the reliability of circulatory assist devices has reached such a high state that a trial of optimal medical treatment versus implantation of a circulatory assist device as final therapy, without resorting to heart transplantation, was considered warranted. The results of the REMATCH trial [208], which encompassed 129 patients in 20 institutions, has shown improved survival in the assist group, with 52% surviving at 1 year as opposed to only 25% in the group with optimal medical treatment ($P = 0.002$). The difference remained at 2 years, with 23% versus 8% surviving in assist and medical groups respectively. Further trials are under way, using newer assist devices (continuous-flow pumps), and impressive clinical results have been observed, with reduction of hospitalizations, improved life quality and improvement in exercise capacity [202]. With wider availability of devices, smaller pumps, lower costs and possibly totally implantable devices with transcutaneous energy transmission, this field can be expected to grow in the near future.

Cellular transplantation

This is one of the most promising fields of translational research, offering substantial possibilities for improving ventricular function in CHF [209]. All cells are autologous, obviating the need for any immunosuppression. Skeletal muscle myoblasts were the first cells to be applied in clinical trials, derived from muscle biopsies, cultured and injected into the ventricular wall [210]. Bone marrow cells are obtained by aspiration, and circulating progenitor cells are isolated from mononuclear cells. Only a minority of trials used surgical implantation methods, and catheter-borne cells can be implanted into the myocardium by direct puncture or injected through the coronary arteries [211]. A clinical trial with surgically implanted myoblasts in an area of scar tissue has demonstrated an unexpected arrhythmogenic potential of these cells, so that defibrillator implantation has been deemed mandatory for these patients. An increase in segmental left ventricular function has been observed in electromechanically guided cell implantation [212]. The mode of action of transplanted cells remains unclear: electromechanical coupling of the transplanted myoblasts has not been demonstrated, and the transformation of progenitor cells into cardiomyocytes has been questioned experimentally, and these cells would still face the problem of electrical coupling. Angiogenesis has been postulated as a mode of action, and other mechanisms by which transplanted cells might improve myocardial function are under investigation.

Ventricular constraint devices

Left ventricular dilatation, combined with increased sphericity of the left ventricle, has been consistently observed in patients with CHF. Several mechanical devices have been developed to prevent this process. In animal experiments these devices were able to reverse the course of CHF [213], and the first human implants have been performed [214]. It is too early to assess the usefulness of Acorn and similar devices [215]; clinical trials are being conducted [216].

Cardiomyoplasty

Wrapping of latissimus dorsi muscle around the heart, coupled with electrical stimulation of the muscle, was developed by Carpentier and Chachques in an effort to provide additional force of contraction to the failing left ventricle [217]. Intensive clinical trials have been

conducted but have failed to produce conclusive results. The method is thought to alleviate symptoms of heart failure by reducing the wall tension of the left ventricle and by reducing its oxygen consumption. However, a limited number of patients have been treated and those with more advanced symptoms seem to do worse. This method is no longer in clinical use.

Ventricular volume reduction

The concept of removing a part of the dilated left ventricle to reduce its wall stress and improve ventricular performance was introduced by Batista *et al*. [218]; the technique met with considerable interest and has been evaluated under strictly controlled conditions at several institutions [219,220]. It is rarely performed today because of the high operative mortality, necessity for addition of left ventricular assist devices to ensure survival, and uncertain long-term results.

Summary of surgical treatment

Surgical treatment of CHF can presently be considered to be reserved for special subgroups of patients with identifiable disorders of left ventricular function. Excellent results can be obtained with properly applied left ventricular restoration, revascularization of hibernating myocardium, and correction of mitral incompetence. Heart transplantation, attractive as it is in substituting a normal heart for a diseased one, remains limited to a small group of selected patients because of a scarcity of donors and complex postoperative immunosuppressive treatment.

Conclusions

CHF is common, disabling, dangerous and costly. However, during the last 10–15 years, management of CHF has improved dramatically, with evidenced-based therapy being able to reduce both morbidity and mortality, improving symptoms as well as cost-effectiveness. The introduction of neurohormonal blockers has resulted in marked reduction in morbidity and mortality together with improved quality of life. In this chapter we have outlined the rationale for managing patients with CHF or left ventricular dysfunction after a recent myocardial infarction including recommendations on non-pharmacological therapies such as pacemakers and surgery.

Personal perspective

The major short-term challenge is to disseminate knowledge about the benefits of pharmacological therapy, as many patients still do not benefit from modern treatment. In order to offer treatment combinations, care must be structured and specialized nurses involved as one physician cannot handle the initiation and up-titration required during regular patient clinics. Implementation and translation of guidelines into primary care is important, in order to offer improved treatment to patients with milder or no symptoms. Traditionally, the medical profession is not very successful in doing this and we need the help of regulatory agencies and the pharmaceutical industry in communicating not only with our colleagues but also with our patients.

The next major challenge is the implementation of device therapy in addition to pharmacological therapy. We have to translate the landmark trials, e.g. SCD-HeFT and CARE-HF, into clinical practice. As the costs are invested up-front, a reasonable time should be allowed for these therapies to act, i.e. it is not an end-of-life option. Further, the priorities within each system must be defined as the investment is considerable once these therapies are disseminated and available resources differ. Closer collaboration between heart failure specialists and electrophysiologists is necessary as implantation will be decentralized, as was done when pacemakers became more widespread.

The challenge over the next 10–15 years will be to define the requirement for the new treatments of advanced heart failure (e.g. cell transplantation). Further, improved understanding of how and why myocardial function deteriorates will allow the prevention of heart failure and left ventricular dysfunction.

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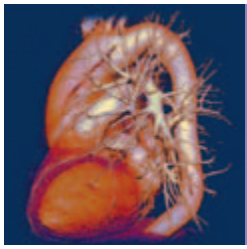

25 Pulmonary Hypertension

Nazzareno Galiè and Gerald Simonneau

Summary

Pulmonary hypertension (PH) is a pathophysiological condition characterized by an increase in pulmonary arterial pressure at rest or during exercise. Clinical conditions with PH are classified in five categories according to similar pathological, pathophysiological and therapeutic characteristics.

Despite possible comparable elevations of pulmonary pressure in the different clinical classes, the underlying mechanisms, the diagnostic approaches and the prognostic and therapeutic implications are completely different. The clinical class 1 defined as pulmonary arterial hypertension (PAH) comprises a group of rare conditions which share comparable clinical and haemodynamic pictures and virtually identical pathological changes in the lung microcirculation. PAH includes the idiopathic and familial forms and PAH associated with various conditions, such as connective tissue diseases, congenital heart defects with systemic-to-pulmonary shunts, portal hypertension, and HIV infection. A sequential diagnostic approach is suggested to identify and characterize the different types. Multiple new medications (prostanoids, endothelin-receptor antagonists, phosphodiesterase-5 inhibitors) have proven to be effective in this severe condition and an evidence-based treatment algorithm is presented. Specific clinical and therapeutic characteristics of each PAH condition are also discussed. Lung transplantation is indicated in case of medical treatments failure and pulmonary endarterectomy is the treatment of choice in cases of chronic thromboembolic PH (clinical class 4). PH is a common complication in patients affected by left heart diseases (clinical class 2). In these cases the treatment is addressed to the underlying heart condition and medications specific for the pulmonary circulation have proven to be non-effective. Also in cases of PH associated with lung diseases (clinical class 3) the use of pulmonary vasodilators is not recommended on the basis of their minimal clinical efficacy and because they may impair pulmonary gas exchange.

Definition and classification of pulmonary hypertension

Pulmonary hypertension is defined by a mean pulmonary artery pressure (PAP) > 25 mmHg at rest or > 30 mmHg with exercise [1]. The current clinical classification of PH is presented in Table 25.1 [2]. Clinical conditions with PH are classified into five categories according to similar pathological, pathophysiological and therapeutic characteristics. Despite possible comparable elevations of PAP and pulmonary vascular resistance (PVR) in the different clinical classes, the underlying mechanisms, the diagnostic approaches and the prognostic and therapeutic implications are completely different [2]. The haemodynamic classification of PH is shown in Table 25.2. Precapillary PH includes the clinical classes 1, 3, 4 and 5, while postcapillary PH includes clinical class 2. The features of each clinical class are discussed in specific sections, with particular attention to clinical class 1, defined as pulmonary arterial hypertension (PAH) in which PH represents the leading pathophysiological feature.

1. Pulmonary arterial hypertension (PAH)
   - 1.1 Idiopathic (IPAH)
   - 1.2 Familial (FPAH)
   - 1.3 Associated with (APAH)
     - 1.3.1 Connective tissue disease
     - 1.3.2 Congenital systemic-to-pulmonary shunts
     - 1.3.3 Portal hypertension
     - 1.3.4 HIV infection
     - 1.3.5 Drugs and toxins
     - 1.3.6 Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliferative disorders, splenectomy)
   - 1.4 Associated with significant venous or capillary involvement
     - 1.4.1 Pulmonary veno-occlusive disease (PVOD)
     - 1.4.2 Pulmonary capillary haemangiomatosis (PCH)
   - 1.5 Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension associated with left heart diseases
   - 2.1 Left-sided atrial or ventricular heart disease
   - 2.2 Left-sided valvular heart disease
3. Pulmonary hypertension associated with lung respiratory diseases and/or hypoxia
   - 3.1 Chronic obstructive pulmonary disease
   - 3.2 Interstitial lung disease
   - 3.3 Sleep-disordered breathing
   - 3.4 Alveolar hypoventilation disorders
   - 3.5 Chronic exposure to high altitude
   - 3.6 Developmental abnormalities
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
   - 4.1 Thromboembolic obstruction of proximal pulmonary arteries
   - 4.2 Thromboembolic obstruction of distal pulmonary arteries
   - 4.3 Non-thrombotic pulmonary embolism (tumour, parasites, foreign material)
5. Miscellaneous: sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumour, fibrosing mediastinitis)

Table 25.1 Clinical classes of pulmonary hypertension, Venice 2003

Table 25.2 Haemodynamic classification of pulmonary hypertension (PH)

Definition	Characteristics	Clinical class number*
Precapillary PH	Mean PAP > 25 mmHg; PWP ≤ 15 mmHg PBF normal or reduced; PVR > 3 mmHg/l/min	1, 3, 4, 5
Precapillary hyperkinetic PH	Mean PAP > 25 mmHg; PWP ≤ 15 mmHg PBF increased; PVR < 2 mmHg/l/min	1.3.2 and 1.3.3 before the development of obstructive changes of pulmonary arteriole
Postcapillary PH	Mean PAP > 25 mmHg; PWP > 15 mmHg PBF normal or reduced *Passive PVR* < 2 mmHg/l/min *Reactive PVR* > 2 mmHg/l/min	2
Postcapillary hyperkinetic PH	Mean PAP > 25 mmHg; PWP > 15 mmHg PBF increased; PVR < 2 mmHg/l/min	2 (condition with high-output heart failure such as anaemia, hyperthyroidism, etc.)

PAP, pulmonary arterial pressure; PBF, pulmonary blood flow; PVR, pulmonary vascular resistance; PWP, pulmonary wedge pressure.
*According to Table 25.1.

Pulmonary arterial hypertension

The clinical class 1 defined as PAH comprises apparently heterogeneous conditions that share comparable clinical and haemodynamic pictures and virtually identical pathological changes of the lung microcirculation [3]. PAH includes idiopathic PAH (IPAH, formerly termed primary pulmonary hypertension), familial PAH (FPAH) [4] and PAH associated with various conditions such as connective tissue disease (CTD), congenital heart defects with systemic-to-pulmonary shunts, portal hypertension, human immunodeficiency virus (HIV) infection, drugs and toxins and other rarer settings [2]. In this section, aspects of the idiopathic and familial forms are discussed while the specific characteristic of the associated conditions are defined in apposite paragraphs.

Epidemiology

PAH is considered a rare condition even if appropriate prospective epidemiological data are lacking. The incidence of IPAH is considered to be 1–2 cases per million or 0.01–0.02 per 10 000 [5]. Assuming that the median survival for IPAH patients (before the recent introduction of the new targeted treatments) is 4 years or less [6], the point prevalence can be estimated to be at least 4–8 cases per million. If we include all PAH categories, the minimal prevalence of the disease has been estimated as 15 cases per million in a recent French registry [7]. Cases of FPAH are considered to be at least 6% of all cases of IPAH [6].

Pathology

The histopathological changes in various forms of PAH are qualitatively similar [3] but with quantitative differences in the distribution and prevalence of pathological changes in the various components of the pulmonary vascular bed (arterioles, capillaries or veins). Four main pathological pictures can be identified: pulmonary arteriopathy (found in the great majority of types of clinical class 1), pulmonary occlusive venopathy (typical of clinical class 1.4.1, also defined as pulmonary veno-occlusive disease), pulmonary microvasculopathy (typical of clinical class 1.4.2, also defined as pulmonary capillary haemangiomatosis) and unclassifiable conditions [3]. Pulmonary arteriopathy is the most frequent pattern and its main histopathological features include medial hypertrophy, intimal thickening and complex lesions of the arterioles (Fig. 25.1). Medial hypertrophy (Fig. 25.1A) is an increase in the cross-sectional area of the media of pre-acinar and intra-acinar pulmonary arteries due to both hypertrophy and hyperplasia of smooth muscle cells as well as an increase in connective tissue matrix and elastic fibres in the media of muscular arteries. Intimal thickening (Fig. 25.1B) may be concentric laminar, eccentric or concentric non-laminar. Adventitial thickening (Fig. 25.1C) occurs in most cases of PAH. Complex lesions include the plexiform lesion (Fig. 25.1D), a focal proliferation of endothelial channels lined by myofibroblasts, smooth muscle cells and connective tissue matrix. The frequency of plexiform lesions in PAH remains undetermined. Arteritis may be associated with plexiform lesions and is characterized by necrosis of the arterial wall with fibrinoid insudation and infiltration with inflammatory cells. Pulmonary occlusive venopathy accounts for a relatively small proportion of cases of PAH; the main histopathological features consist of extensive and diffuse occlusion of pulmonary venules and veins of various sizes. The capillary vessels are engorged and prominent and they may be so tortuous as to mimic pulmonary capillary haemangiomatosis. Pulmonary arterioles can show remodelling, with medial hypertrophy and intimal fibrosis. Plexiform lesions and fibrinoid arteritis are not described in pulmonary occlusive venopathy. The pulmonary interstitium frequently shows oedema in the lobular septa, and lymphatics within the lung and pleura are also dilated. Pulmonary microvasculopathy is another rare condition characterized by localized capillary proliferation within the lung. The abnormal proliferating capillaries infiltrate the walls of arteries and veins, invading muscular walls and occluding the lumen. Similar to pulmonary occlusive venopathy, the pulmonary arteries in pulmonary microvasculopathy show marked muscular hypertrophy and intimal thickening. Finally, there are unclassifiable conditions with atypical histopathological features or inadequate sampling of blood vessels.

Pathogenesis, genetics and pathophysiology

The exact processes that initiate the pathological changes seen in PAH are still unknown even if it is recognized that PAH has a multifactorial pathobiology that involves various biochemical pathways and cell types. The increase in PVR is related to different mechanisms, including vasoconstriction, obstructive remodelling of the pulmonary vessel wall, inflammation and thrombosis.

Pulmonary vasoconstriction is believed to be an early component of the pulmonary hypertensive process. Excessive vasoconstriction has been related to abnormal function or expression of potassium channels in the smooth muscle cells and to endothelial dysfunction [8]. Reduced plasma levels of a vasodilator and antiproliferative substance such as vasoactive intestinal peptide have been demonstrated in patients with PAH [9]. Endothelial

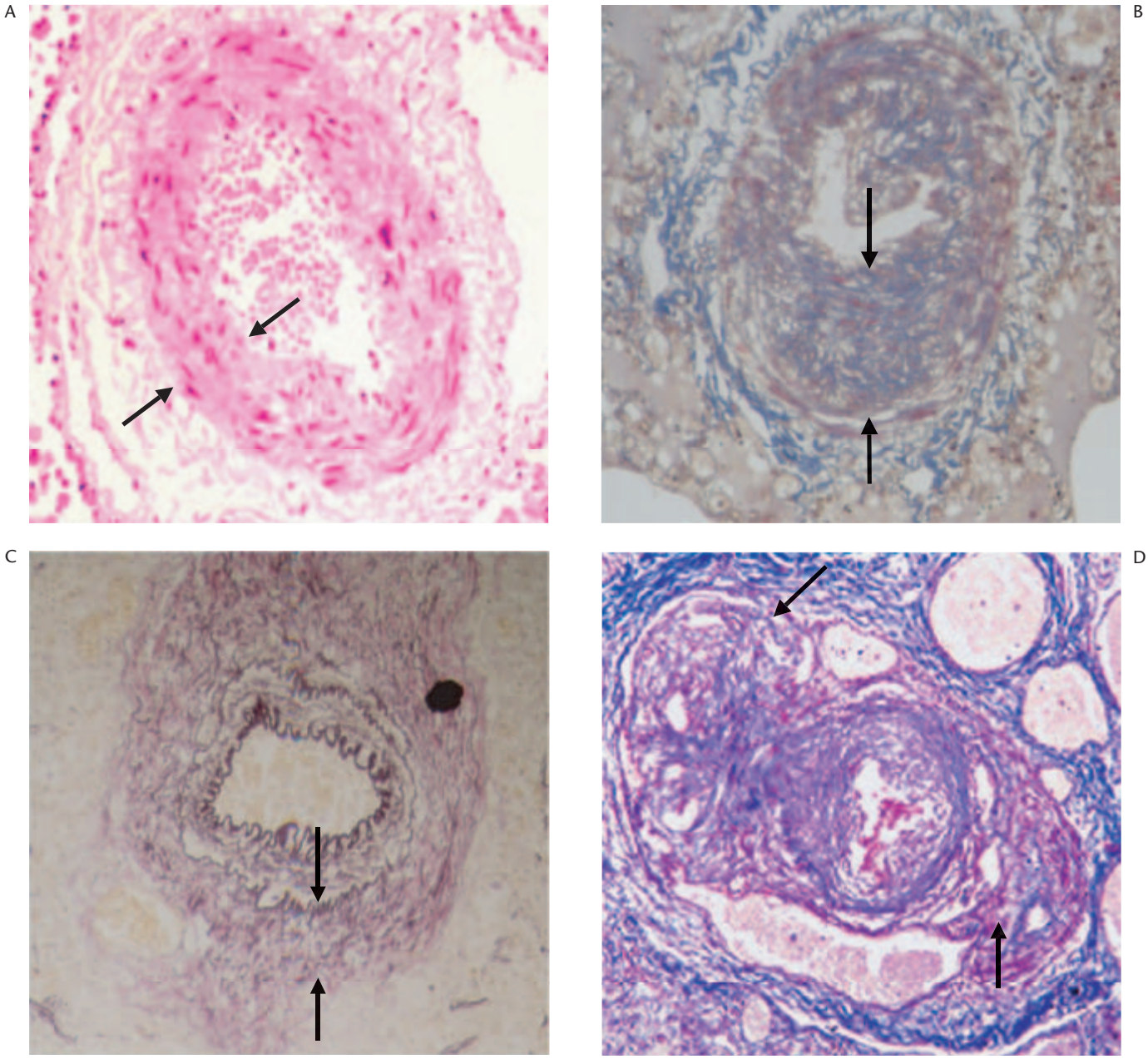

Figure 25.1 Histopathological features of pulmonary arterial hypertension: pulmonary arteriopathy in intra-acinar pulmonary arteries. (A) Medial hypertrophy: increase in the cross-sectional area of the media (between arrows) due to both hypertrophy and hyperplasia of smooth muscle fibres as well as increase in connective tissue matrix and elastic fibres. (B) Intimal thickening (between arrows): eccentric non-laminar thickening due to fibroblasts, myofibroblasts, smooth muscle cells, connective tissue matrix and elastic fibres. (C) Adventitial thickening (between arrows) with its typical ill-defined boundaries. (D) Plexiform lesion: focal proliferation of endothelial channels (arrows) lined by myofibroblasts, smooth muscle cells and connective tissue matrix.

dysfunction leads to chronically impaired production of vasodilators such as nitric oxide and prostacyclin, along with over-expression of vasoconstrictors such as thromboxane A2 and endothelin-1 [8]. Many of these abnormalities both elevate vascular tone and promote vascular remodelling.

The process of pulmonary vascular remodelling involves all layers of the vessel wall and is characterized by proliferative and obstructive changes that involve several cell types, including endothelial, smooth muscle and fibroblast [3,10]. In addition, in the adventitia there is increased production of extracellular matrix including collagen, elastin, fibronectin and tenascin. Angiopoietin-1, an angiogenic factor essential for vascular lung develop-

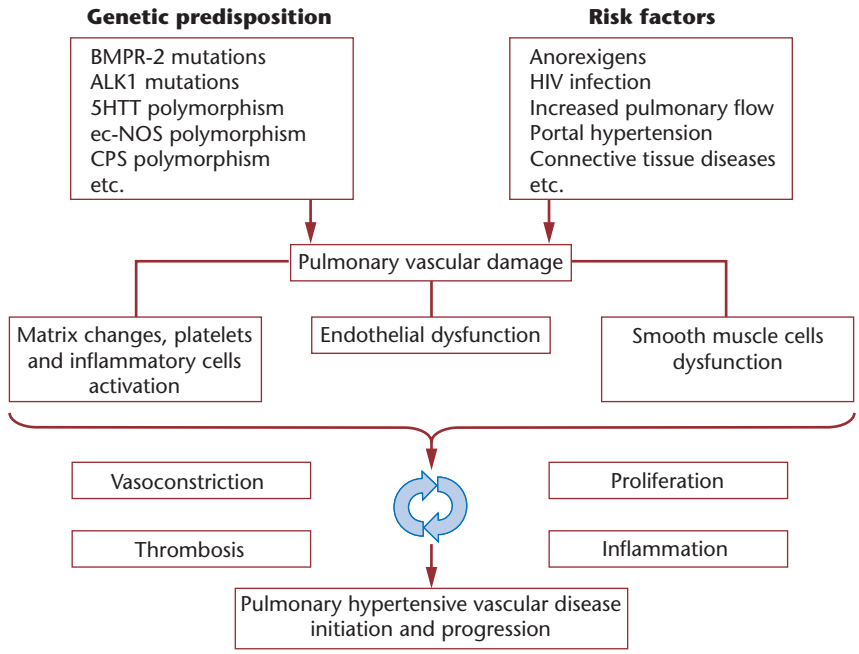

Figure 25.2 Potential pathogenetic and pathobiological mechanisms of pulmonary arterial hypertension: the interaction between genetic predisposition and risk factors may induce changes in different cell types (smooth muscle cells, endothelial cells, inflammatory cells, platelets) and in the extracellular matrix of the pulmonary microcirculation. The imbalance between thrombogenic, mitogenic, pro-inflammatory and vasoconstrictive factors as opposed to anticoagulant, antimitotic and vasodilating mechanisms may initiate and perpetuate interacting processes such as vasoconstriction, proliferation, thrombosis and inflammation in the lung microcirculation. These mechanisms are responsible for the initiation and progression of pathological obstructive changes typical of pulmonary arterial hypertension.

ment, seems to be up-regulated in cases of PH, correlating directly with the severity of the disease.

Inflammatory cells and platelets may also play a significant role in PAH. In fact, inflammatory cells are ubiquitous in the pathological changes of PAH and pro-inflammatory cytokines are elevated in the plasma of PAH patients. Alteration in the metabolic pathways of serotonin, a pulmonary vasoconstrictor substance stored in the platelets, has also been detected in PAH patients [11]. Prothrombotic abnormalities have been demonstrated in PAH patients and thrombi are present in both the microcirculation and elastic pulmonary arteries [3].

FPAH has an autosomal dominant pattern of inheritance with highly variable and incomplete penetrance among families, a female predominance, the suggestion of genetic anticipation, and a clinical course indistinguishable from IPAH [4]. Despite identification of exonic mutations in the bone morphogenetic protein receptor 2 (*BMPR2*) gene in 50–60% of cases of FPAH, the pathobiological linkages between this genetic abnormality and the development of pulmonary vascular hypertensive disease have not been clarified. Interestingly, *BMPR2* exonic mutations have been also identified in about 10% of clinical sporadic IPAH cases. On the other hand, the high frequency of 'true' sporadic IPAH cases (> 90% in most series) and the reduced penetrance of FPAH (only 20% of *BMPR2* gene mutation carriers manifest the disease) suggest that additional triggers are required for the development of the clinical condition. In addition there may be further genes, possibly related to the BMP/transforming growth factor (TGF)-β pathway, yet to be identified. Indeed, mutations in TGF-β receptors, activin-receptor-like kinase 1 (ALK-1) and endoglin have been identified in PAH patients with a personal or family history of hereditary haemorrhagic telangiectasia (i.e. Osler–Weber–Rendu syndrome) [12].

Even if many pathobiological mechanisms have been identified in the cells and tissues of patients with PAH, the exact interactions between them in initiating and progressing the pathological processes are not well understood. Possible theoretical pathways are shown in Fig. 25.2.

The consequent increase in PVR leads to right ventricular overload, hypertrophy and dilatation and eventually to right ventricular failure and death. The importance of the progression of right ventricular failure on the outcome of IPAH patients is testified by the prognostic impact of right atrial pressure, cardiac index and PAP [6], three main determinants of right ventricular pump function. The depression of myocardial contractility seems to be one of the primary events in the progression of heart failure in a chronically overloaded right ventricle. In fact, changes in the adrenergic pathways of right ventricular myocytes leading to reduced contractility have been shown in IPAH patients [13]. However, afterload mismatch remains the leading determinant of heart failure in patients with PAH and chronic thromboembolic pulmonary hypertension (CTEPH) because its removal, as after successful pulmonary endarterectomy or lung transplantation [14], leads almost invariably to sustained recovery of right ventricular function. Therefore, the haemodynamic changes and the prognosis of patients with PAH are related to the complex pathophysiological interactions between the rate of progression (or regression) of the obstructive changes in the pulmonary

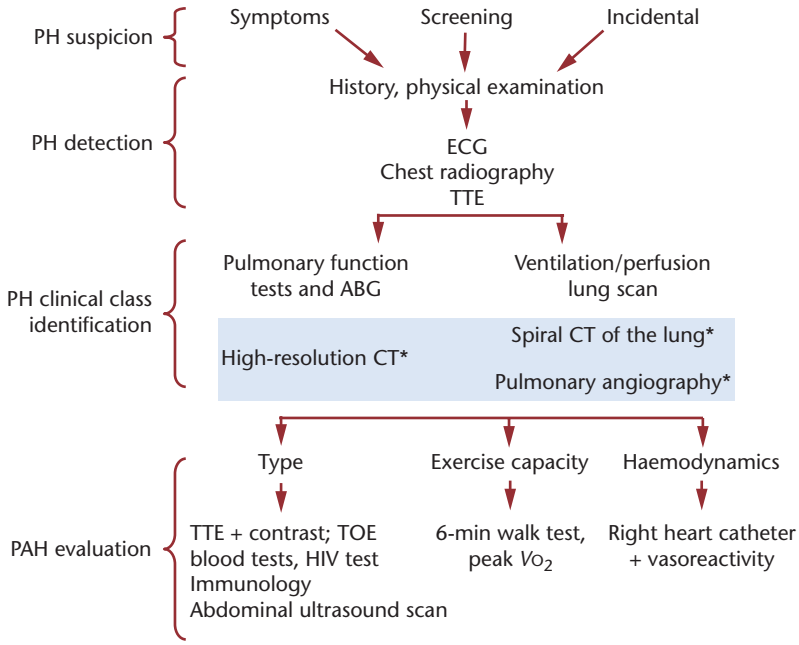

Figure 25.3 Diagnostic algorithm for pulmonary hypertension. ABG, arterial blood gases; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography; *, required in specific circumstances (see text).

circulation and the response of the overloaded right ventricle, which may also be influenced by genetic determinants [15].

Diagnosis

The diagnostic process of PH requires a series of investigations intended to make the diagnosis, clarify the clinical class of PH and the type of PAH, and evaluate the functional and haemodynamic impairment. The various investigative tests can be combined in a diagnostic algorithm (Fig. 25.3), which for practical purposes can be divided into four phases.

1 *Suspicion*. Clinical suspicion of PH should be aroused when there are symptoms such as breathlessness without overt signs of specific heart or lung disease, in cases of screening in predisposing conditions or in cases of incidental findings.
2 *Detection*. The detection of PH requires investigations able to confirm the diagnosis, e.g. clinical examination, ECG, chest radiograph and transthoracic echocardiography (TTE).
3 *Class identification*. The next step is the identification of the clinical class (see Table 25.1) [2]. This is accomplished by the use of essential investigations such as pulmonary function tests, arterial blood gases and ventilation–perfusion lung scan. In particular circumstances, additional tests can be performed such as high-resolution computed tomography (CT) of the chest, contrast-enhanced spiral CT of the lung and pulmonary angiography.
4 *Evaluation*. After the diagnosis of PAH (clinical class 1), additional investigations are required for the exact identification of the type and for the assessment of exercise capacity and haemodynamics.

Symptoms and signs of PH

The symptoms of PH include breathlessness, fatigue, weakness, angina, syncope and abdominal distension [16]. Symptoms at rest are reported only in very advanced cases.

The physical signs of PH include left parasternal lift, accentuated pulmonary component of S_2, pansystolic murmur of tricuspid regurgitation, diastolic murmur of pulmonary insufficiency and right ventricular S_3 [16]. Jugular vein distension, hepatomegaly, peripheral oedema, ascites and cool extremities characterize patients in a more advanced state. Lung sounds are usually normal.

ECG

The ECG may provide suggestive or supportive evidence of PH by demonstrating right ventricular hypertrophy and strain, and right atrial dilation (Fig. 25.4). Right ventricular hypertrophy on ECG is present in 87% and right axis deviation in 79% of patients with IPAH [16]. The ECG has inadequate sensitivity (55%) and specificity (70%) to be a screening tool for detecting significant PH.

Chest radiograph

In 90% of patients with IPAH the chest radiograph is abnormal at the time of diagnosis [16]. Findings include central pulmonary arterial dilatation, which contrasts

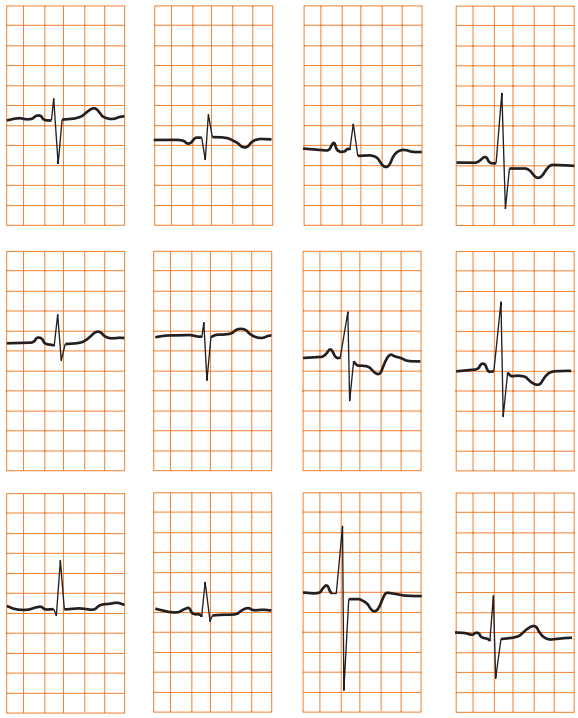

Figure 25.4 ECG of a patient with severe pulmonary arterial hypertension: right atrial enlargement, right axis deviation, right ventricular hypertrophy and strain can be noted.

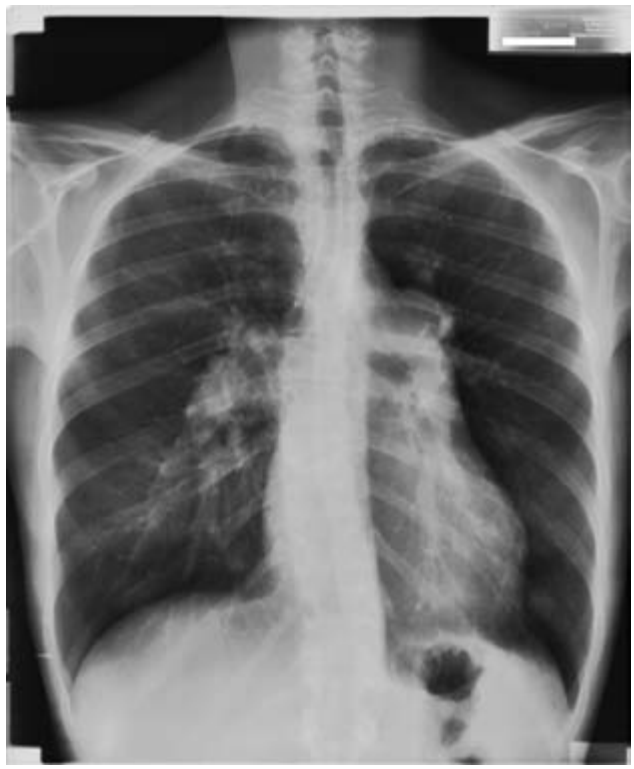

Figure 25.5 Chest radiograph of a patient with severe pulmonary arterial hypertension: central pulmonary arterial dilatation and 'pruning' (loss) of the peripheral blood vessels can be noted.

with 'pruning' (loss) of the peripheral blood vessels (Fig. 25.5). Right atrial and ventricular enlargement may be seen and it progresses in more advanced cases. The chest radiograph allows associated moderate-to-severe lung disease or pulmonary venous hypertension due to left heart abnormalities to be reasonably excluded (see High-resolution CT of the lung, below).

Transthoracic Doppler echocardiography

TTE is an excellent non-invasive screening test for the patient with suspected PH. TTE estimates pulmonary artery systolic pressure (PASP) and can provide additional information about the cause and consequences of PH. PASP is equivalent to right ventricular systolic pressure (RVSP) in the absence of pulmonary outflow obstruction. RVSP is estimated by measurement of the systolic regurgitant tricuspid flow velocity and an estimate of right atrial pressure (RAP) (Fig. 25.6A,B). Tricuspid regurgitant jets can be assessed in 74% of patients with PH [17].

According to data obtained in normal subjects [18], mild PH can be defined as a PASP of approximately 36–50 mmHg or a resting tricuspid regurgitant velocity of 2.8–3.4 m/s (assuming a normal RAP of 5 mmHg). It should also be noted that with this definition a number of false-positive diagnoses can be anticipated, especially in aged subjects, and confirmation with right heart catheterization (RHC) is required in symptomatic patients (New York Heart Association, NYHA, class II/III). In asymptomatic subjects (NYHA class I), a concomitant CTD should be excluded and echocardiography should be repeated in 6 months. Also the possibility of false-negative Doppler echocardiographic results should be considered in cases of high clinical suspicion [19].

Additional echocardiographic and Doppler parameters are important for the confirmation of diagnosis and assessment of the severity of PH, including right ventricular dimensions (enlarged) and function (reduced), left ventricular dimensions (reduced) (Fig. 25.6C) and function (normal), tricuspid [20], pulmonary and mitral valve abnormalities, right ventricular ejection and left ventricular filling characteristics, inferior vena cava dimensions and size of pericardial effusion [21,22].

Besides identification of PH, TTE also allows a differential diagnosis of possible causes. In fact, TTE can recognize left heart valvular and myocardial diseases responsible for pulmonary venous hypertension (clinical class 2), and congenital heart diseases with systemic-to-pulmonary shunts can be easily identified (clinical class 1.3.2). The venous injection of agitated saline as contrast medium can help the identification of patent

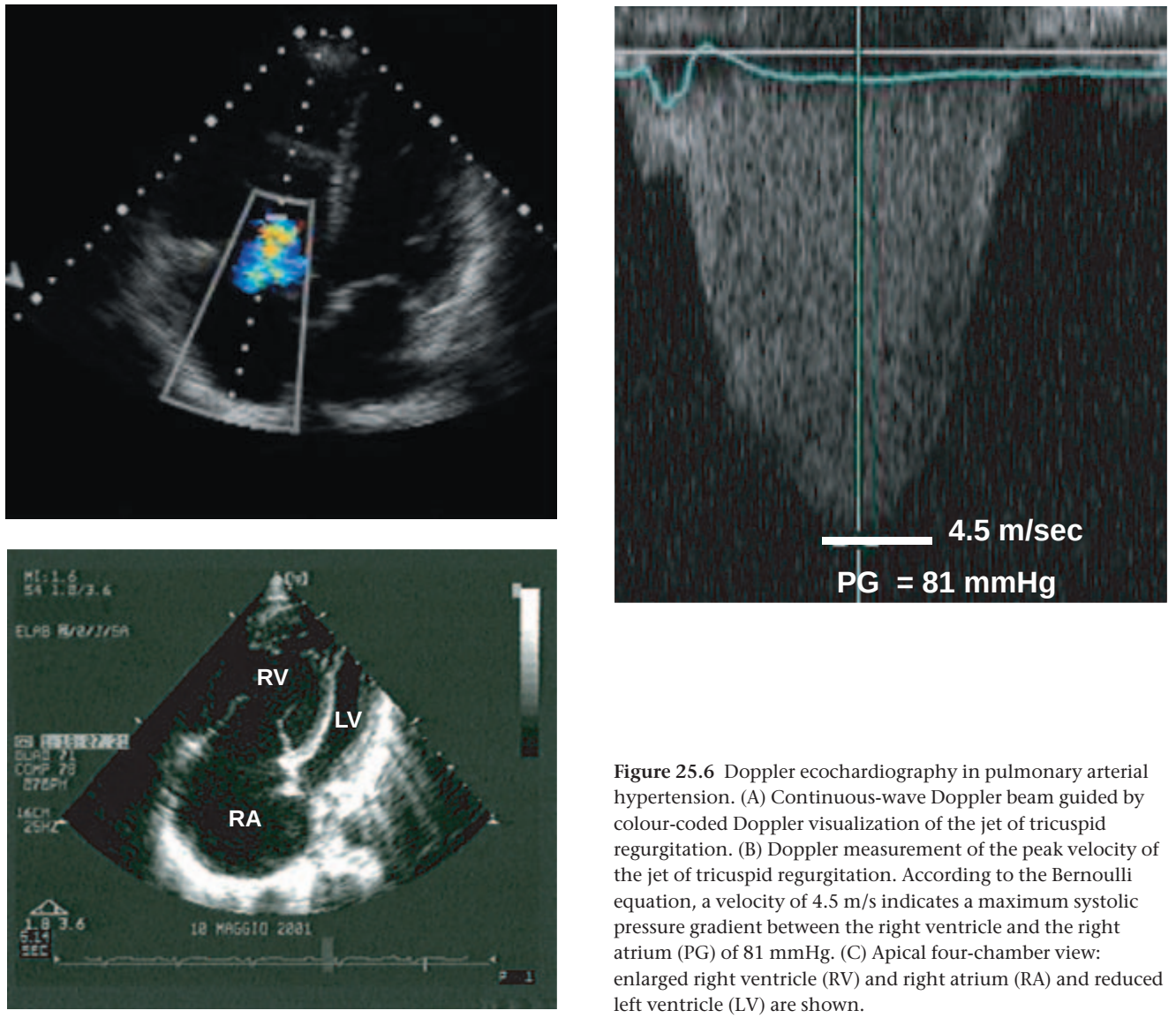

Figure 25.6 Doppler ecochardiography in pulmonary arterial hypertension. (A) Continuous-wave Doppler beam guided by colour-coded Doppler visualization of the jet of tricuspid regurgitation. (B) Doppler measurement of the peak velocity of the jet of tricuspid regurgitation. According to the Bernoulli equation, a velocity of 4.5 m/s indicates a maximum systolic pressure gradient between the right ventricle and the right atrium (PG) of 81 mmHg. (C) Apical four-chamber view: enlarged right ventricle (RV) and right atrium (RA) and reduced left ventricle (LV) are shown.

foramen ovale or sinus venosus-type atrial septal defects that can be overlooked on the standard TTE examination. Transoesophageal echocardiography is rarely required and is used to confirm the presence, and assess the exact size, of small atrial septal defects.

Pulmonary function tests and arterial blood gases

Pulmonary function tests and arterial blood gases will identify the contribution of underlying airway or parenchymal lung disease. Patients with PAH usually have decreased lung diffusion capacity for carbon monoxide (D_{LCO}) (typically in the range of 40–80% predicted) and mild to moderate reduction of lung volumes. Arterial oxygen tension (Pa_{O_2}) is normal or only slightly lower than normal and arterial carbon dioxide tension (Pa_{CO_2}) is decreased as a result of alveolar hyperventilation. Chronic obstructive pulmonary disease (COPD), as a cause of hypoxic PH, is diagnosed on the evidence of irreversible airflow obstruction together with increased residual volumes, reduced D_{LCO} and normal or increased Pa_{CO_2}. A decrease in lung volume together with a decrease in D_{LCO} may indicate a diagnosis of interstitial lung disease (ILD). The severity of emphysema and of ILD can be diagnosed using high-resolution CT. If clinically suspected, screening overnight oximetry will exclude significant obstructive sleep apnoea/hypopnoea.

Ventilation–perfusion ($\dot{V}/\dot{Q}$) lung scan

In PAH, lung $\dot{V}/\dot{Q}$scans may be entirely normal (Fig. 25.7A). However, they may also show small peripheral non-

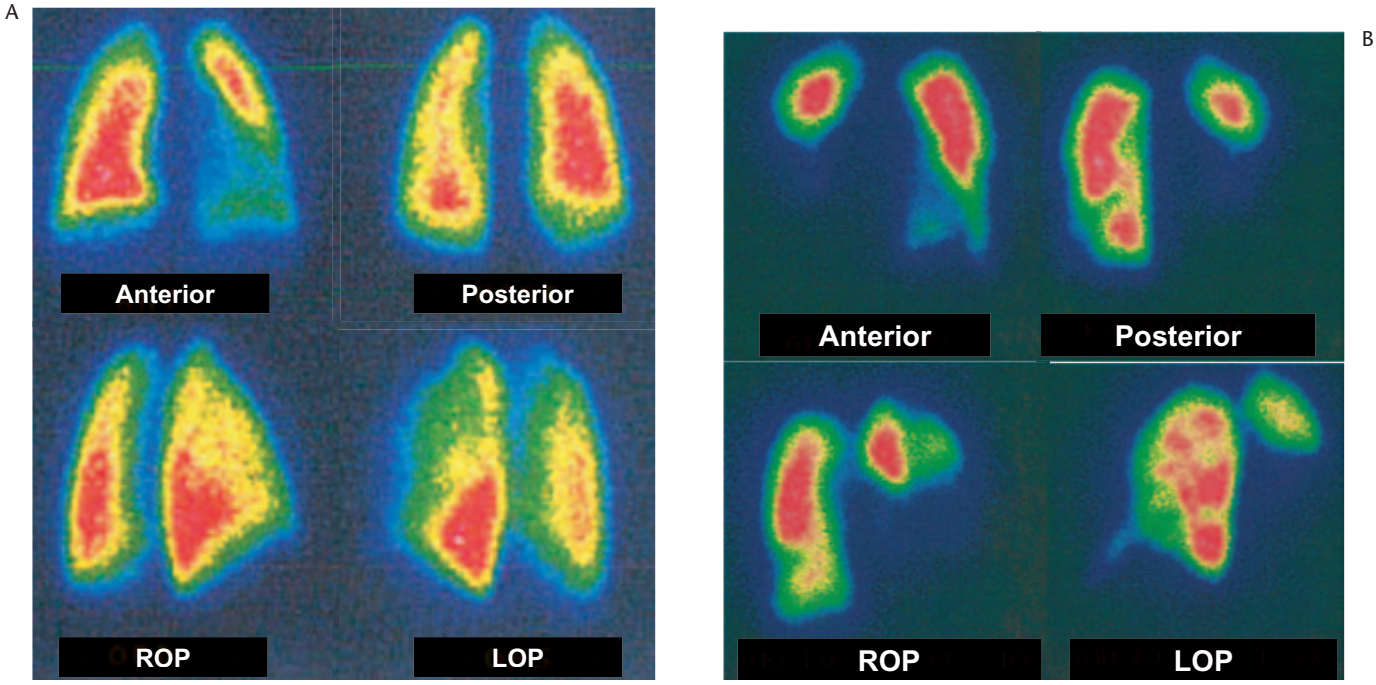

Figure 25.7 Perfusion lung scan. (A) Normal perfusion lung scan of a patient with pulmonary arterial hypertension: anterior, posterior, right (ROP) and left (LOP) oblique posterior views. (B) Lobar and segmental perfusion defects in a patient with chronic thromboembolic pulmonary hypertension.

segmental defects in perfusion. These are normally ventilated and thus represent $\dot{V}/\dot{Q}$ mismatch. Lung $\dot{V}/\dot{Q}$ scan provides a means of diagnosis of CTEPH (clinical class 4) [23,24], showing lobar and segmental defects in the perfusion image (Fig. 25.7B). A caveat is that unmatched perfusion defects are also seen in veno-occlusive disease. In patients with parenchymal lung disease the perfusion defects are *matched* by ventilation defects.

High-resolution CT of the lung

High-resolution CT provides detailed views of the lung parenchyma and facilitates the diagnosis of ILD (Fig. 25.8A) and emphysema. High-resolution CT may be indicated in cases where there is interstitial marking on the chest radiograph without evidence of left ventricular failure. In these cases the confirmation of a diffuse, central, ground-glass opacification and thickening of interlobular septa suggest pulmonary veno-occlusive disease (Fig. 25.8B); additional findings are lymphadenopathy, pleural shadows and effusions [25].

Contrast-enhanced spiral CT of the lung and pulmonary angiography

Contrast-enhanced spiral CT is indicated in patients

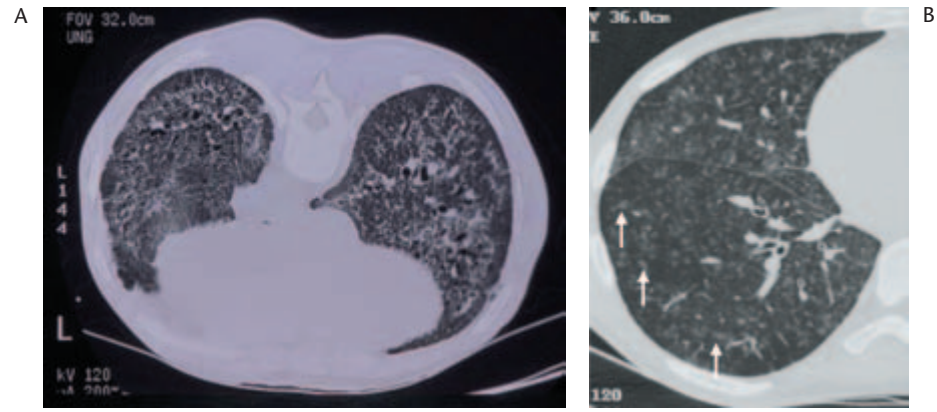

Figure 25.8 (A) High-resolution CT scan of a patient with severe interstitial lung disease: extensive fibrosis and rearrangement of the lung parenchyma is detectable in both lungs. (B) High-resolution CT scan showing ill-defined, patchy and centrilobular ground-glass opacities in a patient with pulmonary veno-occlusive disease (see arrows).

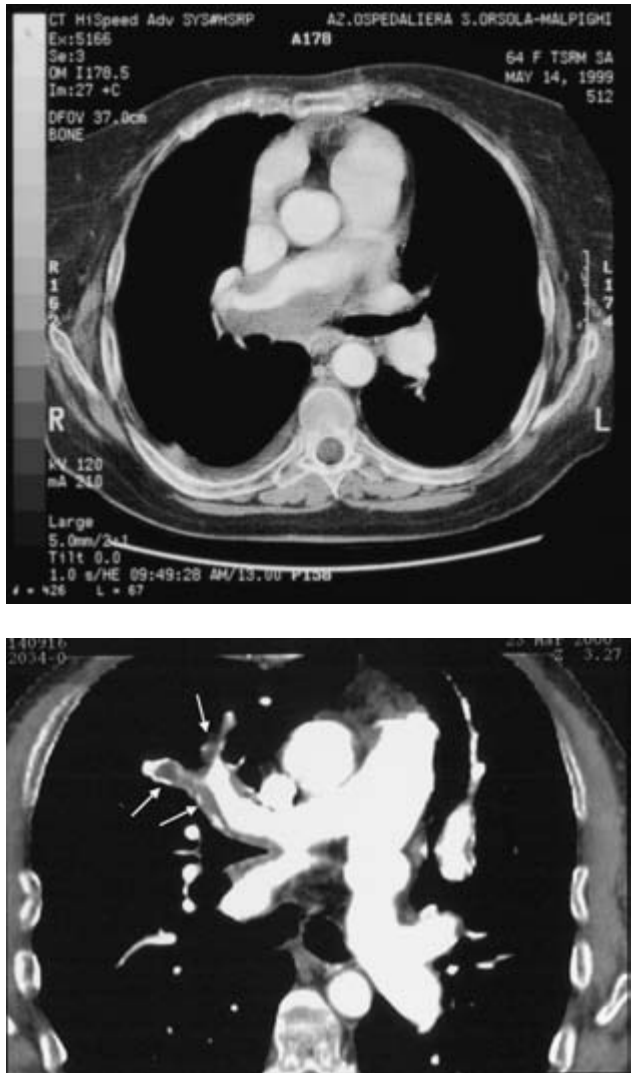

Figure 25.9 Contrast-enhanced spiral CT of the lung of two patients with chronic thromboembolic pulmonary hypertension. (A) Severe reduction of calibre of the right main pulmonary artery by an organized thrombus. (B) Obstruction of two segmental arteries by an organized thrombus which extends proximally to a lobar branch (arrows).

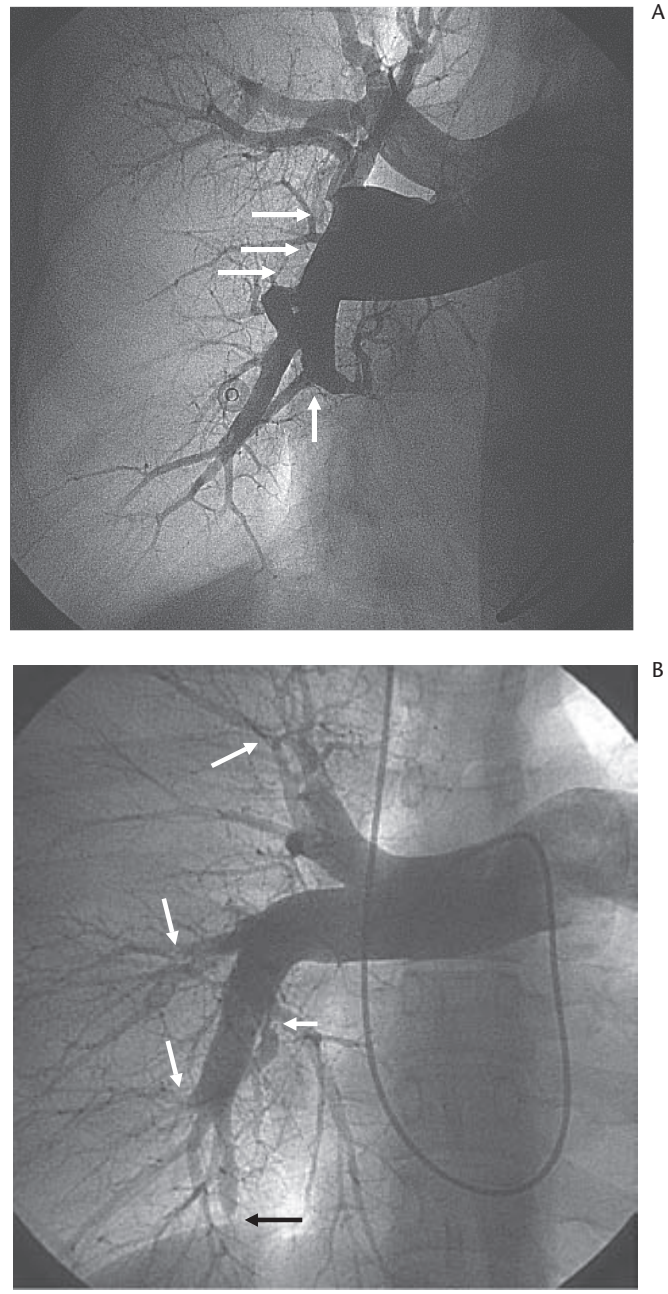

Figure 25.10 Pulmonary angiography of patients with chronic thromboembolic pulmonary hypertension. (A) Proximal obstructions of middle and lower lobe right pulmonary arteries. (B) Distal obstruction/stenosis of multiple segmental and subsegmental right pulmonary arteries.

with PH when $\dot{V}/\dot{Q}$ lung scintigraphy shows segmental defects of perfusion with normal ventilation and may demonstrate central chronic pulmonary thromboemboli. CT features of chronic thromboembolic disease include complete occlusion of pulmonary arteries, eccentric filling defects consistent with organized thrombi, recanalization, and stenoses or webs [24] (Fig. 25.9).

Traditional pulmonary angiography is still required in the work-up of CTEPH to better identify patients who can benefit from the intervention of endarterectomy [22,23] (Fig. 25.10A). Pulmonary angiography is more accurate in the identification of distal obstructions (Fig. 25.10B) and is indicated also in cases of inconclusive contrast-enhanced spiral CT in patients with clinical and lung perfusion scan suspicion of CTEPH.

Blood tests and immunology

Routine biochemistry, haematology and thyroid func-

tion tests are required. CTD are diagnosed primarily on clinical and laboratory criteria and an autoimmune screen consists of antinuclear antibodies, including anti-centromere antibodies, anti-SCL70 and RNP. About one-third of patients with IPAH have positive but low antinuclear antibody titre (< 1 : 80 dilutions). Patients with substantially elevated antinuclear antibodies and/or suspicious clinical features require further serological assessment and rheumatology consultation. Finally, consent of all patients should be obtained and an HIV serology test undertaken.

Abdominal ultrasound scan

Liver cirrhosis and/or portal hypertension can be reliably excluded by the use of abdominal ultrasound. The use of contrast agents may improve the diagnosis. Portal hypertension can be confirmed by the detection of an increased gradient between free and occluded (wedge) hepatic vein pressure at the time of RHC [26].

Exercise capacity

The objective assessment of exercise capacity in patients with PAH is an important instrument for evaluating disease severity [27,28] and treatment effect [29,30]. The most commonly used exercise tests for PH are the six-minute walk test and cardiopulmonary exercise testing with gas exchange measurement.

Haemodynamics

RHC is required to confirm the diagnosis of PAH, to assess the severity of the haemodynamic impairment and to test the vasoreactivity of the pulmonary circulation. PAH is defined by a mean PAP > 25 mmHg at rest or > 30 mmHg with exercise, by a pulmonary wedge (occluded) pressure (PWP) ≤ 15 mmHg (precapillary PH, see Table 25.2) and by PVR > 3 mmHg/l/min (Wood units). Left heart catheterization is required in the rare circumstances in which a reliable PWP cannot be measured. The assessment of PWP may allow the distinction between arterial and venous PH in patients with concomitant left heart diseases.

RHC is also important in patients with definite moderate-to-severe PAH because the haemodynamic variables have prognostic relevance [6]. Elevated mean RAP, mean PAP and reduced cardiac output and central venous oxygen saturation identify IPAH patients with the worst prognosis.

An acute vasodilator challenge performed during RHC [31,32] can identify patients who may benefit from long-term treatment with calcium channel blockers. Acute vasodilator testing should only be done using short-acting pulmonary vasodilators at the time of the initial RHC in experienced centres in order to minimize the potential risks. Currently the agents used in acute testing are intravenous prostacyclin or adenosine and inhaled nitric oxide [33,34]. A positive acute vasoreactive response (positive acute responders) is defined as a reduction of mean PAP ≥ 10 mmHg to reach an absolute value of mean PAP ≤ 40 mmHg with an increased or unchanged cardiac output [32,35,36]. Generally, only about 10–15% of patients with IPAH will meet these criteria [32,33].

Assessment of severity

The variables that have been shown to predict prognosis in IPAH when assessed at baseline or after targeted treatments [30] are listed in Table 25.3. Very little information is available in other conditions, such as PAH associated

Table 25.3 Prognostic parameters in patients with idiopathic pulmonary arterial hypertension

Clinical parameters
Baseline NYHA functional classification [6]
NYHA functional class on chronic epoprostenol treatment [49,50]
History of right heart failure [50]
Exercise capacity
Baseline six-minute walk test distance [27]
Six-minute walk test distance on chronic epoprostenol treatment [50]
Baseline peak Vo_2 [35]
Echocardiographic parameters
Pericardial effusion [84]
Right atrial size [84]
Left ventricular eccentricity index [84]
Doppler right ventricular (Tei) index [35]
Tricuspid regurgitation severity [20]
Haemodynamics
Right atrial pressure [6]
Mean pulmonary arterial pressure [6]
Cardiac output [6]
Mixed venous oxygen saturation [6]
Positive acute response to vasoreactivity tests [33,39]
Fall in pulmonary vascular resistance < 30% after 3 months of epoprostenol [50]
Blood tests
Hyperuricaemia [35]
Baseline brain natriuretic peptide [35]
Brain natriuretic peptide after 3 months' therapy [35]
Troponin: detectable, especially persistent leakage [85]
Plasma noradrenaline (norepinephrine) [35]
Plasma endothelin-1 [58]

NYHA, New York Heart Association.

with CTD, congenital systemic-to-pulmonary shunts, HIV infection or portal hypertension. In these circumstances, additional factors may contribute to the overall outcome. In fact, PAH associated with CTD has a worse prognosis than that of patients with IPAH, whereas patients with PAH associated with congenital systemic-to-pulmonary shunts have a more slowly progressive course than patients with IPAH. In clinical practice, the prognostic value of a single variable in the individual patient may be less than the value of multiple concordant variables.

Pharmacotherapy

Treatments for PAH are discussed according to the level of evidence and grade of recommendation [36] (Table 25.4) and a treatment algorithm is proposed [36] (Fig. 25.11). General measures for patients with PAH include adjustments (reduction) of daily activities, avoiding altitudes above 1500 m, prevention of pulmonary infections, birth control, pregnancy termination, psychological assistance and appropriate management of elective general surgery.

Oral anticoagulant treatment

The evidence for the favourable effects of oral anticoagulant treatment in patients with IPAH or PAH associated with use of anorexigens is based on retrospective analysis of single-centre studies [38,39]. The target international normalized ratio (INR) in patients with IPAH varies somewhat, being 1.5–2.5 in most centres in North America and 2.0–3.0 in European centres. The evidence supporting anticoagulation in patients with IPAH may be extrapolated to other patients with PAH provided that the risk–benefit ratio is carefully considered.

Diuretics

Patients with decompensated right heart failure develop fluid retention that leads to increased central venous

Table 25.4 Grading of recommendations and level of evidence for efficacy in idiopathic pulmonary arterial hypertension

	Grade of recommendation			
Treatment	**I**	**IIa**	**IIb**	**Level of evidence**
General measures		✓		C
Oral anticoagulants		✓*		C
Diuretics	✓			C
Digoxin			✓	C
Oxygen†		✓		C
Calcium channel blockers	✓‡			C
Epoprostenol	✓§			A
Treprostinil		✓		B
Iloprost (inhalation)	✓			A
Iloprost (intravenous)		✓		C
Beraprost			✓	B
Bosentan	✓‖			A
Sitaxsentan¶				B
Ambrisentan¶				C
Sildenafil	✓**			A
Combination therapy		✓		B
Balloon atrial septostomy		✓		C
Lung transplantation	✓			C

*IIa for IPAH, IIb for other PAH conditions.
†If arterial oxygen saturation < 90%.
‡Only in patients responding to acute vasoreactivity tests, I for IPAH, IIb for other PAH conditions.
§IIa C in conditions different from IPAH and PAH associated with connective tissue diseases.
‖IIa B in NYHA class IV, IIa B in conditions different from IPAH and PAH associated with connective tissue diseases.
¶These drugs are currently available only for patients enrolled in randomized controlled trials and no grade of recommendation is given.
**IIa C in conditions different from IPAH and PAH associated with connective tissue diseases.

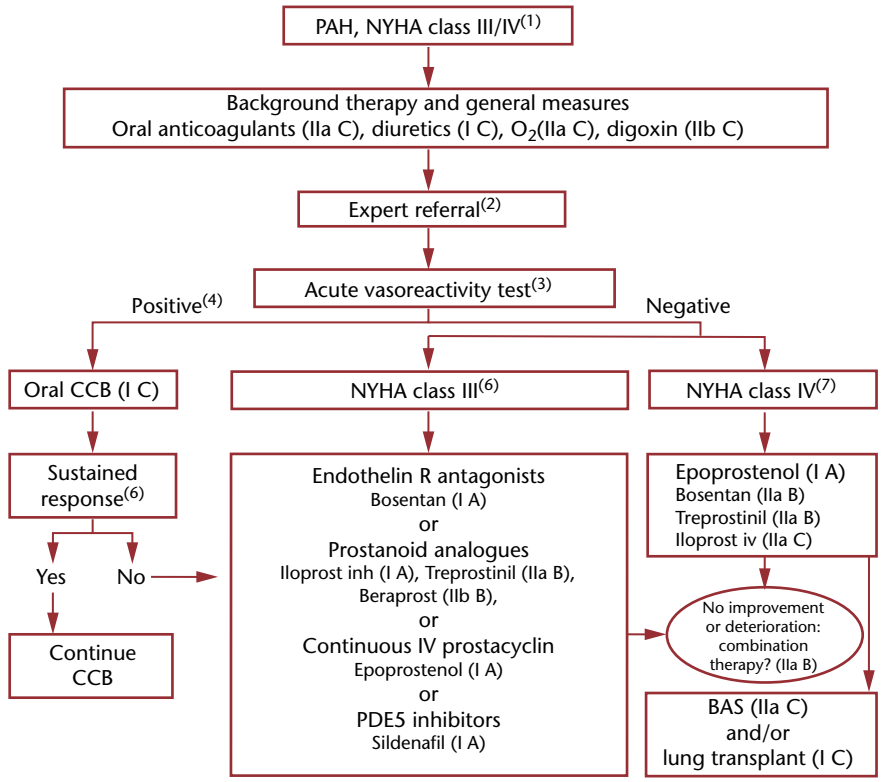

Figure 25.11 Evidence-based treatment algorithm. (1) The algorithm is restricted to patients in NYHA functional class III or IV because they represent the largest population included in controlled clinical trials. For NYHA class I or II very few data are available. In addition, the different treatments have been evaluated mainly in sporadic idiopathic pulmonary arterial hypertension (IPAH) and in pulmonary arterial hypertension (PAH) associated with scleroderma or with use of anorexigens. Extrapolation of these recommendations to the other PAH subgroups should be made with caution. (2) Due to the complexity of the acute vasoreactivity tests and of the treatment options available, it is strongly recommended that consideration be given to referral of patients with PAH to a specialized centre. (3) Acute vasoreactivity test should be performed in all patients with PAH even if the greater incidence of positive response is achieved in patients with IPAH and PAH associated with anorexigen use. (4) A positive acute response to vasodilators is defined as a fall in mean pulmonary artery pressure of at least 10 mmHg to less than or equal to 40 mmHg, with an increased or unchanged cardiac output during acute challenge with inhaled nitric oxide, intravenous epoprostenol or intravenous adenosine. (5) Sustained response to calcium channel blockers (CCB) is defined as patients being in NYHA functional class I or II with near-normal haemodynamics after several months of treatment. (7) In patients in NYHA functional class III, first-line therapy may include oral endothelin receptor antagonists, chronic intravenous epoprostenol, or prostanoid analogues. (7) At present, sildenafil is not approved for PAH by any regulatory agency. (8) Most experts consider that NYHA functional class IV patients in unstable condition should be treated with intravenous epoprostenol (survival improvement, worldwide experience and rapidity of action). I, IIa, IIB, grade of recommendation; A, B, C, grading of level of evidence (see Table 25.4); BAS, balloon atrial septostomy; inh, inhaled; iv, continuous intravenous; PDE, phophodiesterase; R, receptors.

pressure, abdominal organ congestion, peripheral oedema and, in advanced cases, ascites. Appropriate diuretic treatment in right heart failure allows clear symptomatic and clinical benefits in patients with PAH even if specific randomized controlled trials have not been performed.

Oxygen

No consistent data are currently available on the effects of long-term oxygen treatment in PAH. Although improvement in PH with low-flow supplemental oxygen has been reported in some PAH patients, this has not been confirmed in controlled studies. However, it is generally considered important to maintain oxygen saturations at greater than 90% at all times.

Digitalis and dobutamine

Short-term intravenous administration of digoxin in IPAH produces a modest increase in cardiac output and a significant reduction in circulating noradrenaline (norepinephrine) levels [40]; however, no data are available

on the effects of long-term treatment. Patients with end-stage PAH are treated with intravenous dobutamine in most expert centres [41].

Calcium channel blockers

Favourable clinical and prognostic effects of high doses of calcium channel blockers in vasoreactive patients with IPAH have been shown in single-centre, non-randomized, non-controlled studies [32,39]. However, it would appear unethical to withhold therapy with high-dose calcium channel blocker in a patient with a consistent reduction in PAP by acute pharmacological testing and to perform a placebo-controlled clinical trial in these subjects [42]. Empirical treatment with calcium channel blockers without an acute vasoreactivity test is strongly discouraged due to possible severe adverse effects.

The calcium channel blockers that have been predominantly used are nifedipine and diltiazem and the choice can be based upon the patient's heart rate at baseline (relative bradycardia favouring nifedipine, relative tachycardia favouring diltiazem). The doses of these drugs that have shown efficacy in IPAH are relatively high, i.e. up to 120–240 mg/day for nifedipine and 240–720 mg/day for diltiazem [38]. It is advisable to start with reduced doses (i.e. 30 mg of extended-release nifedipine b.i.d. or 60 mg of diltiazem t.i.d.) and then increase cautiously and progressively in the subsequent weeks to the maximal tolerated regimen. About 10–15% of patients with IPAH will meet the criteria for a positive acute vasoreactive response and only about half of these will also be clinical and haemodynamic long-term responders to treatment with calcium channel blockers. It is commonly accepted that only in these cases is continuation of calcium channel blockers as a single treatment warranted.

The usefulness of acute vasoreactivity tests and long-term treatment with calcium channel blockers in patients with PAH associated with CTD or congenital heart disease is less clear compared with patients with IPAH [32,43]. However, experts suggest that in these cases patients should be tested for acute vasoreactivity and the vasoreactive ones treated cautiously with oral calcium channel blockers, monitoring them closely to determine both the efficacy and safety of such therapy.

Synthetic prostacyclin and prostacyclin analogues

Prostacyclin is produced predominantly by endothelial cells and induces potent vasodilatation of all vascular beds studied. This compound is the most potent endogenous inhibitor of platelet aggregation and it also appears to have both cytoprotective and antiproliferative activities [44]. Dysregulation of the prostacyclin metabolic pathways has been shown in patients with PAH as assessed by reduction of prostacyclin synthase expression in the pulmonary arteries and of prostacyclin urinary metabolites [45].

EPOPROSTENOL

Epoprostenol (synthetic prostacyclin) is available as a stable freeze-dried preparation that needs to be dissolved to allow intravenous infusion. Epoprostenol has a short half-life (3–5 min) and is stable at room temperature for only 8 h; this explains why it needs to be administered continuously by means of infusion pumps and permanent tunnellized catheters.

The efficacy of continuous intravenous administration of epoprostenol has been tested in three unblinded randomized controlled trials in patients with IPAH [46,47] and in those with PAH associated with the scleroderma spectrum of diseases [48]. Epoprostenol improves symptoms, exercise capacity and haemodynamics in both clinical conditions, and is the only treatment shown to improve survival in IPAH in a randomized study.

Long-term treatment with epoprostenol is initiated at a dose of 2–4 ng/kg/min, with doses increasing at a rate limited by adverse effects (flushing, headache, diarrhoea, leg pain). Optimal dose is variable between individual patients, ranging in the majority between 20 and 40 ng/kg/min [49,50].

Serious adverse events related to the delivery system include pump malfunction, local site infection, catheter obstruction and sepsis. Abrupt interruption of the epoprostenol infusion should be avoided as this may, in some patients, lead to a rebound worsening of their PH with symptomatic deterioration and even death.

TREPROSTINIL

Treprostinil is a tricyclic benzidine analogue of epoprostenol, with sufficient chemical stability to be administered at ambient temperature. These characteristics allow administration of the compound by the intravenous as well as the subcutaneous route. The subcutaneous administration of treprostinil can be accomplished by microinfusion pumps and small subcutaneous catheters. The effects of treprostinil in PAH were studied in the largest worldwide randomized controlled trial performed in this condition, and showed improvements in exercise capacity, haemodynamics and clinical events [50]. The greatest exercise improvement was observed in patients who were more compromised at baseline and in subjects who could tolerate upper quartile dose (> 13.8 ng/kg/min). Infusion site pain was the most common adverse effect of treprostinil, leading to discontinuation of the treatment in 8% of cases on active drug and limiting dose increase in an additional proportion of patients. Treprostinil has

been recently approved in the USA also for intravenous use in patients with PAH.

BERAPROST

Beraprost is the first chemically stable and orally active prostacyclin analogue. Two randomized controlled studies [52,53] with this compound have shown an improvement in exercise capacity that unfortunately persists only up to 3–6 months.

ILOPROST

Iloprost is a chemically stable prostacyclin analogue available for intravenous, oral and aerosol administration. Inhaled therapy for PAH is an attractive concept that has the theoretical advantage of being selective for the pulmonary circulation. Inhaled iloprost has been evaluated in one randomized controlled trial in which daily repetitive iloprost inhalations (six to nine times, 2.5–5 μg/inhalation, median 30 μg daily) were compared with placebo inhalation in patients with PAH and CTEPH [53]. The study showed an increase in exercise capacity and improvement in symptoms, PVR and clinical events in enrolled patients. A second randomized controlled trial on 60 patients already treated with bosentan has shown increase in exercise capacity in the subjects randomized to the addition of inhaled iloprost in comparison with placebo. Overall, inhaled iloprost was well tolerated. Continuous intravenous administration of iloprost appears to be as effective as epoprostenol in a small series of patients with PAH and CTEPH [55].

Endothelin-1 receptor antagonists

Activation of the endothelin (ET)-1 system has been demonstrated in both plasma and lung tissues of PAH patients [56]. Although it is not clear if the increases in ET-1 plasma levels are a cause or a consequence of PH [57], studies on tissue ET system expression support a prominent role for ET-1 in the pathogenesis of PAH [58].

BOSENTAN

Bosentan is an oral active dual ET_A and ET_B receptor antagonist and is the first molecule of this class of drugs to be synthesized. Bosentan has been evaluated in PAH in two randomized controlled trials that have shown improvement in exercise capacity, functional class, haemodynamics, echocardiographic and Doppler variables, and time to clinical worsening [22,59,60]. Increases in hepatic aminotransferases occurred in 10% of the subjects but were found to be dose dependent and reversible after dose reduction or discontinuation. For these reasons liver function tests should be performed at least monthly in patients receiving bosentan.

SITAXSENTAN

Sitaxsentan, a selective orally active ET_A receptor antagonist, has been assessed in two randomized controlled trials on patients with NYHA class II/III PAH [61]. Aetiology included IPAH and PAH associated with CTD or congenital heart diseases. The studies demonstrated improvements in exercise capacity, haemodynamics and clinical events. Incidence of abnormal liver function tests, which reversed in all cases, was 0–4% for 100 mg and 9.5% for 300 mg. Interaction with warfarin has been reported.

AMBRISENTAN

Ambrisentan, a selective orally active ET_A receptor antagonist, has thus far been evaluated in a pilot blinded dose-comparison study in 64 patients with PAH. The results show improvements in exercise capacity and haemodynamics that appear similar to the results observed with the other ET receptor antagonists [61].

Type 5 phosphodiesterase inhibitors

SILDENAFIL

Sildenafil is an orally active, potent and selective inhibitor of cGMP phosphodiesterase type 5 that exerts its pharmacological effect by increasing the intracellular concentration of cGMP. A number of uncontrolled studies have reported favourable effects of sildenafil in PAH [63,64], CTEPH and PH associated with lung fibrosis. A randomized controlled trial with a crossover design has been recently published: sildenafil 25–100 mg t.i.d. administered in 22 NYHA II and III PAH patients improved symptoms, exercise capacity and haemodynamics after 6 weeks [65]. A pivotal randomized controlled trial on 278 PAH patients treated with sildenafil 20, 40 or 80 mg t.i.d. has confirmed these results.

Combination therapy

Combination therapy is an attractive option to address the multiple pathophysiological mechanisms that are present in PAH. Combination therapy may be considered for patients who fail to improve or who deteriorate with first-line treatment, even though data on this specific strategy are limited. Appropriate protocols for timing and dosing to limit possible adverse effects of the combination have still to be implemented.

Interventions

Balloon atrial septostomy

The role of balloon atrial septostomy in the treatment of patients with PAH is uncertain because its efficacy

has been reported only in small series and case reports, totalling approximately 120 published cases [14,66]. In most circumstances, this intervention has been performed in severely ill patients as a palliative bridge to lung transplantation, which may explain a procedure mortality rate of 5–15%. In addition to symptomatic and haemodynamic improvement, an increase in survival as compared with historical control groups has also been shown.

Lung transplantation

Lung and heart–lung transplantation in PAH has been assessed only in prospective uncontrolled series, since formal randomized controlled trials are considered unethical in the absence of alternative treatment options [14]. The 3-year and 5-year survival after lung and heart–lung transplantation is approximately 55% and 45% respectively [67].

Both single and bilateral lung transplantation have been performed for IPAH and these operations have been combined with repair of cardiac defects in Eisenmenger's syndrome. Recipient survival rates have been similar after single and bilateral lung transplantation and after heart–lung transplantation for PAH. However, many transplant centres currently prefer to perform bilateral lung transplantation. Lung and heart–lung transplantation are indicated in PAH patients with advanced NYHA class III and class IV symptoms that are refractory to available medical treatments. The unpredictability of the period on the waiting list and donor organ shortage complicate the decision-making regarding the appropriate timing of listing for transplantation.

Treatment algorithm

A treatment algorithm based on the grade of recommendation and the level of evidence is shown in Fig. 25.11. The algorithm is restricted to patients in NYHA functional class III or IV because they represent the predominant population included in randomized controlled trials.

For NYHA class I or II patients very few data are available and the most appropriate strategy has still to be determined and possibly validated by specific studies. Currently, NYHA class I and II patients should be treated with background therapy and, if vasoreactive, with calcium channel blockers. In cases with multiple favourable prognostic indicators, a watchful-waiting strategy or inclusion in randomized controlled trials is recommended. The different treatments have been evaluated mainly in IPAH, and in PAH associated with scleroderma or with use of anorexigens. Extrapolation of these recommendations to the other PAH subgroups should be made with caution. Due to the complexity of the additional evaluation and the treatment options available, it is strongly recommended that patients with PAH are referred to a specialized centre.

Balloon atrial septostomy and/or lung transplantation are indicated for refractory PAH or where medical treatments are unavailable.

Associated conditions

Pulmonary arterial hypertension associated with congenital heart defects that have systemic-to-pulmonary shunts and with Eisenmenger's syndrome

The initial left-to-right shunting induces an increase in pulmonary blood flow and a mild elevation of mean PAP with normal or reduced PVR (precapillary hyperkinetic PH, see Table 25.2). The persistent exposure of the pulmonary vasculature to increased blood flow as well as increased pressure may result in the pulmonary arteriopathy (see Fig. 25.1). The initial morphological alterations (medial hypertrophy and intimal proliferation) are potentially reversible. However, as the disease progresses the more advanced morphological changes (plexiform lesions and arteritis) appear to be irreversible. The obliteration of the pulmonary vascular bed leads to increased PVR, and if it approaches or exceeds systemic resistance the shunt is reversed. Eisenmenger's syndrome is defined as a congenital heart defect that initially causes a large left-to-right shunt that induces severe pulmonary vascular disease and PAH, with resultant reversal of the direction of shunting [68]. Eisenmenger's syndrome can be caused by simple or complex (about 30% of cases) congenital heart defects [69]. Among simple defects, ventricular septal defects appear to be the more frequent, followed by atrial septal defects and patent ductus arteriosus [69]. The development of PH appears to be related to the size and type of the defect. It is calculated that 10% of patients with ventricular septal defects of any size who are older than 2 years can develop Eisenmenger's syndrome as compared with 4–6% of subjects with atrial septal defects [70]. In some patients, severe PAH can be detected after correction of the heart defect. Usually an early correction prevents the subsequent development of PAH. Survival of patients with Eisenmenger's syndrome is better than that of subjects with IPAH of comparable functional class [71].

The treatment of Eisenmenger's syndrome is mainly based on the clinical experience of experts and not on specific randomized controlled trials. Phlebotomy with isovolumic replacement should be performed in patients with moderate or severe symptoms of hyperviscosity (e.g. headache and poor concentration) that are usually present when the haematocrit is over 65%; it should not

be performed in asymptomatic or mildly symptomatic patients (regardless of the haematocrit). Diuretics can be used where there are signs of right heart failure.

The use of supplemental oxygen therapy is controversial and should be used only in cases where it produces a consistent increase in arterial oxygen saturation and/or improved clinical well-being (pulmonary restrictive component). In some centres, patients with Eisenmenger's syndrome are anticoagulated similarly to other subjects with PAH in the absence of contraindications. However, other authors suggest that this treatment should be avoided, as it can exacerbate the haemorrhagic diathesis. The use of intravenous epoprostenol has been shown to exert favourable effects on haemodynamics and exercise capacity [72], and the effects of subcutaneous treprostinil in patients with Eisenmenger's syndrome are no different from those in patients with IPAH [51]. A randomized controlled trial to assess the effects of bosentan on 65 patients with Eisenmenger's syndrome has shown favourable results for exercise capacity and haemodynamics (BREATHE-5). Lung transplantation with repair of the cardiac defect or combined heart–lung transplantation is an option for patients with Eisenmenger's syndrome who have markers of poor prognosis (syncope, refractory right-sided heart failure, NYHA functional class III or IV, severe hypoxaemia).

Porto-pulmonary hypertension

PAH is a well-recognized complication of chronic liver diseases [72,73]. Portal hypertension rather than the hepatic disorder itself seems to be the main determining risk factor for developing PH [72]. Two recent studies carried out in patients undergoing liver transplantation found a prevalence of pulmonary hypertension of 4% and 3.5% respectively. The mechanism whereby portal hypertension facilitates the development of PAH remains unknown [72]. The presence of porto-systemic shunt might allow vasoconstrictive and vasoproliferative substances, normally cleared by the liver, to reach the pulmonary circulation. The clinical picture of patients with porto-pulmonary hypertension may be indistinguishable from that of IPAH or may include a combination of symptoms and signs of the underlying liver disease [72]. Echocardiographic screening for the detection of PH in patients with liver diseases is appropriate in symptomatic patients and/or in candidates for liver transplantation. RHC should be performed in all cases with increased systolic PAP in order to clarify the underlying haemodynamic changes and define prognostic and therapeutic implications. Haemodynamically, compared with patients with IPAH, patients with porto-pulmonary hypertension have a significantly higher cardiac output and significantly lower systemic vascular resistance and PVR. In a retrospective study [72], patients with porto-pulmonary hypertension had a better rate of survival than patients with IPAH, although there is some debate on this issue. The treatment of porto-pulmonary hypertension has not been thoroughly studied. Anticoagulant therapy should be avoided in patients at increased risk of bleeding. Patients with porto-pulmonary hypertension seem to respond favourably to chronic intravenous epoprostenol [74]. Despite case series from expert centres with favourable results, the risk–benefit ratio of ET receptor antagonists in patients with liver disease needs to be carefully evaluated on a long-term basis. Significant PAH can substantially increase the risk associated with liver transplantation and usually PAH is a contraindication if mean PAP is ≥ 35 mmHg and/or PVR is ≥ 250 dynes/s/cm^{-5}.

Pulmonary arterial hypertension associated with HIV infection

PAH is a rare but well-documented complication of HIV infection. In a large case–control study, 3349 HIV-infected patients demonstrated a cumulative incidence of PH of 0.57% over a period of 5.5 years, resulting in an annual incidence of 0.1% [75]. The mechanism of the development of PAH is unknown. HIV-related PAH shows similar clinical, haemodynamic and histological findings as IPAH and it does not appear to be related to the route of HIV transmission nor to the degree of immunosuppression. Echocardiographic screening for the detection of PH in patients with HIV infection is required in symptomatic patients. Careful exclusion of other causes for PH such as left heart and parenchymal lung and liver diseases is necessary. RHC is recommended in all cases of suspected PAH associated with HIV infection to confirm the diagnosis, determine severity and rule out left-sided heart disease. PAH is an independent predictor of mortality in this patient population [75]. Therapeutic options are not well established and oral anticoagulation is often contraindicated because of bleeding risk factors, poor compliance and potential drug interactions. Continuous infusion of epoprostenol seems to be effective in improving functional status and haemodynamics. Recently, favourable clinical and haemodynamic results have been shown with the use of bosentan in a series of 16 HIV-related PAH patients.

Pulmonary arterial hypertension associated with CTD

PH is a well-known complication of CTD such as systemic sclerosis [77], systemic lupus erythematosus, mixed CTD and, to a lesser extent, rheumatoid arthritis, dermatopolymyositis and primary Sjögren's syndrome.

In these patients, PAH may occur in association with interstitial fibrosis or as a result of an isolated pulmonary arteriopathy (see Fig. 25.1). In addition, pulmonary venous hypertension from left heart disease can be present. It is imperative to determine which mechanism is operative, as treatment may be quite different for each process. Systemic sclerosis, particularly in its limited variant previously defined as CREST syndrome, represents the main CTD associated with PAH. The recently completed registry study of PH in 722 patients with systemic sclerosis in the UK showed the prevalence at around 12% [76]. Histopathological changes in PAH associated with CTD are generally indistinguishable from those of classical IPAH (see Fig. 25.1). The pathophysiological mechanisms leading to PAH in patients with CTD remain unknown. The presence of antinuclear antibody, rheumatoid factor, IgG and complement-fraction deposits in the pulmonary vessel walls suggest a role for an immunological mechanism. Compared with patients with IPAH, patients with PAH associated with CTD are mainly women, are older and have a significantly lower cardiac output. Symptoms and clinical presentation are very similar to IPAH and occasional patients can be identified as having an associated CTD by immunology screening tests. The mortality was confirmed to be higher than that seen with IPAH (40% 1-year mortality for those with advanced disease), and the predictors of outcome were the same as for IPAH (RAP, PAP and cardiac index). It has been suggested that echocardiographic screening for the detection of PH be performed yearly in asymptomatic patients with the scleroderma spectrum of diseases and only in the presence of symptoms in other CTD. As in other forms of PAH, RHC is recommended in all cases of suspected PAH associated with CTD to confirm the diagnosis, determine severity and rule out left-sided heart disease. Treatment of patients with PAH associated with CTD appears more complex as compared with IPAH. Immunosuppressive therapy seems to be effective only in a minority of patients mainly suffering from conditions other than scleroderma. The rate of acute vasoreactivity and of a long-term favourable response to treatment with calcium channel blockers is lower compared with IPAH. Also, the risk–benefit ratio of oral anticoagulation is not well understood.

Continuous epoprostenol therapy has been shown to improve exercise capacity, symptoms and haemodynamics in a 3-month randomized controlled trial of patients with the scleroderma spectrum of the disease [48]. Some retrospective analysis shows that the effect of intravenous epoprostenol on survival of IPAH patients seems to be better compared with that of scleroderma patients. Subcutaneous treprostinil has been shown to increase exercise capacity, symptoms of PAH, and haemodynamics in 90 patients with CTD. Subgroup analysis of patients with scleroderma enrolled in the randomized controlled trials performed with bosentan [60], sitaxsentan and sildenafil have shown favourable effects with all these medications [61].

Pulmonary veno-occlusive disease and pulmonary capillary haemangiomatosis

Both pulmonary veno-occlusive disease (PVOD) and pulmonary capillary haemangiomatosis (PCH) are uncommon conditions, but are increasingly recognized as causes of PAH [78]. Less than 200 cases of combined PVOD and PCH have been reported in the literature. PVOD and PCH are similar in some respects, particularly in relation to changes in the pulmonary parenchyma, i.e. pulmonary haemosiderosis, interstitial oedema and lymphatic dilatation, and in relation to pulmonary arterial intimal fibrosis and medial hypertrophy [3]. The clinical presentation of these patients is often indistinguishable from that of patients with IPAH. However, physical examination can demonstrate findings suggestive of a diagnosis other than IPAH, such as digital clubbing and/or basilar rales on chest auscultation. Case series indicate that PVOD/PCH is associated with more severe hypoxaemia and reduction of single-breath D_{LCO}, while spirometry and lung volume measurements are generally within normal limits. Haemodynamic data are similar in PVOD/PCH and IPAH, although in some patients the hypoxaemia is out of proportion to the degree of PAH and right heart dysfunction. Interestingly, PWP is often normal despite the postcapillary involvement. Indeed, the pathological changes usually occur in the venules, often without involvement of the larger veins. The static column of blood produced during measurement of PWP is unaffected by the changes in the small pulmonary veins as long as a connection is maintained with the larger unaffected pulmonary veins, which is where the pressure will be measured in the occluded arterial segment. Radiological data may be of great help in detecting PVOD/PCH [25]. The presence of Kerley B lines, pleural effusion and patchy irregularities on a standard chest radiograph may provide important clues that suggest the diagnosis. Thin-section CT of the chest shows characteristic changes (see Fig. 25.8B): the most commonly reported findings are a patchy centrilobular pattern of ground-glass opacities, thickened septal lines, pleural effusion and mediastinal adenopathy. Compared with IPAH, PVOD/PCH is characterized by significantly elevated bronchoalveolar lavage cell counts, with an increased number of haemosiderin-laden macrophages. PVOD and PCH probably require similar management to other PAH subgroups. However, the prognosis seems worse, with a more rapid downhill course. In addition, vasodilators and especially epoprostenol

have to be used with great caution because of the high risk of pulmonary oedema [78]. However, there are reports of sustained clinical improvement in individual patients treated with these medications. There are no data regarding the use of newer medical therapies such as ET receptor antagonists in the treatment of PVOD/PCH. Atrial septostomy may be considered but is limited by hypoxaemia. The only curative therapy for PVOD/PCH is lung transplantation and, as with IPAH, there are no reports of recurrence of disease following transplantation.

Pulmonary hypertension associated with left heart diseases

PH is a common complication in patients affected by left heart diseases. In fact, left ventricular failure or mitral valve diseases may produce an increase in left atrial pressure, pulmonary venous pressure, pulmonary capillary pressure and, in turn, elevation of PAP. The prevalence of PH in patients with chronic heart failure increases with progression of the functional class. In patients referred to transplant clinics, PH with PVR > 2 mmHg/l/min (Wood units) is reported in 19–35% of patients [80]. From the haemodynamic point of view this type of PH is characterized by an increase in PWP and is defined as postcapillary PH (see Table 25.2). The mechanisms responsible for the increase in PAP are multiple and include the passive backward transmission of the pressure elevation (postcapillary passive PH, see Table 25.2). In these cases the transpulmonary pressure gradient (mean PAP—mean PWP) and PVR are within the normal range. In other circumstances the elevation of PAP is greater than that of PWP (increased transpulmonary pressure gradient) and an increase in PVR is observed (postcapillary reactive PH, see Table 25.2). The elevation of PVR is due to an increase in pulmonary artery vasomotor tone and/or to fixed structural obstructive remodelling of the pulmonary artery resistance vessels [81]: the former component of reactive PH is reversible under acute pharmacological testing while the latter, characterized by medial hypertrophy and intimal proliferation of the pulmonary arteriole, does not respond to the acute challenge [80]. Which factors lead to reactive PH and why some patients develop the acutely reversible vasoconstrictive or the fixed obstructive components or both is poorly understood. Pathophysiological mechanisms may include vasoconstrictive reflexes arising from stretch receptors localized in the left atrium and pulmonary veins, and endothelial dysfunction of pulmonary arteries that may favour vasoconstriction and proliferation of vessel wall cells. PH carries a poor prognosis for patients with chronic heart failure: in one study mortality rate after 28 months of follow-up was 57% in patients with moderate PH compared with 17% in patients without PH. In addition, patients who have a PVR exceeding 6–8 Wood units have an increased risk of postoperative right ventricular failure following heart transplantation. When the PVR can be lowered pharmacologically (e.g. with intravenous nitroprusside) this risk is generally thought to be reduced [80]. The treatment of postcapillary PH coincides with appropriate therapy of the underlying condition that aims to normalize PWP. A sustained reduction of PH is expected in weeks to months in most patients successfully operated on for mitral valve disease even if PH represents a risk factor for surgery [82]. The use of interventions that have a theoretical prevalent effect on the pulmonary circulation, such as prostanoids or ET-1 receptor antagonists, has not produced favourable results in patients with chronic heart failure.

Pulmonary hypertension associated with lung diseases and/or hypoxaemia

PH is relatively common in patients with chronic hypoxic lung disease of whatever cause, including COPD, ILD, ventilatory disorders, sleep hypopnoea and apnoea disorders and high altitude. The severity of PH in COPD is generally limited to an increase in mean PAP to 25–35 mmHg; PWP and cardiac output are normal. However, mean PAP > 40 mmHg may occur, especially in patients with at least one previous episode of acute respiratory failure. In addition, transitory increases of PAP may occur during exacerbations, exercise and sleep. On the basis of published series, the incidence of significant PH in COPD patients with at least one previous hospitalization for exacerbation of respiratory failure with or without clinical right heart failure should be around 20%. Pathological changes include medial hypertrophy and intimal obstructive proliferation of the pulmonary arteriole. The pathobiological mechanisms involved in this setting are multiple and include hypoxic vasoconstriction, mechanical stress of hyperinflated lungs, inflammation and toxic effects of cigarette smoke. There are also data supporting an endothelium-derived vasoconstrictor–vasodilator imbalance.

The diagnosis of PH in COPD remains difficult. Echocardiography has made progress, but the performance of this apparently ideal non-invasive test has been reported

variably. Systematic RHC is too invasive in the face of expected benefit to be ethically acceptable.

Even if the progression of PH in patients with COPD is slow, the presence of PH in lung diseases is associated with shorter survival and worse clinical evolution. Long-term oxygen administration has been shown to partially reduce the progression of PH in COPD. Nevertheless, with this treatment PAP rarely returns to normal values and the structural abnormalities of pulmonary vessels remain unaltered. Vasodilators such as calcium channel blockers or prostanoids are not recommended on the basis of their minimal clinical efficacy and because they may impair pulmonary gas exchange. Recognition of the role of endothelial dysfunction in the physiopathology of PH in COPD may open new perspectives for the treatment of this complication.

Pulmonary hypertension due to chronic thrombotic and/or embolic disease

CTEPH is the result of single or recurrent pulmonary thromboemboli arising from sites of venous thrombosis. The natural history of pulmonary thromboemboli is to undergo total resolution, or resolution leaving minimal residua, with restoration of normal pulmonary haemodynamics. For reasons still unclear, thromboemboli in patients with CTEPH fail to resolve and form endothelialized obstructions of the pulmonary vascular bed including the major branches. The estimated incidence of CTEPH is 0.1–0.5% of cases of acute non-fatal pulmonary thromboemboli [23]. More recent studies that report an incidence of CTEPH of 3.8% in this patient population need to be confirmed.

The initial thromboembolic event can also be asymptomatic in most patients with CTEPH [23]. The organized thrombi are tightly attached to the pulmonary arterial medial layer, replacing the normal intima, and can completely occlude the lumen or form different grades of stenosis, webs and bands. Interestingly, in the non-occluded areas, a pulmonary arteriopathy indistinguishable from that of PAH (including plexiform lesions) can develop. The pathogenesis of CTEPH is still unclear. Thrombophilia studies have shown that lupus anticoagulant may be detected in approximately 10% of such patients, and 20% carry anticardiolipin antibodies, lupus anticoagulant, or both. A recent study has demonstrated that the plasma level of factor VIII, a protein associated with both primary and recurrent venous thromboembolism, is elevated in 39% of patients with CTEPH. No abnormalities of fibrinolysis have been detected [83]. The lesion observed in non-obstructed areas may be related to a variety of factors, such as shear stress, pressure, inflammation, and the release of cytokines and vasculotrophic mediators.

From the clinical point of view, after a period of months or years from the initial acute embolic event (when detectable) without symptoms ('honeymoon' period), dyspnoea on exercise develops and progresses. Diagnosis is made by perfusion lung scan (see Fig. 25.7B), contrast-enhanced CT of the lung (see Fig. 25.9) and pulmonary angiography (see Fig. 25.10). The haemodynamic picture is similar to that of IPAH even if some studies have reported a larger pulmonary arterial pulse pressure in CTEPH as compared with IPAH. Pulmonary endarterectomy is the treatment of choice for patients with CTEPH. Detailed preoperative patient evaluation and selection, surgical technique and experience, and meticulous postoperative management are essential prerequisites for success after this intervention [24]. The selection of patients for surgery depends on the extent and location of the thrombus in relation to the degree of PH. Proximal thrombi represent the ideal indication (see Fig. 25.10A) while more distal obstructions may prevent a successful procedure (see Fig. 25.10B). After an effective intervention a dramatic drop in PVR can be expected, with near normalization of pulmonary haemodynamics. Operative mortality in experienced centres today ranges from 5 to 10% according to the severity. In non-operable distal CTEPH, the medical treatment used for PAH can be adopted even if clear data on efficacy are lacking. Lung transplantation can also be performed in the more advanced cases.

Personal perspective

PH is a pathophysiological condition that is classified into five clinical categories according to pathological, pathogenetic and therapeutic characteristics. Substantial differences exist among clinical classes, which may prevent automatic transfer of the progress achieved in one category to another. PAH is the class in which PH represents the leading pathophysiological mechanism and includes conditions that share a severe clinical picture and a downhill course without appropriate interventions. Major advances in our understanding of the mechanism of disease development and in the treatment of PAH have been achieved over the past decade. A variety of cellular pathway abnormalities have been described that may play important roles in the development and progression of this condition. A number of well-designed clinical trials have demonstrated efficacy of several therapies that target specific abnormalities. As a consequence an evidence-based treatment algorithm can currently be proposed for patients with PAH. Despite these successes, the response to therapy of PAH is not universal and is often incomplete. Future studies targeting newly identified alterations in endothelial and smooth muscle cell function, including angiotensin activity, vasoactive intestinal peptide synthesis and activity, and the serotonin pathway, may provide novel treatments. In addition, specific studies targeting the more epidemiologically relevant PH groups, such as those related to left ventricular abnormalities or to COPD, are required. Unfortunately in these settings, preliminary experience with drugs effective in PAH patients has shown unfavourable results.

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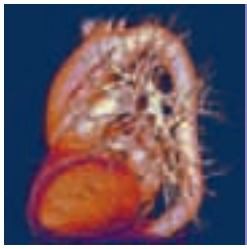

26 Cardiac Rehabilitation

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Summary

Cardiovascular diseases are widely regarded as the most relevant preventable cause of premature death. Prevention should be promoted in two different clinical situations: (1) in apparently healthy individuals to prevent the development of overt atherosclerosis and the related complications/ischaemic events and (2) in patients with documented cardiovascular disease to retard further disease progression. In both situations, *primary and secondary prevention* are effective in lowering cardiovascular morbidity and mortality.

From the traditional exercise training programme, cardiac rehabilitation and prevention have evolved into a *comprehensive intervention*, including optimized medical/interventional treatment to relieve symptoms, appropriate cardiovascular risk evaluation, exercise training, education and counselling. The latter needs to encompass risk reduction and lifestyle changes including the use of appropriate behavioural interventions and involvement of family members to achieve these changes, vocational counselling and adequate follow-up to assure long-term compliance and motivation for adherence to recommended lifestyle changes and pharmacological treatments.

In addition to the preventive approaches, exercise-based intervention programmes are effectively used as an *adjuvant therapy* in a number of cardiovascular diseases, most notably chronic heart failure (CHF). As exercise intolerance in CHF is primarily related to the degree of peripheral changes (such as muscle atrophy, reduced peripheral perfusion due to endothelial dysfunction, abnormalities in ventilation, etc.), pharmacological treatment alone sometimes fails to significantly improve exercise capacity. Regular aerobic endurance training in stable CHF has been shown to improve peak oxygen uptake by 15–25%, to reduce peripheral vascular resistance, to retard or reverse muscle wasting and to reduce morbidity and mortality.

Despite its documented clinical effectiveness, rehabilitation–prevention interventions are still widely underutilized in the clinical context. However, it becomes increasingly clear that the use of interventional procedures, for example in stable coronary artery disease (CAD), is *suboptimal therapy without simultaneous lifestyle modification*, including regular physical exercise and aggressive treatment of cardiovascular risk factors.

The clinical evidence base of cardiac rehabilitation

Definition of rehabilitation

In 1993, the World Health Organization (WHO) defined cardiac rehabilitation as the *'sum of activity and interventions required to ensure the best possible physical, mental, and social conditions so that patients with chronic or post-acute cardiovascular disease may, by their own efforts, preserve or resume their proper place in society and lead an active life'* [1]. The goals of cardiac rehabilitation and secondary prevention are: (1) to prevent disability resulting from coronary disease, particularly in older persons and those with occupations that involve physical exertion and

(2) to prevent subsequent cardiovascular events, hospitalization and death from cardiac causes.

Secondary prevention through cardiac rehabilitation

Secondary prevention through cardiac rehabilitation programmes is now recognized as an essential component of the contemporary management of patients with various presentations of coronary disease and with heart failure, and it should be integrated into the long-term care of all patients with cardiovascular disease [2–5]. Comprehensive cardiac rehabilitation has well-documented effects on the symptoms, exercise tolerance, blood lipid levels and global risk profile, cigarette smoking, psychosocial well-being, progression of atherosclerosis and subsequent coronary events resulting in reduced hospitalization and decreased morbidity and mortality [4].

Target population

After the initial concentration on post-infarction patients and patients recovering from coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA) or other forms of myocardial revascularization changes in demography led to the expansion of cardiac rehabilitative care to older patients, many of whom have severe and complicated coronary illness and serious associated pathologies. Many patients who were once considered to be too high risk for structured rehabilitation programmes [e.g. patients with residual myocardial ischaemia, compensated heart failure, serious arrhythmias and implantable cardioverter-defibrillators (ICDs)] currently derive benefit from more gradual and more protracted, often supervised exercise training. Cardiac rehabilitation is also appropriate for patients with CHF and those who have undergone cardiac transplantation.

Programme components

There is convincing evidence that the combination of regular exercise with interventions for lifestyle changes and modification of risk factors favourably alter the clinical course of cardiovascular diseases. Exercise interventions are therefore combined with education, counselling, behavioural strategies and other psychosocial interventions and vocational counselling strategies to assist the patient to achieve coronary risk reduction and other cardiovascular health-related goals so that these programmes function as comprehensive secondary prevention services (see Table 26.1) [2,3].

Assessment of exercise capacity in the clinical context

The purpose of the various maximal exercise tests in clinical use today is to measure the degree of disease-related exercise limitation in an objective and reproducible way. Performed according to established standard protocols, these tests provide a safe and effective tool to classify the clinical severity of the disease with its implications for prognosis (e.g. in CHF), to monitor the effects of therapeutic interventions and to design individually tailored exercise training programmes in cardiac rehabilitation facilities.

Physiology of maximal exercise testing

Maximal exercise capacity as measured, for example, by maximal oxygen uptake depends on three key physiological systems: (1) the efficacy of the gas exchange by the lungs, (2) the maximal cardiac output and (3) the aerobic metabolic capacity of the working skeletal muscle.

Ventilatory response to exercise

The ventilatory response to a constant work rate is divided into three different phases: (1) an immediate increase in ventilation at the start of exercise lasting for about 15 s, (2) a subsequent slower increase to steady state, lasting 2–3 min and (3) a constant steady-state ventilation, which is reached approximately 3 min after the initiation of exercise for $V\text{O}_2$ and 4 min after exercise begins for $V\text{CO}_2$ and V_E (ventilation L/min).

If the exercise level is further increased the skeletal muscle gradually switches over to anaerobic metabolism as an additional energy source (see Musculoskeletal response to exercise, below), resulting in blood lactate accumulation. Lactic acid is buffered predominantly by the bicarbonate system releasing CO_2 into the bloodstream. CO_2 in turn is a major stimulator of ventilation, leading to a disproportionate rise in V_E in relation to $V\text{O}_2$. Below the anaerobic threshold, CO_2 rises in parallel with oxygen consumption; above the anaerobic threshold, no such correlation exists.

Cardiovascular response to exercise

In the early phases of exercise, the heart increases its output by both increased heart rate and augmented preload with a rightward shift of the Frank–Starling curve. At higher work intensity, the further increase in cardiac

Table 26.1 Programme components of cardiac rehabilitation

Programme component	Tasks	Goals
Initial evaluation	0: Take medical history and perform physical examination 1: Measure risk factors 2: Obtain electrocardiograms (ECGs) at rest and during exercise 3: Determine level of risk 4: Assess occupational status and prepare vocational counselling	Preventive plan in collaboration with primary care physician
Physical activity counselling and exercise training	Assess current physical activity and exercise tolerance with monitored exercise stress test Identify barriers to increased physical activity Provide advice regarding increasing physical activity Develop an individualized regimen of aerobic and resistance training, specifying frequency, intensity, duration and types of exercise	Increases in regular physical activity, strength and physical functioning; more simply, at least 30 min of submaximal work or moderate exercise daily is recommended; greater benefit, however, can be achieved by further increasing physical activity
Management of lipid levels	Assess and modify diet, physical activity and drug therapy	Primary goal: LDL cholesterol level < 100 mg/dl (< 2.6 mmol/l) Secondary goals: HDL cholesterol level > 45 mg/dl (> 1.16 mmol/l), triglyceride level < 200 mg/dl (< 2.26 mmol/l)
Management of hypertension	Measure blood pressure *on ≥ 2 visits* If resting systolic pressure is 130–139 mmHg or diastolic pressure is 85–89 mmHg, recommend lifestyle modifications, including exercise, weight management, sodium restriction and moderation of alcohol intake; if patient has diabetes or chronic renal or heart failure, consider drug therapy If resting systolic pressure is 140 mmHg or diastolic pressure is 90 mmHg, recommend drug therapy Monitor effects of intervention in collaboration with primary care physician	Blood pressure < 140/90 mmHg (or < 130/85 mmHg if patient has diabetes or chronic heart or renal failure)
Smoking cessation	Document smoking status (never smoked, stopped smoking in remote past, stopped smoking recently or currently smokes) Determine patient's readiness to quit; if ready, pick date Offer nicotine replacement therapy, bupropion or both Offer behavioural advice and group or individual counselling	Long-term abstinence
Weight reduction	Consider for patients with BMI > 25 or waist circumference > 100 cm (in men) or > 90 cm (in women), particularly if associated with hypertension, hyperlipidaemia or insulin resistance or diabetes Provide behavioural and nutritional counselling with follow-up to monitor progress in achieving goals	Loss of 5–10% of body weight and modification of associated risk factors with long-term adherence
Management of diabetes	Identify candidates on the basis of the medical history and baseline test Develop a regimen of dietary modification, weight control and exercise combined with oral hypoglycaemic agents and/or insulin therapy Monitor glucose control before exercise sessions and communicate results to primary care physician For newly detected diabetes, refer patient to primary care physician for evaluation and treatment	Normalization of fasting plasma glucose level (80–110 mg/dl, 4.4–6.1 mmol/l) or glycosylated haemoglobin level (< 7.0%) and control of associated obesity, hypertension and hyperlipidaemia
Psychosocial management	Identify psychosocial problems such as denial, depression, anxiety, social isolation, anger and hostility by means of an interview, standardized questionnaire or both Provide individual or group counselling, or both, for patients with clinically significant psychosocial problems Provide stress-reduction classes for all patients Provide family members interventions	Improvement of clinically significant psychosocial problems and acquisition of stress-management skills

output depends largely on increases in heart rate. These adaptations lead to a four- to sixfold increase in cardiac output during maximal exercise. Systolic and mean arterial pressures and pulse pressure increase in parallel, while diastolic pressure remains unchanged or decreases. At higher ages the chronotropic competence and the maximal heart rate reached during exercise are reduced up to 50% compared with young adults, resulting in attenuated cardiac exercise reserve.

During strenuous exercise, a redistribution of cardiac output occurs, induced by selective vasoconstriction of mesenteric/splanchnic arteries and vasodilatation in muscle-supplying arteries. Depending on the extent of the active skeletal muscle mass, a significant net decrease in systemic vascular resistance at submaximal and maximal exercise can be expected.

Musculoskeletal response to exercise

The contracting skeletal muscle depends on a continuous supply of nutrients and oxygen to maintain its work force for extended periods of time. During submaximal exercise, the peripheral oxygen extraction is increased up to twofold and venous oxygen saturation may drop substantially. When the exercise intensity is further increased, the muscle recruits anaerobic metabolism as an additional energy source. In healthy untrained subjects, lactate accumulation starts at approximately 50–60% of maximal exercise capacity.

Safety aspects of exercise testing

Indications/contraindications for exercise testing

Over the last decades, the risk–benefit ratio of exercise testing has been systematically evaluated in a number of disease entities. As a result, the indications and contraindications of exercise testing are now clearly established and laid down in guidelines of the American Heart Association (AHA) and European Society of Cardiology (ESC) (Tables 26.2 and 26.3) [6].

Table 26.2 Contraindications for exercise testing

Acute myocardial infarction < 2 days
Unstable angina with recent rest pain
Untreated life-threatening cardiac arrhythmias
Uncompensated congestive heart failure
Uncontrolled hypertension
Advanced atrioventricular block
Acute myocarditis and pericarditis
Symptomatic aortic stenosis
Severe hypertrophic obstructive cardiomyopathy
Acute pulmonary embolism/pulmonary infarction
Acute aortic dissection
Acute systemic illness

Table 26.3 Indications for exercise testing

Class 1 (clear indication)
Patients with suspected or proven CAD
1 Patients with exercise-related complaints of palpitations, dizziness, or syncope (diagnosis)
2 Men with atypical symptoms (diagnosis)
3 Patients with chronic stable angina or post-myocardial infarction (prognosis, functional evaluation)
4 Symptomatic exercise-induced arrhythmias
5 Evaluation after revascularization procedure

Class 2 (test may be indicated)
1 Women with typical or atypical angina pectoris
2 Functional capacity evaluation to monitor cardiovascular therapy in patients with CAD or heart failure
3 Evaluation of patients with variant angina
4 Follow-up of patients with known CAD
5 Evaluation of asymptomatic men over 40 years who are in special occupations (pilots, firefighters, police officers, bus or truck drivers, railroad engineers) or who have two or more atherosclerotic risk factors or who plan to enter a vigorous exercise programme

Class 3 (test probably not indicated)
1 Evaluation of patients with isolated premature ventricular beats and no evidence of CAD
2 Multiple serial testing during the course of cardiac rehabilitation programme
3 Diagnosis of CAD in patients who have pre-excitation syndrome or complete left bundle branch block or are on digitalis therapy
4 Evaluation

In the context of cardiac rehabilitation, exercise testing is a valuable tool not only to prove or exclude exercise-induced myocardial ischaemia but also to determine the patient's fitness level prior to initiation of a training programme. It is indispensable to recommend a training heart rate for aerobic endurance training and to exclude potential risks during physical exertion, such as exercise-induced arrhythmias or excessive blood pressure increase. Formal indications for exercise testing are to be found in Table 26.3.

Large epidemiological studies clearly indicate a relation between cardiovascular fitness and mortality (Fig. 26.1) [7,8] and exercise testing is widely used to objectively assess disease-related exercise intolerance for risk stratification of heart failure patients.

Statistical risks of adverse events during maximal exercise testing

Despite its undisputed clinical value, maximal exercise

Table 26.4 Criteria for termination of exercise tests [75]

Absolute indications
Drop in systolic blood pressure of > 10 mmHg from baseline blood pressure despite an increase in workload, when accompanied by other evidence of ischaemia
Moderate to severe angina
Increasing nervous system symptoms (e.g. ataxia, dizziness or near-syncope)
Signs of poor perfusion (cyanosis or pallor)
Technical difficulties in monitoring ECG or systolic blood pressure
Subject's desire to stop
Sustained ventricular tachycardia
ST elevation (≥ 1.0 mm) in non-infarct leads without diagnostic Q waves (other than V1 or aVR)
Relative indications
Drop in systolic blood pressure of ≥ 10 mmHg from baseline blood pressure despite an increase in workload, in the absence of other evidence of ischaemia
ST or QRS changes such as excessive ST depression (> 2 mm of horizontal or downsloping ST segment depression) or marked axis shift
Arrhythmias other than sustained ventricular tachycardia, including multifocal PVCs, triplets of PVCs, supraventricular tachycardia, heart block or bradyarrhythmias
Fatigue, shortness of breath, wheezing, leg cramps or claudication
Development of bundle branch block of intraventricular conduction delay that cannot be distinguished from ventricular tachycardia
Increasing chest pain
Hypertensive response (systolic blood pressure > 250 mmHg or diastolic blood pressure > 115 mmHg)

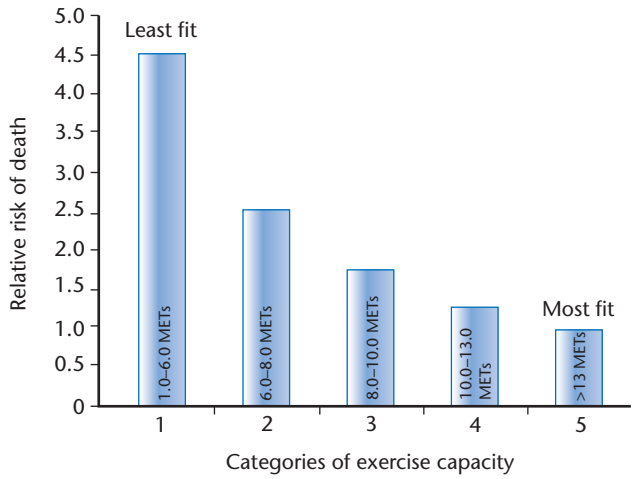

Figure 26.1 In a prospective follow-up study for 6.2 ± 3.7 years in consecutive men referred for treadmill exercise testing the age-adjusted mortality rates in healthy men were categorized by level of fitness. The range of values for exercise capacity (METs) for each category is represented within each bar. A clear relation between fitness level and all-cause mortality is obvious. Reprinted with permission [8].

testing confers a certain measurable statistical risk of adverse events. In an unselected patient population referred for exercise testing, mortality is reported to be below 0.01% and morbidity below 0.05% [9]. When performed in patients within 4 weeks of an acute myocardial infarction, mortality rises to 0.03% and the rate of non-fatal myocardial infarction or need for cardiac resuscitation reaches 0.09% [10].

In patients with stable compensated CHF, no additional risk of maximal exercise testing has been reported, with no major complications reported in one study of 1286 bicycle ergometer tests [11].

The absolute risk of major complications during exercise testing can be greatly minimized by strictly adhering to the established standards with regard to patient selection, careful history and clinical examination, and close monitoring with 12-lead electrocardiogram (ECG) and blood pressure recordings during and in the minutes (minimum of 3 min) immediately after exercise.

Formal requirements for exercise testing facilities

Although rare in absolute numbers major complications of exercise testing can be expected to occur from time to time in high-throughput testing facilities. Everything necessary for cardiopulmonary resuscitation (CPR) must be available at the testing facility, including standard emergency drugs, a defibrillator and equipment for endotracheal intubation. The exercise test must be supervised either by a trained physician or by specially trained assistant personnel with a physician present in calling distance. Regular drills with CPR procedures should be performed to ascertain adequate and quick response in emergency situations. A telephone with emergency numbers on it must be available to call additional assistance.

Criteria for termination of a maximal exercise test

To balance the diagnostic purpose vs. the inherent risks of maximal exercise testing, a comprehensive catalogue of clinical/electrocardiographic criteria for test termination was developed (Table 26.4). It is essential to implement these criteria in clinical practice, as their neglect may have legal consequences if the patient experiences any adverse event due to delayed test termination.

Methodological aspects of exercise testing

Maximal vs. submaximal exercise testing

In the clinical context, maximal exercise tests are clearly dominating. By definition, a test is considered maximal when a patient appears to give a genuine maximal effort or when other clinical end-points are reached. An objective determination of whether an exercise test was indeed maximal can be obtained by ergospirometry: maximal exercise is reached when oxygen uptake does not increase any further despite increasing workload.

A large number of exercise testing protocols has been developed, based on four basic approaches: interrupted stages, stages, ramp and continuous protocols. Today, incremental exercise protocols with discrete stages are most frequently used [as the Bruce protocol for treadmill exercise or the incremental protocol for bicycle ergometer testing with 2- to 3-min increments of 25–50 watts (W)]. When ergospirometry is performed, one has to keep in mind that the maximum oxygen uptake is 5–11% higher when measured on a treadmill than by a cycle ergometer.

Submaximal exercise tests were developed in order to minimize the patient's risk, for example in the immediate period after an acute myocardial infarction or in cases of likely dangerous ventricular arrhythmias. However, the diagnostic potential of the test is limited, as no maximal exercise capacity is reached and the test may therefore be false negative in patients with stenotic CAD.

Treadmill vs. bicycle ergometry

The treadmill uses walking as the exercise mode to be tested and has been in use for decades. The advantages include a higher degree of whole-body exercise during walking, resulting in a greater sensitivity to detect myocardial ischaemia owing to higher peak oxygen uptake [12] and the possibility for the investigator to vary both speed and grade independently. However, some disadvantages need to be mentioned: the treadmill is expensive, frightening for some patients because they cannot control walking speed, and difficult to quantify with regard to workload.

The cycle ergometer has the advantage of being less bulky than the treadmill, offering the patient a seat for support, giving him greater influence on cycling speed, and reducing movement artefacts in ECG and blood pressure recordings.

Supine vs. upright exercise testing

There is a marked difference in haemodynamic response to exercise in the supine or upright position. In supine, cycle ergometry stroke volume and end-diastolic volume remain largely unchanged, whereas in the upright position these parameters increase during mild-to-moderate work, reaching an individual plateau.

When patients with CAD and exercise-induced angina perform a stress test, heart rate is higher in supine position at identical workloads and ST segment depression is generally greater due to higher left-ventricular volume.

Keeping these differences in mind, supine cycle ergometry is the method of choice for patients who have difficulty in keeping balance and for stress echocardiography, when thoracic movements need to be minimized.

Ergometry vs. ergospirometry

The maximal oxygen uptake (V_{O_2}max) defines the upper limit of exercise adaptation of the cardiopulmonary system. It is determined (1) by the potential of the organism to increase cardiac output through augmentation of stroke volume and heart rate, (2) the blood flow redistribution from the splanchnic to the muscular bed and (3) the oxidative capacity of the working skeletal muscle.

The main advantages of ergospirometry over conventional ergometry are: (1) objective determination of maximal exercise capacity and (2) measurement of the maximum oxygen consumption and CO_2 production.

Subjective vs. objective measurements

In order to assess the patient's exercise tolerance it is not always sufficient to determine the maximal exercise capacity in watts. It may also be desirable to obtain information on their subjective exhaustion during the stress test. For this purpose, Borg developed his nonlinear ordinal *Borg Scale of Perceived Exertion*, ranging from 0 to 10 (Table 26.5) [13].

Special methods

Six-minute walk test

The reliability of the *six-minute walk test* depends heavily on the instruction of the patient to walk *as far as he can* in

Table 26.5 Borg scale of perceived exertion

0	Nothing at all
0.5	Extremely light
1	Very light
2	Light
3	Moderate
4	Somewhat heavy
5	Heavy
6	
7	Very heavy
8	
9	
10	Extremely heavy
•	Maximal

the 6-min period. It is recommended that the test be repeated three times with resting periods of 15 min between the walks. The longest distance will be recorded. Immediately after the test, heart rate and blood pressure are taken and the perceived exertion is rated according to the 0–10 Borg scale.

Several studies have confirmed the prognostic value of a properly performed *six-minute walk test* among patients with CHF [14,15].

Exercise therapy

Physical fitness in preventive cardiology

Modern epidemiological studies have confirmed the concept that physical fitness is inversely related with all-cause mortality, mostly as a consequence of reduced prevalence of ischaemic heart disease. However, there is a growing body of evidence to suggest that the incidence of other chronic diseases is also reduced by exercise: type 2 diabetes mellitus, osteoporosis, obesity, depression, and even certain malignancies (breast cancer, colon cancer).

Prognostic implications of exercise capacity

First hints of a beneficial prognostic impact of regular physical exercise were derived from a number of long-term observational studies: Morris [16], Paffenbarger [17,18], Slattery [19] and their colleagues were able to document that increased levels of average daily physical activity correlated to a reduced incidence of coronary heart disease (CHD), reduced cardiac and all-cause mortality. The relative mortality reduction reached was 30–40% in moderately active persons (1000 kcal/week) [19].

Table 26.6 Metabolic equivalents

Exercise intensity	METs	Watt (70 kg)	kcal/min
Low	< 3	< 40	< 4
Moderate	3–6	40–100	4–8
Vigorous	> 6	> 100	> 8

These observations were confirmed by studies that analysed the relation between maximal exercise capacity (as measured by bicycle ergometry) and mortality during long-term follow-up [20,21]. A reduced physical fitness was clearly identified as an independent predictor of mortality [RR in men 1.52 (95% confidence interval 1.28–1.82) and in women 2.10 (95% confidence interval 1.36–3.21)], equal in importance to smoking or hypertension. An increase of exercise capacity by just one metabolic equivalent (MET) conferred a mortality reduction of 12% [7]. One metabolic equivalent was defined as the average resting metabolic rate (3.5 ml of O_2/mL/kg. min). In an average 70-kg man, an exercise intensity of 25 W equals 1.6 METs (Table 26.6).

These and other studies led to the conclusion that men and women should engage in at least 30–45 min of moderate physical activity every day [22]. Exercise intensity should be at 65–70% of the maximal age-adjusted heart rate. Some studies suggest a correlation between exercise intensity and mortality reduction [17,18,23], but the benefits of vigorous exercise should be weighed against the increased risk of trauma and chronic orthopaedic damage.

Traditionally, it has been recommended that a minimum of 1000 kcal of physical activity energy expenditure should be generated per week to obtain a prognostic benefit. New studies suggest that there is an inverse association between relative intensity of physical activity (an individual's perceived level of exertion) and risk of CAD, even among men not satisfying the 1000 kcal/week activity recommendations. Recommendations may therefore need to consider individual fitness levels instead of globally prescribing activities of ≥ 3 METs [23].

Indications and contraindications for exercise training

In general, the contraindications for regular physical exercise training are the same as for exercise testing (see above). Patients should generally be in a stable clinical situation before starting a training programme.

Exercise training for primary prevention—risks and benefits

As outlined above, regular physical exercise confers a significant benefit with regard to lower mortality and morbidity rates. However, the initiation of a regular training programme in a previously sedentary individual is associated with a certain rate of adverse cardiovascular events, including sudden cardiac death, acute myocardial infarction, aortic dissection and cerebrovascular accidents. To minimize the risk of these events, an individual risk stratification is necessary prior to regular physical exercise.

How large exactly is the risk of sudden cardiac death among exercising people? In a 5-year study Thompson recorded all deaths among joggers in Rhode Island. He reported 1 death per year for every 7620 male joggers between age 30 and 65 (= 0.013%). When deaths in persons with known CAD were eliminated, the incidence of cardiac arrest was 1 per year for every 15 240 previously healthy joggers (= 0.0066%) [24]. The risk of myocardial infarction was estimated at 1 myocardial infarction during exertion for every 2142–2571 exercising men (0.039–0.047%). However, the risk was lowest for those regularly engaging in exercise and highest for those with the lowest activity level.

To minimize the risk of any adverse cardiac event, it is recommended by the American College of Sports Medicine that high-risk individuals undergo a maximal exercise test prior to initiation of vigorous exercise. This definition includes men > 40 years and women > 50 years, presence of more than one cardiovascular risk factor and known CAD.

For primary prevention, non-competitive exercise methods with high proportions of aerobic exercise are especially useful. In consideration of the frequency of orthopaedic injuries, swimming and walking are preferable to jogging. The prognostic benefit has so far only been established for aerobic endurance training. Resistance training with a higher proportion of isometric exercise can therefore not be generally recommended in the context of primary prevention. With regard to duration and frequency of training sessions the AHA/ACC propose that each individual should engage in 30 min of moderate intensity physical activity on most, preferably all, days of the week.

Exercise therapy in cardiovascular diseases

Development of exercise therapy from rehabilitation to prognostic intervention

Over the last two decades the clinical application of physical exercise as a therapeutic strategy has developed from rehabilitation to exercise treatment of cardiovascular diseases. This shift in clinical application was accompanied by a more systematic research approach of the involved mechanisms and the objective clinical assessment of sport interventions using prospective randomized clinical trials. This ongoing process established physical exercise as an evidence-based and guideline-orientated treatment option.

In stable CAD, exercise therapy has long been used for rehabilitation purposes following an acute myocardial infarction. A recent meta-analysis revealed a significant 27% reduction of total mortality among training patients and a significant 31% reduction in cardiac mortality [4]. Four mechanisms are considered to be important mediators of the reduced cardiac event rate: (1) improvement of endothelial function, (2) reduced progression of coronary lesions, (3) reduced thrombogenic risk and (4) improved collateralization. The therapeutic benefit of regular physical exercise has also been confirmed in direct comparison with an interventional strategy: a 12-month exercise therapy in stable CAD patients was associated with a higher event-free survival than conventional percutaneous coronary intervention (Fig. 26.2) [25].

In stable CHF, physical activity was traditionally discouraged, with negative consequences for the patients: exercise intolerance worsened and the progression of disease-related muscular atrophy accelerated. A carefully designed exercise programme at 50–70% of the maximal oxygen uptake was effective in improving exercise capacity by 12–32%. In a recent meta-analysis, exercise therapy reduced the relative risk of CHF mortality by 35% and CHF-related hospitalizations by 28% (Fig. 26.3) [26].

Exercise therapy in stable coronary artery disease, after percutaneous transluminal coronary angioplasty and after myocardial infarction

Exercise interventions differ with regard to several aspects:

1. *location:* in-hospital vs. outpatient;
2. *supervision:* supervised vs. non-supervised;
3. *training form:* endurance vs. resistance, steady state vs. interval training.

The diversity has brought with it the necessity to decide which training programme is best suited to the individual patient. The aims of cardiac rehabilitation in patients with recent myocardial infarction or with stable CAD are to improve the patients' angina-free functional capacity and quality of life (symptomatic goals), and to prevent future cardivascular events (prognostic goal). To separate the patients concerned from those with heart failure (see Exercise therapy in chronic heart failure, below) patients with CAD should have a left-ventricular ejection fraction > 40%.

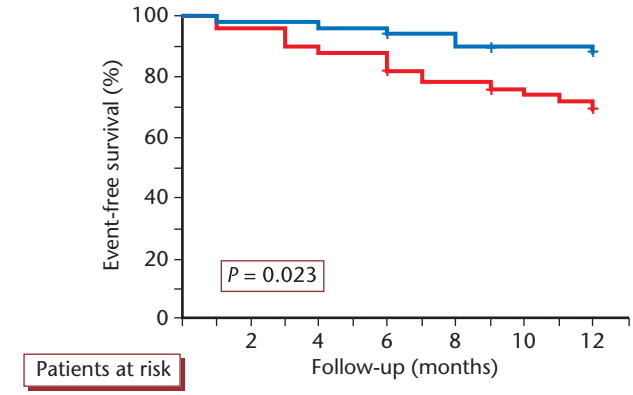

Figure 26.2 In a prospective clinical trial, Hambrecht and colleagues [25] compared the event-free survival in patients with stable angina and a significant coronary stenosis randomized to either percutaneous coronary intervention or 12 months of exercise training. Event-free survival after 12 months was significantly superior in the exercise training group (blue line) vs. the PTCA/stent group (red line) ($P = 0.023$ by log rank test). Reprinted with permission [25].

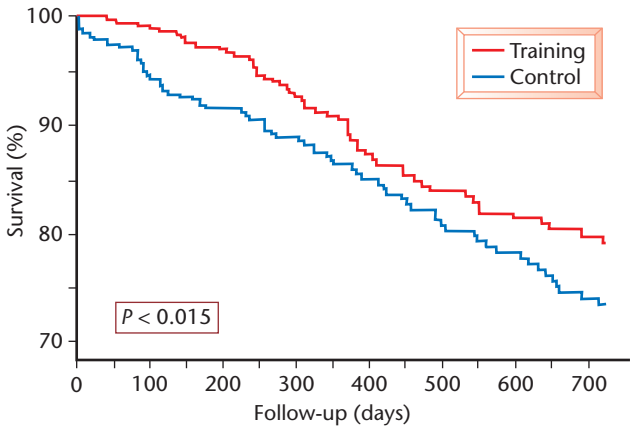

Figure 26.3 In a meta-analysis of 801 patients with CHF who were randomized to either training or control group, long-term follow-up was obtained and a significant mortality reduction could be documented in the intervention group. Reprinted with permission [26].

INDICATIONS/CONTRAINDICATIONS

Starting a training programme in patients with overt CAD is not risk free: based on large clinical databases, one cardiac arrest per 112 000 patients training hours (PTH), one myocardial infarction per 294 000 PTH and one cardiac death per 784 000 PTH can be expected. Although these numbers appear to be small, they add up with increasing training duration and frequency. It has been highlighted that the risk of adverse events is highest when patients exceed their previously determined training pulse. This occurs frequently during competitive games and rarely during steady-state ergometer endurance training.

To minimize the individual risks of participating in rehabilitation programmes, a two-step assessment is recommended. First, to be a candidate for exercise training, certain contraindications must be excluded first (in parallel with the contraindications for exercise testing, see Indications/contraindications for exercise testing, above). Then the risk for adverse events should be stratified according to the patient's medical history and functional parameters (Table 26.7). Although both low- and high-risk patients may participate in training programmes, the degree of supervision and monitoring will be different.

Table 26.7 Risk stratification (AACPR, *Guidelines for Cardiac Rehabilitation and Secondary Prevention Programs*, Champaign, IL: Human Kinetics Publisher, 1999)

Lowest risk
- No significant left-ventricular dysfunction (ejection fraction (EF) > 50%)
- No resting or exercise-induced complex dysrhythmias
- Uncomplicated myocardial infarction, CABG, angioplasty, atherectomy or stent: absence of CHF, absence of signs/symptoms indicating post-event ischaemia
- Normal haemodynamics with exercise or recovery
- Asymptomatic including absence of angina with exertion
- Functional capacity > 7.0 METs
- Absence of clinical depression

Lowest risk classification is assumed when each of the risk factors in the category is present

Moderate risk
- Moderately impaired left-ventricular function (EF = 40–49%)
- Signs/symptoms including angina at moderate levels of exercise (5–6.9 METs) or in recovery

Moderate risk is assumed for patients who do not meet the classification of either highest risk or lowest risk

Highest risk
- Decreased left-ventricular function (EF < 40%)
- Survivor of cardiac arrest or sudden death
- Complex ventricular dysrhythmia at rest or with exercise
- Myocardial infarction or cardiac surgery complicated by cardiogenic shock, CHF and/or signs/symptoms of post-procedure ischaemia
- Abnormal haemodynamics with exercise (especially flat or decreasing systolic blood pressure or chronotropic incompetence with increasing workload)
- Signs/symptoms including angina pectoris at low levels of exercise (< 5.0 METs) or in recovery
- Functional capacity < 5.0 METs
- Clinically significant depression

Highest risk classification is assumed with the presence of any one of the risk factors included in this category

Initiation of training therapy

Based on the risk stratification, different baseline assessments are required for patients entering an exercise-based rehabilitation programme. For most patients (low to moderate risk), history, clinical examination, resting ECG and a reliable exercise test (ergometry with three-lead ECG, 6-minute walk test) are adequate. Complete exercise testing with 12-lead ECG and baseline echocardiography are recommended for high-risk patients or high-intensity exercise training.

With regard to the type of exercise, submaximal strictly aerobic endurance training at 50–80% of the peak oxygen uptake is generally regarded as the gold standard. The prognostic benefits indicated above (see Development of exercise therapy from rehabilitation to prognostic intervention, above) are only established for endurance-type training programmes. Recently, resistance training has been increasingly applied as an additional training modality. It appears to be safe in low-risk populations, but further studies are necessary to determine the risk–benefit ratio in moderate-to-high risk patients.

Among four studies comparing high-intensity and moderate-to-low intensity exercise, three found no difference in mortality, morbidity, physical and psychological outcomes. Therefore, aerobic moderate-intensity exercise training is recommended in patients with CAD. Based on published studies, three to four moderate-intensity exercise training sessions per week, with a duration of 30–40 min each, are necessary to obtain optimal results in phase 3.

Clinical effects of exercise in coronary artery disease

Based on large meta-analyses, exercise-based cardiac rehabilitation is associated with a 27% reduction in total mortality and 31% reduction in cardiac mortality. On the symptomatic level, training interventions led to significant improvements of maximal exercise capacity and muscle strength, and increased the angina pectoris threshold.

The beneficial effect of exercise-only interventions on psychological functioning and social adaptation is less well documented but has been confirmed by observational studies. Training-only interventions have no proven effect on return to work.

Molecular mechanisms of exercise therapy in coronary artery disease

Despite the clear prognostic benefits, the underlying mechanisms have long remained unclear. Basically, regional myocardial hypoperfusion in CAD results from a combination of three basic pathogenetic components: (1) vascular stenosis, (2) microvascular dysfunction and (3) microrheology and haemostasis. All three components may be affected by exercise training in stable CAD:

1 The initial hypothesis that training would lead to a regression of coronary artery stenosis was not substantiated in the majority of patients. Only those with vigorous training programmes were able to actually reverse the process of atherosclerosis. However, training was effective in retarding disease progression. With increasing knowledge about the importance of vascular endothelial dysfunction as an obligatory step for the initiation of atherosclerosis, interactions between training, shear stress and vascular function have received growing attention. Hambrecht [27] was able to show that 4 weeks of training improved coronary vasomotion in patients with stable CAD (Fig. 26.4) and were associated with increased expression and activity of endothelial NO synthase in samples of the left internal mammary artery harvested during bypass surgery. Since others documented the prognostic significance of endothelial dysfunction for occurrence of cardiovascular events, the improvement of endothelium-dependent vasodilatation after

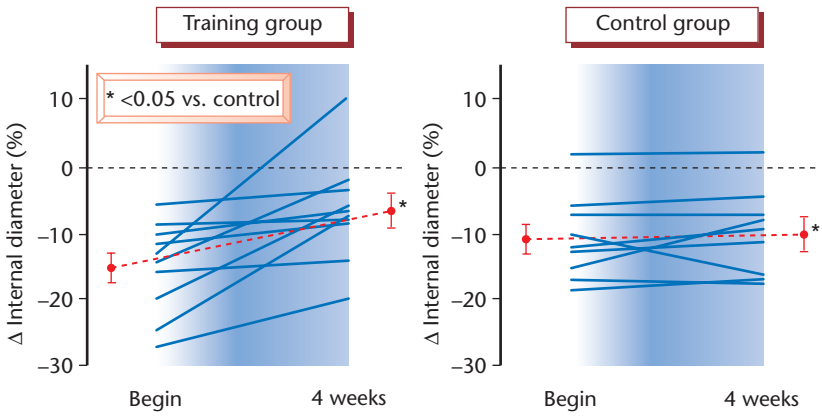

Figure 26.4 Four weeks of exercise training were associated with a significant attenuation of pathological vasoconstriction in patients with stable CAD. This finding confirmed the beneficial effect of training on coronary endothelial function and myocardial perfusion. Reprinted with permission [27].

exercise may represent an important mechanism contributing to the prognostic benefits of training. Other non-specific effects of training include reduction of the incidence of type 2 diabetes, reduction of low-density lipoprotein (LDL) and increase of high-density lipoprotein (HDL) levels.

2 Exercise training increases resistance vessel sensitivity and maximal responsiveness to adenosine. Long-term exercise training induces not only functional, but also morphological changes of the microvasculature by increasing the total vascular bed cross-sectional area by up to 37% after 16 weeks. As a consequence, vascular resistance decreases and maximal flow reserve rises.

3 Chronic endurance training has been shown to attenuate the post-exercise potentiation of platelet function, to increase platelet cyclic guanosine monophosphate (cGMP) content and to suppress coagulability. In summary, a net reduction of thrombogenic risk in CAD by chronic exercise training has been documented. Improvements of blood rheology by reduced viscosity add to these beneficial training effects.

Exercise therapy in chronic heart failure

Any form of strenuous exercise was traditionally discouraged in CHF, a consequence of the concern that any extra haemodynamic workload would lead to further deterioration of cardiac function. However, this concept was shattered by the lack of any correlation between left-ventricular function and exercise capacity in CHF patients. In the 1990s it became increasingly clear that peripheral factors potentially amenable to exercise therapy contribute to exercise intolerance—peripheral hypoperfusion due to impaired endothelium-dependent vasodilatation, reduced strength of respiratory muscles and profound morphological, metabolic, and functional alterations in the skeletal muscles.

INDICATIONS/CONTRAINDICATIONS

Patients with CHF have higher mortality and morbidity rates than most other forms of heart disease (especially stable CAD). Therefore, current guidelines stratify CHF patients as a high-risk group for training interventions. As indicated above, this implies a more detailed diagnostic evaluation before initiation of exercise training, which includes echocardiography and 12-lead ergometry.

In prospectively conducted exercise training studies in stable CHF patients adverse events are, however, surprisingly low, with post-exercise hypotension, atrial or ventricular arrhythmias, and worsening heart failure symptoms being the most common complications.

The same contraindications to exercise as in CAD are also applicable for CHF. Although the risk of patients with ventricular arrhythmias during training interventions has never been prospectively evaluated, most studies excluded patients with evidence of ventricular arrhythmias (> Lown IV during Holter ECG). Training post ICD implantation appears to be safe and feasible [28,29].

Although vigorous uncontrolled exercise may precipitate cardiac decompensation in CHF patients, there are no reports of an increased rate of pulmonary oedema in long-term submaximal training trials in stable CHF patients.

INITIATION OF TRAINING THERAPY

Training interventions in CHF are based on aerobic steady-state exercise sessions at 50–80% of the peak oxygen uptake for 15–30 min 3–5 times per week. In highly symptomatic patients with very low symptom-free exercise tolerance (< 75 W), shorter training sessions at low intensity (50% of Vo_2max) may be required. When patients tolerate this regimen well, first the session duration should be prolonged, then training intensity can be increased.

Recently, resistance exercise has been proposed as an anabolic intervention to antagonize the wasting syndrome often seen in advanced heart failure. Up until now prospective randomized clinical studies documenting the safety and efficacy of resistance training in advanced CHF are lacking. Based on observational studies, single-limb short-term resistance exercise seems to be safe.

CLINICAL EFFECTS OF EXERCISE IN CHRONIC HEART FAILURE

The results of the EXTRA-MATCH meta-analysis of the ESC with a total of 801 CHF patients documented a significant reduction of total mortality by 35% (odds ratio 0.65, CI 0.46–0.92, $P = 0.015$), and of hospitalization by 28% (odds ratio 0.72, CI 0.56–0.93, $P = 0.018$) [26].

With regard to symptomatic benefit, a recent meta-analysis of randomized controlled trials by the European Heart Failure Training Group revealed an improvement of peak Vo_2 by up to 2 ml/kg/min with a range of +14% to +31% increase vs. control patients. Although modest in absolute terms, this increase of about 20% translates into a considerably better quality of life for most patients.

Cardiac function is not worsened by exercise training; in fact a small but significant improvement of ejection fraction and reduction in cardiomegaly was observed in one prospective randomized trial (Fig. 26.5) [30].

MOLECULAR MECHANISMS OF EXERCISE THERAPY IN CHRONIC HEART FAILURE

How does exercise training in stable CHF achieve these beneficial results? Training is a non-specific intervention

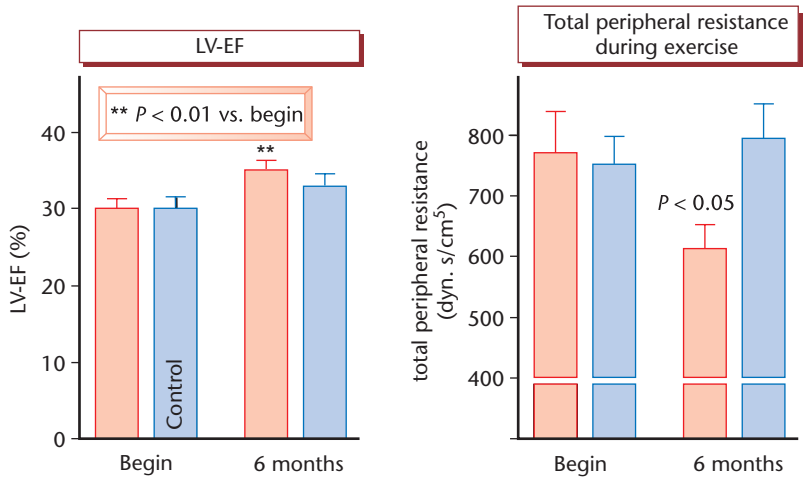

Figure 26.5 A 6-month aerobic training programme in patients with stable CHF was associated with a small but significant improvement in left-ventricular ejection fraction and a concomitant reduction of total peripheral resistance, both at rest and at peak exercise [30].

Figure 26.6 Effects of exercise training on different organ systems in CHF. Note that the effects on cardiac function are probably mediated by decreased neurohormonal activation and reduced afterload. Reprinted with permission from Gielen S, Schuler G, Hambrecht R. Benefits of exercise training for patients with chronic heart failure, *Clin Geriatrics* 2001; **9**: 32–45.

that affects several functional systems: (1) vascular endothelial function, (2) central haemodynamics, (3) the level of neurohumoral activation, (4) the respiratory system and (5), of course, skeletal muscle metabolism and function (Fig. 26.6).

1 Training improves systemic endothelium-dependent vasodilatation, especially during exercise in CHF patients [31,32]. This leads to a reduced cardiac afterload and enhanced peripheral perfusion.
2 Most likely as a consequence of the afterload reduction, a small improvement of cardiac function was observed after a 6-month training programme [30]. So far, no direct training-induced cardiac changes have been reported in CHF patients.
3 Training leads to 25–32% reduction in circulating levels of angiotensin II, aldosterone and atrial natriuretic peptide (Fig. 26.7) [33].

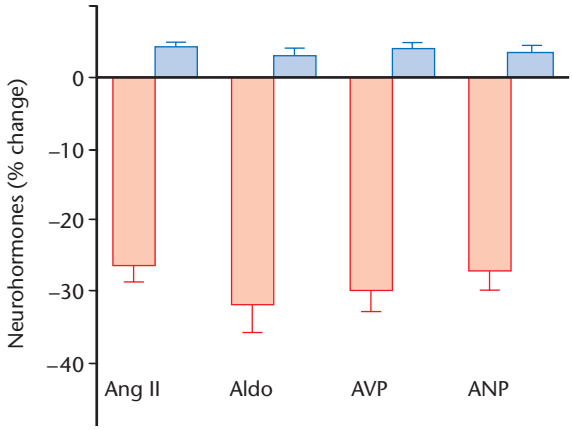

Figure 26.7 Braith and colleagues [33] described dramatic reductions in circulating neurohormones after long-term exercise training in CHF (red boxes, training group; blue boxes, control group, all changes are statistically significant at $P < 0.05$ vs. control group). Ang II, angiotensin II; Aldo, aldosterone; AVP, arginine vasopressin; ANP, atrial natriuretic peptide.

4 In CHF patients, it has been found that dyspnoea is related to the activity and strength of inspiratory muscles, which are significantly weaker in heart failure patients. Both systemic exercise training and selective respiratory muscle training improve ventilation dynamics and exercise performance.
5 CHF causes profound alterations in skeletal muscle morphology, metabolism and function, which are not just a consequence of deconditioning but represent intrinsic changes induced by the systemic neurohumoral and inflammatory response in CHF. All aspects of skeletal muscle characteristics can be positively influenced by training. At the ultrastructural level, the volume density of cytochrome-C-positive mitochondria is increased, permitting an enhanced oxidative phosphorylation. In addition to metabolic improvements, recent studies indicate that training has the potential to reverse the inflammatory activation with increased expression of cytokines like tissue necrosis factor alpha (TNFα), interleukin 1 (IL-1) beta and IL-6 in the skeletal muscle [34]. It is hoped that these changes might also attenuate the pro-apoptotic environment with reduced insulin-like growth factor 1 (IGF-I) in the skeletal muscle [35,36].

Exercise therapy in valvular heart disease

As opposed to CAD and CHF, few studies have specifically evaluated training interventions in patients with valvular heart disease. Therefore, recommendations are necessarily less reliable and are based on pathophysiological considerations rather than on hard clinical evidence.

INDICATIONS/CONTRAINDICATIONS

Clear contraindications to exercise training include all critical and highly symptomatic valvular lesions on the edge to cardiac decompensation. In addition, a stable aortic stenosis with a valvular orifice area of < 0.75 cm^2 and a peak pressure gradient of > 50 mmHg is also generally regarded as a contraindication to training programmes.

Specific risks for special valvular lesions are detailed below.

Mitral valve prolapse Although considered a benign abnormality occurring in up to 5% in the general population, sudden death has been reported as a rare complication. Exercise is considered safe in patients without significant arrhythmias at rest and during exercise, without a family history of sudden cardiac death, and without any previous thromboembolic event or syncope.

Mitral regurgitation In patients with CHF, relative mitral regurgitation is frequent and does not preclude the initiation of training therapy provided the patient is in stable condition (NYHA II–III).

Mitral stenosis Patients with a mitral valve orifice of > 1.5 cm^2 may safely participate in normal exercise training sessions. Those with moderate to severe mitral stenosis (< 1.5 cm^2) are usually limited by exercise-induced dyspnoea and can only tolerate low levels of physical exertion. In these symptomatic patients, treatment of mitral stenosis by balloon valvuloplasty or valve replacement should be performed prior to starting a training programme.

Aortic regurgitation Patients with mild to moderate aortic regurgitation may engage in training without problems. However, left-ventricular diameters need to be reassessed every 3–6 months to watch for worsening of the valve disease.

INITIATION OF TRAINING THERAPY

In valvular heart disease, changes in afterload or preload associated with changes in peripheral resistance may greatly affect cardiac output. Therefore, resistance training of large muscle groups is generally discouraged in valvular heart disease. Endurance training sessions—preferably with ECG and blood pressure monitoring during the initial phase—are better reproducible with regard to haemodynamic load.

CLINICAL EFFECTS OF EXERCISE IN VALVULAR HEART DISEASE

Among patients with valvular heart disease, no prognostic benefit of exercise training has so far been documented. The symptomatic benefits of training are not well established either and are mostly based on anecdotal rather than systematic reports. It therefore seems prudent to opt for curative surgical treatment of the valvular heart disease wherever possible, and to start training programmes after the intervention.

Exercise therapy after cardiac surgery

As opposed to the situation in stable CAD or CHF, after cardiac surgery patients are confronted with several additional problems: open-chest surgery is frequently associated with reduced ventilatory capacity in the immediate postoperative period, pain during respiration and lifting of the arms, weight reduction due to the catabolism associated with major trauma and reduction in muscle strength as a consequence of immobilization.

While the objective in CAD/CHF was to improve exercise capacity to levels above baseline levels, cardiac rehabilitation after cardiac surgery first aims at regaining the pre-surgery levels of physical and social functioning after correction of the exercise-limiting cardiac disorder and at preventing postoperative complications such as pneumonia or deep vein thrombosis. After the completion of wound healing, however, exercise training should be continued to fully recruit the extended cardiovascular exercise capacity.

INDICATIONS/CONTRAINDICATIONS

Limited physical exercise starts immediately after surgery in the form of mobilization on the intensive care unit. In this highly supervised and monitored setting there are very few contraindications to exercise: severe cardiac arrhythmias, overt cardiac decompensation and paralysis or musculoskeletal disorders prohibit exercise. Even in the presence of acute illnesses, i.e. postoperative infections, supervised mobilization/respiratory training can be continued.

To start with, the exercise training indications/contraindications mentioned above need to be observed. Patients should be in stable clinical condition. Risk assessment is according to the low, moderate and high-risk criteria proposed in Exercise therapy in cardiovascular disease, Indications/contraindications, above.

INITIATION OF TRAINING THERAPY

Mobilization including active/passive exercise, respiratory exercise and walking may start immediately after surgery. Formal exercise training with aerobic endurance exercise may be initiated when wound healing is adequately advanced. To mitigate the loss of muscle strength/mass associated with prolonged bed rest, resistance exercises may be introduced into the training programme.

CLINICAL EFFECTS OF EXERCISE AFTER SURGERY

Of the three randomized trials of exercise-based cardiac rehabilitation after bypass surgery, none was powered to analyse prognostic benefits of exercise training. However, exercise capacity and maximal oxygen uptake were significantly improved after training, whereas serum lipids remained unchanged.

Although the number of studies is limited, training seems to be particularly beneficial in patients after cardiac transplantation, owing to the extensive peripheral alterations that persist after transplant if not treated by exercise.

Comprehensive rehabilitation

Definition

Current clinical guidelines recommend that cardiac rehabilitation should be integrated in a multifactorial comprehensive long-term process, which includes clinical assistance and optimized medical or interventional treatment to relieve symptoms, appropriate cardiovascular risk evaluation, exercise training, education and counselling regarding risk reduction, lifestyle changes including the use of appropriate behavioural interventions and involvement of family members to achieve these changes, vocational counselling and adequate follow-up to ensure long-term compliance and motivation for adherence to recommended lifestyle changes and pharmacological treatments [1,3,37,38].

Patient education on heart disease

The behavioural approach to coronary risk reduction encourages and enables coronary patients to manage their illness, adopt and maintain healthy lifestyles and improve adherence to medications and other recommended regimens [37]. Meta-analysis of 28 controlled trials of patient education showed that ‘education programs have demonstrated a measurable impact on blood pressure, mortality, exercise, [and] diet’ and that other parameters are positively affected, although less consistently [39].

Dietary counselling

Epidemiology of overweight/obesity

In many countries, more than half of the adult population is overweight and 20–30% of adults are categorized as clinically obese in Europe, where prevalence has doubled or even risen threefold in less than two decades [40].

Obesity, particularly abdominal obesity, is a substantial risk factor for cardiovascular diseases. In addition, factors such as elevated fasting blood triglycerides, low levels of high-density lipoprotein cholesterol, high fasting blood glucose and hypertension are accentuated markedly by weight gain.

The driving force behind the obesity epidemic and the consequent widespread metabolic syndrome is a diet dominated by an excess of energy-dense foods, high in fat and sugar (and, in addition, salt), and combined with an insufficient consumption of fruits and vegetables. This dysfunctional diet is compounded by predominantly sedentary lifestyles and reduced opportunities for physical activity.

Overweight and obesity in patients with established coronary heart disease

Overweight and obesity are highly prevalent among patients with CAD [41]. Treating overweight patients poses a real challenge to health-care professionals because these patients are more likely to have inadequate blood pressure and cholesterol level control [42].

Prevention of coronary heart disease by diet

Although the relation between overweight/obesity and CHD is well established, research about the effects of specific dietary habits is often difficult. Based on the discovery that increased serum cholesterol predicted the risk of CHD in human populations in the early 1950s, the classic diet–heart hypothesis was developed, which postulated a primary role of dietary saturated fat and cholesterol in the cause of atherosclerosis and CHD in humans [43]. The diet–heart hypothesis gained further support from ecological correlations relating saturated fat intake to rates of CHD in cohorts from different countries and from studies of migrants from low- to high-risk countries [44].

Until recently, most epidemiological and clinical investigations of diet and CHD have been dominated by the diet–heart hypothesis. However, the original hypothesis was overly simplistic because the effects of diet on CHD can be mediated through multiple biological pathways other than serum total cholesterol or low-density lipoprotein cholesterol (LDL-C).

Experimental research was essential to understand the mechanisms by which genes, hormones and diet interact to regulate the serum cholesterol level. LDL cholesterol levels can be increased by saturated fatty acids, especially those with 12–16 carbon atoms, and by trans fatty acids.

MEDITERRANEAN DIET

A common trait of a Mediterranean-style diet is the emphasis on fruits, vegetables, bread, other forms of cereals, potatoes, beans, nuts, seeds, olive oil as an important fat source, dairy products, fish and poultry. In addition, wine is consumed in low to moderate amounts. The Mediterranean-style Step I diet used in the Lyon Diet Heart Study was similar to this pattern but uniquely different in that it was high in α-linolenic acid [45]. Subjects following the Mediterranean-style diet had a 50–70% lower risk of recurrent heart disease.

OMEGA-3 FATTY ACIDS

The fact that omega-3 fatty acids exert cardioprotective effects via multiple mechanisms (i.e. decrease synthesis of cytokines and mitogens, stimulate endothelial-derived nitric oxide and are anti-thrombotic) suggest that they could have accounted for the cardioprotective effect observed. In prevention trials, subjects who took fish oil had a lower rate of primary end-point (death, non-fatal myocardial infarction or stroke) over 1.0–3.5 years than control subjects [46,47].

HIGH-FIBRE DIET

In numerous epidemiological studies, increasing fibre intake was associated with a lower risk of heart disease, possibly as a result of lower LDL levels and improved insulin sensitivity. This relation did not persist after adjustment for CAD risk factors, however [48,49].

ANTIOXIDANTS

Antioxidants also have been proposed for secondary and primary prevention of CAD events. Several large, prospective cohort and randomized controlled studies, however, have shown no benefit from β-carotene, vitamin E, vitamin C, selenium, or multivitamin supplements in reducing the risk of CAD.

Smoking cessation

Epidemiology of smoking

Approximately 1.1 billion people smoke worldwide. By 2025, this number is expected to rise to more than 1.6 billion, with lower income groups being over-represented.

Smoking already kills one in ten adults worldwide. By 2030, perhaps sooner, the proportion will be 1 in 6, or 10 million deaths per year, more than any other single cause.

Smoking as cardiovascular risk factor

The causative relationship between smoking and CHD is well established, with relative risks (RRs) or odds ratios (ORs) estimated at 1.5–3 or higher [50–52]. Observational studies have estimated that smoking cessation reduces the risk of subsequent mortality and further cardiac events among patients with CHD by as much as 50% [53].

In a systematic review from 2003, a 36% reduction in crude RR of mortality for patients with CHD who quit compared with those who continued smoking (RR = 0.64, 95% CI = 0.58–0.71) was documented [54].

Smoking cessation strategies

Smoking cessation should be the primary objective of medical treatment for people who smoke, particularly as most smokers who require treatment are dependent on tobacco. Treatment of the smoker should aim at *complete cessation* and stopping smoking abruptly. Less than 1–2% of heavily dependent smokers achieve this goal without any medical intervention (i.e. through will-power alone), and the number of cigarettes smoked per day need not be a decisive factor. This method of smoking cessation can be achieved with psychological support, but the outcome is better with pharmacological support [55].

Smoking cessation using non-pharmacological methods

Numerous organizations also provide self-help manuals designed to assist smokers who wish to quit. In addition, consulting a therapist may enhance the effectiveness of this method. Standard instructions have been found to be less effective than personalized instructions tailored for a group of smokers. Overall, instructions on smoking cessation are considered useful and more effective than attempting to quit without instructions (Table 26.8).

Pharmacotherapy for tobacco dependence

During the last 20 years, nicotine replacement therapy (NRT) has been used by some 30 million smokers and has been tested in over 34 800 smokers in more than 108 studies [56]. Treatment of the dependent smoker with NRT (in the form of transdermal patches, chewing gum, nasal sprays, sublingual tablets or oral inhalers) can therefore be implemented without any safety concerns.

Table 26.8 Assessment of non-drug treatment modalities to promote smoking cessation, as compiled from the Cochrane Database [59]

	Odds ratio	Assessment
Group therapy (behavioural therapy)	2.19 (1.42–3.37)	*
Aversion therapy (aversive stimulation)	2.66 (1.00–2.78)	†
Physician counselling	1.68 (1.45–1.98)	*
Individual counselling (short counselling session; booklet, etc.)	1.62 (1.35–1.94)	*
Nurse-managed counselling	1.50 (1.29–1.73)	*
Self-help interventions	1.24 (1.07–1.45)	*
Self-help intervention with telephone counselling	—	—
Exercise interventions	§	†
Training by health-care professionals	§	—
Aversion therapy (general)	1.15 (0.77–1.82)	—
Acupuncture	1.22 (0.99–1.49)	‡
Hypnotherapy	§	—
Reduced smoking	—	‡

*Claim (e.g. on efficacy) supported by several suitable, valid clinical studies (e.g. randomized clinical trials) or by one or more valid meta-analyses or systematic reviews. Positive claim clearly confirmed.
†Claim (e.g. on efficacy) supported by at least one suitable, valid clinical study (e.g. randomized clinical trial). Positive claim confirmed.
‡Negative claim (e.g. on efficacy) supported by one or more suitable, valid clinical studies (e.g. randomized clinical trials) or by one or more valid meta-analyses or systematic reviews. Negative claim clearly confirmed.
§No usable studies.

Psychological risk factors and behavioural support

Background

In large cohort studies, psychosocial factors are associated with the prevalence of CAD. This evidence is largely composed of data relating CAD risk to five specific psychosocial domains:

1 depression;
2 anxiety;
3 personality factors and character traits;
4 social isolation;
5 chronic life stress.

Pathophysiological mechanisms underlying the relationship between these entities and CAD can be divided into behavioural mechanisms, whereby psychosocial conditions contribute to a higher frequency of adverse health behaviour, such as poor diet and smoking, and direct pathophysiological mechanisms, such as neuroendocrine or platelet activation and endothelial dysfunction [58].

Depression

In the past years, five out of six community surveys have observed an increased risk of CAD among depressed persons [58]. Research in post-myocardial infarction patients has documented that depression increases the risk of mortality from two to seven times [60]. For clinical purposes and indication for specialized treatment, it may be useful to distinguish minor and major depressive episodes according to the established criteria.

Anxiety

Increasing evidence links anxiety disorders to the development of cardiac events in the general population, with the excess mortality being confined to sudden cardiac death [60,61]. The association between anxiety and sudden death but not myocardial infarction suggests that ventricular arrhythmias may be the mechanism for cardiac death among individuals with anxiety disorders owing to an alteration in cardiac autonomic tone.

Personality factors and character traits

Although type A behaviour characterized by competition, hostility and exaggerated commitment to work continues to receive attention, a series of studies have reported no correlation between type A behaviour and CAD risk [62].

Hostility, a major attribute of the type A behaviour pattern, has received considerable attention as a potential 'toxic' element in this personality construct. The potential for hostility (i.e. aggressive verbal or physical responses when angry) was consistently found to be related to CAD, predicting restenoses and recurrent events. Hostile subjects manifest higher heart rate and blood pressure responses to physiological stimuli, such as mental task, as well as higher ambulatory blood pressure levels during daily-life activity. Preliminary data suggest that hostile individuals may manifest diminished vagal modulation of heart function and increased platelet reactivity.

Social isolation and life stress

An inverse relation has been reported between the magnitude of social support and the incidence of CAD and/or future cardiac events [63,64]. Low socioeconomic status is a significant contributor to increased risk in healthy persons and a contributor to poor prognosis in patients with established CAD.

The effects of acute stress on heart disease are well supported by epidemiological studies regarding life stresses such as bereavement (with a twofold higher risk for men and threefold higher risk for women), anger (twofold increased relative risk of myocardial infarction), earthquakes and terrorist activities [65].

Primary prevention

The prevalence of psychosocial risk factors in the general population can be estimated to be 5%. There is no reliable evidence proving the benefit of interventions on psychosocial risk factors in *primary prevention*. However, patients often know that their lifestyle and psychosocial problems may affect their health, but when physicians do not take these problems seriously, patients are likely to conclude that such problems are not important.

Secondary prevention

Depression and other psychosocial risk factors are highly prevalent in populations with known CAD, varying from 15% to 25% [57]. It has been estimated that psychosocial interventions designed to modify psychosocial risk factors may reduce fatal and non-fatal cardiac events by 30–50% with follow-up intervals equal to or more than 2 years.

The results from meta-analyses [66] suggest that these programmes yielded a 37% reduction in cardiac mortality, a 29% reduction in recurrence of myocardial infarction, and significant positive effects on blood pressure, cholesterol, body weight, smoking behaviour, physical

exercise and eating habits. At the clinical level, it is recommended to routinely include psychosocial components in cardiac rehabilitation programmes, such as stress management, and to offer counselling in selected cases. First results of the Sertraline and Depression in Heart Attack Study (SADHART) suggest a beneficial effect of the antidepressant drug on events and overall clinical well-being over 6-months' follow-up in patients with post-acute myocardial infarction [67].

Sexual problems

Sexual dysfunction is highly prevalent in both sexes and adversely affects patients' quality of life and well-being [68]. Studies have reported erectile dysfunction (ED) rates of 68.3% in patients with hypertension and 40% in patients with CAD. The ED in these cases is usually due to the vascular disease itself, but may also be secondary to the intake of angiotensin-converting enzyme (ACE) inhibitors, diuretics, beta-blockers and other antihypertensive drugs [69]. Treatment options for men with ED include psychosexual therapy, oral sildenafil or vardenafil, transurethral alprostadil, intracavernous alprostadil, vacuum constriction device, surgical treatment (prosthesis) and vascular surgery. The elucidation of the nitric oxide–cyclic GMP pathway for ED and the development of sildenafil and vardenafil have been the most recent advances. However, although their incidence is small, serious cardiovascular events, including significant hypotension, can occur in certain populations at risk. The co-administration of nitrates and sildenafil/tardalafil significantly increases the risk of potentially life-threatening hypotension and must be strictly avoided.

Return to work

Despite the well-documented effects of cardiac rehabilitation on functional capacity and psychological well-being, there is contradictory evidence regarding whether rehabilitation programmes can influence the resumption of gainful employment. In theory, rehabilitation constitutes a pathway from total temporary inability to work to a substantially normal return to the previous habits.

The goals of vocational rehabilitation are to evaluate whether returning to work is safe and realistic, and to expedite the resumption of gainful employment, while assisting individuals to remain at work. It is estimated that up to 80% of patients with uncomplicated myocardial infarction will return to work. Moreover, the time for returning to work and resuming full activities for these patients has decreased from 4 months after an event in 1970 to approximately 60–70 days in 1990. Nevertheless, the socioeconomic consequences of failure to return to work for such a prevalent disease are significant.

Organization of cardiac rehabilitation interventions

Integration of acute care, in- and out-patient programmes

Different patterns of rehabilitative care are currently delivered by specialized hospital-based teams: residential cardiac rehabilitation for more complicated, disabled patients and out-patient cardiac rehabilitation for more independent low-risk and clinically stable patients who require less supervision. There may be variations of individual or group programmes and centre- or home-based activity programmes. Although the objectives are identical to those of the out-patient cardiac rehabilitation programmes, residential rehabilitation programmes are specifically structured to provide more intensive and/or complex interventions to include more complicated high-risk or clinically unstable patients, to include more severe incapacitated and/or elderly patients (especially those with comorbidity) and thus to facilitate the transition from the hospital phase to a more stable clinical condition that may allow the maintenance of an independent life at home. One major disadvantage of in-hospital programmes is the relatively short duration of intervention with regard to risk factor management and lifestyle changes. Therefore, residential cardiac rehabilitation programmes should be followed up by a long-term out-patient risk reduction and secondary prevention programme, with appropriate clinical and functional monitoring.

Formal requirements for in- and out-patient cardiac rehabilitation programmes

The cardiac rehabilitation/secondary prevention programmes should be delivered under the guidance of a cardiologist who is experienced in exercise testing and exercise training of patients with various forms of cardiovascular disease, who are candidates for such programmes, and who have a specific knowledge in all important aspects of rehabilitative and secondary preventative care.

The staff should include a cardiologist, physiotherapists or sports teachers, nutrition counsellor/dietitians,

psychologists/psychiatrists and preferably also a social worker/vocational counsellor.

There are no formal requirements on an international level for equipment, logistic and certification. However, there are national guidelines and recommendations in most European countries. Although life-threatening cardiovascular complications are rare during formal cardiac rehabilitation programmes, a well-designed and regularly controlled emergency concept is crucial for each programme. Staff members should regularly be trained in CPR and basic life support, an alarm system has to be established and also regularly tested, and very early defibrillation and rapid access to advanced life support have to be assured. With regard to equipment, there is consensus in most European countries that easy access to 12-lead ECG, ergometry with either bicycle or treadmill ergometer, two-dimensional Doppler echocardiography, chest radiography and telemetry or Holter-ECG are needed.

Special aspects of cardiac rehabilitation

Congenital heart disease

Evaluation of the patient with congenital heart disease

With an estimated prevalence of 0.8% of all live births, the likelihood of encountering patients with congenital heart disease in the context of cardiac rehabilitation/exercise is higher than expected. In close cooperation with a paediatric cardiologist, the evaluation of these patients should focus on the family history (e.g. history of sudden cardiac death, heart failure, deafness, syncope, etc.) and on current symptoms.

Exercise recommendations for common congenital cardiac defects

ATRIAL SEPTAL DEFECT

In atrial septal defects (ASDs), exercise limitation is caused by the pulmonary volume overload and pulmonary hypertension as a consequence of left–right shunting. Although children will have normal exercise capacities after correction, later repairs in adulthood may leave residual haemodynamic abnormalities (mostly persistent pulmonary hypertension).

Current recommendations indicate that patients with small ASDs without pulmonary hypertension can participate in all sports. If pulmonary hypertension or significant left–right shunting is present ($Q_p/Q_s > 1.5:1$), only low-intensity sports are permitted. In marked pulmonary hypertension, competitive sports need to be discouraged [70].

VENTRICULAR SEPTAL DEFECTS

Ventricular septal defects (VSDs) are the most common congenital cardiac defects (15–20%). Small-moderate VSDs are without haemodynamic significance and patients may participate in all sports when ventricular size and function is normal and no pulmonary hypertension is present. Patients with large VSDs may participate in low intensity sports. Following successful surgical closure (≥ 6 months post surgery) patients with normal pulmonary pressures, normal ventricular function and no evidence of arrhythmias may engage in all sports types.

COARCTATION OF THE AORTA

The main dangers of coarctations of the aorta regarding physical exercise lie in the risk of excessive hypertension in the part of the circulatory bed proximal to the aortic narrowing with stroke, aortic aneurysm and left-ventricular hypertrophy/failure as main complications. Examination should include measurement of blood pressure on all limbs, echocardiography and chest radiograph. Patients with low gradients (≤ 20 mmHg), normal resting blood pressure, systolic blood pressure during exercise of < 230 mmHg, no aortic aneurysm and no large collaterals may engage in all sports. Those with > 20-mmHg gradients, hypertension, systolic blood pressure during exercise of > 230 mmHg and aortic aneurysm or wall thinning should be restricted to low intensity exercises (≤ 3 METs). After surgical correction, sports (except static exercise, i.e. weightlifting) may be started ≥ 6 months post surgery, when no residual hypertension at rest and during exercise is present. In patients with residual gradients of > 20 mmHg, aneurysms or aortic wall thinning, only low-intensity exercise is recommended.

Please refer to Conwell JA, Exercise in children after surgery for congenital heart disease, in: Thompson PD, ed., *Exercise and Sports Cardiology*, McGraw-Hill: New York, and to Kaplan S, Perloff JK, *Congenital Heart Disease in Adults*, Saunders, for exercise recommendations in rare congenital defects.

Morbid obesity

Studies in obese patients suggest that exercise-based rehabilitation (optimally combined with diet programmes) is effective in reducing weight, improving exercise capacity and in normalizing lipid status (LDL↓,HDL↑) [71].

Compared with normal weight rehabilitation participants, the gain in exercise capacity was lower in obese patients (+27% vs. +39%). This may be a consequence of orthopaedic comorbidities, lower baseline fitness or greater difficulties in motivation for starting to exercise.

Women

Despite the advances in cardiac medicine myocardial infarction in women continues to be associated with higher short- and long-term mortality, reinfarction rates and development of congestive heart failure within 6 months, than in men. The old view that CAD is a male disease contributes to the gender differences in cardiac morbidity and mortality, and also affects participation in rehabilitation programmes.

Gender differences in rehabilitation participation

Only approximately 20% of participants in rehabilitation programmes are female, whereas women represent close to 40% of patients with acute myocardial infarction. Women are significantly less likely to be formally informed about rehabilitation interventions and even more rarely receive a referral to a rehabilitation institution by their treating physicians [72]. Among plausible reasons for this gender difference are medical aspects (e.g. the higher prevalence of orthopaedic problems, such as osteoporosis) and social factors (e.g. lack of own car, caring for husband).

The differences in rehabilitation participation are especially unwelcome, as women have more modifiable risk factors than men and are less likely to be physically active.

Gender differences in rehabilitation effects

The preconditions for exercise are different in men and women: women have a lower aerobic capacity, a greater proportion of body fat and smaller muscle cross-sectional areas compared with men. Nonetheless, women benefit as equally as men from exercise-based cardiac rehabilitation with regard to exercise capacity: an increase in Vo_2max ranging from 15% to 30% may be expected.

Exercise effects on lipids are less conclusive in women, partially as a consequence of menopausal status: as oestrogen is associated with lower LDL levels, hormonal status affects the extent of training-induced LDL changes. One long-term study, however, revealed a significant 20% increase in HDL after 5 years of rehabilitation [73]. A combination of diet plus exercise training is effective for weight reduction in overweight women (–5.1 kg within 1 year in a prospective controlled trial) [74].

The elderly

Special considerations for training programmes in the elderly

Among key factors for disability in older people are mental depression, low aerobic fitness levels, low skeletal muscle mass and the presence of orthopaedic comorbidities. Despite these factors, the elderly benefit equally from cardiac rehabilitation; however, from a lower baseline. Evaluation prior to exercise follows the guidelines set above (see Development of exercise therapy from rehabilitation to prognostic intervention, Indications/contraindications and Exercise therapy in chronic heart failure, Indications/contraindications, above). Owing to the higher prevalence of heart failure in older patients, a baseline echocardiography is recommended.

When initiating aerobic exercise, the exercise intensity should be carefully weighed against a higher risk of injuries with higher workloads. Even workloads as low as 60–65% of maximal heart rate have documented effects on exercise capacity. To offset the loss of muscle mass endurance, exercises are often supplemented by moderate intensity resistance training (e.g. elastic bands) with 8–10 set repetitions at 40–60% of the one-repetition maximum.

Evidence base for rehabilitation in the elderly

Over a period of 3 months, 34–53% increases in exercise capacity may be expected from endurance training rehabilitation. The effect of resistance training is similar to the results in younger population, with a 35% increase in leg extension strength.

Although more research in this area needs to be undertaken, current evidence suggests that cardiac rehabilitation in the elderly is cost-effective because even small improvements in exercise tolerance and physical coordination may permit maintenance of independent living and prevent hospitalization.

On a final note, patients from the groups mentioned above are currently under-represented in cardiac rehabilitation programmes. There seems to be a significant level of uncertainty, among many physicians, as regards under which conditions physical activity can be safely recommended in these patients. However, the intuitive reaction of many physicians, namely to discourage training or physical exertion, clearly worsens exercise tolerance and deprives the patient of an important adjunct therapy. Today we are faced with the challenge of putting the guidelines into practice and to convert knowledge into clinical benefit for the patient.

Personal perspective

The impact of physical inactivity weighs heavily on the health-care systems of Western societies: in the USA alone it has been estimated that 18% of heart disease cases (at a cost of $24 billion) and 22% of colon cancer cases (at a cost of $2 billion) in the population may be caused by inactivity. It is now known that the average medical costs for active people are 30% lower than those for inactive people.

Two patient groups are especially on the rise.

1 In secondary prevention and exercise therapy, elderly patients form an important under-represented target population for exercise-based rehabilitation. By improving their exercise capacity they can shift their individual baseline for age-related decline of Vo_2max to a higher level (Fig. 26.8). This exercise-related shift delays physical disabilities by years and permits patients to continue an independent life for a longer period of time.
2 Towards the other end of the age pyramid, a growing obesity epidemic affecting even teenagers is spreading among Western populations. According to the most recent National Health and Nutrition Survey (NHANES III, 1988–1991), 40% of all men and 26% of all women in the USA are overweight; 20% and 26% are obese respectively. Projected adult obesity rates are 30% in 2015 and > 40% in 2025. The direct health-care cost for treating the 15 most common comorbid conditions incurred by adults with obesity [body mass index (BMI) > 30] is $102.2 billion. Patients with obesity have often entered a vicious circle of unhealthy eating habits combined with physical inactivity, which leads to overweight, in turn aggravating inactive lifestyle and accelerating further weight gain. Diet alone is inadequate to achieve a sustained weight loss in obese patients and needs to be combined with intensive aerobic exercise training. It is well established that the incidence of type 2 diabetes and other obesity-related disorders can be dramatically reduced by such an aggressive lifestyle intervention.

In combination, a greater focus on the potentials of physical activity—both in primary and in secondary prevention—would greatly reduce lifestyle-related costs to the health-care system and reduce age-related morbidity. Although obviously not preventing death, physical activity may help us to enjoy an active and fulfilled life for the longest possible period.

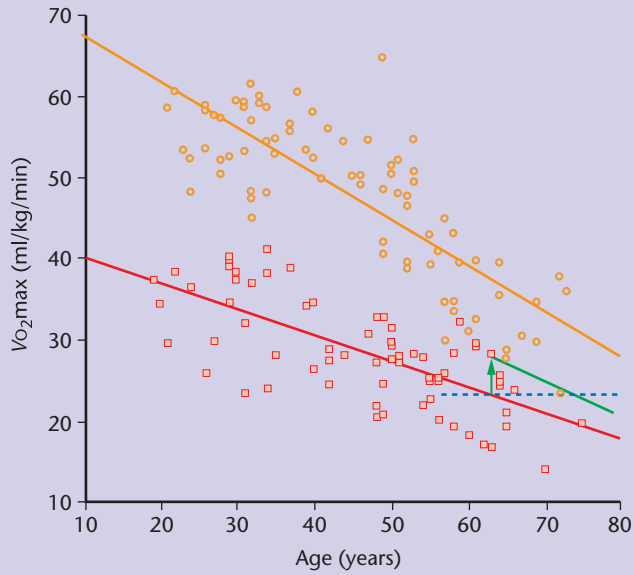

Figure 26.8 In both trained (orange circles) and untrained healthy individuals (red squares) maximal exercise capacity declines by approximately 10% per decade during the ageing process. However, at old age even minor gains in exercise capacity achieved by training interventions may significantly prolong an independent life. Adapted from Tanaka and Seals [77].

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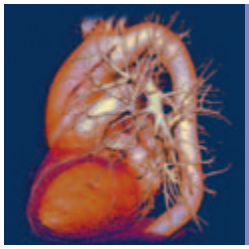

27 Bradycardia

Lukas Kappenberger, Cecilia Linde and William D. Toff

Summary

Bradycardia can present considerable diagnostic and therapeutic challenges to the physician.Bradycardia per se is often a benign observation , but in the context of symptoms suggestive of low cardiac output, may need careful attention and diagnostic accuracy. Pacemakers have become the gold standard for the treatment of sinus node dysfunction and atrioventricular conduction disturbance and they have considerably improved the clinical outcome for patients with symptomatic bradycardia. The past decade has witnessed an increasing level of sophistication of the available pacemaker types and programming options, along with improved understanding of the pathophysiology of the natural activation and electrical stimulation of the heart. New insights have paved the way for increasingly physiological pacing modes, aiming at preserving the natural activation and contraction sequence and protecting the heart from electrical remodelling and its consequences. New data from randomized clinical trials have provided an evidence base to guide the selection of the most appropriate device type but clinical judgment, based on sound experience, remains vital for the optimal programming of the device, which is an essential contributor to what the patient will consider to be a treatment success.

Introduction

Bradycardia is a common finding in daily medical practice and the broad scope of its consequences range from none to a fatal outcome. Understanding the anatomy and physiology of the activating and conduction system of the heart, identifying potentially reversible causes, diagnosing the type of bradycardia, estimating its potential for severe consequences and, finally, choosing the most appropriate therapy for the individual patient are the necessary steps for successful management. More than ever, this represents a considerable clinical challenge for the physician, having evolved from adding years to life in the early days of pacemaker treatment to adding life to years in the 21st century.

Anatomy and physiology of the basic rhythm of the heart

The wedge-shaped sinus node is a collection of specialized cells lying beneath the epicardial surface in the right atrial sulcus terminalis, at the junction of the superior vena cava and the right atrium. Regular spontaneous depolarizations (automaticity) of its P (pacemaker) cells leads via T (transition) cells to a coordinated electrical impulse that initiates depolarization, activation and subsequent contraction of the surrounding atrial myocardial cells. The electrical impulse propagates through the atrial tissue and pathways of preferential conduction from the right atrium to the atrioventricular node [1] as well as to the left atrium. The blood supply of the sinus

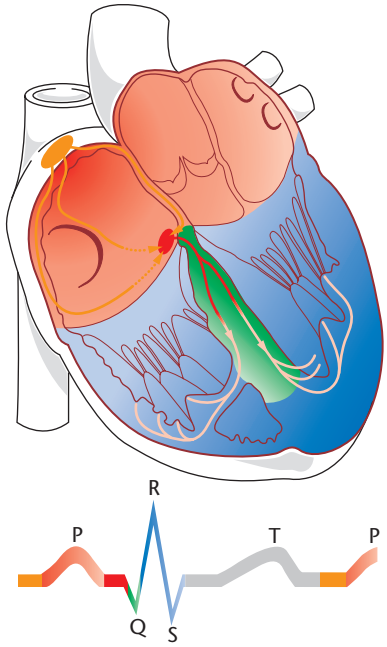

Figure 27.1 Electrical conduction system of the heart. The sinus node is located in the upper part of the right atrium between the superior vena cava and the right atrial appendage. Impulses from the sinus node are conducted to the atrioventricular node. From the atrioventricular node, impulses are conducted through the bundle of His. Below the bundle of His, the conduction system divides into the right and left bundle branches. While the right bundle is quite distinct the left bundle branch divides into one anterior and one posterior hemibranch.

node usually originates from the proximal right coronary artery.

The atrioventricular node is a subendocardial anatomical structure located in the low atrial septum, anterior to the ostium of the coronary sinus and directly above the insertion of the septal leaflet of the tricuspid valve, in the anatomically defined triangle of Koch. It receives its blood supply from the atrioventricular nodal artery, a branch of the posterior descending artery, which arises from the right coronary artery in about 80% and from the circumflex coronary artery in the remainder. Automatic impulse formation may also occur in the atrioventricular node and gives rise to a junctional escape rhythm if the sinus node fails.

From the atrioventricular node, impulses are conducted to the bundle of His, which passes through the annulus fibrosus and penetrates the membranous interventricular septum, before separating into the left and right bundle branches (Fig. 27.1). The bundle of His is predominantly supplied by the atrioventricular nodal artery but also receives a contribution from septal perforators arising from the left anterior descending coronary artery.

The right bundle branch crosses the anterior part of the interventricular septum and reaches the apex of the right ventricle and the base of the anterior papillary muscle. The left bundle branch, which is anatomically less discrete, typically subdivides into an anterosuperior and a postero-inferior fascicle, thereby creating a bifascicular system. Finally, the bundle branches ramify, giving rise to the endocardially located terminal Purkinje fibres, which ensure the activation of both ventricles.

The conduction system is richly innervated by the sympathetic and parasympathetic nervous systems at all levels (sinoatrial, junctional and ventricular), exerting autonomic effects that ensure balanced control of the heart rate and intracardiac conduction. Parasympathetic tone decreases sinus node automaticity and slows atrioventricular nodal conduction, while the sympathetic output increases automaticity and enhances conduction. An imbalance in the neurological control of the heart, as observed during vagal stimulation manoeuvres, after the administration of sympathomimetic or parasympathomimetic drugs, or as a consequence of central nervous system damage, prolonged ischaemia or infection, may therefore result in the development of bradyarrhythmias or tachyarrhythmias.

Definition of bradycardia

The baseline heart rate in an individual patient is determined by the balance between the parasympathetic and the sympathetic nervous systems. The 'normal' heart rate has been defined arbitrarily as 60–100 beats per minute (b.p.m.) at rest, although a range of 50–90 b.p.m. has also been suggested [2]. Interestingly, the 'intrinsic' rate of the sinus node, after sympathetic and vagal blockade, is around 110 b.p.m. [3]. The heart rate may vary from patient to patient depending on age, training status and time-point of the observation [4]. In a healthy asymptomatic population, the 'normal' range of heart rates in the afternoon was found to be 46–93 b.p.m. in men and 51–95 b.p.m. in women [5–7], nocturnal rates being lower. At rest or during sleep, heart rates as low as 40 b.p.m. may be normal, even in healthy subjects. In contrast, sinus or atrial bradycardia below 30 b.p.m. may be of concern in patients with sinus node dysfunction, especially if symptomatic [7]. The heart rate should fluctuate physiologically during respiration, with the Valsalva

Table 27.1 Causes of bradycardia

Intrinsic causes
Idiopathic degeneration (ageing)
Ischaemic heart disease
Infiltrative diseases: sarcoidosis [18,19], amyloidosis [20], haemochromatosis [21]
Collagen vascular diseases: systemic lupus erythematosus [22], rheumatoid arthritis [23], scleroderma
Myotonic muscular dystrophy
Surgical trauma: valve replacement, heart transplantation [24], eye surgery, arteriography
Hereditary diseases, including sinus node and atrioventricular node disease
Infectious diseases: Chagas' disease [25,26], diphtheria, endocarditis, Gram-negative sepsis, typhoid fever [26]
Extrinsic causes
Physical training (sports), possibly via increased vagal tone
Vagal hypertonicity: vasovagal syncope, carotid-sinus hypersensitivity
Vagal hyperreactivity: coughing, micturition, defecation, vomiting
Negatively chronotropic and/or bathmotropic drugs: beta-blockers, calcium channel blockers, clonidine, digoxin, lithium, antiarrhythmic agents (amiodarone, propafenone), including topical application [17]
Drug abuse: cocaine [27]
Electrolyte imbalance: hypokalaemia or hyperkalaemia
Metabolic disorders: hypothyroidism, hypothermia, anorexia nervosa [28,29]
Neurological disorders: increased intracranial pressure, central nervous system tumours
Obstructive sleep apnoea [30,31]

manoeuvre and with other vagal influences, confirming normal autonomic control of the sinus node.

Bradycardia is a frequent finding in trained athletes and heart rates below 40 b.p.m. are often observed at rest [8–10]. Sinus pauses of up to 2.5 s were found in 10% of normal healthy individuals, pauses of more than 2 s in 20% of athletes [8] and pauses of 2–3 s in 37% of athletes during sleep [10]. However, even in athletes, pauses of more than 3 s require further medical attention, especially if associated with a history of syncope [11].

Another important component of the definition of bradycardia is the chronotropic response to exercise, which reflects the ability of the heart to accelerate according to the degree of exertion. An inadequate chronotropic response, together with inability to reach the maximum predicted heart rate (defined as 220 minus age in years) at peak exercise, strongly suggest that a relative bradycardia may require further attention [2,12–14].

During atrial fibrillation, the ventricular rate is determined by atrioventricular nodal refractoriness. Affected patients warrant special consideration, as they exhibit greater beat-to-beat variability than patients in sinus rhythm [15]. During atrial fibrillation, daytime pauses of up to 2.8 s and night-time pauses of up to 4.0 s may be considered as within acceptable limits, if well tolerated by the patient [16].

Reflecting the above, at the individual patient level, bradycardia may be defined as an inappropriately low heart rate in relation to age, gender, activity level and physical training status. Clinical attention is required only if bradycardia is associated with symptoms, at rest or during exercise, that may put the patient at risk.

Causes of bradycardia

Bradycardia may be caused by a variety of intrinsic and extrinsic influences on the heart or by damage to the sinus node or conduction system. The early identification of a potentially reversible cause of bradycardia is the first step towards treatment. Numerous causes have been identified, as shown in Table 27.1. The most frequently identified form of reversible bradycardia is that induced by drugs. Drug interactions and competition for metabolic pathways or elimination routes may promote the negatively chronotropic and bathmotropic effects of drugs. Even locally instilled drugs, such as beta-blockers for the treatment of glaucoma, may cause bradycardia and reveal or aggravate underlying sinoatrial dysfunction or atrioventricular conduction disturbance in susceptible patients [17].

Clinical and electrocardiographic findings in patients with bradycardia

Signs and symptoms

Bradycardia is a frequent finding in daily medical practice. The clinical challenge is to separate those patients who are symptomatic, at risk of complications (low cardiac output, dizziness, heart failure) and in need of further investigation from those who are healthy, in whom the bradycardia is physiological.

Eventual symptoms depend on cardiac output, defined as the product of left ventricular stroke volume and heart rate. As long as changes in stroke volume compensate for the decrease in heart rate, even patients with profound bradycardia may remain asymptomatic, the disorder only being detected as an incidental finding on clinical examination or on ECG performed for other reasons.

At the other end of the clinical spectrum, the patient with bradycardia may present with a variety of signs and symptoms. Amongst these, syncope is the most dramatic, although cardiac standstill of more than 6 s is generally required before loss of consciousness will occur. However, symptoms are often non-specific and chronic, for example transient dizziness, light-headedness or confusional states, reflecting cerebral hypoperfusion due to decreased cardiac output, or episodes of fatigue or muscular weakness with exercise intolerance. Overt heart failure, at rest or on exercise, may also result from underlying bradycardia, especially in patients with impaired left ventricular function. Bradyarrhythmia may also present with palpitation, which simply means a perception of the beating heart. The patient may describe 'pauses' or 'strong beats', which are often manifestations of premature beats or just increased awareness of the action of the heart during a period of emotional sensitivity.

Whatever the patient's presenting symptoms, a causal relationship should only be inferred from the temporal coincidence of documented bradyarrhythmic episodes and the symptoms, whether these are specific or not. This is of particular importance with regard to patients' expectations of treatment benefits.

Sinus node dysfunction

Sinus node dysfunction, also known as sick sinus syndrome, is a common cause of bradycardia, which encompasses a variety of sinoatrial disorders, ranging from the usually benign sinus bradycardia to the more severe and often symptomatic bradycardia–tachycardia syndrome, characterized by paroxysmal, rapid, regular or irregular atrial tachyarrhythmias, alternating with periods of slow atrial and ventricular rates [32,33] (Fig. 27.2A). Other manifestations of sinus node dysfunction include serious, persistent and otherwise inexplicable sinus bradycardia and bradyarrhythmia, sinus arrest with ectopic atrial or nodal escape rhythms, paroxysmal or chronic atrial fibrillation secondary to sinus arrest, sinoatrial exit block and inadequate chronotropic response to exercise. More than one of these conditions may be recorded in the same patient on different occasions. Thus, the clinical entity of sinus node dysfunction encompasses not only inadequate pacemaker function of the sinus node but often also abnormal intra-atrial conduction, which may represent the substrate for atrial fibrillation. The ventricular response to atrial fibrillation will depend on whether the atrioventricular node is also affected, in which case the term 'binodal disease' is used.

Sinus bradycardia is defined by sinus node depolarizations at a rate below 60 b.p.m., with normal P waves before each QRS complex. Sinus bradycardia is a common and usually benign finding [34]. Transient sinus bradycardia may be observed in patients after myocar-

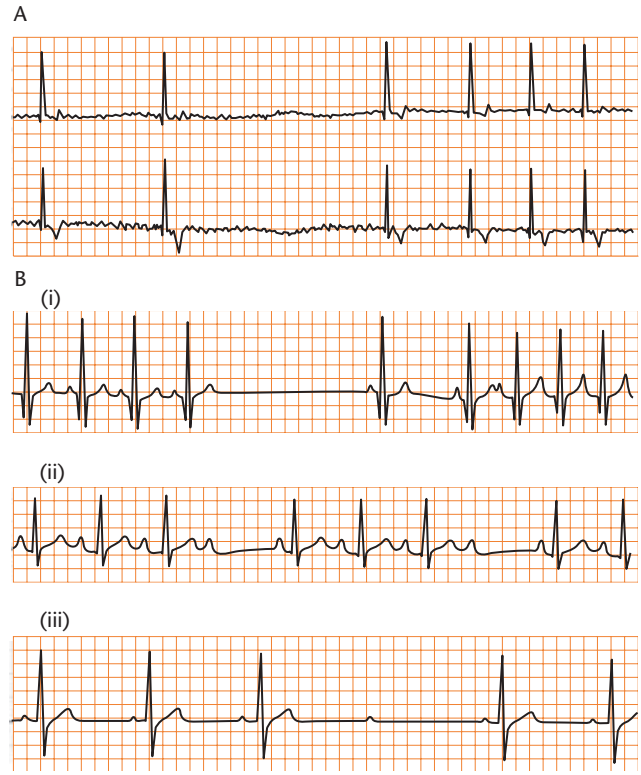

Figure 27.2 ECG appearance in different types of bradycardia. (A) Atrial fibrillation with ventricular pauses: one form of the bradycardia–tachycardia syndrome. (B) (i) Sinus arrest; (ii) Mobitz I second-degree atrioventricular block; (iii) Mobitz II second-degree atrioventricular block.

dial infarction and also following resuscitation from cardiac arrest, in which context it is associated with a poor prognosis [35].

Sinus pauses (standstill of more than 150% of cardiac cycle length) may be due to failure of impulse formation in the sinus node (sinus arrest) or a failure of conduction out of the nodal region to the surrounding atrium (sinoatrial exit block). In pauses due to sinoatrial exit block, the P–P interval during the pause is typically a multiple of the basic P–P interval, whereas in sinus arrest no such relationship is seen (Fig. 27.2B(i)). Although sinus pauses or arrest may have no intrinsic clinical significance, the emergence of surrogate atrial or nodal pacemaker escape rhythms to prevent ventricular asystole increases the risk of atrial fibrillation or flutter [36], thromboembolic events [37] and bradycardia–tachycardia syndrome. The latter, a combination of alternating atrial tachyarrhythmia and sinus bradycardia episodes, is usually symptomatic, since the overdrive suppression of sinus automaticity during the tachycardic phase may result in long pauses due to increased sinus node recovery time and syncope when tachycardia terminates. In addition, attempts to decrease the rapid heart rate (e.g. with beta-blockers or digitalis) may further depress the sinus node or atrioventricular conduction and accentuate the abnormality.

Atrioventricular conduction disturbance

Atrioventricular conduction disturbance may occur at any level, from the atrioventricular junction down to the intraventricular conduction system. It includes varying degrees of block in the atrioventricular node, the His bundle or the right or left bundle branches and/or in the anterior and posterior divisions of the left bundle branch (left anterior or left posterior fascicular blocks). Block may either occur at a single site or affect two or more components of the conduction system [38]. The atrioventricular node and the His bundle are particularly sensitive to ischaemia and to traumatic injury, as they constitute a narrow preferential conduction pathway between the atria and the ventricles.

Atrioventricular block

First-degree atrioventricular block is characterized by a prolonged PR interval, exceeding 210 ms, with normal morphology and duration of the QRS complex and maintenance of 1 : 1 conduction. First-degree atrioventricular block does not cause bradycardia unless it progresses intermittently to second- or third-degree block or is associated with sinus node dysfunction. In patients with anterior myocardial infarction and conduction disturbance located below the bundle of His, first-degree block may progress to complete infra-Hisian block and lead to ventricular asystole, whereas inferior infarction is associated with the more benign intranodal and atropine-sensitive blocks.

Second-degree atrioventricular block is characterized by an atrial rhythm, which is only partially conducted to the ventricles.

- Mobitz type I second-degree atrioventricular block (or Wenckebach block) is characterized by progressively increasing PR intervals, until a P wave is not conducted (Fig. 27.2B(ii)). During the following cycle, the PR interval resumes its original value and progressively increases again until the next P wave is blocked. Observation of the jugular venous pulse may reveal repetitive sudden loss of the v wave, corresponding to the ventricular pause, despite the persistence of an a wave. This type of block, in which the conduction disturbance is localized to the atrioventricular node, rarely manifests with syncope.
- Mobitz type II second-degree atrioventricular block is characterized by abrupt conduction failure (Fig. 27.2B(iii)). Mobitz type II block generally originates from an infra-Hisian lesion, may be associated with a wide QRS complex, often progresses abruptly to complete atrioventricular block and frequently manifests with syncope.

Third-degree atrioventricular block (complete heart block) is characterized by the complete dissociation of atrial and ventricular activity, each following its own rhythm. Usually symptomatic, the patient may have signs and symptoms related to reduced cardiac output, such as syncope or dyspnoea. The escape rhythm may provide an indication of the location of the block: a sustained rhythm between 40 and 60 b.p.m. with narrow QRS complexes suggests a junctional rhythm associated with supra-Hisian block, whereas wide QRS complexes at a slower heart rate indicate block at a lower level in the His–Purkinje system and a more urgent need for therapeutic intervention.

Intraventricular block

Intraventricular conduction delay (bundle branch block) at any level of the His–Purkinje system leads to the loss of synchronous ventricular activation and contraction. Intraventricular block may be fascicular (left anterior or left posterior hemiblock) leading to left intraventricular dyssynchrony, or it may affect the bundle branch itself (left or right bundle branch block) leading to interventricular dyssynchrony. These different types of block may be isolated or combined, rate dependent or not, and may indicate an increased risk of development of high-degree atrioventricular block [39]. However, in the

absence of demonstrated atrioventricular block or unexplained symptoms suggestive of bradycardia, isolated monofascicular or bifascicular block is not usually a major concern. Intracardiac ECG recordings are of limited value, although a His–ventricular conduction time of 100 ms or more is an indication for pacing in a patient with bi- or trifascicular block. Less marked His–ventricular delay is a more common finding but its prognostic significance is uncertain. When investigating unexplained symptoms in this setting, it is important to consider other possible arrhythmic causes, such as paroxysmal tachycardia.

Diagnostic approach to the bradycardic patient

Successful management of bradycardia depends on identification of the right treatment for the right patient, always remembering the option not to treat if there is no need. The aim of the diagnostic work-up is to identify those patients in whom bradycardia impacts upon quality of life and/or puts them at risk of potentially severe complications such as syncope, heart failure, arrhythmias with embolic risk or sudden death.

Patient evaluation begins with a detailed history, including an attempt to identify potentially reversible causes of bradycardia (with a specific focus on drug treatments, including non-cardiovascular drugs), followed by physical examination, including careful cardiac auscultation. Commonly reported symptoms include palpitation, presyncope or syncope, and dyspnoea or fatigue. These symptoms may be paroxysmal or chronic, may be triggered or aggravated by physical exercise, or may occur only in specific situations (e.g. during the night). The standard baseline 12-lead ECG completes the initial diagnostic phase and may usefully be combined with a Valsalva manoeuvre and carotid sinus massage, which may give more detailed information about autonomic function. Exercise testing is often useful, as it may reveal an inadequate chronotropic response and the achieved heart rate should exceed at least 90 b.p.m.

In patients with suspected symptomatic bradycardia, an important determinant of future therapeutic decisions will be to establish a causal relationship between symptoms and bradycardic episodes. The hierarchy of diagnostic testing depends upon sound clinical judgement, as some tests may be more appropriate than others in order to deliver the right diagnosis rapidly.

Long-term ECG recording

HOLTER RECORDING

Ambulatory ECG monitoring over 24–48 h is appropriate for patients with suspected intermittent symptomatic bradycardia in order to correlate the symptoms with the bradycardic episodes [40,41]. Frequently identified forms of bradycardia, such as sinus bradycardia, first-degree atrioventricular block and even second-degree Mobitz I (Wenckebach) atrioventricular block, may be considered as normal in young and/or well-trained subjects. The same findings may be considered as pathological if, for example, their appearance precipitates left ventricular decompensation with symptoms of heart failure. On the other hand, evidence of sinus node dysfunction, bradycardia–tachycardia syndrome, Mobitz II second-degree atrioventricular block or third-degree atrioventricular block with ventricular pauses over 3 s, although less frequently seen, are always pathological.

EVENT RECORDERS AND IMPLANTABLE LOOP RECORDERS

Holter recording, even if prolonged to 48 h, often fails to identify the cause of the patient's symptoms, especially if bradycardic episodes are intermittent, with prolonged periods of normal sinus rhythm and/or a paucity of symptoms. Two other diagnostic devices may help in such cases.

- Transient-event recorders may be kept for a month or more, allowing digital recording of the ECG for up to 30 s initiated by the patient at the time he or she experiences symptoms. This presupposes that the patient remains conscious at the onset of the symptoms but most modern recorders have permanent monitoring for arrhythmic events. A further limitation is that only one ECG channel is usually recorded and detailed interpretation of the findings may be difficult. However, this technique has been shown to be more efficacious and cost-effective than Holter recording in patients with intermittent palpitation [42].
- Implantable loop recorders (e.g. Reveal®) may be particularly useful in the investigation of infrequently recurring symptoms, especially if Holter and transient-event recorders have failed to establish the diagnosis. Implantable loop recorders allow patients to be monitored over a prolonged period, increasing the diagnostic yield to as much as 85% in syncope that is difficult to diagnose [43]. Due to the extended period of observation that it enables, exceeding 1 year, the implantable loop recorder has become a key contributor in establishing the temporal correlation with syncope in patients suspected to have infrequent underlying arrhythmia. It has been shown to be most useful in patients with infrequent unexplained syncope when non-invasive testing is negative [44].

Electrophysiological testing and intracardiac ECG

Electrophysiological testing of sinus node function measures the sinus node recovery time, which is then corrected for the spontaneous sinus rate by subtraction of the sinus cycle length. The normal corrected sinus

node recovery time is below 550 ms and a longer recovery time is observed in patients with sinus node dysfunction. In these patients, atrioventricular and His–Purkinje function should also be evaluated, as coexisting conduction disturbances are frequent.

Electrophysiological testing may be used for the elucidation of atrioventricular or intraventricular conduction disturbance when the level of the block cannot be established from the ECG. Electrophysiological studies may help to identify patients at high risk of progression to complete atrioventricular block, in whom implantation of a pacemaker may be required.

Unexplained syncope may be due to sinus node dysfunction or atrioventricular block and is an indication for electrophysiological testing if non-invasive assessment fails to identify the aetiology [45]. Although the cause of syncope is identified in more than 50% of patients by non-invasive means (history, physical examination, ECG, Holter, loop recording), electrophysiological studies may be indicated in order to establish the cause in the remainder, especially in patients with known heart disease [46]. However, intermittent conduction disturbances are, by their nature, difficult to identify, even by electrophysiological testing, and the diagnosis may occasionally be inferred by exclusion of all other potential causes of syncope of cardiac origin.

Electrophysiological testing is associated with a low risk of complications. However, these include death, arterial injury, thrombophlebitis, systemic arterial embolism, pulmonary embolism and cardiac perforation. In addition, catheter-induced permanent complete atrioventricular block, atrial fibrillation or other tachyarrhythmia, sometimes requiring cardioversion, may occur [47]. Therefore, as with every invasive procedure, careful evaluation of the likely diagnostic benefit and the fully informed consent of the patient is mandatory.

Treatment of bradycardia

The first step in treatment is the identification of reversible, often drug-induced, or situational bradycardia and the elimination of causal drugs or other provocative factors whenever possible.

Drug therapy

Treatment is usually not necessary in patients with sinus bradycardia, sinus bradyarrhythmia, sinus pauses or sinus arrest shorter than 3 s. For more significant bradycardia, intravenous atropine (0.5 mg, repeated if necessary) may be used to accelerate the heart rate and improve cardiac performance in the acute setting, although paradoxical reactions may rarely occur. Some patients may experience relief from bradycardic symptoms with theophylline [48] but this is rarely a reliable long-term therapy. Patients presenting with symptomatic sinus node disease and/or atrioventricular conduction disturbance should therefore be considered and evaluated for the implantation of a temporary or permanent artificial pacemaker.

Implantable pacemakers

Since the early 1950s when pacemakers were large external devices, used principally to ensure survival, implantable pacemakers have become the gold standard for the treatment of symptomatic bradycardia for selected indications. The first pacemaker implantation into a human was performed in 1958 by Elmqvist and Senning [49], followed swiftly by the implantation of the first endocardial lead by Furman and Robinson [50]. Today, millions of patients world-wide have an implanted pacemaker, and with increasingly sophisticated technology the dimension of 'pacing for living' has been added to the initial vision of 'pacing for life'. In the two decades after the first successful implantation, the focus of research was on the development of more reliable power sources and leads. More recently, the concept of 'physiological' pacing has driven the development of sophisticated dual- and even triple-chamber pacemakers, intended to preserve or restore atrioventricular and/or interventricular synchrony, and of sensor-driven heart rate modulation, designed to restore chronotropic competence.

Implantable pacemakers deliver localized electrical stimulation of the cardiac tissue that propagates and activates the myocardium, leading to muscle contraction. The spread of the pacemaker-initiated electrical impulse follows a non-physiological route, which may have important electrical and mechanical consequences, especially with long-term pacing. Therefore 'artificial pacing' should be applied only where and when it is really needed and natural activation sequences should be imitated or conserved whenever possible. Individually adapted pacemaker prescriptions are therefore needed.

Current pacemaker nomenclature

The five-letter code for identifying pacemakers and pacing modes (NBG code) was established by the North American Society of Pacing and Electrophysiology (NASPE) and the British Pacing and Electrophysiology Group (BPEG) in 1987 [51] and revised in 2002 [52].

The first letter indicates the heart chamber(s) being paced (A, atrium; V, ventricle; D, both), the second letter the chamber(s) being sensed and the third letter the

Table 27.2 NBG pacemaker code

I: chamber(s) paced	II: chamber(s) sensed	III: response to sensing	IV: rate modulation	V: multisite pacing
O, none	O, none	O, none	O, none	O, none
A, atrium	A, atrium	T, triggers pacing	R, rate modulation	A, atrium
V, ventricle	V, ventricle	I, inhibits pacing		V, ventricle
D, dual (A and V)	D, dual (A and V)	D, dual (T and I)		D, dual (A and V)
S*, single (A or V)	S*, single (A or V)			

*Used by manufacturers only and indicates that the device can be used in the atrium or the ventricle.
NBG is an acronym of the *N*orth American Society of Pacing and Electrophysiology, the *B*ritish Pacing and Electrophysiology Group, *G*eneric.

response of the pacemaker upon sensing (T, triggered; I, inhibited; D, both). Thus, an AAI pacemaker paces in the atrium, senses in the atrium and inhibits pacing if spontaneous electrical activity is sensed. A DDD pacemaker paces and senses both in the atrium and the ventricle and reacts in a dual fashion: an impulse sensed in the atrium inhibits atrial pacing and triggers ventricular pacing after a delay, mimicking the physiological atrioventricular conduction sequence. The fourth letter indicates the presence (R) or absence (O) of an adaptive-rate mechanism (rate responsiveness), which modulates the heart rate independent of intrinsic cardiac activity (e.g. during exercise). The fifth letter is used to indicate whether multisite pacing is present in the atria (A), the ventricles (V), both (D) or neither (O) (Table 27.2).

Thus the revised code provides for the description of triple-chamber pacemakers used for biventricular pacing or cardiac resynchronization therapy (CRT). In contrast to single- or dual-chamber pacemakers, which have only one or two leads (an atrial and/or a right ventricular lead), triple-chamber devices feature an additional lead to pace the left ventricle, most often located within one of the overlying cardiac veins, which are accessed through the coronary sinus. Whilst right ventricular pacing may result in interventricular dyssynchrony, mimicking the conduction pattern associated with left bundle branch block (LBBB), biventricular pacing can preserve the synchronous activation and contraction of both ventricles, thereby improving cardiac haemodynamics. Biventricular pacing is currently used for CRT in symptomatic heart failure patients with interventricular dyssynchrony but it is possible that it may be considered in the future whenever ventricular stimulation is required. Examples of the ECG during single- and dual-chamber pacing are shown in Figs 27.3 and 27.4 respectively. Figure 27.5 shows the ECG features of CRT.

Indications for pacemaker implantation

Although temporary or external pacemakers can be used for initial stabilization or, in the short term, for reversible or potentially reversible bradycardic episodes, the ther-

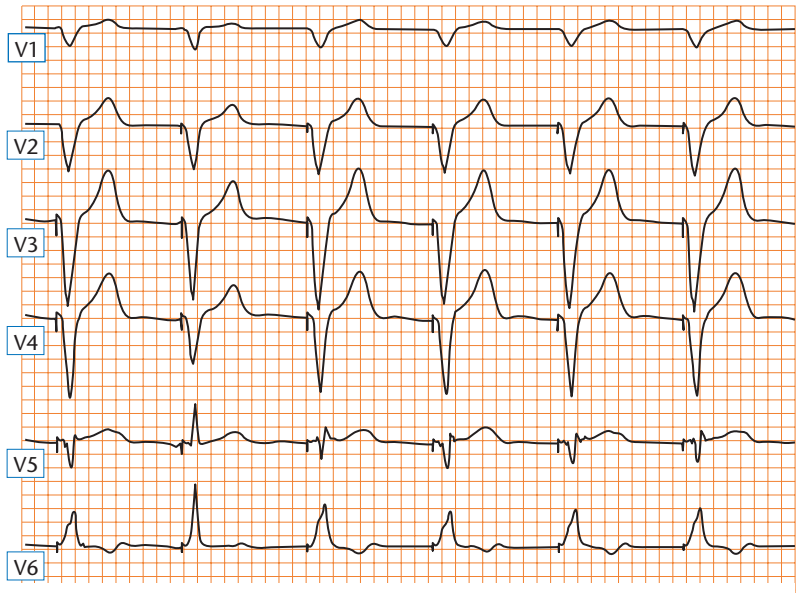

Figure 27.3 ECG during single-chamber ventricular pacing.

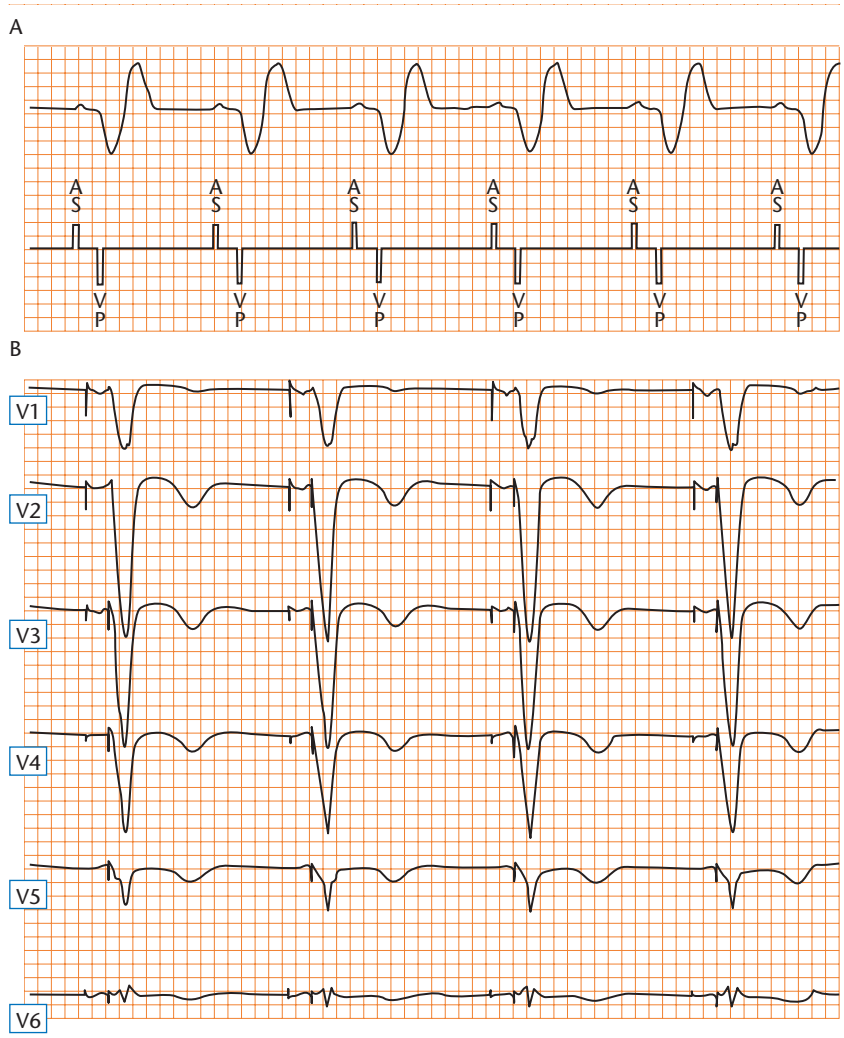

Figure 27.4 ECG during dual-chamber pacing. (A) ECG with simultaneous recording of pacemaker event markers showing atrial sensing (AS) of sinus rhythm and synchronised ventricular pacing (VP). (B) ECG showing synchronised atrial and ventricular pacing.

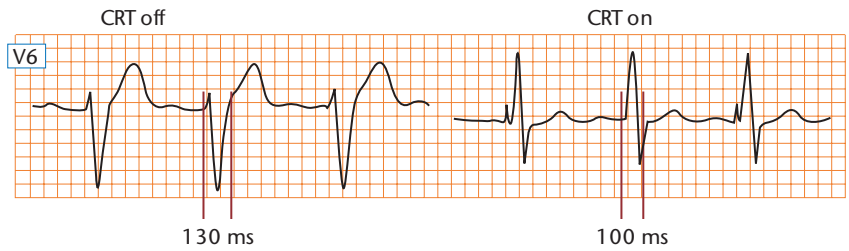

Figure 27.5 ECG features of cardiac resynchronization therapy (CRT), showing shortening of the QRS width.

apeutic challenge is to identify the patient who will benefit from an implanted permanent pacemaker. The indications for permanent pacing are reviewed extensively in the guidelines for implantation of cardiac pacemakers of the American College of Cardiology (ACC), the American Heart Association (AHA) and NASPE [53] (Table 27.3) and in the guidelines of the the European Heart Rhythm Association (EHRA) and the European Society of Cardiology (ESC) [54].

- Class I indications represent conditions where there is general agreement that a permanent pacemaker should be implanted.
- Class II indications are those where there is no such general agreement: class IIa characterizes those indications where the weight of evidence and opinion is in favour of usefulness or efficacy; class IIb characterizes those indications where usefulness or efficacy is less well established.

Sinus node dysfunction (SND)
Class I
SND with documented symptomatic bradycardia, including in patients with iatrogenic SND and no effective alternative drug type or dose
Class IIa
SND with heart rate < 40 b.p.m. and unclear correlation between bradycardia and symptoms
Class IIb
Minimally symptomatic SND with heart rate < 30 b.p.m.
Class III
SND without symptoms or due to non-essential drug therapy

Atrioventricular (AV) block
Class I
Symptomatic third- or second-degree AV block
Asymptomatic third-degree AV block with heart rates < 40 b.p.m., with documented asystole ≥ 3 s or as a consequence of His bundle ablation
Class IIa
Asymptomatic third-degree AV block with heart rates ≥ 40 b.p.m.
Asymptomatic second-degree Mobitz II AV block with narrow QRS
Asymptomatic second-degree Mobitz I intra-Hisian or infra-Hisian AV block found incidentally
Class IIb
Marked first-degree AV block (PR > 0.3 s) in patients with heart failure
Class III
Asymptomatic second-degree Mobitz I supra-Hisian AV block
Asymptomatic first-degree AV block
Potentially reversible AV block (e.g. drug toxicity, Lyme disease, sleep apnoea)

Bifascicular or trifascicular block
Class I
Intermittent third-degree AV block
Second-degree Mobitz II AV block with wide QRS
Alternating bundle branch block
Class IIa
Syncope not demonstrated to be due to AV block when other causes (specifically ventricular tachycardia) have been excluded
Incidental finding of markedly prolonged HV interval (≥ 100 ms) at electrophysiological study in asymptomatic patient
Class III
Asymptomatic fascicular block without AV block or with first-degree AV block

Table 27.3 Abbreviated summary of American College of Cardiology, American Heart Association and North American Society of Pacing and Electrophysiology 2002 recommendations for implantation of permanent cardiac pacemakers in patients with bradycardia, by level of lesion

- Class III indications are those where there is evidence or general agreement that permanent pacing is not needed or may even be harmful.

Evidence-based choice of optimal pacing mode

Once the decision to implant a pacemaker is made, the appropriate pacing mode and type of pacing system must be selected. The choice will be influenced by the primary indication for pacing and by the patient's general health status and anticipated level of activity.

The indications for permanent pacing represent only the most prominent conditions amenable to treatment with a pacemaker. Each indication encompasses a wide variety of patients and the therapeutic goal is to provide the right device and appropriate programming for each individual patient. Cardiologists, electrophysiologists and engineers have developed increasingly sophisticated devices, often exploring the forefront of physiological knowledge, while pushing back the limits of the technical possibilities. The clinical benefit of pacemaker therapy, when first introduced for the treatment of Morgagni–Adams–Stokes attacks [55], was dramatic. Today the indications for permanent pacing have broadened and there has been a proliferation of device types, pacing modes and programming options. This has heralded an era in which the effect sizes of new developments have become less dramatic, albeit still of clinical relevance. Continuing improvements in technology and optimized treatment options will result from innovative thinking

and the accumulation of evidence from well-designed randomized clinical trials.

For patients with normal atrial activity, atrioventricular sequential pacing (DDD) has been shown to be haemodynamically superior to ventricular pacing (VVI), mainly due to preservation or restoration of the atrial contribution to left ventricular filling. This leads to increased stroke volume and improved cardiac output through optimization of the cardiac cycle, with timely closure of the atrioventricular valves. In the absence of atrioventricular synchrony, the coincidence of atrial and ventricular contraction may lead to an abrupt fall in blood pressure and a variety of symptoms, comprising the pacemaker syndrome (discussed below). However, not all patients develop pacemaker syndrome with VVI pacing and some patients have no increase in cardiac output with DDD pacing, observations which may be explained, at least partially, by interindividual variation in left ventricular filling pressure and the ability to adapt stroke volume rapidly [56]. In daily practice, however, DDD pacing has been perceived as the best option for most patients, be it for function or quality of life.

During right ventricular pacing the electrical impulse is usually delivered to the apex of the ventricle, from where it depolarizes the slowly conducting surrounding myocardium (instead of progressing through the fast-conducting His–Purkinje fibres), mimicking LBBB. Patients with LBBB have been shown to have reduced ejection fraction and decreased diastolic filling time compared with patients without LBBB [57], and ejection fraction has been shown to be lowest with ventricular pacing, intermediate with atrioventricular sequential pacing and best preserved with atrial pacing and ventricular activation via the intrinsic pathways [58]. Adverse consequences associated with pacing at the right ventricular apex include pacing-induced mitral regurgitation, decreased ejection fraction and alterations in regional myocardial blood flow, glucose uptake and oxygen consumption, together with regional wall motion and structural abnormalities similar to those observed in patients with intrinsic LBBB. Right ventricular pacing may be considered as causal in the development of interventricular dyssynchrony and its clinical consequences. Therefore, part of the beneficial effect on cardiac output resulting from atrioventricular synchrony in the DDD mode may be offset by the interventricular dyssynchrony induced by pacing at the right ventricular apex.

Over the past decade and for the first time since pacemakers were introduced, several randomized trials have reported the comparative clinical outcomes of atrial-based vs. ventricular-based pacing. In these studies, the specific focus was on the following predefined endpoints and outcomes: all-cause mortality, cardiovascular death, thromboembolism and stroke, atrial fibrillation, development of or hospitalization for heart failure, pacemaker syndrome and quality of life. The patients included suffered mostly from symptomatic bradycardia due to sinus node disease with or without normal atrioventricular conduction [59], although one trial focused specifically on elderly patients with high-grade atrioventricular block [60]. The key features of the study designs and patients included are shown in Table 27.4.

ALL-CAUSE AND CARDIOVASCULAR MORTALITY

The only randomized trial comparing purely atrial pacing (AAI) with purely ventricular pacing (VVI) in patients

Table 27.4 Randomized clinical trials of pacemaker mode selection

Reference (study name)	Year	Pacing modes	*N*	Indication	Mean age (years)	Duration (years)
Andersen *et al*. [61]	1994	AAI vs. VVI	225	SND with normal AV conduction	76	3.3
Andersen *et al*. [62]	1997	—				5.5
Nielsen *et al*. [63]	1998	—				
Andersen *et al*. [64]	1999	—				
Lamas *et al*. [65] (PASE)	1998	DDD(R) vs. VVI(R)	407	SND and AV block	76	2.5
Connolly *et al*. [66] (CTOPP)	2000	AAI(R) or DDD(R)* vs. VVI(R)	2568	SND and AV block	73	3.0
Skanes *et al*. [67] (CTOPP)	2001	—				3.0
Newman *et al*. [68] (CTOPP)	2003	—				N/A
Kerr *et al*. [69] (CTOPP)	2004	—				6.4
Lamas *et al*. [70] (MOST)	2002	DDD(R) vs. VVI(R)	2010	SND	74	2.7
Toff *et al*. [60] (UKPACE)	2005	DDD(R) vs. VVI(R)	2021	AV block	80	4.6

*95% of the patients were paced DDD(R).

AV, atrioventricular; PASE, PAcemaker Selection in the Elderly; CTOPP, Canadian Trial of Physiologic Pacing; MOST, MOde Selection Trial in sinus-node dysfunction; SND, sinus node dysfunction; UKPACE, United Kingdom Pacing and Cardiovascular Events.

with sinus node disease, normal atrioventricular conduction and normal QRS complexes was published in 1994 by Andersen *et al*. [61]. It is also the only trial to date to report a significantly increased cardiovascular death rate in the VVI-paced group, although this only emerged during extended follow-up at 5.5 years (19/110 and 39/115 cardiovascular deaths for AAI and VVI respectively, $P = 0.0065$) [62]. The difference in this end-point did not reach significance 3 years after implantation [61]. The remaining clinical trials compared atrial-based pacing (predominantly DDD(R)) with VVI(R) pacing and found no significant difference in all-cause or cardiovascular mortality between groups after 2.5–4.6 years of treatment [60,65,66,70] nor in the follow-up extension of one trial after 6.4 years [69] (Fig. 27.6).

THROMBOEMBOLISM OR STROKE IN RELATION TO PACING MODALITY

Similar observations apply to the risk of thromboembolism and stroke. In patients with sick sinus syndrome, Andersen *et al*. reported a significant increase in thromboembolic events in the VVI group compared with the AAI group after 3.3 years of observation (20/115 vs. 6/110 events, $P = 0.0083$) [61], confirmed after 5.5 years (39/115 vs. 19/110 events, $P = 0.0065$) [62]. The risk of arterial thromboembolism was primarily associated with the presence of the bradycardia–tachycardia syndrome at randomization and with ventricular pacing, whereas it was small in atrial-paced patients in whom atrial fibrillation had never been documented [64]. No significant differences in thromboembolism or stroke were found in the other trials, comparing DDD(R) with VVI(R) pacing, neither after 2.5–3 years of treatment [60,65,66,70] nor in the follow-up extension of one trial after 6.4 years [69]. The annual rates of stroke ranged from 1% in CTOPP [66] to 2.2% in MOST [70], two of the largest end-point trials published to date in patients with permanent pacemakers. Taking into account the fact that stroke has multiple possible cardiogenic and non-cardiogenic aetiologies in elderly patients and the variable use of antiplatelet therapy, even large clinical trials may lack the power to establish adequately whether one pacing mode is superior to the other with regard to the risk of stroke.

CAN PACING PREVENT OR PROVOKE ATRIAL FIBRILLATION?

The incidence of atrial fibrillation was generally found to be greater in VVI(R)-paced patients than in patients with atrial-based pacing (AAI(R) or DDD(R)), although no significant difference was observed in the UKPACE trial [60] (Fig. 27.6). In the trial reported by Andersen *et al*. [61], 23% of the VVI-paced patients developed atrial fibrillation after 3 years compared with 14% of the AAI-paced patients, an observation that did not reach statistical significance, probably due to the small number of patients included ($n = 225$). However, atrial fibrillation occurred significantly less frequently in the atrial-based pacing group than in the VVI(R)-paced group in CTOPP [66] and the relative risk of developing atrial fibrillation was significantly reduced by 21% ($P = 0.008$) over 2.7 years in the DDD(R)-paced group compared with the VVI(R)-paced group in MOST [70]. This relative risk reduction was consistent with the 20.1% risk reduction ($P = 0.009$) observed after 6.4 years in the extension of CTOPP [69] and the relative risk reduction for chronic atrial fibrillation of 27.1% ($P = 0.016$) in favour of atrial-based pacing in the same trial [67]. The following risk predictors for chronic atrial fibrillation were identified: age ≥ 74 years, sinoatrial node disease and prior episodes of atrial fibrillation [67]. However, in those patients with an intrinsic heart rate ≤ 60 b.p.m., i.e. those most likely to have a predominantly paced rhythm, the benefit of DDD pacing for reduction of atrial fibrillation was even more pronounced [71].

There is therefore consistent evidence that atrial-based pacing reduces the risk of atrial fibrillation in patients with sinus node disease. Several mechanisms have been proposed, such as the suppression of premature atrial beats, which may trigger the development of sustained atrial fibrillation, and the maintenance of optimal ventricular diastolic filling through the preservation of appropriately timed atrial contraction. Indeed, the follow-up observations of Andersen *et al*., 5.5 years after pacemaker implantation, showed that the left atrial diameter increased significantly less in the AAI-paced than in the VVI-paced group [63], a finding consistent with an increased risk of atrial fibrillation in VVI-paced patients. While these studies considered that the reduction in atrial fibrillation was simply a consequence of preventing bradycardia, it has also been proposed that electrical stimulation prevents, reduces or even interrupts atrial fibrillation by a variety of other mechanisms. However, there is presently no convincing evidence for these concepts.

PACEMAKER SYNDROME

Classically, pacemaker syndrome reflects the loss of atrioventricular synchrony resulting in loss of the atrial contribution to cardiac output during ventricular pacing. However, pacemaker syndrome is now recognized as being the result of a complex interaction of neurohumoral, autonomic and vascular changes. It is characterized by: (1) congestive symptoms and signs mimicking heart failure, such as dyspnoea, orthopnoea, distended neck veins, rales, hepatomegaly and oedema of the lower limbs; (2) hypotensive symptoms and signs, such as syncope (or presyncope) at the onset of pacing, with a drop in blood pressure (Fig. 27.7); and (3) non-specific symptoms such as fatigue and dizziness [74]. In clinical studies

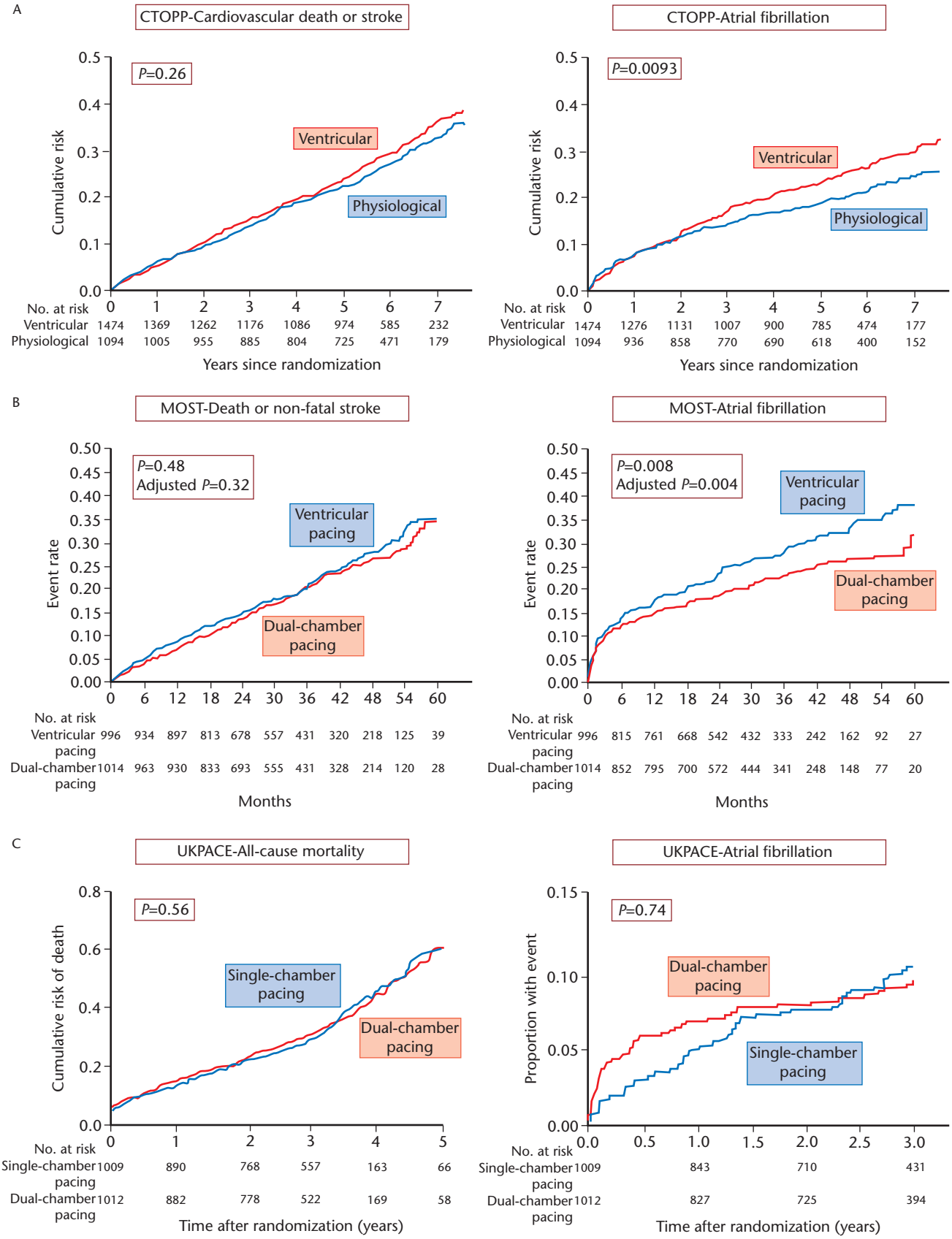

Figure 27.6 Incidence of primary end-points and atrial fibrillation in pacemaker mode selection trials. (A) CTOPP (extended follow-up). Reproduced with permission from Kerr *et al.* [69]. (B) MOST. Reproduced with permission from Lamas *et al.* [70], copyright © 2002 Massachusetts Medical Society. (C) UKPACE. Reproduced with permission from Toff *et al.* [60], copyright © 2005 Massachusetts Medical Society.

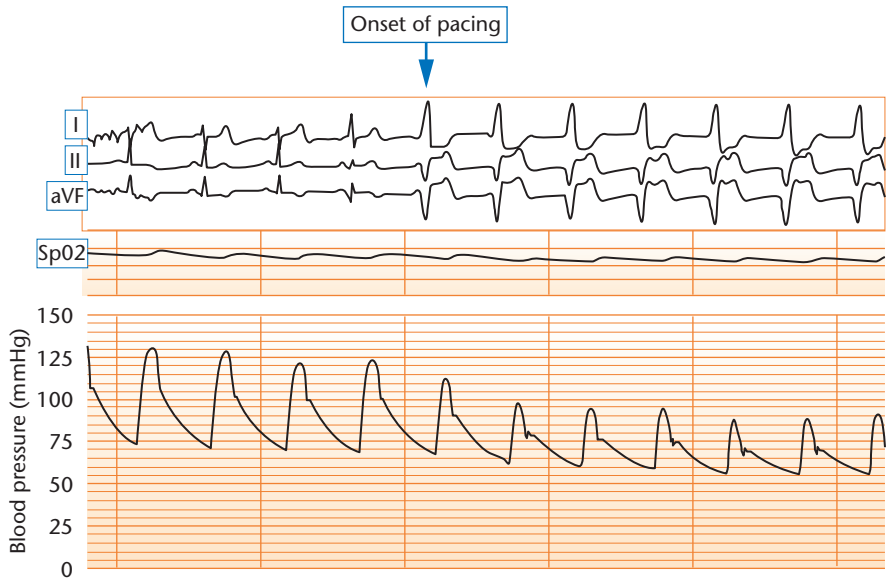

Figure 27.7 Pacemaker syndrome: simultaneous ECG and femoral arterial blood pressure recording in a 64-year-old man presenting with intermittent dizziness, palpitation and dyspnoea 3 years after implantation of a VVI pacemaker for sinus node disease. Arterial blood pressure dropped from 131/72 to 88/55 mmHg with the onset of VVI pacing during slowing of the sinus rate (arrow). Retrograde P waves are discernible after the paced QRS complexes. Reproduced from Ahn and Cho [115] with permission of the BMJ Publishing Group.

where cross-over to the alternate pacing mode (from VVI to either AAI or DDD) required re-intervention, pace-maker syndrome was reportedly rare, with rates of 1.8% over 5.5 years [62] and 5% over 3 years [66]. In contrast, in clinical studies where cross-over required only non-invasive transcutaneous reprogramming of the pacing mode, pacemaker syndrome was reported in 18.3% over 2.7 years [70] and 26% over 2.5 years [65], using a definition based on haemodynamics (elevated right or left filling pressures or hypotension with ventricular pacing). Use of the more common operating definition of pacemaker syndrome (i.e. intolerance of ventricular pacing) would presumably have generated much higher numbers. Figures as high as 83% have been reported with VVI pacing, when patients were given the option to directly compare with DDD pacing [75].

QUALITY OF LIFE

While virtually all patients implanted with a pacemaker have experienced a significant increase in quality of life vs. baseline (i.e. before implantation), large-scale clinical trials published to date have not shown superiority of one pacing mode over another with regard to improvements in generic measures of quality of life [65,68]. However, small single-centre cross-over studies using disease-specific instruments have shown improvement in quality of life with physiological pacing [76,77] and improvements in exercise tolerance have also been reported [78,79].

Patient-based choice of pacing mode

As a general rule, a patient with isolated sinus node dysfunction and no atrioventricular conduction disturbance may be considered for a single-chamber AAI(R) pacemaker, as the annual incidence of second- or third-degree atrioventricular block has been shown to be below 1% [62,80]. The ongoing DANPACE trial will ultimately provide further information about the relative merits of atrial and dual-chamber pacing in this context [81]. For a patient with sinus node dysfunction and concomitant conduction disturbance, a dual-chamber pacing system is most appropriate, with DDD pacing if chronotropic competence of the sinus node is preserved and DDD(R) pacing if it is not. If sinus node disease is associated with the bradycardia–tachycardia syndrome, DDI(R) pacing or a device with mode-switching capability (i.e. automatically switching from an atrial-tracking mode to VVI on detection of atrial tachyarrhythmia) is preferred in order to avoid rapid paced ventricular rates in response to the tracking of high atrial rates [82]. In a patient with atrioventricular or multifascicular block, a dual-chamber device with DDD or DDD(R) pacing is appropriate, although VVI(R) pacing may be an acceptable alternative in the elderly [60]. In the presence of chronic atrial fibrillation, a single-chamber ventricular pacemaker with VVI or VVI(R) pacing should be used. There is no universal pacing mode that suits all patients and careful selection of the appropriate pacing system, with individualized programming to match each patient's needs, is of crucial importance. Not surprisingly, literature on the customization of individual patient settings is scarce and there is no substitute for clinical expertise.

HEART FAILURE INDUCED AND REDUCED BY ELECTRICAL STIMULATION

One of the effects of ventricular pacing, especially with right ventricular apical stimulation, could be the stimulus

for a remodelling process leading to the development of new or worsening heart failure. However, heart failure is a slowly progressive disease and the majority of patients included in the pacemaker end-point trials had normal ejection fractions. In the study by Andersen *et al*., 35/113 patients in the VVI-paced group experienced a deterioration in New York Heart Association (NYHA) class over 5.5 years compared with 19/109 in the AAI-paced group, a highly significant difference ($P < 0.0005$) in favour of AAI pacing [63]. In addition, the increase in dose of diuretics was significantly higher in the VVI group than in the AAI group and left ventricular ejection fraction decreased in the VVI group (–5% compared with baseline over 5.5 years, $P < 0.0005$), whereas it remained unchanged in the AAI group. After adjusting for differences in baseline characteristics (myocardial infarction, diabetes, heart failure and supraventricular tachycardias were more frequent in the DDD(R) group), MOST reported a significant reduction in the incidence of hospitalization for heart failure in the DDD(R)-paced group compared with the VVI(R) group (10.3% vs. 12.3% over 2.7 years, $P = 0.021$) [70], although the unadjusted analysis and other trials did not show a significant difference [60,65,66]. Recent experimental evidence has demonstrated that electrical stimulation of the myocardium has an important influence on structural and metabolic features [72,73].

Two additional considerations may influence the approach to a patient-based choice of pacing mode (Table 27.5).

- Right ventricular apical pacing has been shown to promote electrical remodelling of the heart and to induce interventricular dyssynchrony, both of which may have deleterious effects on cardiac haemodynamics. Physiological pacing should therefore aim to maximize intrinsic rather than paced ventricular activation. The ideally configured pacing system is one that paces only when needed but always when needed. Many pacemaker patients have only transient bradyarrhythmia, with an adequate unpaced heart rate much of the time, and are not pacemaker-dependent. Data from CTOPP showed that the yearly cardiovascular death or stroke rate steadily increased with decreasing unpaced heart rate in the VVI(R) group, whereas there was no such relationship in the physiological (AAI or DDD(R)) pacing group [71]. Recently developed pacemakers with functions aiming at minimizing ventricular pacing and maximizing intrinsic cardiac conduction may represent an important means for preventing the effects of electrically induced cardiac remodelling.
- The interventricular dyssynchrony (cardiac desynchronization) and electrically induced cardiac remodelling associated with right ventricular apical pacing may accelerate the progression of pre-existing heart failure. In patients with congestive heart failure, in NYHA classes III and IV and with wide QRS complexes, an additional left ventricular lead placed through the coronary sinus allows synchronous pacing of both ventricles, resulting in a more normal pattern of ventricular activation and contraction. Cardiac resynchronization therapy, with or without integrated cardioverter–defibrillator capability, has been shown to improve NYHA functional class, six-minute walking distance, quality of life and peak oxygen consumption. Dramatic reductions in heart failure hospitalization [83,84] and the combined risk of death or hospitalization for any cause [85] have also been reported, as has a reduction in total and cardiac mortality [86]. In patients with

Table 27.5 Decision-making elements for physiological pacing. Left ventricular function and the extent of pacemaker dependency (anticipated cumulative percentage of paced right ventricular beats) will determine the attributes of the pacing system most likely to maximize clinical benefit

Left ventricular function	Cumulative percentage of right ventricular pacing	Pacing mode attributes	Expected clinical benefit
Normal ejection fraction	100% (pacemaker-dependent)	Selective-site RV pacing	Preserve LV function
Reduced ejection fraction	Minimal percentage of RV pacing	MVP. AAI pacing with DDD back-up	Reduce RV pacing
Heart failure with LVD	> 40% RV pacing	Selective-site RV or LV pacing	Preserve and support LV function
Heart failure with LVD and interventricular asynchrony	> 40% pacing (resynchronization RV–LV)	LV pacing or biventricular pacing	Restore synchrony, improve LV function and symptoms
			Reduce hospitalizations for heart failure

LV, left ventricle; LVD, left ventricular dysfunction; MVP, minimal ventricular pacing (see ref. 114); RV, right ventricle.

bradyarrhythmia and heart failure, the potential benefits of an additional left ventricular lead for cardiac resynchronization should therefore be considered [86,87].

Complications of pacemaker treatment

The possible complications of pacemaker treatment are many and varied, albeit relatively infrequent. They may occur in either the perioperative period or the months and years that follow (Table 27.6).

The implantation of a pacemaker is an invasive procedure, with the potential for all the general complications of any surgical intervention and for a variety of procedure-specific complications. Human factors related to the implanter, such as operator technique and experience, may influence the risk of complications, as may factors related to the patient, such as comorbidity or concomitant drug therapy.

General perioperative complications include discomfort, infection (typically less than 1% [88]) and bruising or haematoma at the implant site. The risk of haematoma is increased in patients taking antithrombotic or anticoagulant drugs. Although it is customary to discontinue anticoagulant therapy 3–5 days before implantation and provide heparin cover until a few hours before surgery, patients in whom this would pose an unacceptable risk of thromboembolism may be safely implanted whilst anticoagulated, subject to the use of meticulous surgical technique by a skilled operator [89,90]. Specific complications of the implant procedure include traumatic pneumothorax or haemo-pneumothorax (typically less than 2% of implants), brachial plexus injury, arterial puncture and left ventricular incursion or injury, which is associated with an additional risk of thromboembolism. Myocardial perforation with pericardial effusion or, more rarely, tamponade, air embolism, subcutaneous emphysema, or thrombosis of the subclavian vein, superior vena cava, right atrium or right ventricle may also occur. Venous thrombosis may rarely lead to pulmonary embolism or the superior vena cava syndrome.

Amongst the procedure-specific complications, lead dislodgment, loose lead connection to the pacemaker, lead fracture or insulation break deserve special attention. Lead dislodgement has been reported in up to 4.2% of dual-chamber compared with 1.4% of single-chamber pacemaker implantations [66]. As expected, inadequate pacing and sensing was also more frequent with dual-chamber than single-chamber pacemakers. Supraventricular and ventricular arrhythmias are not uncommon during pacemaker implantation but are rarely of clinical consequence. Endless-loop tachycardia, a form of pacemaker-mediated tachycardia, is a well-recognized complication of dual-chamber pacing but is less commonly seen with modern devices and may usually be avoided by careful programming. Diaphragmatic pacing may occur due to phrenic nerve stimulation from a laterally placed atrial lead or to direct activation because of proximity of the ventricular lead. The problem may be resolved by

Table 27.6 Complications of pacemaker treatment

Perioperative
General
Haemorrhage/bruising/haematoma
Pain/discomfort
Infection
Wound dehiscence

Specific
Pneumothorax/haemothorax/haemomediastinum
Arrhythmia (asystole, atrial/ventricular arrhythmia)
Air embolism/subcutaneous emphysema
Myocardial perforation/tamponade
Left-sided lead misplacement
Brachial plexus injury

Mechanical
Lead-related
Lead dislodgement
Conduction break
Insulation failure
Twiddler's syndrome
Venous thrombosis/superior vena cava syndrome/pulmonary embolism

Device-related
Erosion
Migration
Traumatic injury/damage

Functional
Electrical
Diaphragmatic pacing
Pectoral muscle stimulation
Intrinsic electromagnetic interference (myopotential sensing)
Extrinsic electromagnetic interference
Over-sensing
Under-sensing
Threshold rise
Premature battery depletion
Pacemaker failure

Rhythm-related
Pacemaker-mediated tachycardia

Haemodynamic
Pacemaker syndrome
Autonomic dysregulation

Psychological
Anxiety/depression/adjustment problems

decreasing the output voltage (subject to a satisfactory safety margin) or lead repositioning. Pectoral stimulation may be due to incorrect orientation of the pacemaker with its active surface in contact with the muscle or a current leak from a lead insulation failure or exposed connector.

Pacemaker follow-up

Regular and methodical follow-up of the pacemaker recipient is essential for sustained treatment success [91,92]. The principal objectives are to ensure optimal pacemaker function matched to the patient's needs, maximize device longevity, identify any problems or complications, ensure prompt recognition of battery depletion (enabling elective device replacement to be scheduled) and provide patient education and support. The frequency and type of follow-up visit may be influenced by the type of pacemaker implanted (e.g. single or dual chamber), the patient's clinical status (e.g. symptoms, comorbidity, pacemaker dependency) and the original indication for implantation. A typical schedule would include a pre-discharge check, a follow-up visit at 4–8 weeks after discharge and a further visit after 3–6 months. Thereafter, an annual visit is generally sufficient until the time of predicted or observed battery depletion, when follow-up visits will again become more frequent (e.g. 3-monthly or less) until the pulse generator is replaced. For complex dual-chamber pacemakers, additional visits may occasionally be needed during the first 6 months after implantation, for optimization or fine-tuning of the programmed atrioventricular delay and other parameters. When facilities for trans-telephonic monitoring (TTM) are available, more frequent checks may be made (e.g. 3-monthly), as is typically the case in North America. TTM is particularly useful for patients living in remote areas, far from the follow-up centre, and for the prompt evaluation of symptoms arising between visits. Clinic visits are essential for wound assessment, for full evaluation of the patient or the device and for troubleshooting problems detected on TTM. Otherwise, the mode of follow-up will be determined on a case-by-case basis. TTM should include recording of an ECG strip before, during and after magnet application, and measurement of pulse duration (atrial and ventricular channels for dual-chamber pacemakers). This will usually enable confirmation of satisfactory pacemaker function, estimation of battery longevity and detection of any arrhythmia. At clinic visits, a more comprehensive evaluation can be performed, including interrogation of the device memory, measurement of sensing and pacing thresholds, optimization of atrioventricular delay and other parameters, and assessment and optimization of chronotropic response in patients with rate-adaptive devices.

Practical considerations for the patient with a pacemaker

Pacemaker recipients are usually able to resume a full and active life, including return to most forms of employment. Contact sports involving a risk of trauma to the device should be avoided but most other sporting activities may be undertaken. Driving regulations vary between countries and states but commonly permit the resumption of non-commercial driving 1 week after pacemaker implantation, subject to notification of the regulatory authority and the absence of any other disqualifying condition [93]. Patients should be informed of the risk of electromagnetic interference (EMI) and encouraged to avoid strong electromagnetic fields and specific known hazards, such as arc welding machines. Possible effects of EMI include inappropriate pacemaker inhibition or triggering, asynchronous pacing, alteration of programmed settings or damage to the device circuitry, which may lead to a sudden increase in pacing rate, known as 'runaway pacemaker'. In strong magnetic fields there is also the possibility of closure or distortion of magnetic reed switches, displacement of the pacemaker or lead, and heating of the lead tip. The clinical consequences will depend on many factors, the most important being the extent to which the patient is pacemaker dependent [94]. Domestic household appliances rarely give rise to any problems, unless faulty [95]. Cellular telephones do have the potential to affect pacemakers when in close proximity (< 15 cm), although clinically significant EMI is unlikely during normal use [96]. Patients should be advised to use the ear opposite to the side of the implant and not to carry the telephone in a pocket overlying the pacemaker [94]. Electronic article surveillance (EAS) systems, as used in many shops and libraries, may also affect pacemakers but clinically significant EMI is unlikely on walking briskly through. However, patients should be advised not to lean on the EAS gate or linger in close proximity [94].

There are a number of potential hazards for pacemaker patients in the medical and therapeutic environment [97]. Magnetic resonance imaging is contraindicated and should be avoided unless absolutely essential, in which case the patient should be carefully monitored throughout and the pacemaker checked after the procedure [98]. Extracorporeal shock wave lithotripsy, used as a non-invasive treatment for nephrolithiasis or cholelithiasis, is associated with a risk of both EMI and mechanical damage from the hydraulic shock wave. It is, however, relatively safe provided the pacemaker is not in an abdominal position and the shock wave is synchronized to the ECG [99]. In dual-chamber devices, where the shock is synchronized to the atrial pacing pulse, inhibition of the

ventricular channel may occur but this may be avoided by reprogramming to VVI or VOO mode, or by enabling safety pacing. Rate rises in activity-sensing devices may be avoided by temporarily disabling the rate-responsive function. Careful follow-up of the pacemaker over several months is advisable to ensure that there has been no damage to the reed switches. Ionizing radiation in therapeutic doses may cause cumulative damage to the semiconductor circuitry of the pacemaker and the device should be shielded to provide protection during radiotherapy. If the device lies within the field requiring irradiation (e.g. in a patient with ipsilateral breast malignancy), it may be necessary to relocate it, as shielding might compromise effective radiation therapy. Betatron therapy may cause severe EMI and should be avoided [100,101].

For patients requiring surgery, it is important that the surgeon and anaesthetist are aware of the presence and type of the device, the underlying pathology and the possible hazards in the perioperative period [102]. Surgical diathermy and electrocautery are well-recognized sources of EMI. Their use and power output should be kept to the minimum required, using short bursts and avoiding close proximity to the device. With unipolar cautery systems, the indifferent electrode should be placed well away from the pacemaker (e.g. on the posterior thigh), so that the pacemaker does not lie between the electrodes. Bipolar cautery is less hazardous but EMI may still occur. If electrocautery is to be used in a pacemaker-dependent patient, preoperative reprogramming of the device to an asynchronous or triggered mode should be considered. In all other cases, a programmer or magnet should be immediately available to enable asynchronous fixed-rate pacing to be activated in case of pacemaker inhibition. Disabling the rate-adaptive function may also be advisable to avoid the risk of idiosyncratic rate acceleration. Other hazards in the perioperative period include alteration of the pacing threshold by drugs, hypoxia, hypercapnia, metabolic disturbance or electrolyte imbalance. Perioperative ECG and haemodynamic monitoring is essential and the pacemaker should be checked after exposure to perioperative hazards. In patients requiring external cardioversion or defibrillation, the use of anteroposterior paddle positions will reduce the risk of damage to the device or myocardial injury. The pacemaker should always be checked after a shock has been delivered.

New indications for cardiac pacing

The foregoing discussion has focused on the use of pacemakers in the treatment of bradycardia caused by sinus node disease or atrioventricular block. In recent years, a variety of new indications have emerged and it is now clear that cardiac pacing may be of benefit in selected patients with other conditions, even in the absence of bradycardia.

- The use of CRT for selected patients with heart failure has been mentioned above and is considered further in Chapter 24.
- In patients with hypertrophic obstructive cardiomyopathy, pacing-induced pre-excitation of the right ventricular apex may reduce the left ventricular outflow tract gradient and clinical improvement has been reported in randomized trials [103–105]. However, the clinical benefit does not correlate well with gradient reduction and there are no clear predictors of response. Hypertrophic obstructive cardiomyopathy with symptoms refractory to medical therapy is currently a class IIb indication for pacing [53].
- In patients with severe carotid sinus syndrome, the role of pacing is well established [106]. It is also recommended for patients with recurrent syncope without clear provocative events but in whom there is a hypersensitive cardio-inhibitory response to carotid sinus massage [53]. The use of pacing in severe vasovagal syndrome with a cardio-inhibitory response to head-up tilt testing is more controversial. Although some trials have shown a reduction in syncope with pacing, using a specialized rate-drop sensing algorithm [107] or rate hysteresis [108], more recent studies designed to control for a possible placebo effect have shown no clear benefit [109,110].
- The ability of various pacing algorithms and alternative or dual atrial pacing sites to suppress atrial fibrillation has been evaluated in patients with and without bradycardia but clinical benefits have been limited and inconsistent. At present, there is little evidence to support the use of these approaches for suppressing atrial arrhythmia, except in patients with an established indication for anti-bradycardia pacing [111].
- In patients with the long QT syndrome, pacing may be useful as an adjunct to beta-blockade for the prevention of pause-dependent malignant ventricular arrhythmias [112].

Detailed consideration of these new indications for pacing is beyond the scope of this discussion but they are considered elsewhere in this book in the chapters dealing with the specific conditions.

Concluding remarks

A key driver to pacemaker implant success is the experience of the implanter [113]. Similarly, the knowledge and skill of the pacemaker physician contribute to patient satisfaction and well-being at all stages, starting with the

right diagnosis, continuing with the choice of the most appropriate device and pacing mode, the state-of-the-art implantation procedure, and carefully conducted and attentive follow-up. Each of these steps is of crucial importance in achieving what both the physician and the patient will consider to be a treatment success, and at every stage the patient must be kept fully informed regarding all aspects of treatment.

Personal perspective

Implantable pacemakers are the gold standard for the successful management of bradycardia in well-defined indications. Future developments are expected to focus increasingly on mimicking the natural conduction and activation of the heart. Improved knowledge regarding individualized programming of the devices to match patients' needs and optimize long-term results is one avenue to be explored. Another relates to the delivery of the electrical impulse to preserve interventricular synchrony, for example by left ventricular stimulation. Yet another promising possibility is the advent of devices focusing on minimizing ventricular pacing, i.e. devices designed to pace only when needed but always when needed [114]. For decades the implantation technique has utilized subclavian or cephalic venous access. With increasing haemodynamic sophistication, accurate placement of electrodes is of paramount importance. New pericardioscopic approaches may facilitate this and, together with subcostal generator positioning, may make pacemaker or cardioverter–defibrillator implantation an even less invasive procedure.

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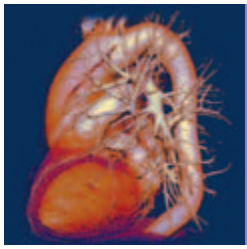

28 Supraventricular Tachycardia

Jerónimo Farré, Hein J.J. Wellens, José A. Cabrera and Carina Blomström-Lundqvist

Summary

Paroxysmal supraventricular tachycardia (SVT) is a common arrhythmia in the emergency room, the outpatients' clinic and the electrophysiology laboratory. While its natural history is often benign in terms of life expectancy, the quality of life of patients suffering paroxysmal SVT is frequently poor. Non-paroxysmal forms of SVT are less frequent. Among the latter, permanent or incessant SVTs can result in a tachycardiomyopathy with systolic left ventricular dysfunction that is usually reversible after permanently abolishing the arrhythmia. Incessant SVT is exceptional in patients aged > 55 years either because of a spontaneous cure or because of a lethal evolution with early death due to heart failure or cardiac arrest. Although paroxysmal and incessant SVT can have various sites of origin and mechanisms, they can usually be cured by catheter ablation techniques. Surgery has no role today in the treatment of SVT.

Introduction

Supraventricular arrhythmias and supraventricular tachycardia

Supraventricular arrhythmias are disorders in the generation of the heart impulse in which structures above the division of the bundle of His are essential for their occurrence. Supraventricular arrhythmia is a wider concept than that of supraventricular tachyarrhythmia (Table 28.1), and the latter is also a broader concept than the more specific supraventricular tachycardia (SVT). Supraventricular tachyarrhythmias, characterized by impulse formation more rapid than expected, can be classified according to various criteria (Table 28.1). Supraventricular tachyarrhythmias comprise all varieties of SVT plus atrial fibrillation (AF). SVT comprises atrial tachycardia (AT), atrial flutter (AFL) and atrioventricular (AV) junctional tachycardias, and excludes AF. AV junctional tachycardias include AV nodal reciprocating tachycardia (AVNRT), AV reciprocating tachycardia (AVRT) incorporating one or more accessory pathways (APs), non-paroxysmal junctional tachycardia (NPJT) and the permanent junctional reciprocating tachycardia (PJRT) [1].

Supraventricular arrhythmias also encompass atrial and AV junctional extrasystoles, sinus node disorders and a number of clinically not very relevant rhythm abnormalities such as wandering sinus pacemaker and low atrial rhythms. This chapter mainly deals with SVT but a brief account of atrial and AV junctional extrasystoles is also given.

Paroxysmal, non-paroxysmal and chronic supraventricular tachyarrhythmias

In medicine, the term 'paroxysmal' is applied to conditions presenting as a sudden episode that is usually recurrent. 'Non-paroxysmal' refers to continuously recurring supraventricular tachyarrhythmias that can be episodic (related to incidental triggers), like NPJT or inappropriate sinus tachycardia (IST), or non-episodic (occurring without precipitating factors) such as primary incessant SVT. Patients with incessant SVT may develop systolic left ventricular dysfunction or tachycardiomyopathy. 'Non-paroxysmal' also describes the continuously recurring runs of AF, sometimes coexisting with periods of

Table 28.1 Classification of supraventricular tachyarrhythmias

Paroxysmal
Paroxysmal atrial tachycardia
Paroxysmal atrial flutter
Paroxysmal atrial fibrillation
Paroxysmal AV junctional tachycardia
  AV nodal reciprocating tachycardia
  AV reciprocating tachycardia utilizing an accessory pathway

Non-paroxysmal
Episodic: non-paroxysmal junctional tachycardia (accelerated junctional rhythm)
Non-episodic
  Inappropriate sinus tachycardia
  Incessant or permanent supraventricular tachyarrhythmias
    Permanent atrial tachycardia
    Permanent atrial flutter and/or fibrillation
    Permanent junctional tachycardia

Chronic
Chronic atrial tachycardia
Chronic atrial flutter
Chronic atrial fibrillation

Note: supraventricular tachycardia comprises atrial tachycardia, including atrial flutter, and AV junctional tachycardias, but excludes atrial fibrillation.

AFL, found in patients with so-called focal AF [2]. Finally, some patients are found to be constantly in AT, AFL or AF without having noticed any significant symptom. These arrhythmias should be classified as chronic since it is not possible to establish their duration (Table 28.1).

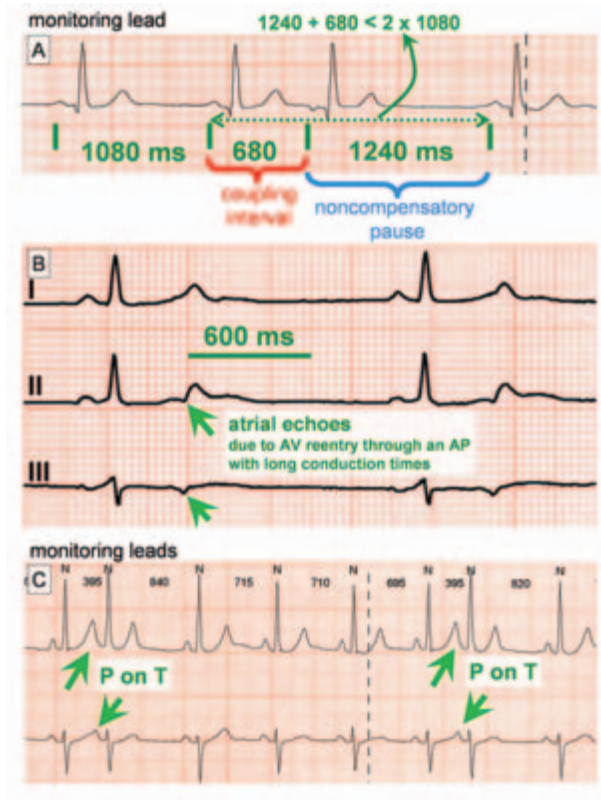

Figure 28.1 (A) Example of 'late' atrial premature beat (APB). The coupling interval measures 680 ms and the post-extrasystolic pause is less than compensatory (see text). (B) Example of atrial echo beats due to AV junctional re-entry, in this case utilizing a retrogradely conducting accessory pathway with long conduction times. Note the retrograde P wave (arrows) as a deformity of the initial forces of the T wave. These atrial echoes are anterogradely blocked in the AV node, thus resulting in an extreme bradycardia of about 38 b.p.m. Also note prolongation of the QT interval. These AV junctional echoes should not be taken as blocked atrial extrasystoles (see text). (C) Example of 'early' APBs with the P-on-T pattern (see text).

Atrial and AV junctional extrasystoles

Definition and epidemiology

Atrial extrasystoles or atrial premature beats (APBs) are depolarizations that occur earlier than the expected normal sinoatrial activation wavefront and are generated without participating structures other than the atrial myocardium. Conceptually, APBs are different from AV junctional echo beats where structures beyond the atria are essential for their development (Fig. 28.1). APBs almost always originate from areas other than the normal sinus node pacemaker and they are also referred to as 'atrial ectopics'. APBs can be isolated or occur as couplets of two consecutive atrial extrasystoles, or may elicit a run of repetitive atrial responses or AF or AFL.

Although APBs are very frequent in the general population, we lack good epidemiological studies on their prevalence and incidence. APBs are rare in healthy young individuals, unless actively engaged in sports or subject to stress and fatigue, such as medical interns and residents during their duty hours [3]. After the fifth decade of life APBs are a relatively common finding in Holter recordings. Their prevalence increases in patients with structural heart disease and in conditions prone to develop AF (hyperthyroidism, hypertension, smoking, alcohol intoxication). In patients with 'lone AF', particularly in those with repetitive recurrent attacks of focal AF, APBs are frequently registered during periods of sinus rhythm.

AV junctional premature beats (AVJPBs) are premature depolarizations arising from the AV node and His

bundle. They should also be differentiated from the AV junctional echoes (Fig. 28.1B). They are less common than atrial or ventricular extrasystoles.

Pathogenesis

APBs originate as a result of enhanced and abnormal automaticity, triggered activity or re-entry. APBs due to re-entry should not be confused with the unusual AV junctional reciprocal echo beats that develop when a sinus impulse finds an anterogradely blocked slow AV nodal pathway or a concealed slow-conducting bypass tract, as in PJRT (Fig. 28.1). The role played by the autonomic nervous system in APBs is controversial. Daytime occurrence, especially with exercise-related preponderance, could suggest an adrenergic dependence, while a higher prevalence at night or rest would indicate a vagal mechanism. AVJPBs are due to increased automaticity or triggered focal activity.

Diagnosis

In many patients APBs are asymptomatic but others may perceive the occurrence of a single atrial extrasystole. Elderly people, particularly with sick hearts, tend not to note the presence of APBs. Other factors influencing symptoms related to APBs are their coupling intervals, AV conduction time following the atrial extrasystole, the circumstances in which they develop (rest or exercise) and the psychological profile of the patient. Often, patients with SVT subjected to a successful catheter ablation procedure notice the occurrence of APBs and complain of a feeling 'as if the tachycardia was going to start'. After 2–3 months, these sensations disappear either due to reassurance in relation with their cure or because the actual density of APBs is reduced. When symptomatic, APBs frequently have a periodic presentation.

Electrocardiographically, an APB manifests itself as a premature P wave different in configuration to the sinus beats. The coupling interval of the APB is the time from onset of the atrial extrasystole to the beginning of the preceding sinus P wave. Most APBs reset the sinus node, so that the pause following the atrial extrasystole is usually less than compensatory (the interval from the sinus P wave preceding the APB to the sinus P wave following it is less than twice the sinus cycle length) (Fig. 28.1A). In APBs with short coupling intervals, the ectopic P wave is coincidental with the preceding T wave. This P-on-T phenomenon may herald the development of AF (Fig. 28.1C). The shorter the coupling interval of the APB, the shorter the atrial refractory period, and the higher the vulnerability of the atrial myocardium to fibrillate. APBs are usually conducted to the ventricles. The QRS complex following an APB may be identical, slightly different or overtly aberrant in comparison with the ventricular complexes following the sinus beats. Aberrant wide QRS complexes may result from the development of a functional bundle branch block or the existence of an AP, as in Wolff–Parkinson–White (WPW) syndrome. Spontaneous APBs may reveal the presence of a non-evident form of pre-excitation. APBs may be blocked in the AV conduction system. Blocked APBs are the commonest reason for 'pauses without apparent cause' in the ECG and it is important to look for deformities in the ST–T segment to identify the atrial extrasystoles in these cases.

Symptoms due to AVJPBs are similar to those of ventricular premature beats (see Chapter 31). The coupling interval is measured from the onset of the premature QRS complex to the onset of the preceding ventricular depolarization. The QRS complex is usually narrow and may be identical to that of normal sinus beats or slightly different in configuration but still < 120 ms. There can be retrograde P' waves visible after the QRS complex, but they can be hidden within the ventricular depolarization or deform the late terminal forces of the QRS. In some 30–50% of cases there is no ventriculo-atrial (VA) conduction. If the AVJPB does not reset the sinus node, the pause will be compensatory.

Treatment

APBs are seldom treated, particularly if the patient is asymptomatic. Some general recommendations can be made (avoid tobacco, alcohol, caffeine, and lose weight). Some bouts of APBs can be terminated with physical exercise. When this fails and the patient is symptomatic, beta-blocking agents may be tried and, if necessary, class I antiarrhythmic drugs. Fortunately, most patients suffering periods of symptomatic APBs are relatively young and have structurally normal hearts so that they can be safely treated with class I drugs. The same can be said in relation to AVJPBs.

Supraventricular tachycardia

Definition

SVT is a tachyarrhythmia in which structures above the division of the bundle of His are essential for its maintenance and comprises AT, AFL, AVNRT, AVRT incorporating one or more APs, NPJT and the primary incessant SVTs [1,4].

Most patients with paroxysmal SVT notice palpitations that have an abrupt onset and frequently, but not always, a sudden termination. While paroxysmal SVT always terminates suddenly, the patient may not perceive the end of the episode if the ensuing sinus rate is elevated secondarily to the anxiety accompanying the crisis. The ventricular rate during SVT is usually > 120 b.p.m. and frequently 140–250 b.p.m. The atrial rate may be higher than the ventricular rate in AT, AFL and exceptionally AVNRT. In AVRT utilizing an accessory pathway (AP), the atrial and ventricular rates are always the same.

The width of the QRS complex during SVT is usually 80–100 ms. Exceptionally, ventricular tachycardias may also have a QRS complex < 120 ms [5]. Conversely, SVT may present with a QRS complex ≥ 120 ms in three situations: (1) if the patient has a permanent left or right bundle branch block (LBBB, RBBB); (2) if during tachycardia a functional bundle branch block (aberrancy) develops; or (3) if AV conduction during tachycardia is over an AV accessory pathway. Pacemaker-related tachycardias are excluded here.

Non-paroxysmal SVTs are continuously recurring tachycardias whose rates may be < 100 b.p.m. but are usually 120–190 b.p.m. They can be episodic and non-episodic. The NPJT is an episodic non-paroxysmal SVT that develops in relation to certain situations such as ischaemia, digitalis intoxication, cardiac surgery, hyperthyroidism or the application of radiofrequency current near the AV node. Primary incessant SVT is a non-episodic non-paroxysmal SVT that electrocardiographically is characterized by runs of SVT that alternate during at least 50% of the time with the normal sinus rhythm or totally replace it [4].

The prevalence of paroxysmal SVT has been estimated to be 2.25 per 1000 persons and the incidence 35 per 100 000 person-years [6]. Non-paroxysmal forms of SVT are less frequent. In patients undergoing an electrophysiological study or a catheter ablation intervention, AVNRT, AVRT utilizing an AP, and AFL are the most frequently encountered arrhythmias (AF excluded) and account for about 90% of the cases. The remaining 10% represents AT and the non-paroxysmal, usually incessant, forms of SVT.

Quality of life and life expectancy in patients with SVT

Most patients with SVT have a normal life expectancy, but their quality of life is frequently poor [7]. The symptoms during SVT (palpitations, syncope or dizziness, polyuria, chest pain, dyspnoea and eventually heart failure, anxiety and fear of developing new crises), the frequency and duration of the attacks, the need to seek hospital treatment for the episodes, the impossibility of participating in certain sports or professional activities, and the feeling of prolonged tiredness after an episode all determine the degree of impairment in the quality of life in these patients, often leading to social isolation. Today, problems derived from the use of antiarrhythmic drugs are minimized if the SVT is cured by radiofrequency catheter ablation (RFCA).

Exceptionally, SVT can compromise life expectancy either directly or indirectly as a consequence of antiarrhythmic drug therapy or complications of catheter ablation procedures. Paroxysmal SVT can be directly fatal in four circumstances: (1) when syncopal and the patient suffers a life-threatening trauma; (2) when SVT degenerates into ventricular fibrillation; (3) when severe embolism occurs (as in AF or AFL); and (4) when SVT precipitates acute pulmonary oedema, as in patients with severe systolic or diastolic left ventricular dysfunction. Incessant SVT can also shorten life expectancy if the patient develops a tachycardiomyopathy. Degeneration of AF into ventricular fibrillation in patients with WPW syndrome is not the only situation in which sudden death can occur during SVT. An enhanced AV nodal conduction facilitates the degeneration of SVT into ventricular fibrillation. SVT can be responsible for 5% of ventricular fibrillations in patients with aborted sudden death and in only 46% of them is an AP involved [8]. Syncope during SVT may be of a vasovagal origin and not only related to very fast ventricular rates during tachycardia [9]. A tachycardiomyopathy state may develop in patients with atrial or junctional incessant tachycardia [10]. This form of left ventricular dysfunction is usually reversible after abolishing the arrhythmia with catheter ablation [10–12].

The 12-lead ECG during sinus rhythm and during SVT

Patients with a history of palpitations should be advised to have a 12-lead ECG obtained during the episode. This tracing, particularly when compared with an ECG during sinus rhythm, can serve to determine the origin and pathway of tachycardia. Not infrequently the ECG will show sinus tachycardia at rates usually < 140 b.p.m. Although most of these patients, particularly females, have anxiety attacks, eventually some will be demonstrated to suffer from paroxysmal SVT if they repeatedly attend an emergency room for electrocardiographic documentation of their episodes, particularly when the latter persist after anxiolytic drug treatment. The ECG during sinus rhythm may demonstrate pre-excitation or signs suspicious of a non-evident form of WPW syndrome, as discussed later in this chapter.

Electrophysiological studies

Catheter mapping and stimulation studies are indicated to define the origin and pathway of SVT when the patient is a candidate for RFCA. In WPW syndrome electrophysiological studies are still used for risk stratification. An electrophysiological study may also differentiate sinus tachycardia from incessant AT in patients with a dilated cardiomyopathy. When there is a history of disabling undocumented attacks of sudden palpitations, the electrophysiological study may establish the correct diagnosis and the appropriate treatment. Paroxysmal tachycardias in patients without structural heart disease are usually supraventricular, although in a few cases an idiopathic right or left ventricular tachycardia might be initiated. Electrophysiological studies differentiate AFL that depends on the cavo-tricuspid isthmus (CTI) from other types of flutters or macro re-entrant AT requiring more complex ablation procedures.

Atrial tachycardia

Definition

AT has been traditionally defined as a rapid atrial impulse formation at rates of 110–240 b.p.m., exclusively maintained by the atrial myocardium, and in which the atrial waves are separated by an isoelectric baseline. The above definition was meant to exclude AFL. As discussed in this chapter, AFL is a form of macro re-entrant AT but is described in a separate section for purely didactic reasons. AT, not including AFL, is the most infrequent type of SVT. The AV relation during AT can be 1 : 1, 2 : 1, higher or variable, depending on the atrial rate, AV nodal function or the effect of drugs on the AV node. Traditionally, paroxysmal AT with block was considered a typical arrhythmia of digitalis intoxication. Today, digitalis is used less frequently and at lower doses than in the past, so that AT with block is rarely related to digitalis intoxication.

Pathogenesis

Paroxysmal, non-paroxysmal and chronic AT can be focal or macro re-entrant. In focal AT there is a relatively circumscribed exit of the atrial activation wavefront from which the rest of the atrial myocardium is depolarized. A few patients present multiple atrial foci [13]. Focal ATs that are induced and interrupted with programmed electrical stimulation are due to triggered focal activity or re-entry and are termed 'non-automatic focal atrial tachycardia' [14]. The remaining forms of focal ATs are most likely due to enhanced or abnormal automaticity. Sinus node reciprocating tachycardia (SNRT) is a non-automatic paroxysmal focal AT whose atrial breakthrough is at the terminal crest, close to the right atrial exit of the normal sinus node impulse (Fig. 28.2A). The precise definition of the re-entry pathway remains unidentified. IST is a rare form of incessant AT whose mechanism may be related to a primary abnormality of the sinus node with an increased automaticity, or to a disturbance of the autonomic balance of the heart [15]. Most forms of focal AT originate from the right atrium, at various sites along the terminal crest or in the vicinity of the tricuspid annulus, including the perinodal region, or at the venous side of different veno-atrial junctions (superior vena cava–right atrium, coronary sinus–right atrium, pulmonary veins–left atrium) (Fig. 28.2A) [13,16,17]. Recently, a new form of incessant focal AT sensitive to lidocaine (lignocaine) has been described [18].

Macro re-entrant AT is a circus movement developing in relation with an anatomically or functionally determined obstacle (Fig. 28.2). AFL is actually the most common form of macro re-entrant AT (Fig. 28.2B). The distinction between AFL and macro re-entrant AT is artificial [13]. Isthmus-dependent AFL uses a circuit present in all hearts and the other forms of macro re-entrant AT develop around or through an atrial scar due to fibrosis of diverse aetiologies or to a surgical incision or patch.

Diagnosis

Clinical characteristics

AT can be paroxysmal, non-paroxysmal (usually incessant) or chronic (Table 28.2). Paroxysmal non-automatic focal AT usually arises in patients without structural heart disease and is most prevalent in females (> 70%) aged over 40 years. SNRT generally occurs in females (80%) who in nearly 20% of cases also present an AVNRT. Focal automatic AT may be paroxysmal and sustained, or may be seen as frequent repetitive runs of various durations. It is usually observed in patients without structural heart disease. The main symptoms in paroxysmal AT are palpitations and anxiety. Occasionally, patients may experience dyspnoea, dizziness or syncope.

Incessant focal AT is a rare arrhythmia usually diagnosed in children and occasionally in young adults that may result in a tachycardiomyopathy [4,18–20]. Incessant AT should always be excluded in patients with a congestive cardiomyopathy and an apparent sinus tachycardia with abnormal P-wave axis or fluctuations in heart rate. The atrial rate during incessant AT ranges from 110 to

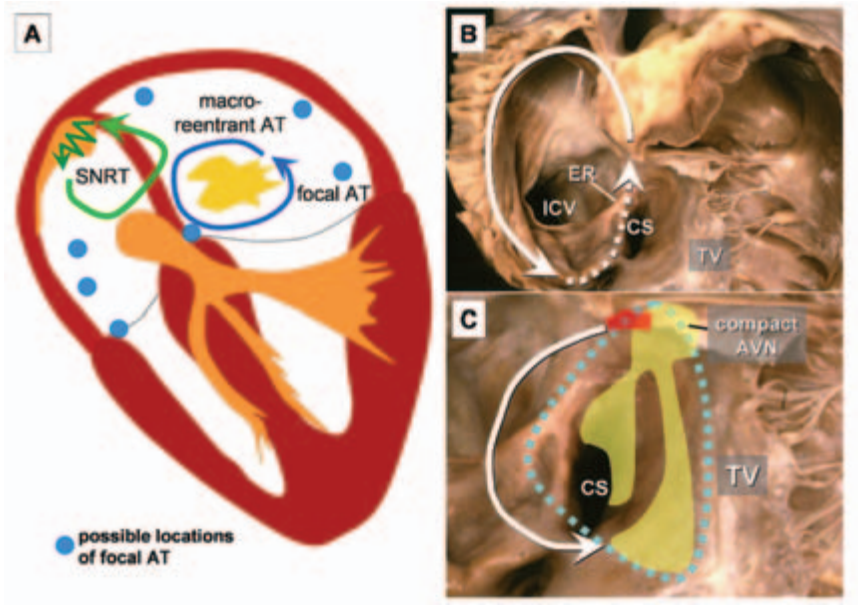

Figure 28.2 (A) Schematic representation of the heart and of three types of atrial tachycardia (AT). Focal AT (blue circles) may arise at various right and left atrial sites (see text) and the spread of atrial activation is from a circumscribed atrial location. Sinus node re-entry tachycardia (SNRT) is a type of focal AT whose atrial breakthrough is high in the terminal crest, near the endocardial site of exit of the normal sinus node impulse. Macro re-entrant AT is a circus movement around an anatomical obstacle, either a post-surgical scar or atrial fibrosis of undetermined aetiology. (B) Necropsy human heart depicting open right atrium. The cavo-tricuspid isthmus is the inferior corridor of the right atrium between the inferior caval vein (ICV) and the Eustachian valve and ridge (ER) posteriorly, and the tricuspid valve (TV) anteriorly. Isthmus-dependent atrial flutter uses this corridor as a compulsory link of its re-entry pathway (interrupted white arrow). Necropsy specimen kindly provided by Professor Sánchez-Quintana, University of Badajoz, Spain. (C) Same specimen as in (B) showing the triangle of Koch (dotted light blue line). This imaginary triangle is located in the inferior paraseptal right atrial region and contains the AV node, its postero-inferior extensions and the transitional fibres that approach the compact nodal area. Its lateral margins are the Eustachian ridge containing the tendon of Todaro, and the attachment of the septal leaflet of the tricuspid valve (TV). The base of the triangle is the orifice of the coronary sinus (CS) and the region from the coronary sinus to the tricuspid valve. The exact mechanism of AV nodal re-entry tachycardia (AVNRT) is not well known. The common type of AVNRT uses the slow AV nodal pathway as anterograde limb of the circuit and the fast pathway retrogradely (see text). The slow pathway is most likely represented by the two inferior extensions of the compact AV node, one coming from the coronary sinus and the other along the tricuspid annulus. The fast AV nodal pathway may be an atrionodal or His–nodal tract but at least in some patients with AVNRT it may have a fully intranodal course.

near 300 b.p.m. and it can vary within the same subject depending on the autonomic tone. Some patients show no evidence of sinus rhythm during Holter monitoring. Others present sinus rhythm only during sleep or the induction of anaesthesia.

Macro re-entrant AT may supervene after corrective surgery for congenital heart diseases (atrial septal defect closure, Mustard or Senning procedures for D-transposition of the great arteries, Fontan operation for tricuspid atresia), causing morbidity and, eventually, mortality. It may be paroxysmal but is frequently chronic. Patients with rheumatic mitral valve disease, even without surgery, may develop a macro re-entrant AT related to electrically silent areas of left atrial fibrosis. Some of the latter patients may present an AT after many years in AF, as an expression of an extremely diseased left atrium. Scar-related right-sided AT may rarely develop in patients without previous heart surgery [13].

Multifocal AT [21] is rare and usually arises in elderly adults with obstructive lung disease, sometimes as a manifestation of theophylline toxicity [22], but is found less frequently in infants, children and young patients. Multifocal incessant AT in children tends to resolve spontaneously but if persistent the patient may develop a tachycardiomyopathy [4]. Infants with multifocal AT may have respiratory diseases and, less commonly, structural heart disease [23].

IST usually appears in females under 50 years of age and more rarely in males and elderly people. Patients with IST complain of palpitations and/or a reduced exercise tolerance. Their resting sinus rate is persistently elevated, with an exaggerated response to minimal physical activities. IST may also temporarily emerge after RFCA interventions close to the compact AV node such as ablation of the fast AV nodal pathway or a peri-Hisian AP [24].

Table 28.2 Characteristics of supraventricular tachycardia

Type of SVT	Varieties	Presentation	Gender dominance	Adenosine	RFCA success	A : V ratio	PR/RP in AV 1 : 1	QRS complex
AT	Focal	Paroxysmal Incessant	Females	Stops	> 90%	1 : 1 or higher	PR < RP PR = RP PR > RP*	Narrow
AT	Macro re-entrant	Paroxysmal Incessant Chronic	Even	No effect	60–80%	2 : 1 or higher	NA	Narrow Wide if organic BBB RBBB if ASD
AFL	Isthmian CCW and CW	Paroxysmal Chronic	Males	No effect	> 98%	2 : 1 or higher	NA	Narrow Wide if BBB
AFL	Non-isthmian	Paroxysmal Chronic	Even	No effect	60–80%	2 : 1 or higher	NA	Narrow Wide if BBB
AVNRT	Slow–fast	Paroxysmal	Females	Stops	~ 100%	1 : 1 2 : 1†	PR >> RP‡	Narrow Wide if BBB
AVNRT	Fast–slow	Paroxysmal Incessant	Females	Stops	~ 100%	1 : 1	PR < RP	Narrow Wide if BBB
AVNRT	Slow–slow	Paroxysmal Incessant	Females	Stops	~ 100%	1 : 1	PR > RP	Narrow Wide if BBB
AVRT	Orthodromic Conventional	Paroxysmal	Males	Stops	~ 100%	1 : 1	PR > RP	Narrow Wide if BBB
AVRT	Antidromic Conventional	Paroxysmal	Males	Stops	~ 100%	1 : 1	PR = RP PR < RP	Wide Maximally pre-excited
PJRT	Orthodromic	Incessant	Even	Stops	~ 100%	1 : 1	PR < RP PR = RP	Narrow
AFRT	Antidromic	Paroxysmal	Males	Stops	~ 100%	1 : 1	PR >>> RP§	Wide (LBBB) Maximally pre-excited

AFL, atrial flutter; AFRT, atriofascicular reciprocating tachycardia; ASD, atrial septal defect; AT, atrial tachycardia; AVNRT, AV nodal reciprocating tachycardia; AVRT, AV reciprocating tachycardia utilizing an accessory pathway; BBB, bundle branch block (either organic or due to aberrant conduction); CCW, counter-clockwise; CW, clockwise; LBBB, left bundle branch block (configuration); NA, not applicable; PJRT, permanent junctional reciprocating tachycardia; RBBB, right bundle branch block; RFCA, radiofrequency catheter ablation; SVT, supraventricular tachycardia.
*PR > RP if concomitant drugs acting on the AV node or if associated AV nodal disease.
†2 : 1 ratio in AVNRT exceptional in the clinical scenario.
‡P waves during slow–fast AVNRT are either hidden within the QRS complex or visible as a continuation of the QRS mimicking terminal s waves in inferior leads or r′ waves in V1.
§P waves are usually hidden within the QRS complex during tachycardia.

Electrocardiographic characteristics

The 12-lead ECG, combined with vagal or pharmacological manoeuvres during tachycardia, usually enables the atrial origin of the arrhythmia to be established. Amplification of the electrocardiographic signals may facilitate P-wave identification. When the AV ratio is 1 : 1, the RP interval is usually longer than the PR (long-RP tachycardia) (Fig. 28.3) [25,26]. This RP/PR relation can change spontaneously or due to drug intervention (Table 28.2).

In patients with tachycardiomyopathy secondary to an incessant AT, the enhanced sympathetic tone shortens AV nodal conduction time, further contributing to the long-RP pattern. However, PR > RP during AT may be observed after the administration of drugs prolonging AV nodal conduction times or because of some degree of AV nodal disease. When the AV ratio is 1 : 1, positive P waves in leads I, II and III exclude a junctional origin. If P waves are negative in lead I and positive in lead III, an AVRT incorporating a left free-wall AP cannot be ruled

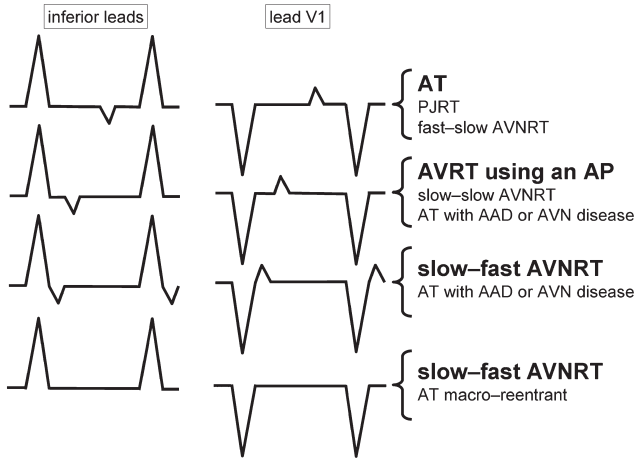

Figure 28.3 Schematic representation of the relations between the P wave and the ventricular complex during narrow-QRS supraventricular tachycardia (SVT) with 1 : 1 AV ratio. The left column represents how the ECG would look in the inferior leads (II, III and AVF) and the right column how it would look in lead V1. The type of SVT typical of each of the electrocardiographic patterns is indicated on the right in bold type, while below this are other SVTs capable of resulting in each of the patterns (for further details see text). Macro re-entrant AT is presented as a possible alternative in the example in which P waves are not apparent because the atrial depolarizations, although frequently between two consecutive QRS complexes, may be barely perceptible due to a very low voltage (see text).

out [25]. AV block during SVT strongly suggests an atrial origin (Fig. 28.4). Vagal stimulation in some patients with AT may prolong the PP interval, and atropine can accelerate the tachycardia [25,26]. When there is a 2 : 1 AV ratio, the identification of two consecutive P waves within the R–R cycle suggests AT. In this situation the PP intervals sandwiching a QRS complex may be 20–40 ms shorter than the PP cycles not comprising a ventricular activation (Fig. 28.4C). This is known as ventriculophasic P–P alternation and although it is often found in digitalis intoxication it may also be seen in AT with 2 : 1 AV block in the absence of digitalis use.

In automatic focal AT the initial P wave is identical to subsequent tachycardia P waves and after its start we can observe a progressive acceleration over a few beats ('warming-up' phenomenon). Preceding the termination of automatic and non-automatic AT there may be a progressive rate decrease ('cooling down'). Identification of the site of origin (atrial breakthrough) of the P wave in AT should be done by examining P-wave morphology and width on the 12-lead ECG. A negative P wave in leads I or aVL indicates a left atrial origin (Fig. 28.4) [27]. The P-wave configuration during SNRT and the normal sinus rhythm is similar. Lidocaine-sensitive AT is characterized by incessant runs of AT of variable duration and rates, firing between very brief phases of sinus beats. The P-wave morphology is sometimes similar to the sinus P waves, but other configurations are possible [18]. In multifocal AT the P waves have three or more different morphologies, with irregular PP intervals at rates of 150–220 b.p.m. There is an isoelectric line between consecutive P waves. The PR intervals and consequently the RR cycle lengths are also variable.

The ECG of macro re-entrant AT has two major manifestations: (1) P waves very similar to those of isthmus-dependent AFL (with caudo-cranial or cranio-caudal atrial activations) (Fig. 28.5) and (2) P waves with very low voltage that are difficult to identify at least in the limb leads (Fig. 28.3) [1,13]. The cranio-caudal P waves of macro re-entrant left AT have bimodal shapes more frequently than the uncommon isthmian AFL. An isoelectric line may be present between consecutive P waves, but a true flutter-like continuous pattern can also be observed.

Electrophysiological studies

Electrophysiological study enables AT to be differentiated from other varieties of SVT [4,13–17,26,28,29]. In addition, we can distinguish automatic from non-automatic forms of AT, and focal from macro re-entrant AT. Finally, macro re-entrant AT unrelated to the CTI can be differentiated from isthmus-dependent AFL. In patients with a dilated cardiomyopathy it may be worth excluding the existence of an incessant AT mimicking sinus tachycardia. The induction of focal AT frequently requires the infusion of isoprenaline or atropine.

Treatment

The management of patients with paroxysmal AT comprises termination of the episode and prevention of its recurrence. In sustained paroxysmal AT, carotid sinus massage should be tried first. The induction of AV block by vagal manoeuvres while the tachycardia persists at the atrial level suggests an atrial origin of the arrhythmia. When vagal stimulation does not terminate AT, adenosine should be used unless contraindicated. Adenosine usually terminates focal AT but not macro re-entrant AT [30]. When adenosine fails, intravenous propafenone or flecainide should be administered, or intravenous amiodarone if the patient has systolic left ventricular dysfunction. DC-shock cardioversion should be considered if AT persists after the use of antiarrhythmic drugs or if there is a history of previous drug failures [1].

If AT is in the form of repetitive runs, vagal manoeuvres and short-acting intravenous drugs such as adenosine,

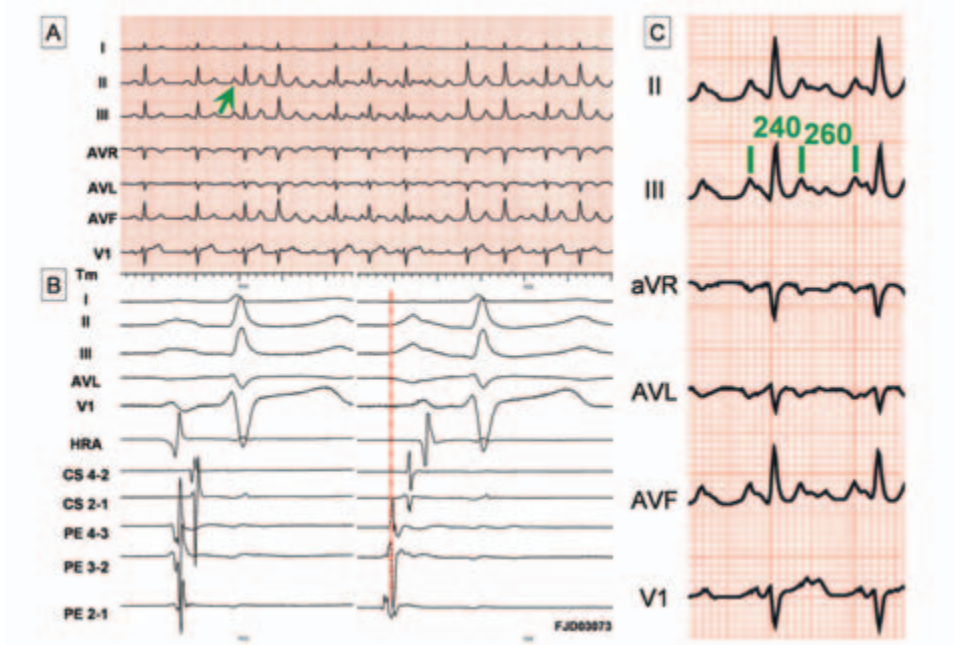

Figure 28.4 (A) ECG of an incessantly recurring focal left atrial tachycardia (AT) originating in the vicinity of the left superior pulmonary vein. AT seemed to be automatic and its runs frequently started by a late ectopic atrial depolarization (green arrow) that was followed by rapid firing at a mean atrial rate of 240 b.p.m. (B) Catheter-electrode mapping during sinus rhythm (left) and during one of the ectopic beats initiating the runs of AT (right). From top to bottom are displayed time marks (Tm), leads I, II, III, aVL and V1, bipolar intracardiac recordings from the high right atrium (HRA) and coronary sinus (CS), and quadripolar probing electrode (PE). Note that at the tip of the probing electrode (PE 2-1) the atrial electrogram is inscribed before the onset of the ectopic P wave in the surface ECG leads (dotted red line). Application of radiofrequency current at this site resulted in cure of the AT (not shown). (C) Detail of the same AT during 2 : 1 AV block. The length of the atrial cycles containing a QRS complex were slightly shorter than the PP intervals not sandwiching a ventricular depolarization (240 vs. 260 ms). This ventriculophasic atrial arrhythmia is frequently found during various types of AT with 2 : 1 AV block (see text). Also note that the ectopic P waves, which have a notched appearance in the inferior leads, are positive in II, III and aVF, negative in aVL and positive in V1. These findings suggest a high left atrial origin.

verapamil or diltiazem are of no practical use. The same applies for DC-shock cardioversion. In these cases the treatment of choice is intravenous administration of flecainide, propafenone or amiodarone.

Radiofrequency catheter ablation

Although various antiarrhythmic drugs have been used to prevent recurrences of AT or to control incessant AT [31–33], the treatment of choice for symptomatic recurrent, chronic and incessant AT is RFCA [13,34]. The success rate of RFCA in AT depends on the experience of the ablation team, the technology available for the ablation, and the type of AT (see Table 28.2). RFCA of IST is associated with poor long-term success rates, even with three-dimensional electro-anatomical mapping [35]. Improved results have been obtained using intracardiac ultrasound to attain transmural lesions [36]. In the long term many patients with IST subjected to RFCA using an endocardial approach develop recurrences because the sinus node is protected against RFCA by the dense matrix of connective tissue in which sinoatrial cells are packed, by the cooling effect of the nodal artery, and by the thick terminal crest interposed between the endocardium and the sinoatrial tissue [37]. Epicardial RFCA using a subxiphoid approach to access the pericardial space has been attempted without encouraging results in IST [38].

The success rate of RFCA in focal AT has been variable in the literature (Fig. 28.4) [1,13,14,16–18,20,34,39–41]. Experienced centres report success rates in excess of 90%, with < 8% of recurrences [42]. RFCA is also the treatment of choice for macro re-entrant AT which is rarely prevented by drugs such as flecainide, propafenone and amiodarone. The latter drugs, by slowing conduction velocity, may even facilitate recurrences of macro re-entrant AT whose atrial rate is then slower than in the basal situation. RFCA in macro re-entrant AT requires identification of a critical isthmus of conduction between anatomical barriers, or an isolated diastolic potential shown to belong to the circuit by entrainment pacing, or a narrow gap in the scar. Electro-anatomical mapping systems facilitate the ablation of these complex ATs (Fig. 28.5) [13,42–44].

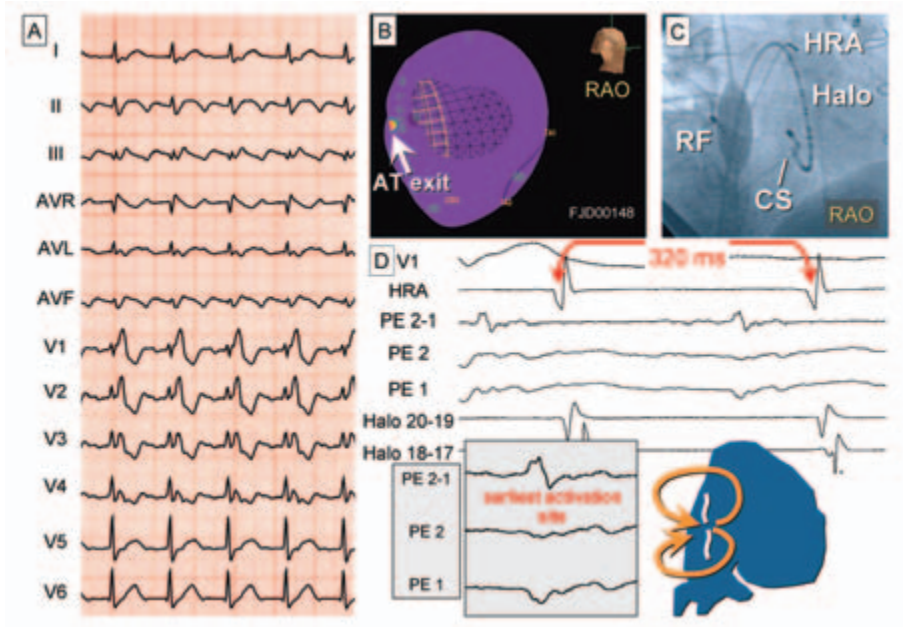

Figure 28.5 (A) ECG of a chronic macro re-entrant atrial tachycardia (AT) in a patient who had undergone repair of an atrial septal defect. The patient who was receiving 300 mg of flecainide daily and had been diagnosed with common slow atrial flutter (AFL), had been subjected to two previous attempts to ablate the cavo-tricuspid isthmus at another centre. The surface ECG is similar to a class IC isthmian AFL. The ventricular rate is approximately 100 b.p.m. due to 2 : 1 AV conduction of a regular atrial tachycardia beating at about 200 impulses per minute. Atrial depolarizations are caudo-cranial, as in counter-clockwise isthmian AFL. During the electrophysiological study the arrhythmia could not be entrained from the cavo-tricuspid isthmus, thus indicating that the tachycardia was not isthmus dependent. (B, C) Using a computerized non-contact mapping system (Ensite, Endocardial Solution) that provides simultaneous recording of the activation of the whole right atrium, we determined that this AT had a rather localized onset of activation from which the rest of the right atrium was activated. This spot was posterolaterally located, in relation with the atriotomy at the time of surgery. In (C) the probing electrode (RF) is shown at the site of earliest atrial activation at one of the sides of a narrow gap in the scar. Other catheters depicted in this fluorographic right anterior oblique view of the right atrium are a quadripolar coronary sinus catheter (CS), a 20-pole Halo catheter and a high right atrial catheter (HRA). (D) Lead V1 is simultaneously displayed with intracardiac recordings from the HRA, PE and Halo catheter. The probing electrode (PE) was positioned at the site of earliest activation of the AT, at one side of the atrial incision where there was a narrow isthmus electrically communicating both sides of the surgical scar [42].

Until recently, patients with incessant AT, even if asymptomatic and without signs of a tachycardiomyopathy, were treated with antiarrhythmic drugs, usually amiodarone, flecainide or propafenone, with a variable success rate [1,2,31–33]. Patients with an asymptomatic incessant AT with normal ventricular function should be followed up carefully to identify early signs of tachycardiomyopathy. When there are signs of systolic left ventricular dysfunction, an ablation procedure should be performed. After abolishing the incessant AT, left ventricular function usually recovers within a few months [2,12,13,20,27].

Treatment of multifocal AT

Infants with multifocal AT are usually treated with digoxin and many of these tachycardias tend to resolve spontaneously [23]. In elderly patients with chronic obstructive lung disease, amiodarone with or without verapamil or diltiazem may be employed for rate control to improve symptoms. Modification of the AV node with RFCA techniques can be used in symptomatic patients not amenable to antiarrhythmic drug treatment [44].

Atrial flutter

Definition

Traditionally, AFL has been defined by the presence of a fast regular atrial rate of 240–350 b.p.m. and the absence

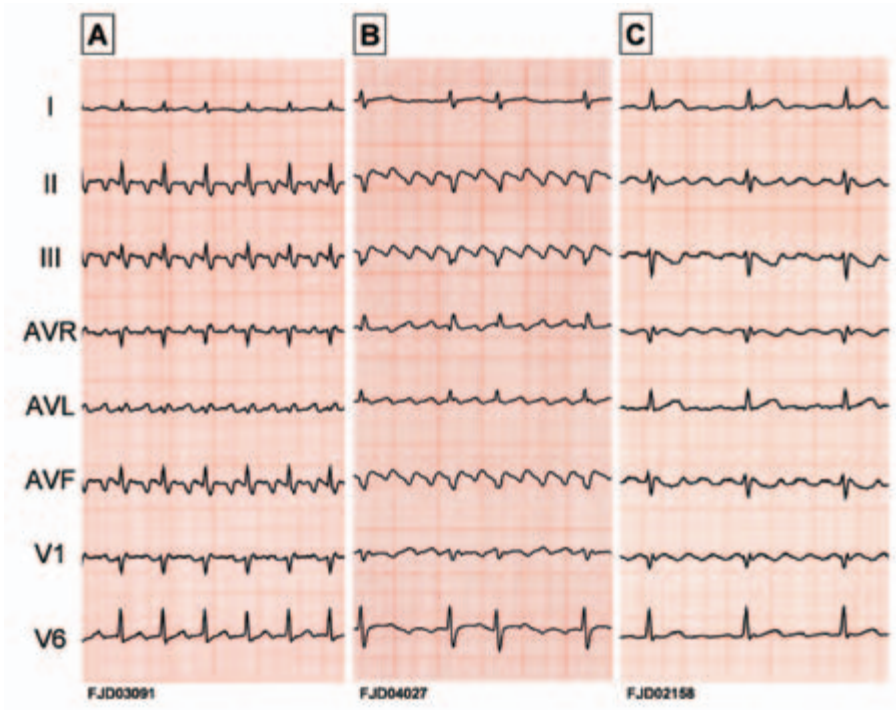

Figure 28.6 Various ECG manifestations of isthmus-dependent atrial flutter (IAFL). (A) Common IAFL with F waves that have a caudo-cranial sequence of atrial activation with an initial negative component, followed by a positive terminal element. In V1 the F waves are positive. The AV ratio is 2 : 1 and because the atrial rate is nearly 300 b.p.m., the ventricular rate is around 150 b.p.m. (B) The typical flutter waves with saw-tooth appearance are very clearly seen because there is a higher degree of AV block due to drugs acting on the AV node. Note the negative initial component of the F waves in the inferior leads followed by a terminal positive deflection. F waves are positive in V1 and negative in V6. (C) Reversed clockwise IAFL. F waves have a cranio-caudal activation pattern and are positive in inferior leads. In V1 they have an initial negative component followed by a terminal positive deflection. The atrial rate is 265 b.p.m. and because of a 4 : 1 AV ratio, the ventricular rate is 66 b.p.m.

of an isoelectric baseline separating atrial deflections (Fig. 28.6). Neither the first nor the second condition is actually required for flutter to exist. Thus, a common isthmus-dependent AFL can have atrial rates of 190–220 b.p.m. in patients with diseased atria, in those receiving drugs that reduce atrial conduction velocity (propafenone, flecainide and amiodarone) or in those developing the arrhythmia after a failed RFCA attempt. An isoelectric baseline between atrial waves can also be present in some relatively slow flutters.

Classically, AFL was classified as common and uncommon [25]. The atrial activation pattern is caudo-cranial in common AFL and cranio-caudal in uncommon AFL. Electrocardiographically, this classification is still valid but does not distinguish right from left AFL, and isthmus-dependent from isthmus-independent AFL. AFL is an 'organic' arrhythmia usually associated with cardiovascular or pulmonary diseases.

Pathogenesis

Right atrial isthmus-dependent atrial flutter

The most common form of AFL, which accounts for about 85% of the total, is the counter-clockwise isthmus-dependent AFL. This is a macro re-entrant AT whose pathway is determined by anatomical and functional right atrial barriers. A key anatomical link of the common AFL circuit is the CTI limited anteriorly by the tricuspid orifice and posteriorly by the inferior vena cava and the Eustachian valve and ridge (Fig. 28.2B). In counter-clockwise CTI AFL, the activation wavefront proceeds in a caudo-cranial direction along the septal aspect of the right atrium, and returns cranio-caudally down the terminal crest and pectinate muscles, towards the CTI. The same circuit can be used in a reverse manner, leading to the inverse or clockwise CTI AFL. In CTI AFL, the terminal crest acts as a barrier to conduction [45] in which block is functionally rather than anatomically determined [46]. Rarely, the CTI is utilized in other varieties of AFL such as the lower-loop CTI AFL in which the circus movement is established around the inferior vena cava [47]. A lower-loop flutter mechanism has also been demonstrated in some apparently clockwise CTI AFL [48].

The re-entry circuit of CTI AFL exists in all hearts but the arrhythmia develops only when the right atrium can accommodate a circulating wavefront not colliding with the tail of refractoriness. This requires some degree of right atrial dilation and/or reduction of conduction velocity in certain segments of the AFL pathway. Using right atrial angiography, the dimensions of the right atrium and the CTI in patients with common AFL are greater than in controls without flutter [49]. Patients with AFL and structural heart disease had an even larger CTI than those with flutter alone.

Atypical atrial flutters: upper-loop CTI-independent right atrial flutter, and left atrial flutter

An atypical upper-loop right AFL which turns around the superior vena cava through the terminal crest in a clockwise direction has been described [13,50,51]. There are left AFLs associated with large 'silent' areas over the posterior left atrium. They are the same type of arrhythmias labelled in this chapter as macro re-entrant AT [13,44,50–52].

Diagnosis

Clinical characteristics

Although common AFL is usually paroxysmal, some patients are found to be in chronic AFL without having noticed any symptoms. Common CTI AFL is 2.5 times more prevalent in males than in females, is very seldom observed in patients aged under 50 years and its incidence increases with ageing, heart failure and chronic obstructive lung disease (see Table 28.2) [53]. AFL can develop in relation to surgical intervention, respiratory infection and, more rarely, acute myocardial infarction. The latter patients may or may not develop recurrences in the future. In children, AFL is episodic and does not tend to recur [54], unless associated with congenital heart disease. Non-episodic AFL tends to recur or to become chronic. In both instances AFL is frequently associated with obstructive lung disease, hypertension, obesity, atrial septal defect (even after repair) or systolic and/or diastolic left ventricular dysfunction of various aetiologies. In patients with mitral valve disease, AFL, particularly when cranio-caudal, must be regarded as left atrial in origin until proved otherwise. Systolic left ventricular dysfunction in patients with chronic AFL may reflect a tachycardiomyopathy state in which the ventricular function improves or is restored after successful ablation [55]. Lone AFL without cardiovascular or pulmonary disease is rare. Not infrequently AFL coexists with AF either spontaneously or after oral treatment with class IC drugs or amiodarone (class IC AFL). Long-term vigorous exercise may predispose to AF [56] but also to the development of CTI AFL.

Patients with paroxysmal AFL usually complain of palpitations and/or nervousness sometimes associated with polyuria [57], dyspnoea, fatigue or chest pain, either at rest or during daily physical activities. Paroxysmal AFL may result in acute heart failure in patients with systolic and/or diastolic left ventricular dysfunction. Exceptionally, if the AV ratio is 1 : 1, AFL may be syncopal and even fatal. Such an event may occur under sympathetic discharge (as during intense physical exercise) usually in combination with enhanced AV nodal conduction or WPW syndrome. Class IC drugs, by reducing atrial conduction velocity, facilitate the development of a form of AFL with relatively slow atrial rates (190–240 b.p.m.). Because these drugs do not significantly prolong the AV nodal refractory period, the patient may develop a life-threatening 1 : 1 AV conduction during AFL. Although a 'slow AFL' can also develop on amiodarone, the AV ratio is usually 2 : 1 or more because of the effects of the drug on AV nodal conduction.

The risk for thromboembolic events in AFL was thought to be low because of a relatively preserved atrial mechanical function. However, transoesophageal echocardiographic examinations have shown atrial thrombi and spontaneous echo contrast in patients with AFL [58–60]. If a previous history of AF or mitral valve disease is excluded, 1.6% of patients with AFL have a left atrial appendage thrombus and 13% significant spontaneous left atrial echo contrast [60]. Precautions similar to those currently advocated for cardioversion in AF are advised in patients with AFL [1,60]. Because more than 50% of patients with lone AFL may also develop AF, the risk of embolic complications in lone AFL must be considered similar to that of AF [61].

Electrocardiographic characteristics

In counter-clockwise CTI AFL the atrial waves (F waves) in the inferior leads have a predominant negative deflection (Fig. 28.6A,B). The initial negative inferior wave, followed by a positive terminal portion without a baseline between consecutive F waves, gives rise to the characteristic 'saw-tooth' morphology (Fig. 28.6B). F waves are usually positive in V1 and negative in V6 (Fig. 28.6B). In counter-clockwise CTI AFL, the atrial rate typically is close to 300 b.p.m., being slower in patients with dilated or diseased right atria or receiving class I drugs or amiodarone, and faster in young people or children. The slower the flutter rate, the higher the probability of having a brief horizontal baseline between the atrial deflections. The AV ratio during AFL is usually 2 : 1. Exceptionally, a 1 : 1 ratio may be observed, most frequently as a complication of class I antiarrhythmic drugs. AV ratios greater than 2 : 1 may be induced by vagal manoeuvres, by drugs acting on the AV node, or because of concomitant AV nodal disease (Fig. 28.6B,C).

In the uncommon clockwise CTI AFL, the initial forces of the atrial F waves are positive in the inferior leads and are usually followed by a terminal negative component (Fig. 28.6C). In V1 the F waves may be negative or positive, and they can be positive in V6. The atrial rate is frequently around 250 b.p.m.

Milliez *et al.* [62] have described three types of counter-clockwise CTI AFL: type 1 has purely negative F waves

inferiorly, while types 2 and 3 have F waves inferiorly with small (type 2) or broad (type 3) positive terminal deflections. Types 2 and 3 counter-clockwise CTI AFL are associated with left atrial enlargement, heart disease and AF. This group has also identified two types of clockwise CTI AFL: type 1 has notched positive F waves in inferior leads with a distinct isoelectric segment, while type 2 has broader F waves which in the inferior leads have a positive and negative component and a short isoelectric segment [62].

Lower-loop CTI AFL may have a surface ECG configuration similar to that of counter-clockwise or clockwise CTI AFL [47,48]. In lower-loop counter-clockwise right AFL using the CTI there is a slight decrease in the amplitude of the late positive deflection in the inferior leads caused by collision over the lateral right atrium that cancels the late cranio-caudal lateral wavefront [51]. Activation of the atrial septum and left atrium during lower-loop counter-clockwise CTI AFL is the same as during common counter-clockwise CTI AFL, thus explaining the similar ECG manifestation of both. Left AFLs (or macro re-entrant AT), positioned septal, mitral annular or around a posterior scar, are electrocardiographically characterized by a variety of patterns sometimes with flat or low amplitude F waves in inferior leads [52].

Electrophysiological studies

Catheter mapping and stimulation studies enable us to differentiate isthmus-dependent from the various varieties of non-isthmian AFLs and macro-reentrant ATs described in previous sections of this chapter. [13,45–48, 50–52]. Patients with AFL unrelated to the CTI or with other forms of macro-reentrant AT should be referred to very experienced centres if they are considered candidates for RFCA.

Treatment

Episodic AFL and recurrent paroxysmal AFL are usually terminated with DC-shock cardioversion or atrial overdrive pacing. When AFL occurs after cardiac surgery it can be terminated by overdrive pacing using the temporary atrial leads customarily left in place by most cardiovascular surgeons. In patients with respiratory failure, atrial overdrive pacing is preferred to DC-shock cardioversion since deep sedation poses additional risks. A spontaneous AV ratio greater than 2 : 1 suggests coexistent AV nodal disease and a potential association with sinus node dysfunction and sinus pauses on restoring sinus rhythm should be anticipated. Adequate rate control with drugs acting on the AV node is frequently difficult if AV nodal function is normal, particularly in patients in cardiac or respiratory failure or in the presence of post-surgical anaemia. Existing guidelines for anticoagulation for patients with AF should be extended to those with AFL. Cardioversion, by electrical, pharmacological or ablation methods, should be considered only if AFL is < 2 days in duration, the patient has been well anticoagulated for 3 weeks or more, or a transoesophageal echocardiogram excludes atrial thrombus. The transoesophageal echocardiogram must be performed after heparinization and be followed by continuous anticoagulation. Oral anticoagulation is maintained for 3–4 weeks after restoring sinus rhythm or permanently in patients aged > 65 years with a history of hypertension, or if there is an associated structural heart disease, especially mitral stenosis or left ventricular dysfunction. Oral anticoagulation can be discontinued 6–12 months after ablation of AFL if the patient remains free from recurrences and does not suffer episodes of AF.

For pharmacological cardioversion of AFL, class III drugs such as ibutilide or dofetilide are superior to class I agents and to amiodarone. Thus, intravenous ibutilide restored sinus rhythm in 76% of AFL as compared with a 14% conversion rate with intravenous procainamide [63]. Class III drugs may produce torsades de pointes and their use is not advocated in patients with systolic left ventricular dysfunction, prolonged QT interval or underlying sinus node disease. We do not encourage the use of intravenous flecainide or propafenone for conversion of AFL since, after reducing the flutter atrial rate, class IC drugs, flecainide in particular, may result in 1 : 1 AV conduction.

Radiofrequency catheter ablation

In patients with recurrent episodes of CTI AFL or with chronic CTI AFL, the treatment of choice is catheter ablation, creating a line of block between the tricuspid annulus and the inferior vena cava or Eustachian ridge (see Table 28.2). Understanding the anatomy of the human CTI, which has recesses, smooth, trabecular and membranous areas and a variable myocardial content, has contributed to a better perception of the ablation needs in these patients [64,65]. Cabrera *et al*. [65] have shown that the central, most inferior, area of the CTI (the 6 o'clock region on a fluoroscopic left anterior oblique view) is thinner and shorter in length than the paraseptal and inferolateral sectors of the isthmus. Conversely, the paraseptal isthmus has the thickest wall and is close to the posterior extensions of the AV node and its arterial supply [65].

Currently, RFCA of AFL is performed with large electrodes or irrigated-tip catheters that offer superior results than conventional 4-mm tip electrodes [42,66]. With these tools a line of bidirectional block across the CTI can

be attained in nearly 100% of patients, with a recurrence rate of less than 5%.

In patients with AF developing CTI AFL on class IC drugs or amiodarone, RFCA of the CTI may avoid AF recurrences in > 70% of cases. In patients who before RFCA for common CTI AFL also had documented episodes of AF, the latter arrhythmia frequently recurs despite a successful bidirectional CTI block [67,68].

RFCA of AFL unrelated to the CTI requires the identification of a critical component of the re-entry pathway suitable for complete linear ablation with a series of radiofrequency applications. This is facilitated with the use of electro-anatomical computerized mapping systems [1,13,42–44,50–52].

Chronic antiarrhythmic drug treatment must be used in patients refusing RFCA. Dofetilide may reduce by 50% the risk of recurrence of AFL as compared with placebo [69]. Although class IC drugs and amiodarone are also used, it is difficult to define the role of these agents in preventing recurrences of AFL [1].

Atrioventricular nodal reciprocating tachycardia

Definition

AVNRT is a re-entrant SVT utilizing the approaches to the AV node and the compact AV node itself. Traditional views on AVNRT considered that AV nodal conduction was functionally dissociated into a fast and a slow pathway with different electrophysiological properties. Two major forms of AVNRT exist. The common AVNRT utilizes the slow pathway anterogradely and the fast pathway retrogradely (slow–fast) (see Fig. 28.2C). Rarely, the reverse form of AVNRT, known as fast–slow, may be observed. Intermediate forms have also been described. AVNRT is the most common paroxysmal SVT in patients without pre-excitation. The rate of AVNRT varies from just above 100 b.p.m. to 250 b.p.m., but the usual rate ranges from 140 to 220 b.p.m.

Pathogenesis

The precise nature of the re-entry pathway in AVNRT is still not completely understood. The fast and slow AV nodal pathways are functionally and anatomically different. It is possible to ablate them at separate topographic sites in the triangle of Koch, without producing AV block. The triangle of Koch is depicted in Fig. 28.2C. The compact AV node results from the merger of the fibres of the right and left postero-inferior nodal extensions that are thought to be the substrate for the slow pathway. These extensions run from the coronary sinus and along the tricuspid side of the triangle of Koch, towards the anterosuperior apex of the triangle (Fig. 28.2C) [70,71]. The fast pathway may be formed by transitional fibres connecting the interatrial septum near the superior apex of the triangle of Koch with the compact AV node.

One area of uncertainty is if the upper link necessary to complete the re-entry loop by connecting the fast and slow nodal pathways is atrial myocardium or an upper common 'intranodal' pathway. Wellens *et al*. [28] described the very rare occurrence of retrograde 2 : 1 block during an AVNRT, a finding that would indicate the existence of an intranodal upper common link between the fast and slow pathways. A similar example was recently reported [72]. Rarely during AVNRT, marked variations and irregularities in atrial activation can exist with a fixed timing of His bundle depolarization, thus showing that the circuit is independent of the timing of atrial activation [73]. Better known is the existence of a lower common pathway that is usually the bundle of His but which occasionally is intranodally located. This may account for the known observation of examples of AVNRT with 2 : 1 AV ratio having the block distal but also proximal to the His bundle (Fig. 28.7) [28,29].

The common slow–fast AVNRT is induced because the fast pathway has an anterograde refractory period that is longer than that of the slow pathway. Therefore, a premature atrial impulse can be blocked in the fast pathway while conduction through the slow pathway is possible. On reaching the lower common pathway of the circuit, the wavefront returns retrogradely to the atria via the fast pathway. The reverse fast–slow AVNRT is rare as a clinical arrhythmia but in the electrophysiology laboratory it can be induced after incomplete ablation of the slow pathway. In the clinical scenario it may develop as the only documented SVT or rarely after RFCA on the slow pathway in patients previously suffering a common slow–fast AVNRT. In any case, the reversed fast–slow AVNRT is elicited when the anterograde refractory period of the slow pathway is longer than that of the fast pathway so that an impulse can be conducted to the His bundle via the fast pathway, returning to the atria via the slow pathway. Patients frequently have more than one functional slow pathway. This probably accounts for the persistence in some patients of a slower slow pathway not sustaining the tachycardia after ablation of the slow pathway. Finally, the so-called slow–slow AVNRT is also rare, but more common than the reversed fast–slow AVNRT. The slow–slow AVNRT was initially described by Ross *et al*. as type B AVNRT (type A being the usual slow–fast AVNRT

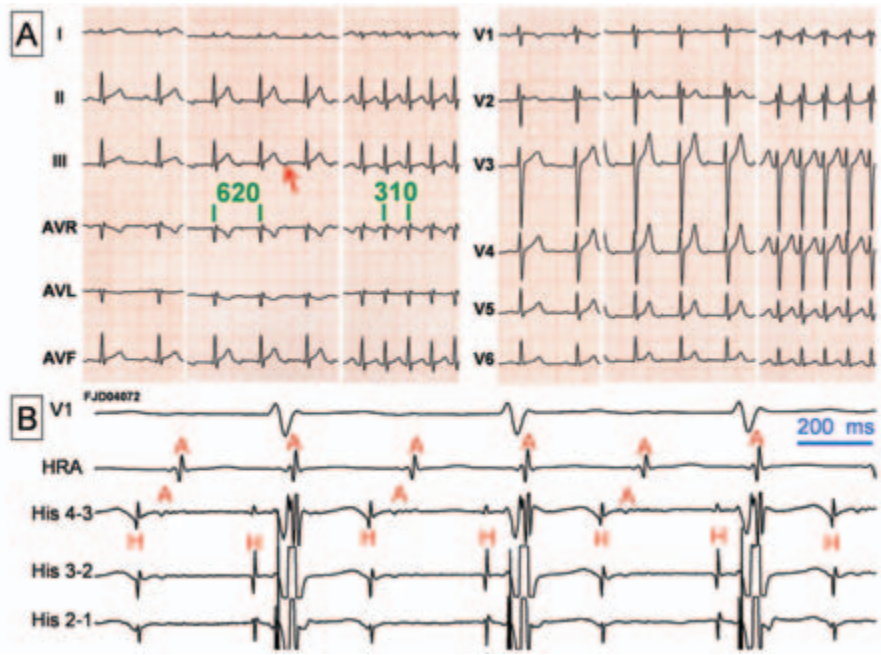

Figure 28.7 AV nodal re-entry tachycardia (AVNRT). (A) Surface ECG during sinus rhythm and in AVNRT. The first tachycardia is in fact AVNRT with 2 : 1 AV block. Note that the ventricular rate is 97 b.p.m. (cycle length 620 ms). The second tachycardia, at 194 b.p.m. (cycle length 310 ms), is AVNRT with 1 : 1 AV ratio. Due to the relatively fast rate of this AVNRT, there is beat-to-beat voltage alternans that is well seen in leads I, II, III, aVL, aVF and V5. As discussed in the text this sign is non-specific and can be observed in both AVNRT and circus-movement tachycardia using an accessory pathway. During AVNRT with 1 : 1 AV ratio the P wave is totally hidden within the QRS complex. The r' wave in V1 is real and belongs to the ventricular complex due to incomplete right bundle branch block (RBBB). The incomplete RBBB is present during sinus rhythm. (B) Intracardiac recordings from the high right atrium (HRA) and the bundle of His during the episode of AVNRT with 2 : 1 AV block. Note that the site of block is below the His bundle.

whose atrial exit was located close to the superior apex of the triangle of Koch). Retrograde conduction times in type B AVNRT are longer than in type A, so that the P waves are recorded immediately after the QRS complex, thus mimicking the ECG pattern typical of a concealed AP. In addition, the retrograde atrial breakthrough of type B AVNRT is located near or within the coronary sinus [74].

The reasons why AVNRT is more common in females than males are not known. Architecturally, the terminal portion of the coronary sinus in patients with AVNRT is wider than that of controls. Females with AVNRT have the widest terminal coronary sinus which adopts a funnel-like shape in venographic studies. Males without AVNRT have the narrowest terminal coronary sinus, which has a tubular shape. Males with AVNRT have intermediate coronary sinus dimensions and shapes that are similar to those observed in females without ANVRT [75].

Diagnosis

Clinical characteristics

Some 70% of patients with AVNRT are females (see Table 28.2). Women start developing AVNRT at a younger age than men (29 ± 16 vs. 39 ± 16 years, respectively) [76]. An associated structural heart disease, which in some early series of AVNRT was found in up to 46% of the patients [77], exists in only about 15% of the cases [76]. AVNRT may be associated with other forms of SVT, such as AFL and SNRT. Whether this is a coincidental association is unknown [78,79]. The meaning of these arrhythmias remains obscure when induced during a stimulation study without previous clinical electrocardiographic documentation. Approximately 20% of patients with idiopathic fascicular left ventricular tachycardia also have an AVNRT, an association with practical relevance since in some patients both arrhythmias have been clinically documented. Patients with WPW syndrome may develop not only tachycardias using the AP but also AVNRT. Indeed, some apparently antidromic AVRT are in fact AVNRT with 'bystander' AV conduction over the AP.

During the common slow–fast AVNRT, atrial and ventricular activations are coincidental and the jugular venous pulse shows an 'a + c' pattern with constant cannon waves and prominent neck pulsations. Patients localize their palpitations on the precordial area, but also in the neck. However, neck palpitations during paroxysmal SVT are not diagnostic for AVNRT. Patients with an AVRT using an AP may also complain of jugular palpitations since the retrograde P wave, although registered after the QRS complex, occurs during mechanical ventricular systole and gives rise to an 'a + v' jugular venous pattern. During episodes of AVNRT, patients may also complain of polyuria, dizziness, chest pain and even syncope.

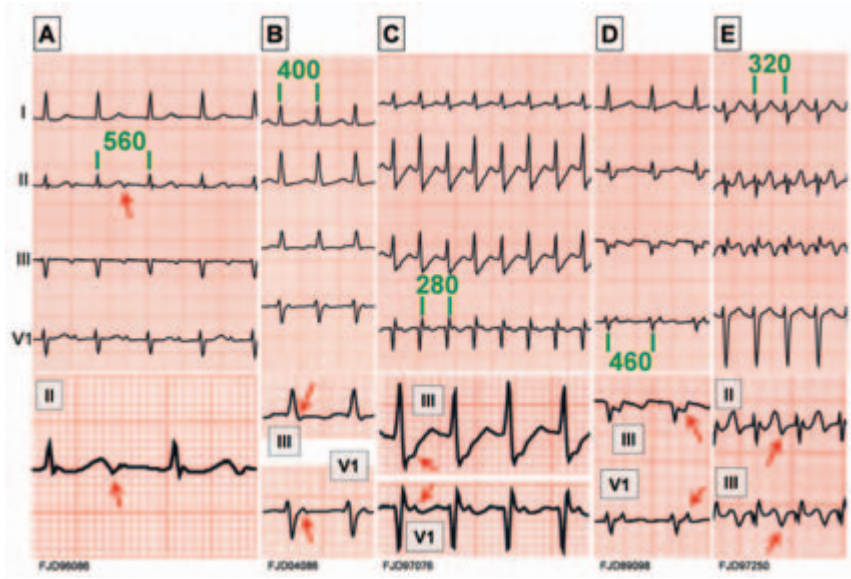

Figure 28.8 Various ECG manifestations of AV nodal re-entry tachycardia (AVNRT). (A–D) Examples of the common slow–fast AVNRT; (E) example of the uncommon fast–slow AVNRT (see text). (A) AVNRT with 2 : 1 AV block. Note that the ventricular rate is relatively slow (107 b.p.m.) and that there is a P wave between two consecutive QRS complexes (arrow). P waves are predominantly negative in the inferior leads and positive in lead V1. A magnified detail showing lead II is shown below. (B) AVNRT in which the retrograde P waves (arrows) mimic terminal forces of the QRS complex (pseudo s waves in the inferior leads and pseudo r′ waves in V1). The rate of this AVNRT is 150 b.p.m. (see text). (C) Relatively fast AVNRT (214 b.p.m.) showing voltage alternans of consecutive QRS complexes. As discussed in the text, although this finding has been said to suggest an AVRT incorporating an accessory pathway, it is a non-specific sign mainly depending on the rate of the tachycardia. Retrograde P waves (negative in the inferior leads and positive in V1) are visible just after the QRS complex. (D) A relatively slow AVNRT (130 b.p.m.) in a 72-year-old woman. P waves are visible just after the QRS complex (arrows). (E) Example of the rare fast–slow AVNRT at a rate of 188 b.p.m. P waves with a PR interval slightly shorter than the RP time are clearly seen (arrows).

Electrocardiographic characteristics

During the common slow–fast AVNRT, retrograde P waves are hidden within the ventricular complex (25%) or are recorded at the end of the QRS, mimicking terminal 's waves' in inferior leads or more frequently 'pseudo r' waves' in lead V1 (60%) (see Table 28.2) (Figs 28.3, 28.7 and 28.8). Exceptionally, P waves may be registered just before the onset of the ventricular complex, simulating initial inferior 'q waves' (2%) or after the QRS offset (8%). The latter variety is the Ross type B or slow–slow AVNRT that electrocardiographically mimics the configuration of an AVRT utilizing an inferior paraseptal AP (Fig. 28.9) [25,76]. The remaining 5% is represented by the reversed fast–slow AVNRT in which the P wave precedes the QRS complex with a PR interval shorter than the RP time, thus mimicking an AT or a PJRT (Figs 28.3 and 28.8E). The P wave during all kinds of AVNRT is negative in leads II, III and aVF, and biphasic with a terminal positive component in V1 (Figs 28.7 and 28.8).

The AV ratio during AVNRT is usually 1 : 1. At the initiation of a fast AVNRT the AV ratio may be 2 : 1. This can occasionally be documented on a Holter recording and more frequently during an electrophysiological study. Electrocardiographically, AVNRT with 2 : 1 AV block manifests as a relatively slow tachycardia (the ventricular rate may be 90–120 b.p.m.) in which negative P waves in the inferior leads appear just in the middle of the ventricular cycle (Figs 28.7 and 28.8A). In these patients it may be possible to identify an additional P wave deforming the terminal forces of the QRS complex. The differential diagnosis is AT with 2 : 1 AV block. Long recordings of AVNRT with 2 : 1 AV block will almost invariably show the abrupt transition to 1 : 1 conduction because block is below the His or below the slow AV nodal pathway (at the level of the lower common pathway), something that would seldom occur in AT where the physiological or pharmacological block is at the nodal level. There are anecdotal reports of a 2 : 1 VA block during an AVNRT [28,72].

Electrophysiological studies

Excellent reviews of the electrophysiology of AVNRT have been published elsewhere [80,81]. Electrophysiological studies in patients with suspected AVNRT are indicated only when RFCA is considered. Both the stimulation study and the ablation must be made during the same

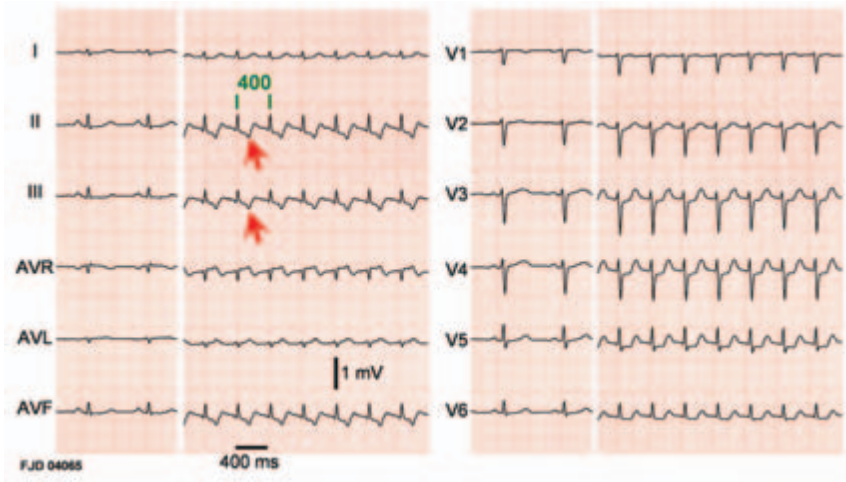

Figure 28.9 Example of the slow–slow or Ross type B AV nodal re-entry tachycardia (AVNRT). The ECG of this form of AVNRT cannot be differentiated from that of an AVRT utilizing a concealed inferior paraseptal accessory pathway. Note the presence of P waves following the QRS complex but starting well after the end of the ventricular depolarization in the surface ECG. The PR interval is longer than the RP time. See text for further explanation.

procedure. Because slow–slow AVNRT may mimic an AVRT utilizing a concealed inferior paraseptal AP and because the ablation approaches are different in both situations, special attention should be paid to making the correct diagnosis. A slow–slow AVNRT is diagnosed if a ventricular premature beat introduced during tachycardia when the His bundle is refractory does not advance the subsequent atrial activity, as would occur in AVRT utilizing an inferior paraseptal AP [74]. The presence of dual AV nodal pathway physiology, defined by a sudden jump of ≥ 50 ms in the AH interval for a 10-ms decrease in the coupling interval of the extrastimulus, is of no diagnostic help. Dual AV nodal pathway physiology is not always present in patients with AVNRT and may be found in patients with other forms of SVT, as well as in subjects without any SVT.

Treatment

Paroxysmal AVNRT can be terminated, but not always, by vagal manoeuvres. Intravenous adenosine and verapamil nearly always terminate AVNRT. These physical and pharmacological interventions terminate AVNRT by inducing block in the anterograde slow AV nodal pathway. Adenosine should not be used in patients with a history of bronchospasm. Verapamil and diltiazem should be avoided in patients using beta-blockers. The intravenous administration of class I antiarrhythmic drugs can also interrupt an AVNRT by blocking the retrograde fast pathway.

The treatment of choice for AVNRT, independently of its variety, is RFCA of the slow AV nodal pathway. When episodes are infrequent, chronic antiarrhythmic drug treatment will impair the quality of life more than the arrhythmia itself. For those patients with frequent episodes of AVNRT who temporarily or permanently refuse RFCA, class IC drugs such as flecainide and propafenone can be recommended. Class IC drugs are particularly effective due to their use-dependent effect on the retrograde fast pathway. Flecainide (200–300 mg/day) prevents recurrences of AVNRT in 65% of patients [82]. If the latter drugs are contraindicated, such as in patients with left ventricular dysfunction or coronary artery disease, beta-blockers, verapamil, diltiazem or amiodarone can be used. Drugs acting on the slow AV nodal pathway, such as verapamil, diltiazem, beta-blockers and digoxin, might prevent recurrences but in some patients they may have the opposite effect. In practice they are successful only when the slow pathway is the weakest link of the AVNRT, a situation that is not always the case. In addition, under physical or psychological stress these drugs may lose their efficacy. Amiodarone is a pharmacological option in patients in whom all other drugs cannot be used or have failed [1].

In patients with infrequent, relatively well tolerated but prolonged episodes of AVNRT and in whom self-performed vagal manoeuvres are ineffective or impossible, the so-called 'pill-in-the-pocket' approach has been advocated. A single oral dose of flecainide (approximately 3 mg/kg) was not much superior to placebo in one study that demonstrated the superiority of the combination of oral propranolol (80 mg) and diltiazem (120 mg) over flecainide and placebo [83]. Since hypotension and sinus bradycardia are potential complications of this approach, its use is not recommended in elderly people who usually refuse to undergo a catheter ablation procedure.

Radiofrequency catheter ablation

RFCA is the treatment of choice for AVNRT after its first recurrence. In patients with infrequent episodes, the use of antiarrhythmic drugs is not acceptable because they do not guarantee prevention of recurrences. The fear of suffering an episode of AVNRT itself deteriorates the

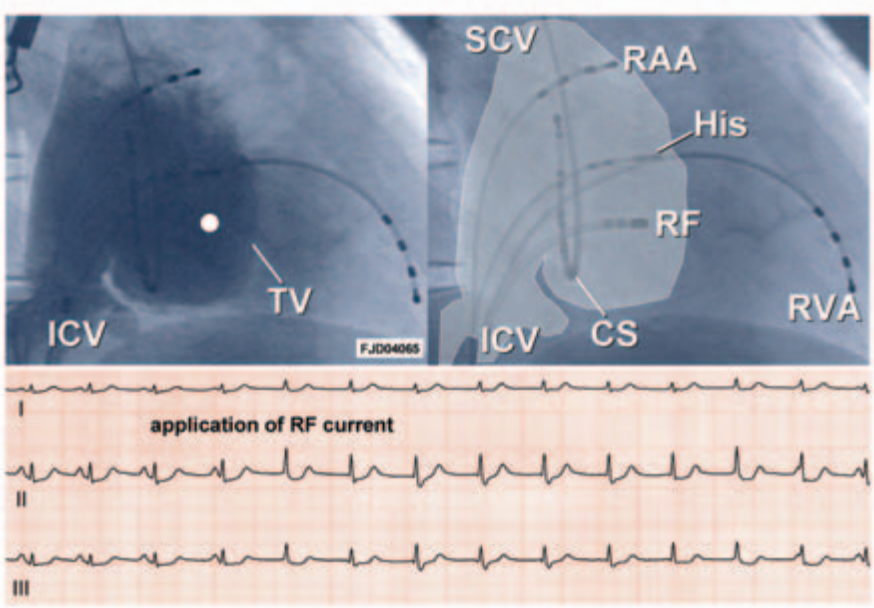

Figure 28.10 Same patient as in Fig. 28.9. The upper left fluorographic image shows a right atrial angiogram depicting the limits of the right atrium (TV, tricuspid valve; ICV, inferior caval vein). The upper right fluorographic image shows a 4-mm tip electrode catheter at the site of ablation of the slow pathway (RF); this point is represented as a white circle on the right atrial angiogram at upper left. A transparent contour of the right atrium and the tricuspid valve limit is superimposed on the fluorographic view at upper right. The lower panel shows an accelerated junctional rhythm at the time of application of radiofrequency current over the slow pathway. SCV, superior caval vein; RAA, right atrial appendage; RVA, right ventricular apex; CS, coronary sinus.

quality of life of these patients. Females of child-bearing age should not take antiarrhythmic drugs permanently.

The ablation of the slow pathway during sinus rhythm is the preferred approach (Fig. 28.10). In experienced centres, slow-pathway ablation can be performed with an almost negligible risk of inducing AV block (< 0.5%) and with a success rate of 98% [67]. However, elimination of AVNRT can be obtained in 100% of patients if the fast pathway is approached in those in whom the slow pathway cannot be ablated. Recurrences of AVNRT after slow-pathway ablation are observed in < 2% and all of them can usually be cured in a repeat procedure [67].

Today, many interventional arrhythmologists do not feel comfortable performing ablation of the fast pathway. The atrial exit of the fast pathway during retrograde conduction is close to the site of recording of the His bundle potential. The risk of inducing AV block during fast pathway ablation is higher than that approaching the slow pathway. With experience, starting with very low temperatures that are very slowly increased, this risk is minimal and obviously lower than the initially reported figure of 5% [84].

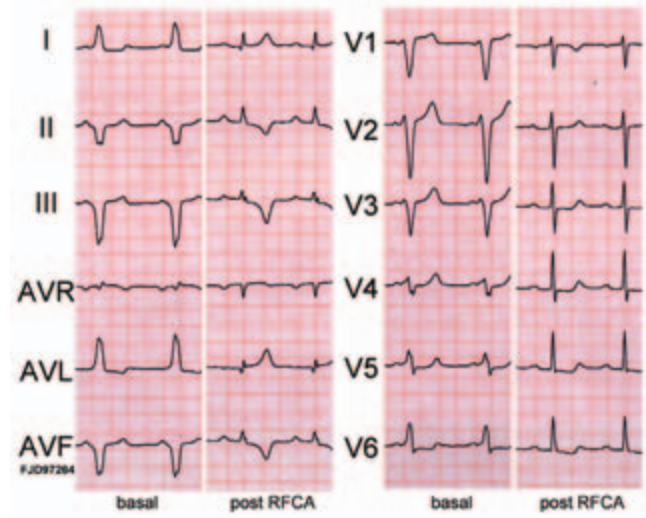

Figure 28.11 Typical patent pre-excitation in a patient with Wolff–Parkinson–White syndrome. ECG in sinus rhythm before (basal) and after the ablation (post RFCA) of a right inferior accessory pathway. The PR interval measures 0.08 s and the width of the QRS complex is 0.16 s. Note the slurring of the initial forces of the ventricular complex that is well seen in I, aVL and V4–V6. After radiofrequency catheter ablation, the PR interval prolongs (0.20 s) and QRS complex becomes normal (QRS width 0.08 s). Note that the T waves after ablation are deeply negative in leads II, III and aVF. These inverted T waves do not reflect ischaemia but the phenomenon of cardiac electric memory (see text).

Accessory pathways, pre-excitation syndromes and their tachycardias

Definition

In 1930, Wolff, Parkinson and White described in 11 healthy young people the association of a short PR interval and a wide QRS complex during sinus rhythm, with a tendency to develop paroxysmal tachycardia [85]. Classical WPW syndrome (Fig. 28.11) is due to the existence of relatively fast-conducting anomalous AV fibres,

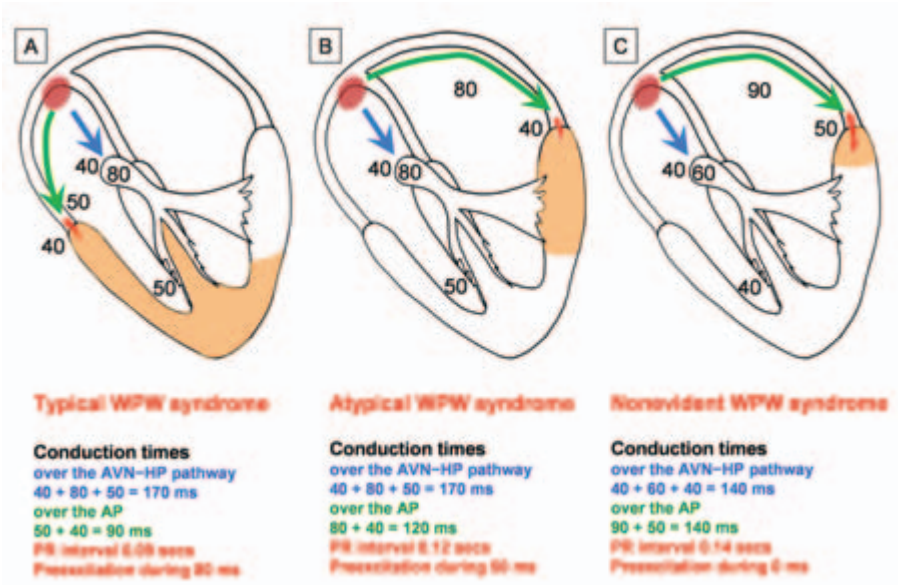

Figure 28.12 Schematic representation of typical, atypical and non-evident pre-excitation in Wolff–Parkinson–White (WPW) syndrome. In the three panels we have estimated the AV conduction times over the normal AV node–His axis and the accessory pathway (AP). (A) Hypothetical scenario of a right-sided AP resulting in a typical WPW pattern. AV conduction times over the AP are much shorter than those over the normal axis. Pre-excitation (defined as the difference between AV conduction times via the AP and over the normal axis) occurs in this example over a period of 80 ms. This means that during this time period the ventricles are activated by the wavefront of depolarization initiated at the ventricular insertion of the AP. The extension of ventricular myocardium that is activated through the AP is represented in orange on all panels. (B) Hypothetical example of an atypical WPW pattern. The atypical feature here is a PR interval of 0.12 s. However, because pre-excitation in this left-sided AP occurs over a period of 50 ms, the configuration of the QRS complex enables a diagnosis of WPW syndrome to be made. (C) Example of non-evident pre-excitation. Here, AV conduction times via the AP and over the AV node–His axis are the same (0.14 s in both instances). The PR interval is not short and the QRS complex is not wide either. Because only a very small amount of ventricular myocardium in the vicinity of the ventricular insertion of the AP will be depolarized by the wavefront conducted by the bypass tract, the diagnosis of pre-excitation during sinus rhythm may be impossible. Sometimes, modification of the initial forces of the QRS complex may prompt consideration of the possibility of non-evident WPW and, if there is a history of tachycardia, to plan further investigations to make a diagnosis. See text for further details.

connecting atria and ventricles at sites where they should be electrically isolated [86]. The existence of atrioventricular APs and their relation with WPW syndrome was verified with the introduction of epicardial excitation mapping, programmed electrical stimulation and intracardiac catheter electrode mapping techniques. The latter methodologies led to the development of 'curative' ablative approaches, first with surgical techniques and subsequently with percutaneous catheter electrode intracardiac procedures.

The term 'pre-excitation' was introduced by Ohnell to indicate that in WPW syndrome ventricular activation starts earlier than expected due to shorter AV conduction times via the AP than over the normal AV node–His axis [87]. Today, pre-excitation syndromes include all situations in which there is an anomalous AV connection that can conduct anterogradely, including instances without actual pre-excitation in which the AV conduction times over the AP are not shorter than those via the normal AV node–His pathway (Fig. 28.12).

There are several anatomical and physiological types of APs (Table 28.3). APs can be patent or concealed. Patent or overt APs conduct in AV direction and have the potential to produce ECG manifestations during sinus rhythm or atrial pacing. They are involved in WPW syndrome and in a form of pre-excitation originally described by Wellens [88] and initially thought to be due to nodoventricular Mahaim fibres although it is actually caused by an atriofascicular bypass tract [89]. Patients with APs frequently develop paroxysmal SVT. Most of these SVTs are due to re-entry utilizing the AP, but in some patients the AP acts as a bystander as when AF supervenes (Table 28.4).

Concealed APs are those that only conduct in retrograde (VA) direction so that during sinus rhythm there are no signs of ventricular pre-excitation. These patients develop a paroxysmal AVRT that utilizes the AP as retrograde limb of the re-entry circuit (Table 28.4). A special type of concealed AP with long conduction times and decremental conducting properties is responsible for

Table 28.3 Types of accessory pathway

Physiological type of AP	Anatomical type of AP	Manifestation
Patent or potentially patent Short conduction times, non-decremental properties	Accessory AV connection of working myocardium	Classical WPW syndrome AVRT (orthodromic or antidromic) AF (with/without pre-excitation)
Long conduction times, decremental properties	Accessory AV conduction axis (AV node–His–Purkinje pathway) or atriofascicular AP	Antidromic AFRT with LBBB configuration AF (with/without pre-excitation)
Concealed Short conduction times, non-decremental properties	Accessory AV connection of working myocardium	AVRT without ventricular pre-excitation during sinus rhythm
Long conduction times, decremental properties	Not yet determined (most likely tortuous fibromuscular tract)	PJRT without pre-excitation during sinus rhythm

AF, atrial fibrillation; AFRT, atriofascicular reciprocating tachycardia; AP, accessory pathway; AVRT, atrioventricular reciprocating tachycardia; LBBB, left bundle branch block; PJRT, permanent junctional reciprocating tachycardia; WPW, Wolff–Parkinson–White.

Table 28.4 Types of Wolff–Parkinson–White (WPW) syndrome

Type	ECG	Tachycardia
Typical WPW	Short PR interval Wide (pre-excited) QRS complex	Without tachycardia With AVRT With AF or AFL
Atypical WPW		
Evident WPW	Normal PR interval Wide (pre-excited) QRS complex	Without tachycardia With AVRT With AF or AFL
Non-evident WPW	Normal PR interval Narrow (not clearly pre-excited) QRS complex	Without tachycardia With AVRT With AF or AFL

AVRT, atrioventricular reciprocating tachycardia; AF, atrial fibrillation; AFL, atrial flutter.

an incessant junctional reciprocating tachycardia, first described by Coumel, and known as PJRT [90]. PJRT may cause a tachycardiomyopathy and electrocardiographically is characterized by negative P waves in the inferior leads with PR < RP.

Epidemiological data with regard to APs and ventricular pre-excitation are scanty. The prevalence of the WPW ECG pattern is said to be 0.1–3 per 1000 tracings [91], a figure that underestimates the reality due to the existence of intermittent and non-evident forms of pre-excitation. In a recent study the annual incidence of new cases of WPW syndrome was 4.4 per 100 000, with more than twice as many males (6.8 per 100 000) as females (2.2 per 100 000) [92]. The WPW pattern is more common in males than in females, with a ratio of approximately 1.5 : 1.

Pathogenesis

Developmental and genetic factors leading to anomalous AV pathways

An AP is usually a congenital defect in AV segmentation and in the development of the fibrous AV rings. While right-sided APs have been said to occur in relation with an ill-formed tricuspid annulus, left-sided pathways probably skirt the annulus [86]. Although the great majority of patients with anomalous AV connections have no other associated cardiac abnormalities, a few have certain congenital heart disorders such as Ebstein's anomaly of the tricuspid valve, L-transposition of the great arteries, hypertrophic cardiomyopathy and coronary sinus diverticulum. Some patients with tuberous sclerosis may

also have an AP and eventually pre-excitation. In most patients there is no family history of similar rhythm disorders. A familial occurrence of the WPW pattern has been reported in about 3% of patients with electrophysiologically demonstrated APs [93]. First-degree relatives of patients with APs have a 0.55% prevalence of a WPW pattern [93], a proportion higher than that in the general population. The inheritance pattern is autosomal dominant in these patients.

Mutations in the γ2 regulatory subunit (PRKAG2) of AMP-activated protein kinase have been described in an exceptional subgroup of patients presenting with a wide spectrum of associated disorders, including conduction disturbances over the normal AV nodal–His axis, atrial flutter or fibrillation in about 40%, and even ventricular hypertrophy, a phenotype that differs from the usual one in WPW syndrome [94,95]. The same group of investigators has developed a transgenic mouse model expressing the human mutant *PRKAG2* gene. As in the human phenotype, this transgenic mouse exhibits pre-excitation with inducible orthodromic AVRT, cardiac hypertrophy and excessive cardiac glycogen [96].

Anatomical types of accessory pathways

The AP involved in WPW syndrome and the conventional type of concealed AP are usually composed of ordinary working myocardium (see Table 28.3) [86]. In the form of pre-excitation initially described by Wellens and today termed Mahaim physiology, the AV bypass is a long tract that represents an anomalous parallel AV conduction system in the free-wall tricuspid annulus. It consists of a proximally decrementally conducting structure (like the AV node) that continues with an anomalous His which through a Purkinje bundle connects distally with the normal right bundle branch or directly with the apical right ventricular myocardium [89]. This AP frequently, but not always, is an atriofascicular bundle. The AP involved in PJRT may be a tortuous fibro-myocardial bundle whose anisotropic properties may account for slow and decremental conduction [97].

Bidirectional or unidirectional conduction over accessory pathways

APs may conduct only in anterograde direction, have bidirectional AV and VA conduction, or can exclusively conduct retrogradely. The anterograde and retrograde conducting properties of APs with bidirectional conduction are frequently different. Moreover, the effects of drugs on the anterograde and retrograde conduction also differ. The reasons for directionally dependent conduction discrepancies in APs are not clear. The concept of mismatch impedance was introduced to explain the unidirectional conduction of AV connections at the level of the junction between the AP and the ventricular myocardium [98]. Alternatively, these directional electrophysiological differences may be related to interactions among branches at the proximal and/or distal insertions of the AP, which would explain the occasional appearance of anterograde conduction after an ablation attempt in a previously concealed AP.

Circus movement tachycardia utilizing an accessory pathway

In patients with bidirectional AP conduction or with a concealed AP, the most frequent arrhythmia is the orthodromic AVRT that utilizes the AP as the retrograde limb of the circuit (Table 28.5). In both instances, an orthodromic AVRT can be induced by an APB that is anterogradely blocked in the AP so that its activation wavefront is conducted to the ventricles via the AV node–His axis. On activating the ventricle the wavefront returns to the atria via the AP. Alternatively, orthodromic AVRT can be induced by ventricular premature beats if they are retrogradely conducted to the atria only via the AP so that the impulse comes back to the ventricles via the AV node–His axis. Orthodromic means that ventricular activation during AVRT is via the normal AV node–His axis, and thereby without ventricular pre-excitation (Figs 28.13 and 28.14).

A few patients with WPW syndrome develop the antidromic AVRT that uses the AP as anterograde limb of the circuit and the normal AV nodal axis, or a second AP, retrogradely (Table 28.5). Some of these apparently antidromic AVRT in WPW syndrome are actually AVNRT with AV conduction over an AP. In the latter, abolition of conduction over the AP (that acts as a mere bystander) will not prevent tachycardia. Pre-excited tachycardias in WPW syndrome can also be observed in patients developing AT, AFL or AF.

Finally, patients with Mahaim physiology may develop a true antidromic AVRT with an LBBB configuration in which AV conduction is via the right-sided AP and retrograde conduction over the normal AV node axis (Fig. 28.14). Exceptionally, there are left-sided slowly conducting AV bypass tracts resulting in a wide QRS complex SVT with an RBBB configuration and an inferior axis. In PJRT the slowly conducting AP is used as the retrograde limb and the AV node as the anterograde arm of the circuit (Fig. 28.14).

Topographic classification of accessory pathways

Initial topographic classifications of APs attended the surgical interest and distinguished four broad insertion

Table 28.5 Tachyarrhythmias in patients with accessory pathways

Tachycardia in patients with WPW syndrome	
Tachycardias utilizing the AP	
Circus movement tachycardia utilizing the AP	
Orthodromic AVRT	AV conduction via the normal AV node–His pathway, VA conduction via AP
Antidromic AVRT	
Conventional antidromic AVRT*	AV conduction via AP, VA conduction via the normal AV node–His pathway
AVRT using two APs	AV conduction via AP1, VA conduction via AP2
Tachycardias modulated by the AP	
AV nodal reciprocating tachycardia	*occasionally manifesting as an antidromic AVRT
Atrial fibrillation	
Atrial flutter	AV conduction varies from exclusively over the AP to exclusively via the normal AV node–His pathway
Atrial tachycardia	
Tachycardia in patients with concealed accessory pathways	
Non-decrementally conducting AP	
Orthodromic AVRT	AV conduction via the normal AV node–His pathway, VA conduction via AP short conduction times
Decrementally conducting AP	
PJRT	AV conduction via the normal AV node–His pathway, VA conduction via AP with long conduction times
Tachycardia in patients with Mahaim physiology	
Antidromic AVRT using a decremental AP	AV conduction via the slowly decrementally conducting AP, VA conduction via the normal AV node–His pathway

AP, accessory pathways; AVRT, atrioventricular reciprocating tachycardia; PJRT, permanent junctional reciprocating tachycardia; WPW, Wolff–Parkinson–White.
*AV nodal tachycardia may manifest with AV conduction over the AP mimicking an antidromic AVRT.

regions: right free wall, left free wall, posteroseptal and anteroseptal. Detailed catheter mapping and ablation techniques led to the definition of a more comprehensive topographic classification of APs in agreement with the fluoroscopic locations of the ablation sites (Fig. 28.15) [99].

The pyramidal space contains septal and paraseptal APs [100,101]. The old term 'posteroseptal' is now named 'inferior paraseptal'. Midseptal APs are located in the pyramidal space between the His bundle and the orifice of the coronary sinus. In the new nomenclature, midseptal APs are named true-septal or septal but the term 'atrioseptal' should be preferred instead [101]. Some APs are unrelated to the AV rings, such as those coursing within the pyramidal space, or the bundles connecting the right or left atrial appendages with their ipsilateral ventricle [101]. Anteroseptal APs are now termed 'superior paraseptal', and in this region there are at least two kinds of AP: (1) peri-Hisian APs that course between the endocardium and the AV node–His bundle and insert distally at the superior summit of the muscular ventricular septum; and (2) superior metaseptal APs whose ventricular insertion is at the supraventricular crest, beyond the ventricular septum [101].

Wolff – Parkinson – White syndrome

Definition

Reserving the name WPW syndrome for patients with the typical ECG in sinus rhythm and a history of palpitations is conceptually inaccurate. Not all the 11 patients in the original publication had paroxysmal tachycardia [85] and not all patients with WPW syndrome have a short PR interval and a QRS complex > 120 ms. WPW syndrome embraces patients with APs with short conduction times that conduct in the AV direction, with or without a history of palpitations. A current asymptomatic status in patients with the 'WPW electrocardiographic pattern' does not exclude the development of tachycar-

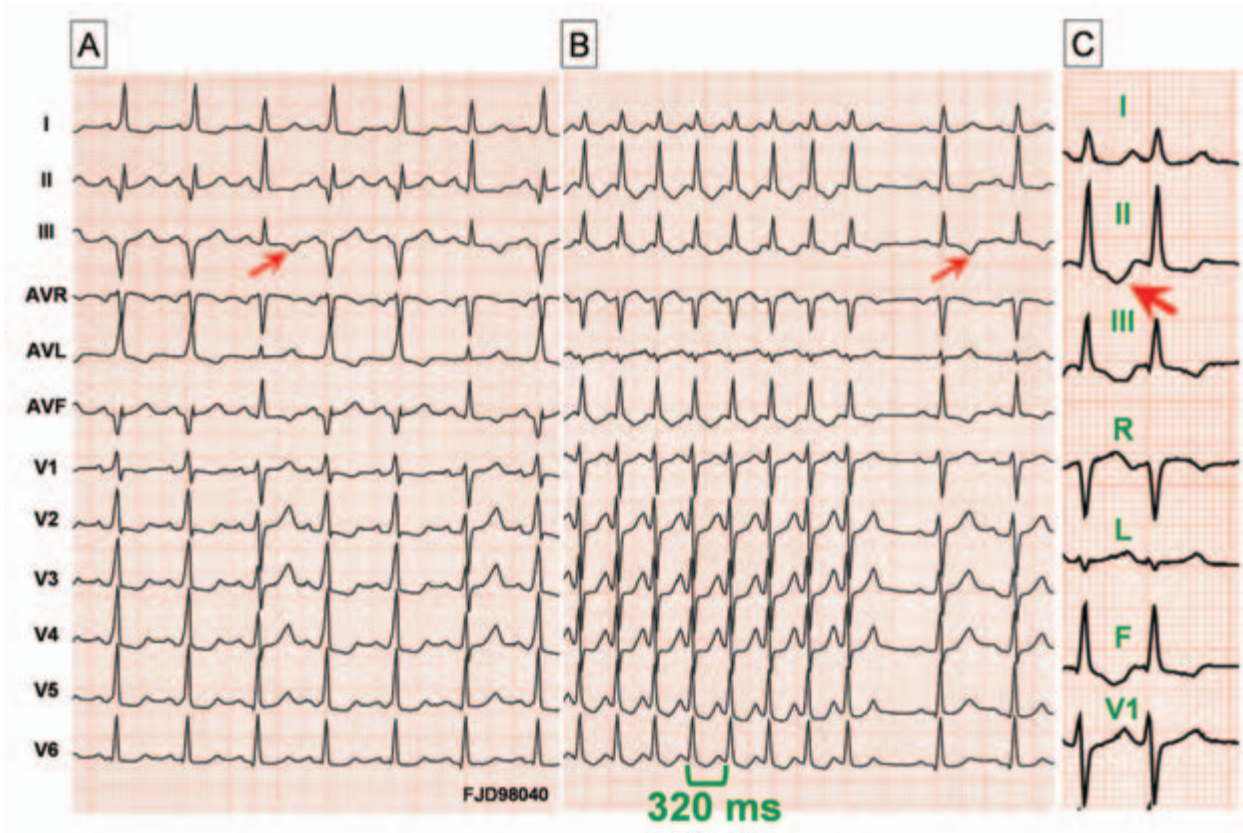

Figure 28.13 Intermittent pre-excitation. (A) A 12-lead ECG in which pre-excited QRS complexes coexist with ventricular depolarizations without pre-excitation. Note that the ventricular complexes conducted via the normal AV node–His axis are followed by an abnormal repolarization with negative T waves in III and aVF (arrow). These repolarization changes are due to cardiac electric memory (see text). (B) ECG during orthodromic AV reciprocating tachycardia (AVRT). This AVRT uses the normal AV node–His axis in anterograde direction so that QRS complexes are narrow, without signs of pre-excitation. The accessory pathway (AP) is used as retrograde arm of the circuit. During AVRT, retrograde P waves are visible after the QRS complex. In this patient with a left inferior paraseptal AP, the P waves during tachycardia are negative in inferior leads. (C) The AVRT terminates spontaneously by block over the AP. The last QRS of the tachycardia is not followed by the negative P wave in leads II and III (arrow pointing to the retrograde P wave in the penultimate QRS of the AVRT).

dias or even sudden death in the future. There are several varieties of WPW syndrome (see Table 28.4). Patients with and without symptoms at the time of diagnosis in whom pre-excitation in sinus rhythm is persistent or intermittent, evident or non-evident, are hereafter included under the umbrella of WPW syndrome. Because the definition of the varieties of WPW syndrome is mainly electrocardiographic, we describe below the ECG during sinus rhythm in these patients.

ECG during sinus rhythm in WPW syndrome

The ECG manifestations of an anterogradely conducting AP during sinus rhythm depend on: (1) the differences in AV conduction times over the normal AV node–His axis and the AP (which determine if the WPW is typical or atypical, and evident or non-evident); and (2) the permanent or transient character of anterograde conduction over the AP (which determines if pre-excitation is permanent or intermittent). The QRS complex during sinus rhythm in WPW is a fusion of two wavefronts, one proceeding over the normal AV node–His axis and the other via the AP (see Fig. 28.12). The degree of pre-excitation on the ECG during sinus rhythm is influenced by the following.

1 *Location of the AP*. The closer the AP to the site of atrial impulse formation, the greater the degree of pre-excitation. Right free-wall APs usually result in very typical forms of pre-excitation (short PR intervals and widely pre-excited QRS complexes) (Figs 28.11 and 28.16) but left free-wall APs can result in an atypical ECG during sinus rhythm with a normal PR interval and minimal or absent signs of ventricular pre-excitation. In these patients

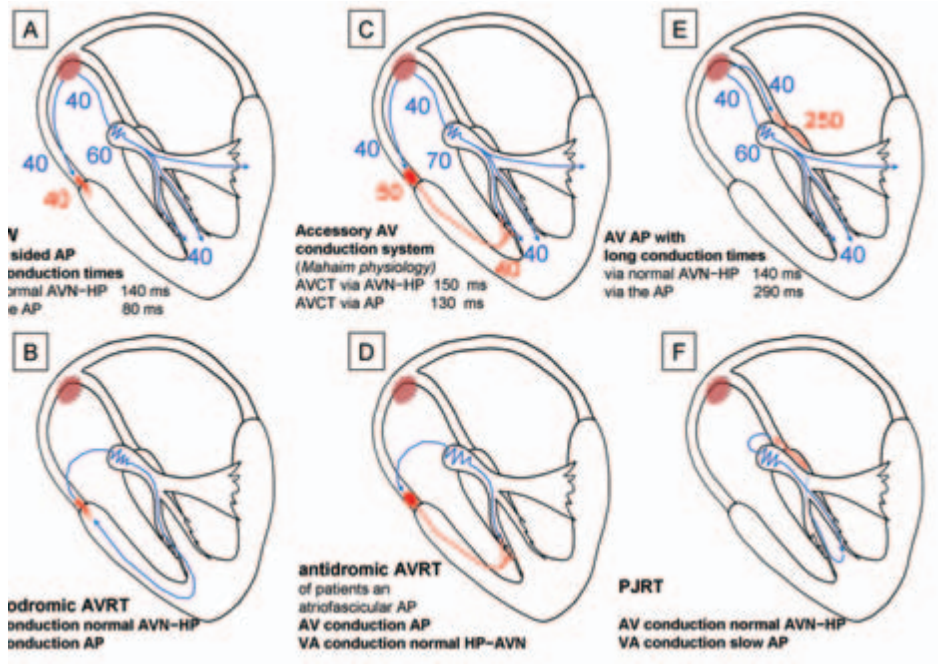

Figure 28.14 Schematic representation of the pathogenesis of the ECG during sinus rhythm and during tachycardia in the three major types of accessory pathway (AP) described in the text. (A, B) Wolff–Parkinson–White (WPW) syndrome: (A) right-sided AP in sinus rhythm (see text); (B) mechanism of AV reciprocating tachycardia (AVRT) using the normal axis in the anterograde direction and the AP retrogradely. (C, D) Mahaim physiology. The AP in these patients is usually a long atriofascicular bypass proximally consisting of an accessory right-sided AV node which through an anomalous bundle of His and a Purkinje bundle connects distally with the normal right bundle branch (see text). During sinus rhythm (C), pre-excitation may be minimal or absent. Because this AP only conducts in AV direction, the induced AVRT is antidromic, utilizing the AP as anterograde arm of the circuit and the normal conduction axis as retrograde limb. Because the AP is right-sided, AVRT has a wide QRS complex with a left bundle branch block configuration. (E, F) Hypothetical explanation of permanent junctional reciprocating tachycardia (PJRT). The AP responsible for PJRT is most likely a tortuous fibromuscular tract with very long conduction times and decremental conducting properties. During sinus rhythm, even if the AP is capable of anterograde conduction, ventricular activation is via the normal AV node–His axis since conduction times via the latter are much shorter than those over the AP. During tachycardia (F), because of the very long conduction times via the AP the P wave is inscribed well after the end of the preceding QRS. The PR interval is shorter than the RP time (see text).

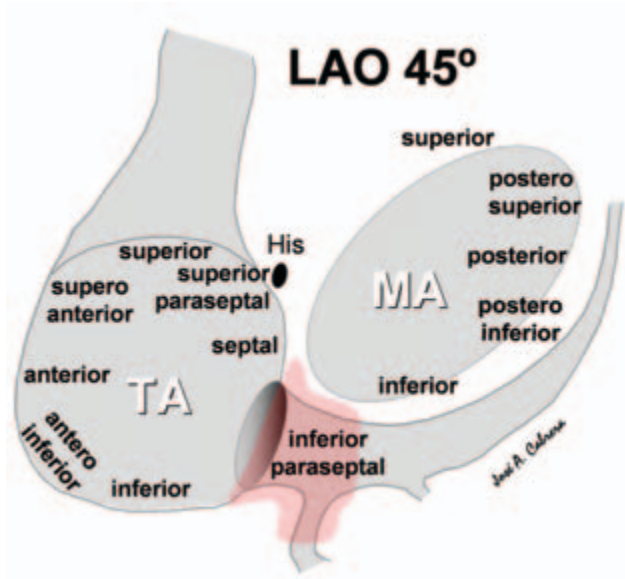

Figure 28.15 Current nomenclature of locations of accessory pathways in both AV grooves based on actual fluoroscopic attitudinal locations [98,100]. LAO, left anterior oblique; MA, mitral annulus; TA, tricuspid annulus.

pre-excitation becomes evident by pacing close to the atrial insertion of the AP (Fig. 28.17).

2 *Intra-atrial conduction times*. Enlarged or diseased atria may result in non-evident pre-excitation in patients with a left free-wall AP because it takes too long for the sinoatrial activation wavefront to reach the atrial insertion of the bypass tract.

3 *Conduction times over the AP*. The time spent by the impulse in travelling from the atrial to the ventricular insertion of the AP depends on the length and conduction velocity of the anomalous bundle. APs involved in WPW syndrome usually have short

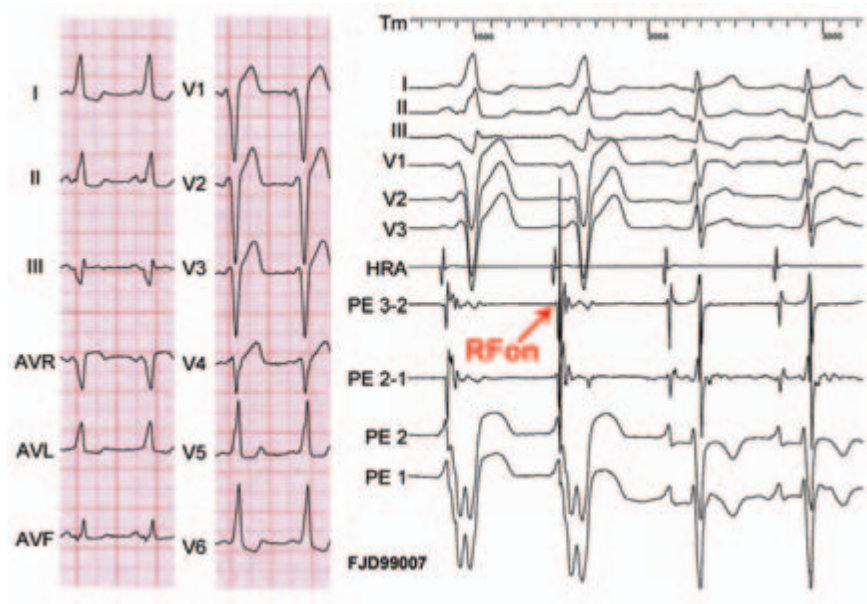

Figure 28.16 ECG during sinus rhythm in a patient with Wolff–Parkinson–White syndrome and a right free-wall (right anterior in location) accessory pathway (AP). On the right, time marks (Tm) are simultaneously displayed with leads I, II, III, V1, V2, V3 and intracardiac recordings from the high right atrium (HRA) and the probing electrode (PE). Bipolar and unipolar recordings from the PE are shown. Less than 1 s after the start of the radiofrequency pulse (arrow), pre-excitation disappears. Note that the T waves in lead III are negative after the loss of pre-excitation.

conduction times (10–60 ms) that may be longer in patients with Ebstein's anomaly or in APs related to the base of the pyramidal space, and in those connecting atrial appendages and ventricles.

4 *Conduction times over the normal AV node–His axis*. When an AP coexists with AV block (usually congenital), pre-excitation is maximal since ventricular activation is exclusively over the bypass tract. Conversely, in some patients with enhanced AV nodal conduction and short AH intervals, combined or not with HV intervals in the low range, particularly when the AP is left superior, the degree of pre-excitation may be minimal or almost absent (non-evident WPW).

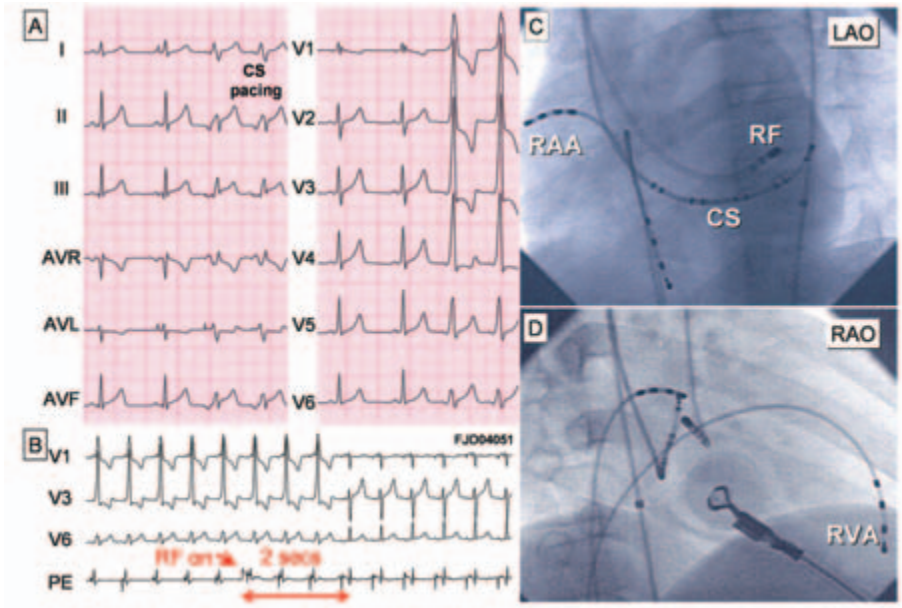

Figure 28.17 Example of atypical Wolff–Parkinson–White syndrome. Pre-excitation is poorly evident. The PR interval may measure 0.12 s or less depending on the leads and the point selected as the origin of the ventricular complex. The QRS complex is not wide and on close inspection it is possible to suspect that there is a delta wave in leads V2, V4 or V5. (A) Two sinus beats are followed by two other beats produced by atrial pacing from the coronary sinus (CS). Because this AP is left posterior (formerly called left lateral), CS pacing results in maximal pre-excitation. Application of radiofrequency current at the site of insertion of the AP resulted in loss of pre-excitation in 2 s (B). (C, D) Position of the ablation catheter (RF) at the site where conduction via the AP was eliminated. RAA, right atrial appendage; RVA, right ventricular apex; RAO, right anterior oblique; LAO, left anterior oblique.

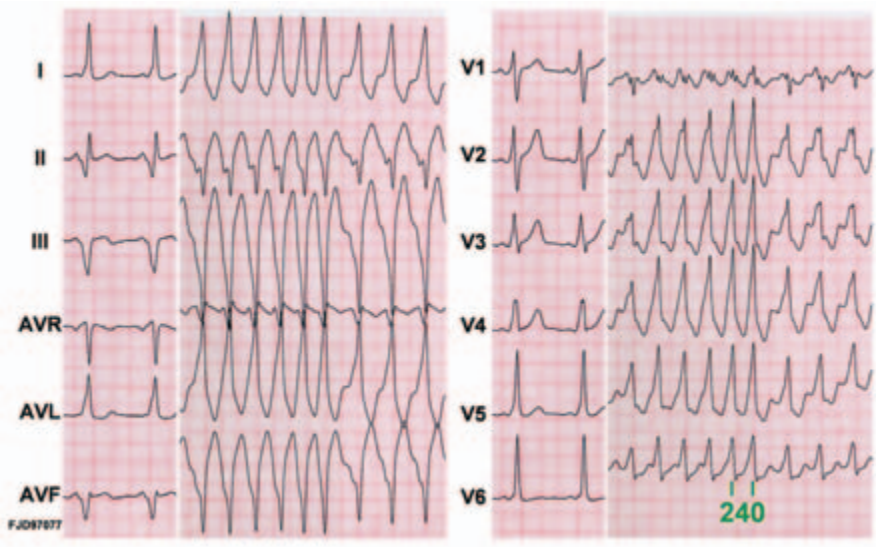

Figure 28.18 Example of typical Wolff–Parkinson–White syndrome due to an inferior paraseptal accessory pathway located within the mid-inferior interventricular vein draining into the coronary sinus. The ECG during sinus rhythm is shown alongside the recording during atrial fibrillation. Note the irregularity of the maximally pre-excited QRS complexes during atrial fibrillation. The shortest pre-excited RR interval during atrial fibrillation was 240 ms. This value has some prognostic implications (see text).

Typical and atypical WPW syndrome

In the typical or classical WPW syndrome the PR interval is short (< 120 ms) and the QRS complex wide (≥ 120 ms), with slow initial forces (delta wave) and repolarization changes (Figs 28.11 and 28.16). Left-sided APs usually show lesser degrees of pre-excitation than right free-wall bypass tracts. Maximally pre-excited QRS complexes in patients with a left free-wall AP can be seen: (1) when there is a conduction defect in the normal AV node–His pathway, and (2) when the atrial driving rhythm is not sinus in origin but left atrial.

WPW syndrome is atypical if the PR interval is ≥ 0.12 s (not short) and/or if there is little or no evidence of ventricular pre-excitation (Figs 28.12 and 28.17). Non-evident pre-excitation should not be confused with a concealed AP. In the former situation the AP conducts in anterograde direction but AV conduction times over the bypass tract and via the normal AV node–His axis are similar so that ventricular pre-excitation is not evident. Non-evident pre-excitation does not mean that the AP cannot allow very rapid ventricular rates during AF [102]. Concealed APs do not conduct in anterograde direction, not even during pacing close to their atrial insertion.

Intermittent pre-excitation

Ventricular pre-excitation is intermittent when QRS complexes with and without pre-excitation coexist on the same ECG tracing (Fig. 28.13) or on ECG recordings obtained on different occasions. In beats without pre-excitation the repolarization may be abnormal due to 'cardiac electric memory', a phenomenon that can also be observed during the usual orthodromic AVRT, and in the ECG following ablation of the AP (see Figs 28.11, 28.13 and 28.16) [103].

Diagnosis

Clinical characteristics

Patients with WPW syndrome may be asymptomatic, oligosymptomatic, symptomatic and severely symptomatic. The ECG pattern of pre-excitation may be an incidental finding during routine examination in an asymptomatic patient or be discovered because of a history of more-or-less frequent episodes of recurrent palpitations with various degrees of haemodynamic intolerance, occasionally resulting in syncope. Syncope may be related to the tachycardia rate but also to a vasovagal mechanism, but lacks prognostic significance in WPW syndrome [104]. Sudden death, which exceptionally occurs in patients with WPW syndrome, is related to degeneration of AF into ventricular fibrillation due to a fast ventricular response over one or more APs with a short anterograde refractory period [102,105]. Risk factors for sudden death in WPW syndrome are the presence of multiple APs, the development of not only AF but also AVRT, and the shortest pre-excited RR interval during AF (≤ 260 ms) (Fig. 28.18) [102,105–107]. Sudden death has been estimated to occur in 1 per 1000 WPW patients per year [107]. Unfortunately, sudden death may be the first manifestation in some patients with WPW syndrome [105–107]. Digitalis and verapamil may increase the ventricular response over the AP during AF in these patients, thus facilitating the development of ventricular fibrillation [108,109]. Myocarditis may be involved in some sudden deaths in young patients with

WPW syndrome [110]. In patients with WPW syndrome, AF is rare under the age of 20 years and sudden death exceptional below 8 years.

Signs indicating a low risk of sudden death in WPW are (1) spontaneous or exercise-induced disappearance of pre-excitation in one beat and, less convincingly, (2) loss of pre-excitation after intravenous infusion of class I drugs (procainamide, ajmaline, flecainide, propafenone). If during exercise the WPW pattern disappears abruptly, in one beat, pre-excitation must be considered intermittent and the patient viewed as low risk. Gradual disappearance of pre-excitation during exercise is of no prognostic value because it is difficult to differentiate actual AV rate-dependent block over the AP from non-evident pre-excitation due to adrenergic-mediated shortening of AV nodal conduction times [111,112]. Although the disappearance of pre-excitation after intravenous infusion of various class I drugs has been suggested as identifying patients with a 'safe' and relatively long AV refractory period of the AP [113], its prognostic significance is debatable [106]. The dose and infusion rate of the drug, as well the precocity and duration of the induced AP block, may play a role in the clinical interpretation of these tests.

The incidence of tachycardia in the WPW population is unclear. Series of patients from referral centres performing electrophysiological studies, AP surgery or catheter ablation are biased towards symptomatic cases. In a prospective population survey, 49% of patients with an electrocardiographic pre-excitation pattern were asymptomatic [92]. An AVRT was documented in 17% of the patients and AF in 8%. The mean age for the first episode of AVRT and AF was 31 and 52 years respectively. During a mean follow-up of 4.5 years, there were no sudden deaths and 4% of previously asymptomatic patients became symptomatic. In a recent study of 212 asymptomatic WPW patients, 84% remained asymptomatic during a relatively brief follow-up of about 3 years, and 16% developed symptoms. In 13% of the patients, pre-excitation disappeared after 5 years [114].

Location of the accessory pathway using the ECG during sinus rhythm

Various algorithms to localize the AP from the ECG during sinus rhythm have been developed [115]. The limitations of these algorithms are the presence of more than one AV-conducting AP, an oblique AP relative to the AV groove (lack of concordance between atrial and ventricular AP insertions) and the presence of structural heart disease or chest deformities. Despite these limitations, it is frequently possible to predict the location of the AP with accuracy from the surface ECG. A detailed description of these algorithms is beyond the scope of this chapter. In brief, pre-excited QRS complexes predominantly positive in V1 are due to left-sided APs. If then the QRS complex is negative in the inferior leads, the AP is left paraseptal or left inferior (formerly called posterior) (Figs 28.13 and 28.18). The more superiorly located a left-sided AP, the more positive the initial forces in inferior leads. Left posterior, left posterosuperior and left superior APs produce predominantly negative QRS complexes in aVL and positive ventricular deflections in II, III and aVF (Fig. 28.16). The last three left-sided locations of an AP may result in minor degrees of pre-excitation due to their distance from the sinus node region. Also, these posterior and superior (formerly left lateral) left-sided APs may not produce predominantly positive QRS complexes in V1 unless pacing is performed from the left atrium (Fig. 28.17). Well pre-excited QRS complexes predominantly negative in V1 are due to inferior paraseptal, septal, superior paraseptal and right free-wall APs. Inferior paraseptal and septal APs produce predominantly negative QRS complexes in leads II, III and aVF with an initial Q wave. A 'w-shaped' morphology in V1 would then suggest a septal (formerly midseptal) location. A well-developed initial R wave in lead V1 (although the QRS complex is predominantly negative) would suggest an inferior paraseptal ventricular insertion of the AP (Fig. 28.18). A low-amplitude initial r wave in V1 with little progression from V1 to V3 suggests a right inferior AP (Fig. 28.11). A well-evident right-sided pre-excitation pattern with positive QRS complexes in I and II, and a QR or qR configuration in III, suggests a right anterior (formerly lateral) AP location (Fig. 28.16). An evident right-sided pre-excitation pattern with positive QRS complexes in leads I, II and III suggests a right superior or right paraseptal (formerly anteroseptal) AP. Some of them are right superior and insert in the supraventricular crest apart from the AV node and His bundle, while others are close to the normal conduction system. They usually have an initial, low-amplitude, relatively broad r wave in V1–V2. The QRS complex of some peri-Hisian APs has three ECG characteristics: (1) although evidently pre-excited, it is not as wide as in superior right free-wall APs; (2) it is predominantly negative in V1 and V2 and positive in I, II, III; and (3) it adopts a characteristic deep negative 'w' shape in V1 and sometimes in V2 as well (Fig. 28.19).

ECG during tachycardia in WPW syndrome

The orthodromic AVRT has a rate generally ranging from 140 to 240 b.p.m. The QRS complex is usually narrow, in which case the P waves are visible and inscribed after the end of the ventricular complex (see Figs 28.13 and 28.14). Characteristically the RP is shorter than the PR (see Figs 28.3 and 28.14). In superior and posterior

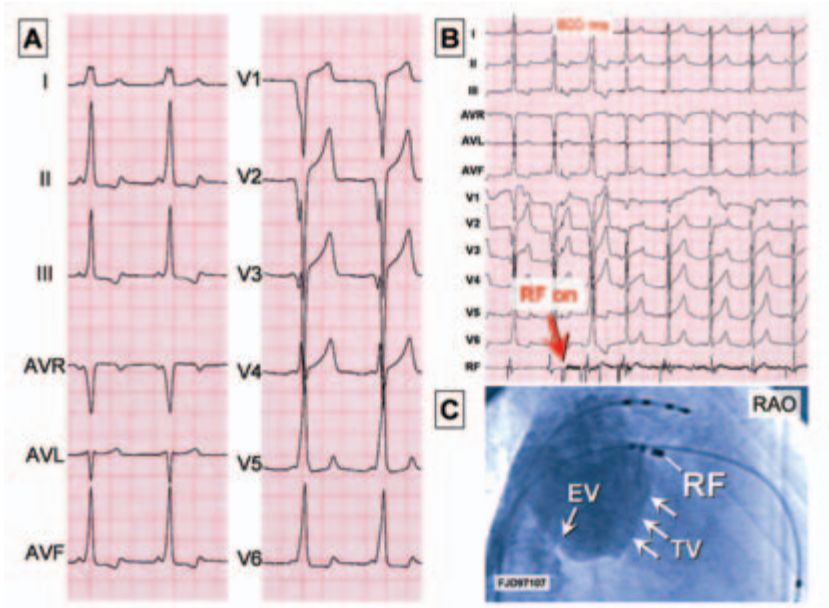

Figure 28.19 Wolff–Parkinson–White syndrome due to a peri-Hisian accessory pathway (AP). (A) The 12–lead ECG during sinus rhythm. Note that the QRS complexes are negative in V1 and V2. Two features are striking: the absence of an initial r wave in V1 and V2 (compare with Figs 28.10 and 28.15) and a 'w-shaped' morphology of the QRS in both leads. This feature, combined with the observation of positive QRS complexes in leads I, II and III, suggest a superior paraseptal location of the AP, and specifically a peri-Hisian course. Finally, note that the width of the QRS complex is 0.12 s, not as wide as with other 'right-sided' APs, including the right superior paraseptal when they have a cristal right ventricular insertion. (B) Disappearance of pre-excitation in less than 1 min after the onset of application of radiofrequency current. After the first non-pre-excited beat there are three QRS complexes that have an AV junctional origin. An accelerated AV junctional rhythm is frequently induced during application of radiofrequency current in peri-Hisian APs. The last beat shown is sinus and conducted without pre-excitation through the AV node–His pathway. (C) Fluorographic image showing the position of the ablation catheter at the site where the AP was coagulated (RF). Right atrial angiography permits identification of the limits of the tricuspid valve (TV) and the Eustachian valve (EV).

left-sided APs (formerly anterolateral or lateral), the retrograde P wave is negative in leads I and aVL and usually positive or isodiphasic in the inferior leads [25]. In inferior paraseptal, right inferior and left inferior APs, the P waves are negative in II, III and aVF. T waves may also be negative in these leads for the same AP locations due to cardiac electric memory. While AVRT using a left-sided AP usually has a predominant positive P wave in V1, those utilizing a right-sided bypass have a negative and bimodal P in V1. When AVRT has a wide QRS complex due to aberrant conduction or concomitant organic bundle branch block, P waves are usually hidden within the terminal forces of the QRS complex.

Antidromic AVRT are maximally pre-excited and P waves are either not visible or precede the QRS complex. The ECG of WPW patients during AF varies according to the electrophysiological properties of the AP and the AV node, the sympathetic tone, the number of APs and the concomitant antiarrhythmic medication (Fig. 28.18). There are patients showing only pre-excited QRS complexes (not infrequently with various degrees of pre-excitation), while others present a conventional AF with no signs of pre-excitation. In many instances AF manifests electrocardiographically as an irregular tachyarrhythmia with wide, pre-excited QRS complexes and a variable number of narrow ventricular activations. 'Capture' beats in a predominantly pre-excited recording of AF are not premature, as in ventricular tachycardia, but usually late as compared with the pre-excited QRS complexes.

Ventricular tachycardia is very rare in WPW syndrome. Bundle branch re-entry ventricular tachycardia exceptionally develops in patient with Ebstein's anomaly of the tricuspid valve. In a few patients with WPW syndrome, an AF with very rapid ventricular response via the AP can degenerate into ventricular fibrillation, particularly when more than one AV-conducting AP is present.

Electrophysiological studies

The aim of catheter-electrode mapping and stimulation studies in patients with WPW syndrome is (1) to confirm the existence of an AV-conducting AP in patients with non-evident WPW syndrome, (2) to establish the location and number of APs, (3) to study the AV and VA electrophysiological properties of the AP, (4) to investigate the mechanism of the tachycardias and (5) to evaluate

the potential risk to the patient. In the past, electrophysiological studies were also carried out to study the effect of antiarrhythmic drugs on the AP, a type of evaluation seldom performed today. A systematic repeat study in patients who have been subjected to catheter ablation is unnecessary. Only in the occasional patient who after RFCA continues to complain of palpitations with a sudden onset is an electrophysiological study required to elucidate the nature of these symptoms.

Treatment

The acute treatment of an episode of orthodromic AVRT consists of vagal manoeuvres and if they fail intravenous adenosine. If the patient is known to have WPW syndrome, the physician may prefer not to use adenosine because it may induce AF. Intravenous flecainide, propafenone or procainamide can be used instead. In patients with AF or pre-excited tachycardias, intravenous flecainide, propafenone, procainamide or ibutilide is the drug of choice. Alternatively, it is possible to proceed to DC-shock cardioversion directly. If the patient is under 60 years old, there are no associated risk factors for systemic embolization and AF has lasted for less than 48 h, electrical cardioversion does not require anticoagulation or a transoesophageal echocardiographic examination. In patients with pre-excited tachycardias, AV nodal-acting drugs should not be used.

The treatment of choice to prevent tachycardia recurrences in WPW patients is catheter ablation. Until the latter intervention is performed, or in patients who refuse the procedure, class IC drugs, amiodarone or sotalol can be used if the frequency and duration of the attacks or the severity of symptoms during the tachyarrhythmia justify constant pharmacological treatment. In the selection of drugs, factors such as age and presence of associated cardiac disorders should be considered. Digitalis, verapamil and diltiazem should be avoided in patients with WPW syndrome. The ability of beta-blockers to prevent tachycardia recurrences in WPW syndrome has not been studied but these agents do not act on the AP and the patient would not be protected if AF supervenes [1,108,109,113]. Class I antiarrhythmic drugs and amiodarone may prolong the anterograde refractory period of the AP, with little change in the retrograde refractory period of the anomalous bundle. This situation can facilitate the induction of orthodromic AVRT and the patient may have an increased number or episodes of palpitations, which although being slower may be more prolonged [113].

Patients in whom chronic antiarrhythmic drug treatment is clearly not indicated include (1) those with infrequent symptomatic episodes, (2) those who have already had recurrences or adverse effects on antiarrhythmic drugs, (3) women considering pregnancy, (4) people with professions or life-styles of risk and (5) those with severely symptomatic episodes or who have been resuscitated from a cardiac arrest.

Radiofrequency catheter ablation

RFCA is the treatment of choice for patients with WPW syndrome and represents cure of the problem (see Table 28.2, Figs 28.16 and 28.17). Single-centre and multicentre studies, and registry reports on RFCA of APs, have shown that this technique safely and effectively abolishes conduction over the bypass tract [116–120]. The success rate in experienced centres is > 98%, with a recurrence rate of about 2–3%, with no mortality and minimal morbidity. Less experienced centres may not be able to offer the same figures and may even have some mortality. Patients with Ebstein's anomaly or other congenital heart disorders are complex and should be referred to experienced centres for ablation. Also complex can be RFCA of some APs within the pyramidal space and in patients with multiple APs or with additional mechanism for tachycardias (usually AVNRT or AFL). Connections between the atrial appendages and the ventricles can be ablated with conventional endocardial catheter techniques.

Left-sided APs are usually ablated using a retrograde aortic approach but can also be ablated with a left-atrial trans-septal method. RFCA of APs related to the left atrial appendage requires trans-septal catheterization. Septal, superior paraseptal and right-sided APs are ablated from the right side of the heart. Inferior paraseptal APs related to the ostium and proximal portions of the coronary sinus and the middle cardiac vein can be ablated from the right side. The rest of the inferior paraseptal APs and exceptionally some true septal (midseptal) APs are best ablated from the left side of the heart. APs related to a coronary sinus diverticulum are ablated from the right side. A venous diverticulum may be seen in a few patients with WPW syndrome and inferior paraseptal APs, but may also be seen in association with right inferior and left inferior APs. The presence of a coronary sinus diverticulum in WPW syndrome does not imply that the AP is anatomically related to this structure.

The recurrence rate after ablation is slightly higher for right-sided than for left-sided APs. The rate of major complications in relation to RFCA in patients with APs is low (0.6%) [67]. Superior paraseptal and peri-Hisian APs have a certain risk for accidental induction of block of the normal AV node–His pathway. In these instances, apart from careful catheter-electrode mapping to localize the AP, RFCA is applied with care, starting with temperatures of about 40°C and which are slowly increased thereafter. Complications can be related to the vascular access

(haematoma, arterial pseudo-aneurysm, arteriovenous fistula, pneumothorax), catheter manipulation (cardiac perforation with pericarditis and eventually tamponade, valvular damage, embolic events, aortic or coronary artery dissection) or delivery of radiofrequency energy (AV block, myocardial perforation, coronary artery spasm or occlusion, embolic events) [1,67,116–120]. Cardiac tamponade can be prevented by avoiding excessively deep levels of heparinization during the procedure, maintaining the activated plasma thromboplastin time between two and three times the control values in left-sided procedures. No heparin is used for right-sided approaches.

Successful RFCA of the AP prevents the recurrence of AVRT. AF recurrences are also prevented with RFCA in relatively young patients with WPW syndrome but less efficiently in subjects ablated at ages over 50 years [121].

The ablation of asymptomatic patients with a WPW pattern is controversial. Young patients engaged in competitive sports or with certain professions (pilots, divers) prefer to be cured. If pre-excitation is persistent and conduction over the AP remains patent during exercise, an electrophysiological study can be performed to further elucidate the risk profile [114]. Tachyarrhythmias can be induced in up to 29% of asymptomatic WPW patients when subjected to programmed stimulation, and 15% develop AVRT or AF during follow-up [114]. In a study by Pappone *et al*., asymptomatic but inducible WPW patients aged ≤ 35 years were randomized to RFCA of the AP or to no treatment. During a median follow-up of 27 months, 5% of the ablated patients and 60% of controls had arrhythmic events [122]. More recently, the same group has completed a randomized study in asymptomatic children with WPW aged 5–12 years and in whom AVRT or AF were inducible during an electrophysiological study. During follow-up, arrhythmic events occurred in 5% of children in the ablation group and in 12% of controls. Two children in the control group had VF, and a 10-year-old boy died suddenly. Arrhythmic events also occurred during follow-up in 8% of the patients without inducible AVRT or AF [123].

Pre-excitation due to Mahaim physiology

Definition and pathogenesis

In 1971 Wellens described an 8-year-old boy with a PR interval of 0.12 s and minor 'type B' pre-excitation during sinus rhythm who developed a wide QRS-complex tachycardia with LBBB configuration [88]. Wellens initially postulated that a nodoventricular Mahaim tract was involved in this form of pre-excitation, but subsequently it has been demonstrated that the conduction bypass in these patients usually consists of a right free-wall anomalous node that continues with an accessory His–Purkinje system distally inserting at the normal right bundle branch or directly at the right ventricular myocardium (see Fig. 28.14C). The term 'Mahaim physiology' frequently used for this condition is a misnomer, since what Mahaim described were nodoventricular and fasciculoventricular connections [124]. The incidence of this form of pre-excitation is low, representing < 1% of all cases of patients with APs studied in the electrophysiology laboratory. These types of APs are often encountered in patients with Ebstein's anomaly of the tricuspid valve.

Diagnosis

There are two electrocardiographic patterns of this form of pre-excitation during sinus rhythm, one with non-evident pre-excitation and the other with a normal PR interval and incomplete LBBB pattern with slightly patent delta wave slurring the initial forces of the QRS complex (Fig. 28.20). Sternick *et al*. recently described that in patients suffering from paroxysmal tachycardia an rS pattern in lead III during sinus rhythm should make one suspicious of an atriofascicular fibre [125]. These patients may develop recurrent attacks of paroxysmal tachycardia having a wide QRS complex with LBBB configuration, and left-axis deviation in the frontal plane. Atrial pacing at increasing rates results in progressive ventricular pre-excitation that finally reproduces the QRS morphology observed during tachycardia. The observation that right atrial pacing pre-excites the ventricles at slower rates than left atrial pacing, and that pre-excitation may disappear during coronary sinus left atrial pacing, indicates that the proximal insertion of the AP is in the right atrium. Following atrial premature stimuli with decreasing coupling intervals, the degree of pre-excitation of the QRS complex progressively increases and AV conduction times become gradually longer, thus showing the decremental conducting properties of the AV bypass. Retrograde conduction over the AP has not been convincingly demonstrated and is typically absent. Tachycardia in these patients is due to a re-entry mechanism utilizing the decrementally conducting AP in AV direction and the bundle branch–His–AV nodal system as retrograde limb of the circuit (a form of antidromic AVRT) or to a coexisting AVNRT using the decrementally conducting AP as an anterograde bystander (see Fig. 28.14D). Exceptionally an AVRT may use the decrementally conducting AP in anterograde direction and a second, conventional, anomalous AV pathway retrogradely. Patients with this

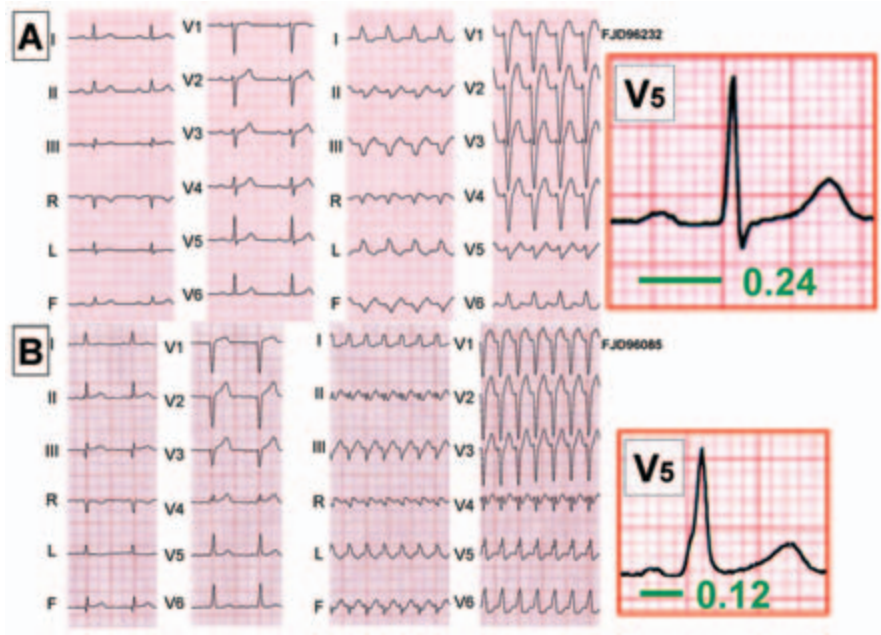

Figure 28.20 ECG of pre-excitation due to atriofascicular accessory pathways. (A, B) Two different patients showing non-evident pre-excitation during sinus rhythm (A) and atypical pre-excitation during sinus rhythm (B). The ECG in lead V5 has been amplified on the right, showing that in (A) the PR interval measures 0.24 s and the QRS complex is narrow, whereas in (B) the PR interval is 0.12 s and the QRS complex shows a kind of incomplete left bundle branch block (LBBB), with slurring of the initial forces. In both instances, the patient developed tachycardias that had a wide QRS complex with an LBBB configuration and left-axis deviation (see text).

syndrome may also develop AF that usually presents AV conduction over the AP with maximally pre-excited QRS complexes.

The site of earliest ventricular activation during right ventricular endocardial catheter-electrode mapping is generally found at the apical one-third of the right aspect of the interventricular septum. At various distances from this site and towards the right free-wall AV ring, it is possible to register Purkinje-like deflections (frequently referred to as Mahaim potentials) preceding the onset of the QRS complex. Mapping the proximal insertion of the AP from the atrial side of the tricuspid annulus can result in catheter-induced block of the anomalous bundle. Mechanical block of the AP may persist for several hours even after isoprenaline infusion.

Treatment

The treatment of choice in these patients is RFCA of the AP. Several approaches have been suggested for guiding RFCA in this syndrome (catheter-induced mechanical block of the AP or identification of the Mahaim potentials) [125–129]. Distal segments of the AP close to its ventricular exit probably branch and are inappropriate targets for RFCA, with only temporary success [128]. Performing the ablation at sites where the Mahaim potential precedes the onset of a maximally pre-excited QRS complex by ≥ 20 ms avoids the more proximal areas that may be encased by a shield of connective tissue and the more distal, potentially branching, portions. Approaching the atrial insertion frequently provokes long-lasting mechanical block, thus making the ablation procedure more difficult.

Concealed accessory pathways

Definition

Patients with an AP that only conducts in the retrograde direction have no pre-excitation during sinus rhythm but may develop an AVRT that utilizes the AV bypass tract as retrograde limb of a re-entry circuit. AVRT using a concealed AP is the underlying mechanism of 27% of the tachycardias in patients with paroxysmal SVT and without pre-excitation during sinus rhythm [130].

Pathogenesis

The reasons why an AP is concealed and conducts only in retrograde direction are still a matter of debate. Mismatch impedance and interconnections and interactions among the branches of bypass tracts at their atrial and ventricular insertions may play a role in the pathogenesis of permanent unidirectional anterograde block in concealed APs. Concealed APs are more frequently related with the left AV ring but right-sided concealed APs also exist.

Diagnosis

This arrhythmia is slightly more prevalent in males than in females, and the age of onset of symptoms is 25 ± 17 years [76]. Most patients have no organic heart disease but if present the profile is similar to that of patients with WPW syndrome. The ECG during sinus rhythm may be normal or show a short PR interval that is due to enhanced AV nodal conduction [130]. Tachycardia usually has a narrow QRS complex and differs from the orthodromic AVRT of patients with WPW in the lack of T-wave changes related to electric cardiac memory. P waves are usually identified following the QRS complex, with RP < PR (see Fig. 28.3). As already stated, the differential diagnosis of this tachycardia is the rare type B, slow–slow AVNRT, a distinction that has practical therapeutic implications for the interventional approach with RFCA (see Figs 28.9 and 28.10). There may be ST-segment depression, particularly if the rate is > 160 b.p.m. RR intervals may all be the same or present alternating cycle lengths. The amplitude of the QRS complex may be constant or show voltage alternans. RR or voltage alternans are more frequently observed in AVRT using an AP than in AVNRT, but they do not exclude the latter, particularly if the rate is > 170 b.p.m. (see Fig. 28.8C).

Treatment

Vagal manoeuvres should be tried to terminate the tachycardia. If unsuccessful, intravenous adenosine should be administered. In this case, concerns regarding the risk of induction of AF do not apply since the AP does not conduct in AV direction.

RFCA is the treatment of choice for the prevention of recurrences. Although there are some technical differences in the ablation of patent and concealed APs, the results and complications are practically the same. Some elderly people may refuse to undergo RFCA. In about 50% of patients with AVRT using a concealed AP, recurrences can be prevented with oral propafenone, flecainide or amiodarone. If the weakest link of the AVRT pathway is the AV node, beta-blocking agents may prevent recurrences. Amiodarone must be considered the last resort when a chronic pharmacological approach is adopted. Propafenone and flecainide may be less appropriate in elderly patients. The 'pill-in-the-pocket' approach is frequently less effective in patients with concealed APs than in those with AVNRT. When episodes of AVRT using a concealed AP are very long-lasting, the conductivity of the AV node and of the AP is usually very good and less sensitive to the effects of antiarrhythmic agents.

Permanent junctional reciprocating tachycardia

Definition

In 1967 Coumel *et al*. described the electrocardiographic characteristics of PJRT, in which the retrograde limb of the re-entry pathway had long conduction times and decremental conducting properties [90]. PJRT is an unusual arrhythmia. Both genders are equally affected and patients with this arrhythmia are usually identified at ages under 50 years.

Pathogenesis

Coumel *et al*. initially thought that PJRT was a fast–slow AVNRT but later they found that the lower common pathway was extranodal, postulating the involvement of a nodoventricular fibre or the existence of longitudinal dissociation within the bundle of His [131]. Subsequently, it was demonstrated that the retrograde limb of the re-entry circuit of PJRT was an inferior paraseptal AV bypass tract with long conduction times and decremental conducting properties [132]. A fibromuscular bundle with a long tortuous course has been found in the only reported necropsy specimen of PJRT (see Fig. 28.14E,F) [97]. These APs were considered 'concealed' but they may have potential for anterograde conduction which does not manifest itself during sinus rhythm due to their very long anterograde conduction times [97]. This is not always the case since in some patients a ventricular premature beat during sinus rhythm at a time when the His bundle is refractory can result in VA conduction via the retrograde slow AP, thus excluding anterograde concealed conduction over the AP.

Diagnosis

Clinical consequences

At rest, despite being in tachycardia, most patients do not perceive palpitations or only notice the scanty normal sinus beats that from time to time are observed between bursts of the arrhythmia. Patients frequently offer a long history of palpitations on exertion or with psychological stress. A few patients have syncope, most likely of vasovagal origin. Cardiomegaly and echocardiographic signs of mild-to-moderate systolic left ventricular dysfunction can be seen in 50–60% of cases [4]. These patients may complain of decreased exercise tolerance or frank dyspnoea on exertion. Some patients are referred

to tertiary centres with the diagnosis of dilated cardiomyopathy [4]. Today this situation is preventable with early treatment with RFCA.

Electrocardiographic diagnosis

PJRT usually has a narrow QRS complex and visible P waves, with PR < RP. P waves are negative in inferior leads and frequently in V6 (Fig. 28.21). There are instances in which the RP and PR intervals have a similar duration and the P wave is in the middle of two consecutive QRS complexes. The rate of PJRT varies from 90 to 250 b.p.m. depending on the autonomic tone. During sleep, PJRT may slow down or even disappear. At rest, tachycardia may be incessantly present or runs of different duration alternate with a few sinus beats. During physical or psychological stress, PJRT becomes truly incessant and its rate accelerates.

At the onset of tachycardia the first RP interval is frequently shorter than the subsequent ones, and in some patients transient oscillations of the RP/PR intervals and of the resulting cycle lengths of the tachycardia can be observed. A few patients show alternating long-to-short RR intervals during tachycardia with an almost constant PR interval and oscillating RP times. The QRS width ranges from 80 to 100 ms and may occasionally show LBBB. Frequent spontaneous tachycardia terminations can be observed, particularly at rest, usually in the form of a QRS complex not followed by a P wave. The VA conduction time is shortened by isoprenaline, atropine and exercise, is prolonged by verapamil and is not affected by ajmaline.

From the electrocardiographic point of view, PJRT is similar to AT and to the uncommon fast–slow AVNRT (see Fig. 28.3). The induction of AV block by vagal or pharmacological manoeuvres without interrupting the tachycardia at the atrial level would indicate an atrial origin. Vagal manoeuvres may terminate PJRT temporarily, usually by inducing retrograde conduction block. The continuously recurring nature of PJRT is very seldom observed in fast–slow AVNRT.

Electrophysiological diagnosis

The complexities of electrophysiological studies in PJRT have been reviewed elsewhere [4,25,89,130,132]. In most PJRTs, an inferior paraseptal AP with long conduction times and decremental conducting properties is demonstrated. Other cases have a left inferior or postero-inferior atrial insertions [4]. Exceptionally, PJRT is based on a fast–slow AV nodal re-entry mechanism.

Treatment

Because of the incessant nature of the tachycardia, no acute treatment should be used in these patients. Due to the risk of developing a tachycardiomyopathy, it is recommended that most asymptomatic patients, as well as all patients with signs of left ventricular dysfunction, should undergo RFCA (Fig. 28.21) [133].

Other non-paroxysmal SVT

Ectopic junctional incessant tachycardia

This type of SVT, first described by Coumel *et al*. in 1976 [134], is also termed 'congenital' when discovered during the first 6 months of life [4]. Congenital junctional ectopic incessant tachycardia has a poor prognosis, with systolic left ventricular dysfunction, heart failure and early death [135]. The ECG shows narrow QRS-complex tachycardia at rates of 140–300 b.p.m. with AV dissociation and exceptionally with intermittent VA conduction. Amiodarone seems to be the drug of choice in these infants, particularly if the tachycardia is fast or when its rate cannot be reduced below 150 b.p.m. with the combination of digoxin and propranolol [4]. Flecainide and propafenone have been reported to slow the tachycardia rate, whereas verapamil causes acceleration of the tachycardia [136]. There are anecdotal reports of successful RFCA of this tachycardia with preservation of AV nodal conduction [137].

Non-paroxysmal junctional tachycardia

NPJT is an accelerated AV junctional rhythm originating at the level of the bundle of His or at the AV node and its approaches. It is usually observed in digitalis intoxication, acute myocardial infarction and in the postoperative period following open heart surgery. Today, runs of this rhythm are observed during the application of radiofrequency current to ablate AVNRT or APs close to the AV node or the His bundle (see Figs 28.10 and 28.19). Although enhanced automaticity may be the underlying mechanism, other causes cannot be excluded. In this regard the term 'focal junctional tachycardia' may be more appropriate [1]. Electrocardiographically, it is characterized by prolonged runs of an accelerated junctional rhythm, at rates of 70–140 b.p.m. During the arrhythmia there is AV dissociation or VA conduction. When there is AV dissociation we can observe capture beats. The QRS complex is narrow except for patients who have an organic bundle branch block. Focal NPJT is usually asymptomatic and does not require treatment.

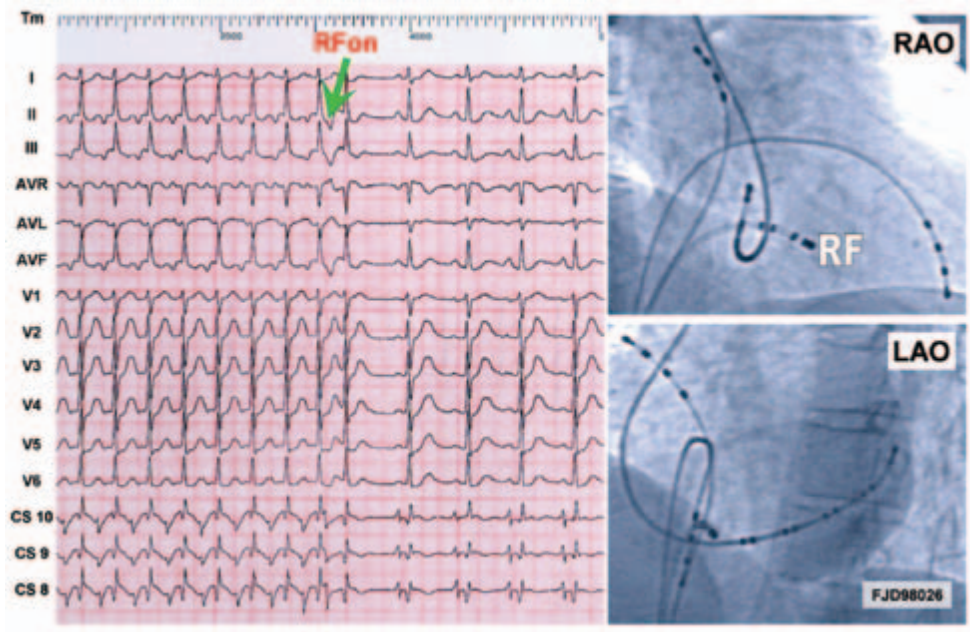

Figure 28.21 ECG of permanent junctional reciprocating tachycardia. This young patient had an incessant almost permanent tachycardia. Immediately after initiation of the pulse of radiofrequency current (which actually advances the atrial activation), tachycardia was not only terminated by block in the retrograde limb of the re-entry pathway but also could not be re-induced again, either spontaneously or with programmed stimulation. Note that during tachycardia the P waves are negative in the inferior leads and in the left lateral precordial leads. The PR interval is shorter than the RP time. On the right are the fluorographic images depicting the position of the ablation catheter (RF) at the site of abolition of conduction over the accessory pathway in the inferior paraseptal area or midseptal (septal) region, just anterior to the ostium of the coronary sinus. RAO, right anterior oblique; LAO, left anterior oblique.

Personal perspective

In few areas has medical progress been more evident during the last 35 years than in the field of SVT. Catheter mapping and stimulation studies performed by a handful of talented pioneers defined the site of origin and pathway of SVT and provided new electrocardiographic signs to diagnose these electric heart disorders. This emerging knowledge and the determination to find a permanent cure for SVT led to the development of ablation techniques, first with surgery and then with catheters. This is a young page in the history of cardiovascular medicine and most of those who made the greatest contributions are still alive. Some, however, have passed away, like Dirk Durrer from Amsterdam and Philippe Coumel from Paris, who in 1967 introduced, simultaneously but independently, the technique of programmed electrical stimulation, one of the foundations on which the investigations that followed in the subsequent three decades built up.

Predicting the future is always difficult. When in 1980 SVT surgery was at its summit, few could forecast that its expiry was only 7 years away. Arrhythmology in general and SVT in particular will be explored from viewpoint of molecular biology, genetics and proteomics. CTI-dependent AFL will become more prevalent due to the longer life expectancy of the population. The strong diagnostic power of the 12-lead ECG will be maintained and hopefully enhanced with future investigations. Interventional arrhythmologists will be helped with newer tools that facilitate more precise, less operator-dependent, catheter manipulation. However, the fine art of electrophysiological diagnosis, a blend of catheter mapping and stimulation criteria, is probably more responsible for operator-dependent results than manual skills. This kind of knowledge, the basis for the current golden age of cardiac arrhythmology, must be reinforced today so that it is not lost tomorrow.

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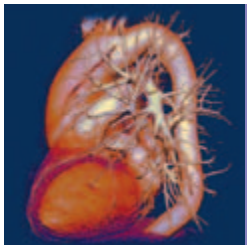

29 Atrial Fibrillation: Epidemiology, Pathogenesis and Diagnosis

Harry J.G.M. Crijns, Maurits A. Allessie and Gregory Y.H. Lip

Summary

The most important threats patients with atrial fibrillation (AF) face are stroke and heart failure. Furthermore, quality of life is diminished due to AF symptoms as well as frequently associated cardiovascular diseases like hypertension, heart failure, coronary artery and valvular disease. Hypertension is the commonest cause and AF is more likely to develop if left ventricular hypertrophy is present. Heart failure may also lead to AF and the risks of stroke in both conditions are additive. Familial AF is becoming more and more recognized as a significant cause of AF but genetic diagnosis and tailored treatment are still remote.

AF mechanisms include focal activity and re-entry, which are clinically difficult to differentiate although focal AF may be recognized from the surface ECG. A re-entrant mechanism is likely in case of coexistent flutter or when the atria are remodelled. Combinations of mechanisms occur frequently.

AF is associated with electrophysiological, contractile and structural remodelling. In most patients structural remodelling occurs long before onset of AF, while in sinus rhythm. This happens in the setting of long-standing hypertension with diastolic dysfunction and chronic atrial stretch. Once present, AF may reinforce itself by inducing electrical remodelling, i.e. shortening of refractoriness due to the high atrial rate ('AF begets AF'). Atrial remodelling in the setting of long standing AF or significant underlying heart disease is associated with failure of antiarrhythmic drugs and electrical cardioversion. In addition, structural and contractile remodelling promote atrial thrombus formation.

Arrhythmia management should be based on a firm clinical characterization of the patients. It must be guided by (a) stroke and bleeding risk factors, (b) symptoms and (c) if a patient is symptomatic by (i) stage of remodelling, (ii) type and (iii) triggers of AF and (iv) the likely arrhythmia mechanism. Up till now, diagnosis and management has relied heavily on characterizing and controlling the arrhythmia itself. However, the very first step a clinician should take is to check stroke and bleeding risks and start antithrombotic treatment if needed. Anticoagulation must be given to all AF patients who possibly have a remodelled thrombogenic left atrium like patients with previous stroke, heart failure and hypertension. Rhythm control should be reserved for symptomatic patients without significant atrial remodelling. Paroxysmal AF needs a different approach than persistent or permanent AF. Concerning triggered AF, in vagal AF a betablocker should be avoided whereas in adrenergic AF this is the drug of first choice.

Epidemiology

Atrial fibrillation (AF) is the commonest sustained cardiac rhythm disorder and is responsible for substantial mortality and morbidity due to stroke, thromboembolism, heart failure, reduced quality of life and impaired cognitive function. This arrhythmia is commonly seen in everyday practice. Indeed it is seen in the context of acute cardiological emergencies as well as in many non-cardiac conditions.

In terms of hospitalization for cardiac arrhythmias, AF is by far the commonest cardiac rhythm disorder [1]. In

a study of acute general medical admissions to a Scottish district general hospital, AF was present in approximately 6% [2]. The presence of AF results in the prolongation of hospital stay, especially postoperatively, and particularly with cardiac surgery. This results in increased morbidity as well as health-care costs.

It should be noted that the epidemiology of AF is predominantly based on Caucasian populations; only limited information is available from non-Caucasian cohorts [3]. Furthermore, there are many differences in the clinical epidemiology of AF based on the type of population studied. For example, studies based on hospital populations tend to have ischaemic heart disease as the underlying aetiological diagnosis, as many such patients tend to be more unwell or have greater comorbidity. In contrast, community or population-based studies tend to list hypertension as the commonest underlying aetiological factor for AF.

Prevalence

There are many common denominators associated with the prevalence of AF. Firstly, AF is more common with increasing age. Since the general population is becoming older, the prevalence of AF correspondingly increases. The improved management of many cardiac disorders, such as heart attack and heart failure, results in greater survival of such patients who subsequently develop AF in later life.

Figure 29.1 illustrates two population-based natural history studies, which clearly show that the prevalence of AF markedly increases after the age of 60 [4,5]. Furthermore, secular trends in the prevalence of AF in subjects aged 65–84 years old appear to show that AF has become more common over the last few decades, particularly among men. In the Framingham study, the prevalence of AF between 1968 and 1970 was 3.2% and this rose consistently to 9.1% between 1987 and 1989 [6]. In women, secular trends in the prevalence of AF show a fairly similar degree of consistency over the years studied. In contrast, the Renfrew–Paisley study reported that the rate of new incident cases of AF detected during rescreening of 8532 men and women showed an increase in both sexes [7].

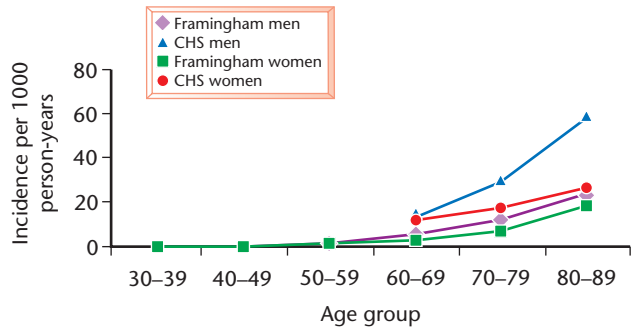

Figure 29.1 Incidence of atrial fibrillation in the Framingham Heart Study [4] and the Cardiovascular Health Study (CHS) [5].

A study of hospital admissions with AF based on Scottish hospital health-care statistics also shows an increasing prevalence of AF among hospital admissions over the last decade, with a clear age gradation, the greatest increase being seen among the elderly with AF [8] (Fig. 29.2).

Incidence

As with prevalence, the incidence of AF also increases with increasing age. In the Renfrew–Paisley study, the rate of incident AF detected during the rescreening of over 8500 men and women (with 34 891 person-years of follow-up) was 0.4 new cases per 1000 person-years in subjects aged 45–49 compared with almost 2.0 new cases per 1000 person-years in subjects aged 60–64 years [7].

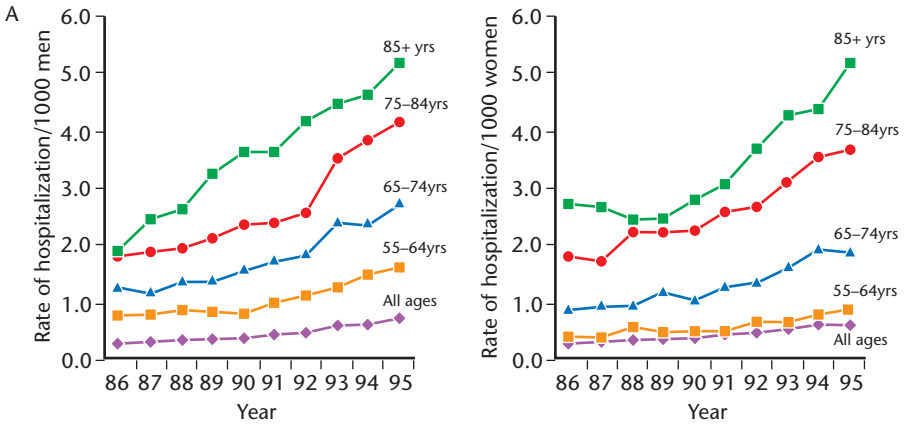

Figure 29.2 Increasing prevalence of atrial fibrillation among first-ever hospital admissions between 1986 and 1995. The greatest increase is seen among the elderly. (A) men; (B) women. Reproduced with permission from Stewart *et al.* [8].

Associations with AF

Table 29.1 shows an overview of causes of AF. AF frequently coexists with common conditions, both cardiovascular and non-cardiovascular. AF also occurs independently in otherwise healthy individuals. As highlighted earlier, there are differences based on the population studied, whether hospital-based or community-based.

In a community study in Rochester, Minnesota, an epidemiological study on the prevalence of AF and comorbidity conditions in 1871 subjects with ischaemic strokes and matched controls reviewed the increasing prevalence of AF during the 1960s, 1970s and 1980s; the commonest comorbid condition in this population was hypertension, followed by coronary heart disease and previous myocardial infarction. Not surprisingly, heart failure, diabetes, valvular heart disease and cardiac surgery were other common conditions [9].

In hospital-based studies, comorbidity conditions such as heart failure and ischaemic heart disease are prevalent. In one study based on the national hospital discharge survey that examined comorbidities among adults aged over 35 years of age hospitalized in 1999 with AF, essential hypertension, ischaemic heart disease and congestive cardiac failure were the commonest comorbidities; the prevalence of all three was greater in those over 65 years of age [10].

Table 29.1 Cardiovascular and non-cardiovascular causes of atrial fibrillation

Lone atrial fibrillation
Focal atrial fibrillation
Pulmonary vein focal activity
Right and left atrial, caval vein foci
Genetic causes: channelopathy
Atrial pressure elevation
Systemic hypertension
Pulmonary hypertension (pulmonary embolism)
Mitral or tricuspid valve disease
Myocardial disease, cardiomyopathy (primary or secondary, leading to systolic or diastolic dysfunction)
Semilunar valvular abnormalities (causing ventricular hypertrophy)
Intracardiac tumours or thrombi
Atrial ischaemia: coronary artery disease
Inflammatory or infiltrative atrial disease
Pericarditis
Amyloidosis
Myocarditis
Age-induced atrial fibrotic changes
Intoxicants
Alcohol
Carbon monoxide
Increased sympathetic activity
Hyperthyroidism
Phaeochromocytoma
Anxiety
Alcohol
Exertion-induced
Drugs
Increased parasympathetic activity
Primary or metastatic disease in or adjacent to the atrial wall
Postoperative
Cardiac and pulmonary surgery
Pericarditis
Cardiac trauma
Hypoxia
Pneumonia
Congenital heart disease, particularly atrial septal defect
Neurogenic: subarachnoid haemorrhage

Hypertension

At a population or community level, hypertension is the commonest aetiological cause of AF. Certainly if we examine AF among some ethnic groups (see later), hypertension is the commonest associated medical condition in AF among Afro-Caribbeans [11]. Prospective studies clearly show a relation between hypertension and AF. Verdecchia *et al*. [12] demonstrated that AF is more likely to develop in hypertensive subjects who were initially in sinus rhythm, especially if echocardiographic left ventricular hypertrophy is present. The 5-year risk of chronic AF in hypertensive subjects is highest in those with the greatest left ventricular mass and largest left atrial diameter [12].

Heart failure

Depending on the severity of heart failure, AF can be present in 10–50% of patients with heart failure, with the highest prevalence seen among those with NYHA grade IV heart failure [13]. Figure 29.3 illustrates the prevalence of AF in clinical trials that examined heart failure. The prevalence of AF was low in those with mild heart failure

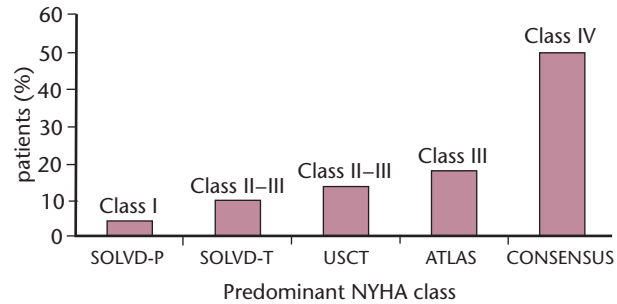

Figure 29.3 Prevalence of atrial fibrillation in heart failure studies. Reproduced with permission from Khand *et al*. [13].

compared with those with severe heart failure. The presence of AF may increase the mortality and morbidity associated with heart failure, and the risk of stroke and thromboembolism in both conditions are additive.

Tachycardiomyopathy

Tachycardiomyopathy indicates that AF may result in heart failure. It may be difficult to recognize this form of congestive heart failure. The diagnosis is made when underlying cardiac disease is absent and cardiac function improves after termination of the arrhythmia or control of the ventricular rate. According to this definition, all patients with AF show some degree of cardiomyopathy [14]. A significant subset of patients who are thought to have idiopathic dilated cardiomyopathy may in fact have tachycardiomyopathy.

Valvular heart disease

AF has traditionally been associated with mitral valve disease, particular mitral stenosis. Although rheumatic fever is becoming less common in the Western world, on a world-wide basis valvular heart disease is still a common aetiological factor for AF. The presence of mitral valve stenosis increases the risk of stroke and thromboembolism in AF 18-fold. Aortic valve stenosis or regurgitation may cause AF through left ventricular hypertrophy and atrial dilatation. The prevalence of AF in aortic stenosis or regurgitation is low.

Coronary artery disease

In patients with uncomplicated coronary artery disease, AF is relatively uncommon. Nonetheless in the context of associated myocardial infarction, especially if there is impaired left ventricular function, the prevalence of AF rises significantly. Certainly the presence of AF after myocardial infarction is an important adverse prognostic factor [15,16].

One common denominator within the above conditions is diastolic dysfunction with raised diastolic pressures. In a cohort study, it appeared that among patients with abnormal left ventricular diastolic relaxation, AF is much more common [17].

Hyperthyroidism

AF occurs in 10–25% of patients with hyperthyroidism [18,19]. Male sex, increasing age, ischaemic heart disease, congestive heart failure and heart valve disease predispose to AF in hyperthyroidism [19]. Patients with hyperthyroidism seem to have a high prevalence of pulmonary hypertension and atrioventricular valve regurgitation, which is reversible after correction of thyroid function [20]. Breakthrough arrhythmias while on amiodarone may relate to hyperthyroidism induced by this agent. The risk of stroke is high in hyperthyroidism complicated by AF and therefore anticoagulation is generally recommended. Recent data in murine experimental hyperthyroidism showed increased delayed rectifier ion channel activity especially in the right atrium, potentially producing dispersion of refractoriness and hence AF [21]. Subclinical hyperthyroidism (serum thyroid-stimulating hormone < 0.1 mU/l) is associated with an increased prevalence of AF, although it is uncertain whether treatment of hyperthyroidism prevents AF [22].

Pulmonary disease

AF occurs frequently in patients with chronic obstructive lung disease [23,24] and is associated with an adverse prognosis in patients with exacerbations [25]. Unfortunately, drugs commonly used in this situation, such as theophylline and beta-adrenergic drugs, can precipitate AF and cause uncontrolled ventricular rate responses. The prevalence of pulmonary disease in patients with persistent AF is relatively high (15–20%) [26]. In the Copenhagen City Heart Study, it was found that reduced lung function is an independent predictor for incident AF [27].

Ethnicity

The literature on ethnic differences in AF is limited. In a prevalence study among a multi-ethnic community in Birmingham, England, hypertension was the commonest aetiological factor among Afro-Caribbeans; in contrast, coronary artery disease was the commonest aetiological factor among Indo-Asians [11]. In the general practice catchment population of this hospital study, there was also a low prevalence of AF among non-Caucasian subjects, with AF being present in only 0.6% of Indo-Asian patients aged over 50 years [28].

Similar ethnic differences are seen in North America. One study of 1373 heart failure patients found a prevalence of AF of 3%, but this was much lower among African-Americans (19.7%) compared with whites (38.3%) [29]. When compared with Caucasians, African-Americans were younger, had more hypertension and had more prior diagnosed heart failure [29]. In the AFFIRM study, ethnicity was examined in an analysis of Caucasians, African-Americans and Hispanics: the African-American and Hispanic subjects were younger, and African-Americans had less ischaemic heart disease but a greater prevalence of hypertension and heart failure. In contrast, Hispanics were younger but had a similar prevalence of ischaemic heart disease and hypertension to Caucasian subjects [30].

Familial AF

In some patients AF appears to run in families. The results have been inconsistent, suggesting that more than one gene may be involved. In familial AF, genetic abnormalities may cause electrical changes directly or indirectly through structural abnormalities. For example, Brugada *et al*. [31] described a family of 26 members of whom 10 had familial AF, segregating as an autosomal dominant disease. Genetic linkage analysis has localized the gene responsible to chromosome 10q in the region 10q22–q24, which may contribute to the substrate for development of AF. Chen *et al*. [32] discovered a gain-of-function gene mutation leading to short atrial refractoriness in one Chinese family.

An example of an indirect genetic defect is AF secondary to one of the many familial cardiomyopathies. There is also a concept that AF is related to an ageing process in the atrial myocardium. A recent paper by Lai *et al*. [33] suggested that AF is commonly associated with accumulation of ageing-related common-type mitochondrial DNA deletion mutation in human atrial tissue. Indeed, the amount of mitochondrial DNA^{4977} correlated positively with the age of the patients, those with AF having the highest amount of these mitochondrial DNA deletion mutations compared with patients without AF in the same age group. Recently, genetic polymorphisms have been related to AF, including the *minK* and the renin–angiotensin gene polymorphisms [34,35].

'Lone' AF

This refers to AF in the absence of detectable associated medical conditions. In the Olmsted County study it referred to patients under 60 years of age without clinical or echocardiographic evidence of cardiopulmonary disease [36]. The more one looks, the fewer 'lone' AF patients one finds. By convention, the term 'non-valvular AF' is restricted to AF in the setting of rheumatic mitral valve disease or a prosthetic heart valve.

Mortality and morbidity

One aspect of the importance of AF is the high mortality and morbidity associated with this cardiac arrhythmia. These can be subdivided into haemodynamic, thromboembolic and treatment causes. Increased morbidity is translated into higher hospitalizations [10], especially among the elderly population (Fig. 29.2). This leads to fewer patients being discharged to their own home and more subjects requiring long-term care. Mortality associated with AF is clearly demonstrated from surveys such as the Framingham Study. AF was associated with an odds ratio for death of 1.5 (95% CI 1.2–1.8) in men and 1.9 (95% CI 1.5–2.2) in women, even after adjustment for major confounding factors [37]. In the AFFIRM study, both rate and rhythm control arms had similar rates of vascular death, as well as arrhythmic and non-arrhythmic cardiac deaths [38].

One analysis suggests that this may be related to the presence of heart failure and conduction abnormalities. For example, Baldasseroni *et al*. [39] reported that the 1-year total mortality and sudden death in patients with heart failure was more common in patients who had AF and associated left bundle branch block. Certainly, the presence of left ventricular dysfunction is an important adverse prognostic factor in AF. In the SOLVD study [40], the presence of AF and left ventricular dysfunction resulted in an increase in all-cause mortality (relative risk 1.34, 95% CI 1.12–1.62), as well as an increased risk of progressive pump failure death (by 42%) as well as death or re-hospitalization (by 26%).

Certainly after a myocardial infarction, the presence of AF substantially increases the case fatality rate [15] and this is also seen in a randomized controlled trial [16]. The presence of AF with a stroke also substantially increases mortality as well as the risk of remaining disabled or handicapped [41]. This probably relates to larger thrombi in stroke due to AF compared with other stroke types. In the European Community Stroke Project, 33% of the AF patients were dead at 3 months compared with 20% of the non-AF patients; furthermore, there was a substantial increased risk of remaining disabled (by 43%) or handicapped (by 51%) [42].

Pathophysiology

The pathophysiology of AF largely encompasses electrophysiological and structural changes. Most of these changes occur long before onset of AF (while in sinus rhythm) but AF itself may reinforce its own arrhythmogenic pathophysiology, i.e. 'AF begets AF'.

Electrophysiology

Electrophysiological mechanisms of AF include focal mechanisms and re-entry, from a single or multiple sources (Fig. 29.4). In focal AF, one or more rapidly firing foci cause fibrillatory conduction over the atria. AF produced by re-entry may involve one or more circuits. A focal origin of AF is supported by experimental models of aconitine-induced and pacing-induced AF [43,44]. The focal origin appears to be more important in patients with paroxysmal AF than in those with persistent AF, and

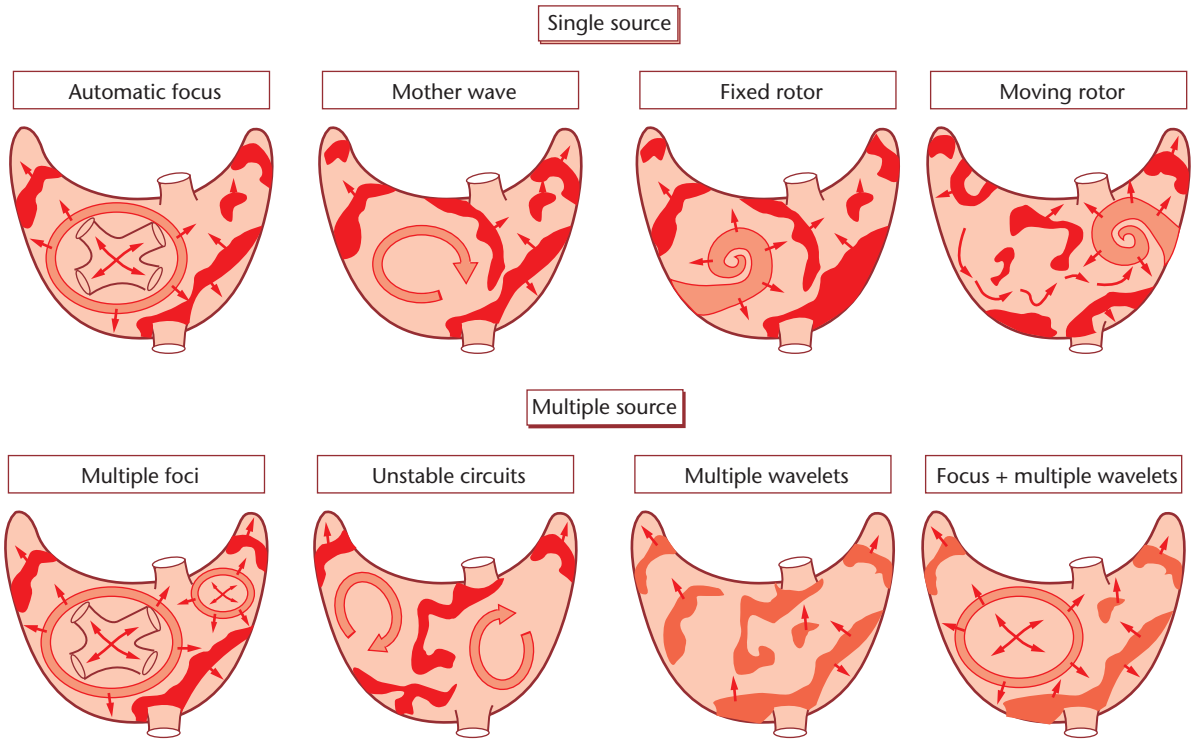

Figure 29.4 Different mechanisms of atrial fibrillation.

ablation of such foci may be curative [45]. The multiple-wavelet hypothesis as the mechanism of re-entrant AF was advanced by Moe [46] and further elaborated by Allessie *et al*. [47]. According to this multiple-wavelet hypothesis, AF will only persist as long as a critical number of wavelets are present in the atria. For stable AF a short wavelength (product of refractoriness and conduction velocity) and a large atrial mass are necessary. Large atria may accommodate many wavelets, even those with a long wavelength since they contain many long pathways.

In recent years much attention has been given to the observation that AF itself causes electrophysiological [48,49] and structural [50] changes in the atrial myocardium (remodelling), which favour the initiation and perpetuation of AF.

AF-induced electrical remodelling

Electrical remodelling is defined as sustained electrophysiological changes occurring in response to an abnormal stimulus. It is due to AF itself or to associated cardiac conditions. It consists largely of changes in refractoriness and conduction. After the causative disease has disappeared, the remodelling may disappear (usually holds for refractory period changes) or persist (usually holds for conduction abnormalities). Table 29.2 shows the different forms this may take.

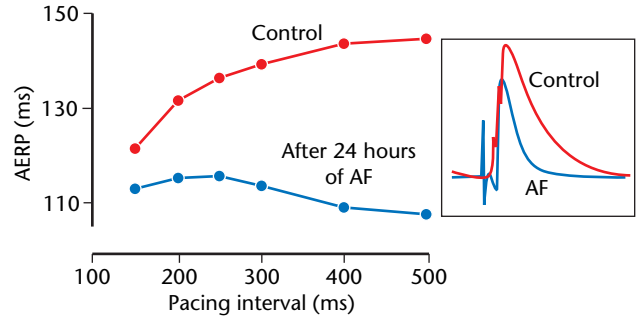

Figure 29.5 Electrical remodelling denotes shortening of refractoriness (left panel, *y*-axis), with reshaping of the atrial action potential from long to short (right panel). In addition, normal rate-related shortening of refractoriness is lost (left panel). AERP, atrial effective refractory period; AF, atrial fibrillation.

The 'AF begets AF' principle has been shown in the goat model using an automatic atrial fibrillator [48]. The increase in AF in this model relates to progressive shortening of the atrial action potential and effective refractory periods (Fig. 29.5). Clinically, it has been shown that the atrial effective refractory period in paroxysmal AF is short and that refractoriness fails to adapt to changes in atrial rate [51]. The duration of the atrial monophasic action potential in AF patients is shorter after cardioversion [52,53]. Lengthening of the atrial refractory period

Table 29.2 Mechanisms of atrial fibrillation (AF)

Mechanism	AERP	Conduction velocity	Wavelength*
High rate†	Shortens markedly	Decreases slightly	Decreases
Atrial dilation‡	Increases slightly	Decreases markedly	Decreases
High vagal tone	Shortens markedly	No change	Decreases

AERP, atrial effective refractory period.
*Wavelength = AERP × conduction velocity. Decrease of wavelength is arrhythmogenic.
†AF begets AF: high rate triggers electrical remodelling (reversible).
‡Hypertension begets AF: high pressure and hence stretch triggers electrical remodelling (largely irreversible).

during the first days after cardioversion further supports the notion of AF-induced electrical remodelling in humans [54]. A decreased inward current through L-type calcium channels has been shown to play a crucial role in action potential shortening [55]. Another feature of tachycardia-induced electrical remodelling is a reduction in, and different distribution of, gap junctional proteins, causing local conduction disturbances [56,57].

Atrial stretch and electrical remodelling

Chronic atrial stretch may also induce electrical remodelling but of a different sort. Electrical remodelling due to chronic atrial dilation is characterized by lengthening rather than shortening of atrial effective refractory period [58–60]. In addition, abnormal conduction caused by muscle fibre disarray and fibrosis causes long conduction pathways and hence favours re-entry. High atrial rate in combination with the development of heart failure is associated with initial shortening followed by lengthening of refractoriness, the net result still being a short refractory period [61]. Acute dilation shortens atrial refractoriness [62–64], prolongs conduction [65] and facilitates AF [64], but does not cause lasting remodelling. Immediately after release of the stretch, atrial electrophysiology normalizes.

Electrophysiological triggers and modulators

Other factors involved in the induction or maintenance of AF include premature beats, autonomic nervous system activity, atrial ischaemia and acute atrial stretch. Atrial fibrillation may result from increased vagal tone, which leads to episodes during sleep or after meals, most often in patients without organic heart disease. In contrast, exercise, emotion, surgical stress or infusion of isoproterenol may provoke catecholamine-induced AF [66]. Half of adrenergic AF patients may have an underlying heart disease.

Atrial premature beats are important initiating events in most cases. In addition, supraventricular tachycardia may cause AF (tachycardia-induced tachycardia) [67]. Ablation of initiating supraventricular tachycardia (e.g. AV node re-entry and AV re-entry) may abolish AF.

Atrial dilation and contractile remodelling

In AF the atria may dilate as a cause but also as the consequence of AF. Atrial dilatation in the setting of hypertension or valvular disease for example predicts future AF [68]. With ongoing AF, however, the atria may dilate further [69]. Similarly, in dogs progressive atrial dilation is seen during rapid atrial pacing [49]. Conversely, it has been demonstrated that atrial diameters may decrease after conversion of AF to sinus rhythm [70,71].

AF may cause loss of contractile function. Even after a few minutes of experimental AF, atrial contractility is impaired but may restore immediately after sinus rhythm has resumed [72]. During the first 3–5 days of AF, atrial contractility largely diminishes. Since the time course of electrical and contractile remodelling is similar, they are most likely due to the same intracellular remodelling process [73]. Contractile remodelling as a result of short-lasting AF (< 1 week) is completely reversible within about 3 days of sinus rhythm [73]. In longer-lasting AF the atria start to hibernate (Fig. 29.6) [50]. This explains why the atria do not contract when brought back to sinus rhythm [74]. This phenomenon has erroneously been termed 'stunning' since it was seen in conjunction with electrical cardioversion. However, 'stunning' suggests an acute insult (as in ischaemic stunning) whereas, if anything, hibernation is the case, the conversion only unmasking the minor metabolic state of the atria. Since the atria hibernate, the recovery of atrial contraction may take weeks to months. As one may expect, the speed of recovery is related to the duration of AF [75]. The atrial contractile dysfunction is considered to be one of the factors responsible for thromboembolism, other factors including atrial endothelial damage and propensity to clot.

Atrial dilation frequently precedes onset of AF

Hypertension precedes AF mainly in patients with

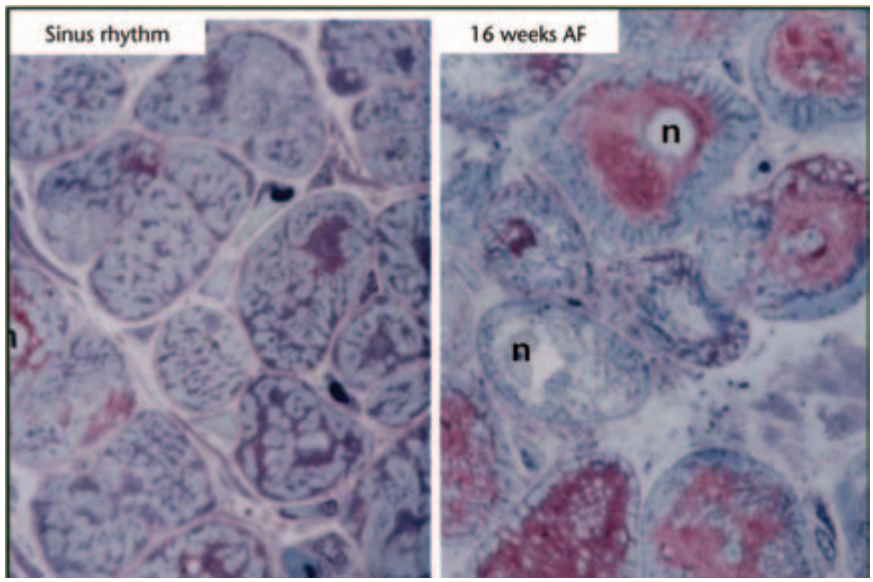

Figure 29.6 Light microscopy of atrial myocardium stained with PAS/toluidine blue. (A) Atrial tissue from goat in sinus rhythm: glycogen is almost absent within the myocytes. (B) Goat atrial tissue harvested after 16 weeks of maintained atrial fibrillation. Myocytes are enlarged and most show myolysis, i.e. loss of myofibrils. In addition, cells have accumulated glycogen (red material). n, nucleus.

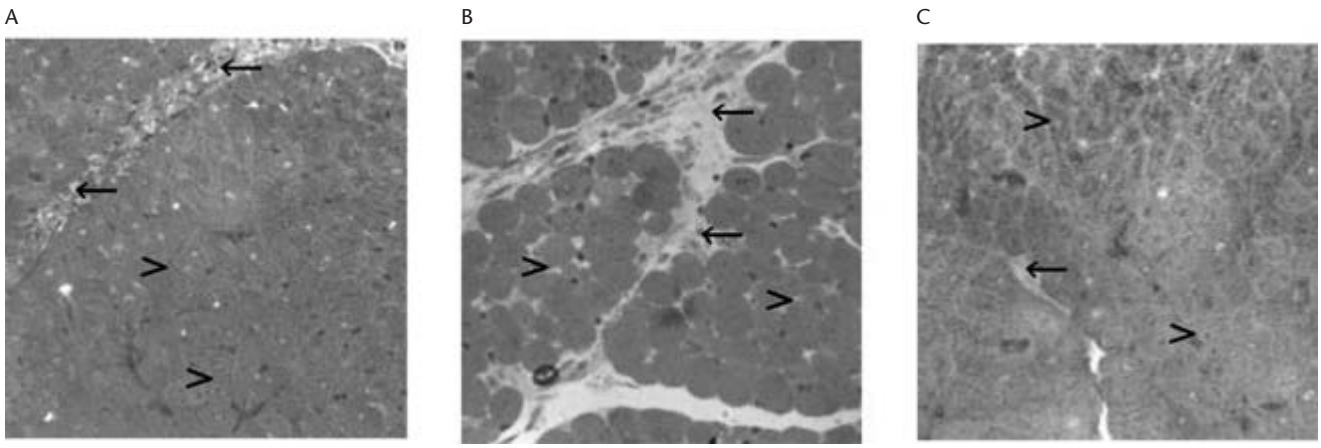

Figure 29.7 Atrial myocardium (×400). (A) Control goat: arrows indicate normal distribution of perimysial interstitial tissue, whereas arrowheads indicate interstitial tissue. (B) Atrial myocardium from an AV-paced goat (heart failure) with prominent structural remodelling showing an increase in connective tissue. Arrows and arrowheads indicate an increased amount of both intermysial and perimysial tissue. (C) Absence of remodelling in atrial tissue from a goat with a high atrial rate when the ventricular rate remained normal (no heart failure). Arrows and arrowhead as in (A). Reproduced with permission from Attuel *et al*. [51].

significant left ventricular hypertrophy [10,76]. This relates to the fact that left ventricular hypertrophy is associated with atrial dilation; in turn, atrial dilation caused by haemodynamic overload is associated with excessive fibrosis (Fig. 29.7) [58,77,78]. The latter strongly promotes AF.

Reversed remodelling

Reversed remodelling relates to reversal of electrical and contractile remodelling, since structural remodelling is usually not reversible except for myolysis and, partly, atrial dilation. Reversed electrical remodelling is important in persistent AF after cardioversion to sinus rhythm [54]. The reversal of electrophysiological abnormalities is associated with high recurrence rates early after conversion and with lower rates subsequently [79]. After electrical cardioversion there are several types of recurrence: immediate recurrences, subacute recurrences and late recurrences (Fig. 29.8). The main pathophysiological basis for subacute recurrence is restoration of membrane channel function, including the L-type calcium channel, as well as recovery of the cellular metabolic machinery, leading to normalization of cellular calcium handling. During the initial weeks after cardioversion, arrhythmogenic calcium handling may lead to arrhythmia recurrences due to calcium-dependent triggered arrhythmias. In addition, spatially differential lengthening of refractoriness may produce temporary dispersion of refractoriness, which in combination with atrial trigger beats is

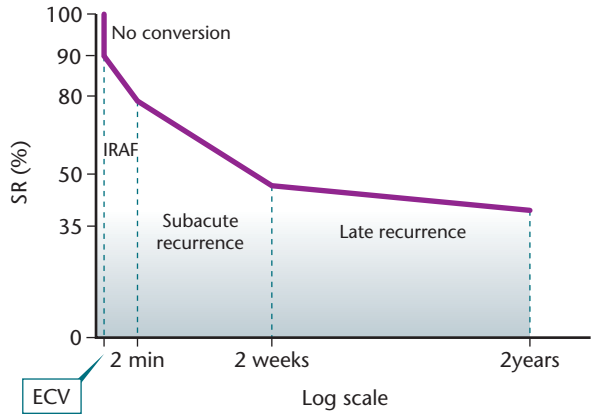

Figure 29.8 Types of recurrences after cardioversion (see text for details). ECV, electrical cardioversion; IRAF, immediate recurrence of atrial fibrillation; SR, sinus rhythm. Adapted with permission from Van Gelder *et al*. [70].

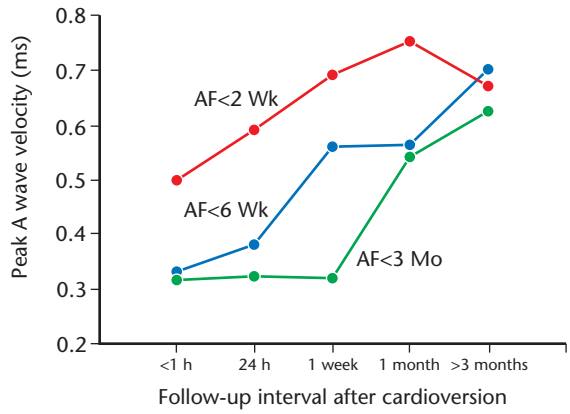

Figure 29.9 Speed of restoration of atrial function (measured as peak A-wave velocity) after cardioversion of atrial fibrillation (AF) depends on the duration of AF before cardioversion. Adapted with permission from Coumel [66].

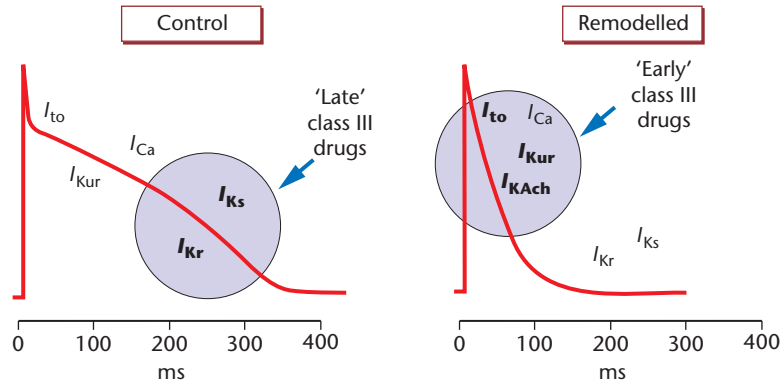

Figure 29.10 Implications of ionic remodelling for class III drug actions. In control cells, classical class III drugs block I_{Kr}, which is abundantly present. I_{Kr} block leads to significant prolongation of the action potential and refractory period. However, in remodelled atria, block of I_{Kr} cannot prolong the action potential significantly. Theoretically, 'early' class III drugs may appear more effective in prolonging the atrial action potential and terminate atrial fibrillation.

extremely arrhythmogenic [80]. Restoration of contractile remodelling may take days to months depending on the time spent in AF before conversion (Fig. 29.9). The long recovery period relates to the time needed for the restoration of myocyte proteins. During the recovery period, thrombus formation and stroke may easily occur, for which anticoagulation is needed.

Clinical consequences

Long-lasting AF and strongly remodelled atria do not respond to the classical antiarrhythmic drugs (Fig. 29.10). Therefore the duration and type of AF should guide the clinician when choosing a drug for termination of AF. Short-lasting AF is always associated with normal atrial refractory periods and relatively short excitable gaps. Vigorous slowing of conduction by class IC drugs is most successful. However, if atrial dilation comes into play, drugs are less effective, especially since these patients tend to have AF of longer duration. Termination may then still be effective using class III drugs or prolonged drug administration (Table 29.3). Atrial flutter resembles AF due to atrial dilation: the excitable gap is short and excitability is normal. Therefore class III drugs like sotalol, ibutilide and amiodarone may easily terminate these arrhythmias [81].

One of the consequences of AF-induced electrical remodelling is that the efficacy of preventive drug treatment after cardioversion may depend on the type of recurrence aimed at. In order to suppress the immediate recurrence of AF, the most effective agents are class IC drugs and amiodarone [80]. In order to suppress subacute recurrences, L-type calcium blockers in combination with class I or III antiarrhythmic drugs reduce immediate and subacute recurrences of AF after cardioversion of persistent AF. This probably relates to amelioration of abnormal calcium handling. Beta-blockers may also reduce subacute recurrences. Amiodarone reduces all types of recurrence.

If a predominant vagal pattern is found, beta-blockers and digitalis should be avoided since these enhance refractory period shortening and possibly also promote atrial trigger beats. Beta-blockers are highly effective in adrenergic AF. Unfortunately, it is not always possible to distinguish the autonomic type of AF especially since the pattern may change over time and with drug treatment.

Mechanism	Target	Drug
High rate (short-lasting AF) Atrial dilation (long-lasting)	Slow conduction* Prolong refractoriness†	Flecainide, propafenone Ibutilide, sotalol, amiodarone

*Slowing of conduction will decrease the wavelength, which promotes AF; however, slowing to the extent that conduction becomes impossible at the high rate of AF (use dependency leading to temporary and instantaneous inexcitability) will terminate AF. In addition, flecainide and propafenone prolong refractoriness in cases of high atrial rate (high efficacy).
†Prolongation of refractoriness will terminate AF because of wavelength prolongation, which will close the short excitable gap (relatively low efficacy).

Table 29.3 Acute termination of atrial fibrillation (AF)

Reducing atrial size or introducing boundaries to the atrial electrical activity may help to eliminate re-entrant AF by reducing the space in which re-entry may take place, thus reducing the number of circulating wavelets below the critical number of 3. This is the principle of the Maze operation [82] and of linear catheter ablation [83].

Curative treatment of AF, such as ablation and rhythm surgery, should start from a firm diagnosis of the underlying mechanism. In patients with atrial flutter or other supraventricular arrhythmias, including Wolff–Parkinson–White syndrome, radiofrequency ablation or cryoablation of the arrhythmia may cure the patient of AF. One important clinical example is ablation of class IC flutter [84]. Similarly, in patients in whom focal AF can be proven, ablation of the foci may lead to elimination of AF.

Acute stretch produces refractory period shortening which may lead to AF. This typically occurs in acute myocardial infarction or cardiac asthma. It should be treated by volume unloading and rate slowing. These manoeuvres may help to increase the refractory period of the atria, which facilitates termination of the arrhythmia due to prolongation of the wavelength.

Slow recovery of atrial function after prolonged AF (Fig. 29.9) predisposes to thrombi and stroke. This is the basis for the 1-month post-cardioversion anticoagulation period. However, after that time risk continues in patients with typical stroke risk factors and anticoagulation should be continued even if sinus rhythm is maintained [85,86].

The structural damage to the left atrium often develops long before AF emerges. Management of hypertension is a very important issue with regard to lowering the incidence of AF in the future. Medical treatment of hypertension is a most important means of primary prevention of AF.

Classification

Classification of AF should focus on symptoms (arrhythmia symptoms as well as symptoms due to associated medical conditions), stroke and bleeding risks as well as type of AF. The first two classifications are rather simple. Thus, patients may be asymptomatic, symptomatic or both (see Diagnosis, below). Further, stroke and bleeding risks may be high or low (see Chapter 30). The type of AF is somewhat more difficult to assess. AF may present as a first attack or as recurrent. Recurrent AF is classified as paroxysmal, persistent or permanent, i.e. the 3P classification introduced in the mid-1990s [87]. This classification, including the notion of 'first attack', has been described extensively in the last AF guideline of the European Society of Cardiology (ESC) [88]. It links presentation of the arrhythmia to management strategy (Fig. 29.11).

Type	Description	Treatment
• First attack	• No previous AF known	• None
• Paroxysmal	• Spontaneous termination within 1–2 days, seldomly attacks longer than 7 days	• Rate or rhythm control
• Persistent	• Not self-terminating, intervention needed to stop AF	• Rate of rhythm control
• Permanent	• AF accepted as the dominant rhythm, conversion not needed or not attempted	• Rate control

Figure 29.11 Different types of atrial fibrillation (AF) and associated treatment strategies.

AF that may be expected to terminate spontaneously is defined as paroxysmal. Paroxysmal AF usually terminates within 24–48 h [89] and rarely lasts longer than 7 days [88]. If AF does not terminate without an intervention, it is indicated as persistent; if intervention fails or AF is deemed refractory, it is classified as permanent. In the latter case, the clinician or the patient has to decide whether to accept the arrhythmia as the alternative to normal sinus rhythm. If paroxysmal AF is terminated by drugs or cardioversion to foreshorten time to conversion, then such a manoeuvre does not change the designation 'paroxysmal AF' since in essence AF would have terminated on its own.

Diagnosis

Clinical history

A complete diagnosis of AF includes an analysis of associated medical conditions (see above) and stroke risk factors (see Chapter 30). This will guide arrhythmia therapy as well as antithrombotic treatment. In addition, the clinician should assess bleeding risk if antithrombotic treatment is indicated. Further, a complete diagnosis includes assessment of whether the patient is symptomatic. In symptomatic patients vagal, adrenergic and potential other trigger mechanisms are considered. Next, symptomatic AF should be typed as first attack or recurrent following the 3P classification (Figs 29.11 and 29.12). Only symptomatic patients with paroxysmal or persistent AF need rhythm control. The type of rhythm control depends on the type of AF. Irrespective of AF type, reporting adequacy of rate control is part of a complete AF diagnosis (Fig. 29.12). AF may be symptomatic and asymptomatic in the same patient [90,91]. Symptoms may relate to the arrhythmia itself or to the complications of AF or the associated medical condition. In addition, modulators may change presentation of symptoms (Table 29.4).

The Euro Heart Survey on AF collected data on 5333 patients in 35 member countries in 2003 and 2004 (unpublished data presented at ESC meeting in Munich, 2004). The data nicely illustrate that type of AF can be determined reliably in clinical practice: first-detected AF was seen in 978, paroxysmal in 1517, persistent in 1167 and permanent in 1547 patients. Concomitant diseases were present in 90% of all patients, causing risk factors for stroke to be also highly prevalent (86%). As many as 69% of patients were symptomatic at the time of the survey, and among asymptomatic patients 54% previously experienced symptoms. Oral anticoagulation was prescribed in 66% of patients with, and 60% of patients without, a risk factor for stroke. A rhythm control strategy was applied in 67% of currently symptomatic patients and in 44% of patients who never experienced symptoms. Strikingly, stroke risk stratification did not play a large role in determining type of antithrombotic treatment. Management schemes (Fig. 29.12) may further improve treatment of AF.

Vagal AF

Vagal AF is a diagnosis made by taking an adequate

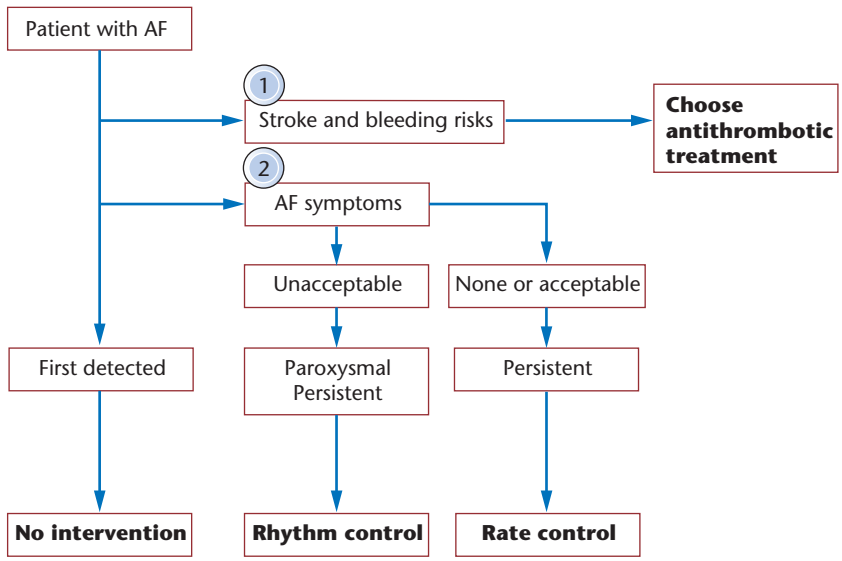

Figure 29.12 Proposed diagnostic and treatment algorithm for patients with atrial fibrillation (AF). The clinician needs to look first at stroke and bleeding risk; thereafter diagnosis and treatment are guided by whether the patient has AF symptoms. In patients with first-detected AF, the need for anticoagulation and treatment of AF is less urgent unless stroke risk is very high and initial symptoms are unacceptable or life-threatening.

Table 29.4 Symptoms in patients with atrial fibrillation (AF)

Typical AF symptoms
Palpitations
Chest pain
'Pain of palpitation'
True angina pectoris
Dyspnoea
Fatigue
During and after an episode (paroxysmal and persistent AF)
Chronic (persistent AF)
Light-headedness
Syncope
Polyuria (atrial natriuretic peptide)
*Symptoms due to AF complication**
Chronic heart failure symptoms (tachycardiomyopathy)
Neurological symptoms (cerebrovascular accident)
Modulators†
Ventricular rate
Duration of AF
Functional status
Neurohumoral activation
Sinus node disease
Associated cardiovascular disease

*These symptoms may be the first manifestation of AF; if so, usually these patients lack typical AF symptoms.
†Modulators act to change symptoms over time, e.g. an increasingly severe aortic stenosis may eventually facilitate syncope during a new AF attack. Or, concomitant coronary artery disease may provoke ischaemic chest pain in addition to chest pain due to the rapid irregular rate ('pain of palpitation').

history. It is important to recognize since it may effectively direct management. One important question to ask is whether palpitations cause disturbed sleep. Another question is to ask the patient about going to bed in normal rhythm and waking up in the morning with arrhythmia complaints, taking into account that some complaints may become manifest only with physical activity. Vagal AF never starts between breakfast and lunch (P. Coumel, personal communication). Pause-dependent AF usually occurs in the elderly in the setting of sick sinus syndrome and is characterized by preceding relatively long sinus pauses or irregular sinus rhythm [88].

Adrenergic AF

Adrenergic AF occurs during exercise or emotion. Most attacks terminate a few minutes after stopping exercise [66]. Van den Berg *et al*. [92] showed that the majority of adrenergic AF patients had associated cardiac disorders, especially coronary artery disease. Beta-blockers are the drugs of choice, whereas the response to amiodarone

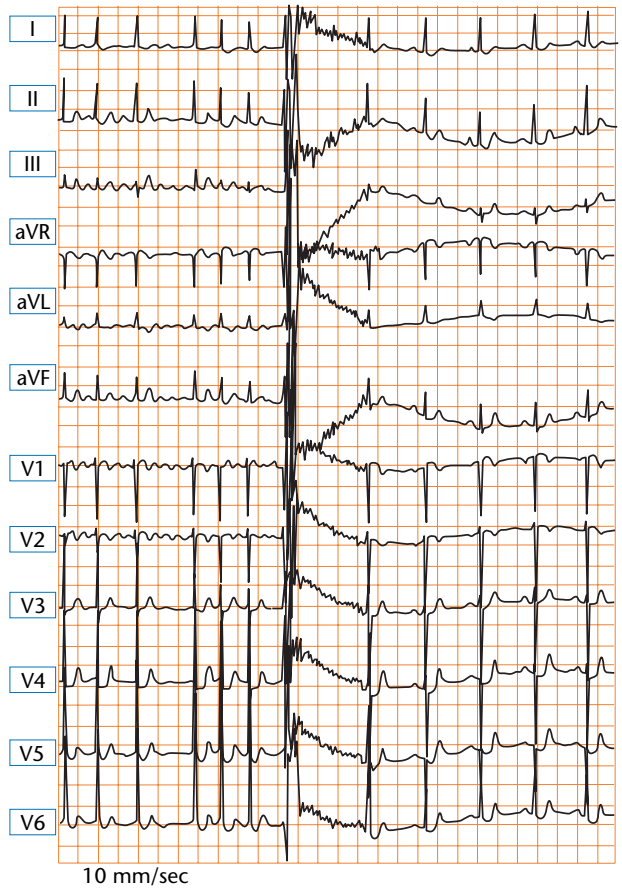

Figure 29.13 The 12-lead ECG of atrial fibrillation and successful cardioversion to sinus rhythm. Note the irregularity of the RR intervals and the fibrillation waves in leads V1 and V2. The artefact in the middle of the tracing represents the moment of DC electrical countershock.

may vary. Considering these findings, it seems advisable to search for associated cardiac disorders.

Physical examination

AF presents with an irregular pulse, irregular jugular venous pulsations and variations in the loudness of the first heart sound and in systolic blood pressure. There may be a deficit between number of heart beats and number of peripheral pulsations, mainly in AF with a high ventricular rate. Signs of valvular heart disease, ventricular dilatation and heart failure may be found.

Surface ECG

The ECG serves to verify AF (Fig. 29.13) or atrial flutter (Fig. 29.14). It may point to an old myocardial infarction, left atrial and ventricular hypertrophy (Fig. 29.15), pericardial disease, cardiomyopathy and ventricular

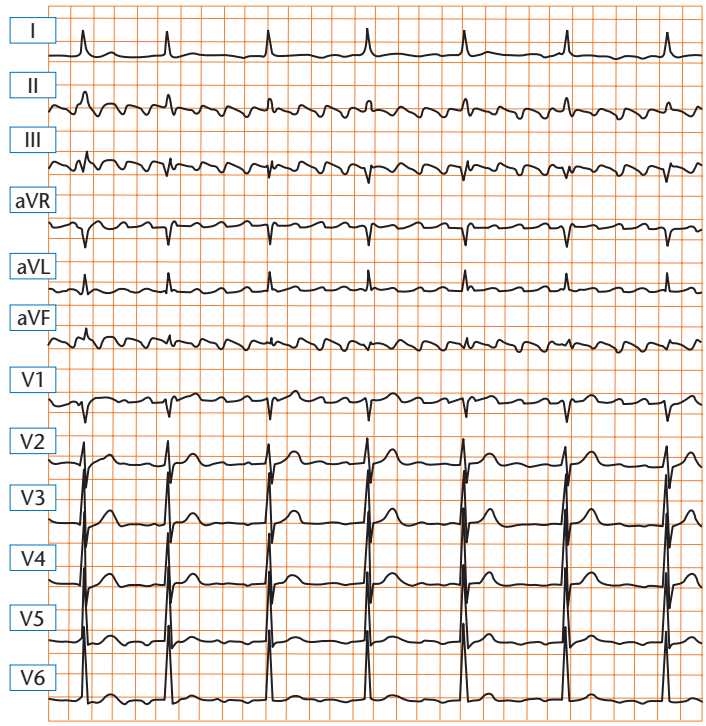

Figure 29.14 Typical atrial flutter with flutter cycle length of 200 ms (atrial rate 300 b.p.m.). The flutter waves show the typical saw-tooth morphology in the inferior leads. The rate is well controlled due to drug-induced 3 : 1 and 4 : 1 AV block.

preexcitation. A long P-wave duration and high or low P-wave voltage may indicate atrial conduction disturbance, or left or right atrial or bi-atrial enlargement. Sometimes an acute atrial infarction can be found in the setting of acute inferior infarction (Fig. 29.16). The ECG may also show other atrial arrhythmias, abnormal sinus node function or ventricular arrhythmias that may trigger AF or be a sign of heart disease. It is always important to distinguish aberrant conduction from ventricular tachycardias, especially when using antiarrhythmic drugs (Fig. 29.17). Finally, the ECG may reveal the morphology of initiating atrial premature beats or even focal AF (Fig. 29.18), although three-lead or even better 12-lead Holter monitoring may be more sensitive. The morphology may be linked to site of origin of focal AF.

Chest radiograph

The chest radiograph may help to reveal cardiac enlargement but is most helpful in detecting intrinsic pulmonary disease and abnormalities of the pulmonary vasculature as in heart failure and pulmonary hypertension.

Echocardiography

A transthoracic echocardiogram should be performed at least once in all AF patients. It is indispensable for the management of AF-associated medical conditions. In addition, markers of thrombosis or even a thrombus may be found. Risk markers for stroke include left ventricular hypertrophy or dysfunction, left atrial enlargement and low flow velocities in the left atrial appendage. Also, aortic plaques are associated with a high stroke risk. New technical developments have improved the performance of transthoracic echocardiography but for detection of thrombi (e.g. for echo-guided cardioversion) transoesophageal echocardiography is the current standard [93].

Laboratory evaluation

Laboratory evaluation may be limited to thyroid function tests, serum electrolytes and haemoglobin levels and, if indicated, markers of heart failure or inflammation or infection. Thyroid function but also other laboratory tests should be repeated when treating patients with amiodarone.

Holter monitoring

This technique may be used for a variety of reasons (Table 29.5). In order to establish the diagnosis of AF, it is sometimes useful to use event recorders rather than Holter. In patients with an implanted device, Holter functions in the device may be very helpful. Adequacy of

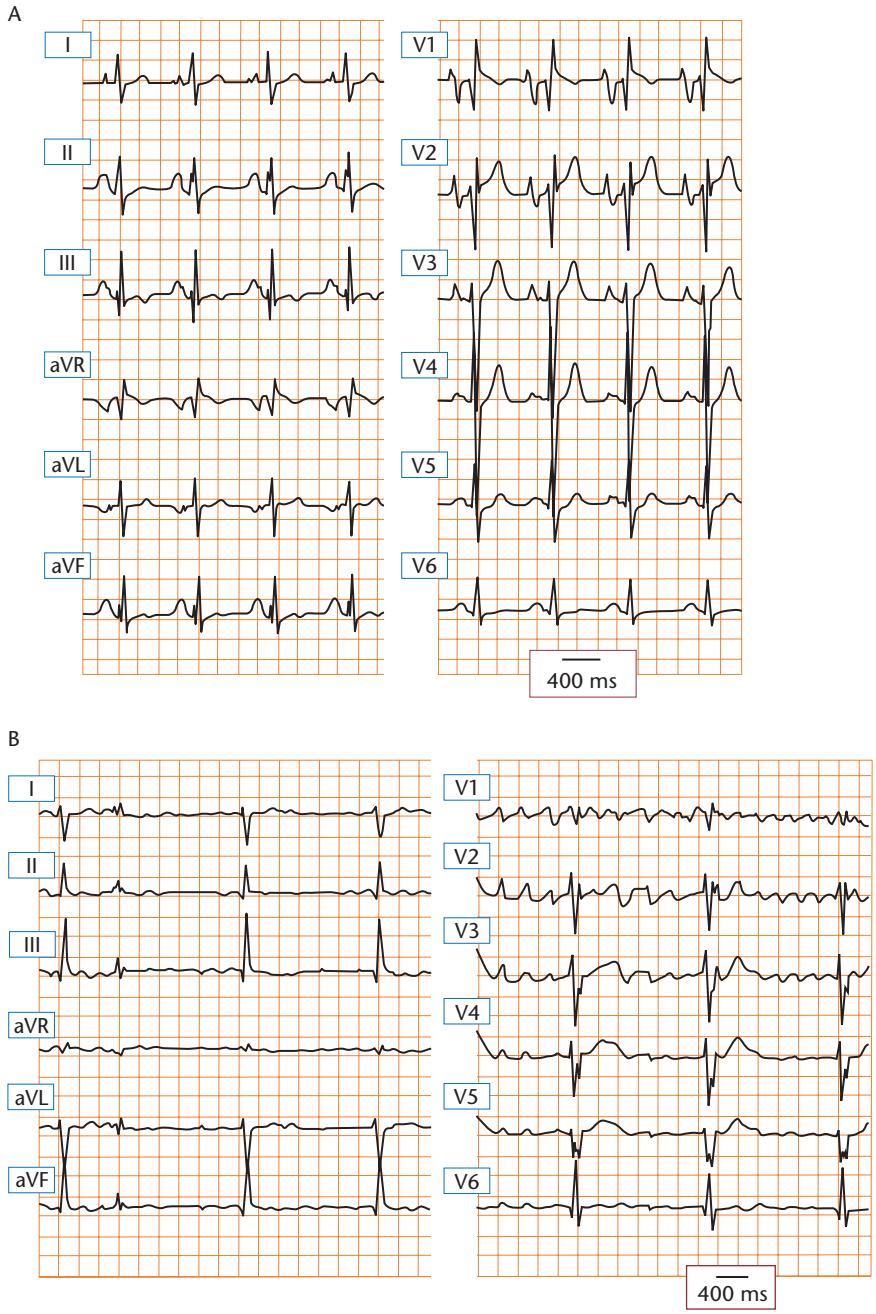

Figure 29.15 (A) ECG of a patient with hypertrophic cardiomyopathy. Note the extreme left atrial involvement (hypertrophy) as evidenced by prolongation of the P wave in leads II, III and aVF and by strong negativity of the P wave in V1. Atrial hypertrophy predisposes to atrial fibrillation (see B). (B) The same patient a few years later. Note that the patient developed atrial fibrillation and AV block with an idioventricular escape rhythm from the left anterior hemibundle (left posterior, right bundle branch block conduction pattern).

rate control may be checked with Holter (or exercise test) if patients remain symptomatic with palpitations or reduced exercise tolerance despite normal resting heart rate. AF may start during (sinus) bradycardia or tachycardia, with single or bouts of atrial ectopic beats, while the start of AF with a supraventricular tachycardia or transitions between AF and atrial flutter may also be seen. Identification of these initiating mechanisms may guide treatment, e.g. vagolytic or beta-blocking agents, atrial pacing or catheter ablation of focal AF or other initiating arrhythmias. The clinical relevance of establishing the AF burden is uncertain at present but it seems especially

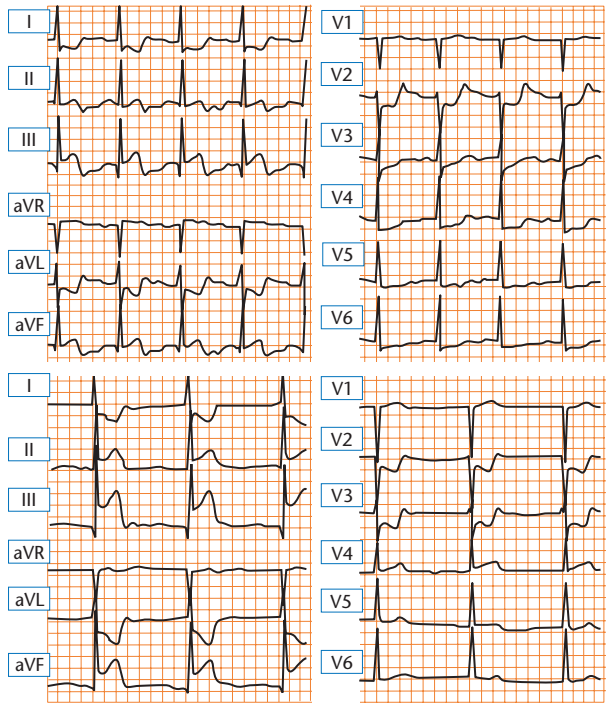

Figure 29.16 Upper panel shows 12-lead ECG of an acute inferoposterolateral myocardial infarction with atrial ischaemia. Note PTa segment abnormalities in inferior leads. Lower panel shows subsequent atrial fibrillation, complete AV block and AV junctional escape rhythm of approximately 30 b.p.m.

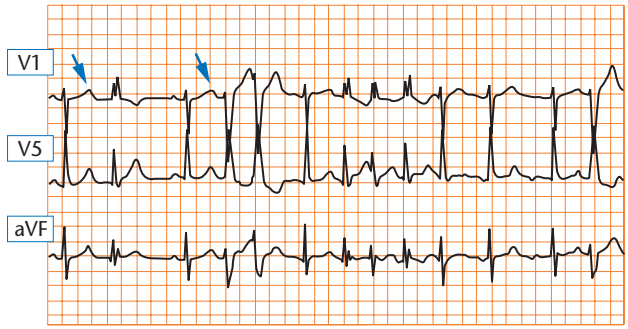

Figure 29.17 Holter strip of modified leads V1, V5 and aVF showing atrial fibrillation (AF) initiated at second arrow (arrows point to atrial premature beats) with left and right aberrant conduction in a patient treated with sotalol for paroxysmal AF. Note the long–short RR sequence at initiation of aberrant conduction. Sotalol may have enhanced onset of aberrancy in this case due to prolongation of refractoriness in the Purkinje system.

important in patients with paroxysmal AF who may have many undetected AF episodes. If the burden appears to be associated with stroke risk, it may become useful for guiding antithrombotic therapy.

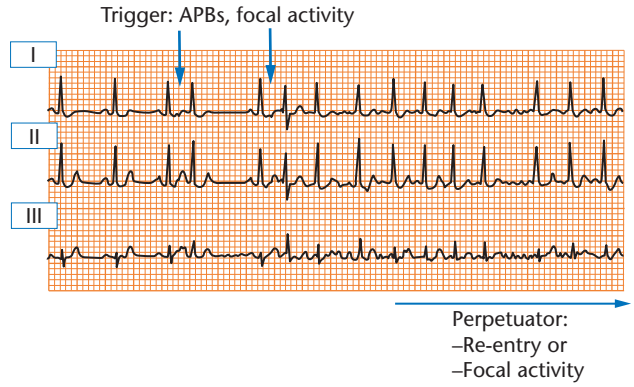

Figure 29.18 Initiation of atrial fibrillation (AF) in a patient with paroxysmal AF. The patient develops monomorphic atrial premature beats (APBs, arrows) presumably due to focal activity. The second APB triggers AF. AF perpetuates because of re-entry or persistent focal activity.

Table 29.5 Role of Holter monitoring in diagnosis and management of atrial fibrillation (AF)

Establish AF diagnosis and determine paroxysmal or persistent nature of AF
Judge adequate rate control
Discover silent ischaemia (ST-segment changes)
Evaluate trigger mechanism
Atrial arrhythmias
Atrial premature beats
Ventricular premature beats
Morphology of atrial premature beats (focal AF)
Supraventricular tachycardias (atrial tachycardia, AV nodal tachycardia, AV nodal re-entrant tachycardia, atrial flutter)
Diurnal onset
Vagal AF: onset during rest or at night, with preceding bradycardia; relative bradycardia during AF
Adrenergic AF: onset during daytime or exercise
Evaluate drug effects
Uncover bouts of (class IC) flutter
Arrhythmia suppression
(Excessive) QT prolongation during slow heart rates (class IA or III drugs)
(Excessive) QRS widening during fast heart rates (class IC drugs)
Sinus node function, AV conduction (class I–IV drugs and digitalis)
Evaluate burden of AF in patients with paroxysmal AF which is the sum of all AF episodes

Exercise testing

Exercise testing is useful in patients with permanent AF who remain symptomatic despite adequate rate control at rest. The test may reveal an excessive heart rate rise during the lower stages of exercise, thereby limiting exercise tolerance due to dyspnoea, fatigue or palpitations.

In these cases, rate-control drugs may be targeted to the heart rate during a lower level of exercise. Exercise testing may be useful in detecting ischaemic heart disease, which has consequences for antiarrhythmic treatment of AF. Finally, exercise testing may be used to evaluate the safety of antiarrhythmic drug treatment, e.g. for detecting excessive QRS widening on class IC drugs.

Electrophysiological evaluation

Electrophysiological evaluation may be needed in selected cases, especially in patients in whom other arrhythmias, sick sinus syndrome or a focal origin is suspected [67]. Many of these patients may receive catheter ablation or a pacemaker.

Personal perspective

After the rate versus rhythm trials it has become apparent that prevention of stroke is most important. In order to reduce strokes, sophisticated tools for detecting stroke risk, including echocardiography and blood tests, are needed. Collaboration with neurologists is also required, since the basis for stroke is not limited to the heart.

The role of echocardiography in defining stroke risk in AF patients needs thorough review. The conventional stroke risk factors assign a high stroke risk to over three-quarters of patients. Echocardiography may help to reduce the number of patients treated needlessly with anticoagulation, for example by showing normal anatomy and function of the heart and aorta in elderly patients with hypertension. According to current guidelines the latter patients have a high stroke risk, whereas on the basis of echocardiography the actual risk is probably low, justifying aspirin or clopidogrel rather than oral anticoagulation. Other imaging techniques such as cardiac magnetic resonance imaging may also be useful.

Asymptomatic AF remains a large problem mainly because of the increased stroke risk. Once asymptomatic AF emerges, this suddenly increases the risk of stroke fourfold without the patient coming to the attention of a physician and receiving anticoagulation. Therefore early detection of AF in hypertensive populations seems important. Intermittent rhythm monitoring using non-invasive detection devices or even implantable loop recorders may reveal the clinical relevance of asymptomatic AF and AF burden. Theoretically, a higher burden represents a higher stroke risk because atrial remodelling may be more marked. In addition, a higher burden may be a marker for a more severe associated medical condition predisposing the patient to stroke. Another approach is to enhance prediction of AF. The big challenge here is to define susceptibility, e.g. genetically or by new imaging techniques.

For symptomatic patients, robust characterization of AF mechanisms, including description of triggers, initiators, perpetuators and their interaction, is needed. It will enhance tailored therapy including the targeting of new antiarrhythmic drugs to relevant ion channels and also improve our ablation techniques. To better characterize AF, the same rhythm monitoring devices mentioned above may be used, but also much more invasive electrophysiological research using new mapping techniques needs to be done.

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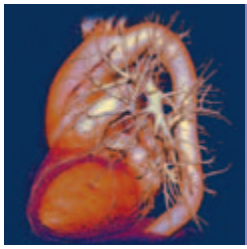

30 Atrial Fibrillation: Treatment

Etienne Aliot, Christian de Chillou, Pierre Jaïs and S. Bertil Olsson

Summary

The main goals of atrial fibrillation (AF) treatment are to reduce symptoms, prevent thromboembolism, and prevent morbidity and mortality. There are three fundamental approaches to the management of AF: rate control, rhythm control, and antithrombotic therapy.

The potential benefits of rate control strategy are that of improved symptom control, lack of antiarrhythmic (AA) drugs with serious adverse events, and simplified and less expensive drug regimen. However, disadvantages of this strategy include negative effects on haemodynamics, atrial remodelling and risks of long-term anticoagulation.

On the other hand, chronic maintenance of sinus rhythm remains the major challenge in this realm. To date there is no AA drug with sufficient efficacy and safety to be administered with confidence to a broad sample of patients. Even with optimal therapy, drug treatment is rarely 'curative'; it's clear that we need better AA drugs with less attendant cardiac and organ toxicity

Warfarin is effective in dramatically reducing the incidence of thromboembolic events in patients with valvular and non-valvular AF, but presents its own complications. New antithrombotic agents with better acceptance and non-pharmacological techniques for elimination of left atrial appendage (LAA) are currently undergoing clinical evaluation.

An increasing variety of non-pharmacological approaches now exists for the management of medically refractory AF patients, spanning devices, surgery, and catheter ablation, which has been proposed since the end of the 1990s and continues to rapidly evolve. Based on pulmonary vein disconnection or substrate modification, catheter ablation of AF has a dramatic and significant positive impact on quality of life of patients and is now performed on a daily basis in electrophysiology (EP) laboratories.

Finally, we have to keep in mind that there are not only one but several AF types and that individualisation of therapy must be based on the type of AF and the patient's characteristics.

Antithrombotic therapy

The inherent risk of arterial embolism linked to atrial fibrillation (AF) has long been recognized. Independent studies, performed before the time when anticoagulation became recommended for these patients, verify a relative risk increase of 2.3–6.9 for patients in AF without signs of rheumatic mitral valve disease (so-called non-valvular AF) compared with arrhythmia-free controls [1]. This risk of embolism is further increased when AF is the consequence of rheumatic mitral valvular disease, estimated to be 17 times the corresponding risk of a healthy person [2].

Risk stratification

The rate of embolism in non-valvular AF depends on the age of the patient and the presence or absence of signs of cardiovascular disease [3]. Patients with non-valvular AF below the age of 60 and who have no clinical history or echocardiographic evidence of cardiovascular disorder carry a very low cumulative stroke risk, estimated to be 1.3% over 15 years [4]. In contrast, the highest risk of stroke in the context of non-valvular AF is seen in those

Risk factor	Risk level
Rheumatic heart disease	Very high
Hypertrophic cardiomyopathy	Very high
Sinoatrial disease	Probably very high
Prior stroke or transitory ischaemic attack	High
History of hypertension	High
Congestive heart failure	High
Age > 65	High
Diabetes	High
Coronary artery disease	High
Hyperthyroidism	Probably high
Age < 65, no concomitant disorder	Low

Table 30.1 Risk levels for ischaemic stroke and systemic embolism in patients with atrial fibrillation

who have already had a stroke or experienced a transient ischaemic attack [3]. Table 30.1 presents the relative risks for stroke or systemic embolism for the patient with non-valvular AF and additional risk factors. However, none of these risk levels reaches the risk observed in AF caused by mitral valvular disease.

The thrombotic mechanism

The markedly increased risk of stroke or systemic embolism in patients with non-valvular AF is linked to two evident unfavourable conditions: the existence of a 'dead-end' part of the circulatory system, namely the left atrial appendix (LAA), together with the markedly reduced atrial myocardial mechanical function caused by the arrhythmia. Indeed, the LAA is the dominant source of embolism in such patients [5]. Thus, following a review of 23 separate studies exploring the origin of arterial emboli in patients with AF, it was concluded that LAA is the embolic source in 91% when AF is of non-valvular origin. In contrast, the importance of the LAA as an embolic source was lower in those with rheumatic mitral valve disease and AF, amounting to 57%. In addition to unfavourable anatomy and impaired mechanical LAA performance, dysfunction of the endothelium as well as of the coagulation system may also participate in thrombus formation [6].

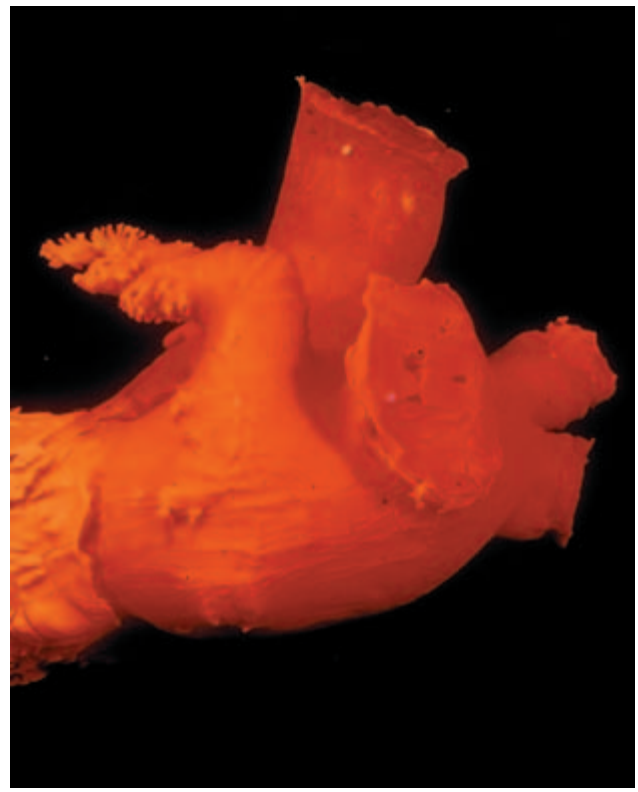

Figure 30.1 Endocardial left heart cast illustrating the profoundly trabeculated left atrial appendix. This is the major source of left atrial thrombi in patients with non-valvular atrial fibrillation. (Courtesy of Dr Yen Ho.)

Left atrial appendix

The LAA is the only part of the circulatory system that has no through-flow of blood. Instead, it is a blind pocket, occupying the three-dimensional space within the surrounding ovoid-shaped pericardial sac and formed by the rounded contour of the left ventricular myocardium, the body of the left atrium and the outflow tract of the right ventricle. Inside, it is markedly trabeculated, as can be visualized by a cast of the cavities of the left heart (Fig. 30.1) [7]. The form of the LAA varies markedly between individuals. Its volume has been measured by cast technique in a necropsy study and found to range between 0.7 and 19.2 ml [8]. The study also documented marked variability in the size of the LAA orifice (5–27 mm) and the maximal diameter (10–40 mm). Interestingly, the LAA of individuals with verified AF during their lifetime had generally larger dimensions than in those known to have been free from the arrhythmia.

It is inappropriate to regard the LAA as only a passive structure, filling the space within the pericardial sac. Its

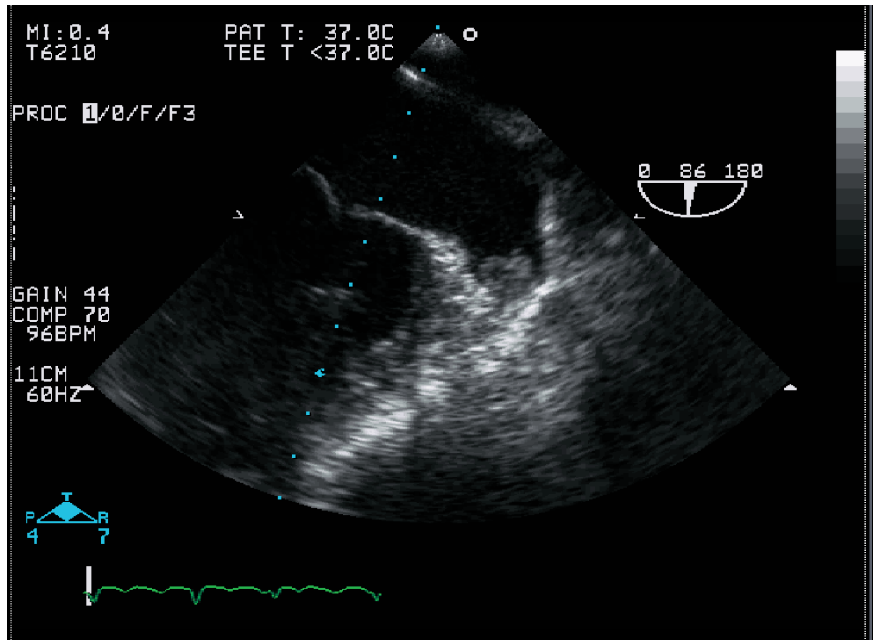

Figure 30.2 TOE view of left atrium with a rounded thrombus within the LAA.

wall stores large concentrations of atrial natriuretic factor and it is supplied by a variety of nerves and receptors [9], reflecting its role in the physiological regulation of blood volume.

Remodelling

Following initiation of AF, the myocardium undergoes within days to weeks both electrical and mechanical remodelling, resulting in further increase of activation rate as well as decreased contractility [10]. Continuation of the arrhythmia for a longer time is followed by structural remodelling [11], further depressing the function of the LAA. This unfavourable development can be verified by transoesophageal echocardiography (TOE), demonstrating a marked decrease of LAA outflow velocity. The more the outflow velocity from the LAA decreases, the higher the risk for development of thrombi within its cavity [12]. Figure 30.2 illustrates a TOE view of an LAA hosting a thrombus.

Embolic targets

An embolus originating from a fibrillating left atrium may follow the bloodstream to any part of the body. However, the relation between the incidence of stroke and of a clinically evident systemic embolism in non-valvular AF differs markedly from the proportion of blood flowing to the brain and to the rest of the body. Thus, the stroke rate is 10 times higher than the rate of systemic embolism in patients with non-valvular AF who have not received any antithromboembolic treatment [13]. This discrepancy can be partly explained by the fact that 'silent' embolism is likely to be more common in the systemic circulation, although this may also occur in cerebral vessels [14].

Permanent AF

Vitamin K is a necessary factor in several steps in the coagulation cascade. Interference with coagulation using a vitamin K antagonist (VKA) has been a therapeutic concept for more than half a century. The principle of this treatment is prevention of the formation of thromboembolic events without affecting coagulation to an extent that causes undesirable bleeding that outweighs the beneficial effect.

The possible benefit of prophylactic VKA therapy in non-valvular AF has been explored in several randomized controlled studies. The first to be published was the Danish AFASAK study, illustrating a 54% relative risk reduction of stroke associated with a VKA regimen [15]. Since then, other randomized controlled studies exploring the role of VKA as stroke prevention in non-valvular AF have been published, in total comparing the benefit of VKA treatment in 1450 patients with AF with that of placebo in a similar-sized group of patients. When pooled together in a meta-analysis (Fig. 30.3), the relative risk reduction was highly significant and amounted to 62%, corresponding to an absolute annual risk reduction of 2.7% [16]. Notably, this was the risk reduction in those patients who were *intended to take* oral anticoagulants. The relative risk reduction for the patients who did indeed use the medication was strikingly high at 85% [17].

The stroke rates referred to above include not only

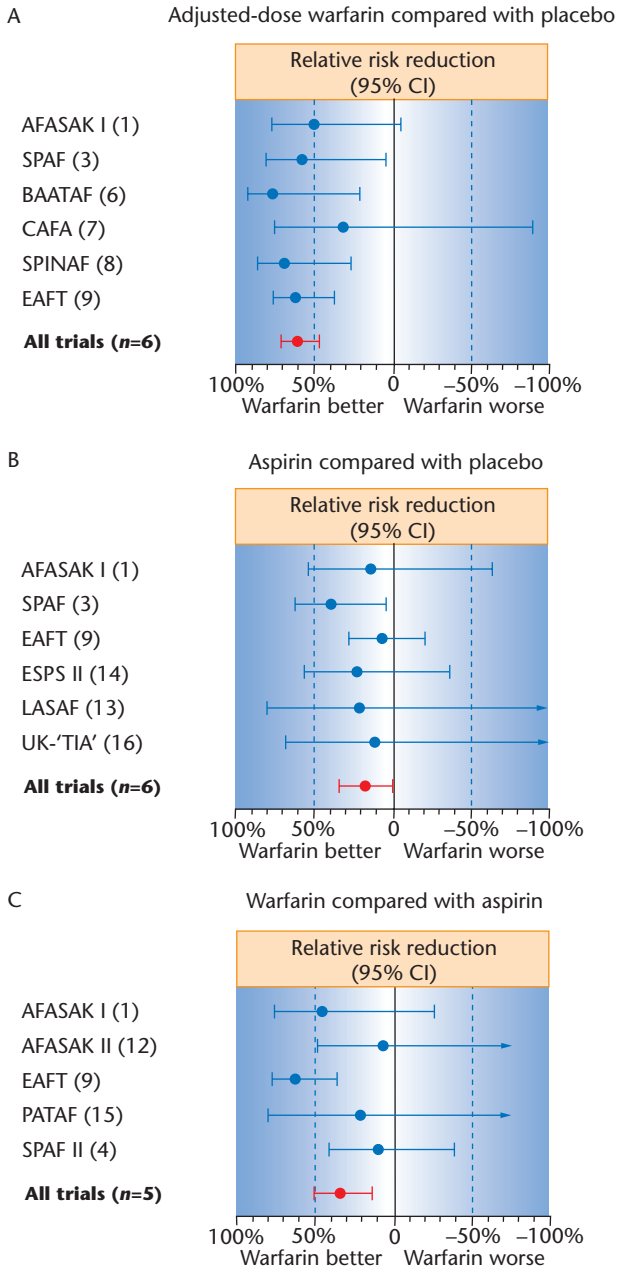

Figure 30.3 Effects on all strokes (ischaemic and haemorrhagic) of therapies for patients with atrial fibrillation: (A) adjusted-dose warfarin compared with placebo (six randomized trials); (B) aspirin compared with placebo (six randomized trials); (C) adjusted-dose warfarin compared with aspirin (five randomized trials). Horizontal lines are 95% confidence intervals around the point estimates. AFASAK, Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation Study; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation Study; EAFT, European Atrial Fibrillation Trial; ESPS II, European Stroke Prevention Study II; LASAF, Low-dose Aspirin, Stroke and Atrial Fibrillation Pilot Study; PATAF, Prevention of Arterial Thromboembolism in Atrial Fibrillation; SPAF, Stroke Prevention in Atrial Fibrillation Study; SPINAF, Stroke Prevention in Non-rheumatic Atrial Fibrillation; UK-TIA, United Kingdom TIA Study. Reproduced with permission from Hart *et al.* [16].

ischaemic strokes but also all types of haemorrhagic strokes, possibly induced by the VKA treatment. Twice as many intracranial haemorrhages occurred in the VKA study arms compared with the placebo arms, although the difference was not statistically significant (6 vs. 3 cases). Furthermore, the VKA treatment was associated with increased risk of major extracranial bleedings, corresponding to an absolute risk level of 0.3% [16].

Importantly, these studies excluded patients with low risk of embolism or markedly increased bleeding risk as well as those with the highest risk of embolism. The latter category, in which VKA treatment is strongly advised (although its benefit has not been illustrated in randomized clinical trials), includes patients who in addition to AF have a prosthetic valve or suffer from rheumatic mitral valve disease or hypertrophic cardiomyopathy. In addition, AF in the setting of hyperthyroidism is often placed in this category.

Supported by the results of the trials cited above, VKA treatment is strongly recommended for patients with AF with additional stroke risk indicators, provided there are no contraindications [18].

What is the optimal INR?

The anticoagulant effect of a fixed dose of a VKA is highly individual and markedly affected by interaction with food components and a large number of drugs. Therefore, the degree of anticoagulation in a given individual necessitates measurement of its biological effect. Currently, the level of anticoagulation in a serum sample is expressed as the international normalized ratio (INR), which is the ratio between the actual prothromin time and that of a standardized control serum. Although arguments have been raised against the accuracy of this comparative technique [19], it has become widely accepted.

The randomized controlled studies that illustrate the benefit of prophylactic VKA therapy in patients with nonvalvular AF have not used similar target anticoagulation levels, nor has a similar coagulation test been used [16]. An effort to recalculate the different target levels to INR values illustrates a possible INR variability of between 1.4 and 4.5 in these studies. Further useful information for deciding the ideal lower and upper INR limits for optimal stroke prevention [21] and avoidance of VKA-associated haemorrhagic strokes [21] has been reached by studying the occurrence of respective events in relation to the INR

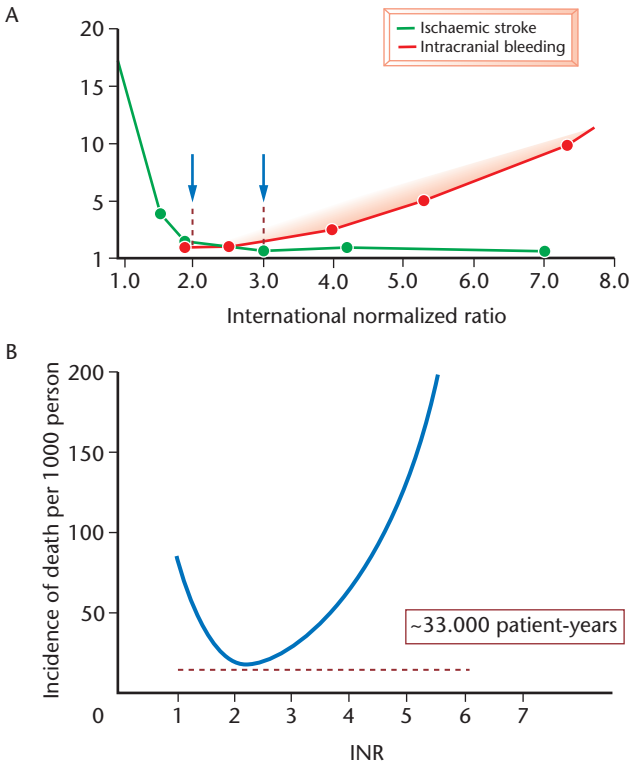

Figure 30.4 (A) Adjusted odds ratios for ischaemic stroke and intracranial bleeding in relation to international normalized ratio (INR). Reproduced with permission from Fuster *et al*. [18]. (B) Risk of death during the month following an INR test in relation to the INR value. The blue line represents the mortality risk for a 71-year-old woman. The horizontal dotted red line represents the mortality risk for the entire population of 71-year-old females. Adapted on invitation from Odén and Fahlén [22].

levels. Based on the pooled information, a consensus has been reached that an INR of 2.0–3.0 is the likely optimal range for prevention of stroke and systemic embolism in patients with non-valvular AF. A mortality risk analysis in a VKA-treated population comprising more than 40 000 patients suggests that the target INR window should be narrower, with a target value close to 2.2–2.3 [22]. Figure 30.4 illustrates the risk of ischaemic stroke and intracranial bleeding relative to the INR level as well as the 1-month mortality risk in relation to INR in patients with AF.

VKA compliance

Since optimal VKA therapy is strictly dependent on maintenance of the anticoagulation level within target INR limits, blood tests for INR measurements should be performed regularly and adjustment of VKA dose performed when necessary. In the clinical routine, attempted INR levels are never entirely reached. During follow-up of almost 13 000 patient-years of warfarin exposure, the INR was below 2.0 for 26.8%, within 2.0–3.0 for 62.5% and above 3.0 for 10.7% of the time [23]. Obviously, drug dosing is more influenced by the possible risk of treatment-induced haemorrhage due to overdosing than by the risk of thromboembolic events due to inadequate dose. Although the limited time within the intended INR range may appear disappointing, similar times in well-controlled large-scale clinical studies illustrate that both under- and over-dosing problems are difficult to avoid. Thus, in the hitherto largest anticoagulation study of non-valvular AF patients with one warfarin-treatment arm, the INR was within the intended range of 2.0–3.0 for 66% of the time [24], and otherwise equally often above as below the range.

In addition to the fear of drug-induced bleeding complications, proper VKA treatment is associated with several other mechanisms that may contribute to the widely verified underuse of this treatment in patients with non-valvular AF [25]. In summary, the barriers to the use of VKA treatment in non-valvular AF patients may relate to the doctor as well as the patient and the health-care system. Together, these factors lead to a 50% or more underuse of VKA treatment in the large cohort of patients with non-valvular AF.

Role of antiplatelet agents

Six independent randomized controlled studies, together including slightly more than 3000 patients, have explored the prophylactic effects of acetylsalicylic acid (ASA) compared with placebo on the risk of embolism in patients with AF (Fig. 30.3) [16]. Although the numbers of events were numerically fewer in the ASA arms of all studies, the difference reached statistical significance in only one of them. When the outcomes of these studies were pooled in a meta-analysis, the difference reached significance, amounting to a relative risk reduction of 22% (Fig. 30.3) [16]. Several important differences exist between the six studies. Three of them, corresponding to about one-third of all patients, studied the role of ASA as secondary prevention. Also, the dose differed markedly between the studies, ranging from 50 to 1300 mg daily.

Direct comparison between the effects of VKA and ASA has been undertaken in five studies, illustrating that the former treatment was significantly superior with a relative risk reduction of 36% [16]. Although the risk reduction following ASA treatment in AF is lower than that of VKA treatment, the risk of major haemorrhage is also lower [16]. ASA is therefore used in patients with a moderate-to-low risk of embolism but also in patients who are concerned about the risk of bleeding due to VKA treatment.

The role of other and new antiplatelet drugs, particularly clopidogrel, for primary or secondary stroke prevention in AF patients awaits further exploration.

Drug combinations

Several attempts have been made to combine drugs with different antithromboembolic mechanisms, mostly low-dose VKA treatment with an antiplatelet drug [3,13,16]. No study has shown any superior outcome for a drug combination compared with dose-adjusted VKA only in preventing stroke or embolism in non-valvular AF.

Investigational drugs

Several oral direct thrombin inhibitors have been developed as possible alternatives to VKA. Presently, ximelagatran is being tested in large-scale clinical studies [24]. The role of this compound as an alternative to VKA has been explored in two parallel studies, including more than 7000 patients with non-valvular AF and at least one additional stroke risk factor. When data from the studies were pooled according to a pre-specified decision, the risk of stroke or systemic embolism was found to be equally low in both treatment arms [26]. Thus, the annual event rate was 1.6%, a figure markedly lower than the anticipated rate of 3.1%, estimated during study planning from the inclusion criteria which were used [27]. A transitory elevation of alanine aminotransferase three times above the upper limit of normal or more was observed in about 6% of the patients, prompting discontinuation of treatment in about half of them according to predefined criteria. The increased alanine aminotransferase values returned towards normal in a similar way, regardless of whether the treatment was continued or not.

Other direct thrombin inhibitors as well as factor Xa inhibitors have been developed with the goal of substituting the present VKA treatment. The possible benefit of these drugs is pending clinical studies.

Paroxysmal atrial fibrillation

Paroxysmal AF (PAF) is not a well-defined entity, comprising a variable number and duration of individual attacks. The rate of embolism has not been adequately explored with regard to this variability. Also, the effect of prophylactic treatment in PAF patients without any obvious underlying disease is much less explored than in permanent AF.

A retrospective hospital record study followed more than 400 individuals with PAF for more than 25 years [28]. All patients had some kind of underlying disorder, most of them being cardiovascular, but no primary VKA prophylaxis was given. The study highlighted a variable risk of embolism with regard to the different stages of the arrhythmia. A distinct clustering of embolism was thus seen at the time of onset of PAF, namely 6.8% during 1 month. Later, the annual embolic rate varied from 0.6 to 2.6%. Following transition to permanent AF, which occurred in every third patient, the rate of embolism rose to a significantly higher level. Another study, exploring the embolic risk factors in more than 700 patients with PAF, verified a 2.2% annual rate of embolism, typically occurring in males above the age of 65 [29]. Importantly, individuals without any underlying disorder had a low embolic event rate (0.7% per year).

Some of the earlier described randomized controlled studies that evaluated the efficacy of VKA treatment against placebo had included patients who suffered intermittent AF, altogether 207 cases [3]. The annual stroke rates in these patients were 1.7% (VKA treated) and 5.7% (controls). Using univariate analysis, intermittent AF did not appear as a significant risk factor within the cohort of control patients.

The evidence for recommendation of prophylactic treatment against embolism in PAF patients is thus very limited. Despite this, current guidelines suggest that prevention of thromboembolism is appropriate in patients with recurrent PAF [18]. Obviously, there is a need for further exploration of the true relation between type and severity of PAF, risk of embolism and the benefit as well as risk of prophylactic VKA treatment.

Atrial flutter

The atrial rate is slower during atrial flutter than during AF. Theoretically, this arrhythmia may have a lower risk for inducing atrial myocardial remodelling, impaired LAA function, thrombus formation and embolism. Large-scale prospective observational or interventional studies on the stroke rate in atrial flutter are lacking. However, the risk of stroke linked to atrial flutter has been studied retrospectively in a large number of older patients [30]. Hospital records of more than 17 000 patients with atrial flutter and 330 000 with AF disclosed a stroke risk ratio between these populations of 0.9.

Although the result of VKA treatment has not been specifically studied in the setting of atrial flutter, it is generally advised that the antithromboembolic treatment of a patient with atrial flutter should follow the same rules as if the patient suffered AF [18].

Cardioversion

The increased risk of embolism following cardioversion is well recognized. An observational study published shortly after the direct-current cardioversion technique became available reported a markedly increased cardioversion-

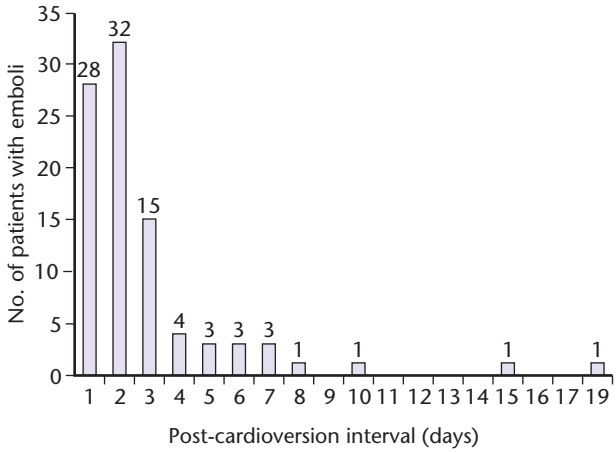

Figure 30.5 Interval between cardioversion and thrombotic events in 92 patients. Reproduced with permission from Berger and Schweitzer [32].

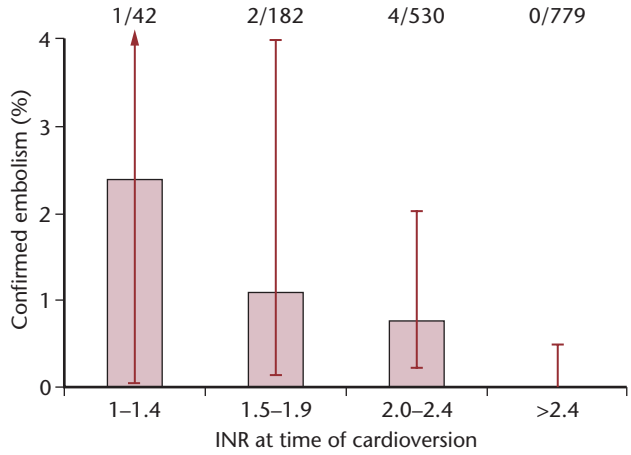

Fig 30.6 Relation between international normalized ratio (INR) at the time of cardioversion and subsequent embolism. Reproduced with permission from Gallagher *et al*. [34].

related embolism rate when no VKA treatment had been given [31]. Therefore, full antithromboembolic treatment is considered mandatory before elective cardioversion in cases where AF duration exceeds 48 h [18]. Despite these precautions, embolism has been reported to occur in up to 2% of all electrical cardioversions [32]. These occur typically during the initial few days following reappearance of sinus rhythm (Fig. 30.5).

The mechanism behind post-cardioversion embolism is complex. Pre-existing thrombi may dislodge from the endocardial wall when the atria resume a slower and regular rhythm. However, following conversion from AF to sinus rhythm, the mechanical function of the atrial myocardium is not immediately restored [33], presenting an opportunity for thrombus formation.

The importance of an adequate anticoagulation level at the time of cardioversion must be stressed. In pooled material, comprising more than 2500 elective direct-current cardioversion attempts in almost 2000 patients, no post-cardioversion embolism could be confirmed when the INR exceeded 2.4 on the day of the procedure [34]. In contrast, embolism was increasingly more common at a lower INR and appeared to increase with decreasing INR (Fig. 30.6).

Current guidelines state that VKA treatment (INR 2.0–3.0) should be given for at least 3–4 weeks before as well as after cardioversion of a patient in whom AF has been maintained for more than 48 h or which is of unknown duration [18]. This regimen is recommended irrespective of whether the cardioversion is performed using a pharmacological or an electrical method.

TOE-guided cardioversion

The 3–4 week period of adequate anticoagulation prior to cardioversion can be shortened with the use of TOE. This technique may not only disclose thrombi within the LAA or the left atrium proper but also identify indicators for thrombus formation. The safety and applicability of TOE-guided cardioversion has been repeatedly verified [35,36]. Following exclusion of any thrombus, anticoagulation can commence with low-molecular-weight heparin [36,37]. The 3–4 week post-cardioversion protection from embolism implies that oral VKA treatment is generally started at the same time. When the INR has reached the intended target level, this is maintained as the sole antithromboembolic treatment.

Non-pharmacological antithrombotic methods

Since the LAA hosts the vast majority of all left atrial thrombi in cases of non-valvular AF [5], different techniques have been developed that aim to eliminate this source of possible embolization. The result of LAA resection in patients who undergo cardiac surgery for other reasons has been tested in a series of more than 400 patients [38]. No strokes were reported following surgery and it has been suggested that the LAA should be resected 'whenever the chest is open'. Arguments against this concept are the potential risk of the procedure, the possibility of incomplete resection and the elimination of a physiological component in body fluid regulation [39]. The possible wider use of this technique is pending the result of an ongoing randomized study [40].

Other non-pharmacological techniques for elimination of the LAA as a possible thrombotic location are currently undergoing clinical evaluation, including thoracoscopic obliteration of the LAA [5] as well as endocardial occlusion of the LAA with different devices [41,42]. Figure 30.7 illustrates three different devices that can be inserted in the LAA as possible stroke prevention in AF.

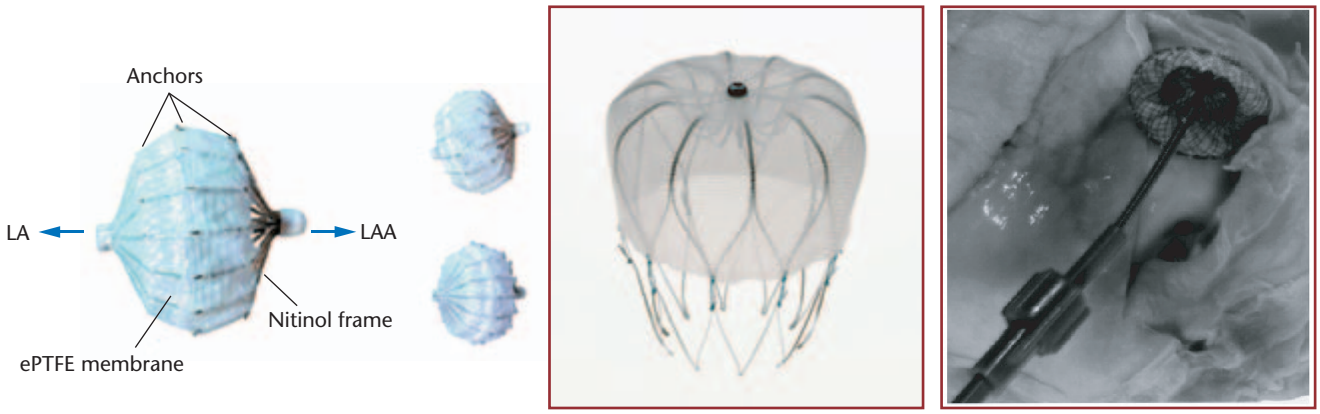

Figure 30.7 Devices used for endocardial occlusion of left atrial appendage. Left to right: PLAATO device, Watchman device and Amplatzer device. The Amplatzer device, originally developed for occlusion of atrial septal defects, is positioned in the opening of the left atrial appendage. Reproduced with permission from Sievert *et al*. [41], Atritec Inc. and Meier *et al*. [42].

Table 30.2 ACC/AHA/ESC recommendations for antithrombotic therapy in patients with atrial fibrillation (AF)

Solid scientific evidence/unanimous agreement

1 Administer antithrombotic therapy (oral anticoagulation or aspirin) to all patients with AF, except those with lone AF, to prevent thromboembolism

2 Individualize the selection of the antithrombotic agent based on assessment of the absolute risks of stroke and bleeding and the relative risk and benefit for a particular patient

3 Chronic oral anticoagulant therapy in a dose adjusted to achieve a target intensity of INR 2–3 in patients at high risk of stroke, unless contraindicated
- (a) The need for anticoagulation should be re-evaluated at regular intervals
- (b) INR should be determined at least weekly during the initiation of oral anticoagulation therapy and monthly when the patient is stable

4 Aspirin in a dose of 325 mg daily is an alternative in low-risk patients or in those with certain contraindications to oral anticoagulation

5 Oral anticoagulation for patients with AF who have rheumatic mitral valve disease or prosthetic heart valves (mechanical or tissue valves)

6 Base the target intensity of anticoagulation on the particular type of prosthesis, but it should not be less than INR 2–3

7 Administer anticoagulation therapy regardless of the method (electrical or pharmacological) used to restore sinus rhythm

8 Anticoagulate patients with AF lasting > 48 h or of unknown duration for at least 3–4 weeks before and after cardioversion (INR 2–3)

9 Perform immediate cardioversion in patients with acute (recent-onset) AF accompanied by symptoms or signs of haemodynamic instability resulting in angina pectoris, myocardial infarction, shock or pulmonary oedema, without waiting for prior anticoagulation
- (a) If not contraindicated, administer heparin concurrently by an initial intravenous bolus injection followed by a continuous infusion in a dose adjusted to prolong the activated partial thromboplastin time at 1.5–2 times the reference control value
- (b) Next, provide oral anticoagulation (INR 2–3) for a period of at least 3–4 weeks, as for patients undergoing elective cardioversion
- (c) Limited data from recent studies support subcutaneous administration of low-molecular-weight heparin in this indication

10 Screening for the presence of thrombus in the left atrium or left atrial apppendix by TOE is an alternative to routine pre-anticoagulation in candidates for AF cardioversion
- (a) Anticoagulate patients in whom no thrombus is identified with intravenous unfractionated heparin by initial bolus injection before cardioversion, followed by continuous infusion in a dose adjusted to prolong the activated partial thromboplastin time at 1.5–2 times the reference control value
- (b) Next, provide oral anticoagulation (INR 2–3) for a period of at least 3–4 weeks, as for patients undergoing elective cardioversion
- (c) Limited data are available to support the subcutaneous administration of low-molecular-weight heparin in this indication
- (d) Treat patients in whom thrombus is identified by TOE with oral anticoagulation (INR 2–3) for at least 3–4 weeks before and after restoration of sinus rhythm

(*Continued on p. 899*)

Table 30.2 (*Cont'd*)

Conflicting evidence but favouring following guidelines

1 Target a lower INR of 2 (range 1.6–2.5) for primary prevention of ischaemic stroke and systemic embolism in patients over 75 years old considered at increased risk of bleeding complications but without frank contraindications to oral anticoagulant therapy
2 Manage antithrombotic therapy for patients with atrial flutter, in general, as for those with AF
3 Select antithrombotic therapy by the same criteria irrespective of the pattern of AF (i.e. for patients with paroxysmal, persistent or permanent AF)

Conflicting evidence, less well established

1 Interrupt anticoagulation for a period of up to 1 week for surgical or diagnostic procedures that carry a risk of bleeding, without substituting heparin in patients with AF who do not have mechanical prosthetic heart valves
2 Administer unfractionated or low-molecular-weight heparin, intravenously or subcutaneously respectively, in selected high-risk patients or when a series of procedures require interruption of oral anticoagulant therapy for a period longer than 1 week
3 Manage patients with coronary artery disease with anticoagulation (INR 2–3) based on the same criteria used for patients without coronary artery disease
   (a) A low dose of aspirin (< 100 mg/day) or clopidogrel (75 mg/day) may be given concurrently with anticoagulation, but these strategies have not been evaluated sufficiently and may be associated with an increased risk of bleeding
4 Treatment with aspirin is optional for primary prevention of stroke in patients under 60 years of age without heart disease or risk factors for thromboembolism (lone AF)
5 Cardioversion without TOE guidance during the first 48 h after the onset of AF
   (a) In these cases, anticoagulation before and after cardioversion is optional, depending on assessment of risk
6 Anticoagulate patients with atrial flutter undergoing cardioversion in the same way as for patients with AF

Evidence/agreement that procedure is not useful, maybe even harmful

1 Long-term anticoagulation for stroke prevention in patients under 60 years of age without heart disease (lone AF) and without risk factors for thromboembolism

INR, international normalized ratio; TOE, transoesophageal echocardiography.
Adapted with permission from Fuster *et al*. [18].

Guidelines

International guidelines for the care of patients with AF provide recommendations for different clinical situations [18]. Table 30.2 presents the recommendations concerning antithromboembolic treatment. Currently, these guidelines are being re-evaluated. The reader is encouraged to visit the most current guidelines via the ESC home page (http://www.escardio.org).

Rhythm versus rate control

Independently of the need for anticoagulation, the two fundamental ways to manage AF are (1) restoration and maintenance of sinus rhythm and (2) ventricular rate control while allowing perpetuation of AF. The theoretical advantages of rhythm control over rate control include relief of symptoms, prevention of embolism and avoidance of cardiomyopathy. Which strategy is preferable on a long-term basis remains debatable despite the publication of recent trials that have addressed this issue [43–46]. These studies have answered some questions but have raised others, precluding definite conclusions in daily practice.

Indeed, all four studies found no difference between the two strategies as far as the various primary end-points were concerned, i.e. symptom improvement [43], overall mortality [46] or a combination of events including death and systemic embolism [43]. However, rhythm control patients required more hospitalization [43,44] and experienced more treatment-related adverse effects [43,45,46]. On the other hand, when analysed by rhythm, the primary end-point occurred less frequently in patients in sinus rhythm both in STAF [44] and AFFIRM [46,47]. Thus the results may have been better in the rhythm control group if sinus rhythm had been maintained in a larger proportion of patients.

A rate-control approach is proposed as first-line treatment in older (> 70 years) or in minimally symptomatic patients, while a rhythm-control strategy is justified after a first episode of AF or when symptoms cannot be satisfactorily improved by rate control [18].

Conversion to sinus rhythm

Cardioversion is generally performed electively to restore sinus rhythm in patients with persistent AF. Occasionally, however, cardioversion has to be performed urgently when the arrhythmia is the main factor responsible for acute heart failure, hypotension or worsening of angina pectoris. The pathophysiology of these clinical conditions is related to a fast ventricular rate driven by AF and/or to the loss of the atrial contribution to left ventricular filling. The latter is of particular importance in terms of haemodynamic impairment in patients with hypertrophic cardiomyopathy, mitral stenosis, restrictive cardiomyopathy, hypertension or in patients with an acute inferior wall infarction with right ventricular involvement. Hence, the need for urgent cardioversion is usually encountered in patients with underlying structural heart disease, although such a situation may also be observed in patients with AF or atrial flutter and a rapidly conducting atrioventricular accessory pathway (Wolff–Parkinson–White syndrome) and an otherwise normal heart. Recommendations for cardioversion of AF emanating from the American Heart Association (AHA), American College of Cardiology (ACC) and European Society of Cardiology (ESC) [18] are listed in Table 30.3.

After resolving to cardiovert the patient, it should be decided whether the procedure should be performed using antiarrhythmic drugs or direct-current shock. For

Table 30.3 ACC/AHA/ESC recommendations for pharmacological or electrical cardioversion of atrial fibrillation (AF). Recommendations are evidence-based and derived primarily from published data

Clinical situations	Type of treatment	Recommendation class*	Level of evidence†
Patients with paroxysmal AF and a rapid ventricular response who have ECG evidence of acute myocardial infarction, or symptomatic hypotension, angina or heart failure that does not respond promptly to pharmacological measures	Immediate electrical cardioversion	I	C
Absence of haemodynamic instability but unacceptable symptoms related to AF	Cardioversion	I	C
First-detected episode of AF	Cardioversion	IIa	C
Patients with persistent AF and low probability of an early recurrence	Electrical cardioversion	IIa	C
Relapse of AF after successful cardioversion in a patient without antiarrhythmic medication	Cardioversion followed by prophylactic drug therapy	IIa	C
Patients with persistent AF	Pharmacological cardioversion	IIb	C
First-detected, paroxysmal or persistent AF in patients without heart disease or when safety of the drug in the particular patient has been verified	Out-of-hospital pharmacological cardioversion	IIb	C
Patients who display spontaneous alternation between AF and sinus rhythm over short periods of time	Electrical cardioversion	III	C
Patients with short periods of sinus rhythm who relapse to AF despite multiple cardioversion procedures and prophylactic antiarrhythmic drug treatment	Additional cardioversion	III	C

*Recommendation classes are defined as follows: I, conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective; II, conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment; IIa, the weight of evidence or opinion is in favour of the procedure or treatment; IIb, usefulness/efficacy is less well established by evidence or opinion; III, conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful.
†Level of evidence is defined as follows: A, data derived from multiple randomized clinical trials; B, data are based on a limited number of randomized trials, non-randomized studies or observational registries; C, the primary basis for the recommendation is expert consensus.
Adapted with permission from Fuster *et al*. [18].

this purpose, the advantages and disadvantages of both techniques should be carefully weighed. Briefly, electrical cardioversion is more effective than medications and has an immediate effect, but it requires general anaesthesia or heavy sedation. With antiarrhythmic drug cardioversion, the time to conversion cannot be predicted and adverse events related to pro-arrhythmic or negative inotropic effects may occur. As regards the choice between pharmacological and electrical approaches, haemodynamic stability and duration of the arrhythmia are the two key parameters in decision-making. Immediate cardioversion using an electrical shock rather than intravenous drugs is indicated when there is haemodynamic instability. Because a successful chemical conversion is less likely, electrical cardioversion may also be a first-line option in patients with long-lasting AF.

Pharmacological cardioversion

Prior to 1963, when electrical cardioversion became available, antiarrhythmic drugs were the first and only option. Self-termination of AF is observed in nearly 70% of patients within 24 h after recent-onset AF [48]. The probability that spontaneous cardioversion will occur decreases in relation to the duration of the arrhythmia, with the result that only 45% of patients with onset of AF 24–72 h previously will have spontaneous termination of the arrhythmia [48]. After 7 days of ongoing AF, the

Table 30.4 ACC/AHA/ESC recommendations for pharmacological cardioversion of atrial fibrillation of ≤ 7 days' duration

Drug*	Route of administration	Recommendation class	Level of evidence
Agents with proven efficacy			
Dofetilide	Oral	I	A
Flecainide	Oral or intravenous	I	A
Ibutilide	Intravenous	I	A
Propafenone	Oral or intravenous	I	A
Amiodarone	Oral or intravenous	IIa	A
Quinidine	Oral	IIb	B
Less effective or incompletely studied agents			
Procainamide	Intravenous	IIb	C
Digoxin	Oral or intravenous	III	A
Sotalol	Oral or intravenous	III	A

*Drugs are listed alphabetically within each category of recommendation and level of evidence.
For definitions of recommendation classes and levels of evidence, see Table 30.3.
Adapted with permission from Fuster *et al*. [18].

Table 30.5 ACC/AHA/ESC recommendations for pharmacological cardioversion of atrial fibrillation of > 7 days' duration

Drug*	Route of administration	Recommendation class	Level of evidence
Agents with proven efficacy			
Dofetilide	Oral	I	A
Amiodarone	Oral or intravenous	IIa	A
Ibutilide	Intravenous	IIa	A
Flecainide	Oral	IIb	B
Propafenone	Oral or intravenous	IIb	B
Quinidine	Oral	IIb	B
Less effective or incompletely studied agents			
Procainamide	Intravenous	IIb	C
Sotalol	Oral or intravenous	III	A
Digoxin	Oral or intravenous	III	C

*Drugs are listed alphabetically within each category of recommendation and level of evidence.
For definitions of recommendation classes and levels of evidence, see Table 30.3.
Adapted with permission from Fuster *et al*. [18].

likelihood that sinus rhythm will resume spontaneously is so low that the arrhythmia is then defined as 'persistent' AF in the current classification [49].

Interestingly, antiarrhythmic drug efficacy for AF cardioversion also depends upon the duration of AF, with the treatment being more effective when initiated within 7 days after the onset of the arrhythmia. Hence, pharmacological cardioversion can be achieved in nearly 71% of patients with recent-onset AF but in only 35% of patients with persistent AF [50].

Antiarrhythmic drugs proven to be effective for cardioversion of AF and recommended by the AHA/ACC/ESC guidelines [18] are summarized in Tables 30.4 and 30.5. The ESC committee and AHA/ACC Task Force members stated that propafenone, flecainide, ibutilide or dofetilide should be the first-line choice (recommendation class I) whereas amiodarone should be the second-line choice (recommendation class IIa) when pharmacological cardioversion of recent (< 7 days duration) AF was considered. In patients with longer (> 7 days) AF duration, the choice of antiarrhythmic drugs is limited to dofetilide (recommendation class I), ibutilide and amiodarone (recommendation class IIa). For each medication, the recommended dosage and administration routes are listed in Table 30.6.

Deneer *et al*. [51] have reviewed clinical studies published between 1966 and 2001 of oral antiarrhythmic drugs for converting recent-onset AF. Oral sotalol, digoxin and verapamil were not effective in converting AF to sinus rhythm. Among the medications proven to be effective (versus placebo) in converting recent-onset AF, the conversion rates of an oral loading dose of propafenone 600 mg varied between 37 and 41% at 4 h and after a single oral dose of flecainide 300 mg sinus rhythm was restored in 59–68% of patients at 3 h.

When given intravenously, antiarrhythmic drugs may restore sinus rhythm within a very short period of time. Conversion rates in relation to time after infusion appear to be higher [52] with class IC drugs (flecainide and propafenone) compared with class IA drugs (procainamide, quinidine) or class III drugs (amiodarone, dofetilide, ibutilide, sotalol) (Fig. 30.8). Hence, within 1 h after infusion, sinus rhythm is restored in 50–90% of patients with flecainide or propafenone. Special attention should be drawn to amiodarone which is associated with a late onset of conversion (Fig. 30.8). Flecainide given intravenously is more effective than placebo, verapamil, digoxin, procainamide, propafenone and amiodarone and as effective and safe as ibutilide [53].

Which medication should be selected to achieve pharmacological cardioversion depends not only on efficacy but also on safety (see Table 30.6), contraindication and cost-effectiveness. As far as this last point is concerned, ibutilide is a rather expensive treatment, since it is about 30 times less cost-effective than other antiarrhythmic drugs. Class IC antiarrhythmic drugs (flecainide and propafenone) should not be administered if heart failure (or impaired cardiac function), acute ischaemia, known sick

Table 30.6 ACC/AHA/ESC recommended doses of drugs proven effective for pharmacological cardioversion of atrial fibrillation

Drug*	Route of administration	Dosage	Potential adverse effects
Amiodarone	Oral Intravenous/oral	200–400 mg/day after loading dose Up to 1.8 g/day using intravenous route	Hypotension, bradycardia, QT prolongation, torsade de pointes (rare), gastrointestinal upset, constipation, phlebitis (when given intravenously)
Dofetilide	Oral	Depending on creatinine clearance	QT prolongation, torsade de pointes
Flecainide	Oral Intravenous	200–300 mg/day† 1.5–3.0 mg/kg over 10–20 min†	Hypotension, rapidly conducting atrial flutter
Ibutilide	Intravenous	1 mg over 10 min	QT prolongation, torsade de pointes
Propafenone	Oral Intravenous	450–600 mg 1.5–2.0 mg/kg over 10–20 min†	Hypotension, rapidly conducting atrial flutter
Quinidine‡	Oral	0.75–1.5 g/day	QT prolongation, torsade de pointes, gastrointestinal upset, hypotension

*Drugs are listed alphabetically.
†Insufficient data are available on which to base specific recommendations for the use of one loading regimen over another for patients with ischaemic heart disease or impaired left ventricular function, and these drugs should be used cautiously or not at all in such patients.
‡The use of quinidine loading is controversial. Quinidine should be used with caution.
Adapted with permission from Fuster *et al*. [18].

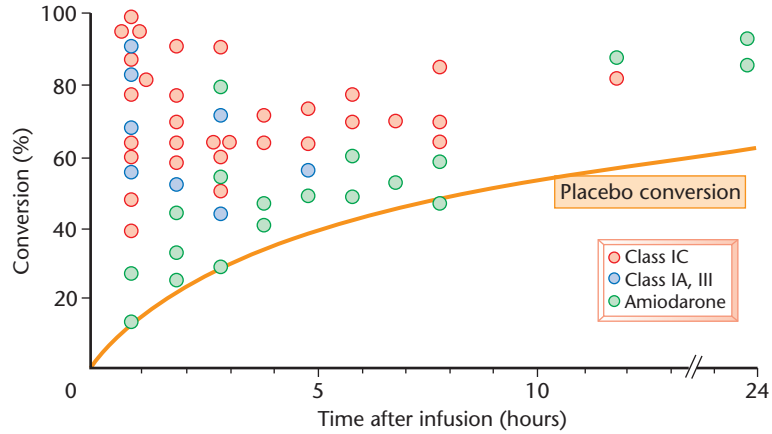

Figure 30.8 Conversion rates of paroxysmal atrial fibrillation (< 3 days) in relation to time after start of the infusion found in studies investigating the efficacy of class IC drugs (flecainide, propafenone), class IA and III drugs (procainamide, quinidine, sotalol, ibutilide, dofetilide), and amiodarone are presented. The curve indicating placebo conversion was constructed from placebo conversion rates. Class IC drugs appear most efficacious. Note the late onset of conversion with amiodarone. Adapted with permission from Fresco *et al*. [52].

sinus syndrome or atrioventricular conduction disturbance is present. Amiodarone is recommended for haemodynamically compromised patients because of its less negative inotropic effect. The other advantage of amiodarone is its ability to slow atrioventricular conduction and control the ventricular rate.

Electrical cardioversion

Direct-current cardioversion of AF was first reported by Lown in 1963 [54]. The term 'direct-current cardioversion' implies delivery of an electrical shock synchronized with the intrinsic activity of the heart to avoid electrical discharge during the vulnerable period, when there is a risk of inadvertent induction of ventricular fibrillation. Usually, the R wave of the surface ECG is chosen for this synchronization since it can be easily sensed by the defibrillator.

External electrical cardioversion is achieved by means of cutaneous electrode paddles positioned directly on the chest wall. Cardioversion is performed with the patient having fasted and under adequate general anaesthesia (or sedation) in order to avoid pain related to delivery of the electrical shock. The success of cardioversion is determined by the current density that traverses the muscle of the chamber to be defibrillated. The intensity of current that flows depends on the output waveform, selected energy level and the transthoracic impedance. The higher the impedance, the lower the current delivered. The determinants of transthoracic impedance mainly include body habitus, the interface between the electrode and skin, and the size and position of the electrode paddles. For successful cardioversion, a critical mass of atrial muscle has to be encompassed by the electrical field. This is the rationale for using the anteroposterior paddle position rather than the anterolateral paddle position. However, some randomized studies [55–57] have shown greater success with the anteroposterior configuration, whereas others [58–60] observed no difference in relation to paddle position. Since the anteroposterior paddle position has never been shown to be worse than the anterolateral, this configuration is the first choice in clinical practice. Because the optimum paddle configuration for a given patient is not known before cardioversion, the clinician should consider an alternative arrangement if the initial position is unsuccessful. To encompass as much atrial muscle as possible, Mehdirad *et al*. [61] have recently shown that optimization of electrode paddle position using fluoroscopy resulted in an improved cardioversion success rate.

Most devices used for external cardioversion deliver current with a monophasic waveform (Fig. 30.9) with a maximum energy output limited to 360 J. The success rate for cardioversion of persistent AF is usually around 80% [62–64]. Success of electrical cardioversion is related to several clinical parameters. Hence, electrical cardioversion of persistent AF is unlikely to succeed in patients with AF duration longer than 3 years or left atrial size larger than 60 mm. Identified predictors of failure include long arrhythmia duration, left atrial enlargement, pres-

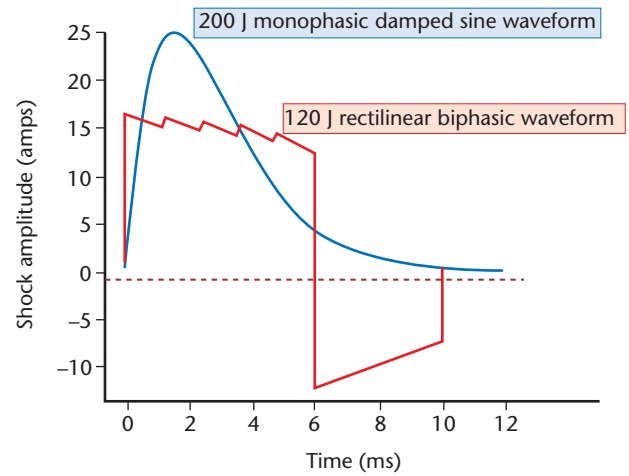

Figure 30.9 Monophasic versus biphasic waveforms. Reproduced with permission from Niebauer *et al*. *Am J Cardiol* 2004; **93**: 1495–1499.

ence of underlying heart disease, cardiomegaly and obesity [62–65]. A 100-J shock is often too low to be successful so an initial energy of 200 J is recommended for electrical cardioversion of AF. Because dermal injury at the interface between electrode and the skin increases with higher energy levels, some physicians use a stepwise energy approach, starting with an initial 200-J shock and increasing the energy output in increments of 100 J until a maximum of 400 J is reached (400 J stored energy is equivalent to 360 J of delivered energy). Alternatively, starting with higher energies may reduce the number of shocks (and thus the total energy) delivered.

The most modern type of external defibrillator delivers the current with a biphasic waveform (Fig. 30.9). The maximum energy output is limited to 200 J. Recent randomized studies [66–68] have shown that biphasic defibrillators have greater efficacy, require fewer shocks and lower delivered energy, and result in less skin burns than monophasic defibrillators. The efficacy of transthoracic cardioversion was more than 90% with a biphasic shock waveform.

After one or two failed cardioversion attempts with maximum energy output at both paddle postions, antiarrhythmic drugs before further shock delivery, double shocks (delivery of energy with the use of two defibrillators) or internal cardioversion may be considered. In 1988, Lévy *et al*. [69] introduced internal cardioversion of AF using high-energy (200–300 J) direct current delivered between a catheter positioned in the right atrium and a backplate. In a randomized trial [70] using a monophasic defibrillator for external cardioversion in the control group, higher acute conversion rates were observed in the biphasic internal cardioversion group (91% vs. 67%, $P = 0.002$), particularly in obese patients and patients with chronic obstructive lung disease. So far, high-energy internal cardioversion has not been tested against external biphasic waveform cardioversion. Other techniques for internal cardioversion apply low-energy (< 20 J) shocks via a large-surface electrode catheter (cathode) in the right atrium and another catheter (anode) positioned in the coronary sinus or the left pulmonary artery [71–73]. One potential advantage is that low-energy internal cardioversion does not require general anaesthesia but can be performed under light sedation. Transoesophageal cardioversion has also been studied as an alternative approach for external cardioversion. With this technique, intermediate-level energy (20–50 J) is delivered between oesophageal electrodes and a mid-sternum patch. It has been proved to be safe and efficacious [74,75] and can be combined with transoesophageal echocardiography [76] to exclude a thrombus just prior to cardioversion.

Use of antiarrhythmic drugs has been proposed as an adjunctive strategy (hybrid therapy) to enhance electrical cardioversion (Table 30.7). One potential advantage

Table 30.7 Pharmacological treatment before cardioversion in patients with persistent atrial fibrillation: effects of various antiarrhythmic drugs on acute and subacute outcome of transthoracic direct-current shock

	Enhance conversion by DC shock and prevent IRAF*	Suppress SRAF and maintenance therapy class	Recommendation class	Level of evidence
Effective	Amiodarone	Y		
	Flecainide	Y		
	Ibutilide	N		
	Propafenone	Y	I	B
	Propafenone/verapamil	Y		
	Quinidine	Y		
	Sotalol	Y		
Uncertain/unknown	Beta-blockers	Y		
	Diltiazem	Y		
	Disopyramide	N	IIb	B
	Dofetilide	N		
	Procainamide	N		
	Verapamil	Y		

*Drugs are listed alphabetically within each recommendation class.
All drugs (except beta-blockers and amiodarone) should be initiated in hospital. IRAF, immediate recurrence of atrial fibrillation; SRAF, subacute recurrence of atrial fibrillation; DC, direct current. For definitions of recommendation classes and levels of evidence, see Table 30.3.
Adapted with permission from Fuster *et al*. [18].

of this approach is that it may prevent subacute recurrences after conversion since adequate plasma levels are present at the moment of sinus rhythm restoration. In contrast, antiarrhythmic drugs are associated with a risk of pro-arrhythmia and may increase the defibrillation threshold (especially with class IC drugs). Of the different randomized clinical trials that have evaluated the efficacy of antiarrhythmic agents before direct-current cardioversion compared with direct-current cardioversion alone, none has demonstrated increased efficacy with the addition of quinidine, propafenone, flecainide or sotalol [77,78]. One study demonstrated improved efficacy with ibutilide pretreatment [79]. Pretreatment with amiodarone [80,81] is also associated with improved efficacy of electrical cardioversion. Although not well demonstrated, antiarrhythmic treatment may be initiated before electrical cardioversion in order to facilitate maintenance of sinus rhythm after cardioversion.

Transient ST-segment elevation may appear on the ECG after cardioversion and serum levels of creatine kinase may be increased whereas troponin-T and troponin-I levels are not. Myocardial damage related to electrical cardioversion is not observed at a microscopic level.

Cardioversion is contraindicated in cases of digitalis toxicity because a malignant ventricular arrhythmia may be triggered by the direct-current shock. However, it is not usually necessary to interrupt digoxin use before elective cardioversion of AF since a serum digoxin level in the therapeutic range is not associated with the induction of malignant ventricular arrhythmias during cardioversion. Because hypokalaemia may precipitate a malignant ventricular arrhythmia after cardioversion, serum potassium levels should be in the normal range before direct-current shock delivery. Appropriate anticoagulation prior to cardioversion is mandatory (see above).

Prevention of recurrences

After successful cardioversion

Post-cardioversion studies [84–87] have established several patterns of recurrence (Fig. 30.10) after electrical cardioversion of persistent AF. In some patients AF reappears within a couple of minutes after a period of sinus rhythm (immediate recurrence of AF, IRAF), in other patients recurrence is delayed from 2 min to 2 weeks (subacute recurrence of AF, SRAF) and finally late recurrence may be observed (> 2 weeks after cardioversion). IRAF occur in approximately 15–20% of patients undergoing electrical cardioversion, SRAF in about 25–35% and late recurrences in 10–20%.

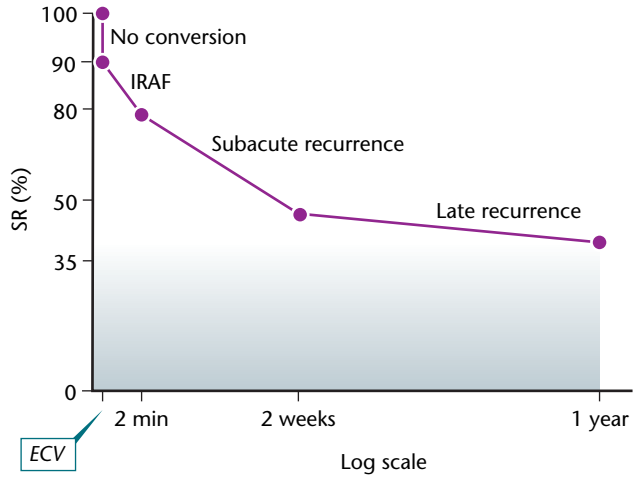

Figure 30.10 Hypothetical illustration of arrhythmia outcome after electrical cardioversion. Three types of recurrence after electrical cardioversion of persistent atrial fibrillation are shown (immediate, subacute and late). ECV, external cardioversion; IRAF, immediate recurrence of AF after cardioversion; SR, sinus rhythm. Adapted with permission from Fuster *et al.* [18] and van Gelder *et al.* [87].

Only recently have randomized studies specifically addressed the issue of IRAF and SRAF and controlled studies are still needed to determine the most effective treatment of these forms of recurrence. Antiarrhythmic drugs proven to be effective in preventing IRAF [18,88] include quinidine, propafenone (alone or in combination with verapamil), flecainide, sotalol, amiodarone and ibutilide. These drugs are approved (see Table 30.7) for prevention of IRAF after electrical cardioversion in the current guidelines [18]. The same medications were also shown to be effective in preventing SRAF, except ibutilide [88]. Two recent publications [89,90] observed that beta-blockers were also efficient in the prevention of SRAF after electrical cardioversion. Beta-blockers, amiodarone, sotalol, flecainide, propafenone and quinidine are approved (see Table 30.7) for prevention of SRAF in the current AHA/ACC/ESC guidelines [18].

Which patient should receive an antiarrhythmic drug treatment prior to cardioversion in order to prevent IRAF or SRAF remains unanswered. Pretreatment seems most appropriate in patients who have previously failed to respond to electrical cardioversion and in those who develop immediate or subacute recurrence of AF.

Combined therapy may also be of interest in preventing early AF recurrences following successful cardioversion. A recent randomized trial [91] has compared amiodarone alone and the association of amiodarone plus

enalapril in preventing AF recurrences in patients with long-standing persistent AF. A tendency to a decrease in IRAF was observed but SRAF was significantly decreased, with the result that 84.3% of patients with the combined therapy remained in sinus rhythm at 4 weeks compared with only 61.3% of patients treated with amiodarone only ($P = 0.002$). Neither enalapril nor any similar medication has been recognized so far as an efficient therapy for the prevention of IRAF or SRAF.

Patients who have been successfully cardioverted are, by definition, those in whom a rhythm-control approach has been chosen to manage their arrhythmia. Therefore, these patients should logically be given antiarrhythmic drug treatment on a long-term basis in order to prevent AF recurrences, with the exception of patients with a newly discovered AF (see below). The 4-year arrhythmia-free survival does not exceed 10% in patients initially treated with a single electrical cardioversion and no prophylactic treatment. However, even in patients exposed to serial drug testing and additional electrical cardioversions when needed, the 4-year arrhythmia-free survival rate is only around 30% (Fig. 30.11).

Prospective studies in patients with persistent AF found most antiarrhythmic drugs equally effective, except for amiodarone which appeared superior as compared with class I antiarrhythmic drugs or sotalol [92–94]. Studies on drug efficacy include a combination of patients with paroxysmal or persistent AF and mostly show overall results (Table 30.8). Therefore, information on drug efficacy is generally not available in the cohorts of patients with persistent AF only. The same holds true for patients with the paroxysmal form of AF. This hampers specific evaluation of treatment strategies. Literature on antiarrhythmic drug efficacy and tolerance for prevention of recurrent AF episodes is discussed below.

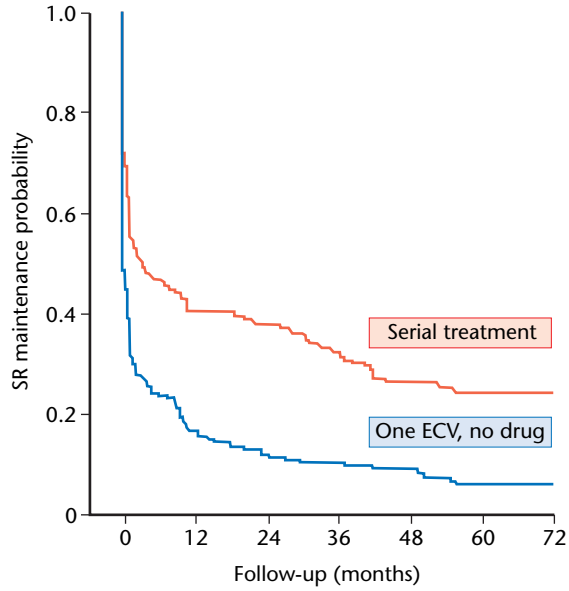

Figure 30.11 Arrhythmia-free survival after electrical cardioversion in patients with persistent atrial fibrillation. The lower curve represents outcome after a single shock when no prophylactic drug therapy was given. The upper curve depicts the outcome with repeated electrical cardioversions in conjunction with antiarrhythmic drug prophylaxis. ECV, electrical cardioversion; SR, sinus rhythm. Adapted with permission from van Gelder *et al*. [64].

In paroxysmal AF

Paroxysmal AF should be considered a chronic disease since over 90% of patients will experience recurrence after a first episode. Most patients with AF will therefore need prophylactic treatment with antiarrhythmic drugs if maintenance of sinus rhythm is clinically relevant. The factors associated with an increased risk of AF recurrence

Table 30.8 Pooled results of randomized controlled trials of drugs for maintenance of sinus rhythm after conversion of atrial fibrillation

Level of evidence	Drug	No. of trials	Trials with control group			All trials that reported adverse effects	
			Patients in drug group	Odds ratio compared with control (95% CI)*	*P*-value	Range of sustained ventricular arrhythmia (%)	Range of cessation or decreased dose of drug (%)
Strong	Amiodarone	2	173	6.8 (4.0–11.4)	< 0.01	0	0–9
	Propafenone	4	228	3.0 (2.0–4.7)	< 0.01	0–3	3–25
	Disopyramide	2	62	2.9 (1.4–6.1)	< 0.01	0	0–55
	Sotalol	4	363	2.5 (1.7–3.7)	0.01	0–5	5–13
Moderate	Flecainide	3	102	4.3 (1.3–14.1)	0.01	0	0–20
	Quinidine	4	218	2.7 (1.1–6.8)	0.02	0–12	4–58
	Azimilide	1	291	1.6 (1.2–2.2)	0.01	1	5

*Control indicates placebo, calcium-channel blockers, beta-blockers or digoxin.
Adapted with permission from McNamara *et al*. [77].

include advanced age, hypertension, left atrial enlargement, history of heart failure and left ventricular dysfunction.

Prophylactic drug treatment is usually not recommended in cases of a first detected episode of AF. Antiarrhythmic drugs may also be avoided in patients with infrequent and well-tolerated paroxysmal AF. The decision to give antiarrhythmic drug therapy in order to maintain sinus rhythm is mainly based on the presence of disabling symptoms related to AF episodes (recommendation class I, level of evidence B, AHA/ACC/ESC guidelines). The selection of a particular pharmacological agent should be based on the arrhythmia burden, type of underlying heart disease, severity of symptoms, risk and type of adverse effects, and patient preferences.

As far as treatment efficacy is concerned, recurrence of AF is not equivalent to treatment failure. Indeed, patients with recurrent AF may prefer to continue treatment with a drug because episodes of AF are less frequent, shorter or associated with milder symptoms. A reduction in arrhythmia burden may constitute therapeutic success for some patients, whereas any recurrence of AF may seem intolerable to others.

A recent meta-analysis of randomized clinical trials [77] could identify 30 trials (18 with a control arm) that had evaluated antiarrhythmic agents for maintenance of sinus rhythm in patients with paroxysmal or persistent AF. Strong evidence for efficacy was observed for amiodarone, propafenone, disopyramide and sotalol, whereas efficacy was deemed moderate by the authors for flecainide, quinidine and azimilide (see Table 30.8). Only three studies that directly compared antiarrhythmic agents found a statistically significant difference between drugs [77]. Two studies reported a higher efficacy for amiodarone compared with sotalol or propafenone and one study found propafenone more efficient than quinidine. Digoxin and calcium channel antagonists (diltiazem and verapamil) are ineffective in maintaining sinus rhythm in patients with paroxysmal or persistent AF [18]. Beta-blockers are usually deemed unsuccessful in preventing AF recurrences, except for patients with adrenergically mediated AF in whom beta-blockers represent the first-line treatment. Typical doses of drugs used to maintain sinus rhythm in patients with AF are presented in Table 30.9.

The antiarrhythmic agents listed in Table 30.8 increase the time to first recurrence of AF and reduce the number of recurrent events as compared with placebo, but these results show generally poor efficacy. Thus, after a 6-month treatment period, relapsed AF is documented in 70% of patients treated with placebo and on average in 50% of patients on active drugs. Depending on both the clinical characteristics of the population studied and the different antiarrhythmic agents, the 6-month AF recurrence rate varies from 23 to 64% in the literature.

Efficacy is not the only conisderation after initiation of antiarrhythmic drug treatment. Indeed, safety is of utmost importance since severe complications may occur in the course of therapy, in particular serious pro-arrhythmia. A meta-analysis [95] of randomized clinical trials found an increased mortality associated with quinidine, and in the AFFIRM trial [46] there was a trend to an increased mortality in the rhythm-control group compared with the rate-control group (hazard ratio 1.15, CI 0.99–1.34,

Table 30.9 Typical doses of drugs used to maintain sinus rhythm in patients with atrial fibrillation*

Drug†	Daily dosage	Potential adverse effects
Amiodarone	100–400 mg	Photosensitivity, pulmonary toxicity, polyneuropathy, gastrointestinal upset, bradycardia, torsade de pointes (rare), hepatic toxicity, thyroid dysfunction
Disopyramide	400–750 mg	Torsade de pointes, heart failure, glaucoma, urinary retention, dry mouth
Dofetilide	500–1000 µg	Torsade de pointes
Flecainide	200–300 mg	Ventricular tachycardia, congestive heart failure, enhanced AV nodal conduction (conversion to atrial flutter)
Procainamide	1000–4000 mg	Torsade de pointes, lupus-like syndrome, gastrointestinal symptoms
Propafenone	450–900 mg	Ventricular tachycardia, congestive heart failure, enhanced AV nodal conduction (conversion to atrial flutter)
Quinidine	600–1500 mg	Torsade de pointes, gastrointestinal upset, enhanced AV nodal conduction
Sotalol‡	240–320 mg	Torsade de pointes, congestive heart failure, bradycardia, exacerbation of chronic obstructive or bronchospastic lung disease

*Drugs and doses given here have been determined by consensus based on published studies.
†Drugs are listed alphabetically.
‡Dose should be adjusted for renal function and QT-interval response during in-hospital initiation phase.
Adapted with permission from Fuster *et al*. [18].

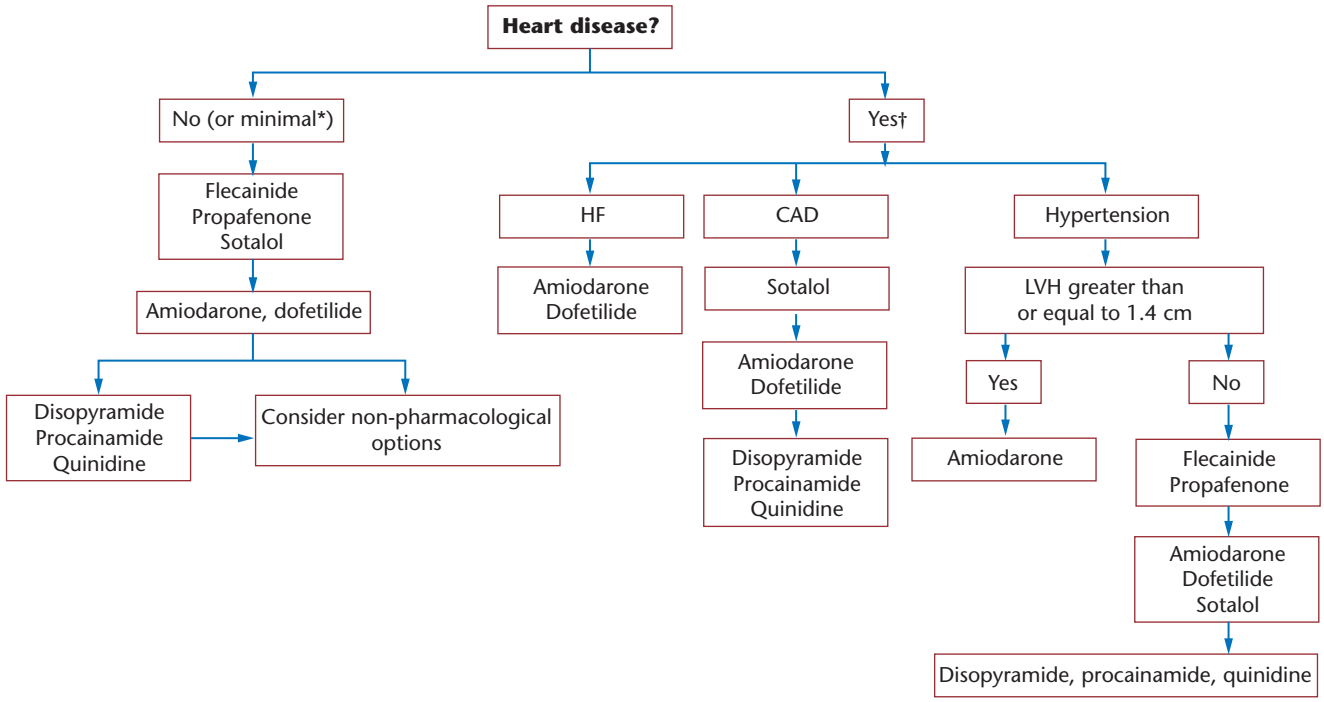

Figure 30.12 Antiarrhythmic drug therapy for maintaining sinus rhythm in patients with recurrent paroxysmal or persistent atrial fibrillation. Drugs are listed alphabetically and not in order of suggested use. *For adrenergic atrial fibrillation, beta-blockers or sotalol are the initial drugs of choice. †Consider non-pharmacological options to maintain sinus rhythm if drug failure occurs. CAD, coronary artery disease; HF, heart failure; LVH, left ventricular hypertrophy. Adapted with permission from Fuster *et al*. [18].

$P = 0.08$), although this was not due to pro-arrhythmia. Table 30.9 lists the potential adverse events for each medication recommended for AF prophylaxis and Table 30.8 shows the range of ventricular arrhythmia reported in the literature for each of these drugs.

Which antiarrhythmic drug treatment should be first given in an individual patient mainly depends on the presence and type of underlying heart disease. Thus, flecainide, propafenone or sotalol should be chosen as first-choice treatment in patients with no or minimal heart disease (Fig. 30.12). Because of the relatively high incidence of non-cardiac adverse effects on long-term treatment, amiodarone is usually used as second-line treatment, except in patients with heart failure or severe left ventricular hypertrophy in whom amiodarone is recommended as first-line treatment. Patients with congestive heart failure are at particular high risk of pro-arrhythmic events related to antiarrhythmic drugs. Randomized trials have demonstrated the safety of amiodarone and dofetilide in patients with heart failure [96,97]. The particular situation of lone AF triggered by autonomic nervous system imbalance deserves a specific approach. In patients with vagally induced AF, disopyramide is considered attractive because of its anticholinergic activity. In patients with adrenergically mediated lone AF, a beta-blocker should be chosen as the treatment of choice.

When treatment with a single drug fails, combinations of antiarrhythmic drugs may be tried. Useful combinations include a beta-blocker, sotalol or amiodarone, plus a type IC agent. On the other hand, patients using class IA or IC drugs (rarely amiodarone) may experience high ventricular rates during breakthrough AF or atrial flutter. These agents may augment atrioventricular (AV) nodal conduction by anticholinergic stimulation, and may transform AF into a more organized arrhythmia, so-called 'class IA or class IC atrial flutter'. Beta-blockers and calcium channel blockers (or digoxin) may be added to class IA or IC agents to avoid such a high ventricular rate. However, this approach is not supported by any clinical data. Moreover, in patients who experience conversion of AF to atrial flutter during antiarrhythmic drug treatment, flutter isthmus ablation (see below) and continuation of the pharmacological therapy has been reported as a safe and effective means of achieving and maintaining sinus rhythm.

Combination with drugs not classified as antiarrhythmic may be another approach for rhythm control. A subanalysis of the TRACE study [98] noticed a reduction in the incidence of AF in patients with left ventricular dysfunction after myocardial infarction who received trandolapril as compared with those treated with placebo. Since then, research studies have demonstrated that

electrical remodelling in AF can be prevented with angiotensin II antagonists [99] as well as with angiotensin-converting enzyme (ACE) inhibitors [100,101], indicating that the renin–angiotensin–aldosterone system plays a role as a mediator of atrial remodelling in AF. Two recent randomized trials have shown that irbesartan [102] and enalapril [91] in addition to amiodarone were more effective compared with amiodarone alone in preventing AF recurrence in patients with persistent AF.

Control of ventricular rate

The first step in the treatment of AF generally is to control the ventricular response rate. Patients who develop rapid ventricular rates during an episode of AF may be highly symptomatic because of reduced cardiac output secondary to a rapid ventricular response. This is particularly significant in patients with underlying heart disease or in elderly patients.

The ventricular rate in patients with AF depends on AV nodal conduction, which in turn is inversely correlated with the refractory period of the AV node. Drugs that prolong the effective refractory period of the AV node control the ventricular response in patients with AF. In the majority of patients with intact AV nodal conduction, some rate-control medication is needed. However, in patients with conduction disease, mostly the elderly, no medication may be necessary to further slow the ventricular rate.

Few patients need rate control as an emergency. When such a clinical situation does occur the alternative approach of immediate cardioversion should be considered. In an individual patient, a careful appraisal of the advantages and disadvantages of each therapy should inform the decision either to control the ventricular rate using rapidly acting drugs or to immediately cardiovert the patient. As previously mentioned (see Table 30.3), immediate electrical cardioversion is recommended in patients with acute AF and a rapid ventricular response associated with acute myocardial infarction, symptomatic hypotension, angina or cardiac failure that does not respond promptly to pharmacological measures (recommendation class I, level of evidence C, AHA/ACC/ESC guidelines). For prompt AV conduction slowing, intravenous administration of either beta-blockers or calcium channel antagonists (verapamil, diltiazem) is recommended in the absence of conduction over an accessory pathway and with great prudence in patients with hypotension or heart failure (recommendation class I, level of evidence B, AHA/ACC/ESC guidelines).

In patients with anterograde conduction over an AV accessory pathway (Wolff–Parkinson–White syndrome) during AF, digoxin and calcium channel blockers are contraindicated for rate control because anterograde conduction through the accessory pathway is facilitated when these agents are administered. This may result in a markedly increased ventricular rate and promote degeneration into ventricular fibrillation. Electrical cardioversion or type I (disopyramide, procainamide, flecainide, propafenone) or type III (ibutilide or amiodarone) antiarrhythmic agents may be used instead in these patients (recommendation class IIb, level of evidence C, AHA/ACC/ESC guidelines). (Note that propafenone is not mentioned in the guidelines because it is not available for intravenous use in the USA.)

Antiarrhythmic drugs recommended by the AHA/ACC/ESC guidelines [18] for ventricular rate control during AF by the intravenous (rapid heart rate control) and oral (chronic heart rate control) routes are listed in Tables 30.10 and 30.11 respectively. The selection of a beta-blocker or

Table 30.10 Intravenous pharmacological agents for heart rate control in patients with atrial fibrillation

Drug*	Loading dose	Onset	Maintenance dose	Recommendation
Diltiazem	0.25 mg/kg i.v. over 2 min	2–7 min	5–15 mg/h infusion	I†
Esmolol‡	0.5 mg/kg over 1 min	5 min	0.05–0.2 mg/kg/min	I
Metoprolol‡	2.5–5 mg i.v. bolus over 2 min	5 min	NA	I†
Propranolol‡	0.15 mg/kg i.v.	5 min	NA	I†
Verapamil	0.075–0.15 mg/kg i.v. over 2 min	3–5 min	NA	I†
Digoxin	0.25 mg i.v. each 2 h, up to 1.5 mg	2 h	0.125–0.25 mg daily	IIb§

*Drugs are listed alphabetically within each recommendation class.
†Class IIb in congestive heart failure.
‡Only representative members of the beta-adrenergic antagonist drugs are listed, and other similar agents could be used for this indication.
§Class I in congestive heart failure.
Adapted with permission from Fuster *et al*. [18].

Table 30.11 Orally administered pharmacological agents for heart rate control in patients with atrial fibrillation

Drug*	Loading dose	Onset	Maintenance dose†	Recommendation
Digoxin	0.25 mg by mouth each 2 h; up to 1.5 mg	2 h	0.125–0.375 mg daily	I
Diltiazem	Not applicable	2–4 h	120–360 mg daily	I
Metoprolol‡	Not applicable	4–6 h	25–100 mg b.i.d.	I
Propranolol‡	Not applicable	60–90 min	80–240 mg daily	I
Verapamil	Not applicable	1–2 h	120–360 mg daily	I
Amiodarone	800 mg daily for 1 week 600 mg daily for 1 week 400 mg daily for 4–6 weeks	1–3 weeks	200 mg daily	IIb

*Drugs are listed alphabetically within each recommendation class.
†Recommended maintenance dosages are the usual ones necessary, but higher doses may be appropriate in some patients.
‡Only representative members of the beta-blocker drugs are listed, and other similar agents could be used for this indication.
Adapted with permission from Fuster *et al*. [18].

calcium channel blocker should be based on the physician's experience and the patient's clinical condition.

Criteria

The adequacy of rate control during AF may be judged from clinical symptoms and heart rate measurements both at rest and during exercise (recommendation class I, level of evidence C, AHA/ACC/ESC guidelines) since an excessive rate acceleration may occur during mild exercise despite the heart rate being well controlled at rest [103]. The rate is generally considered controlled when the ventricular response ranges between 60 and 80 b.p.m. at rest and between 90 and 115 b.p.m. during moderate exercise [104]. Holter monitoring may be helpful for evaluating circadian heart rate control during AF [105].

Drugs

Digoxin

Although digitalis compounds have been used to treat AF for over two centuries, recent studies have shown that digoxin has no effect in terminating the arrhythmia, and may occasionally be harmful. However, digoxin has a negative chronotropic effect and could therefore be given for rate control in patients with AF.

Digoxin helps control symptoms in patients with persistent AF [106] but does not usually reduce symptoms associated with recurrent paroxysmal AF [107]. Indeed, digoxin has little effect on the AV node itself, as has been demonstrated in the transplanted denervated heart [108]. It is now generally accepted that the parasympathetic properties of digoxin are responsible for its indirect mechanism of action. This explains the poor rate control exerted by digoxin during sympathetic stimulation, particularly during exercise, hyperthyroidism or hyperthermia. Digoxin should be considered a weak AV nodal blocker and should not be given orally as first-line treatment to control the ventricular rate in patients with AF, except in patients with heart failure or in those with a limited range of activity. Digoxin should rather be reserved as an efficient adjuvant therapy [109] when another single-drug treatment is insufficient to control the ventricular rate. Administration of digoxin as the sole agent for controlling a rapid rate of ventricular response to AF is not recommended in patients with paroxysmal AF (recommendation class III, level of evidence B, AHA/ACC/ESC guidelines) or persistent AF (recommendation class IIb, level of evidence B, AHA/ACC/ESC guidelines).

When using digoxin in an emergency setting, one must keep in mind that although intravenous digoxin may effectively slow the ventricular rate at rest, there is a delay of at least 60 min before onset of a therapeutic effect in most patients, and the peak effect does not develop for up to 6 h. Given the availability of more effective agents, digoxin is no longer first-line therapy for management of acute AF, except in patients with heart failure or left ventricular dysfunction.

Calcium antagonists

The calcium-antagonist family is a cluster of agents with a wide diversity of pharmacological effects. The non-dihydropyridine calcium channel blockers verapamil and diltiazem are those most commonly used for ventricular rate control in patients with AF. They prolong the effective refractory period of the AV node, with a direct mechanism of action mediated through L-type calcium channels. Dihydropyridine calcium antagonists do not depress the AV node and tend to increase the ventricular rate during AF because of reflex sympathetic activation

secondary to depression of left ventricular function and vasodilation induced by these drugs.

Randomized trials have demonstrated that verapamil and diltiazem reduce heart rate both at rest and during exercise significantly better than does placebo. This is associated with preservation or improvement in exercise tolerance in most patients [110]. Diltiazem and verapamil are also more effective than digoxin in reducing the ventricular rate both at rest and during exercise [111].

In emergency settings, both drugs are rapidly effective in controlling the ventricular rate, but repeated doses or continuous infusion is usually necessary because the induced AV blockade is transient when using the intravenous route [112]. In patients with atrial fibrillation or flutter and a rapid ventricular response, diltiazem given as an intravenous bolus (0.25 mg/kg) induces a significant drop in the mean ventricular rate at 5 min (from 150 to 111 b.p.m.), whereas the decrease in heart rate induced by a 0.25-mg digoxin bolus does not reach statistical significance until 180 min [113].

Verapamil and diltiazem have a negative inotropic effect. Therefore, they should be used cautiously in patients with heart failure and even more so when considering intravenous administration. However, one placebo-controlled randomized trial [114] evaluated intravenous diltiazem for the treatment of AF or atrial flutter associated with a rapid ventricular rate in patients with moderate to severe congestive heart failure (NYHA III or IV). Overall, 97% of the patients had a therapeutic response to intravenous diltiazem, with a median time to response of about 5 min from the beginning of the 2-min bolus injection. No patient had an exacerbation of congestive heart failure due to intravenous diltiazem. Intravenous diltiazem is therefore safe and efficient when given to control a rapid ventricular rhythm in patients with moderate to severe congestive heart failure.

Beta-blockers

Beta-blockers prolong AV refractoriness by targeting β-adrenergic receptors and antagonize the effects of increased sympathetic tone. As for calcium blockers, the beta-blocker family includes a number of agents with different pharmacological profiles, such as partial agonist activity and β_1 selectivity.

Randomized trials have demonstrated that all beta-blockers reduce heart rate both at rest and during exercise significantly better than does placebo, but their range of efficacy is agent specific, with nadolol, atenolol and metoprolol being most efficacious [77,111]. Beta-blockers are also more effective than digoxin in reducing the ventricular rate both at rest and during exercise. Results evaluating exercise tolerance with beta-blockers are inconsistent.

Intravenous beta-blockade with propranolol, atenolol, metoprolol or esmolol may help to control the rate of ventricular response to AF. Beta-blockers may be particularly useful in cases of high adrenergic stimulation, such as after cardiac or non-cardiac surgery. Among the beta-blocker agents available for intravenous use, esmolol has the advantage of easy titration due to its short plasma half-life (9 min).

When given orally, a single therapy may fail to control the ventricular rate and a combination of drugs can be used to improve efficacy. In studies evaluating multiple drug treatment, the combination of digoxin and beta-blockers appeared to be more effective than the combination of digoxin and diltiazem [109].

Beta-blockers should be initiated gradually in patients with heart failure and are recommended in patients with acute myocardial infarction or ischaemic heart disease. On the other hand, calcium antagonists are preferred over beta-blockers for long-term use in asthmatics or in patients with chronic obstructive pulmonary disease.

Other drugs

Amiodarone is effective in controlling the ventricular rate in patients with AF. Indeed, amiodarone depresses AV conduction because of its sympatholytic and calcium antagonist properties. Amiodarone is an alternative therapy in patients with acute AF when conventional drugs are unsuccessful in controlling the ventricular rate. Intravenous amiodarone is both effective and well tolerated in patients with heart failure. Rapid loading of amiodarone with a 30-min infusion has recently been evaluated in a randomized trial [115] and resulted in quicker control of the ventricular rate as compared with digoxin. The benefit of oral amiodarone on AV conduction has not been investigated in prospective studies and it should not be given as a first-line agent because of the adverse effects associated with its chronic administration.

Sotalol, a beta-blocker with predominant class III antiarrhythmic properties, also depresses AV conduction and was shown effective when used intravenously [115] or orally [116]. However, it too has unacceptable adverse effects and its use for long-term control of the ventricular rate cannot be condoned.

Clonidine, a traditional antihypertensive agent, decreases sympathetic outflow and stimulates parasympathetic outflow, resulting in prolongation of refractoriness of the AV node. Clonidine reduces the ventricular rate by 15–20% and may be of interest in hypertensive patients with AF. When given orally, the change in heart rate induced by clonidine is comparable to that induced by intravenous digoxin [117].

Pacemaker and defibrillator therapy

Experimental and clinical data suggest that atrial pacing might prevent AF [118–120] by alleviation of bradycardia-induced dispersion of atrial repolarization and atrial overdrive suppression of supraventricular beats, thus eliminating the trigger of AF. Continuous pacing at selected sites (alternative, dual or biatrial) changes atrial activation patterns, increases homogeneity of left and right atrial electrical properties in conduction and refractoriness, reduces dispersion of refractoriness that occurs with premature atrial contraction (PAC) or with abrupt changes in atrial rate and thus prevents the development of atrial re-entry. The potential to maintain AV synchrony and prevent the development of mitral regurgitation and/or ventriculo-atrial conduction that causes stretch-induced changes in atrial repolarization might also lessen the chance of AF recurrence.

Pacing for rate support: VVIR vs. DDDR

Different modalities of pacing have been assessed with regard to their ability to prevent AF. Atrial pacing has shown some benefit over ventricular pacing alone in decreasing episodes of AF and data from several pacemaker trials support the use of atrial or dual-chamber pacing rather than ventricular pacing for prevention of AF in pacemaker patients [121–125]. It is possible that certain subgroups are more likely to benefit from physiological pacing for AF prevention: those with sinus node dysfunction, those frequently paced in the ventricle and those without any previous history of AF [119].

Multisite or alternative-site pacing

Experimental and clinical studies have demonstrated that septal pacing, dual-site or biatrial-site pacing shortens total atrial activation time and reduces overall dispersion of atrial refractoriness [126–129]. A number of clinical trials have evaluated the effects of selective atrial pacing sites on the prevention of AF in patients with bradycardia as an indication (Bachmann bundle, interatrial septum). However, the largest randomized trial of right atrial pacing versus septal pacing (ASPECT) [130] failed to demonstrate a reduction in AF frequency and burden over a short follow-up.

Multisite pacing has been shown to be effective in reducing AF occurrence in some patients. Several techniques have been used, including dual-site pacing within the right atrium or pacing from the right atrium and coronary sinus in a biatrial fashion [131–135]. In these studies the majority of patients had sinus node dysfunction. In the DAPPAF trial in antiarrhythmic drug-treated patients, dual right atrial pacing increased symptomatic AF-free survival compared with support pacing or high right atrial pacing, supporting the use of a hybrid approach to rhythm management [131].

Results in patients without sinus dysfunction have been reported but are less encouraging [132]. In patients with left atrial delay and AF, the SYNBIAPACE study demonstrated no consistent AF reduction during long-term follow-up between right atrial pacing, demand pacing at 40 b.p.m. or biatrial pacing [136]. Although available studies suggest that biatrial and multisite pacing can be effective in some patients for secondary prevention of AF, there are no clear predictors of which patients will benefit the most.

Preventive algorithms/antitachycardia pacing

A number of selective pacing algorithms have been developed to prevent AF [137]. The potential mechanisms of these algorithms include post-PAC pause prevention, continous atrial pacing, post-PAC overdrive pacing, and transient overdrive pacing after AF. Clinical studies [131,138–140] suggest that AP prevention algorithms have modest to minimal incremental benefit for the prevention of AF. In these studies, benefit was largely observed in patients receiving concomitant antiarrhythmic drugs, suggesting enhanced effectiveness when pacing is used as a 'hybrid' approach. In this regard, these algorithms may be of potential benefit in patients requiring pacemaker or device implantation for non-AF indications [118,119].

In some cases AF can be controlled with antitachycardia devices through the use of antitachycardia pacing, high-frequency atrial burst pacing or atrial defibrillation. This approach is based on the concept that even AF may be sufficiently organized at its onset to allow pacing intervention, tissue capture and arrhythmia termination. It has also been hypothesized that pace termination of atrial tachycardias or atrial flutter would prevent the development of AF and reduce the overall AF burden. Although antitachycardia pacing and high-frequency burst pacing are effective in more than 50% of cases, neither reduction of AF frequency nor AF burden has been consistently observed [141–145].

In summary, although atrial-based pacing is associated with a lower risk of AF and stroke than ventricular-based pacing for patients requiring a pacemaker for bradyarrhythmia, the use of pacing as a primary therapy for prevention of recurrent AF has not been validated.

Atrial defibrillator (within implantable cardioverter–defibrillator)

Initial clinical experience with the 'stand-alone' atrial defibrillator suggested that atrial defibrillation was safe

and effective. The first generation of atrial defibrillator was followed by a commercially available dual-chamber AV defibrillator. The atrial defibrillator component of currently available implantable cardioverter–defibrillators is highly effective in restoring sinus rhythm in most patients. This can be obtained with virtually no risk of ventricular fibrillation. The major drawback of this technique is that the relatively low energy shock is intolerably painful if it is delivered more than occasionally. However, it is possible that the frequency of AF episodes decreases in patients promptly defibrillated. This therapy may be most advantageous when used as a component of hybrid therapy for AF. Ideal candidates seem to be patients with, or at risk of, AF who have an indication for a ventricular defibrillator or biventricular pacemaker [146,147]. Nevertheless, there has been no controlled study that compares efficacy, survival, quality of life or costs in patients with implantable atrial defibrillator versus other therapies.

Hybrid therapy

There is now important interest in combination or 'hybrid' therapy, which emerges from the understanding that different mechanisms may be responsible for initiation and maintenance of AF. The term 'hybrid' implies fundamentally different qualities of treatment that together provide some form of synergism. For example, addition of two or more independent antiarrhythmic actions (pacemaker-induced reduction of PACs and antiarrhythmic drug modification of the substrate), neutralization of a pro-arrhythmic effect of one by the other therapy (pacemaker prevention of antiarrhythmic drug-related bradycardia), and facilitation of the antiarrhythmic effect of one therapy by another (organization of AF with antiarrhythmic drugs to increase the success of antitachycardia pacing). Although interesting, this is a theoretical concept that has not been fully evaluated [118,131,194].

Catheter ablation/modification of the AV node for rate control

There is evidence that AF patients may benefit from control of both the ventricular rate and its regularity. Therefore, pacing after AV junctional ablation to induce heart block ('ablate and pace') is a useful strategy for patients with symptomatic, medically refractory AF (Fig. 30.13). The benefits of this procedure have been demonstrated in many controlled and non-controlled trials [148]. AV nodal ablation is especially useful when an excessive ventricular rate induces a tachycardia-mediated decline in ventricular systolic function despite appropriate medical therapy. The 'ablate and pace' strategy has been shown to improve exercise tolerance, cardiac function, health-care utilization and quality of life. Its safety has been established, and in a meta-analysis the risk of sudden death and total mortality was 2% and 6% respectively at 1 year, figures similar to the mortality observed with medical therapy of AF [149,150].

Of course, AV node ablation and pacing has many disadvantages: creation of irreversible AV block, loss of AV synchrony (an important issue in patients who are most dependent on AV synchrony, such as hypertrophic or restrictive cardiomyopathies), no relief from the need for anticoagulation, and pre-emption of later use of potentially newer and more effective non-pharmacological or pharmacological treatments.

AV node modulation by eliminating the posterior atrial inputs to the AV node has been proposed as a

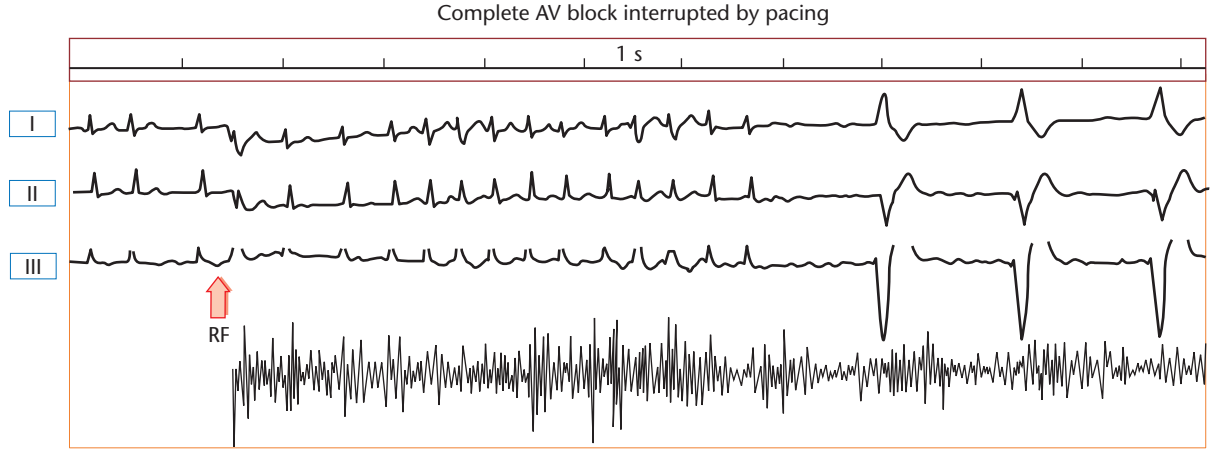

Figure 30.13 Atrial fibrillation and complete radiofrequency (RF)-induced AV block.

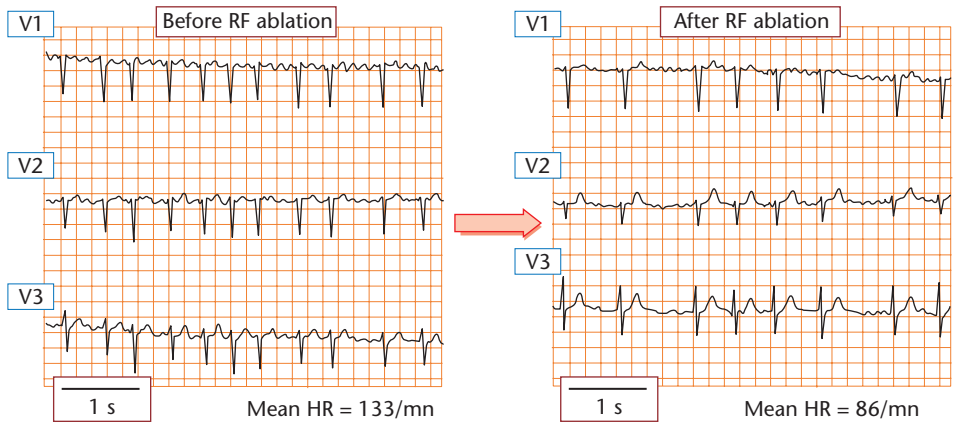

Figure 30.14 Atrial fibrillation and AV nodal conduction modification by radiofrequency (RF) ablation.

means to decrease the ventricular rate during AF, avoiding definite complete AV block and lifetime pacemaker therapy (Fig. 30.14). However, it is less widely accepted because of the lower success rate, the risk of inadvertent AV block and the persistence of symptoms due to irregular beats during AF [151–153].

Ablation of atrial fibrillation

Emerging evidence suggests a significant benefit for the maintenance of sinus rhythm in patients with AF [154]. Although antiarrhythmic drugs have been the mainstay for achieving and maintaining sinus rhythm in such patients, their limited efficacy and potential for significant adverse effects has led to renewed interest in non-pharmacological strategies that maintain sinus rhythm [43,155,156].

Catheter ablation

In the decade since the original description of the success of catheter ablation as a means of maintaining sinus rhythm, our techniques continue to evolve [157,158]. Multiple different strategies and technologies have been investigated over the years with variable success; however, most groups now focus on performing lesions around the pulmonary veins, at least for paroxysmal AF.

Role of the pulmonary veins in AF

It is now recognized that clinical AF results from the complex interaction of triggers with the perpetuators and substrate that then maintain the atria in fibrillation [159]. While a number of structures have been implicated as potential sources of initiating triggers, the pulmonary veins (PVs) are recognized as the dominant source, with focal discharges from the PV musculature being implicated in the initiation of 60–94% of paroxysms of AF [160–162]. Although initially the aim of our procedures was to eliminate these focal triggers by localized ablation, the recognition that multiple sites within a PV and multiple PVs could be arrhythmogenic has led to the strategy of electrically isolating all PVs to prevent any interaction of these triggers with the atrial substrate.

In a small subset of patients, focal triggers from the PVs may also serve as drivers that maintain the atria in fibrillation [160]. In these patients the PVs form both the triggers and substrate that maintain AF, and PV isolation (PVI) is highly effective. However, the role of the PVs exceeds that of initiating triggers. There is now strong evidence suggesting that the veins are in fact critical for maintenance of AF, rendering the classification of trigger versus substrate modification obsolete. This role of the PVs is clearly demonstrated by the observation in patients with paroxysmal AF, undergoing PVI during AF, of a progressive prolongation of AF cycle length (or slowing of the AF process) that culminates in the termination of AF in up to 75% of cases [163]. Furthermore, following PVI of all veins, 54% of patients could no longer sustain induced AF, suggesting that in significant proportions of patients with paroxysmal AF the PVs form the substrate maintaining AF [164].

Why these structures are arrhythmogenic has been an area of intense investigation. Anatomical studies have demonstrated complex and variable extension of the atrial musculature into the PVs, with these anatomical determinants creating the milieu for preferential conduction, unidirectional conduction block and re-entry [165–168]. Clinical studies have demonstrated that the PVs in patients with AF have distinctive electrophysiological properties characterized by shorter refractory periods and greater anisotropy compared with patients

without AF [169]. Indeed, these properties are capable of sustaining high-frequency activity [170,171]. As such, ablation of these arrhythmogenic structures form an essential part of the ablation strategy for AF.

Is it necessary to electrically disconnect the PVs?

Although most groups now agree that lesions around the PVs are able to cure a significant proportion of patients with paroxysmal AF, there remains controversy as to whether complete electrical disconnection is superior to incomplete disconnection. In addition, reports from groups that have advocated the use of a purely anatomical approach have recognized a significant incidence of organized arrhythmias occurring after such ablation. Indeed, a recent study by Pappone *et al.* [172] reports that incomplete encircling lesions ('gaps') were the most predictive factor for the subsequent development of organized arrhythmias. This finding argues further in favour of achieving complete lesions, with complete lesions being crucial for the prevention of macro re-entry; conversely, incomplete lesions promote the occurrence of atrial arrhythmias.

A purely anatomical approach has been advocated (Fig. 30.15), whereby circumferential lesions are deployed without evaluation of the distal PV potentials [173,174]. Using this technique up to 45% of PVs are not isolated, with persistent PV–left atrial conduction, and thus remain potentially arrhythmogenic [175]. Despite the insurmountable evidence demonstrating the arrhythmogenicity of the PVs and the potential consequences of interaction between the PV and the left atrium in the generation and maintenance of arrhythmia, in the absence of studies comparing the outcomes of complete versus incomplete PVI, no definitive statement can be made arguing the need for PVI at this stage. However, theoretically, while incomplete lesions may result in a spectrum of possible PV–left atrial interactions, one could argue that complete isolation results in elimination of all such interaction; thereby, PVI should provide at least a similar if not superior efficacy as compared with incomplete isolation.

Further evidence of the need for PVI is provided by studies that have evaluated the recurrence of AF after ablation. These studies have observed that the vast majority of patients with recurrence of AF demonstrate PV re-conduction. Repeat PVI in these patients has been associated with the elimination of all AF in 90% of patients [176,177]. These data implicate the residual PV–left atrial interaction in the development of clinical arrhythmia and serve to further accentuate the importance of achieving complete isolation.

Techniques for PV isolation

Circumferential mapping has enabled the determination of the perimetric distribution and activation sequence of the PV, identifying the location and extent of the local striated muscle that electrically connects the PV to

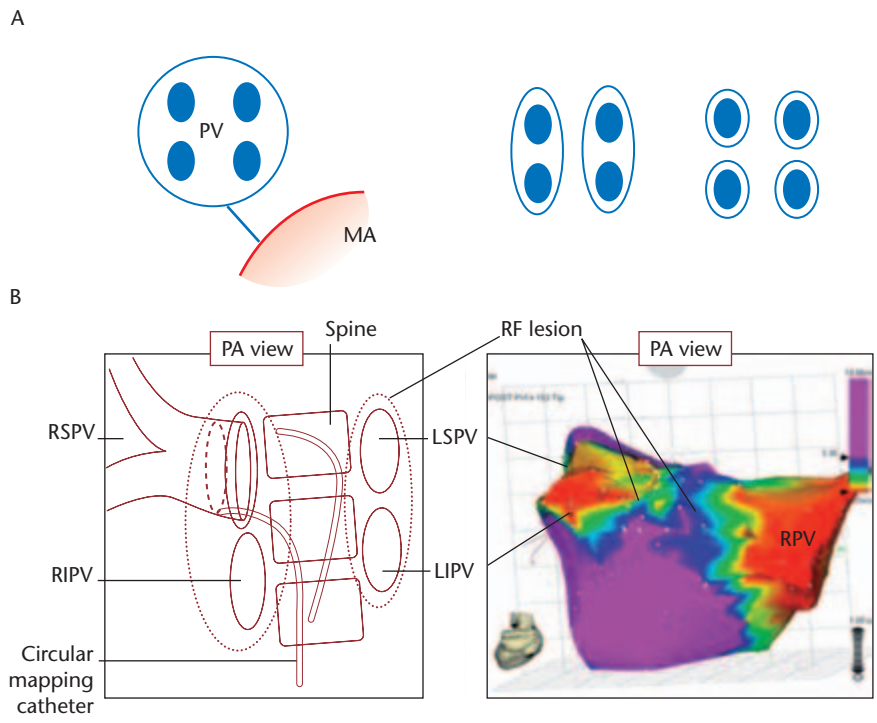

Figure 30.15 Different approaches for pulmonary vein (PV) ablation have been proposed. (A) Anatomical schemata are shown with PV encirclement four by four, two by two or one by one. The most common procedure is ablation of ipsilateral PVs using linear lesions placed at least 1 cm from the PV ostia, in the left atrium. Similar placement of lesions can be used with the electrophysiological approach (B), the main difference being that PV isolation as determined by circular mapping (see Fig. 30.16) is used as a clear end-point in order to maximize procedure efficacy. It should be noted that when ablation is performed along the anterior aspect of the left PVs, infringement of the PV is frequently required in order to achieve catheter stability; ablation in this case is performed with reduced power and is limited by targeting critical PV–left atrial connections. AP, anteroposterior; PA, postero-anterior; RF, radiofrequency; LIPV, left inferior PV; LSPV, left superior PV; RIPV, right inferior PV; RSPV, right superior PV.

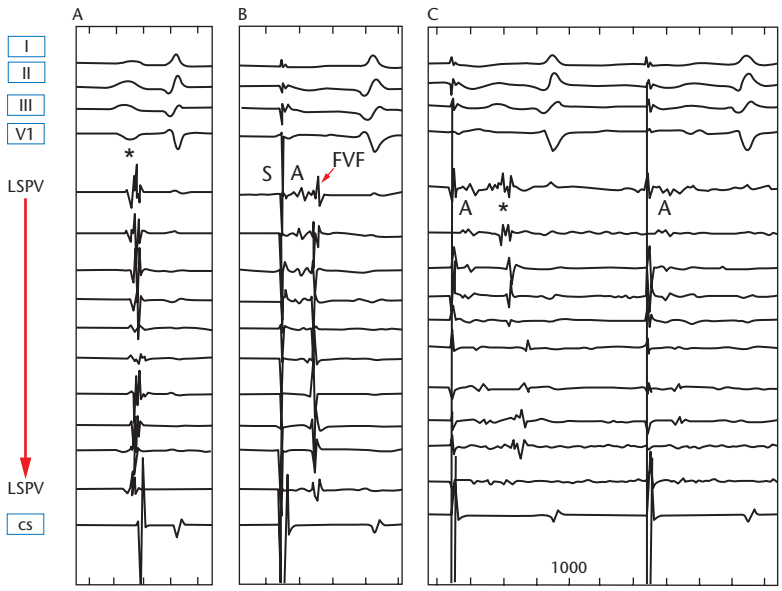

Figure 30.16 Pulmonary vein (PV) isolation can be facilitated by using circular mapping catheters. In this example, the mapping catheter introduced in the left superior PV (LSPV) (A) demonstrates atrial and venous potentials superimposed. By pacing from the coronary sinus (CS), venous potentials (PVP) follow the far-field atrial potential (B). After radiofrequency ablation of the atrial tissue surrounding the vein, complete isolation is demonstrated by the disappearance of venous potentials with persistence of far-field atrial potentials (C).

the left atrium (Fig. 30.16) [178]. By sequential ablation at sites of earliest activity, the PVs can be electrically isolated from the left atrium. While this may be described as segmental, in order to emphasize the need for longer radiofrequency application at critical sites that change PV activation, ablation is performed almost circumferentially by moving around the PV circumference. Ablation can be started in either right or left PVs, and performed individually or en bloc when two or three ostia are coalescent (Fig. 30.15B) [171,178,179].

Most authors agree that lesions performed to isolate the PVs should be placed within the atria or as proximally as possible rather than within the distal PVs. This strategy not only reduces the incidence of PV stenosis but may also improve efficacy by excluding proximal foci of activity from the arrhythmogenic substrate. Ablation is usually started at the posterior wall and then continued around the venous perimeter. However, it should be noted that when ablation is performed along the anterior and inferior aspects of the left PVs, infringement of the PV is frequently required in order to achieve catheter stability; ablation in this case is performed with reduced power and is limited by targeting critical PV–left atrial connections.

It is important to note that the use of a circular mapping catheter does not imply that the ablation lesions are being performed at the PV ostia. A distance greater than 1 or 1.5 cm between both catheters is commonly observed when ablation is performed atrially. Indeed, the circular mapping catheter is used to provide a very clear end-point of complete isolation, which is achieved by wide encircling lesions around the PVs from within the atrium itself, as proposed by Marrouche *et al*. [180] and more recently Ouyang *et al*. [171], at the PV antrum.

Substrate modification

Despite exclusion of triggers initiating AF, most patients with persistent or permanent AF and approximately 20–40% of those with paroxysmal AF have further episodes of AF [181–183]. In these patients, improvement of ablation outcome relies on additional substrate modification. The conceptual basis for substrate modification by compartmentalization of the atria is based on the multiple-wavelet hypothesis of Moe and colleagues, which suggested that AF is maintained by multiple re-entrant wavelets propagating simultaneously in the atria and that a minimum mass of electrically continuous myocardium must be present to sustain the wavelets on re-entry [184]. More recently, other techniques of substrate modification have been evaluated [185,186]. Nademanee *et al*. [186] have proposed the ablation of complex fractionated electrograms, with the hypothesis that they form pivot points for re-entry that result in AF. Pappone *et al*. [185] and more recently the group from Oklahoma (Cardiac Arrhythmia Research Institute) have described the potential role of ganglionic plexi and the efficacy of radiofrequency ablation at atrial sites where a vagal response is observed after local stimulation. However, the long-term results of a procedure limited to these ganglia are not yet available.

Although specific catheters for use in linear ablation remain developmental, conventional catheters have been used to evaluate the role of linear atrial ablation, recently

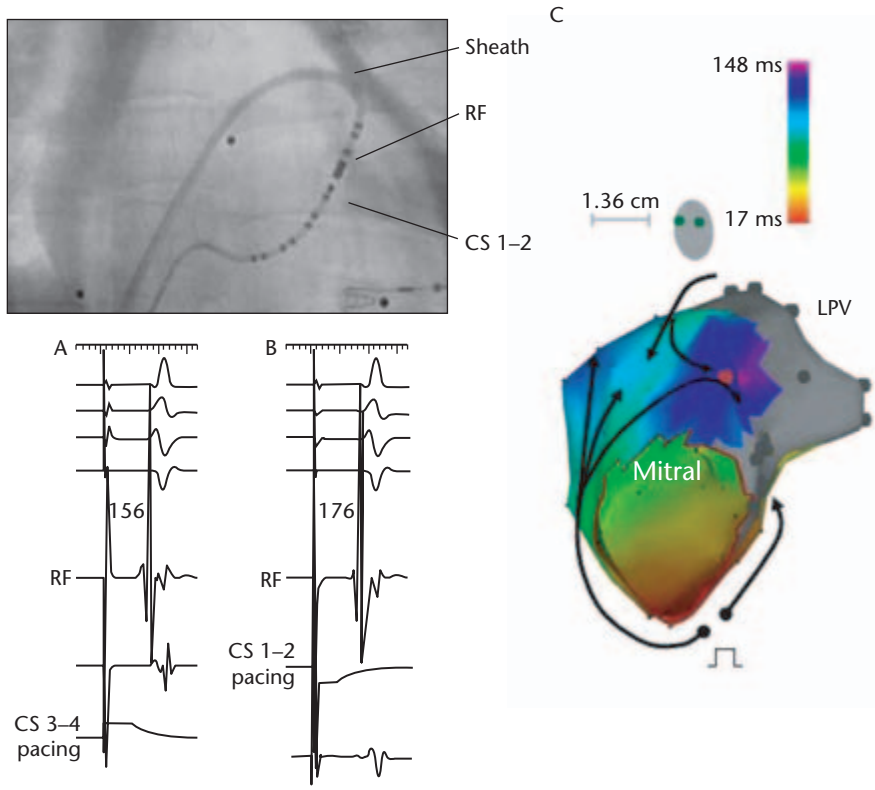

Figure 30.17 Mitral isthmus ablation is performed by stabilizing the ablation catheter (irrigated tip catheter preferably) through a long sheath, extending ablation from the mitral annulus to the ostium of the left pulmonary veins (LPV). (A) Differential pacing (from the CS) is used to exclude slow conduction through the ablation line. A shorter pacing artefact to atrial potential is recorded during pacing from proximal CS (pole 3–4) while pacing from the distal CS (B) is associated with a longer delay as the route of activation travelling from the septal flank of the line around the mitral annulus to the lateral flank of the line is longer. This activation detour can also be demonstrated during CS pacing with the Carto mapping system. The earliest activity is recorded at the pacing site and then travels around the mitral annulus to reach the anterior left atrium where it fuses with an activation front going superiorly in the posterior left atrium. The latest activity displayed in purple is recorded at the septal flank of the mitral isthmus line of block. The achievement of a complete line of block is highly desirable in order to prevent sustained macro re-entry, which frequently propagates through incomplete lines of block. CS, coronary sinus; RF, radiofrequency.

enhanced by the introduction of large tips and irrigated ablation. Linear ablation is performed between anatomical or functional electrical obstacles in order to transect these regions and thereby prevent re-entry. Critical to this concept is that ablation has the requirement to be coalescent and transmural in order to achieve complete lesions and provide better outcomes. This can be challenging, with an increased procedural risk (particularly of tamponade and stroke) and may be pro-arrhythmic in the setting of incomplete or recovered gaps [187–192].

A variety of different linear configurations has been investigated; however, prediction of which line is more suitable in a given patient has been elusive. Linear lesions at the roof of the left atrium connecting both superior PVs are relatively easy to perform, but the demonstration of complete block is not always easy and requires a second catheter for pacing from the left appendage. Recently, when a posterior line has been performed utilizing high power as part of the anatomical ablation strategy, a number of patients have developed atrio-oesophageal fistulae [191]. Lesions connecting the anterior aspect of the mitral annulus to the roof of the left atrium or to the right superior PV to transect the anterior left atrium disrupt sinus activation, resulting in delayed activation of the lateral left atrium with possible deleterious consequence on atrial mechanical function [189].

Ablation of the mitral isthmus (Fig. 30.17), connecting the lateral mitral annulus to the left inferior PV, offers several theoretical benefits to the other left atrial lesions [190]. This line is short but creates a contiguous long lesion with the ablated PVs and does not interfere with normal sinus activation of the atria. In addition, its proximity to the coronary sinus allows positioning of catheters on either side of the line to evaluate the

integrity of the line. However, despite these features, ablation at this site requires 20–25 min of radiofrequency energy application, with 68% requiring ablation within the coronary sinus [190].

When performed with PVI, these linear lesions improve the success rate by 10–20% in paroxysmal AF and by 30–50% in persistent or permanent AF. Although there is no consensus on whether achieving complete block is desirable, incomplete lesions are frequently associated with the development of macro re-entry, which is often more symptomatic.

Complications

Despite significant improvements in recent years, catheter ablation of AF is still associated with significant complications. The most concerning complication of PV ablation has been that of PV stenosis [193]. The current incidence of angiographic PV stenosis (> 50% reduction in PV diameter) is < 2%, with most patients being asymptomatic. This incidence is reduced significantly with lower-power ostial ablation and operator experience. Importantly, none of the localization systems available at present is able to eliminate this risk. Of over 2000 patients having PV ablation so far, we have observed severe symptomatic PV stenosis (> 70%) in only four, the latter requiring PV dilatation and stenting. In addition, five of these 2000 have developed right phrenic nerve injury with complete recovery.

Ablation anywhere within the atria can result in the creation of conduction abnormalities that then may be able to support re-entry. After PV isolation alone we have observed that approximately 12% of patients have inducible macro re-entry and 5% present with spontaneous macro re-entry [194]. Mapping and ablation have demonstrated that the vast majority of these use the ablated zone as a central obstacle, resulting in either perimitral or peri-PV re-entry, the latter being more prevalent in patients with larger atria [177,194]. However, there is a subset of these arrhythmias that utilize the previous ablation lesion or other abnormally conducting zones within the atria to support re-entry [195]. When an anatomical approach of PV encircling has been utilized, the reported incidence of re-entrant arrhythmias has been much higher, with some groups reporting spontaneous arrhythmias in up to 27%, presumably due to the greater and incomplete atrial ablation [196–198].

More recently, a rapidly accumulating number of cases of atrio-oesophageal fistula are being reported, associated with a fatal outcome in many [191]. To date this complication has been observed exclusively in patients undergoing a purely anatomical ablation strategy, and is almost certainly a result of the greater ablation duration required and the higher than required power delivered along the posterior left atrium.

Additional complications that have been recognized include tamponade (0–4%), embolic events (0–1%) and groin injuries (< 5%).

Indications

For paroxysmal AF, there must be sufficient grounds to justify a complex ablation procedure associated with potentially severe complications. In most centres, patients are considered for ablation on the basis of frequent symptomatic episodes of AF (at least two per month) that are resistant to at least one antiarrhythmic drug (class I or III). Ablation is only considered in patients with symptoms, as the benefit of AF ablation has not been demonstrated in asymptomatic patients. Success rates of 70–90% are frequently reported (Table 30.12). Studies comparing the outcome of patients treated with antiarrhythmic drugs versus ablation are ongoing and some results are expected in early 2006.

Table 30.12 Success rate in different series of AF Ablations

Reference	Lesion set	Paroxysmal AF (no.)	AF termination	Inducibility	Follow-up (months)	Success off drugs
Haissaguerre *et al*. [187]	R ± L lines	45	40% RA 80% LA	100% RA	11	13% RA 40% LA
Oral *et al*. [181]	PVI	49	?	27%	5	61%
Nademanee *et al*. [186]	CFAES	57	100%	0%	12	89%
Haissaguerre *et al*. [163]	PVI ± mitral isthmus	70	75%	53/23%	7	74/83%
Oral *et al*. [197]	PVA + lines (anatomical)	100	54/90%	60/10%	6	67/86%
Pappone *et al*. [185]	PVA + lines (anatomical)	297	?	Not used	12	85%
Ouyang *et al*. [171]	PVI	41	?	Not used	6	95%

CFAES, complex fractionated atrial electrogram signals; PVA, pulmonary vein ablation (lesions encircling the pulmonary veins without aim or demonstration to produce complete isolation); PVI, pulmonary vein isolation (lesions encircling the veins are complete, producing the disappearance of venous potentials or their dissociation).

Recently, we have observed that there is a subset of patients, who present with prolonged sinus pauses occurring only on termination of AF (bradycardia–tachycardia syndrome), in whom ablation and cessation of antiarrhythmic agents was associated with recovery of sinus function, such that they no longer required pacing [199]. This subset may constitute a group of patients with paroxysmal AF who would benefit from a primary ablation strategy.

In persistent or permanent AF, ablation is particularly difficult. Consequently, major symptoms must be associated with the arrhythmia to justify the procedure. Once again, the arrhythmia must be resistant to antiarrhythmic drugs, probably including amiodarone. However, there is emerging evidence to suggest that patients with complications related to AF may benefit from a primary ablation strategy; patients with heart failure (Fig. 30.18), even in the absence of obvious symptoms, benefit from ablation as the ejection fraction may improve by about 20% with the maintenance of sinus rhythm (a much greater benefit than that reported with an 'ablate and pace' strategy) [200]. Ablation of persistent and permanent AF is associated with variable but encouraging success rates, usually ranging from 69 to more than 90%. However, these ablation procedures are long, difficult, technically challenging and associated with greater risk than PVI alone. One study by Pappone and Morady (presented at the American College of Cardiology Scientific Sessions, 2005) compared amiodarone with ablation for patients with persistent or permanent AF and observed a superior role for the use of ablation.

Surgical ablation

The pioneers of a surgical approach to AF were Jim Cox (Maze procedure) and Gérard Guiraudon (Corridor procedure) [201,202]. The surgical ablation strategy is relatively similar to that of catheter ablation, and most of the surgical schemata are also centred on the PVs. The veins can be encircled using various methods: one by one, two by two, or four by four. Linear lesions may be used in conjunction with PVI, or used in isolation. For example, linear lesions interconnecting PV ostia, which are then extended to the mitral annulus, have been used with good success rates. However, the first of these lesions has now been abandoned because of the high incidence of fistulae between the posterior left atrium and the oesophagus [203].

Different energy sources have been advocated as replacements for the surgical knife: radiofrequency, cryotherapy, focused ultrasound and microwave. At the present time though, most centres use either radio-frequency and/or cryoenergy. Of these, radiofrequency has had the most widespread use and has a reasonable safety/efficacy ratio. Cryotherapy, although appearing safer with limited risk of PV stenosis, has the disadvantage of long-duration delivery and frequent recovery of the treated area.

The best strategy and technology for surgery remains under evaluation. However, most current surgical schemata include PV encirclement, usually in combination with linear lesions connecting the latter to the lateral mitral annulus (Fig. 30.19). However, it is important to note that most of these approaches are performed under cardiac arrest, preventing the surgeon from using any type of mapping to assess the completeness of the lesions, thereby resulting in an incidence of macro re-entry [203]. However, this drawback must be balanced with the obvious advantage that the surgeon is able to perform the procedure under direct vision. More recently, some investigators have been developing minimally invasive procedures on the beating heart, thus possibly allowing mapping during the procedure [204].

The procedure itself is usually completed within 15–30 min. Postoperative morbidity and mortality was significant 10 years ago, but nowadays is reported to be lower than 1%. The longer-term success rate reported

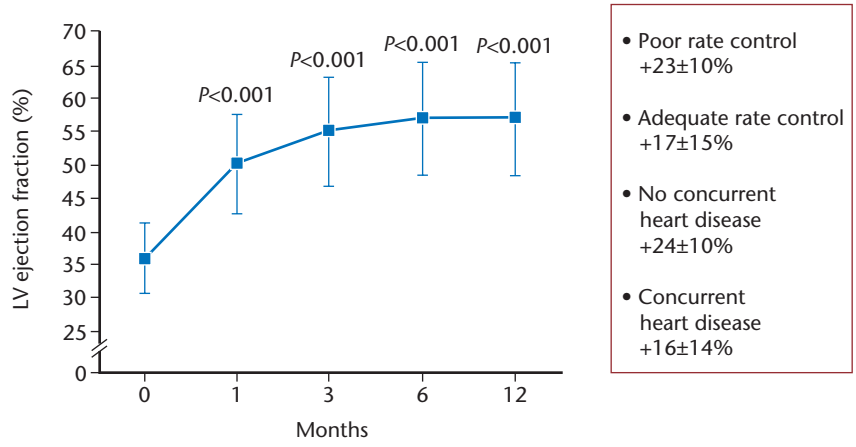

Figure 30.18 Summarized results of catheter ablation in a series of 58 patients with congestive heart failure. Note the important improvement observed in 92% of patients with poor rate control and dilated cardiomyopathy of unknown origin, suggesting a high prevalence of heart failure at least partly attributable to atrial fibrillation in this group of patients.

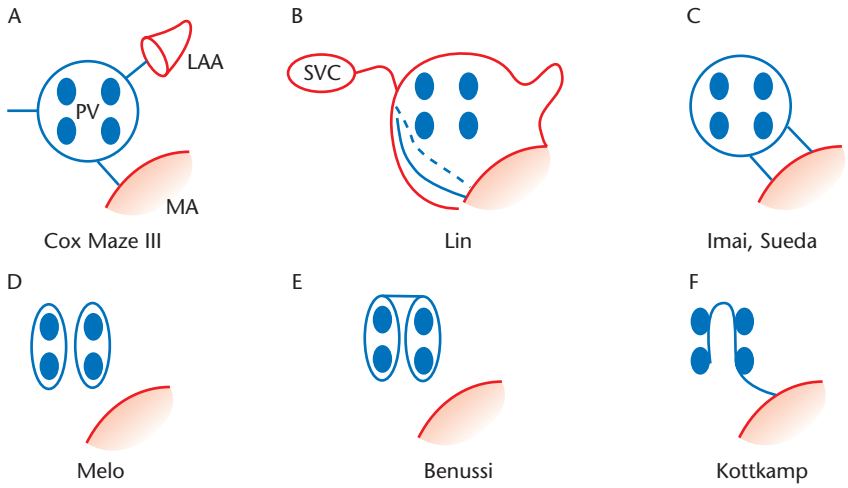

Figure 30.19 Different strategies for the surgical ablation of atrial fibrillation. Note that pulmonary veins are frequently encircled and that linear lesions when used are connected to anatomical areas of block. (A) Cox *et al*. *Ann Surg* 1996; **224**: 267–275; (B) Lin *et al*. *Am J Cardiol* 1997; **79**: 497–499; (C) Imai *et al*. *Ann Thorac Surg* 2001; **71**: 577–581; (D) Melo *et al*. *Eur J Cardiothorac Surg* 2000; **18**: 182–186; (E) Benussi *et al*. *Eur J Cardiothorac Surg* 2000; **17**: 524–529; (F) Kottkamp *et al*. *J Cardiovasc Electrophysiol* 1999; **10**: 772–780. LAA, left atrial appendage; PV, pulmonary vein; MA, mitral annulus.

with surgical intervention is 50–95%, with considerable variability in the incidence of left atrial macro re-entry during follow-up. Currently, this procedure is predominantly advocated in patients with AF who need cardiac surgery for whatever reason. It is generally agreed that in the absence of an indication for cardiac surgery, surgical therapy of AF should not be the first-line approach.

Conclusion

The last decade has seen significant developments in our understanding of AF and has led to catheter ablation and surgical techniques that have demonstrated the feasibility of achieving cure of AF. Ablation limited to the PVs and mappable non-PV foci provides a success rate of approximately 70% in paroxysmal AF and 20–30% in persistent or permanent AF. These results are further improved by additional substrate modification. Emerging evidence and technological improvements will broaden the use of these techniques in patients with AF in the future.

Management strategies according to presentation of atrial fibrillation

The main goals of AF treatment are to reduce symptoms, prevent thromboembolism and prevent morbidity and mortality. Results of multiple trials reinforce the need for continued anticoagulation in both rate and rhythm control strategies in patients with AF and risk factors for stroke.

Independently of the use of anticoagulation (see above), the first step in the treatment of AF is to control the ventricular response rate and to focus on the underlying heart disease. The message of the studies comparing rate control and rhythm control is that in the elderly there is an option for rate control as the primary strategy. On the other hand, this option is valid only for patients who have minimal or no symptoms, as severe symptoms that persist despite good rate control prompt consideration of a rhythm control therapy. Indeed, it is important to distinguish between paroxysmal and persistent AF because the former frequently causes severe symptoms in young active patients, whereas the latter may become less noticed and more amenable to a conservative strategy of rate control [205–207].

The decision to choose a rhythm or rate control strategy should be individualized and based on the expected benefit of restoring sinus rhythm, the likelihood of maintaining sinus rhythm in the long term, and the probability of adverse effects. Moreover, when drugs are unsuccessful, non-pharmacological therapy has to be discussed (Fig. 30.20).

Newly discovered or first-episode AF

In patients with recent-onset AF, it is not always clear whether the initial presentation of AF is actually the patient's first episode, particularly when there are minimal or no symptoms. In patients who have self-limited episodes of PAF, except in patients with severe symptoms, it is not usually necessary to use antiarrhythmic drugs to prevent recurrences, and rate-control and antithromboembolic measures should be used as front-line therapy.

Most patients with persistent AF deserve at least one attempt to convert and maintain sinus rhythm. Further treatment must be based on the likelihood of recurrences and the degree of underlying heart disease (young patients, no hypertension, normal left atrial size, short duration of AF) [18,208].

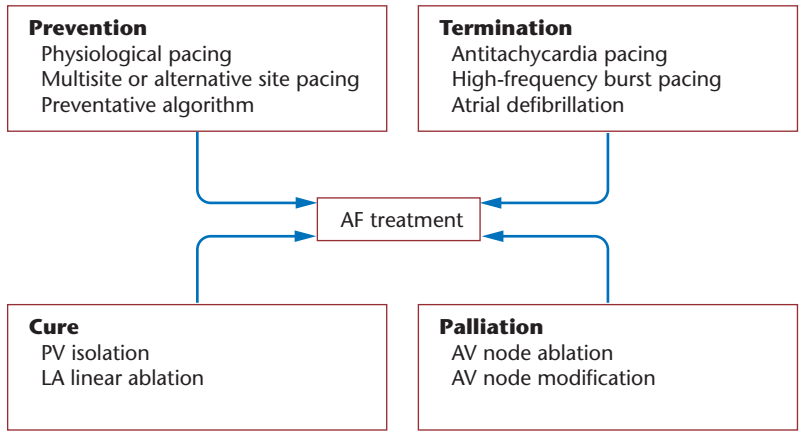

Figure 30.20 Non-pharmacological therapy of atrial fibrillation.

Paroxysmal AF

If the arrhythmia is not self-limiting, antiarrhythmic drugs can be administred to restore sinus rhythm. In this case, ESC/ACC/AHA guidelines [18] state that in patients with AF of less than 7 days' duration, flecainide, propafenone, ibutilide or dofetilide should be the first line if pharmacological conversion is considered. High-dose amiodarone and oral quinidine may be used in selected patients as a second-choice therapy. As the successs rate of pharmacological conversion is progressively reduced with increased duration of the arrhythmia, the choice of drug is then limited to dofetilide, ibutilide and possibly amiodarone (see Table 30.8).

Prophylactic antiarrhythmic drug therapy is usually not recommended after a first episode of arrhythmia, which may self-terminate (or require pharmacological or electrical conversion), and in patients with infrequent, self-limiting, minimally symptomatic episodes of AF. However, PAF is a 'chronic' desease as the arrhythmia tends to evolve to a persistent and, eventually, a permanent form. Moreover, the vast majority of patients experience frequent paroxysms, so that prophylactic antiarrhythmic drug therapy is usually recommended for these troublesome symptoms.

In any given patient several drugs may be effective, and the initial selection is mainly based on safety. Antiarrhythmic drugs recommended by the ESC/AHA/ACC guidelines are summarized in Fig. 30.12 depending on the underlying heart disease. For individuals with minimal or no heart disease, class IC drugs and sotalol are well tolerated and recommended as a first choice. Second or third choice, to be used in case of lack of efficacy or troublesome adverse effects, are amiodarone, disopyramide, procainamide and quinidine.

In patients with vagally induced AF, flecainide, disopyramide and quinidine may be effective due to their vagolytic effects. On the other hand, beta-blockers or sotalol are suggested in patients with adrenergically mediated AF.

Patients with ischaemic heart disease usually require beta-blocker medication, and beta-blockers or sotalol are a first-choice therapy unless heart failure is present. Amiodarone and dofetilide, when available, are proposed as a second choice. The selection of antiarrhythmic drugs in patients with hypertension is compounded by the dearth of prospective antiarrhythmic drug trials comparing their safety and efficacy.

Beta-blockers, calcium blockers or digitalis may be necessary to control the ventricular rate in case of relapse. This holds especially in haemodynamically compromised patients at risk of decompensation. If amiodarone or sotalol are used as a preventive agent, addition of a rate-control agent is not necessary.

A non-pharmacological approach such as AF catheter ablation may be appropriate for PAF, but there must be sufficient grounds to justify a complex ablation procedure associated with relatively rare but potentially severe complications. In most centres, patients are considered for ablation on the basis of frequent symptomatic episodes (at least two per month) that are resistant to at least one antiarrhythmic drug (class I or III). Ablation may be only considered in patients with symptoms, as the benefits of ablation have not yet been demonstrated in asymptomatic patients.

Persistent AF

Persistent AF does not stop spontaneously and is difficult to terminate with pharmacological conversion. First-choice therapy is direct-current electrical cardioversion. As only about 50% of patients will maintain sinus rhythm at 1 year following cardioversion, most patients need prophylactic therapy. Most drugs appear to be equally effective, except for amiodarone which is more efficacious. The selection should be based on the same

algorithms used for patients with PAF (see Fig. 30.12, Tables 30.8 and 30.9).

Rate control appears to be more appropriate as a primary strategy in patients with midly symptomatic long-standing AF, those with persistent AF and failed repeat cardioversions plus serial prophylactic antiarrhythmic drug therapy, and those with an adverse risk–benefit ratio for antiarrhythmic drugs. The results of studies comparing rate control and rhythm control [43–46] pertained to older patients and cannot be extrapolated to younger people, who are more likely to be symtomatic and to have more impaired quality of life when good rate control has been achieved. In persistent or permanent AF, catheter ablation is difficult and consequently major symptoms must be associated with the arrhythmia to justify the procedure. Once again, AF must be resistant to antiarrhythmic drugs including amiodarone.

Permanent AF

Rate control is the primary strategy in patients with permanent AF, i.e. when sinus rhythm cannot be sustained after cardioversion or when it has been decided to abandon efforts to restore sinus rhythm (no symptom improvement, unwanted adverse effects, pro-arrhythmia, sinus node dysfunction). When patients experience symptoms related to a rapid and irregular rate during AF that cannot be controlled by rate-slowing agents or develop a tachycardia-mediated decrease in ventricular function, AV node ablation may be useful (see Table 30.11). Further data are needed to confirm the benefit of primary ablation strategies in patients with heart failure [200].

AF in congestive heart failure

Patients with congestive heart failure are particularly prone to the adverse effects of antiarrhythmic drugs. Electrical cardioversion may be considered in younger patients with a short arrhythmia duration who have compensated heart failure. Repeated cardioversions at intervals longer than 6 months is an appropriate manner to prevent progression of heart failure. In such a case, amiodarone or dofetilide are the drugs of choice to prevent recurrences as they have been shown to be safe and effective in this context [96,97]. Neither drug is associated with deterioration of left ventricular function nor predisposes to pro-arrhythmic effects as long as they have been initiated and followed carefully [18].

All patients with left ventricular dysfunction should also be treated with beta-blockers and ACE inhibitors because not only do they prolong survival but also they provide additional rate control (beta-blockade) or 'antiarrhythmic' (beta-blocker and ACE inhibitor) benefit. Furthermore, non-antiarrhythmic agents may play an important role in rhythm control. Experimental and clinical studies have shown the benefit of ACE inhibitors and angiotensin II receptor blockers [205–207,209]. The magnitude of their effect may be modest but if applied to a very large population, the dividends could be significant. There is increasing evidence that these drugs can be effectively prescribed in patients with AF but without heart failure [205–207,209].

Patients in whom arrhythmia cannot be controlled or who have adverse effects from multiple antiarrhythmic drugs, those who are asymptomatic, the elderly and patients with a major increase in left atrial dimensions are poor candidates for an aggressive approach to the maintenance of sinus rhythm and should be considered for rate control. The 10–15% of patients refractory to drug therapy may be symptomatically improved by AV node catheter ablation, despite the need for pacemaker implantation [150,153]. Preliminary results of primary catheter ablation in the setting of heart failure, although encouraging, need to be confirmed [48].

AF after cardiac surgery

Postoperative AF occurs predominantly during the first 4 days after surgery and is associated with increased mortality and morbidity, and a longer hospital stay. Rate control may be preferable in the absence of haemodynamic compromise or poorly tolerated symptoms as AF after surgery appears to be self-limiting, with a high likelihood of spontaneous conversion to sinus rhythm after a few weeks. In this setting, beta-blockers or sotalol may be considered a first-choice therapy because of the beneficial effect on the hyperadrenergic postoperative state. On the other hand, there is compelling evidence that prophylactic treatment with amiodarone may reduce the incidence and duration of postoperative AF [205].

Conclusions

AF remains a significant challenge due to its increasing prevalence and complex nature. It is unlikely that a single therapy will revolutionize its management. Comprehensive management strategies including new antiarrhythmic and non-antiarrhythmic drugs, non-pharmacological therapy such as catheter ablation, and improved anticoagulation will be needed to provide safe and effective options for the wide spectrum of patients with AF.

Personal perspective

Although several new treatment modalities are available to restore and maintain sinus rhythm in patients with AF, the long-term success remains disappointing. Several clinical trials have concluded that rate control is an acceptable alternative to rhythm control in patients with recurrent AF. Nevertheless AF represents a significant challenge due to its increasing prevalence and heterogeneous and complex nature.

ACE inhibitors and angiotensin receptor blockers appear to be useful in prevention of AF in counteracting stretch-activated channels and/or directly blocking angiotensin II. Advances in molecular biology also hold therapeutic promise. On the other hand, the most significant advances in decreasing mortality and morbidity in AF have come from multiple trials demonstrating the need for chronic and indefinite anticoagulant therapy even in patients controlled with antiarrhythmic drugs if there are risk factors for thromboembolism. The development of new safe anticoagulants such as oral direct antithrombin inhibitors may offer an easier way to prescribe anticoagulation therapy.

Pulmonary vein isolation and substrate modification by catheter ablation (or surgery) have emerged as effective and safe procedures to cure AF. Technological advances will improve efficacy, decrease adverse effects and shorten the procedure time for primary catheter ablation. Shortly this technique will be fully evaluated in randomized trials and it is likely to gain widespread indications.

Individualization of therapy is paramount when treating AF patients. Given the millions of patients at risk of developing AF in the next 10 years, this dramatic progress in its treatment will be very opportune.

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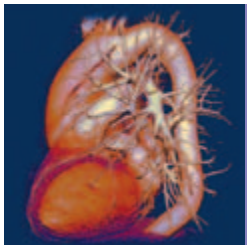

31 Syncope

Michele Brignole, Jean-Jacques Blanc and Richard Sutton

Summary

This chapter summarizes the evidence base which supports accepted standards provided by the Guidelines for the Management (Diagnosis and Treatment) of Syncope of the European Society of Cardiology.

The starting point for evaluation of syncope is the 'initial evaluation', which consists of history, physical examination, including orthostatic blood pressure measurements, and standard electrocardiogram. Differentiating true syncope from other 'non-syncopal' conditions associated with real or apparent transient loss of consciousness is generally the first diagnostic challenge and influences the subsequent diagnostic strategy. The initial evaluation may lead to certain diagnosis, a suspected diagnosis that needs to be confirmed by appropriate diagnostic tests, or no diagnosis (here termed as unexplained syncope). The strategy of evaluation varies according to the severity and frequency of the episodes and to the presence or absence of heart disease. In general, the absence of suspected or certain heart disease excludes a cardiac cause of syncope. Evaluation for neurally mediated syndromes is recommended only in those patients with recurrent or severe syncope. It includes tilt testing, carotid sinus massage and prolonged ECG monitoring including loop recorder. Conversely, the presence of heart disease at the initial evaluation is a strong predictor of a cardiac cause of syncope and includes virtually all cardiac syncopes, but its specificity is low because about half of patients with heart disease have a non-cardiac cause of syncope. In these patients, cardiac evaluation (echocardiography, stress testing, electrophysiological study and prolonged ECG monitoring including loop recorder) is recommended. Neurological disease may cause transient loss of consciousness (e.g. certain seizures), but is almost never the cause of syncope. Thus, neurological testing (electroencephalography, computerized tomography and magnetic resonance imaging of the brain) may be needed to distinguish seizures from syncope in some patients, but these should not be considered as essential elements in the evaluation of the basis of true syncope. In recent population-based studies, neurally mediated and orthostatic hypotension were the most frequent causes of syncope, accounting for 56% of cases; cardiac syncope accounted for 14% of cases; and neurological and psychiatric causes were found in 9% of patients, with the mechanism remaining unknown in 20% of cases. Determining the mechanism is a prerequisite for advising patients with regard to prognosis and to developing an effective treatment strategy.

Definition, pathophysiology, epidemiology and prognosis

Syncope is a symptom, defined as a transient, self-limited loss of consciousness, usually leading to falling. The onset of syncope is relatively rapid, and the subsequent recovery is spontaneous, complete and usually prompt. The underlying mechanism is a transient period of global cerebral hypoperfusion [1–3]. Presyncope or 'near-syncope' refers to a condition in which patients feel as though syncope is imminent.

In healthy younger individuals with cerebral blood flow in the range of 50–60 ml/100 g tissue/min, about 12–15% of resting cardiac output, minimum oxygen

requirements necessary to sustain consciousness (approximately 3.0–3.5 ml O_2/100 g tissue/min) are easily achieved. However, in older individuals, or those with underlying disease, the safety margin for oxygen delivery may be more tenuous. A sudden cessation of cerebral blood flow for 6–8 s has been shown to be sufficient to cause complete loss of consciousness. Experience gained during head-up tilt-table testing has shown that a decrease in systolic blood pressure to 60 mmHg or less is usually associated with development of syncope. Further, it has been estimated that as little as a 20% drop in cerebral oxygen delivery is sufficient to cause loss of consciousness [1–3]. Thus, whatever the mechanism of syncope is in a given clinical circumstance, it is transient global cerebral hypoperfusion (most often due to diminished systemic arterial pressure) that is the principal factor leading to loss of consciousness. Furthermore, it is the global cerebral hypoperfusion that differentiates syncope from the non-syncopal causes of transient loss of consciousness (Tables 31.1 and 31.2).

In some forms of syncope, there may be a premonitory warning of an impending syncopal event, whereas in others the loss of consciousness occurs without warning. Recovery from syncope is usually accompanied by rapid restoration of appropriate behaviour. Retrograde amnesia, although believed to be uncommon, may be more frequent than previously thought, particularly in older individuals. Typical syncopal episodes are brief and usually last no longer than 20 s. Rarely, syncope duration may be longer, even lasting for several minutes. In such cases, distinguishing between syncope and other causes of loss of consciousness can be difficult.

Syncope is a common problem. In the Framingham study [4], the 10-year cumulative incidence of syncope was of 6%. However, the incidence was not constant, but increased rapidly starting at the age of 70 years. The 10-year cumulative incidence of syncope was 11% for both men and women at age 70–79, and 17% and 19% respectively for men and women at age ≥ 80.

Structural heart disease is a major risk factor for sudden death and overall mortality in patients with syncope. Conversely, young patients without structural heart disease and patients affected by neurally mediated syncope or orthostatic hypotension have an excellent prognosis with respect to mortality, but syncope recurrences remain a concern.

Approximately 35% of patients have had recurrences of syncope at 3 years of follow-up; 82% of recurrences occur within the first 2 years. Predictors of recurrence of syncope include having had recurrent syncope at the time of presentation. Major morbidity such as fractures and motor vehicle accidents were reported in 6% of patients, and minor injury such as laceration and bruises in 29%. Recurrent syncope causes impairment of quality of life similar to that of chronic illnesses such as rheumatoid arthritis, low back pain and psychiatric disorders. Further, patients with syncope are often admitted to hospital and undergo expensive and repeated investigations.

Table 31.1 Causes of syncope

Neurally mediated (reflex)
Vasovagal syncope (common faint)
Classical
Non-classical
Carotid sinus syncope
Situational syncope
Acute haemorrhage
Cough, sneeze
Gastrointestinal stimulation (swallow, defaecation, visceral pain)
Micturition (post-micturition)
Post-exercise
Post-prandial
Others (e.g. brass instrument playing, weightlifting)
Glossopharyngeal neuralgia
Orthostatic hypotension
Autonomic failure
Primary autonomic failure syndromes (e.g. pure autonomic failure, multiple system atrophy, Parkinson's disease with autonomic failure)
Secondary autonomic failure syndromes (e.g. diabetic neuropathy, amyloid neuropathy)
Drugs and alcohol
Post-exercise
Post-prandial
Volume depletion
Haemorrhage, diarrhoea, Addison's disease
Cardiac arrhythmias as primary cause
Sinus node dysfunction (including bradycardia/tachycardia syndrome)
Atrioventricular conduction system disease
Paroxysmal supraventricular and ventricular tachycardias
Inherited syndromes (e.g. long QT syndrome, Brugada syndrome)
Implanted device (pacemaker, ICD) malfunction
Drug-induced arrhythmias
Structural cardiac or cardiopulmonary disease
Obstructive cardiac valvular disease
Acute myocardial infarction/ischaemia
Obstructive cardiomyopathy
Atrial myxoma
Acute aortic dissection
Pericardial disease/tamponade
Pulmonary embolus/pulmonary hypertension
Cerebrovascular
Vascular steal syndromes

Table 31.2 Causes of non-syncopal attacks (commonly misdiagnosed as syncope)

Disorders without any impairment of consciousness
Falls
Cataplexy
Drop attacks
Psychogenic pseudosyncope
Transient ischaemic attacks (TIAs) of carotid origin
Disorders with partial or complete loss of consciousness
Metabolic disorders, including hypoglycaemia, hypoxia, hyperventilation with hypocapnia
Epilepsy
Intoxications
Vertebrobasilar transient ischaemic attack

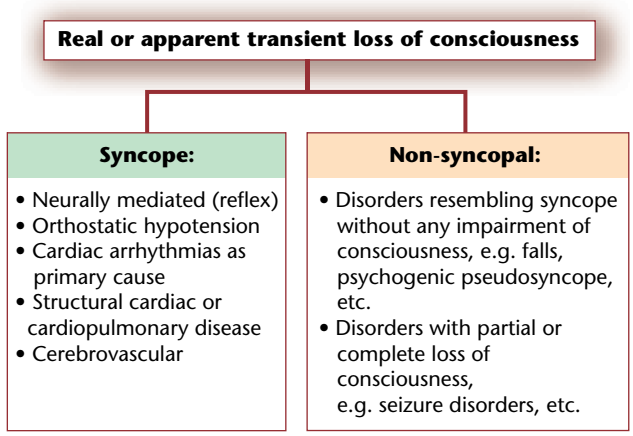

Figure 31.1 Classification of transient loss of consciousness.

Often, these investigations are not well considered in terms of currently recommended optimum diagnostic strategy for the evaluation of the causes of syncope in a given individual [2], and as a result frequently do not provide a definite diagnosis.

The diagnostic strategy based on the initial evaluation

The *initial evaluation* of a patient presenting with syncope consists of careful history, physical examination including orthostatic blood pressure measurements, and standard electrocardiogram (ECG) [1–3].

Three key questions should be addressed during the initial evaluation:

1 Is loss of consciousness attributable to syncope or not? Differentiating true syncope from 'non-syncopal' conditions associated with real or apparent transient loss of consciousness is generally the first diagnostic challenge and influences the subsequent diagnostic strategy (Fig. 31.1).
2 Are there features in the history that suggest the diagnosis? Accurate history-taking alone is a key stage and often leads to the diagnosis or may suggest the strategy of evaluation.
3 Is heart disease present or absent? The absence of signs of suspected or overt heart disease virtually excludes a cardiac cause of syncope, with the exception of syncope accompanied by palpitations which could be due to paroxysmal tachycardia (especially paroxysmal supraventricular tachycardia). Conversely, the presence of heart disease at the initial evaluation is a strong predictor of cardiac cause of syncope, but its specificity is low as about half of patients with heart disease have a non-cardiac cause of syncope [5].

Table 31.1 provides a clinical classification of the principal known causes of syncope [1–3]. The subdivision of syncope is based on pathophysiology as follows:

- 'Neurally mediated (reflex) syncope' refers to a reflex response that, when triggered, gives rise to vasodilatation and/or bradycardia; however, the contribution of each of these two factors to systemic hypotension and cerebral hypoperfusion may differ considerably. The triggering events might vary considerably in individual patients. The 'classical vasovagal syncope' is mediated by emotional or orthostatic stress and can be diagnosed by history-taking. 'Carotid sinus syncope' is defined as syncope which, by history, seems to occur in close relationship to accidental mechanical manipulation of the carotid sinuses, and can be reproduced by carotid sinus massage. 'Situational syncope' refers to those forms of neurally mediated syncope associated with specific scenarios (e.g. micturition, coughing and defaecating). Often, however, neurally mediated reflex syncopes have 'non-classical' presentations. These forms are diagnosed by minor clinical criteria, exclusion of other causes for syncope (absence of structural heart disease) and positive response to tilt testing or carotid sinus massage. Examples of non-classical vasovagal syncope include episodes without clear triggering events or premonitory symptoms.
- 'Orthostatic hypotension' refers to syncope in which the upright position (most often the movement from sitting or lying to an upright position) causes arterial hypotension. This occurs when the autonomic nervous system is incapacitated and fails to respond

to the challenges imposed by upright position. A second major cause is 'volume depletion', in which the autonomic nervous system is itself not deranged but is unable to maintain blood pressure as a result of decreased circulating volume. Note that vasovagal syncope can also be provoked by standing (e.g. soldiers fainting on parade), but these events are grouped under 'neurally mediated (reflex) syncope'.

- 'Cardiac arrhythmias' can cause a decrease in cardiac output, which usually occurs irrespective of circulatory demands.
- 'Structural heart disease' can cause syncope when circulatory demands outweigh the impaired ability of the heart to increase its output.
- 'Steal' syndromes are rare, but can cause syncope when blood supply is diverted from the brain to another organ. The most common example is the so-called 'subclavian steal syndrome'.

Table 31.2 lists the most common conditions misdiagnosed as causes of syncope. Such a differentiation is crucial because the clinician is usually confronted with patients in whom sudden loss of consciousness has been provoked by causes not associated with decreased cerebral blood flow such as seizure and/or conversion reaction. Several disorders may resemble syncope in two different ways. In some, consciousness is truly lost, but the mechanism is not related to cerebral hypoperfusion, such as epilepsy, metabolic disorders (including hypoxia and hypoglycaemia) and intoxications. In several other disorders, consciousness is only apparently lost; this is the case in 'psychogenic pseudosyncope', cataplexy and drop attacks.

The initial evaluation may lead to certain or suspected diagnosis or no diagnosis (here termed as unexplained syncope) (Fig. 31.2).

Certain diagnosis

Initial evaluation may lead to a certain diagnosis based on symptoms, physical signs or ECG findings. Under

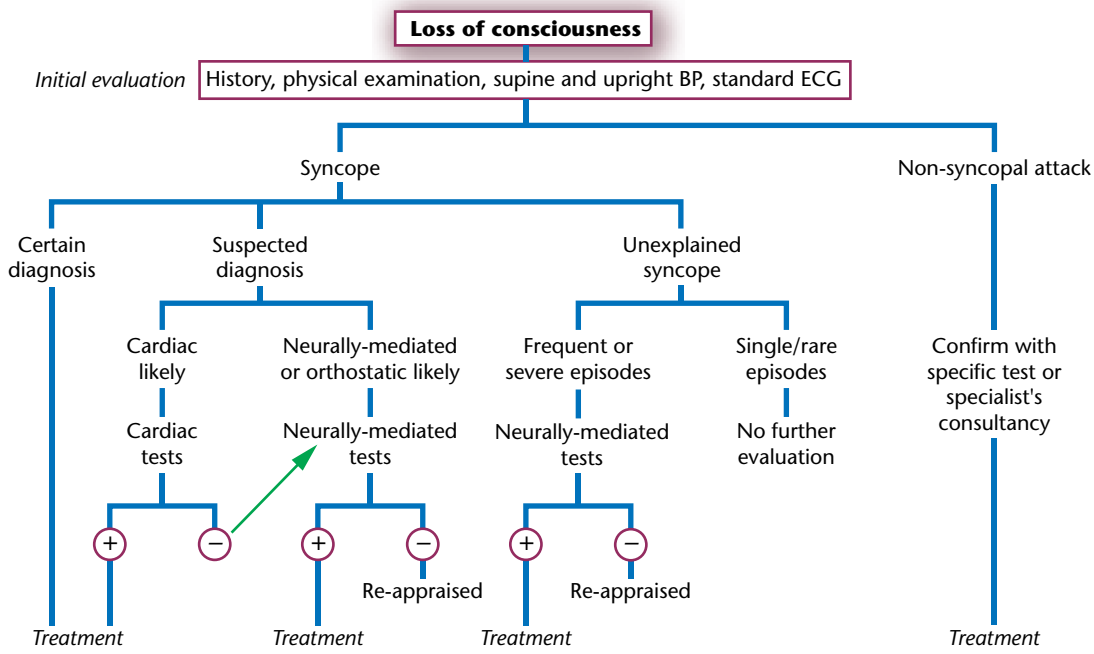

Figure 31.2 The flow diagram proposed by the Task Force on Syncope of an approach to the evaluation of loss of consciousness based on the initial evaluation. Differentiating true syncope from other 'non-syncopal' conditions associated with real or apparent transient loss of consciousness is generally the first diagnostic step and influences the subsequent diagnostic strategy. For the classification of syncope, refer to Table 31.1, and for the classification of non-syncopal attack refer to Table 31.2. The conditions in which the results of the initial evaluation are diagnostic of the cause of syncope and no further evaluation is required are listed as recommendations in The diagnostic strategy based on the initial evaluation. The features that suggest a cardiac or a neurally mediated cause of syncope are listed in Tables 31.3 and 31.4. Among cardiac investigations, echocardiography, prolonged electrocardiographic monitoring, stress test, electrophysiological study and implantable loop recorder are most useful. Among neurally mediated investigations, tilt test, carotid sinus massage and implantable loop recorder are most useful. When a cardiac diagnosis cannot be confirmed, neurally mediated tests are usually performed. Once the evaluation, as outlined, is completed and no cause of syncope is determined, reappraisal of the work-up may be needed. BP, blood pressure; ECG, electrocardiogram.

such circumstances, no further evaluation may be needed and treatment, if any, can be planned. The results of the initial evaluation are most often diagnostic of the cause of syncope in the following situations [1–3]:

- *Classical vasovagal syncope* is diagnosed if precipitating events such as fear, severe pain, emotional distress, instrumentation or prolonged standing are associated with typical prodromal symptoms.
- *Situational syncope* is diagnosed if syncope occurs during or immediately after urination, defaecation, coughing or swallowing.
- *Orthostatic syncope* is diagnosed when there is documentation of orthostatic hypotension (defined as a decrease in systolic blood pressure ≥ 20 mmHg or a decrease of systolic blood pressure to < 90 mmHg) associated with syncope or presyncope.
- *Cardiac ischaemia*-related syncope is diagnosed when symptoms are present with ECG evidence of acute ischaemia with or without myocardial infarction. However, in this case, the further determination of the specific ischaemia-induced aetiology may be necessary (e.g. neurally mediated hypotension, tachyarrhythmia and ischaemia-induced AV block).
- *Arrhythmia*-related syncope is diagnosed by ECG when there is:
  (a) sinus bradycardia < 40 beats/min or repetitive sinoatrial blocks or sinus pauses > 3 s in the absence of medications known to have negative chronotropic effect
  (b) second-degree Mobitz II or third-degree atrioventricular block
  (c) alternating left and right bundle branch block
  (d) rapid paroxysmal supraventricular tachycardia or ventricular tachycardia
  (e) pacemaker malfunction with cardiac pauses.

However, it is important to bear in mind that syncope is often multifactorial. The latter is especially true in older individuals. Thus, careful consideration should be given to multiple potentially interacting factors (e.g. diuretics in older patients already susceptible to orthostatic hypotension and myocardial ischaemia in the setting of moderate aortic stenosis).

Table 31.3 Clinical features suggestive of specific causes of syncope

Neurally mediated syncope
Absence of cardiac disease
Long history of syncope
After sudden unexpected unpleasant sight, sound, smell or pain
Prolonged standing or crowded, hot places
Nausea, vomiting associated with syncope
During or in the absorptive state after a meal
With head rotation, pressure on carotid sinus (as in tumours, shaving, tight collars)
After exertion
Syncope due to orthostatic hypotension
After standing up
Temporal relationship with start of medication leading to hypotension or changes of dosage
Prolonged standing especially in crowded, hot places
Presence of autonomic neuropathy or Parkinsonism
After exertion
Cardiac syncope
Presence of severe structural heart disease
During exertion, or supine
Preceded by palpitation or accompanied by chest pain
Family history of sudden death
Cerebrovascular syncope
With arm exercise
Differences in blood pressure or pulse in the two arms

Table 31.4 ECG abnormalities suggesting arrhythmic syncope

Bifascicular block (defined as either left bundle branch block or right bundle branch block combined with left anterior or left posterior fascicular block)
Other intraventricular conduction abnormalities (QRS duration ≥ 0.12 s)
Mobitz I second-degree atrioventricular block
• Asymptomatic sinus bradycardia (< 50 b.p.m.) or sinoatrial block
• Pre-excited QRS complexes
• Prolonged QT interval
• Right bundle branch block pattern with ST elevation in leads V1–V3 (Brugada syndrome)
• Negative T waves in right precordial leads, epsilon waves and ventricular late potentials suggestive of arrhythmogenic right ventricular dysplasia
• Q waves suggesting myocardial infarction

Suspected diagnosis

Commonly, the initial evaluation leads to a suspected diagnosis when one or more of the features listed in Tables 31.3 and 31.4 are present [1–3]. The presence of suspected or certain heart disease is associated with a higher risk of arrhythmias and mortality at 1 year. In these patients, cardiac evaluation (echocardiography, stress testing, electrophysiological study and prolonged ECG monitoring including loop recorder) is recommended. If cardiac evaluation does not show evidence of arrhythmia as a cause of syncope, evaluation for neurally mediated syndromes is recommended only in those with recurrent or severe syncope. It includes tilt testing, carotid sinus

massage and ECG monitoring, and often further necessitates implantation of an implantable loop recorder (ILR). The majority of patients with single or rare episodes in this setting have a high likelihood of neurally mediated syncope, and tests for confirmation are usually not necessary.

If the diagnosis is confirmed, treatment may be initiated; if not, a reappraisal process may be useful.

Unknown diagnosis

The cause of syncope may remain unexplained after the initial evaluation. The strategy varies according to the severity and frequency of the episodes (Fig. 31.2) (see above). For patients with unexplained syncope, the most likely diagnosis is neurally mediated, for which the appropriate tests are described above. The majority of patients with single or rare episodes in this category probably have neurally mediated syncope and tests for confirmation are usually not necessary [1–3].

Reappraisal

If the cause of syncope is undetermined once the evaluation is completed, reappraisal of the work-up is needed because subtle findings or new historical information may change the strategy. Reappraisal may consist of obtaining additional details of history and re-examining the patient, placement of an ILR if not previously undertaken, as well as review of the entire work-up. If new clues to possible cardiac or neurological disease are yielded, further cardiac and neurological assessment are recommended. In these circumstances, consultation with appropriate specialists may be useful. Psychiatric assessment is recommended in patients with frequent recurrent syncope who have multiple other somatic complaints and in whom initial evaluation raises concerns about stress, anxiety and possible other psychiatric disorders [1–3].

Diagnostic tests

Echocardiogram

Echocardiography is diagnostic of the cause of syncope in the presence of severe aortic stenosis and atrial myxoma. This investigation also provides information about the type and severity of underlying heart disease. If moderate to severe structural heart disease is found, evaluation is directed towards a cardiac cause of syncope, whereas in the presence of minor abnormalities the probability of cardiac cause of syncope is low and the evaluation proceeds as in patients without structural heart disease.

Carotid sinus massage

Carotid sinus syndrome is diagnosed in patients who have an abnormal response to carotid sinus massage (carotid sinus hypersensitivity) and an otherwise negative work-up for syncope. Carotid sinuses (alternatively right and left) are firmly massaged for 5–10 s. The site for massage is the anterior margin of the sternocleomastoid muscle at the level of the cricoid cartilage. Both a cardioinhibitory reflex and a vasodepressor reflex are usually evoked with the massage (mixed form) but their relative contribution varies. A correct determination of the vasodepressor component of the reflex is of practical importance for the choice of pacing therapy, which is more effective in dominant cardioinhibitory forms (Fig. 31.3). A positive response is defined as a ventricular pause > 3 s and/or a fall in systolic blood pressure > 50 mmHg [6,7]. However, abnormal responses are frequently observed in patients without syncope. The specificity of the test increases if reproduction of spontaneous syncope during carotid massage is a requisite for positivity of the test. The syndrome is misdiagnosed in half of the cases if the massage is not performed in the upright position [8]. There is a relationship between carotid sinus hypersensitivity and spontaneous, otherwise unexplained, syncope [9]. Carotid sinus syndrome is a frequent cause of syncope, especially in elderly men, ranging from 4% in patients < 40 years to 41% in patients > 80 years [8]. In a large population of 1719 consecutive patients with syncope uncertain after the initial evaluation (mean age 66 ± 17 years), carotid sinus hypersensitivity was found in 56% and syncope was reproduced in 26% of cases [8]. The response was cardioinhibitory in 46% of patients, mixed in 40% and vasodepressor in 14%. The main complication of carotid sinus massage is neurological, i.e. transient ischaemic attack (TIA) and stroke, its incidence ranging in three studies between 0.17% and 0.45% [8–10]. If there is a risk of stroke due to carotid artery disease, massage should be avoided. Therefore, carotid sinus massage is recommended in patients over the age of 40 years with syncope of unknown aetiology after the initial evaluation [1–3].

Tilt testing

On changing from supine to erect posture, there is a large gravitational shift of blood from the chest to the venous capacitance system below the diaphragm. Failure of compensatory reflexes to orthostatic stress is thought to play a predominant role in a large number of patients with

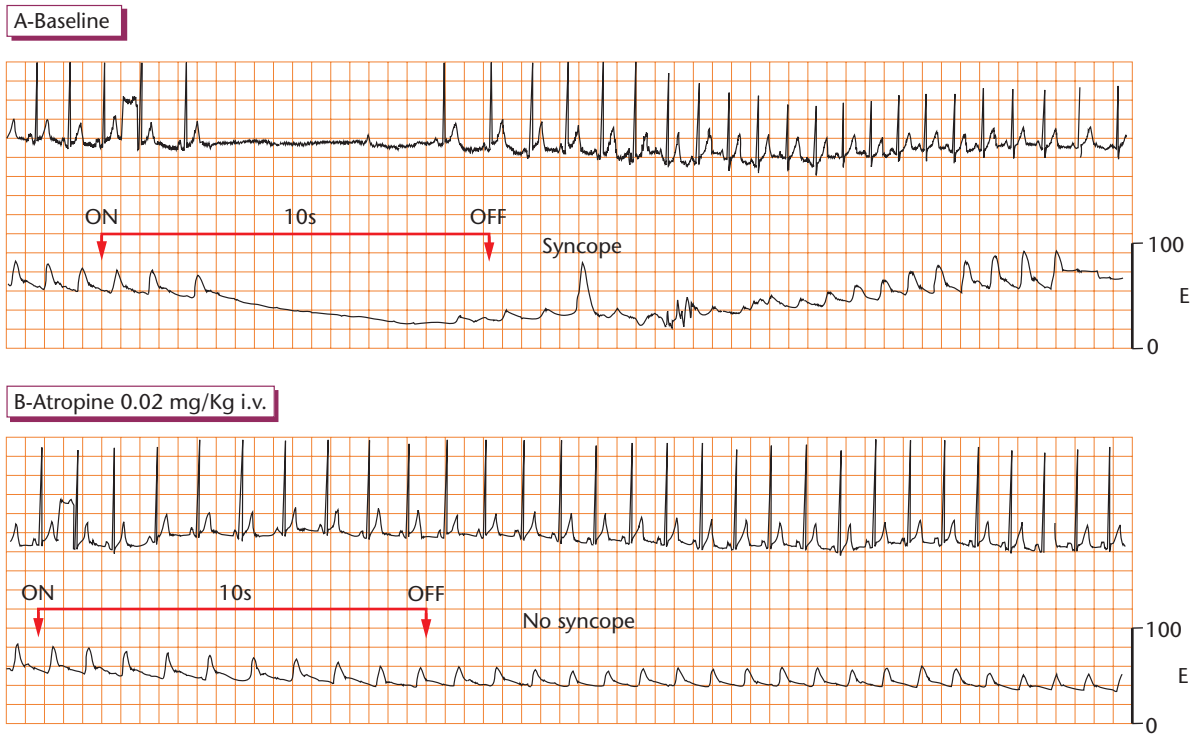

Figure 31.3 Dominant cardioinhibitory form of carotid sinus syndrome diagnosed by carotid sinus massage performed according the 'method of symptoms' [8–9]. (A) The massage was performed during beat-to-beat, electrocardiographic (top trace) and systemic blood pressure monitoring (bottom trace) with the patient lying on a tilt-table in upright 60° position (arrows). The massage was continued for 10 s. A 6.5-s asystole was induced soon after the beginning of the massage. The systolic blood pressure felt below 50 mmHg; the vasodepressor reflex persisted longer than the cardioinhibitory reflex. Syncope occurred after the end of the massage when heart rhythm had already recovered. (B) In order to determine the relative contribution of the two components of the reflex, the cardioinhibitory component was suppressed by means of i.v. infusion of 0.02 mg/kg atropine and the massage repeated. Despite a marked blood pressure fall, syncope could not be reproduced, thus showing that the cardioinhibitory component of the reflex was the major determinant of syncope in this patient.

suspected vasovagal syncope. This forms the basis for the use of tilt testing.

Protocols

In 1986, the initial tilt protocol consisted of a passive phase of tilting with an inclination of 60° for 60 min [11]. In 1989, a drug challenge with isoproterenol (isoprenaline) was added [12]. After several protocol variations tested to maximize its diagnostic value, the most valuable seemed to be the 'shortened' low-dose isoproterenol tilt testing, in which the rate of positive responses was of 61% with a specificity of 92–93% [13,14]. In 1994, a drug challenge with nitroglycerine was proposed [15]. After several protocol variations, the most valuable seems to be a 'shortened' protocol using 400 µg nitroglycerine spray sublingually after a 20-min baseline phase (Fig. 31.4). Pooled data from three studies [16–18] show a positive response rate of 69% with a specificity of 94%.

To summarize, the widely accepted protocols consist of [1–3]:

- supine pre-tilt phase of at least 5 min when no venous or arterial cannulation is performed, and at least 20 min when cannulation is undertaken;
- tilt angle is 60–70°;
- passive phase ≥ 20 min and ≥ 45 min;
- use of either intravenous isoproterenol or sublingual nitroglycerine for drug provocation if the passive phase has been negative; drug challenge phase duration should be 15–20 min;
- for isoproterenol, an incremental infusion rate from 1 up to 3 µg/min, in order to increase average heart rate by about 20–25% over baseline, should be administered without returning the patient to the supine position;
- for nitroglycerine, a fixed dose of 400 µg nitroglycerine spray sublingually should be administered in the upright position;

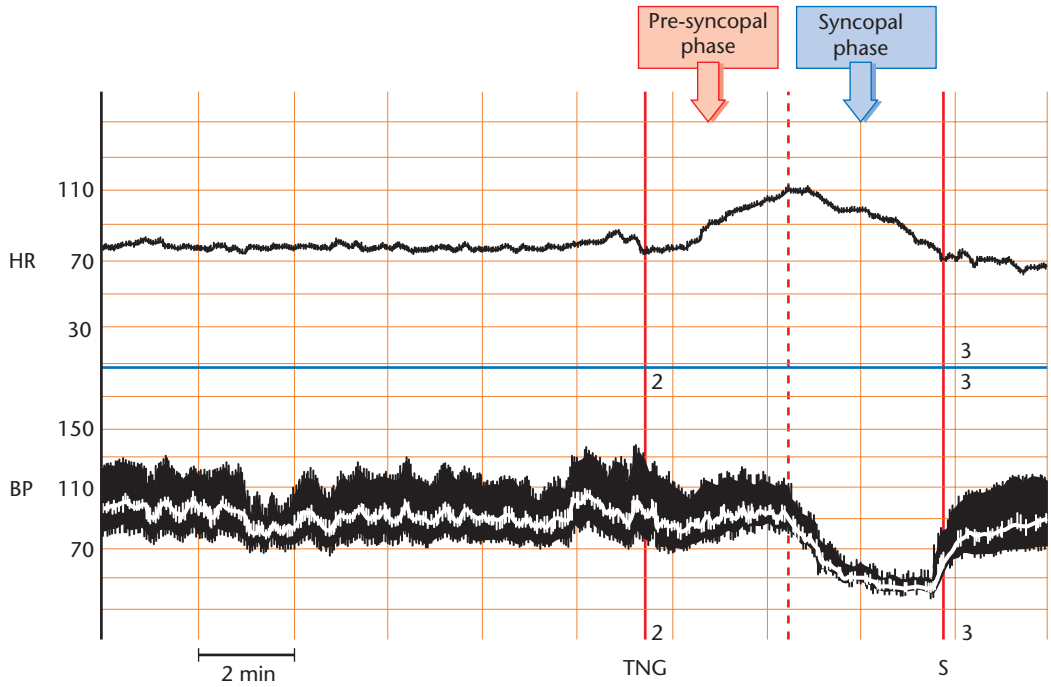

Figure 31.4 A case of classical (vasovagal) syncope, mixed pattern, occurring during nitroglycerine (TNG) challenge. The figure is expanded and the first part of the passive phase of the tilt testing is not shown. The top trace shows the heart rate curve; the bottom trace shows systolic, diastolic and mean blood pressure curves. Immediately after the administration of 0.4 mg of TNG, there is a mild decrease in blood pressure as a consequence of the haemodynamic effect of the drug. The presyncopal phase lasts about 2 min and is characterized by an increase in diastolic blood pressure of 15 mmHg, which indicates a full compensatory reflex adaptation with peripheral vasoconstriction. The heart rate rises approximately 35 b.p.m. The vertical dashed line indicates the time of onset of the vasovagal reaction, which is characterized by a rapid fall in both blood pressure and heart rate that leads to syncope in about 3 min. HR, heart rate; BP, blood pressure; TNG, trinitroglycerine; S, syncope.

- end-point of the test is the reproduction of syncope or completion of the planned duration of tilt, including drug provocation.

In patients without structural heart disease, tilt testing can be considered diagnostic, and no further tests are need when syncope is reproduced. In patients with structural heart disease, arrhythmias or other cardiac causes should be excluded prior to considering positive tilt test results. The clinical meaning of abnormal responses other than induction of syncope is unclear.

Responses to the tilt test

Experience from tilt testing showed that the vasovagal reaction lasts roughly ≤ 3 min before loss of consciousness. A decrease in systolic blood pressure ≤ 90 mmHg is associated with symptoms of impending syncope reproducing the patient's previous experience, and ≤ 60mmHg is associated with syncope. Prodromal symptoms are present in virtually all cases of tilt-induced vasovagal syncope, which occurs, on average, 1 min after the onset of prodromal symptoms. During the prodromal phase, blood pressure falls markedly; this fall frequently precedes the decrease in heart rate, which may be absent at least at the beginning of this phase. During the syncopal phase, a cardioinhibitory reflex of variable severity (ranging from slight heart rate decrease up to prolonged asystole) is frequent and contributes to the loss of consciousness (Fig. 31.4). Unusual response patterns include cases of chronotropic incompetence or of excessive heart rate rise (the so-called postural orthostatic tachycardia syndrome) [19].

Role of tilt test for assessing the effectiveness of the treatment

Data from controlled trials showed that approximately 50% of patients with a baseline positive tilt test became negative when the test was repeated with treatment or with placebo [20–22]. The mechanism of tilt-induced syncope was frequently different from that of the spontaneous syncope recorded with the ILR [23]. Moreover, acute studies were not predictive of the long-term outcome of pacing therapy [24]. These data show that the

use of tilt testing for assessing the effectiveness of different treatments has important limitations.

Complications

Tilt test is a safe procedure and the rate of complications is very low. The presence of prolonged asystole during a positive response cannot be considered a complication because this is an end-point of the test.

Electrocardiographic monitoring (non-invasive and invasive)

ECG monitoring is indicated only when there is a high pre-test probability of identifying an arrhythmia responsible for syncope. These conditions are listed in Tables 31.3 and 31.4. ECG monitoring is diagnostic when a correlation between syncope and electrocardiographic abnormality (brady- or tachyarrhythmia) is detected. Conversely, ECG monitoring excludes an arrhythmic cause when there is a correlation between syncope and no rhythm variation. Presyncope may not be an accurate surrogate for syncope in establishing a diagnosis and, therefore, therapy should not be guided by presyncopal findings. In the absence of such correlations, additional testing is recommended with the possible exception of ventricular pauses longer than 3 s when awake; periods of second-degree Mobitz II or third-degree atrioventricular block when awake; and rapid paroxysmal ventricular tachycardia [1–3].

In-hospital monitoring (in bed or telemetric) is warranted only when the patient has important structural heart disease and is at high risk of life-threatening arrhythmias. A few days of ECG monitoring may be of value, especially if the monitoring is applied immediately after syncope.

The vast majority of patients have a syncope-free interval measured in weeks, months or years, and therefore symptom–ECG correlation can rarely be achieved with Holter monitoring. In an overview [25] of the results of eight studies of ambulatory monitoring in syncope, only 4% of patients (range between 1% and 20%) had correlation of symptoms with arrhythmia. The true yield of conventional ECG monitoring in syncope may be as low as 1–2% in an unselected population. Therefore, Holter monitoring is indicated only in patients who have very frequent syncopes or presyncope. Holter monitoring may also be useful in patients who have the clinical or ECG features suggesting an arrhythmic syncope in order to guide subsequent examinations (i.e. electrophysiological study) [2–3].

In one study [26], external retrospective loop recorders showed relatively higher diagnostic yield in syncope, 25% of enrolled patients having syncope or presyncope recorded during the monitoring period up to 1 month. In a recent study [27], the external loop recorder yielded a low diagnostic value in patients with 3 ± 4 syncopal episodes (more than 2) during the previous 6 months, no overt heart disease and negative tilt test. Therefore, the external loop recorder may be indicated in patients who have an intersymptom interval of ≤ 4 weeks [2,3]. Newer, internet-based ambulatory monitoring systems offer the potential for continuous out-patient telemetry, thereby providing rapid recognition of arrhythmias without the need for the patient to return to the hospital for data downloading.

Patients with infrequent syncopes are unlikely to be diagnosed by the above systems. In such circumstances, consideration should be given to implantable ECG loop recorder (Fig. 31.5). In the initial clinical experience [28], correlation between symptoms (syncope or presyncope) and ECG was achieved in 59% of 85 patients within a mean of 10 months of implantation. Pooled data from four studies [23,28–30] comprising 247 patients with unexplained syncope at the end of a complete conventional investigation showed that correlation between syncope and ECG was found in 84 patients (34%); of these, 52% had bradycardia or asystole at the time of the recorded event, 11% had tachycardia and 37% had no rhythm variation. Therefore, when the mechanism of syncope remains unclear after full evaluation, an ILR is indicated in patients who have clinical or ECG features suggesting arrhythmic syncope (Tables 31.3 and 31.4) or a history of recurrent syncopes with injury (Fig. 31.6) [2,3]. The ILR may also be indicated in an initial phase of the work-up instead of at completion of conventional investigations. This is particularly the case for patients with preserved cardiac function who have clinical or ECG features suggesting an arrhythmic syncope [31], and in order to confirm suspected bradycardia before embarking on cardiac pacing in patients with suspected or certain neurally mediated syncope presenting with frequent or traumatic syncopal episodes [23].

Electrophysiological testing

The diagnostic efficiency of the invasive electrophysiological study is not only highly dependent on the degree of suspicion of the abnormality (pre-test probability) but also on the protocol (Table 31.5) and the criteria used for diagnosing clinically significant abnormalities. Positive results at electrophysiological study occur almost exclusively in patients with overt heart disease or conduction defects [32]. It must be emphasized that normal electrophysiological findings cannot completely exclude an arrhythmic cause of syncope. When an arrhythmia is

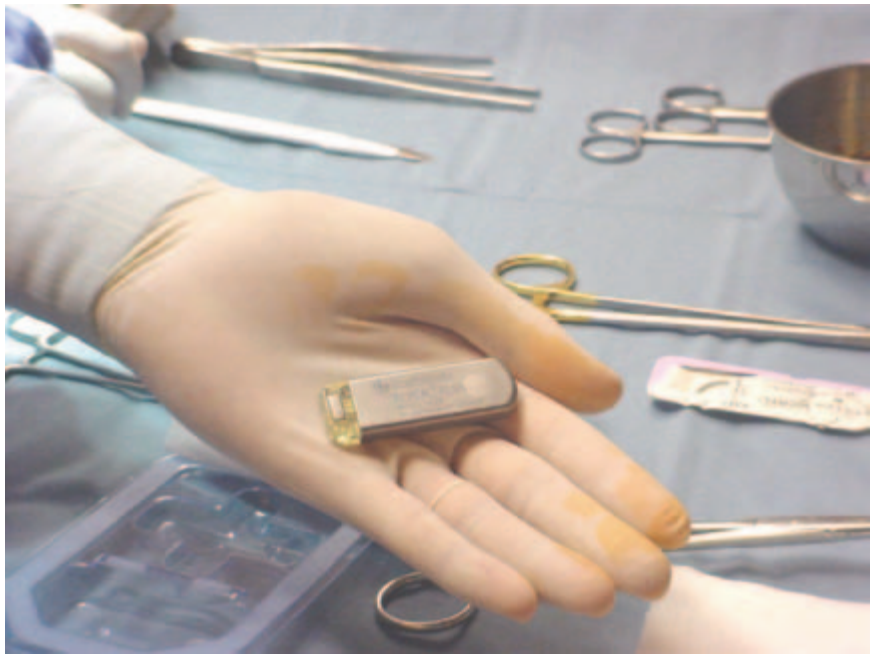

Figure 31.5 Implantable loop recorder. The implantable loop recorder (Reveal) is placed subcutaneously under local anaesthesia, and has a battery life of 18–24 months. The device has a solid-state loop memory, and the current version can store up to 42 min of continuous single-lead electrocardiogram. Retrospective ECG allows activation of the device after consciousness has been restored. Automatic activation is also available in case of occurrence of predefined arrhythmias.

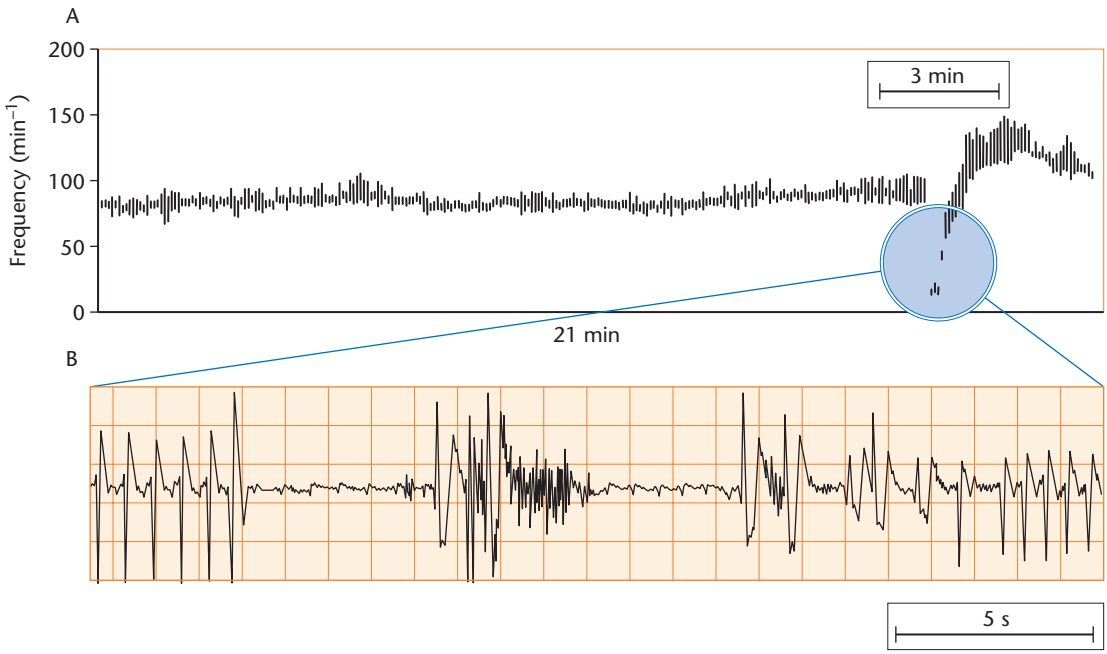

Figure 31.6 Implantable loop recorder documentation of a syncope episode due to a paroxysmal AV block. (A) Heart rate trend during the whole 21-min loop recording. Initially, the heart rate is stable at approximately 80 b.p.m. and suddenly falls at the time of the syncope. (B) The expanded ECG shows blocked P waves with two main pauses of 5 and 6 s duration. The sinus rate increases during AV block. The noise recorded during the second pause probably reflects jerking movements of the patient. The sudden onset AV block (and ventricular pause) with concomitant increase in sinus rate suggests an intrinsic disease of the His–Purkinje system as observed in Stokes–Adam attacks.

Table 31.5 Minimal suggested electrophysiological protocol for diagnosis of syncope

Measurement of sinus node recovery time and corrected sinus node recovery time by repeated sequences of atrial pacing for 30–60 s with at least one low (10–20 beats/min higher than sinus rate) and two higher pacing rates*
Assessment of the His–Purkinje system includes measurement of the HV interval at baseline and pseudosyncope conduction with stress by incremental atrial pacing; if the baseline study is inconclusive, pharmacological provocation with slow infusion of ajmaline (1 mg/kg i.v.), procainamide (10 mg/kg i.v.) or disopyramide (2 mg/kg i.v.) is added unless contraindicated.
Assessment of ventricular arrhythmia inducibility performed by ventricular programmed stimulation at two right ventricular sites (apex and outflow tract), at two basic drive cycle lengths (100 or 120 beats/min and 140 or 150 beats/min), with up to two extra stimuli†
Assessment of supraventricular arrhythmia inducibility by any atrial stimulation protocol

*When sinus node dysfunction is suspected, autonomic blockade may be applied and measurements repeated.
†A third extra stimulus may be added. This may increase sensitivity, but reduces specificity. Ventricular extra stimulus coupling intervals below 200 ms also reduce specificity.

likely, further evaluations (e.g. loop recording) are recommended. Finally, depending on the clinical context, even apparently abnormal electrophysiological findings (e.g. relatively long HV interval, inducible ventricular fibrillation with aggressive stimulation) may not be diagnostic of the cause of syncope [1–3].

There are four areas of particular pertinence to electrophysiological testing in syncope patients: suspected sinus node disease, bundle branch block (impending high-degree AV block), suspected supraventricular tachycardia and suspected ventricular tachycardia.

Suspected sinus node disease

The pre-test probability of a transient symptomatic bradycardia as the cause of syncope is relatively high when there is asymptomatic sinus bradycardia (< 50 b.p.m.) or sinus pauses in the absence of negatively chronotropic medications. Sinus node dysfunction can be demonstrated by abnormal beat-to-beat variability and chronotropic incompetence, and by a prolonged sinus node recovery time. The prognostic value of a prolonged sinus node recovery time is largely unknown. It is widely accepted that, in presence of an SNRT > 2 s or corrected SNRT > 1 s, sinus node dysfunction may be the cause of syncope [1–3].

Bundle branch block

In patients with syncope and bifascicular block, an electrophysiological study is diagnostic and, usually, no additional tests are required when the baseline HV interval is ≥ 100 ms, second- or third-degree His–Purkinje block is demonstrated during incremental atrial pacing, or high-degree His–Purkinje block is provoked by intravenous administration of ajmaline, procainamide or disopyramide [1–3]. An electrophysiological study is highly sensitive (> 80%) in identifying patients with intermittent or impending high-degree AV block, but, when negative, it cannot rule out paroxysmal AV block as the cause of syncope. This block is the likely cause of syncope in most cases but not of the high mortality rate observed in these patients, which is mainly related to underlying structural heart disease and ventricular tachyarrhythmias. Unfortunately, ventricular programmed stimulation does not seem to be able correctly to identify these patients, and the finding of inducible ventricular arrhythmia should therefore be interpreted with caution [33].

Suspected supraventricular tachycardia

Supraventricular tachycardia presenting as syncope without accompanying palpitations is probably a rare event. The induction of rapid supraventricular arrhythmia that reproduces hypotensive or spontaneous symptoms is usually considered diagnostic [1–3]. The combination of supraventricular tachycardia and orthostasis may be responsible for syncope.

Suspected ventricular tachycardia

The outcome largely depends on the clinical features of the patients. Inducibility of sustained monomorphic ventricular tachycardia and/or very depressed systolic function are the two strongest predictors of life-threatening arrhythmic cause of syncope; conversely, their absence suggests a more favourable outcome [1–3].

Electrophysiological study with programmed electrical stimulation is an effective diagnostic test in patients with coronary artery disease, markedly depressed cardiac function and unexplained syncope (Fig. 31.7). For example, in the ESVEM trial [34], syncope associated with induced ventricular tachyarrhythmias at electrophysiological testing indicated high risk of death, similar to that of patients with documented spontaneous ventricular tachyarrhythmias. The specificity of the induction of ventricular tachycardia (as stated above) has been questioned in patients with syncope and bifascicular block [33]. The specificity of the induction of polymorphic ventricular tachycardia and ventricular fibrillation

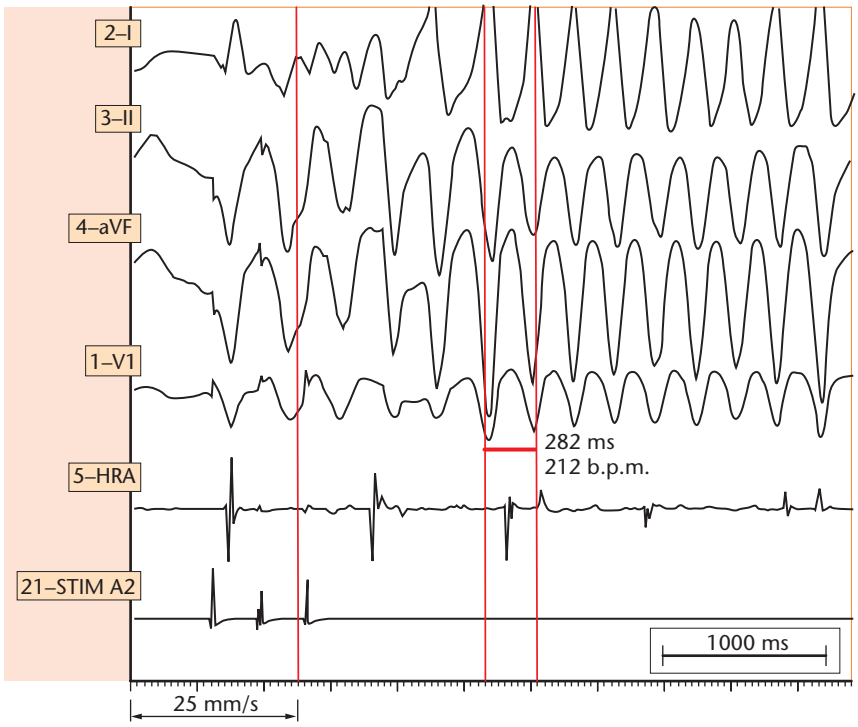

Figure 31.7 Induction of ventricular tachycardia by means of premature ventricular stimulation during an electrophysiological study in a patient with suspected cardiac syncope, coronary artery disease and markedly depressed cardiac function. Three ventricular premature extra stimuli (S2, S3 and S4) cause the induction of a monomorphic ventricular tachycardia with a cycle length of 282 ms (212 b.p.m.). Atrial rhythm is dissociated from ventricular rhythm (HRA trace).

probably depends on the clinical setting. On one hand, in coronary artery disease and syncope, the follow-up of patients with and without inducible ventricular fibrillation did not demonstrate any difference in survival between the two groups [35]. On the other hand, the induction of polymorphic ventricular arrhythmias has been reported to have a predictive value in patients with Brugada syndrome, in survivors of cardiac arrest with significant coronary artery disease undergoing coronary bypass surgery and in idiopathic ventricular fibrillation.

The predictive value of non-inducibility depends on the aetiology of the underlying heart disease, e.g. ischaemic versus non-ischaemic heart disease. In patients with syncope, coronary artery disease and preserved cardiac function, non-inducibility at electrophysiological study predicted a low risk of sudden death and ventricular arrhythmias [36]. Conversely, programmed ventricular stimulation has a low predictive value in patients with non-ischaemic dilated cardiomyopathy [37].

Exercise testing

Exercise testing should be performed in patients who have experienced episodes of syncope during or shortly after exertion.

The following two situations should be separately considered. Syncope occurring during exercise in the presence of structural heart disease is likely to have a cardiac cause. Tachycardia-related (phase 3), exercise-induced second- and third-degree AV block has been shown to be invariably located in the His–Purkinje system and is an ominous finding of progression to chronic AV block. The resting ECG frequently shows an intraventricular conduction abnormality [38]. In the absence of structural heart disease, syncope occurring during exercise may be a manifestation of an exaggerated reflex vasodilatation [39]. By contrast, postexertional syncope is almost invariably due to autonomic failure or to a neurally mediated mechanism [40]. Syncope in athletes may be an important problem. However, in the absence of structural heart disease, syncope occurring during or immediately after exercise in athletes is a benign condition, with a good long-term outcome. The likely final diagnosis is neurally mediated [39].

ATP test

Intravenous injection of adenosine triphosphate (ATP) has recently been proposed as a tool in the investigation of patients with unexplained syncope [41,42]. The test requires the rapid injection of a 20-mg bolus of ATP during electrocardiographic monitoring. Asystole lasting more than 6 s or AV block lasting more than 10 s is considered abnormal. ATP testing produces an abnormal response in some patients with syncope of unknown origin, but not in controls (Fig. 31.8). ATP testing identifies a group of patients with otherwise unexplained syncope with definite clinical features and benign prognosis but

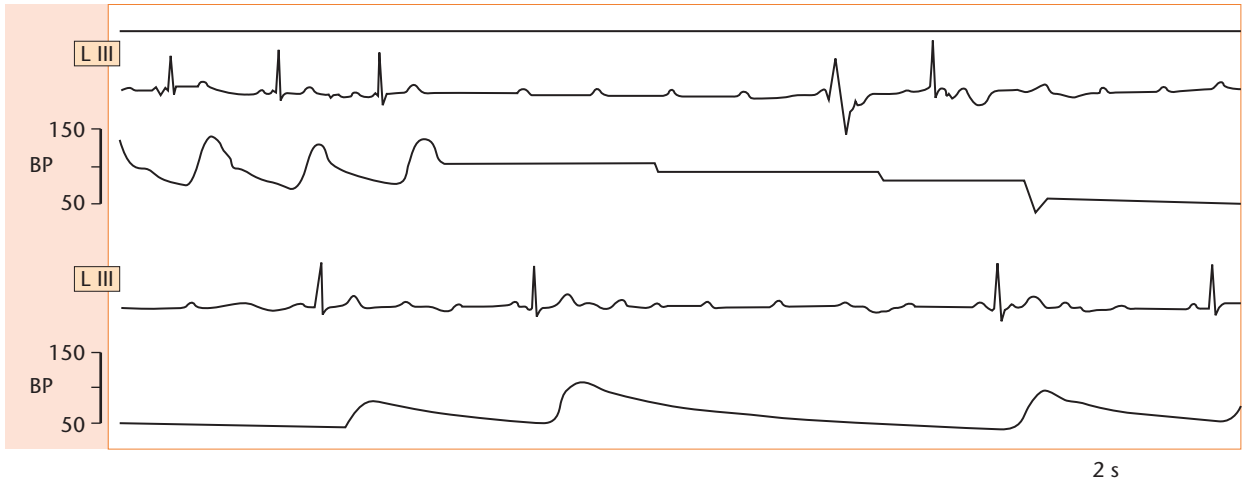

Figure 31.8 ATP test. The continuous tracing of ECG and non-invasive blood pressure (Finapres method) is shown. The bolus of 20 mg of ATP causes abrupt third-degree AV block with long ventricular asystoles of 5.2, 6.0 and 4.5 s. Sinus rate increases during the block. Thus, the effect of the drug is limited to the AV conduction system. Systolic blood pressure drops from an initial value of 140 mmHg to values ranging between 80 mmHg and 110 mmHg.

possibly heterogeneous mechanism of syncope [43]. The diagnostic and predictive value of the test remains to be confirmed by prospective studies.

Other tests

Ventricular signal-averaged electrocardiogram and T-wave alternans are not diagnostic of the cause of syncope and their systematic use is not recommended [2,3].

In patients with syncope suspected to be due, directly or indirectly, to myocardial ischaemia, coronary angiography is recommended in order to confirm the diagnosis. However, angiography alone is rarely diagnostic of the cause of syncope [1–3].

Neurological disease may cause transient loss of consciousness (e.g. certain seizures), but is almost never the cause of syncope. Thus, neurological testing may be needed to distinguish seizures from syncope in some patients, but these should not be considered as essential elements in the evaluation of the basis of true syncope. The possible contribution of electroencephalography (EEG), computerized tomography and magnetic resonance imaging of the brain is to disclose abnormalities due to epilepsy; there are no specific EEG findings for any loss of consciousness other than epilepsy. Accordingly, several studies [32] conclusively showed that EEG monitoring was of little use in unselected patients with syncope. Thus, EEG is not recommended for patients in whom syncope is the most likely cause for a transient loss of consciousness [1–3].

Carotid TIAs are not accompanied by loss of consciousness. Therefore, carotid Doppler ultrasonography is not required in patients with syncope [1–3].

Diagnostic yield and prevalence of causes of syncope

Figure 31.9 shows the prevalence of the causes of syncope as determined by pooling the data of four recent population-based studies that included a total of 1640 patients [5,44–46]. Neurally mediated and orthostatic hypotension were the most frequent causes; cardiac syncope accounted for 14% of cases and neurological and psychiatric causes were found in 9%. Compared with six older studies performed in the 1980s (total 1499 patients) [32], the proportion of unexplained syncope despite a complete work-up has decreased from 36% to 20% and the percentage of neurally mediated syncope increased from 37% to 50%. In more recent studies, there was a more extensive use of carotid sinus massage and tilt testing.

Treatment

Treatment of the syncope patient comprises, first, the care of the fainter at the time of the event, and thereafter consideration of strategies for prevention of recurrences. This section focuses primarily on the latter. In this regard, the principal goals of long-term treatment of the 'syncopal patient' are prevention of syncopal recurrences and injuries and diminution of mortality risk.

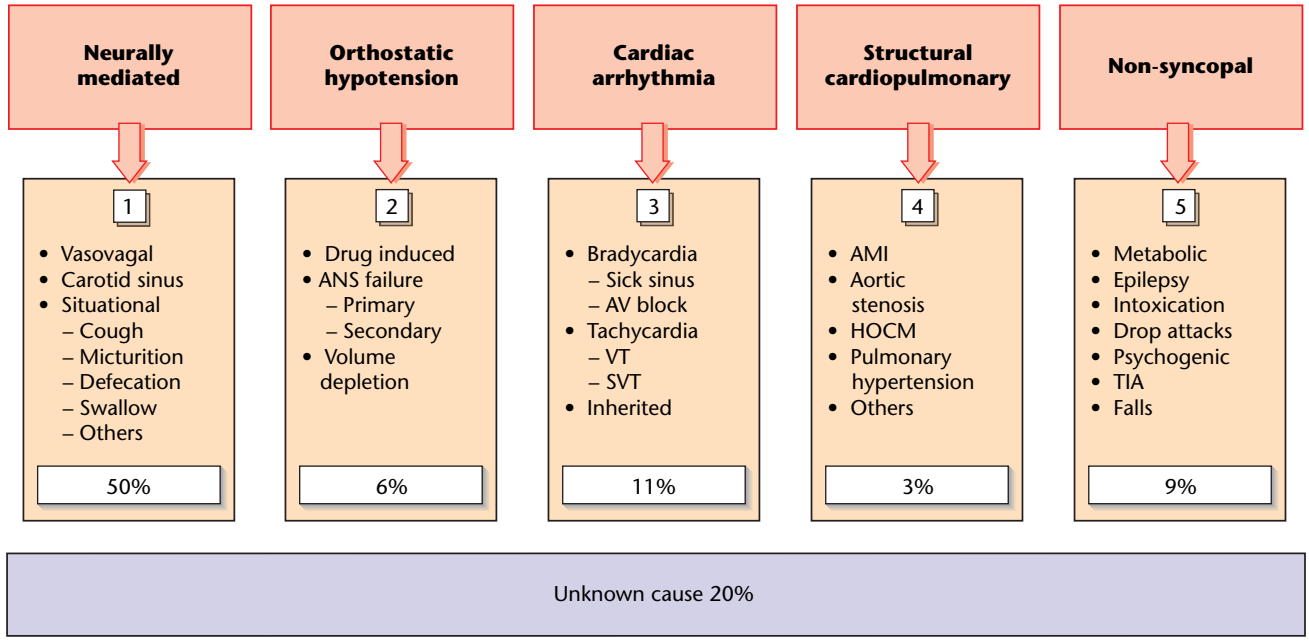

Figure 31.9 Prevalence of the causes of syncope. AMI, acute myocardial infarction; HOCM, hypertrophic obstructive cardiomyopathy.

Neurally mediated (reflex) syncope

Patients who seek medical advice after having experienced a vasovagal faint require reassurance and education regarding the nature of the disease and the avoidance of triggering events. In general, education and reassurance are sufficient for most patients. Modification or discontinuation of hypotensive drug treatment for concomitant conditions is another first-line measure for the prevention of syncope recurrences. Treatment is not necessary for patients who have sustained a single syncope and are not having syncope in a high-risk setting [1–3].

Additional treatment may be necessary in high-risk or high-frequency settings when [2,3]:

- syncope is very frequent, e.g. alters the quality of life;
- syncope is recurrent and unpredictable (absence of premonitory symptoms) and exposes patients to a 'high risk' of trauma;
- syncope occurs during the prosecution of a 'high-risk' activity (e.g. driving, machine operation, flying, competitive athletics).

Non-pharmacological 'physical' treatments are emerging as a new front-line treatment of vasovagal syncope. In highly motivated patients with recurrent vasovagal symptoms, the prescription of progressively prolonged periods of enforced upright posture (so-called 'tilt-training') may reduce syncope recurrence. However, this treatment is hampered by the low compliance of patients in continuing the training programme for a long period [47]. Two recent clinical trials [48,49] have shown that isometric counterpressure manoeuvres of the legs (leg crossing), or of the arms (hand grip and arm tensing), are able to induce a significant blood pressure increase during the phase of impending vasovagal syncope that allows the patient to avoid or delay losing consciousness in most cases.

Many drugs have been used in the treatment of vasovagal syncope (beta-blockers, disopyramide, scopolamine, clonidine, theophylline, fludrocortisone, ephedrine, etilefrine, midodrine, clonidine, serotonin reuptake inhibitors, etc). In general, although the results have been satisfactory in uncontrolled trials or short-term controlled trials, long-term placebo-controlled prospective trials have failed to show any benefit of the active drug over placebo. Beta-adrenergic blocking drugs have failed to be effective in five of six long-term follow-up controlled studies [50–55]. Vasoconstrictor drugs are potentially more effective in orthostatic hypotension caused by autonomic dysfunction than in the neurally mediated syncope. Etilefrine proved to be ineffective [22]. To date, there are insufficient data to support the use of any other pharmacological therapy for vasovagal syncope.

Pacing for vasovagal syncope has been the subject of five major multicentre randomized controlled trials [24,56–59]. Three gave positive and two gave negative

results. The two trials in which there was no statistically significant difference differed from the three 'positive' reports in that both 'paced' and 'unpaced' groups had undergone pacemaker implantation (i.e. device inactive in the controls for the duration of the study). Adding together the results of the five trials, 318 patients were evaluated; syncope recurred in 21% (33/156) of the paced patients and in 44% (72/162) of unpaced patients ($P < 0.001$). However, all the studies have limitations; in particular, those concerning the preimplant selection criteria of the patients who might benefit from pacemaker therapy. Therefore, the role of pacing is not yet established.

Cardiac pacing appears to be beneficial in carotid sinus syndrome and, although only one relatively small randomized controlled trial has been undertaken, pacing is acknowledged to be the treatment of choice when bradycardia has been documented [1–3]. Single-chamber atrial pacing is not appropriate for vasovagal syncope, and dual-chamber pacing is generally preferred over single-chamber ventricular pacing [9].

Orthostatic hypotension

Drug-induced autonomic failure is probably the most frequent cause of orthostatic hypotension. The principal treatment strategy is elimination of the offending agents, mainly diuretics and vasodilators. Alcohol is also commonly associated with orthostatic intolerance [1–3].

Additional treatment principles, used alone or in combination, are appropriate for consideration on an individual patient basis [1–3]:

- chronic expansion of intravascular volume by encouraging a higher than normal salt intake and fluid intake of 2–2.5 l/day;
- fludrocortisone in low dose (0.1–0.2 mg/day);
- raising the head of the bed on blocks to permit gravitational exposure during sleep;
- reduce vascular volume into which gravitation-induced pooling occurs by use of abdominal binders and/or waist-height support stockings or garments;
- introduce physical countermanoeuvres such as leg crossing, gripping or squatting;
- use of drugs which increase peripheral resistance (midodrine 5–15 mg t.i.d.).

Cardiac arrhythmias as primary cause

Syncope due to cardiac arrhythmias must receive treatment appropriate to the cause in all patients in whom it is life-threatening and when there is a high risk of injury.

Treatment may be warranted when:

- the culprit arrhythmia has not been demonstrated conclusively, but a diagnosis of life-threatening arrhythmia is presumed from surrogate data;
- the culprit arrhythmia has been identified but is not life-threatening or presenting a high risk of injury [1–3].

Cardiac pacing, implantable cardioverter defibrillators and catheter ablation are the usual treatments of syncope due to cardiac arrhythmias, depending on the mechanism of syncope. Table 31.6 provides commonly accepted indications for ICD therapy for the prevention of sudden death in patients with syncope. It is important to bear in mind, however, that although pacing or ablation may prevent arrhythmias and thereby eliminate syncope the ICD-treated patient may remain at risk for fainting because only the sudden-death risk is being addressed. In the latter group of patients, additional treatment steps (e.g. antiarrhythmic drugs) may also be needed to reduce the risk of syncope.

Table 31.6 Situations in which implantable cardioverter defibrillator (ICD) therapy is likely to be useful

Documented syncopal ventricular tachycardia or fibrillation without correctable causes (e.g. drug induced)
Undocumented syncope likely to be due to ventricular tachycardia or fibrillation
Inducible sustained monomorphic ventricular tachycardia with severe haemodynamic compromise, in the absence of another competing diagnosis as a cause of syncope
Very depressed left ventricular systolic function in the absence of another competing diagnosis as a cause of syncope
Established long QT syndrome, Brugada syndrome, arrhythmogenic right ventricular dysplasia, or hypertrophic obstructive cardiomyopathy, with a family history of sudden death, in the absence of another competing diagnosis for the cause of syncope
Brugada syndrome or arrhythmogenic right ventricular dysplasia and inducible ventricular tachyarrhythmias with severe haemodynamic compromise in the absence of another competing diagnosis for the cause of syncope

Structural cardiac or cardiopulmonary disease

Treatment is best directed at amelioration of the specific structural lesion or its consequences.

Personal perspective

A major issue in the use of diagnostic tests is that syncope is a transient symptom and not a disease. Typically, patients are asymptomatic at the time of evaluation, and the opportunity to capture a spontaneous event during diagnostic testing is rare. This type of reasoning leads, of necessity, to uncertainty in establishing a cause. Establishing the basis for syncope (i.e. determining the 'diagnosis') is a prerequisite for advising patients with regard to prognosis and to developing an effective treatment strategy. However, arriving at the diagnosis can be difficult, and is often marked by the undertaking of costly and often useless diagnostic procedures.

In the evaluation of patients with syncope, the critical first step is a detailed medical history. A diagnostic strategy based on initial evaluation is warranted. In this regard, the development and evaluation of thoughtful, evidence-based (when possible), diagnostic guidelines for the evaluation of syncope patients has been of great support. Heart disease is an independent predictor of cardiac cause of syncope; by contrast, the absence of heart disease allows exclusion of a cardiac cause of syncope. The importance of the initial evaluation goes well beyond its capability to make a diagnosis as it determines the most appropriate subsequent diagnostic pathways and risk evaluation.

The ultimate goal of diagnostic testing is to establish a sufficiently strong correlation between syncope and detected abnormalities to permit both an assessment of prognosis and initiation of an appropriate treatment plan. Knowledge of what occurs during a spontaneous syncopal episode is ideally the gold standard for syncope evaluation. For this reason, it is likely that implantable monitors will become increasingly important in the assessment of the syncope patient, and their use will increasingly be appropriate instead of, or before, many current conventional investigations. This early ILR approach implies the need for a careful initial risk stratification in order to exclude from such a strategy patients with potential life-threatening conditions. Ultimately, technology may allow recording of multiple signals in addition to the ECG (e.g. blood flow or pressure and EEG) and the automatic immediate wireless transmission of pertinent data to a central monitoring station. Such advances will permit greater emphasis on the documenting and characterizing of spontaneous episodes. Conversely, they will result in less reliance for current diagnostic testing techniques which are largely designed to assess susceptibility to the provocation of syncope in the laboratory.

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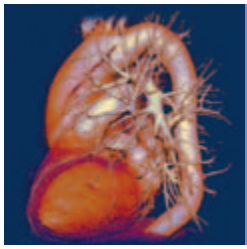
Suggested Reading

For a detailed overview, the authors suggest the following:

Benditt DG, Blanc JJ, Brignole M, Sutton R. *The Evaluation and Treatment of Syncope. A Handbook for Clinical Practice*. Blackwell Futura, New York, 2003.



32 Ventricular Tachycardia

Lars Eckardt, Pedro Brugada, John Morgan and Günter Breithardt

Summary

Ventricular arrhythmias are the major cause of morbidity and mortality in patients with structural heart disease, but can also be a mechanism of sudden death in patients with structurally normal hearts (e.g. channelopathies such as long or short QT syndrome, Brugada syndrome). Infrequently, they can be generated by mechanisms that are amenable to curative catheter ablation. Overall, ventricular tachycardia and ventricular fibrillation are the major cause of sudden unexpected death. Ventricular tachycardias are relatively organized tachyarrhythmias with discrete QRS complexes. They can be either sustained or non-sustained, and can be monomorphic or polymorphic. Polymorphic ventricular tachyarrhythmias tend to be faster and less stable than monomorphic. The correct diagnosis of a ventricular tachycardia remains a challenge despite numerous established criteria for the differentiation of ventricular from supraventricular tachycardia with aberrant conduction. A history of heart disease has a positive predictive accuracy of 95% for a ventricular tachyarrhythmia. A re-entry mechanism accounts for the majority of ventricular tachyarrhythmias in patients with structural heart disease. The spectrum of therapies for ventricular tachycardias includes drug therapy, device implantation and surgical or catheter ablation techniques. In patients with chronic coronary heart disease, the magnitude of the survival benefit from the implantable cardioverter-defibrillator is directly related to the severity of cardiac dysfunction. The management challenge is to deal both with the ventricular tachycardia as the presenting symptom, and the pervading sudden cardiac death risk that may be the consequence of the arrhythmogenic substrate.

Introduction

Ventricular arrhythmias are the major cause of morbidity and mortality in patients with structural heart disease, but can also be a mechanism of sudden death in patients with structurally normal hearts. Infrequently they can be generated by mechanisms that are amenable to curative catheter ablation. Overall, ventricular tachycardia (VT) and ventricular fibrillation (VF) are the major cause of sudden unexpected death. Ambulatory ECG recordings at the time of sudden death have shown that, in approximately 60% of sudden cardiac death victims, an episode of VT was identified as the initial event [1]. Major studies of heart failure therapy have shown that ventricular arrhythmia is the commonest cause of death, whatever the functional class of the patient.

Definitions

Ventricular tachycardia is a relatively organized tachyarrhythmia with discrete QRS complexes. It can be either sustained (lasting longer than 30 s) or non-sustained (defined as three or more beats but less than 30 s), and can be monomorphic or polymorphic. If the same patient has monomorphic ventricular tachycardias with different morphologies, it is termed pleomorphic. Polymorphic

ventricular tachycardias tend to be faster and less stable than monomorphic. The rate of ventricular tachycardia can range from 100 beats per minute (b.p.m.) to more than 300 b.p.m. At faster rates (usually 220 b.p.m. or faster), ventricular tachycardia is so rapid that it may be impossible to distinguish the QRS complex from the T wave. This type of ventricular tachycardia is referred to as ventricular flutter. Ventricular fibrillation is a completely disorganized (chaotic) tachyarrhythmia without discrete QRS complexes. When it begins, it is associated with a coarse electrical pattern. As the heart becomes less viable, the fibrillation becomes fine, and then, as an agonal event, all electrical activity ceases (flat line).

Electrocardiographic diagnosis of ventricular tachycardia

The correct diagnosis of a wide complex tachycardia (QRS duration > 120 ms) remains a challenge despite numerous established criteria for the differentiation of ventricular from supraventricular tachycardia with aberrant conduction. Ventricular tachycardia is the most common cause of wide complex tachycardia, accounting for up to 80% of all cases [2]. A history of heart disease (prior myocardial infarction or heart failure) has a positive predictive accuracy of 95% for ventricular tachycardia [3]. On the other hand, if a patient has had similar episodes during previous years, a supraventricular origin is more likely than a ventricular tachycardia. Termination of a tachycardia by physical manoeuvres, such as the Valsalva manoeuvre or adenosine injection, strongly suggests a supraventricular origin, although some ventricular tachycardias can also terminate by these manoeuvres (e.g. fascicular ventricular tachycardia). A wide complex tachycardia in a patient who is alert and haemodynamically stable is not necessarily of supraventricular origin. If it is a ventricular tachycardia in a patient with reduced systolic function, an i.v. injection of, for example, verapamil may result in severe hypotension and haemodynamic instability.

In general, if an electrocardiogram (ECG) showing a wide complex tachycardia does not look like aberration, it is most likely a ventricular tachycardia. If there is any doubt about the origin of a broad complex tachycardia, the patient should be treated as if the rhythm is ventricular tachycardia because it is by far the more common diagnosis. The absence of a RS complex in any precordial lead or an interval of the R-wave onset to the S-wave nadir of more than 100 ms strongly suggests a ventricular tachycardia [4]. In addition, the following ECG criteria have been suggested to distinguish between a ventricular and a supraventricular tachycardia with aberration.

- *QRS complex duration*. Ventricular tachycardia is the probable diagnosis when the QRS duration with right bundle branch block (RBBB) is greater than 140 ms, and greater than 160 ms with left bundle branch block (LBBB) morphology [2].
- *QRS axis*. A frontal axis of between –90 and ±180 degrees cannot be achieved by any combination of bundle branch block and therefore suggests ventricular tachycardia. Thus, predominantly negative QRS complexes in leads I, II and III are useful criteria for identifying a ventricular tachycardia.
- *Concordant negative ECG patterns in the precordial leads*. If all precordial leads are predominantly negative, a ventricular tachycardia is the likely diagnosis. If all precordial leads are predominantly positive, the differential diagnosis is an antidromic tachycardia using a left-sided accessory pathway or a ventricular tachycardia.
- *QRS morphologies in V1 and V6* (Fig. 32.1). In RBBB pattern, a monophasic R wave, a broad (> 30 ms) R or a QR in V1 strongly suggests ventricular tachycardia. A monophasic R wave or an S greater than an R in V6

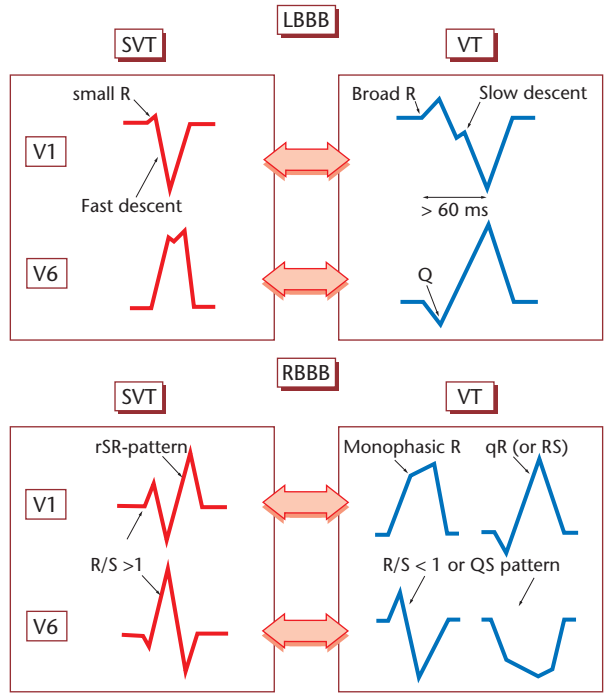


Figure 32.1 QRS criteria for differential diagnosis in broad complex tachycardia: ventricular tachycardia (VT) vs. supraventricular tachycardia (SVT) with left (LBBB) or right (RBBB) bundle branch block.

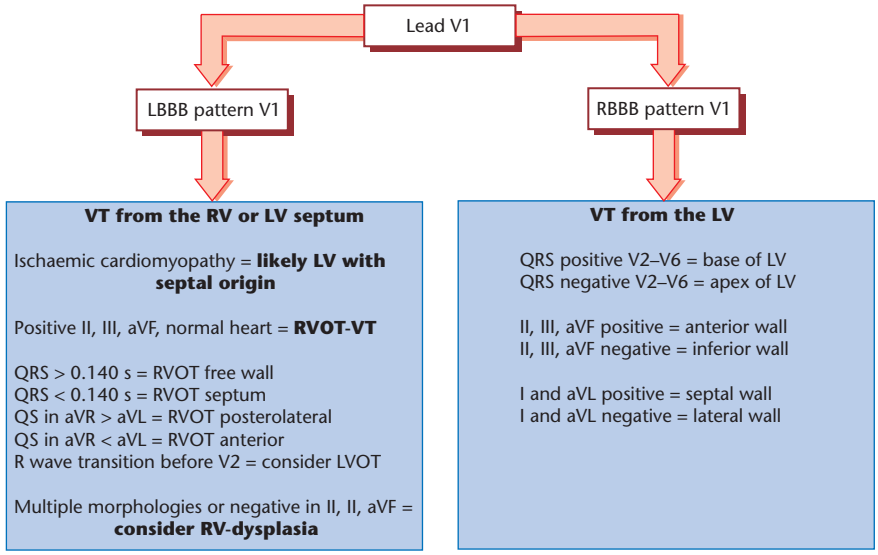


Figure 32.2 Algorithm for localization of the exit site of ventricular tachycardia.

also suggests ventricular tachycardia. In the presence of a LBBB pattern, a broad R wave (usually greater than 30 ms [5]) and/or a slow descent to the S wave nadir in V1 and a Q in V6 point towards a ventricular tachycardia.

- *Atrioventricular dissociation*. This is one of the most useful criteria for distinguishing ventricular tachycardia from supraventricular tachycardia (SVT). It occurs in 20–50% of ventricular tachycardia and almost never in SVT [2,6,7]. Atrioventricular dissociation may be diagnosed by a changeable pulse pressure, irregular canon A waves in the jugular veins and a variable first heart sound. It is often very difficult to ascertain, particularly in rapid tachycardias. It often demands long 12-lead ECG recordings and careful ECG analysis. In addition, about 30% of ventricular tachycardias have 1:1 retrograde conduction. In the presence of AV dissociation, one may also observe *fusion beat*, which may result from the fusion of a P wave conducted to the ventricles.

The 12-lead ECG during ventricular tachycardia can be helpful in providing an approximation of the site of origin, which may be helpful for guiding ablation (Fig. 32.2). In general, ventricular tachycardias that have a left bundle branch block-like morphology in V1 have an exit in the right ventricle or the interventricular septum. A QRS axis that is directed superiorly generally indicates an exit in the inferior wall; an axis directed inferiorly indicates an exit in the anterior (superior) wall. In V2–V4, dominant R waves usually indicate an exit near the base of the ventricle. In idiopathic right ventricular outflow tract tachycardia (see RVOT ventricular tachycardia, below), the QRS duration during ventricular tachycardia is usually greater than 140 ms if it originates from the free-wall of the RVOT, and less than 140 ms if the arrhythmia originates from the septal site of the RVOT. Furthermore, if the QS amplitude in aVR is greater than in aVL, the initial activation occurs more posterolateral, whereas if the QS amplitude in aVL is greater than in aVR, the origin is more anterior in the RVOT. The precordial R-wave transition in RVOT-ventricular tachycardia usually occurs in leads V2–V4 and becomes earlier as the site of origin advances more superiorly along the septum. An R-wave transition in lead V2 suggests a site of origin immediately inferior to the pulmonic valve or the left-ventricular outflow tract [8].

Electrophysiological mechanisms of ventricular tachycardia

Re-entrant ventricular arrhythmias

Monomorphic ventricular tachycardia is the most common form of sustained ventricular tachycardia and usually occurs after myocardial infarction. A re-entry mechanism accounts for the majority of these ventricular tachycardias. In contrast with automatic arrhythmias, the conditions for re-entry tend to be associated with chronic rather than acute disease. Endocardial catheter mapping and intraoperative mapping have shown that these arrhythmias originate within or at the border zone of the diseased myocardium. The size of the re-entrant circuit may be large, especially in patients with a left-ventricular

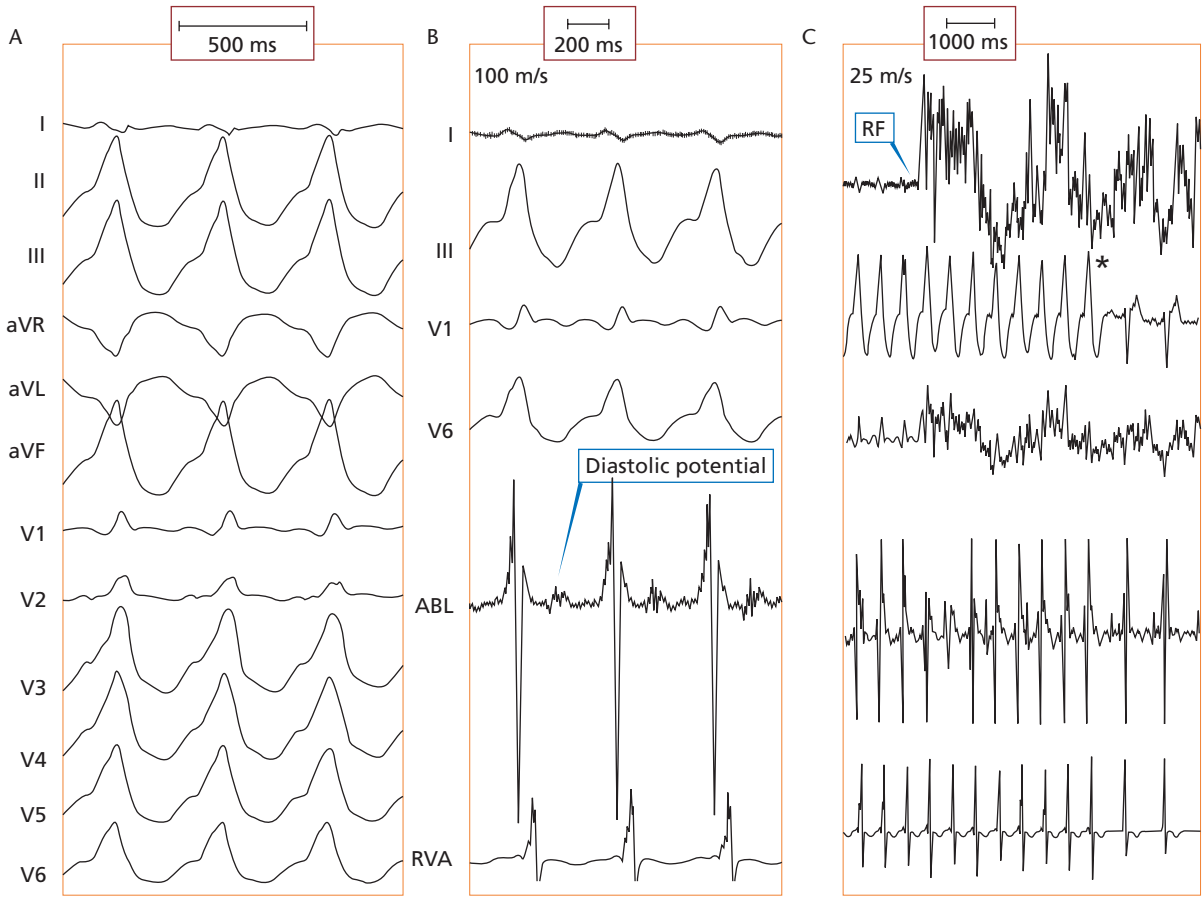


Figure 32.3 ECG recording in a patient with previous anterior myocardial infarction and recurrent sustained ventricular tachycardia. (A) Catheter mapping and subsequent catheter ablation were performed. (B) Leads I, III, V1 and V6, as well as intracardiac signals from the right ventricular apex (RVA) and the ablation catheter at the successful ablation site (ABL) anteroseptal at the left-ventricular base are displayed. Note: the fragmented diastolic potential at the successful ablation site (for further details, see text), where the ventricular tachycardia terminated a few seconds after starting radiofrequency (RF) ablation (C).

aneurysm, or may be confined to a small area. Re-entry requires a series of conditions to be satisfied for its occurrence: (1) two potentially conducting pathways or more; (2) unidirectional block must occur in one pathway; (3) an activation wavefront that travels around that zone of unidirectional block over the alternative pathway; (4) then activation of myocardium distal to the zone of unidirectional block with delay (i.e. with slow conduction), so allowing (5) the activation wavefront to invade the zone of block retrogradely and re-excite the tissue where the activation wavefront originated. For re-entry to occur, the impulse that is conducting around the re-entrant circuit must always find excitable tissue in the direction in which it is propagating. This constellation frequently occurs in the context of myocardial scarring.

An understanding of these electrophysiological phenomena is critical to the diagnosis and successful ablation of re-entrant ventricular arrhythmias. Initiation and termination of ventricular tachycardia by pacing stimuli, the demonstration of electrical activity bridging diastole and a variety of other clinically used techniques are consistent with a re-entry mechanism. Entrainment by pacing is considered the most reliable clinical method to demonstrate the presence of a re-entry mechanism. The areas of slow conduction have been shown to be desirable targets of ablation. Zones of slowly conducting myocardium may be identified during endocardial catheter mapping by fractionated and/or mid-diastolic electrograms (Fig. 32.3), continuous electrical activity or a long delay between a stimulus artefact and the resulting QRS complex. However, not all areas of slow conduction participate in the re-entry circuit, i.e. 'dead end' or 'bystander' pathways may exist. Therefore, for successful ablation, localization procedures have to provide evidence that a mapping site is actually within the re-entry circuit and is critically linked to the perpetuation of the arrhythmia. Ischaemia seems to be less frequently involved in the initiation of monomorphic ventricular

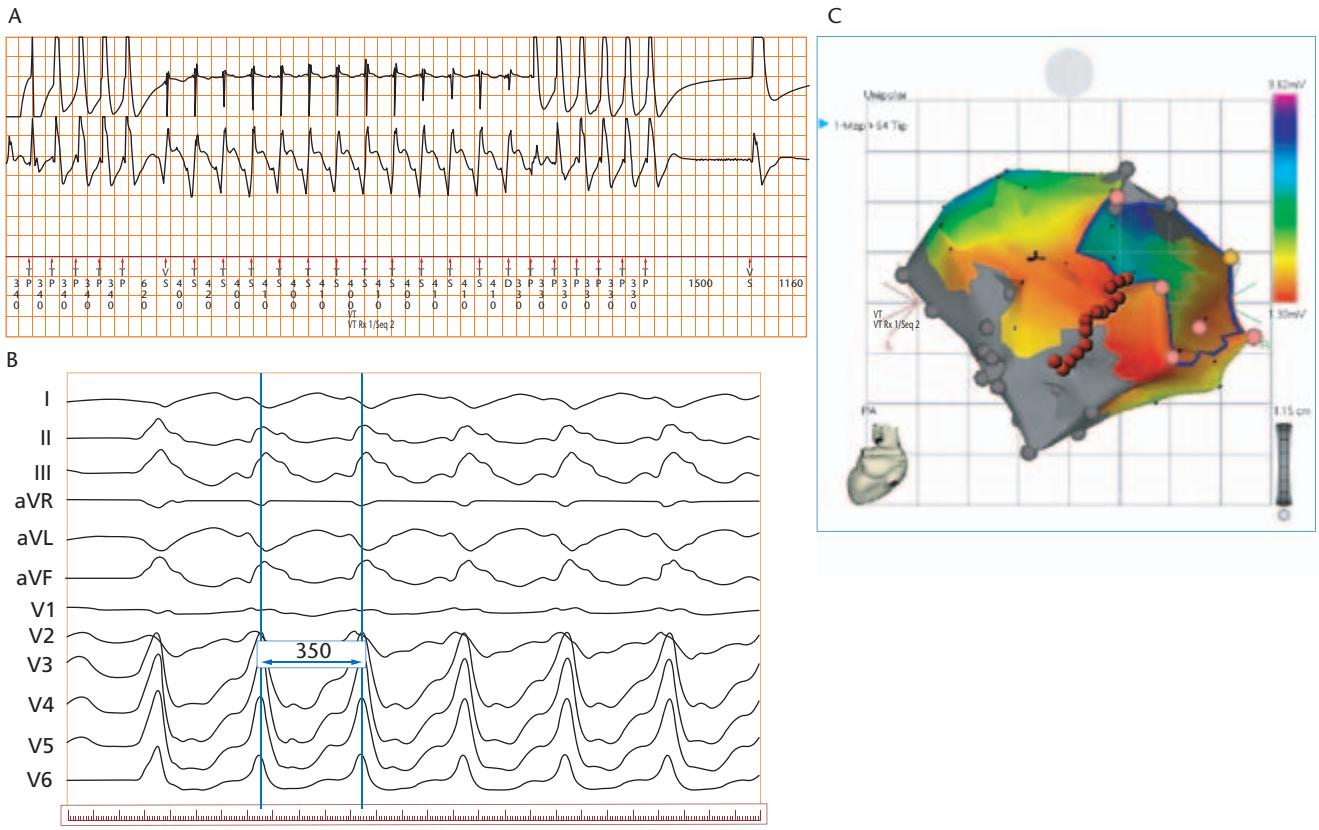


Figure 32.4 (A) Episode of ventricular tachycardia (cycle length ~ 400 ms) detected and terminated by an implantable cardioverter-defibrillator in a patient with a remote inferior myocardial infarction who experienced recurrent VT episodes. (B) Twelve-lead ECG of the VT in the same patient. (C) Posterior view of an electroanatomic voltage map (Carto) of the left ventricle. Electroanatomic mapping can be used to define isthmus boundaries and thus guide successful ablation. Colour range represents voltage amplitude. Grey denotes dense scar tissue. A linear ablation lesion was placed from the mitral annulus to the edge of the scar tissue to prohibit mitral 'isthmus' re-entrant tachycardias (around the mitral valve and/or around the posterior scar).

tachycardia. If a VT is not inducible or haemodynamically not tolerated during an ablation procedure, electroanatomical mapping systems can be used to locate critical isthmus regions, such as the mitral isthmus (Fig. 32.4) and to guide successful ablation. Occasionally, ischaemia has been found to precede the onset of a monomorphic ventricular tachycardia. More commonly, however, acute ischaemia triggers the occurrence of polymorphic ventricular tachycardia, which may degenerate to ventricular fibrillation rather than a sustained monomorphic ventricular tachycardia.

The underlying mechanisms of ventricular tachycardia in dilated cardiomyopathy are less well understood than they are in coronary artery disease. As heart failure is not a specific disease but a syndrome, there are no specific anatomical or pathological changes in failing hearts. The occurrence of ventricular tachycardia in heart failure is a result of a complex interplay between a pathological substrate and numerous environmental triggers and facilitators evoked by left-ventricular dysfunction and medical therapy. The non-specific cardiac changes include diffuse interstitial fibrosis, myofibrillar degeneration and myocyte hypertrophy. All known non-specific alterations result in disparity of electrophysiological properties within the myocardium, which provide an appropriate abnormal substrate for arrhythmogenesis. Also, a tachyarrhythmia itself may cause reversible heart failure, including myocardial changes such as dilatation and hypertrophy. Incessant or intermittent tachyarrhythmias present for months to years are known to cause reversible cardiomyopathy in experimental heart failure models as well as in patients ('tachycardiomyopathy').

Noteworthy in the presence of heart failure due to idiopathic dilated cardiomyopathy, re-entry in the His–Purkinje system (bundle branch re-entry, Fig. 32.5) accounts for a substantial number of monomorphic ventricular tachycardias. The re-entry wavefront proceeds down one bundle branch (mostly the right bundle branch), and up the contralateral bundle. This creates a QRS complex that has a LBBB contour and a normal

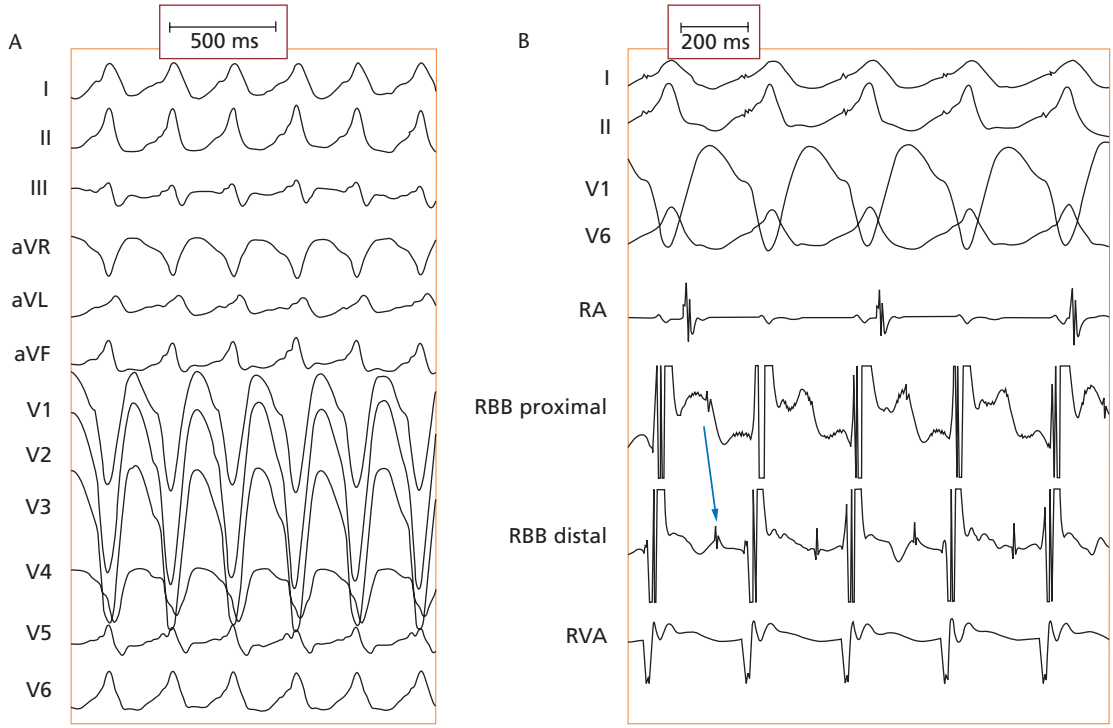


Figure 32.5 ECG recording in a patient with dilated cardiomyopathy and recurrent sustained ventricular tachycardia. (A) A sustained bundle branch re-entry tachycardia with a LBBB morphology is displayed. Intracardiac signals (B) reveal ventriculo-atrial dissociation (RA, right atrial catheter; RVA, right ventricular apex) and activation of the right bundle branch (RBB) from proximal (RBB prox) to distal (RBB dis). The tachycardia was successfully ablated at the distal right bundle branch using radiofrequency current.

or leftward frontal plane axis. Its significance lies in the fact that it can be easily cured by catheter ablation of the right bundle branch.

Automatic ventricular arrhythmias

Abnormal automaticity accounts for a minority of ventricular tachycardias. Automatic ventricular tachycardia tends to be associated with conditions such as acute myocardial infarction, hypoxaemia, electrolyte abnormalities and a high adrenergic tone. Automatic ventricular tachycardias that occur during the first 24–48 h after an acute myocardial infarction are a major cause of sudden cardiac death. They are probably related to the residual ischaemia seen acutely in the zone of infarction. Once the infarction heals, the substrate for these arrhythmias disappears (but the one for re-entry evolves). Because automatic arrhythmias generally occur secondarily to metabolic abnormalities, treatment should be aimed at identifying and reversing the underlying cause whenever possible.

Triggered activity

Although ventricular tachycardias based on triggered activity are uncommon, two distinct clinical syndromes involving triggered activity have been identified: pause- and catecholamine-dependent arrhythmias. In each syndrome, patients develop polymorphic ventricular tachycardia. These arrhythmias tend to occur in relatively short bursts that may be accompanied by lightheadedness or syncope, but may also degenerate into ventricular fibrillation and cause sudden death.

Pause-dependent triggered activity is caused by afterdepolarizations that occur during phase 3 of the action potential (early afterdepolarizations). If these afterdepolarizations reach the threshold potential of the cardiac cell, another action potential can be generated. Pause-dependent triggered activity may be related to congenital ion-channel abnormalities (long QT syndrome, see p. 961) and/or to specific conditions (hypokalaemia and hypomagnesaemia), and/or the use of non-cardiovascular or cardiovascular drugs (e.g. class IA or class III antiarrhythmic agents, i.e. acquired QT syndrome) that prolong repolarization. Individuals who develop ventricular arrhythmias (i.e. torsade de pointes) [9] in the presence of these conditions have a reduced repolarization reserve. Torsades de pointes (Fig. 32.6) is a rapid, irregular nonsustained polymorphic ventricular tachycardia that appears to twist around the isoelectric line and may

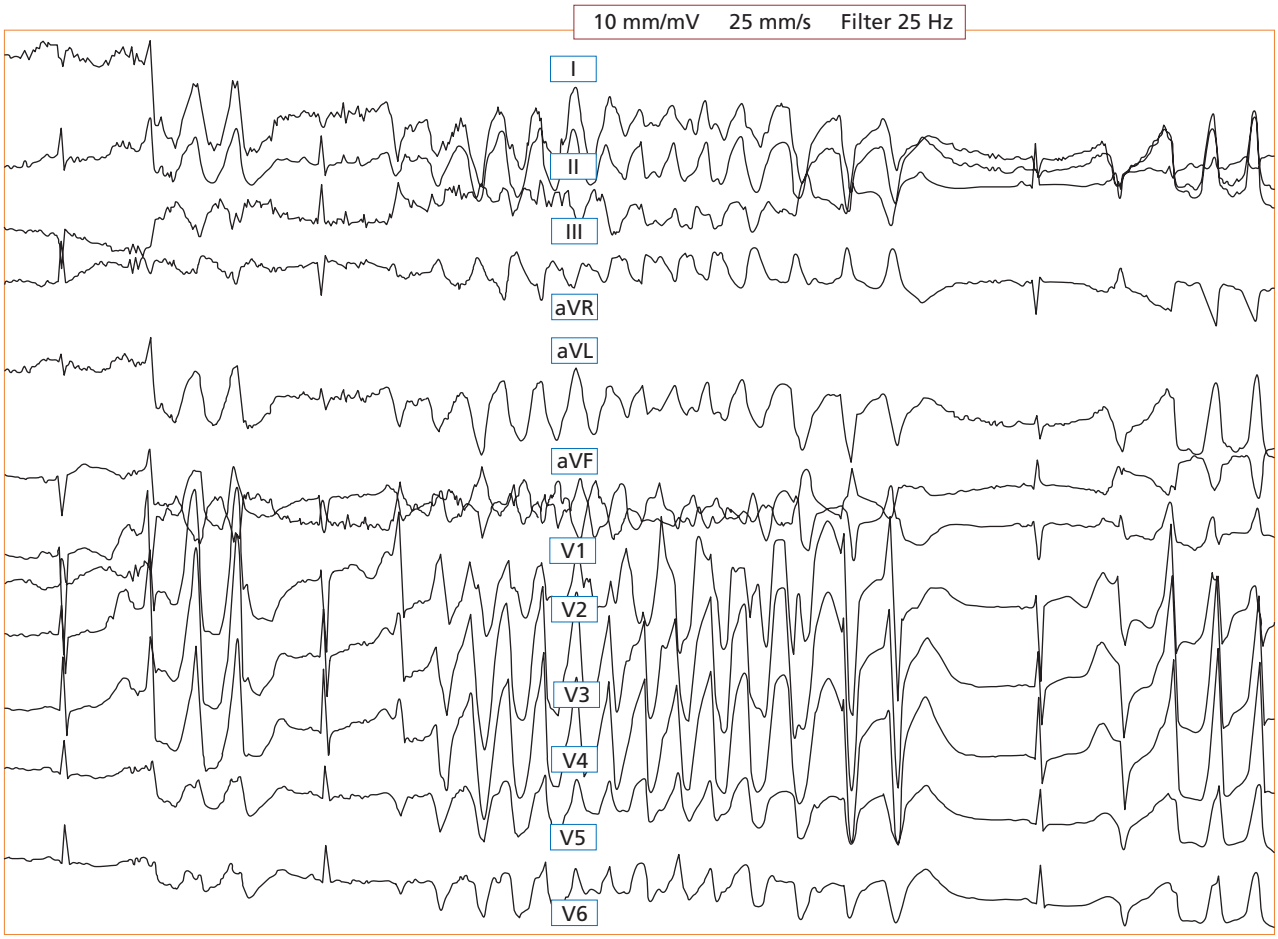


Figure 32.6 Recurrent episodes of torsade de pointes in a patient with long QT syndrome.

degenerate into ventricular fibrillation. The ECG, while in sinus rhythm, usually shows prolongation of the QT interval (see long QT syndrome, p. 961). In addition, distortion of the T wave and often distinct U waves may occur. The longer the previous cycle length, the more exaggerated the TU wave aberration of the following complex, hence the condition is 'pause-dependent'. The treatment of pause-dependent triggered activity is aimed at reducing the prolonged repolarization. Drugs that prolong the QT interval should be discontinued and avoided. Electrolyte abnormalities should be rapidly corrected. Intravenous magnesium sulphate ameliorates these arrhythmias. In addition, pauses can be eliminated by either atrial or ventricular pacing, or by beginning an isoproterenol infusion.

Catecholamine-dependent triggered activity is caused by afterdepolarizations that occur during phase 4 of the cardiac action potential (delayed afterdepolarizations). They occur in the setting of congenital ion-channel abnormalities, digitalis toxicity or cardiac ischaemia. Catecholamine-dependent triggered activity generally is not dependent on pauses. Instead, these arrhythmias may arise in conditions of high sympathetic tone. Thus, patients experience ventricular tachycardia (manifested by syncope or cardiac arrest) during times of exercise or of emotional stress.

Ventricular tachycardia clinical presentation

The clinical presentation of ventricular tachycardia depends on the haemodynamic consequences it produces. These depend partly on ventricular tachycardia rate, the degree of myocardial dysfunction, the circumstances and suddenness of initiation, and autonomic factors. Physical examination in a patient presenting with ventricular tachycardia often indicates haemodynamic distress (low blood pressure, heart failure or cardiogenic shock). When cardiac output and blood pressure are

maintained and/or when the ventricular tachycardias are short-lived, the arrhythmia may present as palpitations, breathlessness or chest pain. Sometimes, especially in patients without structural heart disease, no symptoms are reported during ventricular tachycardia.

The rate of ventricular tachycardia is a major factor in determining clinical symptoms. Among 1130 patients with ventricular tachycardia, the average ventricular tachycardia rate was 163 b.p.m. in asymptomatic patients, 170 b.p.m. in patients who had lightheadedness, 191 b.p.m. in patients presenting with presyncope and 224 b.p.m. in those with syncope [10]. Persistent, slow (< 150 b.p.m.) ventricular tachycardia may lead to dyspnoea, pulmonary congestion and oedema. Patients with heart failure were more likely to present with syncope regardless of ventricular tachycardia rate. Rapid and/or persistent ventricular tachycardia, impaired left-ventricular function and atrioventricular dissociation contribute to haemodynamic collapse, which may result in presyncope, syncope or sudden death.

Syncope is the single most important clinical event for grading sudden cardiac death risk in heart failure [11]. Ventricular tachycardia was found to be the cause of syncope in 35% of these patients [12]. Patients with heart failure and unexplained syncope have a 1-year sudden death rate of up to 45% [12]. The frequency and complexity of ventricular tachycardia parallel the severity of ventricular dysfunction. In total, 15–20% of patients with NYHA class I–II heart failure have non-sustained ventricular tachycardia compared with 50–70% of patients with class IV heart failure. *Sustained polymorphic ventricular tachycardia* is less stable than monomorphic ventricular tachycardia. It is usually rapid and often degenerates into ventricular fibrillation. *Sustained monomorphic ventricular tachycardia* may be haemodynamically tolerated, but may also precipitate ventricular fibrillation or may cause syncope before terminating spontaneously. Patients presenting with haemodynamically tolerated ventricular tachycardia have a lower risk of sudden cardiac death than patients whose initial episode causes cardiac arrest, but the risk is still substantial.

Therapy of ventricular tachycardias in patients with structural heart disease

The spectrum of therapies for ventricular tachycardias includes drug therapy, device implantation and surgical or catheter ablation interventional techniques. The management challenge is to deal with both the ventricular tachycardia that is the presenting symptom and the pervading sudden cardiac death risk that may be the consequence of the arrhythmogenic substrate.

Device and drug therapy of ventricular tachyarrhythmias in patients with structural heart disease

When ventricular tachycardia is the consequence of structural cardiac disease, persistence or evolution of an arrhythmogenic substrate, even after successful treatment of a presenting ventricular tachycardia, militates against any *curative* therapy. For a long time, therapy of ventricular tachycardia was dominated by drug therapy or anti-tachycardic surgery. However, nowadays the implantable cardioverter-defibrillator (ICD) is the best available therapy to prevent sudden cardiac death from ventricular tachycardia. In clinical use since 1980, the ICD is a self-contained device that is capable of identifying ventricular tachycardia and ventricular fibrillation and automatically terminating these arrhythmias by anti-tachycardic pacing or delivering a shock, usually about 35 J, directly to the heart.

Ischaemic heart disease and idiopathic dilated cardiomyopathy

Implantable cardioverter-defibrillator trials for secondary prevention of sudden cardiac death

The antiarrhythmics vs. implantable defibrillator (AVID) trial [13] was the first large-scale randomized study that compared ICD therapy with antiarrhythmic drug treatment in patients with documented symptomatic ventricular tachycardia (55%) or ventricular fibrillation (45%). Patients with ventricular tachycardia also had either syncope or other serious cardiac symptoms, along with a left-ventricular ejection fraction of < 40%; 81% of these patients had coronary artery disease. In total, 1016 patients with documented ventricular tachycardia were randomized to ICD or antiarrhythmic drug therapy, almost exclusively with amiodarone. Mortality in the group treated with antiarrhythmic drugs was 17.7%, 25.3% and 35.9% after 1, 2 and 3 years respectively. The total death rate was significantly reduced by 39% in the

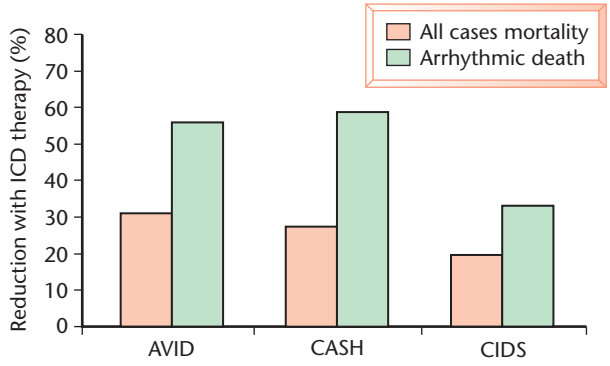


Figure 32.7 Relative risk reduction of total death rate by ICD implantation in secondary prevention trials (for details, see text).

ICD group after 1 year and by 27% and 31% after 2 and 3 years respectively. The results of AVID were consistent among all prespecified subgroups: coronary artery disease vs. other diseases, ventricular fibrillation vs. ventricular tachycardia, all age groups, and all ejection fractions. There was a small trend towards less benefit in patients with an ejection fraction above 35%.

The Canadian Implantable Defibrillator Study (CIDS) [14] and the Cardiac Arrest Study Hamburg (CASH) [15] recruited similar patient cohorts as AVID (Fig. 32.7). CIDS [14] randomized 659 patients with symptomatic ventricular tachycardia, aborted sudden death or syncope in the presence of inducible ventricular tachycardia to ICD treatment or empirical amiodarone. Two-year mortality in the drug arm was about 22%. There was a reduction of total death rate by ICD implantation (risk reduction 19.6% at 3 years) but this did not reach statistical significance.

In CASH [15] a total of 346 patients with a history of cardiac arrest were randomized to ICD or treatment with metoprolol, amiodarone or propafenone. After inclusion of 230 patients that were randomly assigned to propafenone, amiodarone, metoprolol or the implantable defibrillator, the propafenone arm was stopped because of excess mortality compared with the ICD group [15]. This study demonstrated a 37% survival benefit of patients receiving ICDs in comparison with metoprolol or amiodarone at 2 years. Two-year mortality in these arms was 19.6%. Noteworthy, the ejection fraction of the patients in CASH (0.46) was much higher than in AVID (0.32) or CIDS (0.34). In CASH primary ventricular fibrillation patients were also included.

Data from AVID, CIDS and CASH (only amiodarone and ICD arms) were merged into a meta-analysis [16]. This analysis showed a significant reduction in death from any cause, with the ICD having a mean hazard ratio of 0.72. This 28% reduction in the relative risk of death with the ICD was largely the result of the reduction in arrhythmic death. Survival was extended by a mean of 4.4 months by the ICD over a follow-up period of 6 years. Patients with left-ventricular ejection fraction of ≤ 35% had a significantly higher benefit from ICD therapy than those with a better-preserved left-ventricular function. This was also found in a *post hoc* analysis of CIDS [17]. This analysis showed that three clinical risk factors were predictors of death and benefited from the ICD: age ≥ 70 years, left-ventricular ejection fraction ≤ 35% and New York Heart Association class III or IV.

In contrast with patients with coronary artery disease, risk stratification in patients with *idiopathic dilated cardiomyopathy* is much more difficult. These patients are under-represented in all ICD studies. In AVID, CASH and CIDS only 15%, 11% and 10%, respectively, of all patients had idiopathic dilated cardiomyopathy. All of these studies showed a reduction of total mortality in patients with non-ischaemic dilated cardiomyopathy of 20–40% compared with conventional therapy [13–15]. However, the confidence intervals for patients with non-ischaemic dilated cardiomyopathy was much wider than for patients with coronary artery disease. In the meta-analysis of these three studies, only 225 out of 1832 patients had non-ischaemic cardiomyopathy [16]. These patients had a hazard ratio for reduction of total mortality of 0.78, which was very similar to the total cohort (0.72). However, the 95% confidence intervals for these patients ranged from 0.45 to 1.37. The significance of syncope in dilated cardiomyopathy without documented ventricular tachycardia is still unclear. A non-randomized study showed similar event rates of appropriate ICD discharges in patients who received an ICD because of syncope, and patients who received a defibrillator after aborted sudden death or episodes of ventricular tachycardia or ventricular fibrillation [18]. Another study showed significantly lower event rates in a series of consecutive patients treated with an ICD than in conventionally treated patients [19]. Hence, it seems reasonable to treat patients with non-ischaemic dilated cardiomyopathy and syncope similar to those after aborted sudden cardiac death if other causes of syncope are excluded.

Implantable cardioverter-defibrillator trials for primary prevention of sudden cardiac death
(Fig. 32.8)

The Multicenter Automatic Defibrillator Implantation Trial (MADIT) [20] was the first study that showed a benefit of implanting an ICD in patients with coronary heart disease and left-ventricular dysfunction, whereas the CABG-Patch trial [21] (ICD therapy vs. no specific antiarrhythmic therapy—the other studies compared

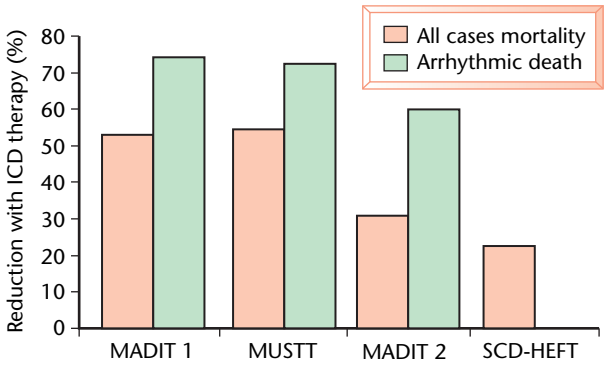


Figure 32.8 Relative risk reduction of total death rate by I CD implantation in primary prevention trials (for details, see text).

the ICD with antiarrhythmic drugs—for the primary prophylaxis of sudden cardiac death) in patients with impaired left-ventricular function scheduled for elective bypass surgery demonstrated no benefit. MADIT [22] enrolled patients after myocardial infarction (in 75% of the patients, the interval between infarction and enrolment was more than 6 months) with an ejection fraction below 0.36, non-sustained ventricular tachycardia and inducible ventricular tachycardia (not suppressible by a class I drug). During an average follow-up of 27 months, the risk of death was reduced by 54% in the ICD arm.

MADIT II [23] was designed to investigate whether the ICD would be effective in the prevention of all-cause death in patients after myocardial infarction, with a low ejection fraction (≤ 30%) as the only inclusion criterion. A randomization ratio of 3:2 to receive an ICD or conventional therapy was selected. After inclusion of 1232 patients, the trial was terminated because of a significant (31%) reduction in all-cause death in patients assigned to ICD therapy.

In a *post hoc* analysis, Moss and colleagues [22] found that patients with an ejection fraction of less than 26% had a far greater benefit from ICD implantation than patients with an ejection fraction of between 26% and 35% [24]. Later they identified three independent risk factors: ejection fraction < 26%, QRS duration ≥ 120 ms and a history of heart failure treatment [25]. The benefit from ICD treatment increased with the number of risk predictors. Thus, in patients with chronic coronary heart disease, the magnitude of the survival benefit from the ICD is directly related to the severity of cardiac dysfunction and its associated mortality risk. The same was found in a *post hoc* analysis of the Multicenter Unsustained Tachycardia Trial (MUSTT) [26]. The combination of an ejection fraction of ≤ 30% and an abnormal signal-averaged ECG identified a subgroup of particularly high risk, constituting 21% of the total study population.

In contrast with MADIT and MADIT II, where 85% of the patients were included > 6 months post myocardial infarction, the yet unpublished DINAMIT study, which included patients within the first 40 days after a myocardial infarction, failed to demonstrate a benefit from prophylactic ICD implantation, despite the fact that most patients had a large anterior infarction and left-ventricular ejection fraction was low (average 28%) (for comment, see ref. no. 27).

Very recently, the first results of SCD-Heft trial have been presented. This trial determined if amiodarone or an ICD reduces all-cause mortality compared with placebo in patients with either ischaemic or non-ischaemic NYHA class II and III heart failure and an ejection fraction of < 35%. The ICD decreased mortality by 23%, whereas amiodarone, when used as a primary preventative agent, did not improve survival. Two other prospective studies in patients with *non-ischaemic cardiomyopathy* without prior arrhythmias and one in patients with asymptomatic non-sustained ventricular tachycardia have been reported.

The Cardiomyopathy Trial (CAT) [28] was a pilot study in patients with a recently diagnosed (< 9 months) non-ischaemic dilated cardiomyopathy (EF < 30%) that included 102 patients. Patients were randomized to ICD therapy or no antiarrhythmic drug therapy. The primary end-point was total mortality after 2 years. In contrast with the investigators' expectations, the total mortality after 2 years was only 8–9% in both groups. The study was terminated, as more than 1300 patients would have been needed to demonstrate a significant difference between the two groups. In the first 2 years after inclusion into the study, there was not a single case of sudden death in the control group. In the ICD group, there were 11 patients with a ventricular tachycardia faster than 200 b.p.m. All ventricular tachycardias were terminated by the ICD. Nevertheless, after 5 years only 50% of those patients with appropriate ICD discharges survived, in contrast with 85% of the patients without appropriate ICD discharges. This finding is in analogy to the finding of an association between appropriate ICD discharges and death from progressive heart failure [29].

The findings of the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) [30,31] trial are in contrast with the results of the CAT trial. DEFINITE was the first large-scale trial investigating the use of ICD for the primary prevention of sudden cardiac death in patients with non-ischaemic dilated cardiomyopathy. It enrolled a total of 458 patients with non-ischaemic dilated cardiomyopathy, left-ventricular dysfunction (ejection fraction < 35%), NYHA class I–III heart failure and spontaneous ventricular tachycardia (premature ventricular complexes or non-sustained ventricular tachycardia).

Patients with unexplained syncope within 6 months, prior cardiac arrest or ventricular tachycardia of > 15 beats at a rate of > 120 b.p.m. or those on amiodarone treatment for ventricular tachycardia were excluded from the study. Patients were randomized to drug therapy with beta-blockers and ACE inhibitors (if tolerated) or drug therapy plus an ICD. The study's primary end-point was total mortality; the secondary end-point was arrhythmic death. During a mean follow-up of 26 months, total mortality observed in the ICD group was 8.1%, a result that did not reach statistical significance when compared with control subjects (although there was a clear trend toward a benefit). The absolute mortality benefit in the ICD group was 5.7% at 2 years and the relative risk reduction was 34%. ICDs were associated with a significantly lower rate of arrhythmic death, the study's secondary end-point. Use of an ICD was associated with a 74% relative reduction in arrhythmic death (P = 0.01). Subgroup analyses uncovered that patients with class III heart failure who received an ICD had a 67% relative risk reduction in all-cause mortality compared with those who received drug therapy alone (P = 0.009).

As ICD therapy has been shown to be beneficial in patients with impaired left-ventricular function and non-sustained ventricular tachycardia in the MADIT and the MUSTT trials [22,26], the hypothesis that ICD therapy would be superior to antiarrhythmic drug therapy also in patients with non-ischaemic dilated cardiomyopathy and non-sustained ventricular tachycardia was tested in the AMIOVIRT study [32]. Patients (n = 103) with non-ischaemic dilated cardiomyopathy, left-ventricular ejection fraction of < 35% and asymptomatic non-sustained ventricular tachycardia were randomized to receive either amiodarone or an ICD. The primary end-point was total mortality. The study was stopped because of the unexpectedly low total mortality in both arms. The percent of patients surviving at 1 year (90% vs. 96%) and three years (88% vs. 87%) in the amiodarone and ICD groups, respectively, was not different. As there was no true placebo group in this study, it cannot be clarified whether non-sustained ventricular tachycardia is useful as a risk predictor in non-ischaemic dilated cardiomyopathy or whether amiodarone is highly efficient in this patient cohort. The latter had already been suggested retrospectively by the CHF-STAT trial, when amiodarone proved more effective in non-ischaemic vs. ischaemic patients [33]. However, in a prospective registry including 343 patients with idiopathic dilated cardiomyopathy, only reduced left-ventricular EF and lack of beta-blocker therapy were predictors of an increased arrhythmic risk [34]. Signal-averaged ECG, QTc dispersion, heart rate variability, baroreflex sensitivity and microvolt T-wave alternans did not predict arrhythmia risk, and non-sustained ventricular tachycardia on Holter was associated only with a trend towards higher arrhythmia risk. In contrast with these findings, patients with non-sustained ventricular tachycardia in the CAT trial had a markedly increased total mortality rate with only 63% surviving after 6 years compared with 77% of the patients without non-sustained ventricular tachycardia. However, in CAT, even in this subgroup, there was no benefit from ICD implantation. In patients with non-ischaemic dilated cardiomyopathy, non-sustained ventricular tachycardia seems to be more a marker for increased total mortality than for a high arrhythmic risk.

Catheter ablation or surgical treatment of ventricular tachyarrhythmias

Catheter ablation might be an adjunctive but rarely curative option for a highly select group of patients with refractory or incessant ventricular tachycardia (i.e. patients with multiple ICD discharges due to ventricular tachycardia—Fig. 32.3). Catheter ablation has been successfully applied in ventricular tachycardia that is caused by ischaemic heart disease. Results with computerized mapping systems and mapping techniques using non-contact mapping systems that do not require sustained ventricular tachycardia during the ablation procedure have demonstrated promising results in ventricular tachycardia ablation. Surgical techniques for treatment of ventricular tachycardia may be effective in ICD carriers with sustained monomorphic ventricular tachycardia resulting from coronary artery disease, especially when a discrete left-ventricular aneurysm and inducible monomorphic ventricular tachycardia are present [35]. In selected patients, anti-tachycardia operations can be carried out with an acceptable mortality and a relatively high long-term survival rate. However, these procedures cannot be expected to alter the natural history of the underlying heart disease. Bundle branch re-entry ventricular tachycardia, which may be relatively commoner in idiopathic dilated cardiomyopathy, is particularly amenable to catheter ablation (see above).

Other cardiomyopathic conditions

Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC) was first described in 1982 [36] and since

then has been diagnosed with increased frequency. ARVC is a primary myocardial disorder with a genetic background. In recent years, the disease has been recognized as a major cause of ventricular arrhythmias and sudden death, particular in young patients and athletes with apparently normal hearts. ARVC is characterized by localized or diffuse atrophy of predominantly right-ventricular myocardium, with subsequent replacement with fatty and fibrous tissue, and usually manifests with ventricular tachycardia and/or sudden death, frequently before structural abnormalities become apparent [36–38]. Diagnostic criteria of ARVC were proposed by an international study group [39] and include major and minor criteria in different categories. Eight chromosomal loci for autosomal dominant forms of ARVC and two loci for autosomal recessive inheritance (one of which is Naxos disease) have been reported. In Naxos disease, a syndromic variant of ARVC with palmoplantar keratosis and woolly hair, a mutation in the gene encoding the cytoskeletal protein plakoglobin was identified. Several years later, a mutation in the desmoplakin gene, another protein involved in cell-to-cell junctions (adherens junctions and desmosomes), was identified in a classical form of ARVC (ARVC-8), with frequent left-ventricular involvement. In a rare and rather atypical subgroup of ARVC (ARVC-2) with minor right ventricular abnormalities and polymorphic ventricular arrhythmias, a mutation in the gene encoding the cardiac ryanodine receptor (RyR2) was identified.

In ARVC, episodes of ventricular tachycardia are frequently well tolerated, mainly due to the preserved left-ventricular function. Antiarrhythmic treatment of ARVC includes drug therapy, catheter ablation and ICD implantation. The available but limited data on risk stratification indicate that patients with severe right ventricular dysfunction, left-ventricular involvement, a history of syncope or cardiac arrest, family history of sudden cardiac death, inducible ventricular tachycardia/ventricular fibrillation and ECG abnormalities (epsilon potential, late potential) are more prone to life-threatening ventricular tachycardia and sudden death. In patients with ARVC and low risk of sudden death, antiarrhythmic drug therapy is an alternative option. Low-risk cohorts include patients with localized right-ventricular disease and monomorphic ventricular tachycardia suppressed by antiarrhythmic drugs.

Despite high efficacy rates of radiofrequency catheter ablation in abolishing regional sites of ventricular tachycardia, there is a high recurrence rate due to new ventricular tachycardia morphologies and origins. Main indications for catheter ablation in ARVC include monomorphic ventricular tachycardia in localized right-ventricular abnormalities and incessant or frequent ventricular tachycardia not suppressed by antiarrhythmic treatment. Recent studies [40,41] in high-risk patients with ARVC after resuscitated cardiac arrest, life-threatening ventricular tachycardia or drug-refractory ventricular tachycardia demonstrated the high efficacy of ICD implantation in the prevention of sudden death. The estimated survival benefit of ICD therapy was 21%, 32% and 36% after 1, 3 and 5 years, respectively, of follow-up. The role of ICD therapy for primary prevention of sudden death in ARVC remains unclear to date because only very preliminary data are available. Patients with well-tolerated and non-life-threatening ventricular tachycardia are usually treated empirically with antiarrhythmic drugs, including amiodarone, sotalol, beta-blockers, flecainide and propafenone, alone or in combination. ICDs are usually reserved for patients with life-threatening ventricular tachycardia, in whom drug therapy is either ineffective or undesirable. Wichter and colleagues [41] found that, in a series of 60 patients in a single centre during a mean follow-up of 80 ± 43 months, event-free rate after 5 years was only 26% for ventricular tachycardias and 59% for potentially fatal ventricular tachycardias with a rate > 240 b.p.m. Extensive right-ventricular dysfunction was identified as a predictor for appropriate ICD discharges.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is an inherited myocardial disorder with an autosomal dominant trait and is caused by mutations in one of 10 genes known so far, each encoding for protein components of the cardiac sarcomer. There is broad heterogeneity not only concerning disease-causing genetic mutations, but also in terms of phenotypic expression, treatment and prognosis. Patients with hypertrophic cardiomyopathy often present with ventricular ectopy or non-sustained ventricular tachycardias that are associated with a high risk of sudden cardiac death. Symptoms of HCM range from dyspnoea and angina pectoris to palpitations, dizziness and syncope [42]. Treatment of symptomatic HCM patients includes drugs (verapamil, beta-blockers or disopyramide) or non-pharmacological options (septal myectomy, DDD pacing, alcohol septal ablation) in those with obstructive HCM [43]. These treatment options are targeted to reduce symptoms and improve quality of life, but have not been shown to have an impact on survival.

Sudden cardiac death may occur without warning signs or symptoms, as the initial disease manifestation, and may be triggered by vigorous exercise or competitive sports activity. The highest risk for sudden cardiac death has been associated with prior cardiac arrest or spontaneous sustained ventricular tachycardia/ventricular

fibrillation. In such patients, the implantation of an ICD is strongly recommended for secondary prevention of sudden death. In a multicentre retrospective study in high-risk HCM patients, appropriate ICD interventions occurred in 25% of patients after a follow-up period of only 3 years. Potentially life-saving ICD therapies were reported at a rate of 11% per year in patients receiving the ICD for secondary prevention (aborted sudden death or sustained ventricular tachycardia/ventricular fibrillation), compared with a rate of 5% per year in the primary prevention cohort (based solely on non-invasive risk factors) [44].

In the setting of primary prevention, major risk factors for sudden death in HCM include a high-risk mutant gene, a family history of premature sudden death, unexplained syncope, abnormal exercise blood pressure, non-sustained ventricular tachycardia (Holter), and severe left-ventricular hypertrophy (≥ 30 mm). In individual patients, atrial fibrillation, myocardial ischaemia, left-ventricular outflow-tract obstruction and vigorous physical exertion or competitive sports may be additional risk factors [45,46]. ICD implantation is considered the most effective and reliable treatment option and has been recommended in HCM patients at high risk of sudden death [44–46]. HCM patients without risk factors are at low risk of sudden death and should be reassured and followed clinically. Little or no restriction is necessary with regard to employment and recreational activities but patients should be excluded from strenuous exercise and competitive sports.

Ventricular tachycardia in patients without structural heart disease: 'idiopathic' ventricular tachycardia

'Idiopathic ventricular tachycardia' is a non-specific term that represents a heterogeneous group of arrhythmias. Awareness of this entity has existed since it was first described by Gallavardin [47] in 1922. Patients can be completely asymptomatic or have transient symptoms including palpitations, dizziness or presyncope, but these arrhythmias, with the exception of rapid polymorphic ventricular tachycardia or idiopathic ventricular fibrillation occurring in the setting of inherited arrhythmic syndromes, are rarely life threatening. The underlying mechanisms include re-entry, triggered activity and catecholamine-mediated automaticity. Idiopathic ventricular tachycardia can be categorized according to the clinical presentation (non-sustained vs. sustained), precipitating factors (e.g. exercise), site of origin (i.e. left or right ventricle), by response to antiarrhythmic drugs (e.g. adenosine or verapamil) or on the basis of an underlying organic heart disease (primary electrical disorder vs. inherited myocardial disease—Table 32.1).

Table 32.1 Ventricular tachycardias in patients with primary electrical disease and inherited myocardial diseases

'Primary electrical disorders', in which an organic heart disease is not detectable
Long QT syndrome (LQTS)
Short QT syndrome (SQTS)
Catecholaminergic polymorphic ventricular tachycardia (CPVT)
Idiopathic right-ventricular outflow tract tachycardia (RVOT-VT)
Idiopathic left-ventricular tachycardias (ILVT)
Idiopathic ventricular fibrillation (IVF)
Brugada syndrome
'Arrhythmogenic cardiomyopathies', in which an inherited myocardial disease may primarily manifest with ventricular tachyarrhythmias
Arrhythmogenic right ventricular cardiomyopathy (ARVC)
Hypertrophic cardiomyopathy (HCM)
Dilated cardiomyopathy (DCM)

Ventricular tachycardia in patients without structural heart disease but not currently amenable to curative therapies

Long QT syndrome (LQTS) is characterized by a prolonged QT interval in the surface ECG, recurrent syncope or sudden death resulting from torsade de pointes (Fig. 32.6) [48–51]. The incidence of LQTS has been estimated as 1 in 7000 to 1 in 10 000 live births. More than 250 mutations in seven genes (LQTS 1–7) have been described. Mutations involve genes encoding potassium channels [LQT1, 2, 5 and 6, Jervell Lange–Nielsen (JLN) 1 and 2], sodium channels (LQT3) and ankyrin B (LQT4), which acts as a targeting and anchoring molecule for the sodium channel. In 30–40% of all patients with LQTS, no gene defect can be found, pointing towards a large heterogeneity of gene loci. The term acquired LQTS [52,53] is reserved for a syndrome similar to the congenital form but caused by exposure to drugs that prolong the duration of the ventricular action potential or to QT prolongation secondary to bradycardia or an electrolyte

imbalance. Drugs that prolong the QT interval, and thereby predispose to torsade de pointes, are listed on websites such as www.qtdrugs.org.

Associations between genotype and phenotype have been investigated based on the International LQTS Registry, which was started in 1979. Moss and colleagues [54] identified a gene-specific phenotype in the repolarization pattern of the surface ECG. Patients with LQT1 show a broad and prolonged T wave, whereas LQT2 patients have a notched, low-amplitude T wave. Patients of the LQT3 demonstrate a long isoelectric ST segment with a delayed, peaked narrow T wave. In LQT3, cardiac events occur more frequently at rest or during sleep, whereas they are typically related to emotion or exercise (in particular, swimming) in LQT1 and auditory stimuli in LQT2 [55,56]. Of 533 genotyped index patients (243 LQT1, 209 LQT2, 81 LQT3) and 1842 family members mortality was highest in patients with LQT3 followed by male patients with LQT1 and 2 and female patients with LQT1 and 2, but arrhythmic events occurred more frequently in LQT1 and LQT2 [57]. Priori and colleagues [55] presented a scheme for risk stratification, based on analysis of 647 patients. High risk was considered in patients with LQT1 and $QT_c > 500$ $ms^{1/2}$ and in male patients with LQT2 or LQT3 and $QT_c > 500$ $ms^{1/2}$.

High-risk patients should be treated prophylactically using beta-blockers [58], although the effect is less beneficial in patients with LQT3 [59]. Beta-blocker therapy is associated with a significant reduction in the rate of cardiac events. Event rates within 5 years while on beta-blocker were higher in those patients who were symptomatic before starting this therapy (32%) than in those who had been asymptomatic (14%) [60]. Subgroup analysis in genotyped patients with LQT1, LQT2 and LQT3 showed that beta-blocker therapy had only minimal effects on QT_c in all three genotypes. Treatment was associated with a significant reduction of events in LQT1 and LQT2 patients, whereas there was no evident effect in LQT3 [60]. In selected patients with LQT1, LQT2 and LQT5, potassium channel openers (i.e. pinacidil, nicorandil) may become a therapeutic option [61,62]. In LQT3, mexiletine may selectively suppress the mutant channel phenotype by inhibition of late openings [63,64] and lidocaine showed similar effects [65]. Priori and colleagues [66] were able to show a significant reduction of QT_c prolongation in LQT3 patients carrying mutant sodium channels that were known to be influenced by mexiletine *in vitro*. Similar effects were reported with flecainide [67].

There is only limited information available on the role of ICD therapy in patients with LQTS. The ACC/AHA 2002 guidelines have designated the ICD for primary prevention of SCD as a class IIb indication. In clinical practice, the decision for prophylactic ICD implantation is not based on gene analysis. Usually, prophylactic ICD implantation is considered in patients with syncope despite beta-blocker therapy or in patients with syncope and with a family history of sudden death. A benefit from ICD has been suggested by retrospective analyses. Zareba and colleagues [68] compared 73 LQTS patients who were treated with ICD because of prior cardiac arrest (n = 54) or recurrent syncope despite beta-blocker therapy (n = 19) with 161 LQTS patients who had similar indications (89 cardiac arrest and 72 recurrent syncope despite beta-blocker therapy) but did not receive ICD. There was one (1.3%) death in 73 ICD patients following an average of 3 years, whereas there were 26 deaths (16%) in non-ICD patients during a mean 8-year follow-up. However, it was noted by Viskin [69] that, after exclusion of the patients who died within 1 month after inclusion and therefore likely from residuals of their first aborted sudden death, the difference between both groups was only marginal. Hence, a long-term prospective study is needed to determine the benefit of ICD therapy in LQTS.

Short QT syndrome

Very recently, a new syndrome associated with sudden cardiac death in otherwise healthy patients with structurally normal hearts has been described, the short QT syndrome [70,71]. The prevalence of this syndrome is unknown. Patients with the short QT syndrome (SQTS) present with a short QT interval on the 12-lead ECG, familial sudden death and palpitations, syncope or sudden cardiac arrest. Six patients from two European families were extensively tested by non-invasive and invasive methods. Mean QT intervals were 252 ± 13 ms (QT_c = 287 ± 13 ms). In four patients, electrophysiological studies were performed, revealing short atrial and ventricular refractory periods in all and an increased propensity to ventricular vulnerability to fibrillation in three out of four patients [70,71]. The genetic basis has only recently been uncovered. In two families, two different missense mutations of the cardiac potassium channel HERG (KCNH2) were identified, resulting in the same amino acid change. These mutations dramatically increase the potassium current I_{Kr}, leading to heterogeneous abbreviation of action potential duration and refractoriness. The affinity of the affected channels to I_{Kr} blockers is markedly reduced [72]. Currently, ICD implantation is the only therapeutic option. First experience with ICD therapy in SQTS indicates an increased risk of inappropriate device discharge owing to atrial fibrillation and T-wave oversensing, which constitutes a significant and specific risk in patients with SQTS [73].

Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a clinically and genetically heterogeneous disease. It is characterized by episodes of syncope or sudden death in response to physiological or emotional stress occurring in structurally normal hearts [74–79]. Documented arrhythmias include bidirectional ventricular tachycardia, polymorphic ventricular tachycardia and, in rare patients, catecholaminergic idiopathic ventricular fibrillation. CPVT was first described in a Bedouin tribe from Israel [80] but has also been identified in other populations [77,81,82]. A family history of juvenile sudden death and stress-induced syncope is present in approximately one-third of cases. Mortality is high and reaches up to 30–50% by the age of 30 years [83]. Around 40–60% of the patients with CPVT carry mutations in the cardiac ryanodine receptor gene (RyR2) [82] or in the calsequestrin 2 gene (CASQ2) [84]. Genotype–phenotype analysis showed that men are at higher risk of cardiac events (i.e. syncope) and that mutation carriers became symptomatic at a younger age [76]. Current treatment of CPVT consists of β-adrenergic blockers [76,80], antiarrhythmic drugs and/or ICD implantation, mainly based on empirical grounds or the results of serial exercise/pharmacological testing [83].

Idiopathic ventricular fibrillation

In 5–10% of survivors of cardiac arrest due to ventricular arrhythmias, no structural abnormality of the heart as the underlying cause is found. In the absence of demonstrable structural heart disease, myocardial ischaemia, drug effects, electrolyte or metabolic abnormalities and toxicity, and ventricular fibrillation and unexplained cardiac arrest is rare [85–88]. However, it appears to be more frequent than previously thought and accounts for approximately 6–12% of all sudden deaths (lifetime prevalence < 0.5 in 10 000), with a higher percentage in the young population below the age of 40 years. Ventricular fibrillation in patients with apparently normal hearts may represent a true 'primary electrical disease', but it may also be the first manifestation of a cardiomyopathy. The diagnosis of idiopathic ventricular fibrillation must therefore be made by exclusion, implying that adequate and extensive diagnostic evaluation is necessary in order to rule out subclinical structural heart disease. Idiopathic ventricular fibrillation is associated with a high mortality rate. Available data suggest an 11% rate of sudden death within 1 year of diagnosis or recurrence rates of up to 30% 5 years after an initial episode of survived cardiac arrest [85]. Therefore, effective treatment is mandatory to improve the long-term prognosis. In one report, quinidine (class IA antiarrhythmic agent) was highly effective in preventing arrhythmia re-induction during electrophysiological study [88]. ICD implantation is currently the treatment of choice in patients with idiopathic ventricular fibrillation in order to prevent sudden death from recurrent episodes of ventricular fibrillation. In selected patients, catheter ablation may be a potential new option in the treatment of idiopathic ventricular fibrillation by targeting premature ventricular beats arising from the Purkinje conducting system, which have been observed to trigger polymorphic ventricular tachycardia [89].

Brugada syndrome

In 1992, Brugada and Brugada [90] reported a new clinical entity with a RBBB pattern and ST segment elevation in right precordial ECG leads (Fig. 32.11) and a high incidence of sudden cardiac death in patients with structurally normal hearts. The disease is considered as a subgroup of idiopathic ventricular fibrillation and has been referred to as *Brugada syndrome*. It manifests with episodes of polymorphic ventricular tachycardia, syncope, and cardiac arrest during adulthood at a mean age of 40 years but within a large age range. Because symptoms occur mostly at night, this syndrome is also assigned as 'sudden unexpected nocturnal death syndrome'. It accounts for approximately 4–12% of sudden deaths and for 20–40% of sudden cardiac arrest in patients without structural heart disease. It dominantly occurs in males and appears to be most prevalent in South-East Asia and Japan, where the disorder is a leading cause of natural death among young men with an estimated annual mortality rate of 26–38 per 100 000 [91].

Diagnostic criteria were recently proposed and reported in a consensus document [92] and mainly rely on electrocardiographic abnormalities after exclusion of structural heart disease by detailed cardiac investigation. Before making the diagnosis of Brugada syndrome, it is mandatory to exclude myocardial ischaemia and organic heart disease, particularly affecting the right ventricle (i.e. arrhythmogenic right-ventricular cardiomyopathy) as well as extracardiac and electrolyte abnormalities. Brugada syndrome is considered a 'channelopathy' that belongs to the group of 'primary electrical diseases' of the heart. In familial Brugada syndrome (20–30%), genetic mutations identified so far refer to the alpha-subunit of the cardiac sodium channel (SCN5A) [93]. Assessment of these mutations in expression systems demonstrated loss of function of the sodium channel.

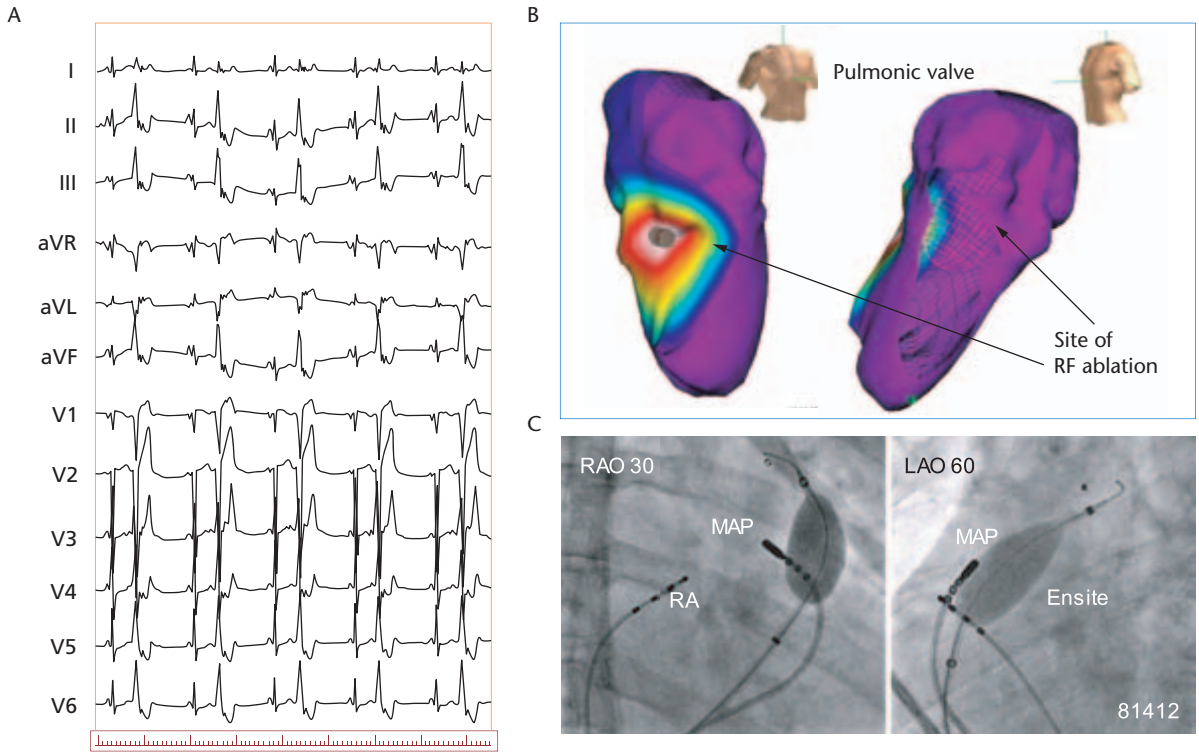


Figure 32.9 Non-contact mapping of a ventricular bigeminus with LBBB inferior axis morphology originating from the right ventricular outflow tract in a highly symptomatic patient (A). The multielectrode array catheter (MEA) is part of the non-contact mapping system (EnSite 3000; Endocardial Solutions). The system permits mapping of a single complex. The MEA, which is filled with a contrast saline medium, is positioned in the right-ventricular outflow tract (RAO/LAO, right/left anterior oblique views). The system calculates electrograms from 3000 endocardial points simultaneously by reconstructing far-field signals. Non-depolarized myocardium is shown in purple in this three-dimensional isopotential map (B). The map also shows the site of earliest depolarization (white circle). At this site the extrasystoles were successfully ablated using radiofrequency ablation. The ablation catheter is located at the successful ablation site. RA, diagnostic catheter in the right atrium (C).

However, mutations in the SCN5A gene have been detected in only a minority of patients, thus indicating genetic heterogeneity. In the more common sporadic disease (70–80%), mutations in the SCN5A gene are very infrequent [94]. Although, at present, genetic testing is not helpful in risk stratification and clinical decision-making, it is important for the expansion of pathophysiological knowledge and understanding of genotype–phenotype correlations [95].

Three types of repolarization patterns can be described in Brugada syndrome [92]. Type 1 demonstrates a coved ST segment elevation of ≥ 2 mm (0.2 mV) and negative T waves in the right precordial leads (Fig. 32.11). Type 2 is characterized by a saddleback appearance with a high take-off ST segment elevation (≥ 2 mm) followed by a gradually descending ST segment (remaining ≥ 1 mm above baseline) and positive or biphasic T waves. Type 3 has either coved or saddleback morphology, with an ST segment elevation of < 1 mm. These electrocardiographic manifestations of Brugada syndrome may be transient or concealed but can be unmasked or challenged with sodium channel blockers (i.e. ajmaline, flecainide and others) [96,97], vagotonic stimulation [98] or fever [99]. Only type 1 should be considered diagnostic. Types 2 and 3 must be considered suspicious and an ajmaline test has to be performed to uncover type 1 for the diagnosis. The diagnostic and prognostic impact of an incidental finding of Brugada-type ECG signs in asymptomatic individuals without a family history represents a controversial and currently unresolved yet growing problem in clinical decision-making. Because ventricular fibrillation is the most important and frequently first manifestation of Brugada syndrome, appropriate diagnosing and early risk stratification are vital for patient management and prevention of sudden cardiac death.

Brugada and colleagues [100] identified male gender,

spontaneous ST segment elevation and inducible ventricular tachycardia/ventricular fibrillation as indicators of high risk. In their study population, patients with a family history of Brugada syndrome appeared not to be at increased risk when compared with those with sporadic disease. Patients with an episode of aborted sudden death were at highest risk for recurrent arrhythmic events, whereas symptomatic (i.e. syncope) and asymptomatic patients with spontaneous ST segment elevation were at moderate risk. In these patients, the result of programmed electrical stimulation appeared to be helpful in clinical decision-making. Asymptomatic patients with ST segment elevation only after challenge with sodium channel blockers were at low risk for life-threatening arrhythmias [100]. The role of programmed electrical stimulation for risk stratification has been a matter of controversial discussion. Some studies [96,101,102] failed to find a correlation between ventricular tachycardia/ventricular fibrillation recurrence and inducibility of ventricular tachyarrhythmias. Priori and colleagues [102] collected clinical data from 200 patients with Brugada syndrome and identified patients with the combined presence of a spontaneous right precordial ST segment elevation and the history of syncope at highest risk of sudden death (hazard ratio 6.4; $P < 0.002$). Spontaneous ST segment elevation of ≥ 2 mm without history of syncope indicated intermediate risk (hazard ratio 2.1, not significant). A history of syncope per se and the results of programmed electrical stimulation were not helpful in identifying individuals at higher risk of major arrhythmic events [102]. Very recently, Eckardt and colleagues [103] reported data on a large population of individuals with a type 1 Brugada ECG pattern. During a mean follow-up of 40 ± 50 months, 4 out of the 24 patients (17%) with aborted sudden cardiac death and 4 out of 65 (6%) with a prior syncope had a recurrent arrhythmic event, whereas only 1 out of 123 asymptomatic individuals (0.8%) had a first arrhythmic event. A previous history of aborted sudden death or syncope and the presence of a spontaneous type 1 ECG were the only significant predictors of adverse outcome. The results of programmed electrical stimulation correlated only poorly to outcome. Hence, available data on risk stratification for symptomatic and asymptomatic patients in Brugada syndrome are inconclusive, and patient management and therapeutic strategies are controversial and under constant debate and refinement. β-Adrenergic (i.e. isoproterenol) or anticholinergic agents may be helpful in restoring the balance of currents during phase 1, whereas beta-blockers and amiodarone have demo strated no clinical efficacy [104]. Reports from Belhassen and colleagues [105,106] indicate a potential efficacy of quinidine in the treatment of ventricular tachycardia and prevention of sudden death in Brugada syndrome [107]. However, systematic or randomized studies on the clinical efficacy of quinidine in Brugada syndrome are not available. Currently, ICD implantation is the treatment of choice in secondary and primary prevention of sudden death in high-risk patients with Brugada syndrome [105,108].

Ventricular tachycardia in patients without structural heart disease, who are amenable to curative therapies

Idiopathic right-ventricular outflow-tract ventricular tachycardia

This arrhythmia, which has also been termed *repetitive monomorphic ventricular tachycardia*, usually originates in the right ventricular outflow tract. It is usually seen in younger patients (female > male) without structural heart disease and accounts for up to 70% of idiopathic ventricular tachycardia. Although the majority of cases appear to occur sporadically rather than on a familial basis, the condition is generally considered as a 'primary electrical disease'. It is important in the differential diagnosis of various entities, in particular mild or subclinical forms of arrhythmogenic right ventricular cardiomyopathy [109]. Most data suggest that the mechanism of RVOT-ventricular tachycardia is triggered activity due to adenylcyclase-mediated delayed afterdepolarizations [110]. They are usually exertion- or stress-related arrhythmias. They can also present as recurrent extrasystolies (Fig. 32.9) or non-sustained arrhythmias tending to occur at rest ('repetitive monomorphic ventricular tachycardia'), or provoked only with exercise (Gallavardin's tachycardias [47]). However, these forms may just represent different spectra of the same arrhythmia. Idiopathic RVOT-ventricular tachycardia is usually well tolerated, probably owing to the preserved ventricular function. Hence, RVOT-ventricular tachycardia has a favourable long-term prognosis compared with ventricular tachycardia in structural heart disease. It manifests as a left bundle branch block ventricular tachycardia with an inferior axis (Fig. 32.9). Pacing the heart at a rapid rate or isoproterenol infusion can often induce the arrhythmia. The arrhythmia is responsive to therapy with beta-blockers [111], sotalol [111,112] or calcium channel blockers [110,113] and can also be amenable to transcatheter ablation (Fig. 32.9) [109,114].

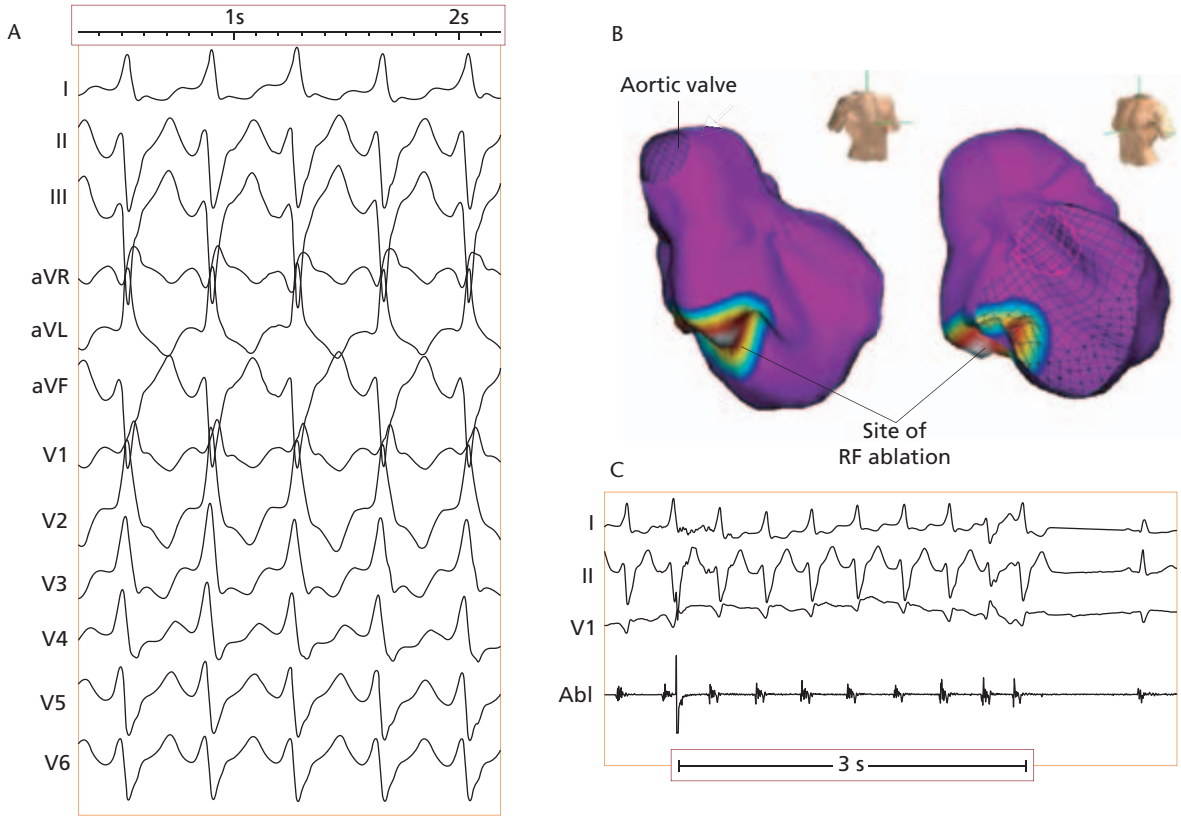


Figure 32.10 Non-contact mapping of an idiopathic left-ventricular tachycardia with RBBB left axis deviation (A). The multiple electrode array (Ensite 3000, Endocardial Solutions) was placed in the left ventricle (for details, see legend to Fig. 32.9). At the distal part of the left posterior fascicle, radiofrequency ablation almost immediately terminated the ventricular tachycardia (C), which, thereafter, was no longer inducible.

Idiopathic left-ventricular tachycardias (fascicular ventricular tachycardia)

This arrhythmia tends to occur in younger, predominantly male patients, without structural heart disease [115,116]. An association with exertion or stress is uncommon. The arrhythmia has a relatively narrow (0.10–0.14 s) RBBB morphology with a rapid downstroke of S waves in the precordial leads and a left superior axis (Fig. 32.10). It is inducible with programmed stimulation. ILVT is thought to have a re-entrant basis or derives from triggered activity secondary to delayed afterdepolarizations [117]. It arises on or near to the septum near the left posterior fascicle [118–121]. Rarely, ventricular tachycardia can arise from the left anterior fascicle [115] and thus produce an RBBB pattern with right-axis deviation. Catheter ablation (Fig. 32.10) [122] offers curative therapy and should be considered early in the management of symptomatic patients. It can be performed using pace mapping [118,123], presystolic Purkinje potential [123,124] or diastolic potential during ventricular tachycardia [120,120]. Alternatively, ILVT tends to respond to therapy with beta-blockers and calcium channel blockers [112,115].

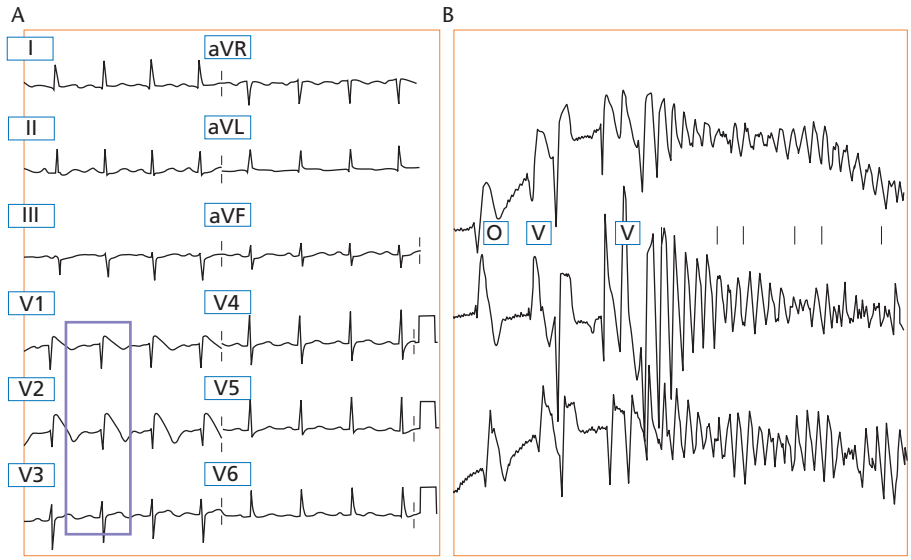


Figure 32.11 Twelve-lead ECG of a resuscitated patient with Brugada syndrome. The ECG is characterized by a prominent coved ST segment elevation displaying a J wave amplitude or ST segment amplitude elevation of ≥ 0.2 mV at its peak, followed by a negative T wave, with little or no isoelectric separation (A). Patients with such an ECG may develop syncope or sudden cardiac death due to fast polymorphic ventricular tachycardia (B: for details, see text).

Personal perspective

During the recent decades, our understanding of the clinical problem of ventricular tachycardia has markedly changed. At the beginning of my training in the early 1970s, ventricular tachycardia was a problem that seemed to represent a common entity. It took some time to understand that the mechanisms and the prognostic implications of sustained ventricular tachycardia often were markedly different, despite similar electrocardiographic appearances. Our understanding was greatly improved by experimental and clinical–electrophysiological studies for which the introduction of programmed electrical stimulation by the late Philippe Coumel and by Hein J.J. Wellens was of paramount importance. Experimental and clinical work, often done by the same persons or at least the same groups, have fertilized each other and have contributed to the rapid expansion of electrophysiological studies, drug assessment, techniques for localization of the underlying electrophysiological substrate, anti-tachycardia surgery, catheter ablation and, finally, as the now established therapy of first choice in most cases, the implantable cardioverter-defibrillator pioneered by Michel Mirowski. We had to learn that not everything is re-entry but that abnormal automaticity, especially after depolarization, plays an important role, too. Seminal observations, such as the one by Dessertenne, describing torsades de pointes as a specific type of ventricular tachycardia, were followed by decades of clinical observations and experimental and pharmacological studies, which finally led to the identification of the underlying molecular genetic background of long QT syndromes.

Nowadays, ventricular tachycardia, appearing under different aetiologies, can frequently be viewed as separate entities with different electrophysiological substrates, different arrhythmia mechanisms and often markedly different prognosis. The spectrum of therapy has changed with almost complete disappearance of anti-tachycardia surgery and, instead, dominance of the implantable cardioverter-defibrillator in patients at risk of sudden cardiac death. For me, the field of experimental and clinical research on ventricular tachycardia is one of the almost ideal examples of translational research 'from bench to bedside' and vice versa.

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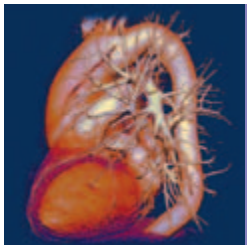


33 Sudden Cardiac Death and Resuscitation

Stefan H. Hohnloser, Alessandro Capucci and Peter J. Schwartz

Summary

Sudden cardiac death (SCD) continues to be a leading cause of death in Western countries, most often caused by ventricular tachyarrhythmias, such as ventricular tachycardia or fibrillation, in the setting of structural heart disease. Risk stratification for SCD remains a major challenge despite the development of new non-invasive risk assessment methods, i.e. baroreflex testing, assessment of microvolt T-wave alternans. A plethora of cardiovascular drugs such as beta-blockers, ACE inhibitors and statins have been shown to reduce the risk for SCD, whereas antiarrhythmic drugs, in general, have yielded disappointing results. The implantable defibrillator has been demonstrated to be an effective treatment modality not only for secondary, but also for primary prevention of SCD in selected patient populations. However, primarily owing to cost implications, this therapeutic modality still needs to be further refined, particularly by developing better ways of identifying those patients at highest risk for ventricular tachyarrhythmias. As only a minority of victims of cardiac arrest survive to receive secondary preventive therapy, recent years have seen strong efforts to improve cardiopulmonary resuscitation (CPR). Probably the most important aspect in this regard is represented by the development of the automatic external defibrillator, which has been shown in prospective trials to effectively improve the outcome of victims of cardiac arrest. Future research is necessary to further increase our knowledge concerning the pathophysiology of SCD and the identification of high-risk patients, and to develop therapeutic modalities which can be applied to large patient populations.

Sudden cardiac death

SCD remains one of the major challenges in cardiovascular medicine today. This chapter summarizes the present state of knowledge regarding the epidemiology, pathophysiology and therapeutic approaches to this important clinical syndrome. In large parts, this chapter is based on the recently published report of the Task Force on Sudden Cardiac Death of the European Society of Cardiology [1]. This comprehensive document provides in-depth review of all-important aspects of SCD and contemporary guidelines concerning risk stratification and therapeutic approaches.

Definition

SCD is defined as 'Natural death due to cardiac causes, heralded by abrupt loss of consciousness within one hour of the onset of acute symptoms; preexisting heart disease may have been known to be present but the time and mode of death are unexpected' [2]. The key concepts that are central in the definition of SCD are the non-traumatic nature of the event and the fact that SCD should be unexpected and instantaneous. In order to limit sudden death to heart diseases, the word 'cardiac' has been added to forge the term SCD. The classification of deaths that occur unwitnessed, such as being found dead in bed, has been a difficult issue to deal with. Most investigators have elected to classify such events as SCDs,

even although it is often impossible to define when the patient was last alive or for what duration he suffered any symptoms prior to death.

Definition of cardiac arrest

Cardiac arrest is defined as an abrupt cessation of cardiac pump function, which may be reversible by a prompt intervention but will lead to death in its absence [2]. The most common electrophysiological mechanisms of cardiac arrest leading to SCD are ventricular tachyarrhythmias [ventricular fibrillation (VF) or ventricular tachycardia (VT)], but primary non-tachyarrhythmic events are also common [3]. These include pulseless electrical activity (PEA), asystole or bradycardias that are severe enough to result in loss of adequate cerebral and other organ perfusion.

Epidemiology

Annual incidence rates of SCD ranging between 0.36 and 1.28 per 1000 inhabitants have been reported [4–6]. The incidence of SCD occurring out-of-hospital varies with age, gender and presence or absence of a history of cardiovascular disease. For instance, a population-based study undertaken in Maastricht [7] monitored all cases of out-of-hospital cardiac arrest occurring in individuals aged 20–75 years. An overall yearly incidence of SCD of 1 per 1000 was observed. Overall, 21% of all deaths were sudden and unexpected in men and 14.5% in women. Most deaths occurred at home (80%) and only about 15% in public places; 40% of deaths were unwitnessed.

In the USA, there is an estimate of 300 000 cases of SCD per year. Myerburg and colleagues [8] reviewed the issue of risk of SCD in population subgroups. The population incidence of SCD was just over 1 in 1000 per year, implying that any intervention applied to the general population to reduce the risk of SCD would therefore be given to 999 out of 1000 individuals who will not die suddenly in order to prevent one instance of SCD. Subgroups with progressively greater annual SCD risk comprise a progressively smaller proportion of the total numbers of SCDs in the population. As pointed out in the recent ESC guidelines on SCD [1], the logical conclusion of these figures is that the greatest opportunity to reduce the population burden of SCD lies in the reduction of coronary artery disease in the population at large.

Causes

The single most important cause of death in the adult population of the industrialized world is SCD due to coronary artery disease. Although estimates vary, approximately 75–80% of SCDs are due to this one underlying aetiology [8]. Accordingly, population studies in many industrialized countries have demonstrated that the risk factors for SCD are predominantly the same as those for atherosclerotic coronary disease, such as increasing age, male gender, family history of coronary artery disease, increased low-density lipoprotein cholesterol (LDL-C), hypertension, smoking and diabetes mellitus [9–11].

Idiopathic dilated cardiomyopathy (DCM), a chronic heart muscle disease characterized by left-ventricular dilatation, impairment of systolic function and congestive heart failure, is the second largest cause of SCD. DCM accounts for approximately 10–15% of all SCDs [3]. Despite a gradual decline in 5-year mortality from 70% in the early 1980s to approximately 20% in recent time, SCD accounts for at least 30% of all deaths in DCM.

In about 5–10% of cases, SCD occurs in the absence of coronary artery disease and congestive heart failure; Table 33.1 provides a summary of the clinical syndromes that constitute this proportion of SCD cases. Despite the relatively low absolute number of SCDs due to these clinical entities, identification of individuals at risk is of paramount importance, as many of the afflicted individuals are destined to die at young age.

Pathological anatomy

Most knowledge available on the pathology of SCD

Table 33.1 Cardiovascular diseases and SCD

Coronary artery disease
Dilated cardiomyopathy
Together, these two diseases account for > 90% of all SCDs
Other cardiomyopathies
Hypertrophic cardiomyopathy
Arrhythmogenic right ventricular cardiomyopathy
Primary 'electrical' disorders
Long QT syndrome
Brugada's syndrome
Catecholaminergic polymorphic VT
Wolff–Parkinson–White syndrome
Sinus node and AV node conduction disturbances
Mechanical cardiovascular diseases
Aortic stenosis
Mitral valve prolapse
Myocardial bridging
Anomalous origin of coronary arteries
Miscellaneous disorders
Myocarditis
Chest trauma
Drug-induced torsade de pointes and SCD
Trained heart
SCD in the normal heart

reflects the predominance of coronary artery disease as the most important underlying aetiology. Extensive coronary atherosclerosis is the primary anatomic hallmark of SCD in patients with coronary heart disease. More recently, the presence of plaque fissuring and/or erosion, platelet aggregation and acute thrombosis within the matrix of coronary atherosclerosis have been described in association with SCD [12,13]. This feature of coronary artery anatomy, superimposed upon chronic lesions, does not differ among the three primary expressions of acute coronary syndromes: namely SCD, acute myocardial infarction and unstable angina pectoris. Myocardial pathology reflects the presence and extent of chronic coronary atherosclerosis, which is characterized by myocardial scars as a result of healed myocardial infarction. The association between extensive coronary disease and left-ventricular hypertrophy is mainly a reflection of the presence of longstanding arterial hypertension as a risk factor in coronary heart disease patients. Both myocardial scars and left-ventricular hypertrophy are considered important factors in arrhythmogenesis during transient ischaemia.

Among the less prevalent causes of SCD, anatomy depends upon the underlying aetiology. In dilated cardiomyopathy, pathological findings are unspecific, characterized by interstitial fibrosis and myocyte degeneration. In hypertrophic cardiomyopathy, there are obstructive and non-obstructive forms with apical vs. concentric hypertrophy patterns.

In the small fraction of SCDs that is due to the rare genetically determined disorders such as the long QT syndrome or Brugada's syndrome, there may be no or only minimal myocardial pathology. A number of cases of SCD in infancy (often labelled as sudden infant death syndrome), and even of stillbirths, are actually due to the long QT syndrome [14–16].

Risk stratification

Risk stratification has always been important in medicine and in cardiology but its interest has taken a sudden twist in the last few years, largely as a consequence of the results of the major implantable cardioverter-defibrillator (ICD) trials (MADIT I, II, SCD-HeFT) [17–19]. Indeed, the emerging indication of considering for ICD implant all post-myocardial infarction patients with a left-ventricular ejection fraction (LVEF) below 31% is causing havoc in the national health services of European countries because of the almost unmanageable increase in medical costs that such a policy would produce if followed blindly. Accordingly, this section will focus primarily on this issue. For more general and traditional risk stratification, the reader is referred to major reviews [3,20,21].

As depressed LVEF represents the key factor in the current decision-making process, a sound approach appears to be that of considering which combination of cardiovascular markers carries the highest probability of identifying, within the population with a markedly depressed LVEF, a subgroup at relatively low risk in which the ICD would save very few lives and in which the number needed to treat would be excessively high.

Owing to space limitations, here we will examine only those markers that, besides LVEF and with data obtained in the thrombolytic era, have received a class IA recommendation by the Task Force Report of the ESC [1]. These markers are the demographic variables and heart rate variability or baroreflex sensitivity. As the increased risk with advancing age relates more to all-cause mortality than to sudden death, our analysis will predominantly focus on the autonomic parameters. Other markers that could contribute to better risk stratification, in association with low LVEF, include the following: ECG variables such as QRS duration, ventricular premature beats, nonsustained ventricular tachycardia, late potentials, microvolt T-wave alternans (MTWA) and electrophysiological testing [1]. For example, a recent publication from the MUSTT trial indicates that the presence of left bundle branch block or intraventricular conduction defect assessed from the surface in 1638 coronary patients with depressed left-ventricular function carried a 50% increased risk of total and arrhythmic mortality [22]. This prognostic information was independent of other risk markers such as LVEF or results of electrophysiological evaluation. In addition, ECG signs of left-ventricular hypertrophy were also a significant predictor of arrhythmic mortality (hazard ratio 1.35, 95% CI 1.08–1.69).

Similarly, the presence of subtle changes in the repolarization phase of the ECG, termed microvolt T-wave alternans, has been shown to be associated with an increased risk of SCD or other serious ventricular tachyarrhythmic events [23]. MTWA refers to the presence of changes in T-wave amplitude on an every-other-beat basis, which are not detectable on the surface ECG. Utilizing contemporary signal processing techniques, however, these changes can be detected upon an increase in heart rate. This heart rate increase is produced either by atrial pacing or, preferably, non-invasively by means of exercise testing. In Fig. 33.1, examples of a positive, negative and indeterminate MTWA testing are shown.

Several clinical studies have demonstrated that assessment of MTWA in patients with structural heart disease may yield prognostic information. Particularly in patients with ischaemic and non-ischaemic cardiomyopathy, assessment of MTWA has been shown to be useful for prediction of arrhythmic complications during the subsequent course of these patients. For instance, a recent

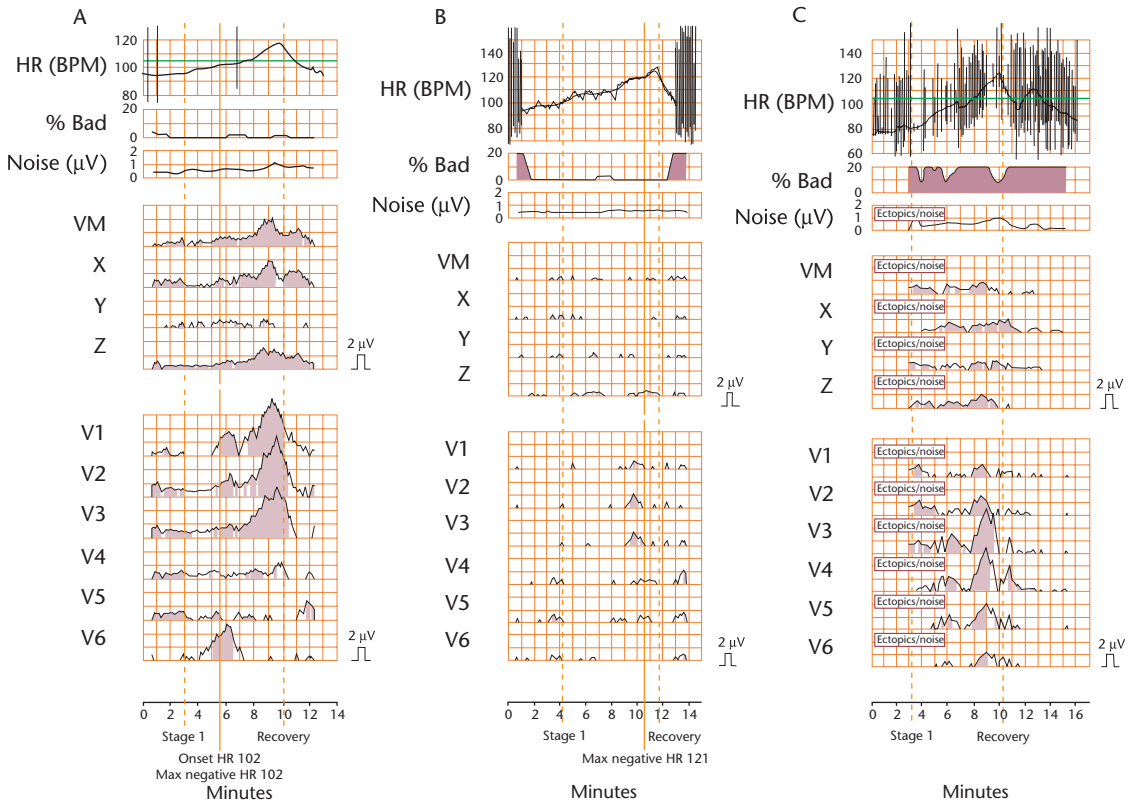


Figure 33.1 Examples of MTWA-positive, -negative and indeterminate test results. Shown from top to bottom: heart rate trend, percentage of bad beats, noise level, MTWA amplitudes in vector magnitude lead VM, orthogonal leads X, Y and Z and from ECG leads V1–V6. (A) Example of bicycle exercise-induced sustained MTWA (grey shaded area), which starts at an onset rate of 102 b.p.m. (B) Absence of MTWA during exercise-induced elevation of heart rate to a maximum rate of 121 b.p.m. (C) Indeterminate MTWA test due to the presence of frequent ectopic beats that are indicated by the vertical lines in the heart rate trend pictogram.

report on 129 patients with ischaemic cardiomyopathy found that over a 24 months' follow-up no major arrhythmic event or SCD occurred in those patients who tested negative; on the other hand, in MTWA-positive patients or in those with an indeterminate test result, the event rate was 15.6% (Fig. 33.2) [24]. These findings have recently been confirmed in a prospective study [25]. Bloomfield and co-workers [25] recently reported their findings in 177 MADIT II-like patients in whom they assessed MTWA and whom they followed for 2 years.

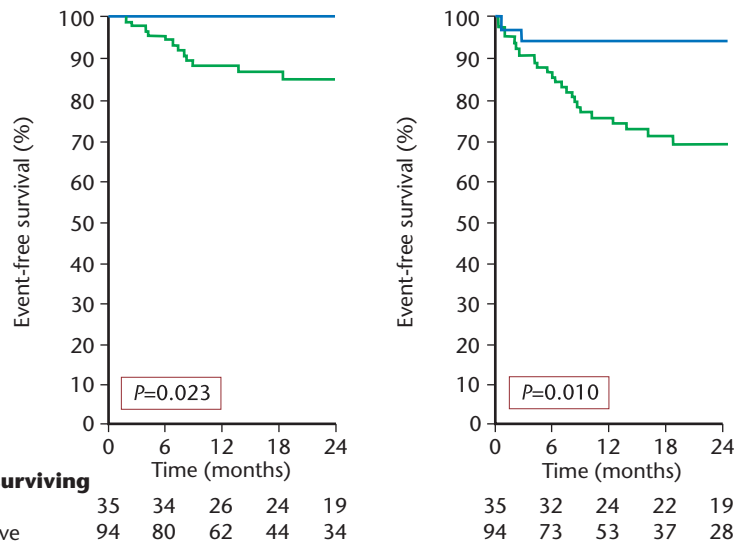


Figure 33.2 Event-free survival for sudden cardiac death or cardiac arrest (left) and for SCD, cardiac arrest and documented sustained ventricular tachycardia (right), according to outcome of MTWA assessment [24]. Blue, MTWA negative; green, MTWA not negative.

They found that a positive MTWA was associated with a higher mortality rate than that associated with a prolonged QRS duration of > 120 ms. In fact, the actuarial mortality was 17.8% in patients with a positive MTWA compared with only 3.8% in those patients who tested negative for MTWA (hazard ratio 4.8, 95% CI 1.1–20.7, $P = 0.02$). Of particular note is the high negative predictive value of between 96% and 100%, which MTWA carried in this and in all other studies. This indicates that analysis of MTWA may be particularly helpful to avoid unnecessary ICD implantations in patients with depressed left-ventricular function who test negative for MTWA.

Both heart rate variability (HRV) and baroreflex sensitivity (BRS) have been assessed prospectively, with cut-off values determined *a priori*, together with LVEF in a population of 1284 post-MI patients. This was done in the ATRAMI study [26,27]. Also, the predictive value of HRV was assessed using the dataset from the European Myocardial Infarction Amiodarone Trial (EMIAT) [28]. Finally, HRV was prospectively used in the randomized clinical trial ALIVE to identify a subgroup at higher risk for sudden death, in which to assess the potential value of the antiarrhythmic drug azimilide [29]. We will briefly review the main findings of these studies, prior to examining how the use of autonomic markers may impact on the use of the ICD.

In ATRAMI, both HRV and BRS—when depressed, thus indicating reduced vagal tone and reflexes [30]—were associated with an increased risk for cardiac mortality and arrhythmic deaths [26,27]. When examined in conjunction with depressed LVEF, it was especially BRS that contributed in a novel way to risk stratification. Specifically, within the patients with LVEF of < 35%, those with preserved BRS had a significantly better 2-year survival than patients with depressed BRS (7% vs. 18%). This was even more evident for major arrhythmic events (3% vs. 16%) (Fig. 33.3).

The Holter data obtained in 1216 post-myocardial infarction patients enrolled in EMIAT represented the first evidence of the 'golden group' postulated by the Sicilian Gambit as the ideal target for clinical trials on sudden death [31], namely a subgroup—within a population at risk—in which risk was markedly higher, thus offering better chances to demonstrate efficacy of any given intervention of between 15% and 35%. Indeed, it was observed that within patients with an LVEF of < 30%, those who also had a depressed HRV had a much higher mortality in the placebo group (14.9% vs. 8.4%) and the best protection by amiodarone, as shown by a reduction in mortality of 56% vs. 33% [31]. This last observation was rapidly translated in the design of clinical trials. This happened with the AzimiLide Post Infarct surVival Evaluation (ALIVE) study, a trial aiming at assessing the efficacy of the antiarrhythmic drug azimilide in 3717 patients [29].

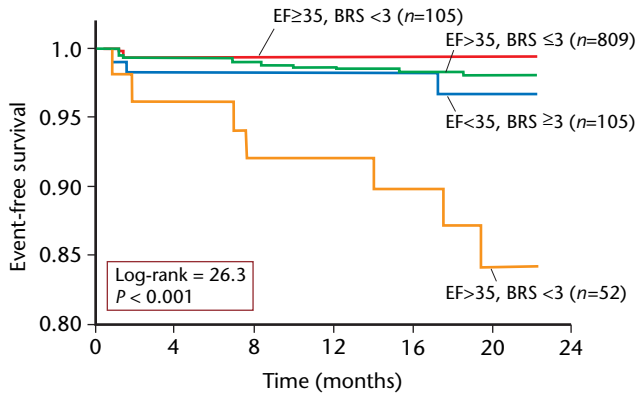


Figure 33.3 Risk prediction for major arrhythmic events according to determination of LVEF and assessment of BRS.

A unique feature of this study was that although the HRV measurement results were not part of the eligibility requirements, they were used to prospectively stratify the at-risk trial population. Patients with baseline HRV = 20 U were assigned to the high-risk cohort, whereas patients with HRV > 20 U were considered as 'low risk'. This allowed different alpha values for the statistical analysis [29]. The validity of the hypothesis was confirmed by the finding that in the placebo group the 1-year mortality rate was significantly higher in the 'high' group than in the 'low'-risk group (15% vs. 9.5%, $P = 0.0005$). This result shows how risk stratification based upon a combination of LVEF and autonomic markers, in this case HRV, can usefully contribute to the often daunting problem of combining the feasibility of a clinical trial (in terms of the necessary number of patients to be enrolled), with a high probability of attaining statistical significance.

The evidence that autonomic markers could differentiate groups at markedly different risk for cardiac and arrhythmic death within the population of post-myocardial infarction patients with depressed LVEF has raised the question of whether this information might be useful for the best selection of the patients for whom an ICD should be recommended. The first approach to this important question has been recently provided by an analysis of the ATRAMI data, limited to the small group ($n = 70$) of patients with an LVEF of < 30% [31]. The hypothesis was tested that within this 'high-risk' group, the presence of a 'well preserved autonomic balance' (BRS > 6 ms/mmHg, standard deviation of normal-to-normal RR intervals (SDNN) > 105 ms, both values corresponding to the median for the entire population of 1284 patients) would have identified a group with very few fatal events. During a mean follow-up of 24 months there were 11 cardiac deaths (16%). None of them occurred in the patients with well-preserved HRV and only one occurred in the patients with well-preserved BRS (7%) compared with eight (40%) in the group with depressed BRS (< 3 ms/mmHg).

It follows that by using the autonomic markers it would be possible to reduce by 20% the number of ICDs to be implanted in MADIT-like patients [32].

The latter analysis, certainly to be repeated in larger patient populations, well summarizes our concepts for risk stratification. This is because it shows how one can move from pathophysiology [33] to clinical trials [26,29] and use a rational combination of parameters, such as LVEF and autonomic markers, to improve risk stratification with the very pragmatic and useful consequence of decreasing costs for society without reducing the number of individuals protected.

Prevention

As SCD has a multifactorial aetiology, a variety of therapeutic targets may be considered [1]. For instance in the case of coronary artery disease, the most prevalent underlying cause of SCD, such therapeutic interventions may range from limitation of infarct size and prevention of new ischaemic events, resulting from progression of disease and plaque instability, to modulation of neuroendocrine activation, and antiarrhythmic and antifibrillatory actions. All of these treatment modalities are designed to either prevent or terminate ventricular tachyarrhythmias.

The terms 'primary' and 'secondary' prophylaxis of SCD usually refer to whether or not a patient has a history of sustained hypotensive ventricular tachycardia or aborted SCD due to ventricular fibrillation. In patients without prior sustained ventricular tachyarrhythmias who are nevertheless deemed to be at high risk for SCD, therapy that is given to prevent such arrhythmias is usually described as 'primary' prophylaxis. Similar prophylactic therapy recommended for patients who have already suffered a cardiac arrest or sustained VT is termed 'secondary' prophylaxis.

Primary prophylaxis

There are three different therapeutic modalities by which primary prevention of SCD in patients with structural heart disease is pursued: therapy using drugs that have no electrophysiological properties, therapy using drugs with distinct electrophysiological properties and use of implantable cardioverter-defibrillators (ICDs).

According to the recently published report of the Task Force on Sudden Cardiac Death of the European Society of Cardiology, there are at least three different drug classes that do not have electrophysiological properties but have been shown to reduce not only all-cause mortality, but also SCD. Treatment with angiotensin-converting enzyme (ACE) inhibitors in patients after myocardial infarction and/or congestive heart failure has resulted in a reduction in SCD in the range of 30% to 54%, which was statistically significant in some studies [34,35]. The second class of drugs without electrophysiological effects which have been shown to reduce SCD are aldosterone receptor blockers. The RALES study [36] has demonstrated a 30% reduction in the relative risk of SCD. The mechanism of this protection is not entirely clear but may include prevention of hypokalaemia and regression of aldosterone-related interstitial fibrosis. More recently, these results were substantiated in a much larger study comprising 6632 survivors of acute myocardial infarction with left-ventricular dysfunction [37]. In this large-scale randomized trial, the aldosterone blocker eplerenone reduced all-cause mortality, which was the primary endpoint of the trial, significantly (relative risk 0.85, 95% CI 0.75–0.96, $P = 0.008$). Mortality from SCD was also significantly reduced by eplerenone (relative risk 0.79, 95% CI 0.64–0.97, $P = 0.03$). Finally, there is evidence from several randomized controlled clinical trials that lipid-lowering agents may not only reduce overall mortality but also SCD mortality in coronary patients. More recently, supplemental n-3 polyunsaturated fatty acids were reported to be effective in improving the clinical outcome of patients by reducing SCD [38].

With respect to drugs with distinct electrophysiological properties, there is ample evidence that treatment with beta-blockers is associated with an improved outcome in several patient groups. A recent analysis of 31 beta-blocker trials showed that only 13 trials reported data on reduction of SCD [39,40]. These 13 trials indicated a reduction in SCD from 51% in the control patients to 43% in patients receiving antiadrenergic therapy. The greatest beneficial effect in terms of mortality reduction was shown in patients with congestive heart failure or depressed left-ventricular function. Importantly, concomitant therapy with important other categories of drugs such as ACE inhibitors, aldosterone receptor blockers or aspirin does not appear to limit the independent benefit on clinical outcome provided by beta-blockers, as suggested by the evidence of residual risk reductions of between 30% and 50% [41]. Accordingly, beta-blocking drugs are to be regarded as a cornerstone in the prophylactic treatment of survivors of myocardial infarction and in patients suffering from congestive heart failure.

In recent years, consistent evidence has accumulated that therapy with sodium channel blockers has no beneficial effects in patients after myocardial infarction (Table 33.2). In fact, there is strong evidence that these drugs are potentially harmful when given in the early post-myocardial infarction period. They should also not be administered for suppression of symptomatic ventricular or supraventricular arrhythmias in patients with coronary artery disease and/or congestive heart failure.

Amiodarone, which is predominantly a class III antiarrhythmic compound but also possesses antiadrenergic,

Table 33.2 Primary prevention antiarrhythmic trials: relative risk for all-cause mortality

Antiarrhythmic compound	No. of patients	Relative risk of death (95% CI)	*P*-value
Sodium channel blockers post-myocardial infarction			
Class IA	6582	1.19 (0.99–1.44)	0.07
Class IB	14 033	1.06 (0.89–1.26)	0.50
Class IC	2538	1.31 (0.95–1.79)	0.10
Flecainide and encainide	1455	**3.6 (1.7–8.5)**	**0.0006**
Beta-blocker			
During myocardial infarction	28 970	0.87 (0.77–0.98)	0.02
After myocardial infarction	24 298	0.77 (0.70–0.84)	< 0.001
Carvedilol	1959	0.77 (0.60–0.98)	0.03
		0.74 (0.51–1.06)	**0.098**
Beta-blocker in CHF			
Carvedilol	1094	0.44 (0.28–0.69)	< 0.001
		0.51 (0.28–0.92)	NA
Bisoprolol	2647	0.66 (0.54–0.81)	< 0.0001
		0.56 (0.39–0.80)	**< 0.01**
Metoprolol	3991	0.66 (0.53–0.81)	0.0009
		0.59 (0.45–0.78)	**0.0002**
Class III antiarrhythmic drugs			
Amiodarone	6500	0.87 (0.78–0.99)	0.03
		0.71 (0.59–0.85)	**0.0003**
D-Sotalol	3121	1.65 (1.15–2.36)	< 0.006
		1.77 (1.15–2.74)	**0.008**
Dofetilide	1518	0.95 (0.81–1.11)	> 0.05

Figures relating to sudden death appear in bold text.
NA, not applicable.
Adapted from ref. [1].

sodium-channel and calcium-channel blocking properties, has been subjected to a number of randomized controlled trials evaluating the primary preventive efficacy of this drug in various patient subsets. Although early studies showed a reduction in SCD in patients receiving amiodarone [28], more recent trials demonstrated that amiodarone has little or no effect on all-cause mortality. A meta-analysis comprising data from 13 randomized controlled trials in 6553 patients with various forms of heart disease reported a small albeit significant reduction in all-cause mortality in favour of amiodarone over placebo (hazard ratio 0.87; 95% CI 0.78–0.99, $P = 0.03$) (Fig. 33.4) [42]. Recently, however, a definitive study of amiodarone vs. placebo reported its results in 2521 patients with reduced LV function [19]. Release of the results of the SCD-HeFT trial in which patients with

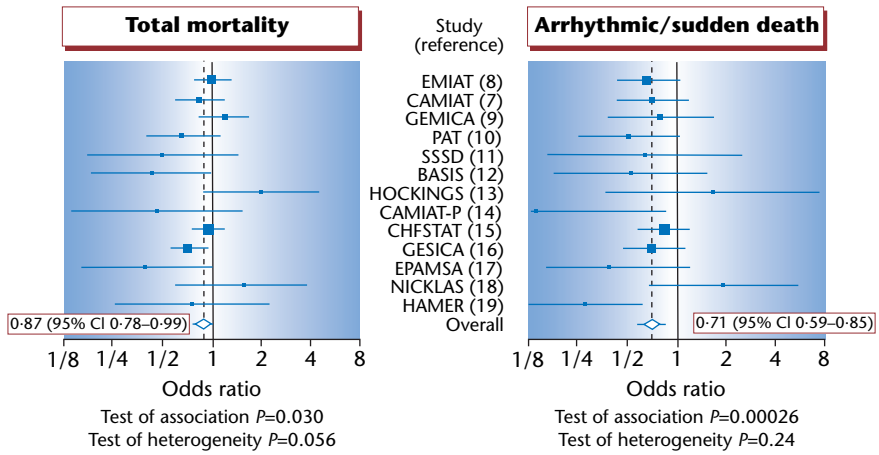


Figure 33.4 Meta-analysis of 13 studies comparing the effects of amiodarone to placebo on all-cause mortality (left) and arrhythmic mortality (right). Overall mortality showed a 13% decrease for patients who received amiodarone compared with control subjects [42].

Figure 33.5 Example of a three-chamber implantable cardioverter-defibrillator (ICD) capable of providing cardiac resynchronization therapy in addition to anti-bradycardia and anti-tachycardia stimulation, cardioversion and defibrillation (size, 36 cc; weight, 73 g; maximal high energy output, 30 J).

congestive heart failure were randomized to best medical therapy alone or in addition to amiodarone or the ICD demonstrated that amiodarone-treated patients had the same mortality compared to patients who received double-blind placebo therapy [19]. SCD-HeFT is by far the largest trial examining the preventive efficacy of amiodarone; its results demonstrate that there is no indication for amiodarone administration for primary prevention of sudden death in patients with congestive heart failure [19]. However, the neutral effect on mortality and the good cardiovascular safety profile indicate that amiodarone can be safely administered to treat non-sustained ventricular arrhythmias or atrial fibrillation in patients after myocardial infarction or congestive heart failure.

Over the last two to three decades, the introduction of the ICD has revolutionized the world of electrophysiology (Figs 33.5, 33.6 and 33.7). Originally designed to prevent SCD in patients with a history of life-threatening ventricular arrhythmias, more recently the impact of device therapy in primary prevention of SCD has been evaluated in patients deemed to be at high risk of serious ventricular tachyarrhythmias (Table 33.3). The MADIT I [17] and the MUSTT [43] trial used invasive electrophysiological testing to identify coronary patients at risk for SCD. In both trials, the ICD was clearly superior to conventional antiarrhythmic therapy (mostly amiodarone) in reducing not only sudden death but more importantly all-cause mortality. A similar effect was demonstrated in MADIT II, a trial which randomized coronary patients only on the basis of a reduced left-ventricular function (LVEF < 31%) without using other risk stratifiers [18] (Fig. 33.8). More recently, the DEFINITE trial showed in patients with non-ischaemic cardiomyopathy a strong trend towards a reduction in all-cause mortality in patients randomized to receive the ICD compared with medically treated patients [44]. In a subset of patients with NYHA class III heart failure, the ICD caused a significant reduction in all-cause mortality. Desai and co-workers [45] performed a meta-analysis of five randomized trials that evaluated the benefits of prophylactic ICD therapy in 1854 patients with non-ischaemic cardiomyopathy. There was a 39% reduction in all-cause mortality in patients fitted with an ICD (hazard ratio 0.61, 95% CI 0.55–0.87, $P = 0.002$) (Fig. 33.9). The largest of these trials, the SCD-HeFT trial [19], randomized patients with ischaemic and non-ischaemic cardiomyopathy and a LVEF < 36% to placebo, amiodarone or device therapy on top of optimal medical therapy. A total of 2521 patients were included. A significant reduction in all-cause mortality (RR 0.77, 95% CI 0.62–0.96; $P = 0.007$) was observed in patients randomized to ICD therapy. The beneficial effect of device therapy was similar regardless of the presence of ischaemic or non-ischaemic cardiomyopathy.

The majority of ICD trials reporting benefit of ICD therapy is contrasted by two trials that could not demonstrate a survival advantage of ICD-treated patients compared with control subjects. The CABG-Patch trial used the presence of late potentials on the signal-averaged ECG and reduced LVEF to randomize patients who were scheduled for elective coronary artery bypass grafting [46]. The study was terminated prematurely because an interim analysis showed no benefit of device therapy. More recently, the DINAMIT trial results were published [47]. In this trial, patients who had survived a recent myocardial infarction (6–40 days enrolment window) with a LVEF of < 36% and signs of autonomic imbalance were randomized to best medical therapy with or without ICD implantation. A total of 674 patients were followed for a mean of 2.5 years. Whereas the ICD was associated with a significant reduction in arrhythmic mortality, there was no effect on all-cause mortality (Fig. 33.10). This neutral effect was due to an unexpected increase in non-arrhythmic mortality in patients randomized to

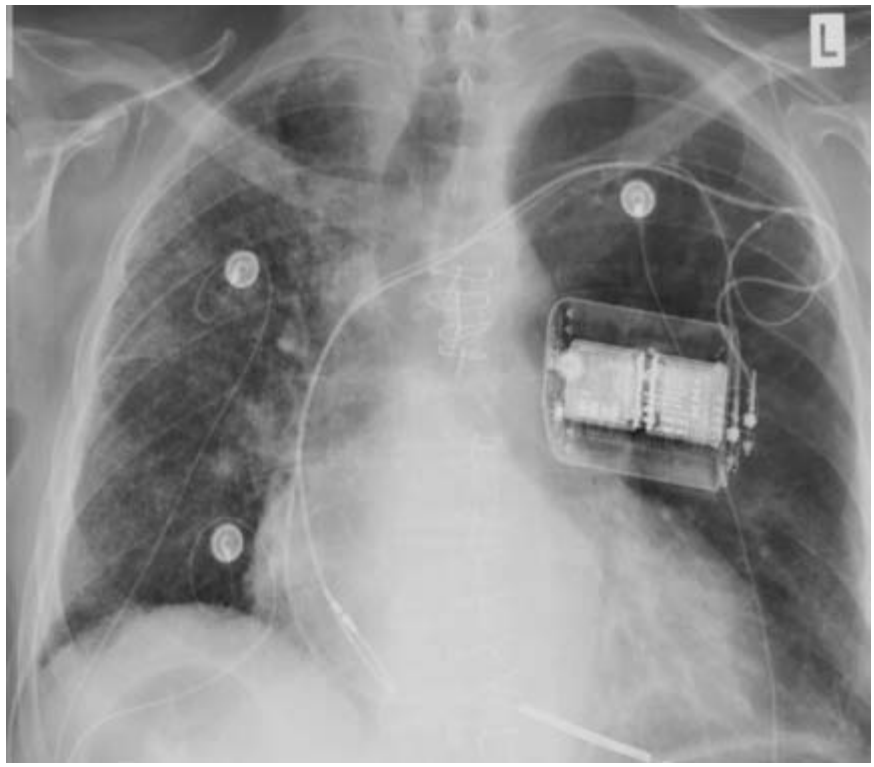


Figure 33.6 Example of a dual-chamber ICD implanted in a patient with ischaemic cardiomyopathy and prior coronary artery bypass grafting.

Counter

Last test: 24 Sept 2004 10:26;08

	Since last test	Since last clearance	Since implantation
Episodes	01, Apr 2004	09, Oct 2002	
VF	0	3	3
FVT	0	0	0
VT	1	3	3
SVT/NST	3	582	582
% Stimulation			
Sensed	98%	99%	99%
Paced	1%	0%	0%
Additional counters			
Single	313667	430195	430195
VES salvos	7958	17542	17542
V. freq stabilizing stimuli	0	0	0
Salvos of V freq. stab. stimuli	0	0	0

Episode report

Last test: 24 Sep 2004 10:26:08

VT/VF-episodes

ID	Date/time	Art	V. cycle	Last Rx	Success	Duration
6	27 Aug 23:51:09	VT	300 ms	VT Rx 1	Yes	27 Sec

SVT/NST-episodes

ID	Date/time	V. cycle	Duration	Reason
582	06 Aug 20:41:58	360 ms	5 strikes	Non-sustained
581	12 Jul 21:38:37	340 ms	5 strikes	Non-sustained
580	28 Jun 16:55:09	370 ms	7 strikes	Non-sustained

Figure 33.7 Read-out of the device memory including number and timing of device-delivered therapy for VT and VF .

receive the ICD. The reason for this surprising observation is not clear at present. Importantly, however, DINAMIT contrasts all other primary preventive ICD trials in coronary patients by the fact that it included patients early after a myocardial infarction, whereas patients entering the other trials were for the most part years after their last infarct. It appears therefore that survival benefit of the ICD in infarct survivors accrues after a considerable time having elapsed from the most recent myocardial infarction, presumably 6 months or perhaps more. Importantly, this notion is supported by evidence stemming from the MADIT II trial. Wilber and colleagues [48] examined the relationship between ICD-associated survival benefit and the time interval from the most recent myocardial infarction to study enrolment in MADIT II. They found that patients who entered the trial within 18 months of their last infarction had no benefit from device therapy as opposed to those who entered the study years after their last myocardial infarction.

In summary, therefore, there is a sound database on the efficacy of ICD therapy for primary prevention of SCD in various patient populations. This database can

Table 33.3 Primary prevention ICD trials: relative risk for all-cause mortality in ICD patients vs. control subjects

Trial	CAD/ NICM	Entry criteria	Control group	Mean LVEF	Time post AMI	Mean follow-up	No. of patients	RR (95% CI)	*P*-value
MADIT I	CAD	LVEF ≤ 35%, nsVT, EP inducibility	80% amiodarone	26%	> 6 months in 75% of patients	27 months	196	0.46 (0.26–0.92)	0.009
MADIT II	CAD	LVEF ≤ 30%	No antiarrhythmic therapy	23%	> 6 months in 88% of patients	20 months	1232	0.69 (0.51–0.93)	0.016
MUSTT	CAD	LVEF ≤ 40%, nsVT, EP inducibility	No antiarrhythmic therapy	30%	> 1 year in 60% of patients	39 months	704	0.73 (0.53–0.99)	0.04
CABG-Patch	CAD	LVEF ≤ 35%, positive SAECG	No antiarrhythmic therapy	27%	NA	32 ± 16 months	900	1.07 (0.81–1.42)	0.64
DEFINITE	NICM	LVEF ≤ 35%, VPBs and/or nsVT	No antiarrhythmic therapy	21%	NA	29 ± 14 months	458	0.65 (0.40–1.06)	0.08
SCD-HeFT	CAD/ NICM	LVEF ≤ 35%, history of CHF	Amiodarone or placebo*	25%	4.3 years	NA	2521	0.77 (0.62–0.96)	0.007
DINAMIT	CAD	AMI 6–40 days, LVEF ≤ 35%, depressed HRV	No antiarrhythmic therapy	28%	18 ± 10 days	30 ± 13 months	674	1.08 (0.76–1.55)	0.66

*Double-blind assignment.
AMI, acute myocardial infarction; NA, not applicable; NICM, non-ischaemic cardiomyopathy; nsVT, non-sustained VT; RR, relative risk ICD vs. Control; VPB, ventricular premature beat; 95% CI, 95% confidence interval.

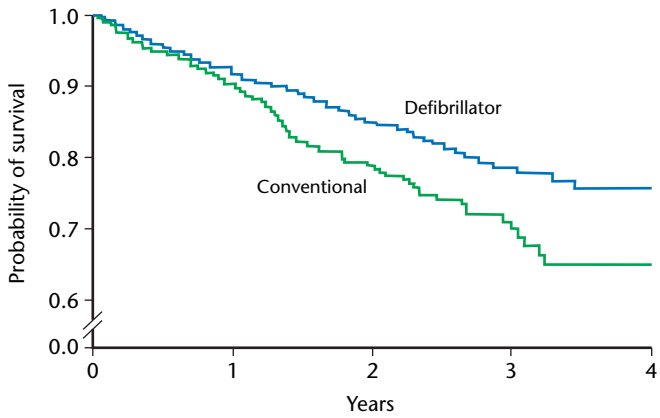


Figure 33.8 Probability of survival in patients with coronary disease and reduced left-ventricular function who received a prophylactic ICD compared with patients treated conventionally [18].

and must be used to tailor ICD therapy to those patient groups in which the benefit is greatest. As all positive trials reported relatively small absolute reductions in all-cause mortality, it is of paramount importance to tailor device therapy to individuals who are most likely to receive the largest benefit. Even then, the cost associated with device therapy is extraordinary and all societies will face enormous problems in translating trial results to everyday clinical practice. The most reasonable approach to reduce costs without affecting benefit lies in the improvement in risk stratification, with the goal of reducing the number of 'false-positives'.

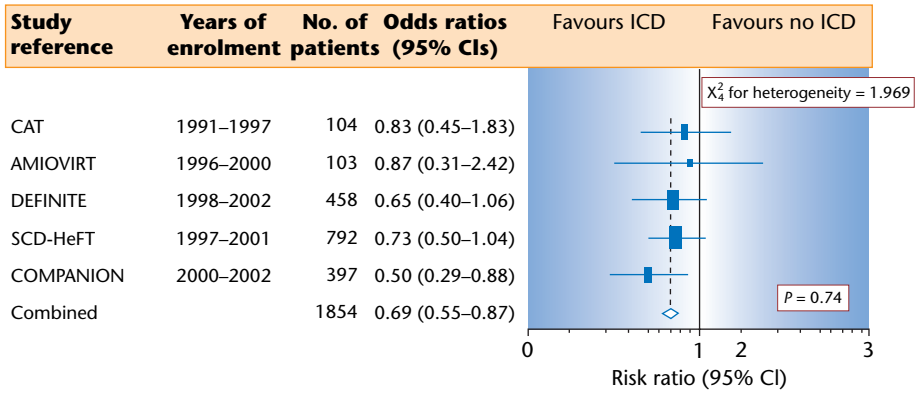
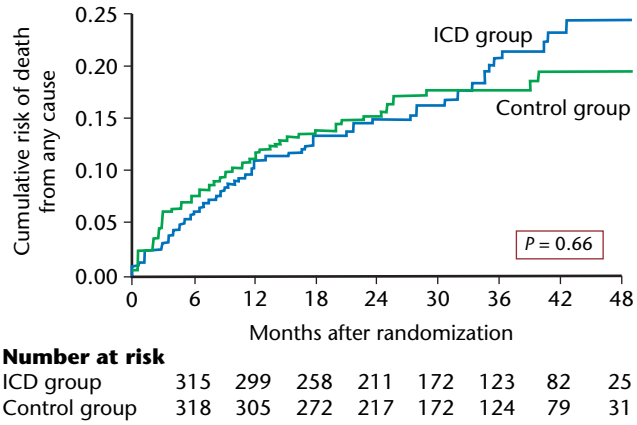


Figure 33.9 Overall mortality among patients with non-ischaemic cardiomyopathy randomized to ICD (or CRT-D) vs. medical therapy in five primary prevention trials [45].



Number at risk

ICD group	315	299	258	211	172	123	82	25
Control group	318	305	272	217	172	124	79	31

Figure 33.10 Cumulative risk of death from any cause according to treatment assignment in the DINAMIT trial [47].

Secondary prophylaxis

Patients with documented sustained ventricular tachycardia or resuscitated cardiac arrest have been traditionally treated with drugs with electrophysiological properties to prevent recurrent ventricular tachyarrhythmic events. With the advent of the ICD, device therapy has become the cornerstone of treatment of these patients (Figs 33.11 and 33.12). Three randomized clinical trials have compared the efficacy of the device to the efficacy of amiodarone in prolonging life in such high-risk patients [49–51]. The largest of these three trials, the AVID study, randomized 1016 patients to receive the ICD or medical therapy, which was amiodarone in the vast majority of subjects [49]. The trial reported a significant risk reduction for all-cause mortality of 31% in favour of the ICD.

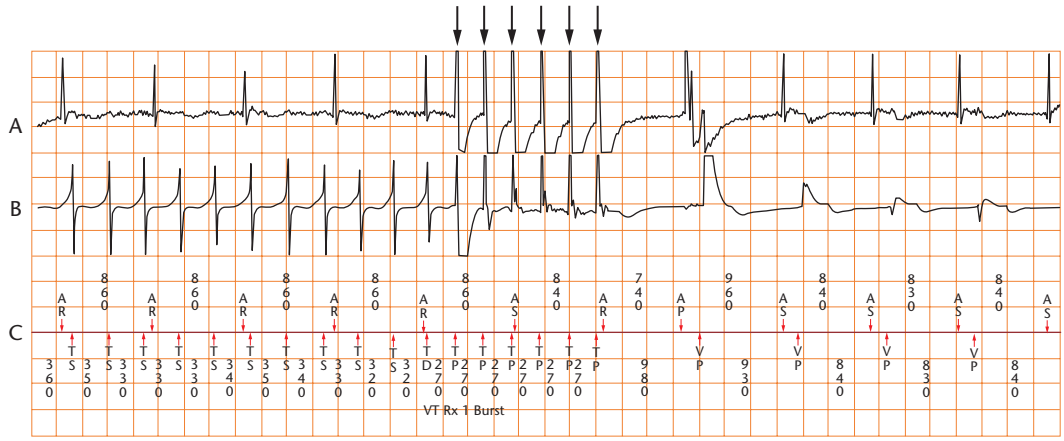


Figure 33.11 Example of an electrogram read-out of a dual-chamber ICD. (A) Atrial electrograms; (B) ventricular electrograms; (C) marker annotations. Note the VT on the left-hand side of the tracing (AV dissociation), which is terminated by anti-tachycardia pacing (arrows).

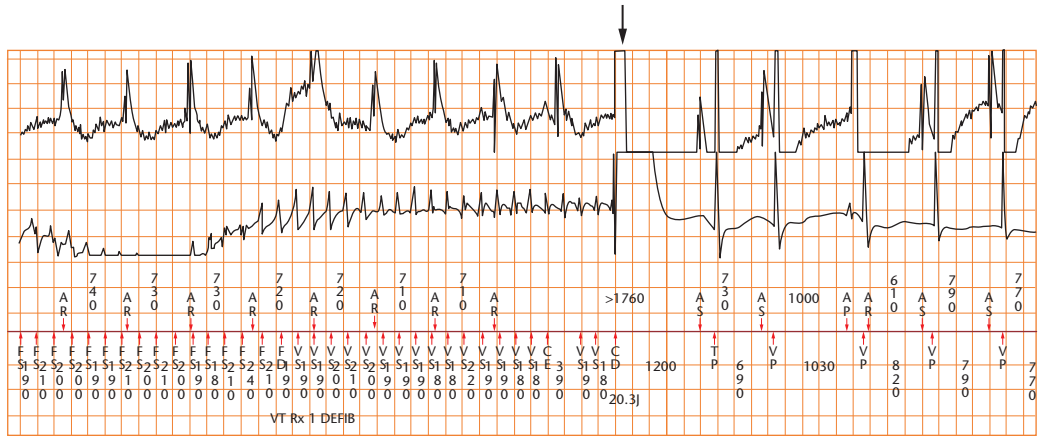


Figure 33.12 Example of an electrogram readout of a dual-chamber ICD (settings identical to Fig. 33.4). Note the presence of VF on the left-hand side of the tracing which is terminated by the ICD delivering a high-voltage shock (arrow).

Although the two other trials did not achieve statistically significant results when analysed separately, a recent meta-analysis of all trials convincingly demonstrated the benefit of ICD therapy [52]. The hazard ratio for all-cause mortality was 0.72 (95% CI 0.60–0.87, $P = 0.0006$) for the ICD over amiodarone therapy (Fig. 33.13). Particularly in patients with an ejection fraction of < 36%, the ICD yielded a significant survival benefit. In individuals with a LVEF > 35%, there was no significant difference in survival between patients treated with amiodarone or the ICD [52].

A recent study, however, compared the long-term outcome of 120 patients who were enrolled in the Canadian defibrillator trial and who were followed for 11 years [53]. One-half of these patients had been implanted with the device; the other half had been randomized to receive amiodarone and were kept on the drug after the official end of the CIDS trial. After a mean follow-up of 5.6 years, 28 deaths occurred in the amiodarone group (47%) compared with 16 deaths (23%) in the ICD group ($P = 0.021$). Over the observation time, 49 patients (82%) developed side-effects related to amiodarone, which required drug discontinuation. Although this study has limitations owing to the small patient population, it suggests that the strategy of using amiodarone as first-line monotherapy for secondary prevention of SCD results in a substantial arrhythmogenic risk and a high incidence of side-effects necessitating drug discontinuation. In this small study, the benefit from the ICD in reducing all-cause mortality extends to more than 10 years of follow-up. This may be particularly relevant to patients after a survived cardiac arrest with only moderately impaired LV function in whom benefit of ICD therapy may only accrue after a prolonged time period.

Among apparently non-traditional therapies, there is a special place, due to the inferences on mechanisms, for left cardiac sympathetic denervation (LCSD). LCSD was actually introduced in 1916 for the management of angina pectoris and was widely used until the early 1960s, when it was superseded by beta-blockers [54]. The antifibrillatory properties of LCSD, along with its lifelong effects (pre-ganglionic denervation prevents re-innervation and

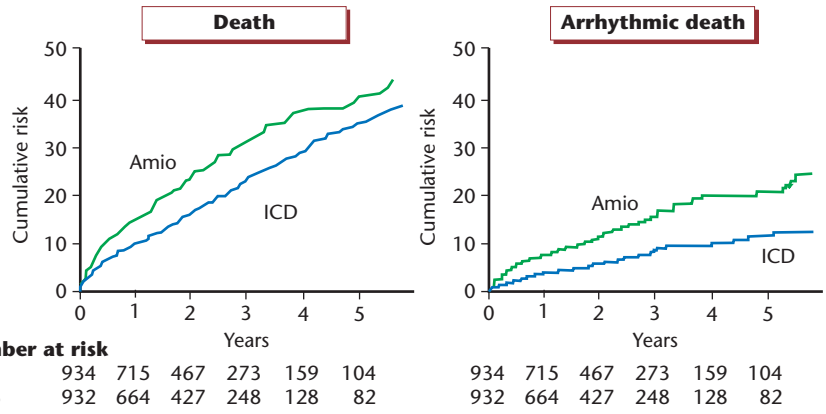


Figure 33.13 Cumulative risk for all-cause mortality (left) and arrhythmic mortality (right) for ICD vs. amiodarone therapy in the three randomized controlled secondary prevention trials [52].

does not produce post-denervation supersensitivity) are of interest in specific groups of patients. Its overall efficacy has been demonstrated in a randomized clinical trial in post-myocardial infarction patients at high risk for SCD, in which it reduced the incidence of sudden death from 22% in the placebo group to 3.5% during a 21-month follow-up; beta-blockers provided a similar reduction [55]. The rationale for LCSD has been strengthened by the recent evidence that myocardial infarction leads to nerve sprouting from the stellate ganglia and that this effect is quantitatively dominant on the left side, with significant arrhythmogenic effects [56]. There is one group of patients for whom LCSD is an integral part of the therapeutic strategy, namely patients affected by long QT syndrome, who continue to have syncope despite beta-blockers. A recent worldwide analysis has shown that these patients have a reduction of 90% in the incidence of cardiac events, with a 3% risk of sudden death at 5 years [57]. Long-term survival is especially good when within 6 months from surgery QTc shortens below 500 ms. A unique aspect of LCSD is the fact that it can effectively complement other therapies. The best example is when it is used in patients with frequent ICD shocks: whereas the ICD ensures survival, LCSD effectively prevents or minimizes the risk of arrhythmias requiring shocks [57].

Resuscitation

Out-of-hospital resuscitation

Survival of cardiac arrest outside the hospital continues to be very poor. In general, survival is critically depending on the characteristics of the cardiac arrest (i.e. cardiac aetiology or not, ventricular fibrillation vs. pulseless electrical activity, witnessed or not, etc.) and on the patient's condition prior to cardiac arrest. Before the introduction of the automated external defibrillator (AED), only approximately 15% of all out-of-hospital cardiac arrest victims had restoration of spontaneous circulation and reached the hospital alive. However, only one-half of these survived to discharge (= 5–7%). Survival rates were somewhat better if only patients with documented ventricular fibrillation as the cause of their cardiac arrest are considered. In areas with early defibrillation programmes in place, more patients are found in ventricular fibrillation owing to shorter arrival times or use of the automated defibrillator; in such areas, higher hospital discharge rates reaching 20–25% have been reported [58,59].

Most instances of cardiac arrest occur at home, in men aged > 50 years and during daytime. As recently pointed out, this profile of the cardiac arrest victim is useful to identify the profile of the potential bystander of such an event. These persons constitute the primary target group for teaching CPR to laypersons.

The International 2000 Guidelines for Basic Life Support [60] are basically a step moving towards simplicity and thus making public CPR education more feasible. The main principles are shown in Fig. 33.14. Basic life support has to be followed by advanced cardiac life support (ACLS). Such guidelines have been established by the American Heart Association and other societies [60–64] and are regularly updated. Figure 33.15 depicts the current algorithm for ACLS.

Electrical means of resuscitation

Cardiac arrest is most often due to ventricular fibrillation that does not end spontaneously in the human heart. When ventricular fibrillation continues for more than 3–4 min, there is irreversible damage to the central nervous

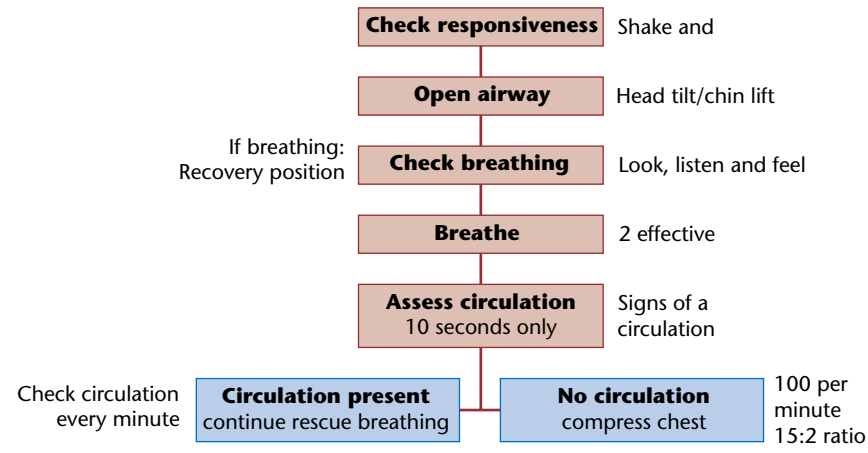


Figure 33.14 Main principles of basic life support according to the International 2000 Guidelines.

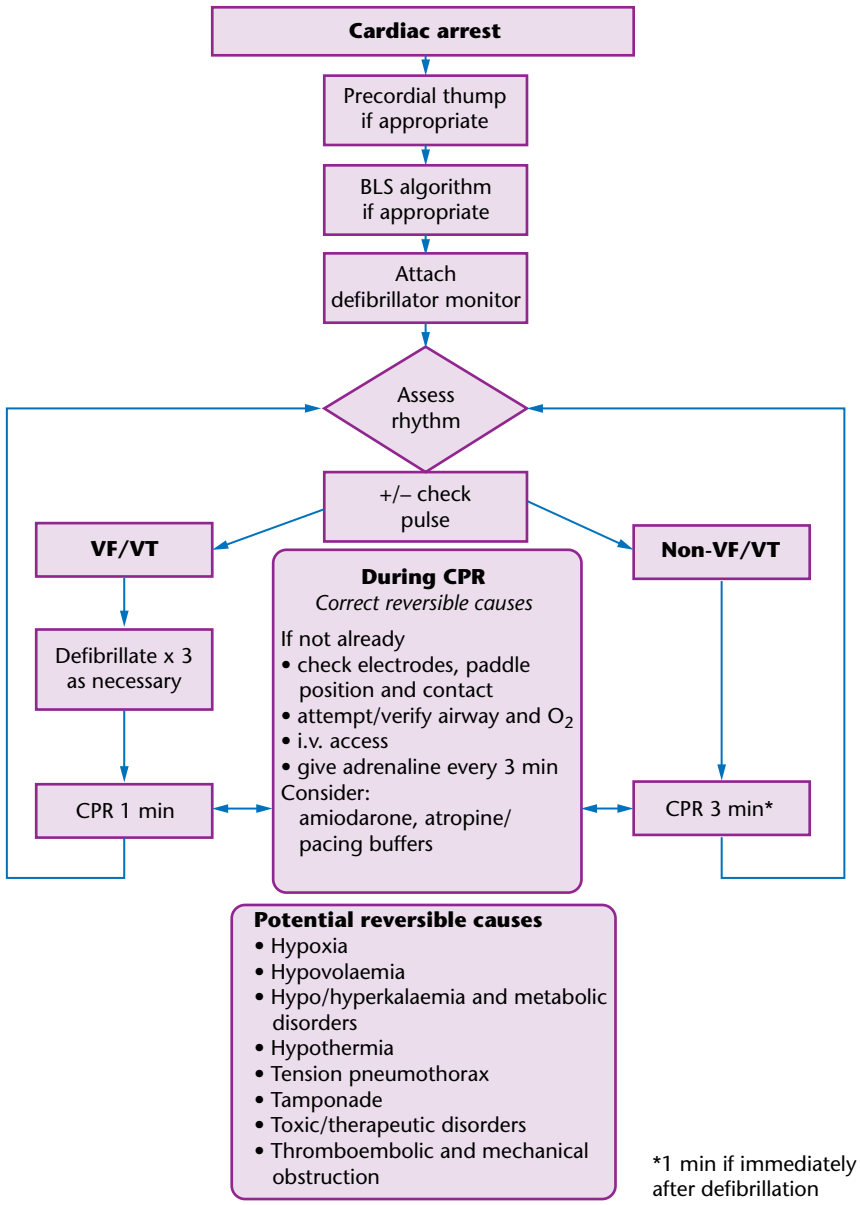


Figure 33.15 Main principles of advanced life support according to the International 2000 Guidelines.

system and other organ systems, which affects survival even in the case of successful defibrillation. Accordingly, the most important therapeutic means to prevent death from cardiac arrest is to accomplish successful and early termination of ventricular fibrillation by prompt defibrillation [65–67]. It has been estimated that for each minute of delay of defibrillation, survival rate drops by about 7–10%, even if CPR is started immediately. The relation between delay time to defibrillation and survival explains, to a large extent, the variation in survival in different published studies. The regions with high survival rates have a shorter delay time to defibrillation. Prior to the initial development of the community-based emergency rescue system in Seattle [68], out-of-hospital cardiac arrest was nearly uniformly fatal.

'Defibrillation' means 'reversal of the action of fibrillation'. Defibrillation does not mean 'shock' but 'termination of fibrillation' and should not be confused with other resuscitation outcomes, such as restoration of a perfusing rhythm, recovery of spontaneous circulation or admission to hospital and discharge survival [69]. These end-points may occur during resuscitation as a consequence of many other variables such as collapse to shock time and drug therapy during resuscitation attempt. These different end-points should be taken into account when considering clinical research results.

Defibrillation consists of the passage of sufficient electric current (amperes) through the heart. The energy chosen (joules) and the transthoracic impedance (ohms) or resistance to current flow determine effective current flow. Factors that determine transthoracic impedance include energy selected, electrode size, paddle skin coupling material, number and interval of previous shocks, size of the chest, phase of ventilation and paddle electrode pressure [70]. New defibrillators, including AEDs, may provide monophasic and biphasic energy waveforms. Monophasic waveforms deliver current that is primarily of one polarity: the direction of current flow is one-way. The recommended energy for monophasic waveforms is 200 J followed by escalating energy dosage (up to 360 J) with the intent to maximize shock success with termination of ventricular fibrillation/ventricular tachycardia while minimizing shock toxicity [71]. Biphasic waveform is a sequence of two current pulses of two different polarity (the current flows in a positive direction for a specific duration, then reverses and flows in a negative direction for the remaining time of the electrical discharge): the polarity of the second flow is opposite that of the first. The first successful experience with biphasic waveforms stems from implantable defibrillators [72]. Subsequently, many studies using implantable but also external biphasic defibrillators have clearly demonstrated the superiority of this particular waveform over monophasic shocks in terminating ventricular fibrillation [73].

Adjunctive drug therapy during resuscitation

Although various pharmacological interventions have been recommended in various older versions of resuscitation guidelines, most of these do not have sufficient evidence to support their routine use. From the various interventions, only the administration of adrenaline is recommended in the most recent guidelines for ACLS (see Figs 33.14 and 33.15). Routine administration of sodium bicarbonate is no longer advised, as one prospective randomized trial failed to demonstrate improved survival by using buffering agents during CPR [74]. Probably the longest controversy in this regard exists with respect to the use of antiarrhythmic drugs to improve outcome of cardiac arrest victims. From the published literature, however, there is no evidence that administration of lidocaine (lignocaine), bretylium or procainamide has any beneficial effect during resuscitation. Two prospective randomized controlled trials, however, strongly indicate that the administration of intravenous amiodarone may improve chances of survival to hospital admission [75,76]. Accordingly, administration of amiodarone has been incorporated in the latest recommendations of ACLS of the American Heart Association.

Automatic external defibrillator

Automatic external defibrillators (AEDs) are considered to be one of the key links in the chain of survival. AEDs were first developed in the 1970s and pre-hospital care systems in various locations in the USA and the UK began to use them in the early 1980s. Since that time, research has established that AEDs are among the most successful technological innovations in emergency cardiac care. AED devices include an automated rhythm analysis system and a shock delivery system. The AED automatically 'analyses' the rhythm of a patient and 'advises' a shock. Fully automated external defibrillators do not require pressing the shock button, but are available only for specific situations. The commonly used AED is better defined as 'semi-automatic' as the operator needs to press the 'shock' button to deliver electric shock. AEDs are programmed to detect and analyse multiple features of surface ECG signal through a highly sophisticated microprocessor-based system. Frequency, amplitude and slope or wave morphology are the ECG features analysed in order to classify the rhythm as 'shockable' or 'non-shockable'. When a shockable rhythm is recognized, the AED charges and shock delivery is permitted.

Some devices are programmed to recognize patients' movements (spontaneous or by others) and to filter them out from ECG analysis. The diagnostic accuracy of AEDs is high, with a specificity of the diagnostic algorithm for ventricular fibrillation of about 100%, along with a sensitivity of about 90–92%. If it fails, it fails only to shock fine ventricular fibrillation, which is more properly termed *coarse asystole* [77]. Rarely, when used improperly in patients who are not in cardiac arrest, AEDs have been reported to deliver shocks to non-ventricular fibrillation/ventricular tachycardia rhythm. However, these events are rare and represent an improper use of the device by the operator rather than a low diagnostic accuracy of the AED. The AED should be operated only on patients who are unresponsive, not breathing and who have no signs of circulation.

The incremental survival benefit associated with early defibrillation using the AED was recently demonstrated in a large randomized multicentre trial [78]. The Public Access Defibrillation (PAD) trial involved more than 19 000 volunteer responders from 993 community places in the USA. One-half of these responders were trained in CPR alone and the other half were trained in CPR plus the use of the AED. There were more survivors to hospital discharge in the units assigned to have volunteers trained in CPR plus the use of the AED (30 survivors among 128 cardiac arrests) than there were in the units assigned to have volunteers trained only in CPR (15 out of 107; relative risk 2.0, 95% CI 1.07–3.77, $P = 0.03$).

No inappropriate shocks were delivered in the entire study. Thus, this trial proves the concept of trained laypersons being able to safely and effectively use the AED.

Based on results from controlled studies [65,73,77–84], first responders to cardiac arrest who should undergo training in the use of the AED according to the recent ESC guidelines may be subdivided into the following categories:

- *traditional first responders*: ambulance personnel;
- *non-traditional first responders*: firefighters, police, security personnel, airline cabin crew, first-aiders;
- *targeted lay first responders*: trained citizens at work sites or public places, family of high-risk patients.

The same guidelines recommend that:

- every ambulance must carry a defibrillator on board, with personnel who are trained in its use;
- defibrillation should be one of the core competencies of doctors, nurses and other health-care professionals;
- defibrillators should be widely placed on general hospital wards;
- the feasibility and efficacy of allowing lay rescuers in the community to be trained and permitted to defibrillate should be investigated.

Personal perspective

Basic and clinical research efforts over the last 20 years have led to a tremendous increase in our knowledge on the pathophysiology of SCD, on identification of patients at risk for this event, and on secondary and primary preventive therapeutic modalities. Along with this, awareness of the problem of SCD not only among patients with cardiovascular diseases, but also among the general population, has resulted in better ways of delivering basic and advanced cardiac life support to the victim of cardiac arrest. The development of the AED has clearly been a milestone in that respect. For the future, many tasks remain to be fulfilled. Among these, probably the most important one, besides further improvement of resuscitation means, remains the identification of those patients who are indeed at highest risk of developing SCD. The process of risk stratification needs to be refined to avoid unnecessary therapeutic interventions, most importantly the unnecessary implantation of defibrillators. At the same time, better implantable devices need to be developed, for instance leadless implantable defibrillators, to make this therapy even safer than it is at present. We have been very successful in fighting the problem of SCD over the last two decades but we need to vigorously continue our efforts. The theme for these activities has perhaps been best expressed by a citation of Michel Mirowski, the inventor of the implantable defibrillator, who used to say: 'The bumps in the road are not bumps, they are the road!'

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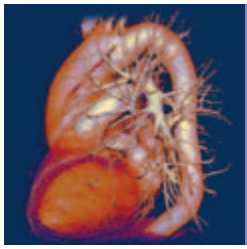


34 Diseases of the Aorta and Trauma to the Aorta and the Heart

Christoph A. Nienaber, Axel Haverich and Raimund Erbel

Summary

Both chronic and acute diseases of the aorta, including trauma, are attracting increasing attention both in the light of an ageing Western population and with the advent of modern diagnostic modalities and therapeutic options to manage aortic pathology. For aortic aneurysm, an individual rate of expansion and the risk of rupture may be assessed from co-morbidities, hypertensive state or connective tissue disease, and may be quantified regardless of anatomic location for timely selection and treatment. Acute aortic syndrome, a new term comprising acute dissection, intramural haematoma and penetrating aortic ulcers, may share common ground by the observation of microapoplexy of the aortic wall, eventually leading to higher wall stress, facilitating progressive dilatation, intramural haemorrhage, dissection and rupture; chronic hypertension and connective tissue disorders are likely to promote this mechanism as well.

While classical surgical strategies still dominate care for acute and chronic pathology of the ascending aorta and the arch region, new endovascular concepts are emerging and are likely to evolve as primary treatment for descending and abdominal aortic pathology in selected and suitable patients. Whereas life-threatening aortic emergencies, including aortic trauma involving the descending aorta, are accepted indications for endovascular stentgrafts, the endovascular concept is not established yet in chronic and stable scenarios of aortic pathology.

In summary, the newly discovered field of clinical aortic pathology is unfolding; optimized multimodality diagnostic and therapeutic strategies require the collaborative effort of a multidisciplinary approach probably organized best in association with a chest pain unit and close ties to cardiology.

Aneurysms of the thoracic aorta

Definition

Enlargement of the aortic diameter exceeding at least 50% of the normal range represents ectasia, which may eventually result in aneurysm formation [1]. The normal diameter of the ascending aorta can be calculated [2,3] and has been defined as 2.1 cm/m^2; the value for the descending aorta is 1.6 cm/m^2 [4]. The normal diameter of the abdominal aorta is regarded to be less than 3.0 cm. The normal expansion rate is 1–2 mm/year. The aortic wall consists of the intima, media and adventitia, with a thickness of about 4 mm. The intima is thin, the media contains elastic fibres and smooth muscle cells forming a spiral layer of tissue that provides the strength of the aortic wall, and the adventitia provides the nutrition with arterial and venous vasa vasorum.

Various forms of aneurysm have to be separated: 'true aneurysm' denotes enlargement of the inner lumen due to vessel wall expansion, whereas 'false aneurysm' (also called pseudo-aneurysm) denotes lumen enlargement due to perforation (penetration) of all parts of the vessel wall, forming an outer sac in communication with the inner lumen of the aorta. The term 'dissecting aneurysm' should be replaced:

- 'circumscript (localized) aneurysm' denotes involvement of only segments of the entire aorta;

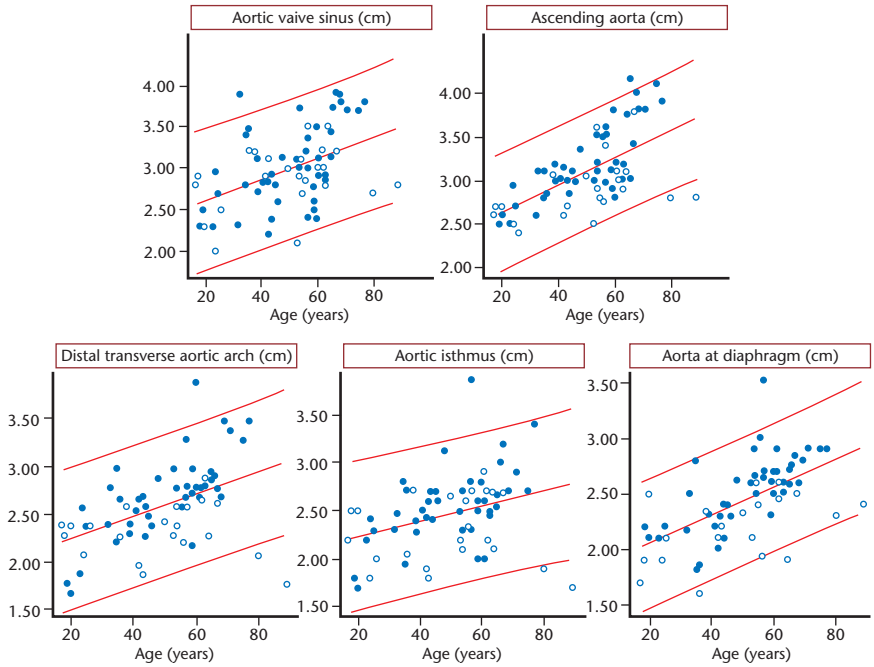


Figure 34.1 Changes in aortic size during life illustrated for the following aortic segments: aortic root, ascending aorta, transverse descending aorta, aortic isthmus and aorta at diaphragm. Reproduced with permission from Hager *et al*. [3].

- 'diffuse aneurysm' denotes enlargement of the ascending aorta, aortic arch, descending thoracic or abdominal aorta, or even the whole aorta.

Aetiology

During life, typical ageing of the aorta is present [3–5]. This involves all segments, with an increase in the luminal diameter of the entire aorta during childhood and young adulthood (Fig. 34.1). Ageing processes are gender specific (Fig. 34.2). In adulthood, aortic size is related to exercise and workload. During further ageing, vessel wall stiffness increases due to structural changes induced by aortic sclerosis [3]. Risk factors include

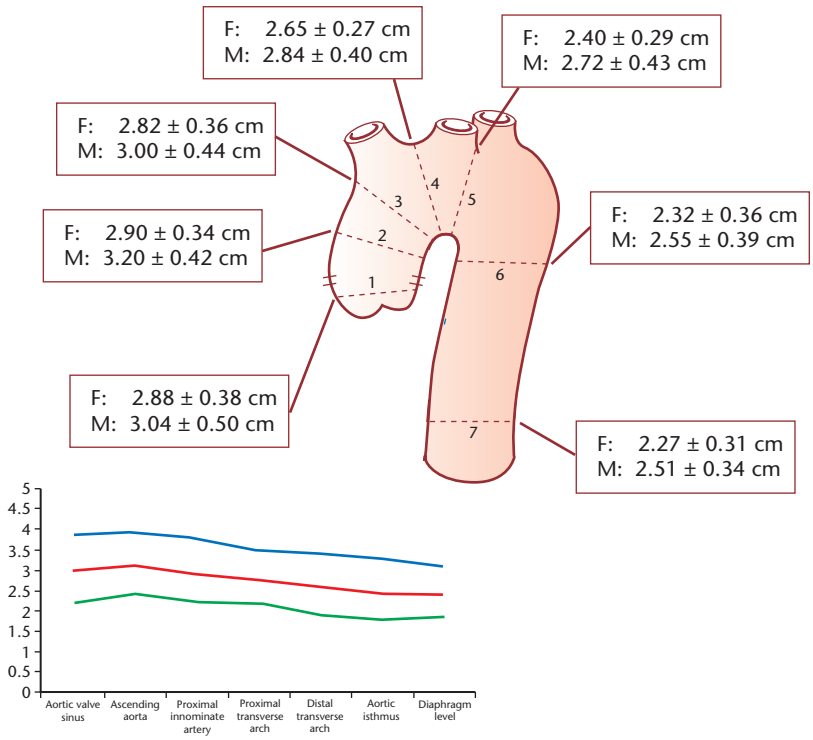


Figure 34.2 Gender-related normal values for the diameter at seven aortic segments. Mean values ± standard deviation. Reproduced with permission from Hager *et al*. [3].

hypertension, hyperlipidaemia, diabetes mellitus and smoking. Aortic wall components demonstrate increasing amounts of collagen and lipids as well as calcium deposits. Aortic wall thickness increases; up to 7 mm is regarded as the upper normal tolerance limit [4]. As a result pulse pressure is enhanced and pulse wave velocity elevated, decreasing the resulting organ perfusion, particularly diastolic myocardial perfusion. The further development of aortic sclerosis is characterized by intimal thickening, plaque formation, ulceration and thrombus formation.

Aneurysm formation of the ascending aorta has been regarded as a forme fruste of Marfan's syndrome, but actually represents a specific genetically determined disease. The aortic arch is usually not involved [6]. There is a 1% prevalence of bicuspid aortic valve (BAV) in these patients [7]. In a review of 21 417 cases with 161 patients suffering from aortic dissection, BAV was tenfold more prevalent than in controls [8] and found in 6–10% of all dissections [9]. Patients with BAV have a ninefold higher risk of dissection than those with tricuspid aortic valves [6]. There is also a high incidence of BAV in patients with aortic coarctation. In patients with BAV enlarged aortic diameters are reported [10].

Three major inherited disorders are known to cause aortic diseases: Marfan's syndrome, Ehlers–Danlos syndrome and other familial forms of connective tissue diseases. In Marfan's syndrome more than 100 mutations have been identified at one locus on the fibrillin gene [11]. The prevalence is about 1 in 5000 [12]. It accounts for 6–9% of all dissections [13]. Complications are aortic aneurysms, aortic regurgitation due to aortic ring dilatation, and aortic dissection. Other familial clusters of thoracic aortic aneurysm have also been identified in about 20% of 1600 patients [14].

Annulo-aortic ectasia affects 5–10% of patients undergoing valve replacement and has been described in association with a familial sex-linked aggregation with the probable existence of genetic heterogeneity [15,16]. Abdominal aortic aneurysm formation is uncommon before the sixth decade. The process is often combined with more proximal disease [17]. The prevalence in men over the age of 50 years is 5% [18,19]. A familial aggregation is suggested that predominantly affects women, whereas men who are affected tend to be younger [20]. A genetic mutation has been described [21].

Pathological–anatomical studies demonstrate typical cystic degeneration of the aortic media, mucoid material and loss of elastic fibres (Fig. 34.3). The loss of elastic fibres, deposits of mucopolysaccharide-like material and cystic anomalies are found in Marfan's syndrome as well as annulo-aortic ectasia [22]. This leads to a weakening of wall strength and consequent vessel dilatation. The circumferential wall stress (W) can be calculated according to Laplace's law for thin-walled structures:

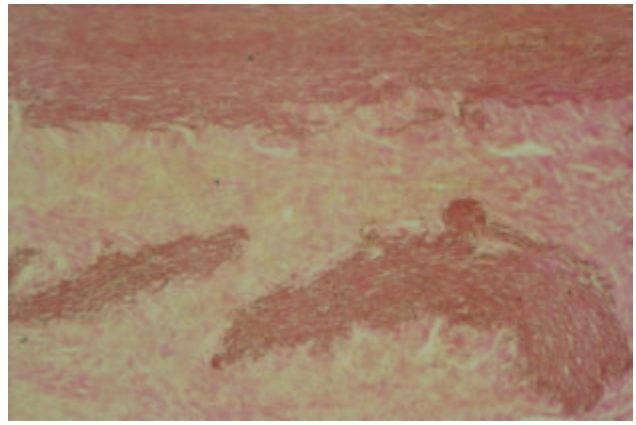


Figure 34.3 Aortic aneurysm specimen: histological view of aortic wall structure with mucoid medial degeneration and fibre rupture.

$$W = Pr/2h$$

where P is pressure, r radius and h wall thickness.

Hypertension, wall thinning and aortic enlargement are the most important factors increasing wall stress leading to aortic rupture or dissection [23,24]. Aortic diameter is a marker of risk but is not always enlarged. In connective tissue disease up to 40% of cases show aortic enlargement of more than the normal range, although in other forms this degree of enlargement is found in only 10%. The critical point of rupture (Fig. 34.3) is at 6 cm for the ascending aorta and 7 cm for the descending aorta [14]. When this point is reached, up to 30% with enlargement of the ascending aorta and 40% with enlargement of the descending aorta suffer rupture or dissection [14]. The yearly risk of complications can be calculated as follows:

$$\begin{aligned} \text{Ln} = &-21.055 + 0.0093\ (\text{age}) \\ &+ 0.842\ (\text{pain}) + 1.282\ (\text{COPD}) \\ &+ 0.643\ (\text{descending aortic diameter}) \\ &+ 0.405\ (\text{abdominal aortic diameter}) \end{aligned}$$ [25]

Aortic sclerosis of the thoracic but also the abdominal aorta is only a weak predictor of expansion [26,27]. Patients with the most atherosclerotic burden have the slowest growth of the abdominal aorta [27]. Smoking increases growth rate by 15–20%.

Weakening of the aortic wall can also be induced by inflammation. This can be the result of microbiological diseases or multisystem vasculitic disorders. Well known is the aortitis induced by syphilis and *Staphylococcus aureus* infection. Kawasaki's syndrome is characterized by more circumscript aneurysm formation, whereas syphilis

can induce diffuse wall thickening and aneurysm formation of the ascending aorta, but penetrating ulcers can also be observed. The risk of rupture increases with the diameter of the aorta. Inflammatory cells and elevated levels of cytokines within the aneurysm wall have been observed [28]. Cytokines may trigger increased production of matrix metalloproteinase (MMP) by macrophages and smooth muscle cells [29]. There is a strong relation between infiltration and MMP activation [28]. Behçet's disease, like other forms of vasculitis, may lead to local aneurysm formation and perforation rather than dissection [30]. Kawasaki's syndrome has an incidence of 135 per 100 000 children, with 8–17 cases in 100 000 children under the age of 5 years [31]. Coronary aneurysm is the leading sign, but other arterial segments can also be involved. In giant-cell arteritis, thoracic and abdominal aneurysm may develop [32]. The use of cocaine and amphetamines can also lead to aortic wall thinning and aneurysm formation.

In aortic stenosis, poststenotic aneurysm formation can occur, which may even be enhanced after aortic valve prosthesis implantation [33]. Previous surgery accounts for 2–4% of patients receiving aortic root surgery [27]. An important cause of aneurysm formation is related to trauma, particularly high-speed deceleration trauma involving the aortic isthmus in 95% [34]. About 15–20% of deaths are related to aortic trauma in these patients.

Clinical features

Aortic aneurysms are silent as long as no complications occur, because symptoms are not produced by enlargement of the aortic diameter. Aortic regurgitation is a typical consequence of ascending aortic aneurysm formation, as a result of aortic ring dilatation with or without valve degeneration. Circumscript pseudo-aneurysm of the aortic root can also lead to aortic regurgitation when the aortic ring is destroyed, which is more often seen in mycotic aneurysm, particularly related to endocarditis involving the aortic–mitral triangle. Aortic regurgitation may even be the first sign of disease.

Aortic dissection and rupture may develop and is related to aortic diameter and expansion rate. The increase in diameter accelerates as the aneurysm enlarges [27]. The main risk factor is smoking. The risk of complication accelerates with a diameter beyond 6 cm for the ascending aorta and 7 cm for the descending aorta [14]. The annual risk of rupture, dissection and death is 5–6.5% with a diameter below 6 cm and > 14% with a diameter above 6 cm [14] (Fig. 34.4).

In some patients, compression of mediastinal organs as well as of neural or bony structures leads to symptoms such as dyspnoea, pain or hoarseness. Pain occurs when the pain receptors in the adventitia of the aortic wall are irritated. Pain is always a sign of emergent or ongoing expansion or trauma to the aortic wall. Penetration and perforation of the oesophagus may be a sudden deleterious event [35] (Table 34.1).

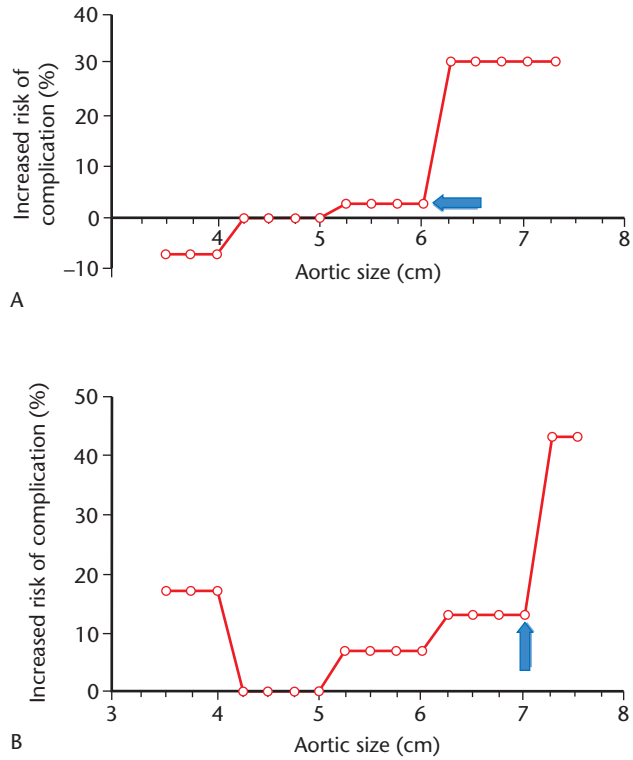


Figure 34.4 Influence of aortic size on cumulative lifetime incidence of natural complications of aortic aneurysm: *y*-axis, incidence of natural complications (rupture/dissection); *x*-axis, aortic size. (A) Ascending aorta, hinge point at 6 cm. (B) Descending aorta, hinge point at 7 cm. Reproduced with permission from Elefteriades [14].

Diagnostic procedures

Many imaging techniques can be used to diagnose aortic aneurysm formation, which in many instances is an accidental finding. Chest radiography may reveal widening of the mediastinum, left-sided visible enlargement of

Table 34.1 Annual risk (%) of complications based on aortic size

	Aortic size (cm)			
	> 3.5	> 4	> 5	> 6
Rupture	0	0.3	1.7	3.6
Dissection	2.2	1.5	2.5	3.7
Mortality	5.9	4.6	4.8	10.8
Any event	7.2	5.3	6.5	14.1

Reproduced with permission from Ellis *et al.* [15].

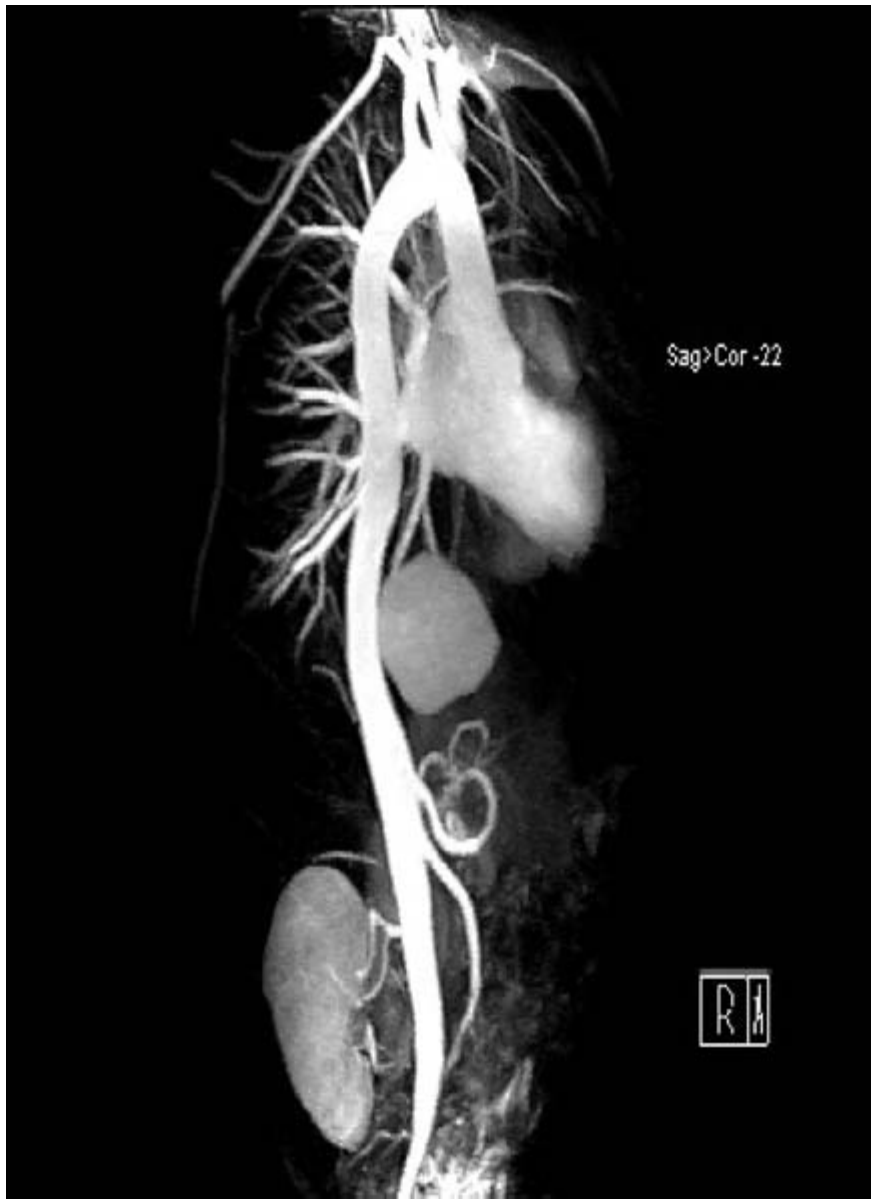


Figure 34.5 Magnetic resonance image of discrete false aneurysm of the descending aorta reconstruction.

the ascending aorta, changes in the aortic knob, or an enlarged and often elongated descending aorta. Circumscript aneurysm formation may result in multiform chest radiographic abnormalities.

Computed tomography (CT), especially with contrast image enhancement, can aid in determining location, size and/or complications. Aortic wall thickness, calcium deposits in the area of the coronary arteries and aortic wall, and side-branch anatomy is clearly visualized. The use of standardized techniques yields high reproducibility for follow-up studies in order to estimate changes over time. Complications such as perforation with mediastinal haematoma, pleural effusion, pericardial effusion and signs of aortic syndrome are detected [5,36,37]. Disadvantages are the use of potentially toxic contrast agents and the inability to visualize aortic regurgitation and left ventricular wall motion abnormalities.

Magnetic resonance imaging (MRI) produces unrestricted high-resolution views of the aorta in transverse, sagittal and coronal planes. Because of its higher quality images, MRI provides optimal delineation of the origin and extent of aneurysm formation (Fig. 34.5). Left ventricular wall thickness and function can be studied. Less accurate is the visualization of coronary or aortic sclerosis. The size of an aortic aneurysm, its location and extent is easily measured [38–40]. A big advantage is the lack of radiation burden, which allows multiple follow-up studies particularly in young adults and women of childbearing age. Renal failure occurs to a lesser extent than with radiographic contrast material injection.

Ultrasound can visualize the whole aorta using transthoracic, suprasternal, subcostal and abdominal, as well as duplex sonography. However, the ascending part of the aortic arch cannot be imaged even by transoesophageal echocardiography because of the interposition of the trachea and the right mainstem bronchus between the oesophagus and the aorta at this location [41,42]. This technique has high resolution but spatial orientation is limited. Aneurysms can be detected but the full extent and size are difficult to assess. With endovascular interventions, however, intravascular ultrasound and transoesophageal echocardiography are of great importance [43,44].

The invasive technique most widely used is aortography, which allows visualization of aortic regurgitation, ventricular function, coronary artery disease, side-branch involvement and aneurysm location, size and extent. The disadvantage is the exposure to radiation and the use of contrast agents. The technique is the basis for interventional procedures [45–48]. Moreover, intravascular ultrasound using transducers of 7–10 MHz also has great diagnostic potential. Mechanical and electronic sector scanners are available which show cross-sectional images but without flow imaging. This disadvantage can be eliminated with the use of flexible, steerable, linear 8F ultrasound catheters (Fig. 34.6), which have all the capabilities of other echocardiographic and sonographic machines.

Positron emission tomography (PET) is able to detect increased metabolic activity in thoracic and abdominal aneurysms [49]. [^{18}F]-Fluorodeoxyglucose uptake at the level of the aneurysm is a strong predictor of aneurysm expansion and rupture, and the combination of PET and CT may potentially offer new insights.

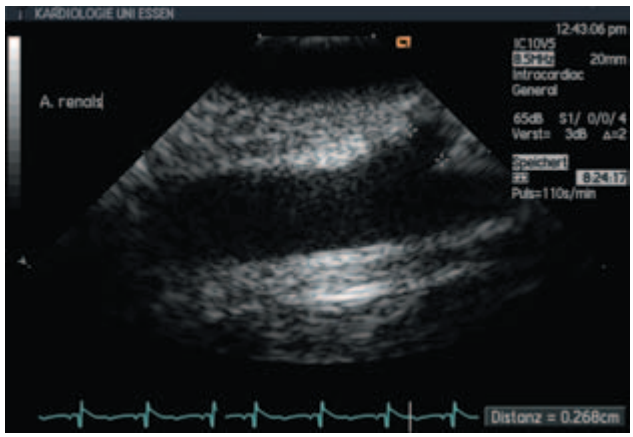


Figure 34.6 Intravascular ultrasound catheter positioned within the lumen of the inferior vena cava showing the descending aorta and longitudinal-sectional scanning of the descending aorta (AcuNav catheter, Siemens, Erlangen, Germany).

Besides imaging techniques, laboratory tests may be helpful for identifying active inflammatory processes [50]. Elevated levels of fibrinogen, orosomucoid, α_1-antitrypsin, haptoglobin and ceruloplasmin were observed in 63 of 6075 men with an event [51]. The risk for events increased with the number of factors found, from 0.4 to 2.3% with more than three risk factors in the top quartile. In aortic dissection, elevated levels of C-reactive protein and D-dimers are frequently found [52]. The detection of elevated levels of MMP (MMP-2 and MMP-9) products or their tissue inhibitors (TIMP-1 and TIMP-2) may be a useful marker in the near future [29].

Surgical and endovascular management

Important measures for preventing enlargement and progression of aneurysm include cessation of smoking and lowering of blood pressure. Beta-blocking agents or other agents that lower blood pressure may be used in combination. For abdominal aneurysms, smoking and hypertension were predictors of late death after aortic surgery [53]. In addition to medical treatment with beta-blocking agents, surgical and/or endovascular management may become necessary. Aortic dissection and rupture are the most severe complication of aortic aneurysm formation, leading to high operative risk in urgent or emergency situations [54]. Operative mortality has been reported to be 1.5% for elective, 2.6% for emergency and 11.7% for urgent surgery. Thus, elective surgery has been recommended for aneurysms of the ascending aorta > 5.5 cm diameter and for those > 4.5 cm in Marfan's syndrome or other connective tissue disease [5,14].

Composite mechanical valve conduits have been used since their introduction by Bentall and De Bono in 1968 [55]. Most often, modified procedures are used [53]. The open technique has replaced the inclusion wrap technique, with the Carrel button technique to reattach the coronary ostia [56]. In order to create an optimal sinutubular junction with a 1 : 1 relation to the valve cusp's free margin and annulus diameter, Dacron tubes of 26–30 mm are chosen [53]. Valve-preserving procedures would be ideal because anticoagulation can be avoided, but often the valve apparatus itself contains connective tissue abnormalities [57,58]. If the aortic root exceeds 6 cm, most of the cusps demonstrate abnormalities [59]. Therefore, it is not surprising that in 203 patients operated in the Mayo Clinic, composite valve conduit reconstruction resulted in a more durable result during a follow-up period of 20 years [53]. After 5 years, 12% versus 40% were free from reoperation. Sarsam and Yacoub [60], as well as David and Feindel [61], have developed a valve-preserving reconstruction technique. The reoperation rate was reported to be 11% at 10 years [62] and only 3% at 10 and 8 years,

respectively [63]. However, a high rate of residual aortic regurgitation developed in 25–45% at 8–10 years [59,63].

Reoperation is necessary in 10–20% of the patients during a follow-up of 10–20 years, with a trend for more reoperations in those with valve-preserving aortic root reconstruction versus composite graft replacement (16% vs. 5%) [64]. A predictor for reoperation was found to be an annulus diameter > 25 cm [65]. Other predictors were found to be Marfan's syndrome, mitral valve prolapse, preoperative atrial fibrillation, aortic valve-preserving operation and concomitant procedures performed, with a mean time to reoperation of 4.5 ± 5 years [53]. Recurrent aortic aneurysm was found in 3.5%, mitral valve disease in 2%.

Long-term problems can arise from anticoagulation. Thromboembolism is reported in up to 0.42 per 100 patient-years [66], depending on whether patients with atherosclerotic aneurysms are included in the analysis [53]. Valve thrombosis was observed in 1% and life-threatening haemorrhage in 2% of 203 patients, with a time of 5.4 ± 4.9 years to the event. Endocarditis was found in only 1%, but usually within 1 year after surgery. Main predictors of late death are female sex, increased age, untreated with beta-blockers, mitral regurgitation +3–4 at presentation, mitral ring calcification, postoperative dysrhythmia, and postoperative inotropes. The overall 20-year survival rate reaches 50% [53].

For the aortic arch, surgical intervention is most likely to be the method of choice, which nowadays is more frequently combined with stentgraft implantation in order to seal the distal aortic arch to the descending aorta. Special systems have been designed so that implantation can be performed via an antegrade strategy [67].

For thoracic descending or thoraco-abdominal aortic aneurysms, the current surgical strategy has been developed over the last 15 years in order to prevent ischaemic complications and includes permissive mild hypothermia (32–34°C nasopharyngeal), moderate heparinization with 1 mg/kg, renal artery perfusion with 4°C crystalloid solution, aggressive reattachment of segmental arteries (especially between T8 and L1), sequential aortic clamping as well as cerebrospinal fluid drainage, left heart bypass during proximal anastomosis, and selective perfusion of coeliac and superior mesenteric arteries during intercostal, visceral and renal anastomosis [67]. The technique for spinal cord protection can reduce the rate of paraplegia from about 15 to less than 5% [68]. Also renal failure (serum creatinine elevation > 50% above baseline value) could be reduced from about 60 to 20% [69]. The 5-year survival of 1773 patients reached nearly 75% compared with only 20% [67,70].

For circumscript localized aneurysm formation, whether true or false aneurysms, percutaneous stentgraft implantation has become an alternative option. Despite the limited experience at present and limited follow-up, this technique appears attractive in emergency situations, with high procedural and clinical success rates [70,71]. The prerequisite is close cooperation of cardiologists, radiologists, anaesthesiologists and cardiovascular surgeons for optimal results (Fig. 34.7). The intervention is mostly performed under general anaesthesia, but local anaesthesia has also been used [72]. Access to the peripheral artery requires surgical cut-down for the 22–24F sheaths. Under fluoroscopic guidance the stentgraft is advanced using a stiff wire in order to overcome the elongation of the iliac arteries and the aorta, which can be difficult [48]. Today, the technical success rate reaches 95% [45,46]. Positioning of the customized stentgraft is regarded as crucial and can be aided by transoesophageal ultrasound, whereas for surgery of the abdominal aorta it is helpful to have the intravascular ultrasound probe located in the inferior vena cava. Lowering the blood pressure to 50 mmHg or application of adenosine to lower heart rate is essential before deploying a stentgraft. Angiography after implantation will reveal satisfying wall apposition of the stent. If endoleaks are found, additional balloon inflations may be necessary to obtain good strut apposition to the wall. After stenting, patients can usually be rapidly extubated and discharged after a few days. In some patients inflammation is seen, described as graft disease, leading to some chest discomfort that responds to indometacin.

Meanwhile hybrid techniques, i.e. the combination of stentgraft placement and open visceral bypass grafting, have been described [73–75]. For the abdominal aorta, even fenestrated grafts and additional visceral grafts are on the horizon [76,77].

Dissection of the thoracic aorta

Aetiology

All mechanisms that weaken the aorta's media layers via micro-apoplexy lead to higher wall stress, facilitating aortic dilatation, aneurysm formation, intramural haemorrhage, aortic dissection or rupture (Table 34.2). Moreover, besides chronic repetitive trauma resulting from long-standing arterial hypertension, three inherited connective tissue disorders are currently known to affect the arterial wall: Marfan's syndrome, Ehlers–Danlos syndrome and familial forms of thoracic aneurysm and dissection [78–100].

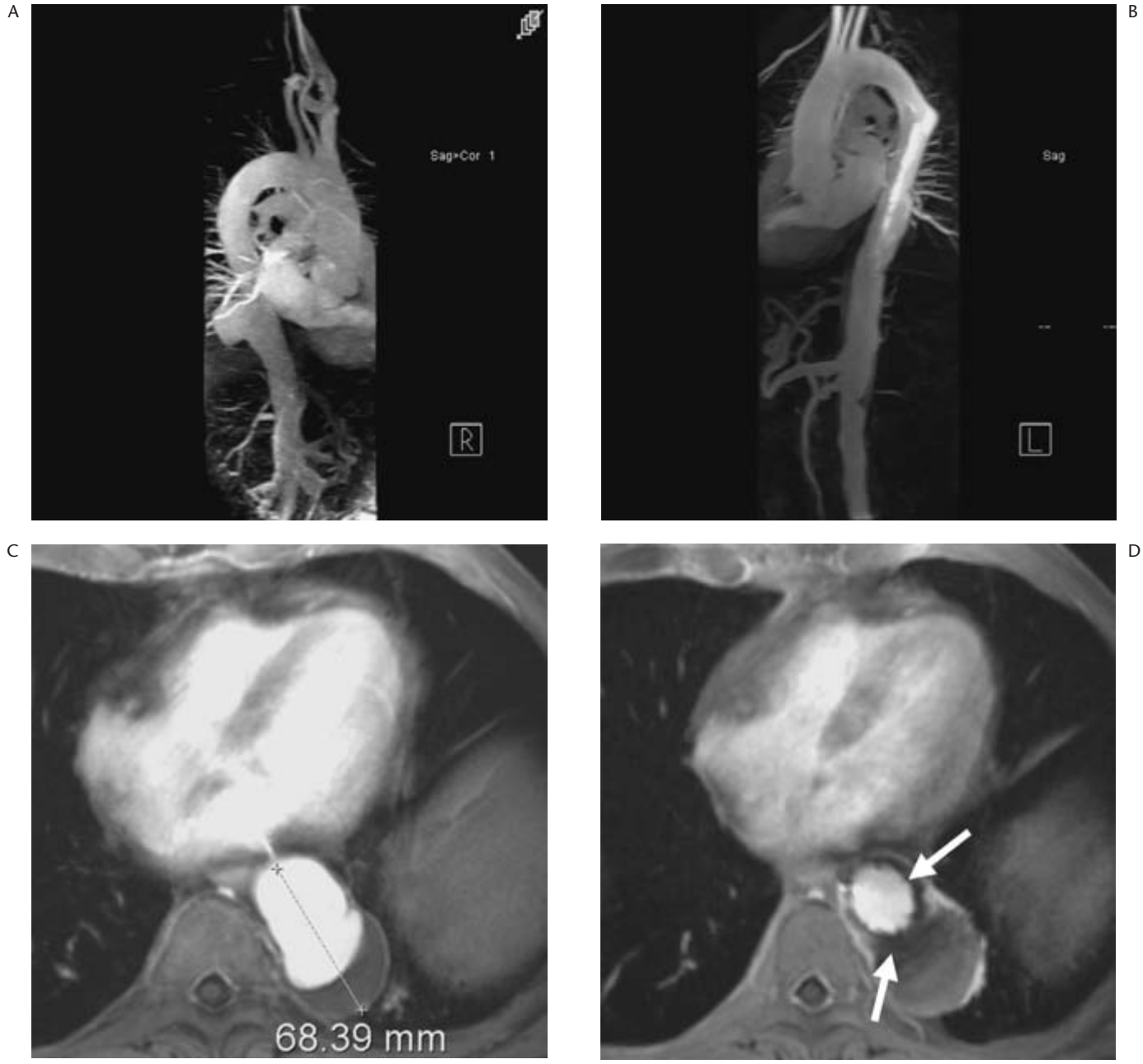


Figure 34.7 Magnetic resonance images of false aneurysm with complete thrombus formation shown in longitudinal view (A, B) and cross-section (C, D) before (A, C) and after (B, D) implantation of a stent (3.6 cm diameter, 10 cm length).

Acquired conditions

Chronic hypertension affects arterial wall composition, causing intimal thickening, fibrosis and calcification, and extracellular fatty acid deposition. In parallel the extracellular matrix undergoes accelerated degradation, apoptosis and elastolysis with hyalinization of collagen. Both mechanisms may eventually lead to intimal disruption. Moreover, adventitial fibrosis may obstruct nutrient vessels feeding the arterial wall as well as small intramural vasa vasorum. Both result in necrosis of smooth muscle cells and fibrosis of elastic structures, rendering the vessel wall vulnerable to pulsatile forces and creating a substrate for aneurysms and dissections [7,88–91]. In addition to chronic hypertension, smoking, dyslipidaemia and, potentially, the use of crack cocaine are modulating risk factors. On rare occasions, inflammatory diseases destroy the media layers and cause weakening, expansion and dissection of the aortic wall. Iatrogenic aortic dissection may occur in association with invasive retrograde

Table 34.2 Risk conditions for aortic dissection

Long-standing arterial hypertension
Smoking, dyslipidaemia, cocaine/crack
Connective tissue disorders
Hereditary fibrillinopathies
Marfan's syndrome
Ehlers–Danlos syndrome
Hereditary vascular disease
Bicuspid aortic disease
Coarctation
Vascular inflammation
Giant-cell arteritis
Takayasu's arteritis
Behçet's disease
Syphilis
Ormond's disease
Deceleration trauma
Car accident
Fall from height
Iatrogenic factors
Catheter/instrument intervention
Valvular/aortic surgery
Side- or cross-clamping/aortotomy
Graft anastomosis
Patch aortoplasty
Aortic wall fragility

catheter interventions, or during or after valve or aortic surgery [7,92–94]. Given the morbidity and mortality of iatrogenic aortic dissection, careful assessment is strongly encouraged in patients with unexplained haemodynamic instability or malperfusion syndromes following invasive vascular procedures or aortic surgery (Table 34.3).

Finally, pregnancy-related dissection, although a dramatic scenario, is a rare event as long as the patient is not affected by any form of connective tissue disease. The putative association of pregnancy in otherwise healthy women and acute dissection may largely be an artefact of selective reporting. Pregnancy is a common condition and may coincidentally occur only with concomitant existence of other risk factors, such as long-standing or pregnancy-associated hypertension, or Marfan's syndrome. Preliminary data from the International Registry of Aortic Dissection show that pregnancy in Marfan's syndrome is not associated with aortic tears unless root size exceeds 40 mm.

Marfan's syndrome

Among hereditary diseases, Marfan's syndrome is the most prevalent connective tissue disorder, with an estimated incidence of 1 in 7000 and autosomal dominant inheritance with variable penetrance. More than 150 mutations on the fibrillin-1 (*FBN-1*) gene have been identified encoding for a defective fibrillin in the extracellular matrix, which may affect the ocular, cardiovascular, skeletal and pulmonary systems, as well as skin and dura mater. The diagnosis of Marfan's syndrome is currently based on the revised clinical criteria of the 'Gent nosology' [95]. The Gent criteria pay particular attention to genetic information, for example the appearance of Marfan's syndrome in kindreds of an unequivocally affected individual. Moreover, both skeletal and cardiovascular features are major (i.e. diagnostic) criteria if four of eight typical manifestations are present. However, borderline manifestations such as the MASS phenotype or subtle phenotypic features (forme fruste), the molecular analysis of suspected Marfan's syndrome and the delineation of criteria for differentiating other inherited conditions (genotypes) from the Marfan phenotype are attracting interest [11,96–99]. The clinical variety of Marfan's syndrome is only partially explained by the number of mutations on the *FBN-1* gene. Genetic heterogeneity and the involvement of a second gene (*MFS2*, Marfan's syndrome type 2) may further add to the broad spectrum of symptoms [100].

A common denominator of all phenotypic forms of aortic wall disease is the dedifferentiation of vascular smooth muscle cells, not only with classic aneurysm formation but also from enhanced elastolysis of aortic wall components [101], as shown in a fibrillin-1-deficient

Table 34.3 Aetiology of iatrogenic aortic dissection in International Registry of Aortic Dissection

Cause	Type A	Type B
Cardiac surgery	18 (69%)	1 (12%)
Coronary angiography/intervention	7 (27%)	7 (87%)
Renal angioplasty	1 (4%)	–
Complication	Iatrogenic	Spontaneous
Myocardial ischaemia	36%*	5%
Myocardial infarction	15%*	3%
Limb ischaemia	14%	8%
Mortality (30 days)	35%	24%

*$P = 0.001$.

animal model [102]. Moreover, enhanced expression of metalloproteinases in vascular smooth muscle cells of the Marfan aorta may promote both fragmentation of medial elastic layers and elastolysis, thus initiating an activated phenotype of smooth muscle cells [103]. In parallel, expression of peroxisome proliferator activated receptor (PPAR) is up-regulated in smooth muscle cells of Marfan's aorta and with cystic medial degeneration and correlates with clinical severity, while vascular smooth muscle cell apoptosis is likely to be related to progression of aortic dilatation. Thus, PPAR expression might reflect the pathogenesis of cystic medial degeneration and disease progression in the aorta of both Marfan's syndrome and non-Marfan's disease without any vascular inflammatory response [104].

Ehlers–Danlos syndrome

Ehlers–Danlos syndrome is a heterogeneous group of hereditable connective tissue disorders characterized by articular hypermobility, skin hyperextensibility and tissue fragility. Eleven types of Ehlers–Danlos syndrome have been characterized; the true prevalence is unknown. An aggregate incidence of 1 in 5000 births is often cited, with no racial or ethnic predisposition. Aortic involvement is seen primarily in autosomal dominant Ehlers–Danlos syndrome type IV [105].

Annulo-aortic ectasia and familial aortic dissection

More than five mutations in the *FBN-1* gene have now been identified in patients presenting with either sporadic or familial forms of thoracic aortic aneurysm and dissection [106,107]. Histological examination of the aortic wall reveals elastolysis or loss of elastic fibres, deposits of mucopolysaccharide-like material and cystic medial degeneration similar to that in Marfan's syndrome. However, no abnormalities of types I and III collagen or any specific fibrillopathy have been found in fibroblast cultures.

Abdominal aortic aneurysm and dissection

Careful examination of family pedigrees often reveals both involvement of the abdominal aorta and disease in proximal aortic segments, or other features suggestive of Marfan's or Ehlers–Danlos syndrome. Differentiation of familial forms of abdominal aortic aneurysm/dissection from thoracic aortic aneurysm/dissection with an abdominal component is difficult considering that only one mutation within the *COL3A1* gene is known [107]. In fact, many candidate genes encoding for collagens, fibrillins, fibrullins, microfibril-associated glycoproteins, and MMPs and their inhibitors have been investigated but no mutation has been identified. Similar pathogenetic processes have been described with coarctation [88] and with the bicuspid aortic valve architecture [89].

Definition and classification

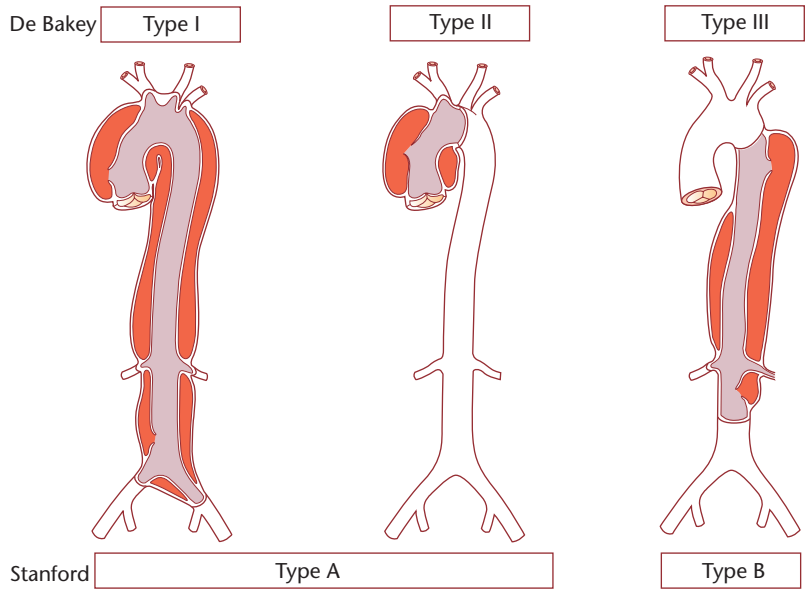
The Stanford classification of aortic dissection distinguishes between type A and type B (Fig. 34.8) [108,109]. Type A involves the ascending aorta, while type B dissection does not involve the ascending aorta. The De Bakey classification subdivides the dissection process into type I dissection involving the entire aorta, type II dissection involving only the ascending aorta, and type III dissection sparing the ascending aorta and the arch. Various attempts to further subdivide both classification systems have not been established [110,111], although the arch region deserves integration into a modern classification system. Recent observations highlight the importance of precursors of typical aortic dissection such as intramural haematoma, penetrating aortic ulcers or localized intimal tears as variants of a wall-dissecting process [112,113] (Fig. 34.9).

Classic aortic dissection

Acute aortic dissection is characterized by the rapid development of an intimal flap separating the true and false lumen [114–116]. In the majority of cases (~ 90%) intimal tears are identified as sites of communication between true and false lumen. The dissection can spread in an antegrade or retrograde fashion, involving side branches and causing complications such as malperfusion syndrome by dynamic or static obstruction (from coronary to iliac arteries), tamponade or aortic insufficiency. The arbitrary classification of acute, subacute or chronic dissection appears helpful for neither didactic nor differential therapeutic considerations, but may rather be used to describe the individual situation and time span of survival of a given patient. From a pathophysiological point of view, progression of dissection is difficult to predict once a patient with dissection has survived the initial 2 weeks after its inception, although false lumen expansion is likely to develop over time. Several clinical features may be used to roughly estimate late risk, including evidence of persistent communication, patent false channel, and others [111,114,115].

Intramural haematoma

Aortic intramural haematoma is considered a precursor of classic dissection, and originates from ruptured vasa vasorum in medial wall layers, eventually provoking a secondary communication with the aortic lumen



De Bakey

Type I	Originates in the ascending aorta, propagates at least to the aortic arch and often beyond it distally
Type II	Originates in and is confined to the ascending aorta
Type III	Originates in the descending aorta and extends distally down the aorta or, rarely, retrograde into the aortic arch and ascending aorta

Stanford

Type A	All dissections involving the ascending aorta, regardless of the site of origin
Type B	All dissections not involving the ascending aorta

Figure 34.8 The most common classification systems of thoracic aortic dissection.

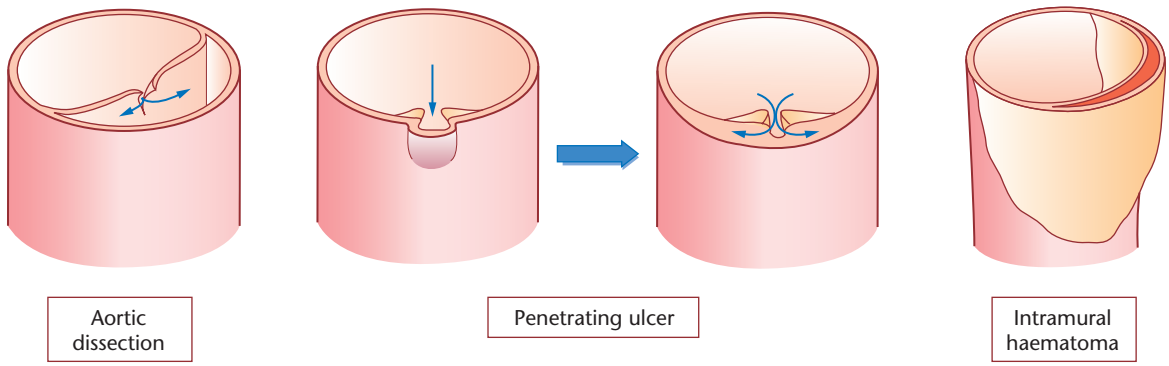


Figure 34.9 Schematic representation of aortic dissection (left), penetrating ulcer (middle) and intramural haematoma (right).

[113,117,118]; this process may be initiated by an 'aortic wall infarction'. Similar to classic dissection, intramural haematoma may extend along the aorta or may progress, regress or reabsorb. The prevalence of intramural haemorrhage is 10–30% [113,118–120]. Intramural haematoma can lead to acute aortic dissection in 21–47% of patients or to regression in about 10%. Involvement of the ascending aorta is considered an indication for expeditious surgery due to the inherent risk of rupture, tamponade or compression of coronary ostia. Distal intramural haematoma may warrant watchful waiting and, potentially, stentgraft placement [118,121–123] (Fig. 34.10). Studies in Asian patients from Japan and Korea have argued that wall haematoma reflects a more benign condition, in which aggressive medical therapy and serial imaging allow a watchful waiting strategy [121,122]. The reasons

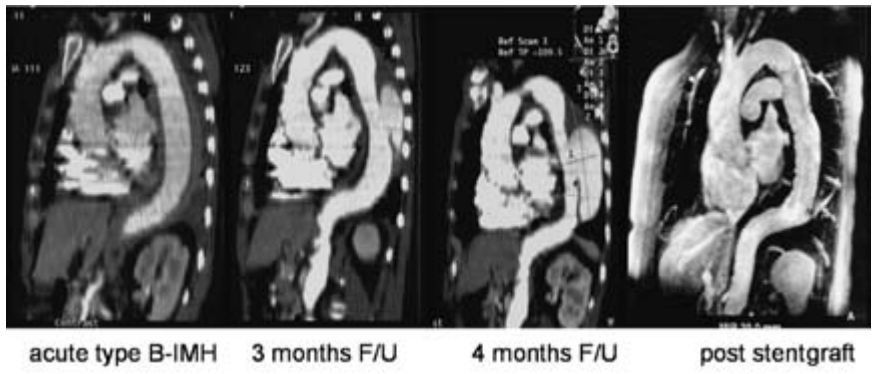


Figure 34.10 Spiral contrast-enhanced CT scans showing evolution of acute intramural haematoma (IMH) of the descending aorta (left) into growing local dissection and formation of an aneurysm within 4 months, and reconstruction of the dissected aorta and exclusion of aneurysm after interventional stentgraft placement (right).

for this disparity may relate either to a different gene pool of Asian and white patients or to semantic differences. However, at present the cardiological and surgical communities have generally concluded that acute intramural haematoma involving the ascending aorta should be managed surgically in the same way as type A dissection.

Plaque rupture/ulceration

Ulceration of atherosclerotic aortic plaques can lead to aortic dissection or perforation [124–126]. Non-invasive imaging of aortic ulceration has been improved by tomographic scanning and has shed light on pathophysiology and aetiology. Aortic ulcers occur predominantly in the descending thoracic and abdominal aorta, penetrate intimal borders and appear in nipple-like projections with an adjacent haematoma [127,128]; symptomatic ulcers and/or with signs of deep erosion are more likely to rupture than others.

Clinical features

The challenge in managing acute aortic syndrome, and especially dissection, is appropriate clinical suspicion and action in pursuing diagnosis and therapy [129,130]. Typical features of dissection are the acute onset of chest and/or back pain of blunt, radiating and migrating nature. Chronic hypertension is common if obvious signs of connective tissue disorders are absent. Clinical manifestations of acute aortic dissection are often explained by specific malperfusion syndrome from dissection-related side-branch obstruction. Every fifth case of acute aortic dissection may present with syncope from tamponade, severe hypotension or carotid obstruction [78–84]. Emerging heart failure is usually related to severe aortic regurgitation or coronary obstruction. Cerebrovascular manifestations, limb ischaemia or pulse deficits are caused by involvement of a side-branch orifice into the dissection or obliteration of the true lumen by an expanding false lumen [85,131]. Paraplegia may emerge if too many pairs of intercostal arteries are separated from the aortic lumen.

Recurrent abdominal pain, elevation of acute-phase proteins and increase of lactate dehydrogenase are indicators of involvement of either the coeliac trunk (observed in ~ 8%) or superior mesenteric artery (in 8–13%). Involvement of renal arteries may result in oliguria or anuria and propagation of dissection is heralded by repetitive bouts of pain or a deteriorating clinical picture [11,96].

Pulse deficits on physical examination occur in about 20% and are important clues heralding complications and bad outcome (Fig. 34.11). A diastolic murmur indicative of aortic regurgitation is seen in approximately 50% of patients with proximal dissection. Signs of pericardial effusion, jugular venous distension or a paradoxical pulse should provoke confirmation of the diagnosis. Shock may be a presenting sign, resulting from tamponade, coronary compression, acute aortic valve incompetence, or loss of blood and imminent exsanguination [78,85,87,129].

Consequently, the differential diagnosis of acute aortic dissection should always be considered in patients presenting with chest pain, back pain, unexplained syncope, abdominal pain, stroke, acute onset of congestive heart

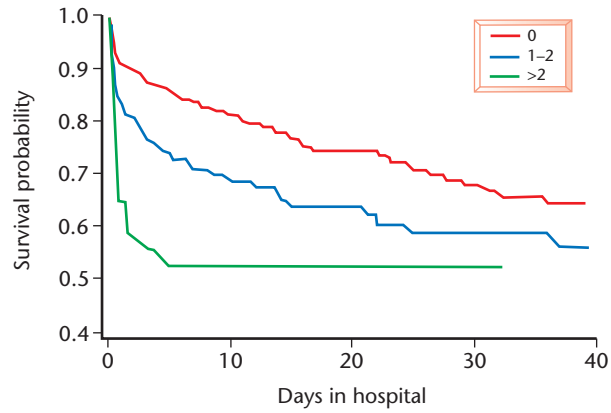


Figure 34.11 Kaplan–Meier survival curves for patients with and without pulse deficits; log-rank for curves of patients with one, two or three or more pulse deficits differ from patients with no pulse deficits ($P < 0.03$).

Table 34.4 Life-threatening causes of acute chest pain

Acute coronary syndromes
Aortic dissection
Pulmonary embolus
Tension pneumothorax
Oesophageal rupture

failure, pulse differentials, or malperfusion syndrome of extremities or viscera (Table 34.4). In the present absence of useful specific biomarkers for aortic dissection, interpretation of positive cardiac markers may be even more complex in the scenario of aortic dissection compromising coronary ostia.

Diagnostic procedures

Considering the differential diagnosis of acute aortic dissection, its aetiology and the wide spectrum of symptoms, it is not surprising that 70% of ECG findings are pathological [87]. ECG finding are non-specific, with misleading normal results in type B dissection or acute ischaemic changes with involvement of the coronary arteries in type A dissection.

Moreover, routine chest radiography is abnormal in 56% of cases of suspected aortic dissection [87]. Transthoracic echocardiography has a sensitivity of 60% and a specificity of 83% for type A dissection and also shows aortic regurgitation, pleural effusion and pericardial effusion/tamponade [132]. Transoesophageal echocardiography with colour Doppler interrogation overcomes the limitations of transthoracic echocardiography, with a sensitivity of 94–100% for identifying an intimal flap and 77–87% for identifying the site of entry; specificity ranges from 77 to 97% [80].

Multislice CT is available in many hospitals and is usually offered on an emergency basis [36]. It provides complete anatomical information of the aorta including branch vessel involvement and enables visualization of the ostium and proximal part of both coronary arteries. CT has a sensitivity of 83–100% and a specificity of 90–100% for aortic dissection [78–80]. In randomized trials, cardiac MRI was more precise than transoesophageal echocardiography and CT and nearly 100% specific for aortic dissection. For identifying the site of entry, sensitivity was 85% and specificity 100% [81,83]. Aortography, an invasive procedure, is no longer required for diagnosing aortic dissection. Coronary angiography adds little to the decision-making process and should generally be avoided in type A dissection [80].

Medical management

Acute aortic dissection of the ascending aorta is highly lethal, with a mortality rate of 1–2% per hour early after symptom onset [78,133]. Acute type A dissection is a surgical emergency. Medical management alone is associated with a mortality rate of nearly 20% by 24 h after presentation, 30% by 48 h, 40% by day 7 and 50% by 1 month. Even with surgical repair, mortality rates are 10% by 24 h, 13% by 7 days and nearly 20% by 30 days, as recently documented in the largest registry of aortic dissection, although randomized data are not available [85,87,134].

Acute aortic dissection affecting the descending aorta is less lethal than type A dissection. Patients with uncomplicated type B dissection have a 30-day mortality rate of 10% [78]. Conversely, those who develop an ischaemic leg, renal failure, visceral ischaemia or contained rupture often require urgent aortic repair; their mortality rate is 20% by day 2 and 25% by day 30. Not surprisingly, advanced age, rupture, shock and malperfusion are the most important independent predictors of early mortality [80–82].

Patients with suspected acute aortic dissection should be admitted to an intensive care or monitoring unit and undergo diagnostic evaluation immediately. Pain and blood pressure control to a target systolic pressure of 110 mmHg can be achieved using morphine sulfate and intravenous beta-blockers (metoprolol, esmolol or labetalol) or in combination with vasodilating drugs such as sodium nitroprusside or angiotensin-converting enzyme inhibitors. Intravenous verapamil or diltiazem may also be used if beta-blockers are contraindicated. Monotherapy with beta-blocking agents may be adequate to control mild hypertension and, in concert with sodium nitroprusside at an initial dose of 0.3 μg/kg/min, is often effective in a severe hypertensive state (Table 34.5). In normotensive or hypotensive patients, careful evaluation for loss of blood, pericardial effusion or heart failure (by cardiac ultrasound) is mandatory before administering volume. Patients with profound haemodynamic instability often require intubation, mechanical ventilation and urgent bedside transoesophageal echocardiography or rapid CT for confirmatory imaging. In rare cases, the external ultrasound diagnosis of cardiac tamponade may justify immediate sternotomy and surgical access to the ascending aorta to prevent circulatory arrest, shock and ischaemic brain damage. Percutaneous pericardiocentesis as a temporizing step has often failed, and can accelerate bleeding and shock [135].

Surgical management

The aim of surgical therapy in proximal type A (type I, II) aortic dissection is prevention of rupture or development of pericardial effusion, which may lead to cardiac tamponade and death. Similarly, sudden onset of aortic

Table 34.5 Management of patients with suspected aortic dissection

Class	Recommendation*
I	ECG: documentation of ischaemia
I	Heart rate and blood pressure monitoring
I	Pain relief (morphine sulphate)
I	Reduction of systolic blood pressure using beta-blockers (i.v. metoprolol, esmolol or labetolol)
I	In patients with severe hypertension despite beta-blockers, additional vasodilator (i.v. sodium nitroprusside) to titrate blood pressure to 100–120 mmHg
I	Diagnostic imaging (non-invasive)
II	In patients with obstructive pulmonary disease, blood pressure lowering with calcium channel blockers
II	Imaging in patients with ECG signs of ischaemia before thrombolysis if aortic pathology is suspected
III	Chest radiography

*All recommendations are level of evidence C.

regurgitation and coronary flow obstruction require urgent surgical intervention, with the aim of resecting the region of intimal tear in dissection limited to the ascending aorta and replacement by a composite or interposition graft (if the aortic valves are intact or resuspendable). When the dissection extends to the aortic arch or the descending aorta, resection of the entire intimal flap may not be possible or the patient may require partial or total arch replacement [136]. A recent report highlights the problem of either resecting or leaving unrecognized intimal tears in the arch or descending thoracic aorta, which is seen in 20–30% and predisposes to later distal aortic reoperation [137]. With an operative mortality of 15–35% even in centres of excellence, adjunctive measures such as profound hypothermic circulatory arrest and selective retrograde perfusion of head vessels have been used in the surgical management of arch repair or an open distal anastomosis [138]. Although the latter is gaining growing acceptance for improved outcome (5-year survival of 73 ± 6%), profound hypothermic circulatory arrest has failed to improve early complications, survival and distal reoperation rates in patients with acute type A dissection; 30-day, 1-year and 5-year survival estimates are 81 ± 2%, 74 ± 3% and 63 ± 3%, no different from other techniques using propensity-matched retrospective analysis [136]. The key to success is rapid surgery prior to any haemodynamic instability or deterioration (Table 34.6).

Table 34.6 Surgical therapy of acute type A (type I and II) aortic dissection

Class	Recommendation*
I	Emergency surgery to avoid tamponade/aortic rupture
I	Valve-preserving surgery: tubular graft if normal-sized aortic root and no pathological changes of valve cusps
I	Replacement of aorta and aortic valve (composite graft) if ectatic proximal aorta and/or pathological changes of valve/aortic wall
IIa	Valve-sparing operations with aortic root remodelling for abnormal valves
IIa	Valve preservation and aortic root remodelling in Marfan patients

*All recommendations are level of evidence C.

Once the patient is on extracorporeal circulation and preferably antegrade cerebral perfusion, which is usually established after cannulation of one femoral artery and the right atrium, the aorta is mobilized to visualize the innominate artery and the aortic root. If the valve leaflets are intact, aortic valve reconstruction using David's or Yacoub's resuspension technique is gaining growing acceptance over valve replacement [61,62] (Fig. 34.12).

The approach to an acute type A (type I, II) dissection (see Fig. 34.8) in a previously ectatic proximal aorta requires a different approach. In such instances, mostly in patients with Marfan's syndrome, a composite graft (aortic tube graft with integrated valve) is preferred, with coronary reimplantation [55,56,139]. Surgical allografts and xenografts are experimental since late postoperative degeneration may require reoperation on the aortic root. Valve-sparing operations are delicate endeavours in an emergency and require great surgical competence in centres with expertise in elective cases. If the dissection compromises the left or right ostium without disrupting the coronary vessel, the ostium can usually be preserved. An ostium completely surrounded by dissected aortic wall may be excised in button form. The dissected layers around the ostium are conjoined using tissue adhesive and over-and-over suturing before the anastomosis to a tube graft is accomplished. Bypass grafting of coronary arteries using saphenous vein segments is limited to those instances where a small torn ostium precludes reconstruction.

Aortic arch in acute type A (type I and II) dissection

Treatment of the acutely dissected aortic arch remains an unresolved issue. At present there is growing consensus

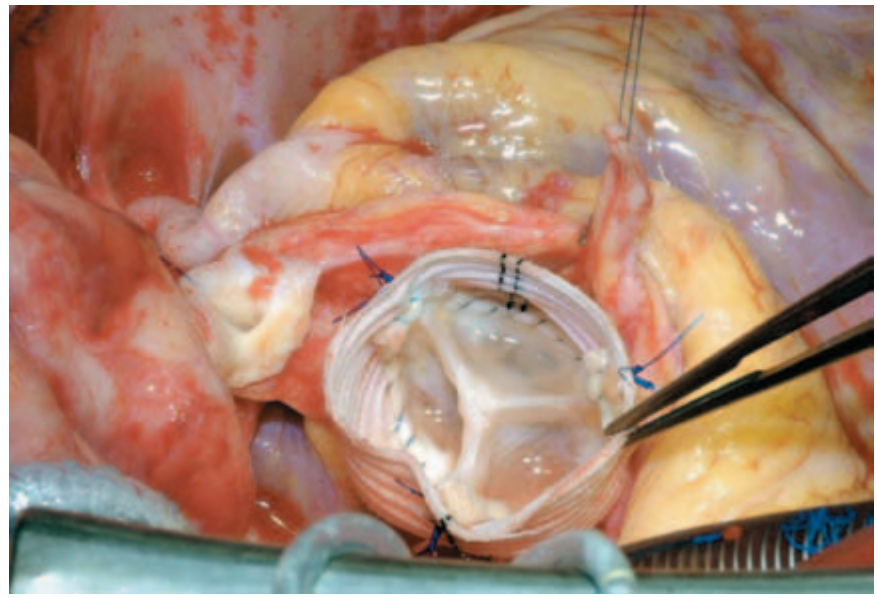


Figure 34.12 Intraoperative view of a re-implanted aortic valve (David technique).

that any dissected arch should be explored during hypothermic circulatory arrest [139,140]. In the absence of an arch tear, an open distal anastomosis of the graft and the conjoined aortic wall layers at the junction of the ascending and arch portions is justified. Arch tears occur in up to 30% of patients with acute dissection [140,141]. Whenever extensive tears are found that continue beyond the junction of the transverse and descending aortic segments, or with acute dissection of a previously aneurysmatic arch, subtotal or total arch replacement may be required, with reconnection of some or all supra-aortic vessels to the graft during hypothermic circulatory arrest and antegrade head perfusion [142].

In dissecting and non-dissecting aneurysms extending to the downstream aorta, an elephant trunk extension of the arch graft is an option described by Borst *et al*. [143]. This technique greatly facilitates later procedures on the downstream aorta. Instead of performing a conventional anastomosis between the end of the graft and the descending aorta, the graft is allowed to float freely in the aortic lumen. In a later procedure the elephant trunk section of the graft may be either connected surgically to the distal descending aorta directly or extended with another tubular prosthesis or interventionally by a customized endovascular stentgraft that may then be anastomosed at any desired downstream level of the aorta (Fig. 34.13).

In summary, surgery is advised without delay in acute type A (type I and II) dissection in order to prevent aortic rupture, pericardial tamponade and death, and to relieve aortic regurgitation.

Surgery in type B (type III) aortic dissection

In the current era, the indications for operative treatment in patients with acute type B (type III) are limited to the prevention or relief of life-threatening complications such as intractable pain, a rapidly expanding aortic diameter or signs of imminent aortic rupture, although these can also be managed by interventional stentgraft placement. The onset of complications such as malperfusion of vital aortic side branches warrants interventional therapy via stentgrafting to improve distal true lumen flow or, in rare instances, via catheter-guided fenestration of an occlusive lamella. When this approach does not lead to prompt relief of symptoms, surgical intervention may still be required. At present uncomplicated type B (type III) aortic dissections are usually treated conservatively, since surgical repair has no proven superiority over medical or interventional treatment in stable patients. In complicated cases, the concept of interventional stentgraft placement is currently being explored [46,144,145].

Interventional endovascular strategy

Conventional treatment of Stanford type A (De Bakey type I, II) dissection consists of surgical reconstruction of the ascending aorta with complete or partial resection of the dissected aortic segment; endovascular strategies have no clinical application except for relief of critical malperfusion prior to surgery of the ascending aorta by distal fenestration in cases of thoraco-abdominal extension

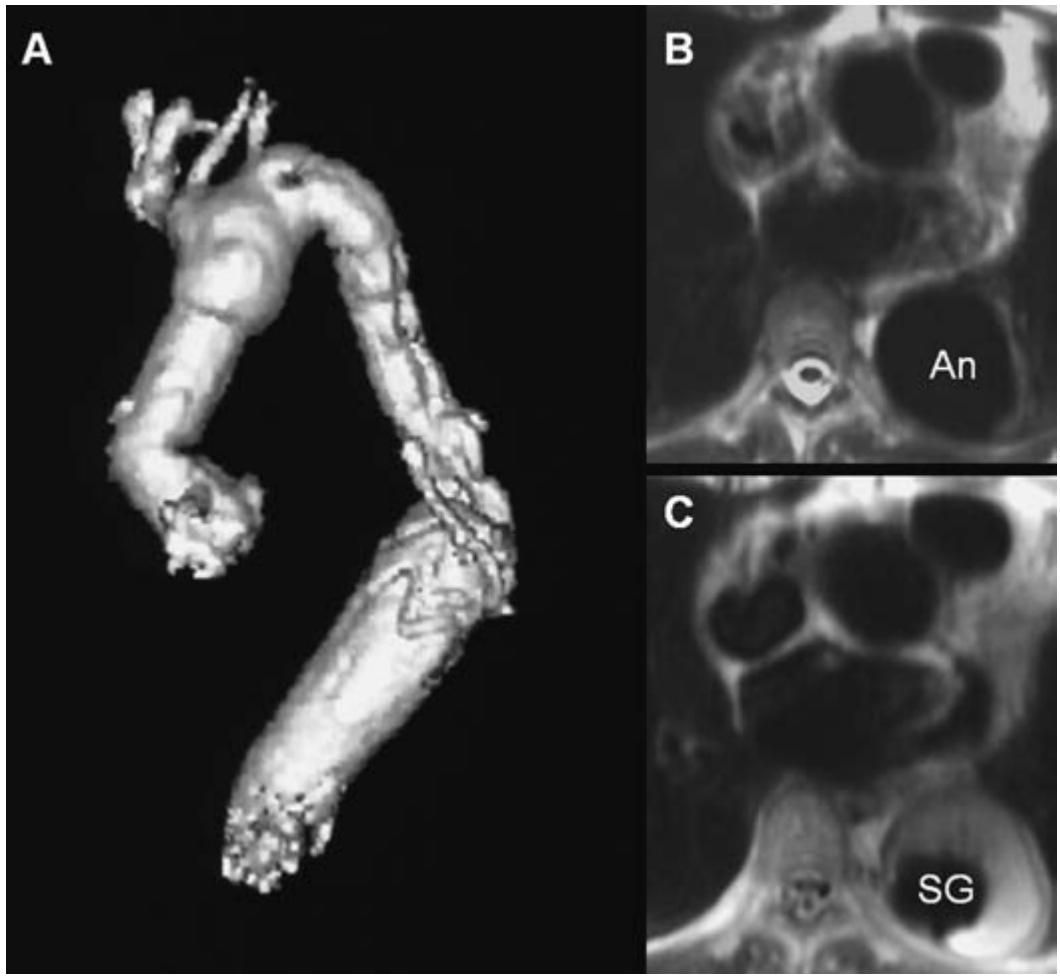


Figure 34.13 (A) Reconstructed three-dimensional magnetic resonance image after percutaneous use of a customized stentgraft to connect a surgically inserted 'elephant trunk' with the upper abdominal aorta in order to exclude an aneurysm that had formed at the distal end of the 'elephant trunk'. (B) After placement of the customized stentgraft, the thoracic aneurysm was successfully excluded from circulation, with thrombus formation around the stentgraft prostheses (C). An, aneurysm; SG, stentgraft.

(De Bakey type I) and peripheral ischaemic complications. However, endovascular stentgraft placement, typically in type B dissection, has the potential to reconstruct the aorta by sealing one (or multiple) proximal entry tears with a Dacron-covered scaffold, thus initiating thrombosis of the false lumen [46,144–146]. Reconstruction of a collapsed true lumen might result in re-establishment of side-branch flow (Fig. 34.14). Most scenarios of malperfusion syndrome are amenable to endovascular management, considering that surgical mortality rates in patients with acute peripheral vascular ischaemic complications are similar to those in patients with mesenteric ischaemia, reaching 89% in-hospital mortality [147,148].

The interventional management of Stanford type B (De Bakey type III) dissection and the use of stentgrafts evolved to avoid the risk of paraplegia from spinal artery occlusion, as seen in up to 18% after open surgery [88,89]. In the near future, combined surgical and interventional procedures even for proximal dissection are likely to emerge [149,150].

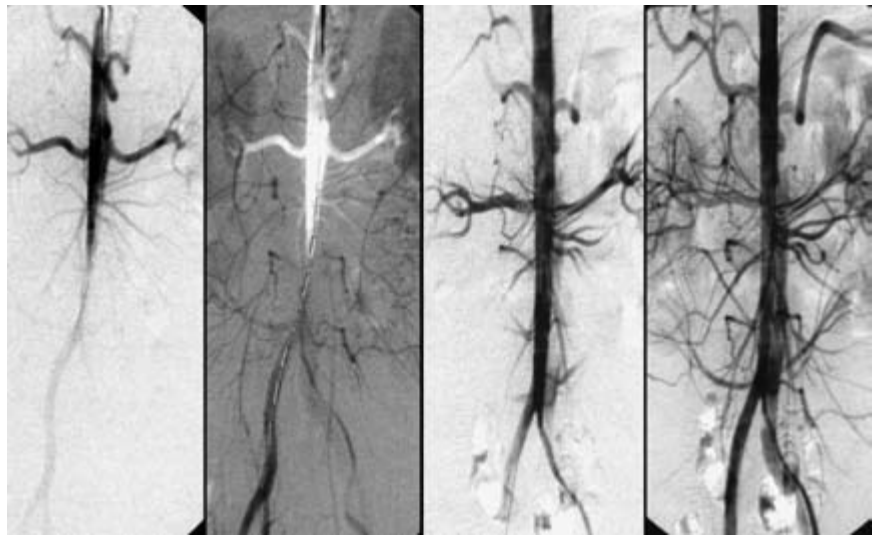


Figure 34.14 Malperfusion of distal aorta by occlusive type B dissection. Stentgraft placement in the true lumen of the proximal descending aorta re-established flow to the abdomen and legs.

Indications for stentgraft placement

There appears to be a role for interventional concepts in the treatment of static or dynamic obstruction of aortic branch arteries: static obstruction of a branch can be overcome by placing endovascular stents in the ostium of the compromised side branch, and dynamic obstruction may benefit from stents in the aortic true lumen. In classic aortic dissection, successful fenestration leaves false lumen pressure unchanged [92]. Sometimes bare stents deployed from the true lumen into side branches are useful for buttressing the flap in a stable position [151]. Conversely, fenestration may increase the long-term risk of aortic rupture because a large re-entry tear promotes flow in the false lumen and provides the basis for aneurysmal expansion of the false lumen; moreover, there is a risk of peripheral embolism from a perfused but partially thrombosed false lumen.

The most effective method for excluding an enlarging and aneurysmal dilated false lumen is the sealing of proximal entry tears with a customized stentgraft; the absence of a distal re-entry tear is desirable for optimal results but not a prerequisite. Adjunctive treatment by fenestration and/or ostial bare stents may help establish flow to compromised aortic branches. Compression of the true aortic lumen cranial to the main abdominal branches with distal malperfusion (so called pseudo-coarctation) may also be corrected by stentgrafts that enlarge the compressed true lumen and improve distal aortic blood flow [46,144,145,148]. Depressurization and shrinking of the false lumen is the most beneficial result to be gained, ideally followed by complete thrombosis of the false lumen and remodelling of the entire dissected aorta; on rare occasions, this even occurs in retrograde type A dissection [151]. Similar to previously accepted indications for surgical intervention in type B dissection, scenarios such as intractable pain with descending dissection, rapidly expanding false lumen diameter, extra-aortic blood collection as a sign of imminent rupture or distal malperfusion syndrome are accepted indications for emergency stentgraft placement [145,151–153]. Moreover, late onset of complications such as malperfusion of vital aortic side branches may justify endovascular stentgrafting as a first option (Table 34.7).

Interventional therapy in an elective setting

With both bare stents in side branches and sometimes fenestrating manoeuvres, compromised flow can be

Table 34.7 Interventional therapy in aortic dissection

Class	Recommendation*
IIa	Stenting of obstructed branch origin for static obstruction of branch artery
IIa	Balloon fenestration of dissecting membrane plus stenting of aortic true lumen for dynamic obstruction
IIa	Stenting to keep fenestration open
IIa	Fenestration to provide re-entry tear for dead-end false lumen
IIa	Stenting of true lumen to enlarge compressed true lumen
IIb	Stenting of true lumen to seal entry (covered stent)

*All recommendations are level of evidence C.

restored in more than 90% (range 92–100%) of vessels obstructed by aortic dissection. The average 30-day mortality rate is 10% (range 0–25%) and additional surgical revascularization is rarely needed [106]. Most patients remain asymptomatic over a mean follow-up time of about 1 year. Fatalities related to the interventional procedure may occur as a result of non-reversible ischaemic complications, progression of the dissection or complications of additional reconstructive surgical procedures on the thoracic aorta. Potential problems may arise from unpredictable haemodynamic alterations in the true and false lumen after fenestration and side-branch stenting. These alterations can result in loss of previously well-perfused arteries or initially salvaged side branches.

Recent reports suggest that percutaneous stentgraft placement in the dissected aorta is safer and produces better results than surgery for type B dissection. Paraplegia may occur after use of multiple stentgrafts but still appears to be a rare phenomenon, especially with stented segment of less than 16 cm. Results of short-term follow-up are excellent, with a 1-year survival rate of > 90%; tears can be re-adapted and aortic diameters generally decrease with complete thrombosis of the false lumen. This suggests that stent placement may facilitate healing of the dissection, sometimes of the entire aorta, including abdominal segments (Fig. 34.15). However, late reperfusion of the false lumen has been observed occasionally, underlining the need for stringent follow-up imaging.

Interventional therapy in an emergency setting

The concept of emergency stentgraft placement for urgent endovascular aortic repair of dissection is attractive, and a growing number of acute type B aortic dissections undergo endovascular repair (with little evidence of periprocedural morbidity, aborted malperfusion or leakage) and reconstruction of the dissected aorta; stentgraft placement in complicated distal aortic dissection is an emerging concept not associated with excessive peripheral or neurological complications in experienced hands [152–154].

In conclusion, current advances with stentgraft thoracic intervention must be viewed as exciting new developments that offer hope to many patients with type B dissection. Technical strategies and devices continue to evolve and it is likely that these techniques will soon become first-line therapy for most patients presenting with anatomically suitable thoracic and thoraco-abdominal aortic lesions.

Long-term therapy and follow-up

The long-term approach to patients with successful initial treatment of acute aortic dissection begins with the appreciation of a systemic illness. Systemic hypertension, advanced age, aortic size and presence of patent false lumen are all factors which identify higher risk, as does the entire spectrum of Marfan's syndrome [155–157]. All patients merit aggressive medical therapy, follow-up visits and serial imaging. It has been estimated that nearly one-third of patients surviving initial treatment for acute dissection will experience extension of dissection or aortic rupture, or require surgery for aortic aneurysm formation within 5 years of presentation. Treatment with effective beta-blockade is the cornerstone of medical therapy. By lowering both blood pressure and dP/dt, beta-blockers have been shown to retard aortic expansion in Marfan's syndrome [158] and that associated with chronic abdominal aortic aneurysms. Blood pressure should be titrated to less than 135/80 mmHg in usual patients and to less than 130/80 mmHg in those with Marfan's syndrome [4,159,160].

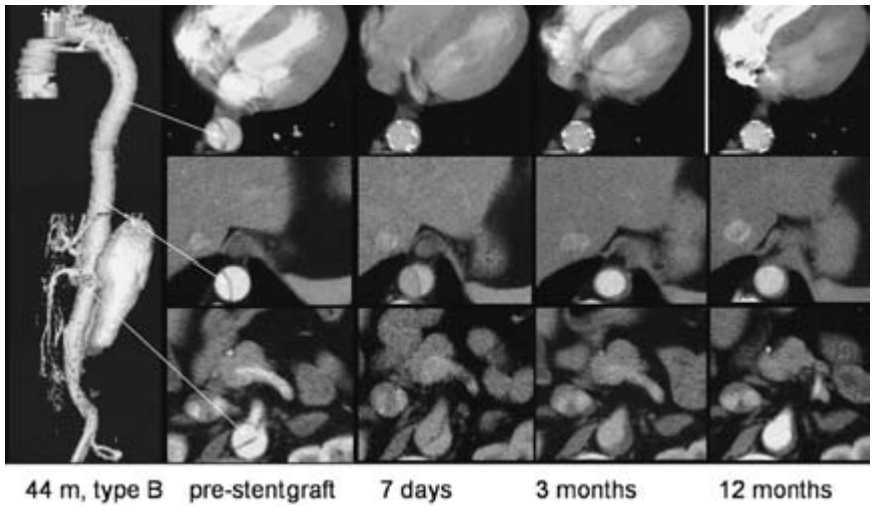


Figure 34.15 Acute type B aortic dissection in a 44-year-old man; note the communications between the true and false lumen at the thoracic and abdominal level. After stentgraft placement across the proximal thoracic entry, the entire aorta including the abdominal segment is reconstructed, with complete 'healing' of the dissected aortic wall and closure of distal communication.

Serial imaging of the aorta is an essential component of long-term management (before and after surgery or stentgraft placement) in Marfan's disease and in all cases of chronic dissection. Choice of imaging modality is dependent on institutional availability and expertise. Previous recommendations suggest follow-up imaging at 1, 3, 6, 9 and 12 months following discharge, and annually thereafter [4]; this aggressive strategy underlines the observation that both hypertension and aortic expansion/dissection are common and not easily predicted in the first months following hospital discharge. Imaging should not be confined to the region of initial involvement since both dissection and aneurysm formation may occur anywhere along the entire length of the aorta.

Development of an ascending aortic diameter of 4.5–5.0 cm is an indication for surgical repair in Marfan's syndrome. In non-Marfan patients, an aortic diameter of 5.5–6 cm warrants repair, as does distal aortic expansion to 6.0 cm or more in all types of patients. As with non-dissecting aneurysms, rate of growth and size of the aorta are both important factors to consider when it comes to prophylactic vascular surgery. An ascending aortic aneurysm of 5.0 cm may merit urgent repair in a young patient with Marfan's syndrome [159]. Conversely, an aneurysm of 5.0 cm present for 3 years in an elderly person with well-controlled blood pressure is unlikely to rupture. Patients who have been treated with surgery and/or endovascular stentgrafting warrant similar follow-up to those whose initial treatment was limited to medical therapy.

Aortic atheromatous disease: thrombotic or cholesterol emboli

Thrombotic or cholesterol emboli of peripheral organs can arise from atheromatous disease of the aorta, with morphological or functional alterations of the aortic wall. Most frequently, atheromatous plaque or ulcers are encountered in the aortic arch and the descending aorta. Aortic intimal morphology is graded according to plaque characteristics.

- Grade I: normal intima.
- Grade II: increased intimal echo-density without lumen irregularity.
- Grade III: increased intimal echo-density with single or multiple well-defined atheromatous plaque of 3 mm.
- Grade IV: atheroma > 3 mm or mobile or ulcerated plaque [161].

Interestingly, reduced compliance of the aortic wall is considered an early expression of atheromatous disease and may promote atheromatous progression. Certainly, dissection membranes and aneurysmatic widenings will alter the laminar flow profile of the aorta and therefore cause mostly thrombotic emboli.

Spontaneous emboli frequently have their origin in ulcerated plaque or plaque with pedunculated or mobile parts [162]. These mobile parts consist of atheromatous material or adhesive thrombotic material; embolic events arise more from plaques without calcifications than from calcified lesions. In echocardiographic images the structures appear mostly echolucent. The incidence of aortic thrombus has been estimated as 2–5% [163–165].

Besides being spontaneous, emboli can be provoked by iatrogenic manipulations. Mechanical manipulation with wires or catheters, for instance during cardiac catheterization, can loosen mobile parts or even cause limited dissections, especially in diseased regions of the aortic wall [166]. Showering of cholesterol crystals occur especially during cardiac catheterization in 1–2%, often with cutaneous signs, renal insufficiency [167] and elevation of C-reactive protein (CRP) [168]. Surgical manipulations during cardiovascular interventions and aortic cannulation or cross-clamping can likewise cause detachment of aortic debris.

Risk factors for such emboli include smoking, hypercholesterolaemia, hypertension, diabetes, elevated homo cysteine levels and increased fibrinogen levels. Furthermore, hormone therapy and procoagulative disease can increase aggregation of thrombocytes and promote thrombotic events. While embolic events into the lower limbs or the abdominal organs rarely cause significant clinical symptoms, embolic events to the brain and the retina are symptomatic. Amarenco *et al.* [169] have identified aortic plaque (measured as aortic wall thickness) of 4 mm as a major risk factor for cerebral stroke besides the occurrence of atrial fibrillation and internal carotid stenosis. In patients with such atheromatous plaques, the annual risk of an embolic stroke is 12% [170].

The diagnosis of patients at risk for embolic events is often prompted when the first embolic event has already occurred. Transoesophageal echocardiography is the first modality to be employed and gives adequate image quality for assessment of the aortic valve, the ascending aorta, as well as the descending part to the level of the diaphragm (Fig. 34.16). However, it should be noted that the transoesophageal echo is unable to analyse the abdominal aorta or parts of the aortic arch as the left main bronchus is interposed between the oesophagus and the aortic arch [4]. The aorta can be further analysed by contrast-enhanced CT and by MRI using 1.5-T

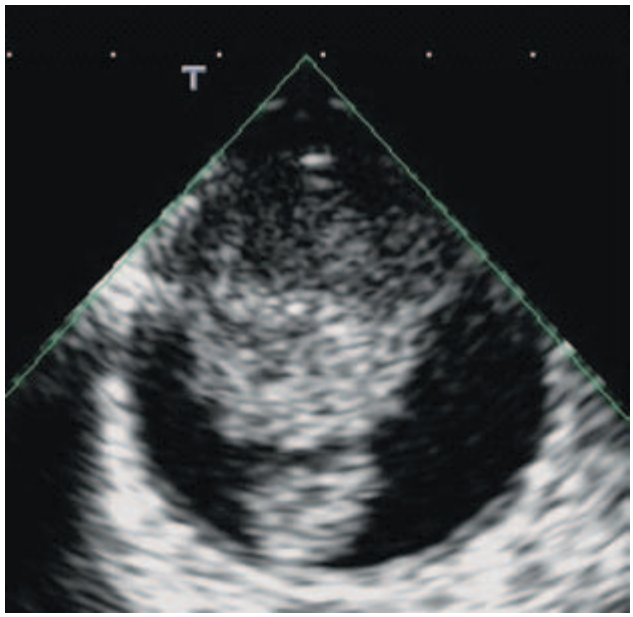


Figure 34.16 Transoesophageal echocardiography of mobile plaque with thrombus.

machines with good resolution especially for small pathological changes of the aortic wall. Experimental studies reveal that the diagnostic use of small iron oxide particles can improve plaque imaging of the aortic wall [171].

Intravascular ultrasound certainly has a higher risk of complications than non-invasive techniques but is clearly superior in imaging quality and is suited for differential diagnosis. In addition to superb image quality of the aortic wall and plaque characteristics, intravascular ultrasound allows imaging of the whole aorta. The newer AcuNav System (Acuson, Malvern, PA, USA) is a 10F miniaturized steerable echo-probe that can nevertheless only reach the descending aorta [172].

As there is no clear therapy for emboli, medical strategies should be clearly directed towards risk factor management and prevention. In this context, blood pressure control and cholesterol reduction using statins as well as optimization of blood glucose are considered important. Moreover, platelet inhibition is recommended as a preventive measure, while the use of antiaggregatory agents or anticoagulant drugs is controversial. Only few authors see a clear risk reduction in cerebral events with an INR value between 1.5 and 3 [173]. In general, a note of caution is raised on the use of anticoagulant drugs. Anecdotal reports have indeed suggested that in patients with cholesterol emboli, anticoagulation may favour further embolization (e.g. blue-toe syndrome). The hypothesis is that anticoagulation prevents thrombus formation on ulcerated plaques, allowing the release of atheromatous material contained in the plaques. Although the value of antithrombotic drugs is controversial, such patients are at high risk of vascular events [174]. In patients with atheromatous disease of the aorta or at risk for embolic events, statin therapy has shown superior outcome than warfarin or antiaggregation [175].

In summary, thrombotic or cholesterol emboli are a clearly underestimated clinical entity. In particular, cholesterol embolization is a rare but serious complication of cardiac catheterization. Our goal should be directed at the identification of risk groups and individual patients at risk for such events. Patients with suspected aortic disease should undergo a detailed analysis of the entire aorta using transoesophageal echocardiography and non-invasive tomographic imaging modalities. The therapy should be individualized and aimed at the reduction of risk factors and should include the use of statins.

Aortitis

Definition

Aortitis is defined by inflammation of the aorta, categorized by the underlying aetiology into (1) infective syphilitic aortitis, (2) infective non-syphilitic (bacterial or fungal) aortitis, or (3) non-infective aortitis due to large-vessel vasculitis (e.g. Takayasu's arteritis, giant-cell arteritis) or atherosclerosis. Determining the individual aetiology of aortitis is of particular importance because immunosuppressive therapy can aggravate an active infectious process.

Pathophysiology

Infectious agents can destroy the medial layers of the aortic wall by direct invasion and subsequent inflammatory reactions. Bacterial or fungal infections may trigger non-infectious vasculitis by generating immune complexes or by cross-reactivity. By analogy with infective endocarditis, bacterial or fungal aortitis often develops following bacteraemia in the place of least resistance (e.g. pre-existing atherosclerotic lesions or aneurysms) [176,177].

Aortitis is the principal cardiovascular manifestation of tertiary syphilis, found mainly in the ascending aorta [4]. Whereas cardiovascular syphilis was a relatively frequent disorder at the beginning of the last century, tertiary syphilis has been almost eradicated with the use of penicillin and is today a medical curiosity. However, tertiary syphilitic lesions may persist despite treatment in patients with compromised immune status [178].

Staphylococcus aureus accounts for the majority of Gram-positive infections; aortitis has also been observed in association with streptococci [179,180]. Gram-negative bacilli such as *Salmonella* and *Proteus* species, and *Escherichia coli* have been described [177]. Less common causes include tuberculous infections and fungal agents such as *Candida*, *Cryptococcus* and *Aspergillus* species [180–182].

Autoimmune disorders can severely affect the vasa vasorum, and decrease the blood supply of the media [4]. Diseases affecting the aorta are diverse and include serum sickness, cryoglobulinaemia, systemic lupus erythematosus, rheumatoid arthritis, relapsing polychondritis, Behçet's disease, Henoch–Schönlein purpura and postinfectious or drug-induced immune complex disease [30,183–187]. Also, antineutrophil cytoplasmic autoantibody (ANCA)-associated small-vessel vasculitides can affect the large vessels, as in Wegener's granulomatosis, microscopic polyangiitis and Churg–Strauss syndrome [188]. Other antibodies, such as antiglomerular basement membrane (Goodpasture's syndrome) and anti-endothelial (Kawasaki's disease), can also be targets. Transplant rejection, inflammatory bowel diseases and paraneoplastic vasculitis also may afflict the large vessels.

The causes of aortitis in Takayasu's arteritis and giant-cell arteritis (temporal arteritis, granulomatous arteritis) are unknown. Takayasu's arteritis is a chronic inflammatory disease of the large vessels that mainly affects the thoracic aorta and its branches, but can also occur anywhere in the vascular system [189]. Giant-cell arteritis usually affects the medium-sized extracranial arteries but may also affect the aorta in 10–15% of patients [190,191].

Histologically, aortitis is characterized by inflammatory lymphocytic infiltrates within the medial layers of the aortic wall and around the vasa vasorum, smooth muscle and fibroblast necrosis, and fibrosis of the vessel wall [4]. In syphilitic aortitis, *Treponema pallidum* invades the vasa vasorum, initiating inflammatory changes consisting of lymphocytic and plasma cell perivascular infiltrates that lead to endarteritis obliterans, adventitia scarring, and patchy necrosis of the medial layer with elastic fibre destruction [192]. The inflammatory reactions within the aortic wall may cause local weakening resulting in aortic dilation up to aneurysm formation [4]. 'Mycotic' aneurysms are often characterized by rapid expansion. Moreover, aortitis can cause fibrous thickening of the aortic wall and subsequent ostial stenosis of major branches up to chronic arterial occlusions [193].

Clinical presentation

Diagnosing aortitis is clinically challenging because symptoms are non-specific and present as fatigue, malaise, joint aches and low-grade fever as well as raised serum markers of inflammation. Carotidynia due to vascular inflammation presenting as neck pain can be an important clue. These symptoms can be accompanied by more specific clinical symptoms due to inflammatory stenoses of major arterial branches, such as reduced or absent peripheral pulses, ocular disturbances, neurological deficits, claudication up to ischaemic gangrene, or angina pectoris up to myocardial infarction in cases of coronary ostial involvement [192]. Aortitis-related aneurysm of the ascending aorta may become clinically overt with the appearance of new-onset diastolic murmur and signs of heart failure in cases of severe aortic regurgitation. However, the combination of clinical signs of infection (fever, raised laboratory markers), new-onset murmur and multiple ischaemias may mimic infective endocarditis. Syphilitic or mycotic aneurysms are often indolent and show rapid progression [192,194].

Diagnostic procedures

On physical examination, patients appear chronically ill with mild fever. Reduced blood pressure or laterality (i.e. a difference > 10 mmHg between left and right arms) suggests vascular obstruction. Arterial pulse intensity in any of the limbs may be diminished. Bruits may be audible at carotid arteries, abdominal aorta and even the subclavian and brachial arteries.

Laboratory examination may reveal elevated acute-phase proteins (CRP, fibrinogen) and erythrocyte sedimentation rate as evidence of inflammatory processes. In patients with clinically diagnosed Takayasu's arteritis, high titres of anti-endothelial antibodies have been detected.

Traditionally, angiography was used as the imaging 'gold standard' for diagnosing aortitis by detecting luminal abnormalities (aneurysms or ostial stenosis of major branches) but is not useful for detecting early mural findings. Nowadays, modern tomographic imaging techniques are considered the method of choice, as they allow evaluation of early changes within the vessel wall [195,196]. Characteristic features on contrast-enhanced CT, MRI or transoesophageal echocardiography include thickening of the aortic wall with or without stenosis of major adjacent aortic branches, irregular enhancement of peri-aortic tissue, aortic dilatation or (irregular) aortic aneurysms [197–199]. A peri-aortic collection of blood, fluid or gas or adjacent vertebral osteomyelitis may suggest infectious aortitis [177]. These modalities are also used in the follow-up of patients, because MRI and CT are able to show reduction of wall thickening after initiation of treatment [195]. Recently, [^{18}F]-fluorodeoxyglucose PET has been shown sensitive

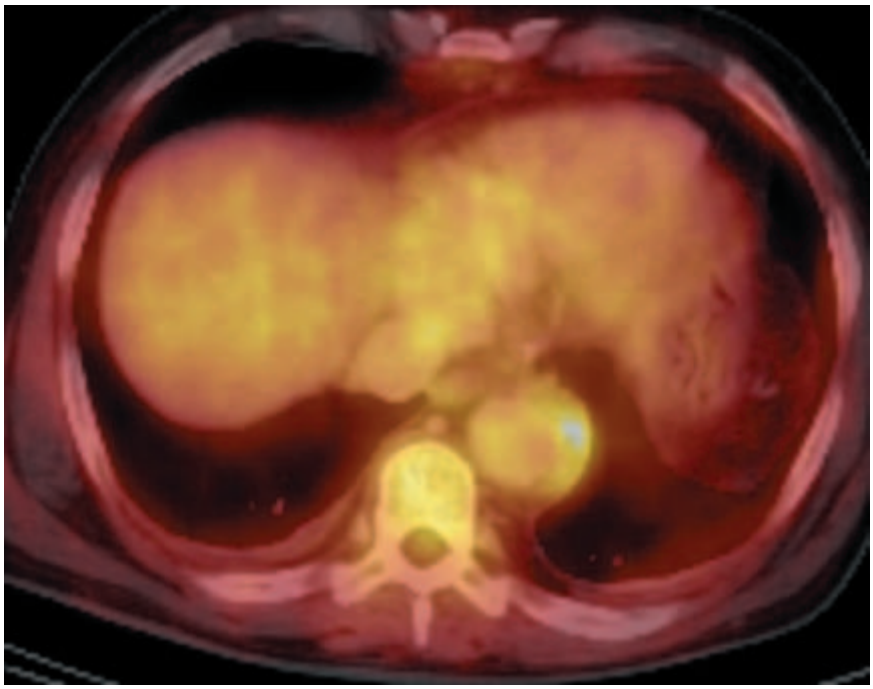


Figure 34.17 Demonstration of increased ^{18}F-deoxyglucose uptake within the wall of the descending thoraco-abdominal aorta by positron emission tomography/computerized tomography indicating non-infective aortitis due to severe atherosclerosis and inflammation.

in detecting inflammatory aortic changes (Fig. 34.17) [195].

Therapy

In syphilitic aortitis, antibiotic treatment with benzylpenicillin 10–20 million units is the widely accepted treatment, although no controlled trials have shown its efficacy [192]. The optimal management of infective non-syphilitic aortitis requires early surgical intervention in addition to prolonged antibiotic/antimycotic administration [177,180,200]. With mere antimicrobial therapy, the mortality rate of infective aneurysms approaches 90% due to continued aneurysm growth and subsequent rupture [180]. Early surgical intervention with resection of the infected aorta with wide débridement and extra-anatomical bypass grafting has greatly increased survival [201,202]. Recently, endovascular stentgraft placement has been suggested as a novel, less invasive alternative [203]. After surgery, bactericidal antibiotic therapy is usually continued for at least 6 weeks [204]. The mainstay of therapy for patients with non-infective aortitis is corticosteroids; however, a substantial percentage of patients require additional immunosuppressive agents such as cyclophosphamide, methotrexate or mycophenolate mofetil. Daily prednisone in doses of 1 mg/kg, not to exceed 60 mg/day, should be given for 1–3 months to patients with active arteritis. Long-term low-dose prednisone therapy may be necessary to prevent progression of arterial stenoses. Balloon angioplasty, stenting or bypass surgery may be necessary for revascularization of aortitis-related arterial stenosis [205,206]. In cases of enlarging aortic aneurysms due to non-infective aortitis, radical surgical resection is indicated [193].

Traumatic rupture of the aorta

Aetiology

Traumatic aortic rupture (TAR) is a lesion due to blunt trauma involving the aortic wall, from the intima to the adventitia. The first annotation of TAR was in 1557 by Vesalius, who described a patient with an aortic rupture after falling off a horse. In 1923 Dshanelidze in Russia reported the first successful repair of TAR in a penetrating lesion of the ascending aorta, followed by pioneering reports in the 1950s [207]. A pathological study, which is still the largest series of 296 cases, clearly defined the characteristics of aortic lesions and emphasized the time relationships between the trauma and subsequent death. The era of high-speed motor vehicles has brought an increased incidence of TAR [208]. Between 1936 and 1942 in a cohort of 7000 autopsies, Strassman [209] found only 51 patients with TAR secondary to vehicular collision,

whereas several recent investigations have shown that TAR occurs in 10–30% of adults sustaining fatal blunt trauma. Richens *et al*. [210] reported 21% of mortality due to aortic rupture in a sample of 613 fatalities of road traffic accidents and accounts for 8000 victims per year in the US [209,211].

Pathogenesis

TAR can result from car and motorcycle collisions, falls from a height or blast injuries, airplane and train crashes, and skiing and equestrian accidents. In a demographic analysis of 144 patients with aortic rupture, Hunt *et al*. [212] reported motor vehicle crash in 83%, motorcycle in 4.9%, pedestrian in 7% and falls in 2.1% of cases. Even lateral impact accounts for 20–40% of cases in recent studies [211]. The shearing forces in lateral collision seem to produce most frequently a partial laceration involving the lesser curvature of the distal part of the aortic arch, just above the isthmus [213,214]. Airbags and seatbelts do not protect against this type of impact [211,213]. The region subject to the greatest strain is the isthmus, where the relatively mobile thoracic aorta joins the fixed arch and the insertion of the ligamentum arteriosus. Aortic ruptures occur at this site in 80–95% [34,210,212,213]. Because of the high immediate mortality of traumatic rupture of the ascending aorta, this location has been reported in 10–20% of the autopsy series vs. 5% of the surgical cases [34,213,215]. Other less common locations are distal segments of the descending aorta (12%) or the infrarenal segment (4.7%). Multiple sites of aortic tears are found in some reports [34]. Different theories have been advanced to explain the mechanism of aortic injury. Considering different causes and types of impact that produce the aortic lesion, it is reasonable to claim not only one mechanism but a combination of many [216–220].

Mechanisms of rupture

A traumatic lesion may be classified as (1) intimal haemorrhage, (2) intimal haemorrhage with laceration, (3) medial laceration, (4) complete laceration of the aorta, (5) false aneurysm formation and (6) peri-aortic haemorrhage [34]. Intimal haemorrhage may leave an intact endothelial layer or may be associated with circumscribed laceration of the endothelial and internal elastic lamina of the intima. When the lesion involves intimal and medial layers, false aneurysm formation can occur. The aneurysm is fusiform in the case of a circumferential lesion, involving the entire wall on the transversal plane, while in a partial lesion in which only a portion of the wall is lacerated, it appears as a localized diverticulum. Peri-aortic haemorrhage occurs independently of the type of lesion. While complete rupture of the aorta including adventitia and peri-adventitial connective tissue leads to immediate death, formation of an aneurysm or occlusion of the site of rupture may permit temporary survival.

Clinical features

Clinical presentation

Despite the severe nature of injury, clinical signs may not be impressive and thus it is imperative to mantain a high index of suspicion in victims of high-speed decelerating injuries, regardless of external evidence of thoracic injury.

The signs of aortic rupture are not specific, and the presence of coexisting head, facial, orthopaedic and visceral lesions dominates the physician's attention. Dyspnoea and chest pain are prominent symptoms, localized in the back in 20–76% of cases. Loss of consciousness and hypotension are also frequent, as generally reported in polytraumatized patients, while generalized hypertension is reported in about 17% [221]. Systolic blood pressure < 90 mmHg despite adequate fluid resuscitation is considered to be a sign of haemodynamic instability and associated with higher mortality [210]. Less frequent symptoms include dysphagia and hoarseness. A small number of patients (6%) have paraplegia without obvious spinal malperfusion [222]. Difference in pulse amplitude between upper and lower extremities from compression of the aortic lumen by a peri-aortic haematoma is seen in 23% [221] to 37% [223]. If the intimal and media tear forms a flap which acts as a ball valve, partial aortic obstruction occurs, with upper extremity hypertension reported as 'acute coarctation syndrome' or 'pseudocoarcation' [224]. Hypertension may be secondary to stretching or stimulation of the cardiac plexus. Hypotension < 90 mmHg despite adequate fluid volume resuscitation and free exsanguination into the pleural space, often worsening despite thoracotomy, are considered to be signs of forthcoming free aortic rupture [210,225–228]. Likewise, vocal cord palsy, or tracheal and superior vena cava compression may herald severe expansion [223].

Associated lesions are present in almost all patients with TAR, ranging from fractures and head injuries to spleen, liver and cardiac as well as lung contusion [221,229,230]. The latter can cause respiratory insufficiency, while cardiac contusion results from compression of the heart between the sternum and the vertebral column in 20% of cases, frequently if the ascending aorta is involved. Finally, normal physical findings are reported in 5–14% of cases [215,221].

Diagnostic procedures

The common denominator of TAR is its unpredictable and unfavourable outcome. Therefore, early diagnosis and appropriate treatment are essential. The most important diagnostic imaging modalities are transoesophageal echocardiography, contrast-enhanced CT, MRI and contrast angiography. There is growing interest in, and use of, three-dimensional MRI and CT due to the high sensitivity of reconstruction. Computer-enhanced three-dimezsional reconstruction of the aorta can serve as a blueprint for surgical or interventional therapeutic procedures.

Management

With improved resuscitation and transport logistics, almost all patients with TAR who reach the hospital alive are candidates for aortic repair. Until recently, emergency surgery was universally accepted for TAR [34]; however, immediate surgery has been characterized by high mortality and morbidity. Surgery within 6 h of arrival had an intraoperative mortality of 10.2%, postoperative mortality of 18.4% and major postoperative morbidity (e.g. paraplegia) of 10.5% [212]. Because of these unsatisfactory results of surgery, alternative treatment protocols have been explored [229–233].

Maggisano *et al*. [234] showed that there are two populations of patients with TAR. The first group is represented by patients who reach the hospital in an unstable haemodynamic condition with signs of active bleeding; the survival rate of these patients is low at 17.7%. The second group includes haemodynamically stable patients in whom the diagnosis is obtained by chest radiography and aortography. Surgical repair can be delayed if coexisting injuries increase the risk of operative mortality and morbidity. The risk of fatal free rupture in these patients is low (4.5% within 72 h) and justifies waiting.

If complete rupture of the aorta does not occur with the traumatic impact, the adventitia and the surrounding mediastinal structures guarantee continuity of the aortic wall. This first phase after the trauma is life-threatening and victims should be taken to hospital as quickly as possible. Prompt diagnosis of aortic wall injury is mandatory and therapeutic hypotension with vasodilators and beta-blocking drugs should reduce aortic wall stress and the risk of lethal aortic rupture. Pate *et al*. [230] analysed 15 years of data and their own experience of risk of free haemorrhage in patients affected by acute TAR in the interval between diagnosis and delayed surgical repair. Of the 492 patients in reports specifying the cause of death, 22 (4.5%) died of aortic rupture, mostly presenting with haemodynamic instability and active bleeding into the pleural space on arrival; in patients in whom the pseudo-aneurysm or haematoma was contained within the mediastinum and who did not present with signs of haemodynamic instability or exsanguination, rupture appeared to be uncommon.

On subsequent days after the trauma, a process of organization of the haematoma usually develops and with time it will turn into strong fibrous tissue, with the formation of a pseudo-aneurysm, which has the same risk of rupture as a true aneurysm of similar size. An arterial systolic pressure exceeding 90 mmHg should be an indication to limit fluid replacement for haemodynamic support in hypotensive patients. Monitoring of respiratory function and eventual intubation and mechanical ventilation are fundamental in polytraumatized patients with respiratory insufficiency from injury to the central nervous system, pulmonary contusion and pleural effusion [235,236].

The strategy of delaying surgical repair of post-traumatic aortic aneurysms in selected patients offers clear advantages. The overall mortality and incidence of major complications are reduced in an elective scenario compared with an emergency operation. All the necessary procedures of distal aortic perfusion can be safely performed and the mortality is also reduced by prior treatment of potentially lethal associated lesions in polytraumatized patients [225,237]. Therefore, the treatment of associated lesions is fundamental in these patients and is another incentive to delay surgical intervention in the aorta. However, delayed surgery cannot be applied in every case [238–240]. Even if the majority of traumatic aortic ruptures are stable lesions, in approximately 5% of them the risk of rupture may be high in the acute phase. Signs of impending rupture, such as peri-aortic haematoma, repeated haemothorax, contrast medium extravasation and uncontrolled blood pressure, are considered signs of instability. Sometimes the aortic tear, acting as a valve mechanism, may cause a pseudo-coarctation syndrome, producing a reduction of flow in the descending aorta with lower extremity ischaemia. This complication, which represents a surgical emergency, accounts for 10% of victims.

Endovascular techniques offer a less invasive option for these patients in whom emergency treatment is necessary. By avoiding thoracotomy and heparin, this technique can be applied in the acute phase without the risk of destabilizing pulmonary, head or abdominal traumatic lesions. The correct timing of aortic repair in a polytraumatized patient should be balanced against other injuries, without a fixed priority.

Surgical and interventional procedures in typical TAR

For surgery the patient is positioned in the right lateral

decubitus position with the left hip rolled back to expose the left groin sufficiently to allow access to the femoral vessels. The aortic isthmus is approached via a left posterolateral thoracotomy through the fourth or fifth intercostal space. After opening the pleural space and removing any clots that may be present, the aorta must be controlled above and below the adventitial haematoma. The damaged aortic wall is manipulated only after vascular clamping. The proximal clamp can be positioned below or above the left subclavian artery depending on its involvement within the rupture; various techniques can ensure perfusion of the distal aorta and are discussed below. Once the haematoma is opened, the margins of the rupture can be identified; if the aortic tear is sufficiently limited, a primary wall repair with stitches reinforced with Teflon pledgets should be considered. Frequently, an interposition of preclotted Dacron graft is required. The choice of surgical technique is based on the type of lesion and the time of execution: primary sutures (also with pledgets) (Fig. 34.18A) and end-to-end anastomoses are suitable in patients with linear lesions without extensive dissection and in young patients with an easily mobilized aorta (Fig. 34.18B). A tube prosthesis is recommended in lacerated or multiple lesions, with wide intimal dissection, and in elderly patients with atherosclerotic lesions (Fig. 34.19).

Rupture involving the anterior portion of the aortic arch is usually characterized by partial or complete avulsion of the brachiocephalic trunk. In these cases the surgical approach is via a median sternotomy and the

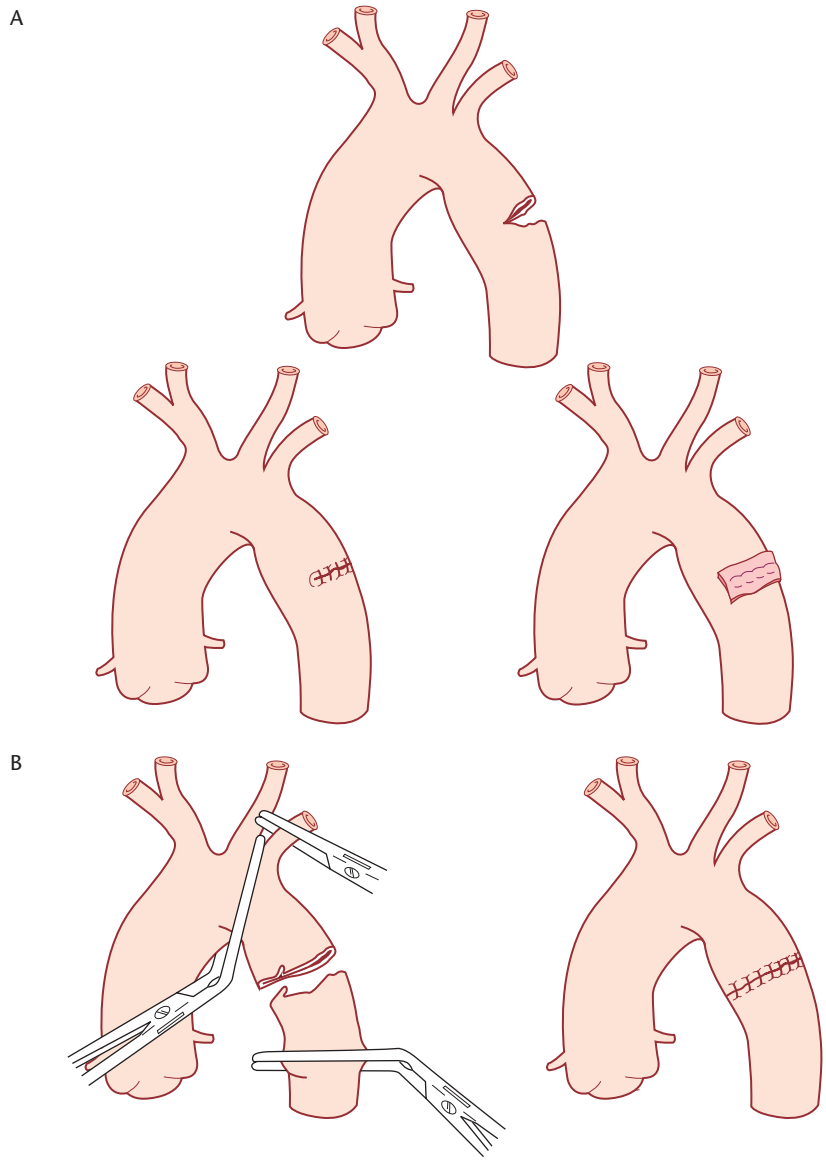


Figure 34.18 (A) Surgical patch repair after traumatic rupture of the descending aorta at the isthmus. (B) Clamping and end-to-end anastomosis after complete transsection of the aorta.

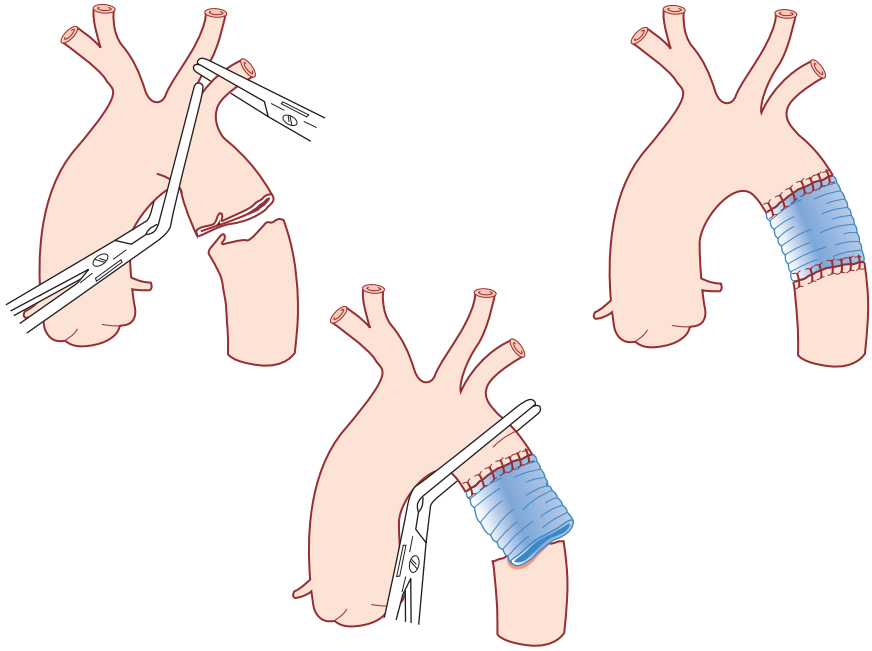


Figure 34.19 Surgical repair by clamping and insertion of an inter-position graft for complete traumatic transsection of the aorta.

operation is performed with the patient in cardiopulmonary bypass and deep hypothermia with complete circulatory arrest. The extracorporeal circulation can be right atrium–femoral artery or femoral vein–femoral artery to be implanted before sternotomy. The operation involves completely detaching the brachiocephalic trunk, repairing the aortic arch with a Dacron patch or replacing it with a Dacron tube prosthesis and re-implanting the brachiocephalic trunk on the ascending aorta with the interposition of a prosthesis. In the case of rupture of the ascending aorta, the involved segment needs to be replaced during heart cardioplegic arrest and extracorporeal circulation, either right atrium–femoral artery or femoral vein–femoral artery.

Spinal cord protection

All surgical techniques that use aortic clamping at the level of the descending aorta disrupt spinal cord perfusion and blood pressure; hypertension is extensive above the cross-clamp while hypotension may compromise the spinal cord, kidneys and other abdominal organs below the clamp. The risk of paraplegia, common in operations on the thoracic descending aorta, is particularly elevated in patients with traumatic aortic rupture. Katz *et al*. [241] found a 24% incidence of ischaemic damage to the spinal cord with postoperative paraplegia. This complication is directly correlated with the length of flow interruption and increases proportionally beyond 30 min. Efforts to reduce the incidence of cordal ischaemia by whole-body surface hypothermia, localized cooling of the spinal cord, intrathecal administration of drugs, systemic administration of steroids and perfusion of the distal aorta were not all convincing [242–244]. An extracorporeal circulation can be used with partial bypass between the femoral vein and artery; this procedure implies total heparinization of the patient and therefore carries a risk of haemorrhage. Left atrium–femoral artery bypass with partial or without heparinization performed with a centrifugal pump offers an adequate blood flow to the distal aorta and the abdominal organs, reduces blood volume overload and the overall pressure to the cardiocirculator system above the cross-clamp, and prevents possible haemorrhagic complications [245].

An overview by von Oppel *et al*. in 1994 [228] disclosed a 25% incidence of paraplegia when the surgical repair was performed by simple cross-clamping. By significantly increasing the distal perfusion the incidence of paraplegia was reduced to 5.2%. Moreover, the two types of distal perfusion differed significantly, because paraplegia developed in 15.6% of patients submitted to 'passive' perfusion and in 2.5% of patients submitted to 'active' perfusion. However, overall operative mortality is still 18.2% for cardiopulmonary bypass, 11.9% for perfusion without heparin, 12.5% for shunts and 16% for simple aortic cross-clamping.

Outcomes

After initial limited series and case reports, endovascular treatment is going to become the method of choice in the management of TAR [246–250]. By avoiding

thoracotomy and the use of heparin, endovascular repair can be applied in the acute patient without the risk of threatening pulmonary, head or abdominal traumatic lesions. The risk of paraplegia seems to be very low in endovascular techniques. Therefore we may expect a very low rate or absence of paraplegia when using short stentgraft coverage of a post-traumatic aneurysm.

Trauma to the heart

Aetiology

Trauma is the most common cause of death for men under 40 years of age, with 25% related to chest trauma. Isolated chest trauma is responsible for 10% of all fatal traumas [251] as a result of penetrating or non-penetrating injuries or blunt trauma to the heart. For penetrating injuries, the underlying cause may be stab wounds from knife, ice pick, stiletto or screwdriver that has been violently driven into the chest. Other causes are missiles, shotgun wounds or iatrogenic injury such as chest tubes or needle biopsy. While stab wounds most commonly injure the right ventricle, high-velocity missiles rupture the heart.

The most common cause of blunt cardiac injury is a high-speed motor vehicle crash in which the driver's chest impacts the steering wheel. Motor vehicle accidents are responsible for 70% of all chest wall injuries [252]. Other causes are falls from height, blast injuries, sports collisions and assaults. The incidence of blunt cardiac injury, formerly called myocardial contusion, ranges from 8 to 71% after blunt chest trauma [253]. Blunt cardiac rupture is almost immediately fatal in more than 90% of victims and may be directly responsible for 10–30% of all deaths after blunt chest injury [251,254].

Pathophysiology

Penetrating cardiac trauma is caused by direct injury of cardiac structures due to penetration of a foreign body. The result may be injury to the pericardium, laceration of the epicardium with possible damage to the coronary arteries, and penetration through the myocardial wall opening a connection between the chambers and the pericardium. All structures of the heart can be injured directly and may cause the specific pathophysiological patterns observed for myocardial infarction, acute valvular insufficiency, creation of intracardiac shunts and injury to the conduction system (Fig. 34.20). However, most stab wounds result in acute pericardial tamponade, although rapidly exsanguinating haemorrhage into the pleural space is also possible. Therefore, the clinical presentation of patients with stab wounds is dominated by the typical signs of cardiac tamponade and/or haemorrhagic shock. Cardiac wounds caused by missiles usually result in acute haemorrhagic shock with frequently fatal outcome. The clinical status is typically profound hypotension with tachycardia and collapsed veins. On their way to the heart, penetrating foreign bodies frequently injure the pleural space, internal mammary vessels, lung

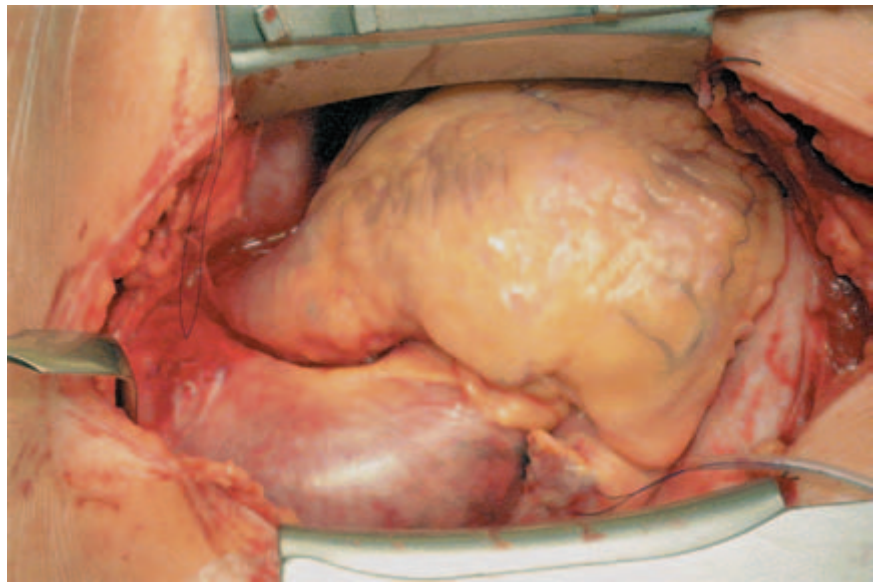


Figure 34.20 Intraoperative aspect of a 'blue aorta' after acute aortic dissection Stanford type A.

including pulmonary vessels and/or occasionally structures of the abdominal viscera.

Blunt cardiac injury may be caused by compression of the heart between the sternum and vertebral column, or by sudden deceleration of the chest causing the heart to be thrust forward against the sternum with consequent sudden increase in intracardiac pressure. The possible result may be rupture of the free cardiac wall, the ventricular septum, the tensor apparatus or leaflets of the atrioventricular valves or the cusps of the aortic valve. Also described are coronary artery fistula to a cardiac chamber, injury with coronary artery thrombosis, and damage to the conduction system causing bundle branch block or arrhythmias with cardiac arrest or ventricular fibrillation. If the blunt chest impact is less violent, contusion of the myocardium may be the result. Myocardial contusion may result in subepicardial and myocardial haemorrhage and disruption, inflammatory cell infiltration and interstitial oedema.

Clinical features

Penetrating cardiac injury

The diagnosis of cardiac injury must be considered any time the chest is penetrated by a missile or a knife. This is especially true when the entry is medial to the nipple anteriorly or medial to the scapula posteriorly. Careful inspection of the undressed chest is mandatory since stab wounds of stilettos may be missed. The clinical presentation of penetrating cardiac injuries ranges from complete haemodynamic stability to acute cardiovascular collapse and frank cardiopulmonary arrest. Distended neck veins, muffled heart sounds and hypertension represent the classical Beck's triad [255] of patients presenting with full-blown pericardial tamponade. Kussmaul's sign (paradoxical inspiratory distension of neck veins upon expiration) is another classic sign attributed to pericardial tamponade. When blood loss exceeds 40–50% of intravascular blood volume, cessation of cardiac function will occur. It has been controversially discussed that pericardial tamponade has protective as well as negative impacts on outcome after penetrating cardiac injury, i.e. avoidance of exsanguination versus compression of the heart leading to cardiopulmonary arrest [256]. However, medical staff of emergency departments should be aware that cardiac injuries can be extremely deceptive in their clinical presentation. If the patient's condition permits, chest radiography and techniques of cardiac investigation are helpful, such as transthoracic echocardiography, MRI and/or CT. However, the majority of patients with penetrating cardiac injury will reach the emergency room in an unstable condition, often under resuscitation or presenting with pericardial tamponade [259]. Therefore, diagnostic procedures are restricted to the identification of the cause of haemodynamic instability or shock.

The established standard for diagnosis of pericardial tamponade remains subxiphoid access with transthoracic echocardiography [257–260]. Surgical inspection has been relegated to a second line of evaluation. Two-dimensional echocardiography is also the tool of choice for diagnosis of penetrating cardiac injuries, with 90% accuracy, 97% specificity and 90% sensitivity in haemodynamically stable patients [261]. When a haemopneumothorax is associated, the usefulness and value of echocardiography declines significantly [253]; however, echocardiography should be employed both in stable and unstable patients with suspected penetrating cardiac injury, allowing the surgeon to proceed directly to median sternotomy. If diagnostic tools fail to show definite evidence of cardiac penetration in patients presenting with penetrating thoracic injury, diagnostic sternotomy or thoracotomy should be considered liberally.

Blunt cardiac trauma

Blunt cardiac trauma manifests as a variety of clinical conditions, usually in association with multiorgan injuries. The patient with blunt cardiac injury may exhibit severe (or no) symptoms of precordial pain, dysrhythmias, symptoms of acute valvular incompetence, myocardial infarction, intracardiac shunts or the complete picture of cardiac tamponade or shock due to exsanguinating haemorrhage. The most important determinant for diagnostic management is haemodynamic stability. A normal ECG and blood pressure virtually excludes significant injury to the heart. Haemodynamic instability may be related to blood loss caused by additional injuries, but cardiac tamponade must be excluded. The classic 'bruit de Moulin' demonstrates the sound of the heart beating in a pericardium partially filled with air and blood and sounds like a splashing millwheel. Immediate objective assessment of unstable patients suspected of blunt cardiac injury is provided in the majority of cases by echocardiography in the emergency room. If echocardiography shows a mechanical cause for hypotension, rapid surgical intervention is warranted.

The significance of making the diagnosis in asymptomatic patients is not clear, nor is the best method. Probably only 1–20% of asymptomatic patients will develop complications that require treatment [253]; one scenario may be the development of an aneurysm of the left ventricle after cardiac contusion. Therefore, transthoracic ultrasound, ECG, measurement of cardiac enzymes and use of echocardiography in selected cases

are all useful for assessment of stable patients. A normal ECG helps to identify a very-low risk patient. ECG changes are neither specific nor sensitive for significant myocardial dysfunction but have a high negative predictive value for cardiac complications [265]. Routine measurement of cardiac enzymes such as cardiac troponin I in asymptomatic patients suspected of cardiac trauma is recommended [251,253,262,263] but evidence for benefit in the accurate diagnosis of cardiac trauma in asymptomatic patients is lacking [254]. At present, an admission ECG should be performed on all patients in whom there is suspected blunt cardiac injury, and echocardiography should be obtained in haemodynamically unstable patients. If aortic rupture is a potential differential diagnosis, echocardiography and CT should be performed. A normal ECG should terminate the pursuit of diagnosis since the risk of having blunt cardiac injury that requires treatment is insignificant. No other imaging studies or measurement of cardiac enzymes are recommended for screening of cardiac injury or for predicting complications related to blunt cardiac injury [254].

Management and results

Medical treatment

In this era of progressively earlier ambulation of patients with acute myocardial infarction, a similar approach appears to be reasonable after several days of close observation for myocardial contusion. Several groups have concluded that in trauma patients in stable condition, contusion neither increases the complication rate nor necessitates monitoring [264,265]. In a study from the Boston City Hospital, Jimenez *et al*. [261] prospectively divided 336 patients admitted to the surgical intensive care unit with possible myocardial contusion into three groups: (1) those with a normal ECG, (2) those with an abnormal one and (3) those with either normal or abnormal ECG but with many associated thoracic or extrathoracic injuries. Non-invasive studies were abnormal most often in the latter group, while cardiac complications were absent in groups 1 and 2. The authors concluded that young patients with minor blunt trauma and a normal or slightly abnormal ECG do not benefit from cardiac monitoring and should be subject to regular mobilization and rehabilitation. However, treatment with anticoagulants, and clearly with thrombolytics, is contraindicated because intramyocardial or intrapericardial haemorrhage may be precipitated or exacerbated. Atrial fibrillation, when present, usually reverts to sinus rhythm spontaneously; digitalis glycosides may be used to slow the ventricular rate and accelerate reversion to sinus rhythm. Chest pain is best treated with analgesics; non-steroidal anti-inflammatory agents are not advised because they might interfere with myocardial healing. Corticosteroids have proved helpful [17] only in Dressler's syndrome [266].

As already noted, the prognosis for complete or partial recovery is generally excellent but careful follow-up to screen for late complications, ranging from ventricular arrhythmias to cardiac rupture, is recommended. Coronary occlusion [266–269], aorta–right atrial fistula [270] and ventricular aneurysms [257] are occasional sequelae.

Although many analogies can be drawn between cardiac necrosis caused by trauma and that caused by ischaemic heart disease, a number of crucial differences must be emphasized. Paitients with acute myocardial infarction secondary to coronary artery disease generally have diffuse, obstructive, gradually progressive coronary atherosclerosis, are frequently middle-aged or elderly, and may have underlying heart disease. Patients with traumatic myocardial contusion generally have normal coronary vessels and only a discrete area of myocardial damage; most often, they are young and without underlying cardiovascular illness. Hence, the long-term prognosis in surviving patients with myocardial necrosis secondary to trauma tends to be far better than in patients with myocardial infarction and coronary disease.

Patients with external rupture of the heart obviously require emergency surgery if they reach a hospital. Pericardiocentesis and expansion of the intravascular volume can be carried out while the most rapid preparation possible for operation is undertaken [271–276]. In contrast, patients with rupture of the interventricular septum do not always require emergency operation. Indeed, many defects are small, with minimal left-to-right shunts, and may even heal spontaneously. If heart failure develops subsequently, as occurs in many patients, surgical correction should be carried out promptly and is often successful [274].

Surgical management

In the majority of patients with cardiac trauma, surgical intervention is aimed at preserving life in patients with a poor prognosis. Recently, the American Association for the Surgery of Trauma and its Organ Injury Scaling Committee have developed a cardiac injury scale for uniformly describing cardiac injuries [277]. It remains questionable if this complex but comprehensive scale will be usable for emergency situations in the emergency or operating room, but it defines the severity, mechanism and location of both penetrating and blunt trauma in a scale from I to VI. Treatment strategies could be developed

with regard to the heart injury scale, and prognosis of mortality becomes predictable to a certain degree [257].

In stable patients with evidence of penetrating cardiac injury, immediate transport to the operating room, general anaesthesia and thoracotomy is mandatory. Median sternotomy is the incision of choice. This is especially true in stable patients with stab wound. If the stabbing device is still in place when the patient is admitted to the emergency room, it is not removed until the surgical approach has been made and ideally not until the pericardium has been opened [278]. In unstable patients who arrive in the emergency room *in extremis*, unconscious, with or without reduced vital signs but with evidence of cardiac or great vessel wound as the cause, immediate thoracotomy in the emergency unit is indicated. Left anterolateral thoracotomy remains the incision of choice, and can be extended across the sternum as bilateral anterolateral thoracotomies if the patient's injuries extend into the right hemithoracic cavity [256]. Evaluation of the extent of haemorrhage present within the left hemithoracic cavity is then carried out. If necessary, the descending aorta can be reached and cross-clamped, the location of penetrating injury found and immediate digital control can be established. If the repair appears to be a simple one, repair is then performed. Otherwise, the patient is transferred to a prepared operating room while digital control of the haemorrhage is maintained. Atrial wounds can be controlled by partial occlusion with a Satinsky vascular clamp or Allis clamps followed by a closing suture line; total inflow occlusion by clamping of both venae cavae should be avoided since the acidotic and ischaemic heart will not tolerate the manoeuvre [256,257]. Ventricular wounds are best controlled by digital occlusion while placing running or horizontal mattress sutures with 2-0 Prolene. If coronary arteries are injured, either ligation (of distal portion) or immediate establishment of cardiopulmonary bypass and coronary artery bypass grafting are indicated (Fig. 34.21). Since most septal injuries from penetrating trauma close spontaneously, no patient should be considered for operation acutely. Only if an intracardiac shunt greater than 2:1 is confirmed by cardiac catheterization should surgery be considered in a stable patient.

Cardiac contusion is no indication for surgery [266, 267]. Close follow-up management is indicated in order to detect delayed cardiac rupture, valvular dysfunction or aneurysm formation. Rupture of atrioventricular and aortic valves requires surgical repair, but proper timing of the procedure may improve results. Stabilization of a traumatized patient prior to surgery is attempted, although left ventricular failure may require immediate operation. If possible, septal defects with a left-to-right shunt and a $Q_p : Q_s$ ratio greater than 2 : 1 should be repaired electively to improve long-term outcome. Immediate surgery for blunt cardiac trauma is mandatory in both cardiac rupture and injury or occlusion of a coronary artery. In contrast to penetrating cardiac injuries, pericardiocentesis should not be used to diagnose haemopericardium in a stable patient with suspected cardiac injury; instead, the patient should be transported to the operating room with cardiopulmonary bypass equipment available. The operative approach for repairing cardiac injury is a median sternotomy. Surgical techniques are similar to those used for penetrating cardiac injuries; use of cardiopulmonary bypass is required for coronary artery bypass grafting of valve repair but rarely for the repair of cardiac rupture [267].

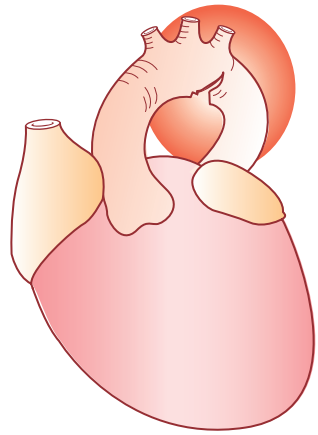


Figure 34.21 Schematic view of a typical aortic rupture.

Outcome after cardiac trauma

Survival after penetrating cardiac trauma is directly related to the patient's status on presenting to the emergency department. Of those who reach the emergency room alive, 80% of patients survive. Survival of patients with cardiac missile wounds is poor, with 40% of these reaching the emergency room. Generally, stab wounds have a better outcome than missile wounds [278]. In a prospective study, a total of 105 patients sustained penetrating injuries over a 2-year period, with 65% due to gunshots and 35% to stab wounds [257]. Survival of patients with gunshot wounds was 16% but was 65% in those with stab wounds. Emergency department thoracotomy was performed in 71 patients (68%), but only 10 patients survived. The site of injury and the presence of tamponade did not predict survival.

Outcome after blunt heart trauma depends on the severity of the injury. The prognosis after myocardial contusion is generally benign. A prospective study of

118 patients with blunt chest trauma revealed 14 patients (12%) with myocardial contusion. All but one patient survived the acute hospitalization and 1-year follow-up without new cardiac pathologies [279]. However, cardiac rupture may be a diagnostic challenge since institutional algorithms may not identify those patients with remarkably few symptoms before [269]. Cardiac rupture has a poor prognosis, with a mortality of more than 90% [254]; if patients showing vital signs at admission reach a surgical unit, prognosis increases significantly. Outcome of emergency thoracotomy after blunt chest trauma in the admission room is poor [280–282].

Personal perspective

Cardiovascular and aortic disease, in both acute syndromes and chronic stages, will constitute an increasing share of cardiology and vascular medicine. With improved awareness and easy access to non-invasive tomographic imaging, aortic pathology emerges as a major focus and will require more attention than before; cardiology in particular will shoulder the major burden of the multifaceted acute and chronic aortic pathology. Thus the cardiovascular community has to handle the complexity and the challenges with regard to screening patients at risk, rapid and reliable diagnosis and, eventually, competent interventional or surgical treatment. The spectrum will encompass young patients with hereditary vascular diseases, a middle-aged cohort with hypertension and elderly patients with advanced general atherosclerosis. This variety calls for multidisciplinary cooperation and formation of 'aortic centres' to concentrate competence and offer special diagnostic and interventional skills for treating delicate patients.

In the near future, miniaturization and refinement of endovascular technology will allow endo-aortic interventions to be performed percutaneously under local anaesthesia, and more physiological stentgrafts will even mimic the rotational three-dimensional systolic twist of the thoracic aorta, while contemporary surgical techniques are less likely to improve. More importantly, even successful aortic surgery will not abolish any of the associated risk factors from comorbid conditions and therefore late outcome will remain dominated by the individual prognosis (comorbid state). As a consequence, in centres of excellence for aortic disease the endovascular treatment options are more likely to prevail even in highly comorbid subsets of patients, since at least the surgical risk will be eliminated with endovascular techniques. A definitive answer to the ethical justification for treatment in the very old patient is not established, because prospective data from randomized studies or registries are scarce in aortic diseases. However, when insisting on strict proof (or disproof) in empirical science, one will never benefit from experience. In a world of rapidly advancing technology, it is wise to remember the old principles of responsible use of clinical judgement and experience for the benefit of our patients. The growing segment of older patients with multiorgan comorbidities deserve an holistic approach, the intelligent use of prognosticating tools and close interdisciplinary cooperation.

Acknowledgements

We are indebted to Mrs J. Heine for her professional support in preparing the manuscript and the artwork. We would like to thank the following for their contribution to this chapter: Dr Dietrich Baumgart, Dr Holger Eggebrecht, Dr Rosella Fattori, Dr Huseyin Ince, Dr M. Karck, Dr Stephan Kische, Dr Alexander Lind, Dr Michael Petzsch, Dr Tim C. Rehders and Dr Frank Weber.

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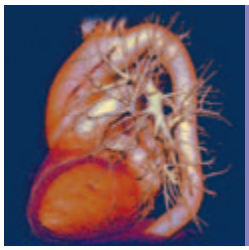


35 Peripheral Arterial Occlusive Disease

Giancarlo Biamino, Andrej Schmidt, Iris Baumgartner, Dierk Scheinert, Marco Roffi and Felix Mahler

Summary

The management of patients with peripheral arterial occlusive disease (PAD) has to be planned in the context of natural history, epidemiology of disease, and apparent risk factors predicting deterioration. The ankle-brachial index (ABI) to date has proved to be the most effective, accurate and practical method of PAD detection. Given that PAD is a powerful indicator of systemic atherosclerosis and, independent of symptoms, it is associated with an increased risk of myocardial infarction and stroke as well as a six times greater likelihood of death, the prevalence and demographic distribution of measurable PAD becomes relevant.

Reliable information on symptom relief is weaker and illustrates discrepancies between published reports of specific treatment from centres of excellence and what happens to patients routinely treated in communities around the world. However, endovascular interventions have greatly changed the current therapeutic spectrum, and many indications such as for renal, pelvic and femoro-popliteal arteries are today regarded as standard. Because of the limited space this chapter could not consider the surgical aspects of treatment of obstructive arterial disease, which is of course in many cases still the standard of care.

Introduction

Peripheral arterial occlusive disease (PAOD) is a disorder of the peripheral arteries, defined as all the arteries of the body except the coronary vessels. However, it is the circulation of the lower limb that is most frequently involved. Atherosclerosis is the major cause of chronic PAOD [1]. General interest in the management of patients with PAOD has increased in recent years, and there has been a shift from vascular surgical domination to comprehensive vascular centres integrating surgical, endovascular and medical services. Patients afflicted with PAOD are recognized as a cardiovascular high-risk population, and therefore primary and secondary prevention, endovascular treatment options and novel gene therapeutic approaches, in addition to classical vascular surgery, may hold potential for the future. This chapter deals with the lower limb, renal and carotid arteries, with emphasis on endovascular therapy.

Epidemiology and risk factors

Epidemiology

Epidemiological studies have documented that 2–3% of men and 1–2% of women over 60 years of age have intermittent claudication (IC). The prevalence of PAOD is three- to four-fold higher when sensitive tests such as ankle–brachial pressure index (ABI) (see Diagnosis, below) are applied [2], and increases with age. The Rotterdam study, a population-based analysis of 7715 individuals, documented a frequency of IC ranging from 1 to 6% in the 55–60 and 80–85 age groups respectively [3]. Despite this rather low frequency of IC, 17% of men and 21% of women aged 55 years and older had PAOD as defined by an ABI < 0.90. This observation confirms that most patients with PAOD are asymptomatic.

The infrarenal abdominal aorta and the iliac arteries are among the most common sites of involvement. In

contrast to the usual male predominance, almost half of patients with localized aorto-iliac disease (type I) are women around 50–60 years of age and heavy smokers, frequently with findings of a hypoplastic aorta. In 65% of cases, distribution of atherosclerotic disease is diffuse, involving arteries both above and below the inguinal ligament (type III). Patients in the latter group with multilevel disease are typically older and more commonly male and there is a much higher propensity for diabetes, hypertension and concomitant cerebral, coronary and visceral artery involvement. Distal to the inguinal ligament, stenoses and occlusions are more common in the superficial femoral artery (SFA) at the level of the adductor canal. An exception to these rules is found in patients with diabetes mellitus or end-stage renal disease, where there is a predilection for below-knee sites [1].

Although PAOD is progressive in the pathophysiological sense, the natural history and prognosis in the involved lower extremities is relatively benign in most cases with IC. Large population-based studies such as the Basle study have documented angiographic progression of the disease in 63% of patients 5 years after presentation, although 66% still did not have disabling or lifestyle-limiting IC [4]. One-quarter of claudicants deteriorate and ultimately require revascularization, with only 5% developing critical limb ischaemia (CLI). Deterioration is most frequent during the first year after initial diagnosis (6–9%) compared with 2–3% per annum thereafter [5]. Progression of disease is greatest in patients with multilevel arterial involvement, low ABI, renal failure, diabetes mellitus and, possibly, heavy tobacco abuse. Major amputation is required in 1–3% of patients over a 5-year period [6,7], primarily in patients with progression resulting in CLI.

A more serious prognosis of CLI has been demonstrated in other series. A multicentre observational study in Italy reported 12% major amputations and 18% persistent CLI in 574 patients after 3 months [8]. Despite the rather benign prognosis for the limb, IC is an ominous sign of systemic atherosclerosis with considerable overlap of disease manifested in multiple vascular beds, coupled with an increased cardiovascular morbidity and mortality especially for coronary and carotid artery disease [9,10]. Two years following a below-knee amputation, no more than 40% of amputees will have reached full mobility and 15% will have had a contralateral and 15% an above-knee amputation, of whom 30% will have died [11].

Risk factors

Atherosclerosis in the lower extremities is more common in elderly individuals and men [1,3,4,7,11]. Smoking ranks as the most punitive modifiable risk factor, increasing both the risk of development and progression of disease [12]. The diagnosis of PAOD is typically made up to a decade earlier in smokers compared with non-smokers. Major amputation is more common in patients who are heavy smokers. In diabetics, the prevalence of PAOD has been reported to be one and a half to six times higher compared with their non-diabetic counterparts, IC to be two to four times more common, and major amputation 10 times more likely [7]. The Framingham Heart Study provided the most convincing link between PAOD and hypertension, with a 2.5-fold risk for men and a 3.9-fold risk in women [7,11]. Lipids and atherothrombotic biomarkers were assessed in a recent cohort of 14 916 healthy US male physicians aged 40–84 years [13]. Of 11 atherothrombotic biomarkers measured at baseline, the ratio of total cholesterol to high-density lipoprotein (HDL)-C ($P < 0.001$) and level of high-sensitivity C-reactive protein ($P = 0.006$) were the strongest independent predictors of the development of PAOD. Hyperhomocysteinaemia was not among them, although a meta-analysis from the 1990s gave an odds ratio of 6.8 [14].

Diagnosis

A comprehensive physical examination including pulse palpation and vessel auscultation remains the cornerstone of the evaluation of patients at risk for PAOD [1,7,15]. The two clinical classification systems based on physical examination and the patient's history are shown in Table 35.1.

Doppler ultrasound measurement of ankle artery pressure and its relation to brachial pressure (ABI) has proved to be the most effective, accurate and practical non-invasive vascular laboratory test for detecting PAOD (Fig. 35.1). It can be performed by the primary care provider in the office and at the bedside in hospitalized patients. A resting ABI of less than 0.90 approaches 95% sensitivity for PAOD and 99% specificity in excluding healthy individuals [15].

Exercise testing is an important adjunct to the diagnostic armamentarium when assessing a patient with normal pulses at rest and a normal resting ABI but who claims typical IC [7]. Patients with IC will typically exhibit a greater than 20-mmHg drop in ankle pressure 1 min after exercise. Walking on a treadmill is the most commonly used exercise test for this purpose, although it is not the only form of exercise that may be employed. Active pedal plantarflexion, which involves repeatedly standing up on the toes, may be a simpler and more cost-effective but non-quantitative alternative. In cases of medial calcification, often seen in diabetic patients or

Table 35.1 Classification of chronic peripheral arterial occlusive disease

Fontaine		Rutherford		
Stage	Clinical description	Grade	Category	Objective description
Stage I	Asymptomatic	Stage 0		Asymptomatic, normal treadmill test
Stage IIa	Intermittent claudication, pain-free walking distance > 200 m	Stage I	Grade 1	Mild intermittent claudication, treadmill exercise limited to 5 min; ankle pressure after exercise > 50 mmHg, but at least 20 mmHg lower than at rest
			Grade 2	Moderate intermittent claudication, between Rutherford 2 and 3 disease
Stage IIb	Intermittent claudication, pain-free walking distance < 200 m		Grade 3	Severe intermittent claudication, treadmill exercise limited to < 5 min; ankle pressure after exercise < 50 mmHg
Stage II (complicated)	Trophic lesions with intermittent claudication but without critical leg ischaemia			
Stage III	Rest pain	Stage II	Grade 4	Rest pain, ankle pressure < 40 mmHg and/or great toe pressure < 30 mmHg; pulse volume recording barely pulsatile or flat*
Stage IV	Ischaemic lesion (ulcer, gangrene, necrosis)	Stage III	Grade 5	Limited ischaemic lesion, ankle pressure < 60 mmHg and/or great toe pressure < 30 mmHg; pulse volume recording barely pulsatile or flat*
			Grade 6	Extended ischaemic lesion (above metatarsal level)*

*Chronic critical limb ischaemia.

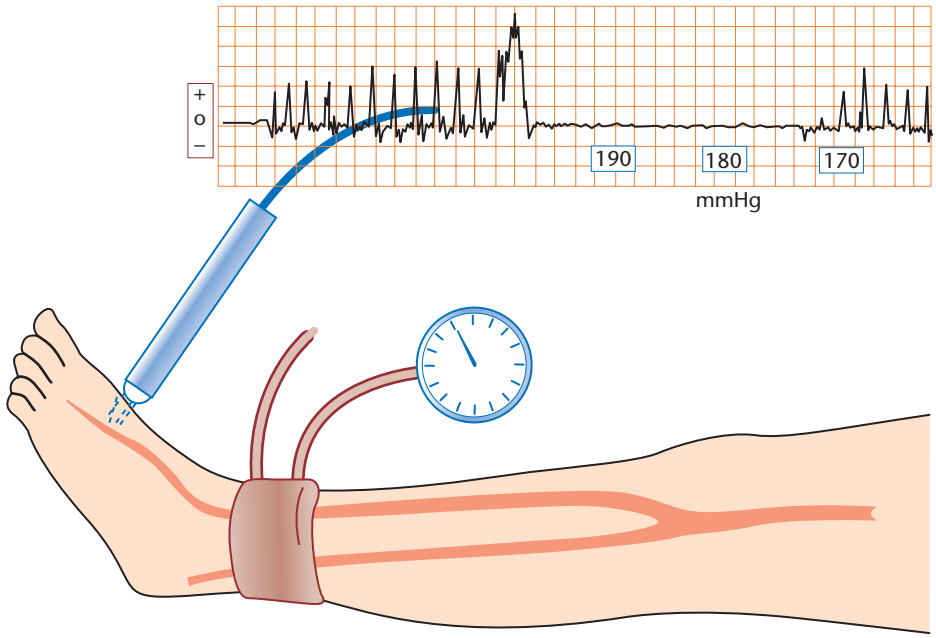


Figure 35.1 Measurement of the ankle–brachial index (ABI): systolic ankle pressure is determined by Doppler ultrasound. The higher value of either dorsalis pedis (d.p.) or tibialis posterior (t.p.) divided by the systolic upper arm pressure represents ABI. Reproduced with permission from Holstein and Sorensen [36].

those with chronic renal failure, the ankle pressures are spuriously elevated due to incompressible vessels. Vessel non-compressibility should be suspected when the ABI exceeds 1.30 or shows discrepancy from the clinical findings, e.g. pulse palpation. In these situations, toe pressure measurements utilizing photoplethysmography or pulse volume recordings are necessary for diagnosing and accurately assessing the severity of PAOD.

Colour-flow duplex imaging of the lower extremity vasculature is useful for assessing candidacy for either surgical or endovascular revascularization in patients with PAOD or as an adjunct to, or possibly as a replacement for, conventional arteriography [16]. Magnetic resonance angiography (MRA) has been promoted as an excellent method of evaluating the anatomy of the lower extremities. Recent comparative trials of MRA and standard contrast arteriography have revealed high sensitivity and specificity (97% and 99% respectively) for MRA in patients suspected of having PAOD [17]. Intra-arterial digital subtraction arteriography using iodine contrast is still considered the gold standard for evaluation of patients with PAOD despite a certain morbidity risk and additional expense.

Given the fact that PAOD is a powerful indicator of systemic atherosclerosis and, independent of symptoms, is associated with an increased risk of myocardial infarction and stroke as well as a six times greater likelihood of death within 10 years than patients without PAOD, the following patients should be considered at risk for PAOD: those with exertional leg pain, those over 50 years of age with associated risk factors, diabetics with greater than 20 years' duration of disease, and all those over 70 years of age.

Periodic duplex ultrasound examination of patients who have undergone an endovascular or lower extremity arterial bypass procedure accurately detects evidence of restenosis or a failing bypass graft [18].

Acute limb ischaemia

Acute limb ischaemia is defined as a sudden decrease or worsening in limb perfusion that results in a potential threat to limb viability [1,7]. Acute limb ischaemia is caused by either arterial embolization or thrombosis of an already diseased artery, whether stenotic or aneurysmal. Prompt reconstruction of perfusion is the most effective treatment in terms of maintaining a viable limb. Pain, pulselessness, pallor, paraesthesia and paralysis (the five Ps) reliably demonstrate severity and dynamics of acute limb ischaemia. Sensory loss, muscle weakness, pain with compression of the calf and elevation of creatinine phosphokinase indicate immediate limb-threatening ischaemia and urgent need for revascularization possibly within 6 h. Most large series published report a 30-day mortality of approximately 15%. The amputation rate over the same period varies from 10 to 30% [7]. Arteriography remains the preferred modality of imaging for the pre-interventional assessment based on its track record of safety, availability and usefulness in facilitating a diagnosis. In infra-inguinal occlusions, catheter therapy (aspiration, local thrombolysis and percutaneous transluminal angioplasty) may often be performed successfully within the same session [19]. In limbs acutely threatened by supra-inguinal occlusions, surgical thromboembolectomy should be performed directly, during which intraoperative arteriography can be performed.

Chronic critical limb ischaemia

CLI is defined as those patients with ischaemic rest pain, ulcers or gangrene at risk of major amputation [7,20]. It coincides with stages III and IV of the Fontaine classification and categories 4, 5 and 6 of the Society for Vascular Surgery/International Society for Cardiovascular Surgery reporting standards (see Table 35.1). An objective measure of CLI at risk of major amputation without revascularization is an absolute ankle pressure ≤ 50 mmHg and/or toe pressure ≤ 30 mmHg and these measurements should be obtained in all patients [7,20]. A transcutaneous oxygen partial pressure (tcPo_2) below 20–30 mmHg suggests severe ischaemia and non-healing of wounds or minor amputations. The tcPo_2 is helpful for estimating the degree of ischaemia and has a high positive predictive value (77–87%) for classifying patients with severe ischaemia [21].

Conservative treatment

The goal of treatment in patients with PAOD is two-pronged, addressing the systemic risk of generalized atherosclerosis and the relief of lower extremity symptoms. The key element in prevention and management of cardiovascular complications in PAOD is risk-factor modification and treatment with antiplatelet agents. The Heart Protection Study has demonstrated that lowering total cholesterol and low-density lipoprotein (LDL) by 25% with statin therapy reduces cardiovascular mortality and morbidity in patients with PAOD by 21% irrespective of age, sex or baseline cholesterol. Reduction of LDL by statins can reduce the risk of PAOD by 30–40% [22–24]. Data on diabetes control and direct effect on PAOD are not clear. However, any other risk factor should be treated vigorously in the presence of diabetes. Appropriate blood pressure control, especially with angiotensin-

converting enzyme (ACE) inhibitors, will also contribute to the prevention of PAOD [26].

Regular exercise, such as walking or treadmill use, should be encouraged (30–40 min daily, four to five times a week). Exercise therapy for IC is ideal in a supervised vascular rehabilitation programme [27]. It provides a 24% reduction in relative risk of cardiovascular mortality, and a meta-analysis of randomized trials found that exercise training increases maximal treadmill walking distance by 179 m [28].

Revascularization should be considered in patients with IC as long as catheter therapy offers favourable results [7] (see below). Any kind of revascularization must be attempted in patients with CLI, since the risk of amputation is excessive at this stage. Limb salvage by means of revascularization is cost-effective, provides improved quality of life and is associated with lower morbidity and mortality than amputation [29].

Antithrombotic therapy

Patients with PAOD are at high risk of future cardiovascular events and therefore lifelong aspirin therapy (75–150 mg/day) is recommended. A reduction in the relative risk by 23% has been shown for aspirin [30], perhaps even more for clopidogrel [31]. In a recent meta-analysis by the Peripheral Vascular Disease Group of the Cochrane Collaboration of peripheral angioplasty trials it was shown that there was a 30% reduction in relative risk for recurrent stenosis or occlusion comparing aspirin and placebo. The result did not achieve statistical significance because of the relatively small sample size.

A report on the post-interventional and postoperative regimens has recently been published by the ACCP consensus conference on antithrombotic therapy [32]. In bypass surgery the general recommendation is for aspirin to be started preoperatively in order to improve graft patency and reduce the risk of cardiovascular events. Exceptions are perhaps patients with femoro-distal bypass procedures that may be at increased risk for graft thrombosis, defined as those with marginal-quality vein, poor arterial run-off and previously failed bypass, with a recommendation for oral anticoagulation in combination with aspirin (Table 35.2). Clopidogrel or oral anticoagulation is often given after stenting or complex endovascular therapy without direct evidence of benefit but in analogy to coronary or surgical data.

Adjunctive pharmacotherapy and gene therapy

Pharmacotherapy for the treatment of IC could be added, but the lack of robust clinical data and high costs have

Table 35.2 Antithrombotic therapy in peripheral arterial occlusive disease (PAOD)

Clinical situation	Antithrombotic therapy	Level of evidence*
Chronic PAOD	Aspirin Clopidogrel	1C 2A
Acute limb ischaemia	Heparin Intra-arterial thrombolytic therapy	1C 2B
Vascular surgery (intraoperative)	Heparin	1A
Infra-inguinal vein bypass	Aspirin (started before operation) Clopidogrel, if unable to take aspirin (started before operation)	1C 1C
Infra-inguinal prosthetic bypass	Aspirin (± dipyridamole)	1A
Infra-inguinal bypass at high risk for thrombotic occlusion	Aspirin and oral anticoagulation	1B

*Level of evidence: grade 1, multiple randomized trials supporting use; grade 2, few randomized trials, mostly observational data that suggest use may be beneficial; grade 3, data exist to recommend against use.
Adapted with permission from Clagett *et al.* [32].

limited the widespread use of these agents as summarized in a review [33]. A meta-analysis of pentoxifylline found a net benefit of only 44 m in the maximal distance walked on a treadmill [28]. In a trial of 698 patients with stable IC, it was found that cilostazol significantly ($P < 0.05$) increased maximum walking distance and pain-free walking distance on a treadmill compared with pentoxifylline and placebo.

Because of their antiplatelet and vasodilatory effects, prostaglandins have been administered either intravenously or intra-arterially in advanced stages of PAOD and have been shown to relieve rest pain and heal ischaemic ulcers. In current practice, the lack of available oral forms of these agents and the lack of robust superiority over conventional therapy have resulted in limited use of these compounds [33].

Therapeutic angiogenesis is a new area in cardiovascular medicine that has received attention in recent years. Isner's group has proposed intramuscular injection of naked plasmid expressing vascular endothelial growth factor in order to stimulate collateral growth in PAOD [34]. Preliminary studies in patients with CLI have shown improvement in rest pain and ulcer healing [35]. Several randomized controlled studies in patients with CLI are under way but have not given convincing clinical results so far.

Diabetic foot

More than 120 million people in the world suffer from diabetes mellitus and 25% incur diabetic foot ulcer at some point, with 40–60% of all non-traumatic lower leg amputations performed in diabetic patients. Limb salvage seems to be best in centres with a multidisciplinary approach to ischaemic, orthopaedic and infectious problems of the diabetic foot. In a consecutive series of 162 patients, major amputation was avoided in approximately 80% of patients with limb-threatening ischaemia, and in about 95% with foot ulceration complicated by infection [36].

The Trans Atlantic Inter-society Consensus (TASC) paper recommends that with a balanced choice between endovascular therapy and surgery, the former is preferred for treating limb ischaemia because of lower systemic stress and less serious complications [7]. Recent reports show remarkably good results with regard to limb salvage by balloon catheter interventions [37,38] or laser techniques. Late recurrence after angioplasty may result in recurrent ulceration in some patients, but it rarely precludes subsequent surgery or compromises additional vascular segments. Patients with end-stage renal disease (who are often diabetic) appear to be the most difficult to treat because of the presence of diffuse disease, greater involvement of the distal and pedal vessels, and superimposed heavy calcifications [29].

Renal arteries

Epidemiology

Even though renovascular hypertension is a relatively rare condition (1–2% of all hypertensive patients), renal artery stenosis (RAS) is by no means uncommon. Significant RAS is found in 4% of autopsy reports in general and in 8% of diabetic patients [39]. In patients undergoing coronary angiography, mild RAS (< 50%) was present in 53%, moderate RAS (50–70%) in 12% and severe RAS in 7% [40]. Most renal artery stenoses are of atherosclerotic origin, with only about 10% due to fibromuscular dysplasia [39]. In our own patient population, the mean age of patients with atherosclerotic RAS undergoing percutaneous transluminal renal angioplasty (PTRA) is 69 years with equal gender distribution, while that of patients with RAS due to fibromuscular dysplasia is 49 years and the gender predominantly female [41]. Progression of atherosclerotic RAS to full occlusion is well documented, ranging from 6 to 16% occlusions per year depending on the degree of initial RAS [39,42].

Haemodynamically, significant RAS produces renovascular hypertension and/or renal dysfunction. Thus, RAS due to fibromuscular dysplasia may be suspected in young, severely hypertensive, mostly female patients, and RAS due to atherosclerosis in patients with newly appearing hypertension above the age of 50 years. Haemodynamic significance is assumed to start at a diameter reduction of 60% (cross-sectional area reduction > 80%), possibly stimulating the renin–angiotensin system. The presence of this mechanism may be proven by selective renal vein renin determination, an examination rarely performed at present [39,43]. In patients with two kidneys, one-sided RAS does not impair kidney function as long as the contralateral kidney compensates for the underperfused partner. However, in patients with a single kidney, such as those with unilateral kidney or transplanted kidneys, RAS may well be the determinant of kidney function. In this situation, water excretion may be impaired by the renin–angiotensin–aldosterone axis since no contralateral organ can compensate. The

same mechanism is active when bilateral RAS is present in those with two kidneys. In the more frequent situation with impaired renal parenchymal function, severe unilateral RAS may accelerate the progression of renal insufficiency, and its reconstruction may improve or stabilize kidney function [39].

Renal artery reconstruction

Renal artery reconstruction may be performed either surgically (aortic endarterectomy or bypass) or by transcatheter techniques (PTRA/stenting) (Fig. 35.2). In the surgical era the indications for renal artery reconstruction were very restrictive with regard to the severity of the operation, whereas the indications for catheter revascularization are now more liberal.

The effects of catheter intervention have been described in terms of blood pressure (Fig. 35.3) and/or renal function in many series by single centres of excellence [43–49]. Results after introduction of stents for ostial lesions [46–50] are technically excellent (success rate > 95%), durable (12-month restenosis rate about 15%) and complications are low (death rate < 1%). However, with regard to the effect of hypertension a few controlled studies that compared conservative with transcatheter treatment have produced controversy about whether the intervention is beneficial [42,51,52]. These studies included small numbers of patients and have important flaws, such as including those with moderate RAS (≥ 50%) and cases where stents were not used. Nevertheless, a recent meta-analysis showed a net benefit for interventions despite the afore-mentioned confounders [53]. The results on hypertension are summarized in Table 35.3, based on more concise clinical studies and our own experience [41]. In general, the benefit in fibromuscular dysplasia is markedly better than in atherosclerosis.

In clinical practice the main indication for revascularization of RAS has recently changed from hypertension to renal insufficiency. There are clear data on transplanted or single-kidney RAS which indicate marked improvement with PTRA and/or stenting. More complex is the situation with kidney insufficiency in the presence of

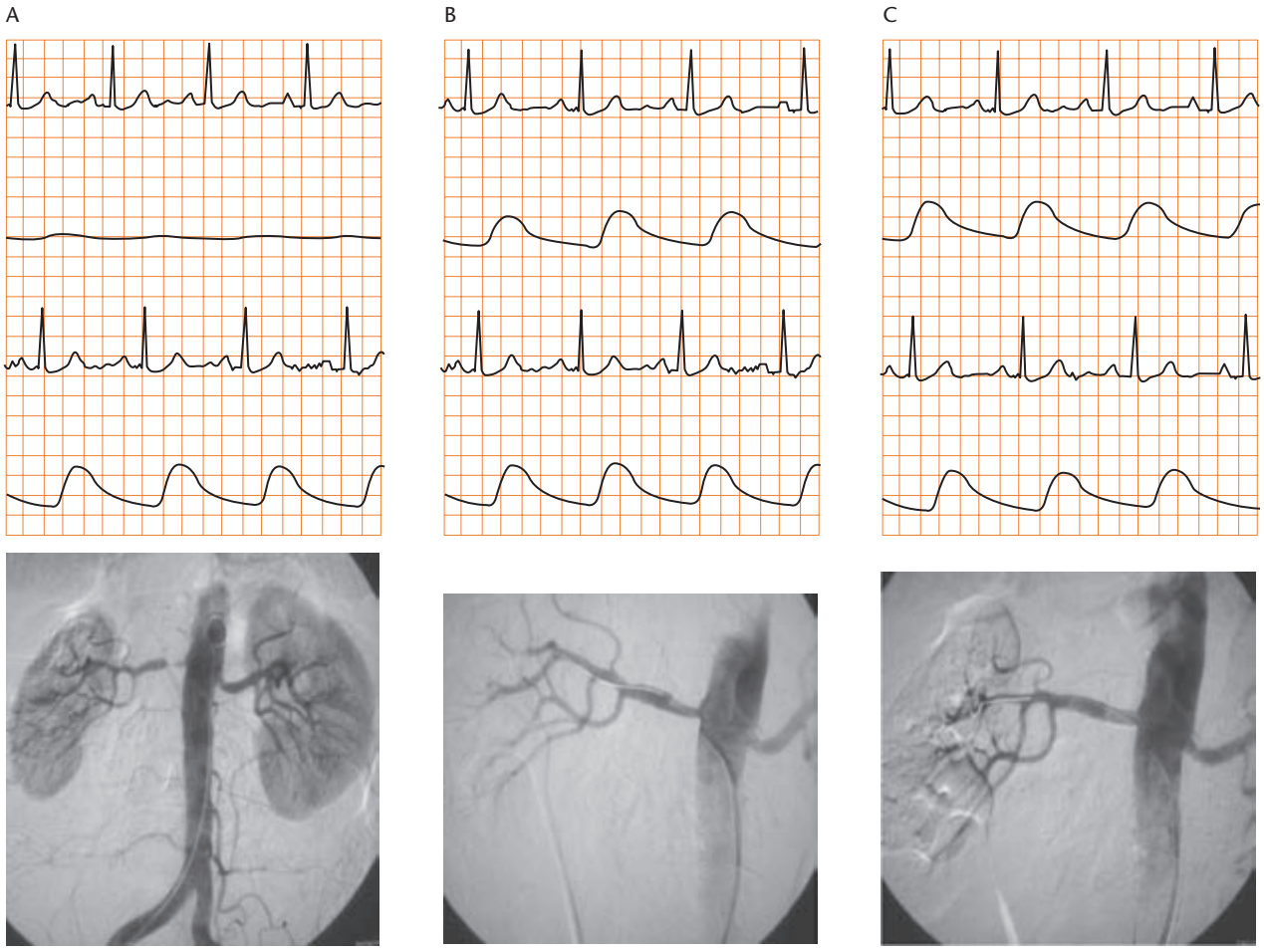


Figure 35.2 Renal artery (A) before and (B) after percutaneous transluminal renal angioplasty, and (C) after stenting.

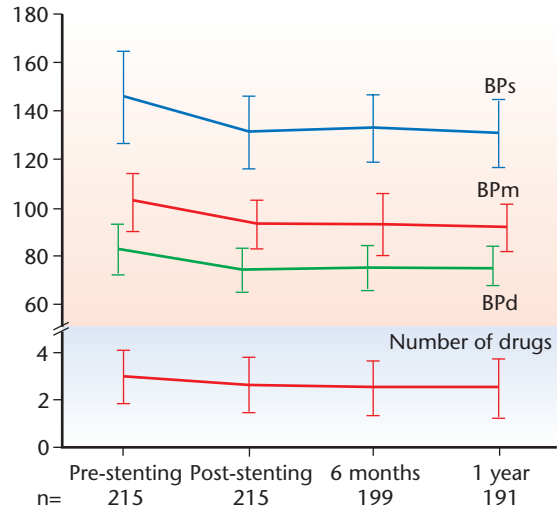


Figure 35.3 Time course of blood pressure and number of antihypertensive drugs in 215 patients with atherosclerotic renal artery stenosis before renal artery intervention and during 1 year after. All comparisons with pre-interventional values are statistically significant ($P < 0.0001$). Reproduced with permission from Zeller *et al.* [57].

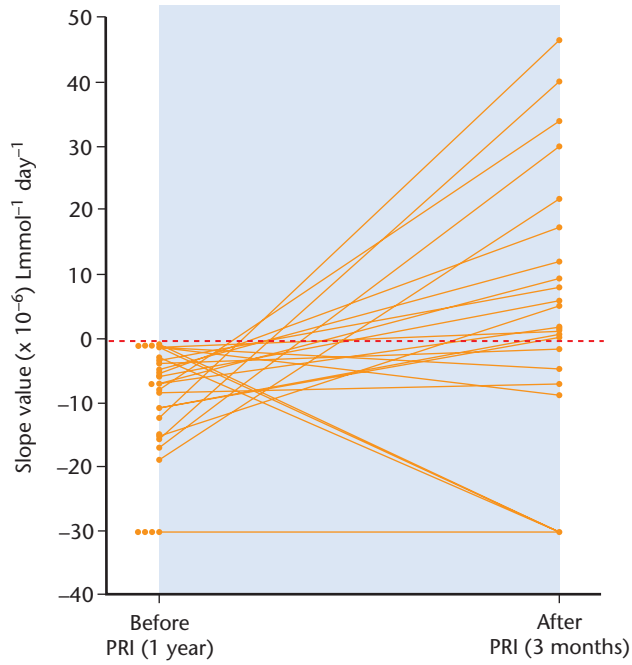


Figure 35.4 Change in slope of reciprocal serum creatinine (creatinine clearance analogue) 1 year before and 3 months after renal artery stenting in 22 patients with renal insufficiency (serum creatinine > 300 µmol/l) undergoing renal artery stenting. Negative slopes indicate decreasing values over 2 years previously, zero slope indicates stabilization and positive slopes indicate increasing values of serum creatinine after intervention. Reproduced with permission from Korsakas *et al.* [56].

two kidneys and one-sided RAS. However, several papers addressing this problem show that in patients with moderately elevated serum creatinine, stabilization or improvement of renal insufficiency may be achieved in more than 70% [54–57]. Even in a group of patients with severely impaired renal function, catheter revascularization achieved functional improvement or at least stabilization of deterioration in 50% [56] (Fig. 35.4). Even when renal function is rapidly deteriorating prior to intervention, as long as glomerular filtration rate (GFR) remains above 10 ml/min, revascularization has a positive effect [56,57]. Perhaps when the renal parenchyma is damaged so much that GFR is below this value, and the Doppler flow velocity resistance index above 0.80 [58], that revascularization of RAS comes too late to achieve functional improvement.

Conclusions

1 The technique of catheter revascularization (stent-assisted PTRA) has greatly improved, especially with the introduction of low-profile instruments and stents.
2 Hypertension with significant RAS may respond well (cure or improvement) in two-thirds of patients with atherosclerosis and in 80% of those with fibromuscular dysplasia.
3 Renal insufficiency may be improved by renal artery revascularization. Rapid deterioration prior to intervention but with GFR above 10 ml/min is a positive predictive factor.
4 Revascularization should be performed as soon as haemodynamically significant stenosis has been documented in order to avoid progression to full occlusion.

Results	Renal artery stenosis (%)	Fibromuscular dysplasia (%)
Cured	10	80
Improved	40	10
Unchanged/worse	50	10

Table 35.3 Hypertension after renal artery intervention

Carotid arteries

Epidemiology

A significant (> 50%) stenosis of the internal carotid artery may account for 5–10% of all strokes [59]. The prevalence of carotid disease increases with age. Even though half of men over 75 years of age may have evidence of carotid atherosclerosis, stenoses of > 50% are detected in only approximately 5% [60]. The highest prevalence (12.5–28%) of carotid stenosis is found in patients with PAOD, whereas carotid stenosis among unselected patients with coronary disease is rare (< 5%) [61]. Conversely, even in the absence of cardiac symptoms, patients with carotid disease frequently (25–60%) have significant coronary artery disease [62]. The risk of stroke in patients with carotid disease is predicted by recent neurological symptoms and the degree of stenosis. In asymptomatic patients it is estimated to be less than 2% per year but may increase to as high as 5.5% per year among individuals with stenosis > 75% [63]. In patients with severe carotid stenosis presenting with transient ischaemic attacks, the risk of subsequent stroke is approximately 10% at 1 year and 30–35% at 5 years [64].

Diagnosis

The clinical presentation of carotid disease includes stroke or transient ischaemic attack, characterized by motor and sensory loss of the contralateral face and body. Dysphasia, contralateral visual field loss and ipsilateral amaurosis fugax may be additional presentations. The clinical examination, particularly auscultation of neck bruits, has poor sensitivity and specificity for the detection of significant internal carotid stenosis [65]. Therefore, all patients with suspected carotid territory ischaemia should be further investigated independently of the presence or absence of carotid bruits.

The diagnostic tool of choice for assessing carotid stenosis is duplex ultrasonography (DUS). A systematic review of the literature addressing the efficacy of DUS in discriminating between severe (70–99%) and moderate (< 70%) stenosis compared with digital subtraction angiography (DSA) yielded a pooled sensitivity and specificity of 87% and 86% respectively [66]. In the same analysis, the sensitivity and specificity of MRA was 95% and 90% respectively. Although currently somewhat less reliable, computed tomography angiography may be used as an alternative non-invasive imaging modality in addition to DUS [67]. Improvements in non-invasive carotid diagnostics have lowered the need for DSA, which remains the gold standard for the diagnosis of carotid stenosis. Since DSA even in experienced hands carries a risk of stroke (< 1%), diagnostic angiography should be performed only in selected cases [68].

Therapy

Antiplatelet drugs, lipid-lowering agents and antihypertensive therapy are the mainstays of medical treatment in patients with carotid disease. The efficacy of antiplatelet therapy has not been specifically addressed in this patient population. Nonetheless, based on the efficacy of these agents in both stroke and coronary prevention, they should be administered in all patients with carotid stenosis [62]. Similarly, the clinical benefit of statins has not been studied in patients with significant carotid disease. A histological analysis performed on endarterectomy specimens has suggested that statin therapy may have a beneficial effect on carotid plaque stabilization [69]. Aggressive lipid management is indicated based on the high-risk status for cardiovascular events in this patient population [62].

Large-scale randomized trials have compared carotid endarterectomy and medical management in patients with carotid stenosis. Overall, the benefit of surgery in terms of stroke prevention has been greater among patients with symptomatic disease than among asymptomatic individuals. In symptomatic disease, endarterectomy is superior to medical management in the presence of carotid stenosis > 50%, and particularly if the luminal narrowing is more than 70% [70]. Among asymptomatic patients, clinical trials detected a moderate but significant benefit for patients with stenosis > 60% [71,72]. These data were obtained by selected surgeons operating on selected patients, resulting in low perioperative morbidity and mortality, and may therefore not be applicable to everyday clinical practice. According to the American Heart Association (AHA) guidelines, carotid endarterectomy in asymptomatic patients is indicated in the presence of carotid stenosis of 60%, as long as the estimated perioperative risk of stroke or death is < 3%. Recent results of the ACST study clearly indicate that in asymptomatic patients under 75 years of age with an internal carotid stenosis of 70%, immediate carotid endarterectomy, taking into account a 3% perioperative hazard, halved the net 5-year stroke risk from about 12% to about 6% [73].

Endovascular carotid intervention (Fig. 35.5) has been increasingly used as an alternative treatment for carotid disease, particularly in patients at high risk for surgery. Over the last few years, neurological complications associated with angioplasty and stenting have decreased. Putative explanations include greater experience of the

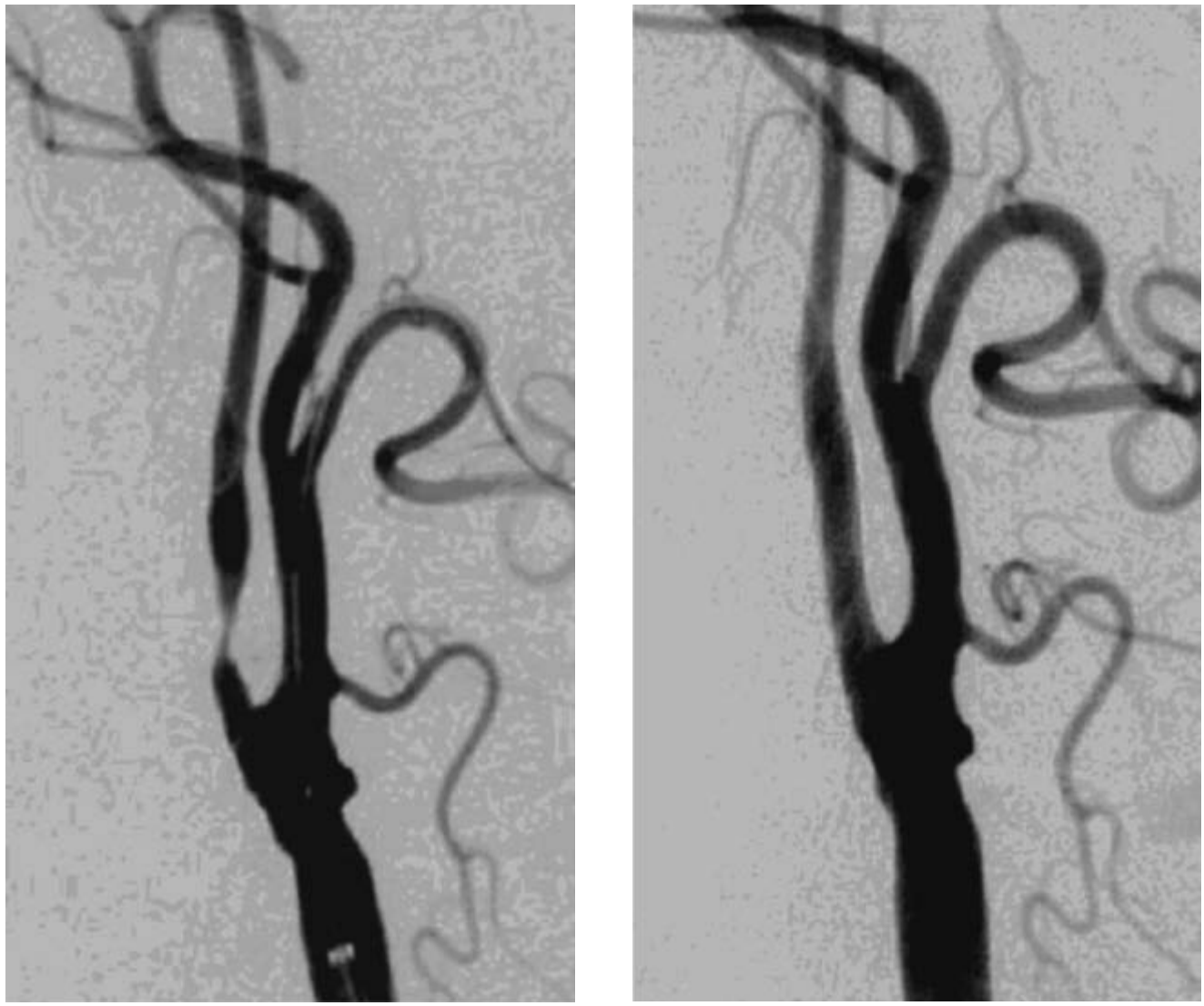


Figure 35.5 (A) High-grade stenosis of the internal carotid artery. (B) Result after stenting.

operators, optimization of antiplatelet therapy and the better equipment. Specifically, the introduction of neuroprotective devices, such as filters and distal or proximal occlusion balloons, has been a major breakthrough [74,75]. Although no randomized study has been performed to compare 'protected' and 'unprotected' carotid stenting, there is substantial evidence that the use of emboli protection devices reduces neurological events associated with percutaneous carotid intervention [76].

Thus far two published large-scale randomized trials have compared endovascular carotid intervention and endarterectomy. In the CAVATAS (Carotid and Vertebral Artery Transluminal Angioplasty Study) trial the two strategies resulted in comparable event rates up to 3 years among 504 patients with symptomatic carotid stenosis [77]. The SAPPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) study randomized 334 symptomatic or asymptomatic patients deemed to be at high risk for surgery to endarterectomy versus carotid stenting with distal emboli protection [78]. At 1 year, carotid stenting was associated with significantly fewer neurological or cardiovascular complications than surgery (Fig. 35.6). Carotid stenting with emboli protection performed by an experienced operator should be viewed as a valid alternative to surgery for patients at high risk for endarterectomy. The results of ongoing randomized trials should be awaited before expanding the indications for carotid stenting to a lower-risk population.

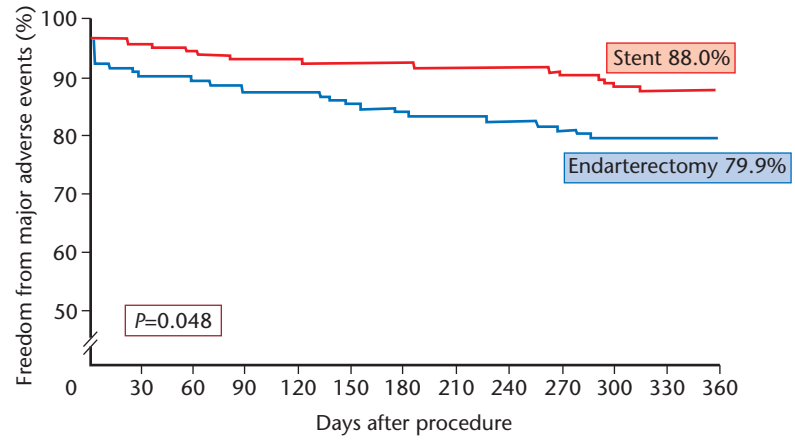


Figure 35.6 Freedom from major adverse events at 1 year in the actual-treatment analysis of the SAPPHIRE trial. Major adverse events were defined as death, stroke or myocardial infarction at 30 days plus ipsilateral stroke or death from neurological causes within 31 days to 1 year. Reproduced with permission from Yadav *et al*. [78].

Recanalization of pelvic arteries

About one-third of the obstructive lesions in PAOD affect the aorto-iliac segment. Iliac artery obstructions have traditionally been treated by open interventions, e.g. aorto-femoral or aorto-bifemoral bypass grafting. This treatment is highly effective, with patency rates of 85–89% after 5 years and 70–74% after 15 years. However, surgical interventions are associated with a substantial procedure-related risk for the patient, leading to aggregated mortality rates of up to 8% [79].

Percutaneous transluminal angioplasty (PTA) is a less invasive treatment alternative, and in the last few years has proven to be an effective technique for the treatment of focal iliac artery stenosis [80,81]. The reported procedural success rate is 85–99% (mean 95%). Adjunctive stent implantation has even increased the primary success rate to 97–100% (mean 99%). Patency rates of 80–90% after 5 years for short iliac stenoses are comparable to surgical results. Furthermore, PTA is associated with a much lower complication rate, with a mortality rate of 0.2% [82–84].

The TASC recommendations attempt to define a treatment of choice, depending on the morphological stratification of iliac lesions (Table 35.4). Thus, PTA is generally considered for focal lesions (type A and B lesions). For diffuse, extensive, complex multilevel, multifocal or totally occluded segments of the iliac arteries (type C and D lesions), surgery is recommended as the procedure of choice [7]. The TASC document may be a good guideline for institutions with a low volume of interventions or during the initial phase of a PAOD programme. Completed in mid-1999, the consensus process represented the most up-to-date view at that time. However, with the new endovascular devices available to experienced and skilled interventionalists, the length and morphology of iliac lesions has less influence on technical success and long-term results (Fig. 35.7).

Clinical manifestation and non-invasive work-up

Lifestyle-limiting claudication is the leading symptom of

Table 35.4 TASC recommendations for the treatment of iliac lesions*

Type A iliac lesions
Single stenosis < 3 cm of CIA or EIA (unilateral/bilateral)
Type B iliac lesions
Single stenosis 3–10 cm in length not extending into CFA
Total of two stenoses < 5 cm long in CIA and/or EIA and not extending into CFA
Unilateral CIA occlusion
Type C iliac lesions
Bilateral 5–10 cm long stenoses of CIA and/or EIA not extending into CFA
Unilateral EIA occlusion not extending into CFA
Unilateral EIA stenosis not extending into CFA
Bilateral CIA occlusion
Type D iliac lesions
Diffuse, multiple, unilateral stenoses involving CIA, EIA and CFA (usually > 10 cm)
Unilateral occlusion involving both the CIA and EIA
Bilateral EIA occlusions
Diffuse disease involving the aorta and both iliac arteries
Iliac stenoses in a patient with abdominal aortic aneurysm or other lesion requiring aortic or iliac surgery

*An endovascular procedure is the treatment of choice for type A lesions, while surgery is the procedure of choice for type D lesions. More evidence is needed to make firm recommendations about the best treatment for type B and C lesions.
CFA, common femoral artery; CIA, common iliac artery; EIA, external iliac artery.

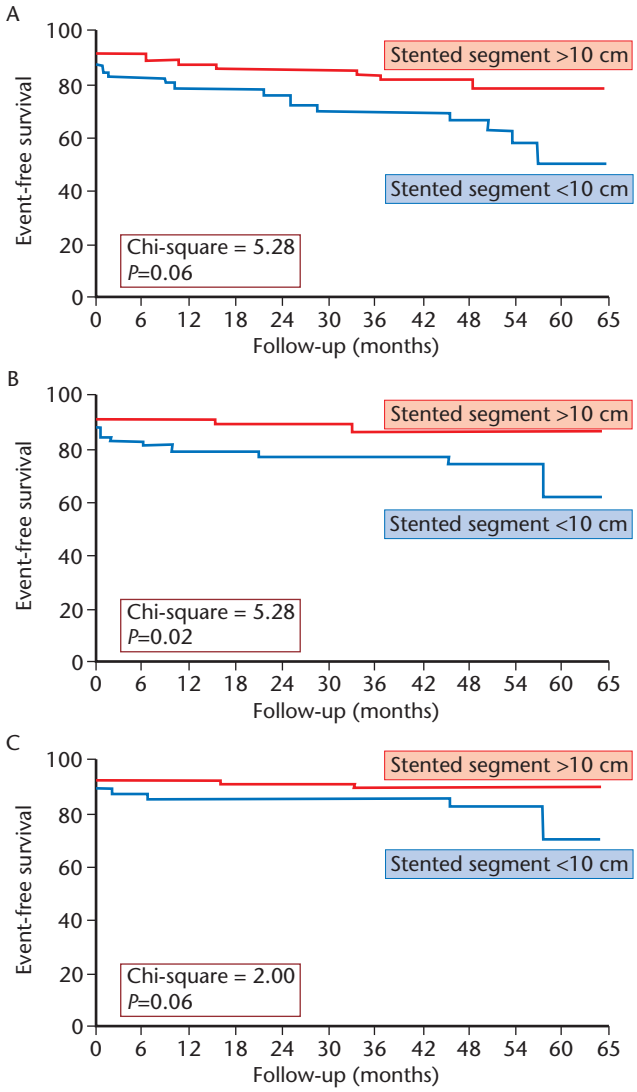


Figure 35.7 Kaplan–Meier curves comparing (A) primary, (B) assisted primary and (C) secondary patency rates for stented iliac segments after recanalization of total occlusions greater or less than 10 cm in length.

patients with pelvic obstructions. Whereas patients with femoral obstructions nearly uniformly present with pain in the calf during exercise, the complaints of patients with aorto-iliac disease may be more unspecific, with pain in the thigh or even in the back and the hips besides claudication of the calf. Furthermore, obstructions involving the internal iliac artery may cause claudication of hips and buttocks. Even though these complaints typically occur during exercise, they are frequently misdiagnosed as orthopaedic or ischiadic problems.

Procedure

Angiography

Once there is an indication for interventional therapy, intra-arterial angiography will clarify the morphological situation during the therapeutic session. Depending on the anatomical location of the lesion and the tortuosity of the iliac arteries, a single posterior–anterior projection may be insufficient. Additional lateral views may be helpful for optimal imaging of specific arterial segments: 30–45° contralateral angulation for imaging of the bifurcation of the iliac artery; 30–45° ipsilateral angulation for visualization of the external iliac artery and the femoral bifurcation.

Retrograde iliac approach

In most cases, iliac artery stenoses can be treated using ipsilateral retrograde access. Initial passage of the stenosis can be performed using a standard 0.46-mm (0.018-inch) or hydrophilic 0.89-mm (0.035-inch) angled-tip guidewire. For PTA of the stenosis, the dimensions of the balloon should be chosen to match the length of the lesion and by comparison with the proximal and distal reference segment (mostly 7–10 mm for the common iliac artery, 6–8 mm for the external iliac artery). If primary stent implantation is considered, predilatation of the stenosis should be performed with an undersized balloon and low dilatation pressure.

Balloon-expandable stents should be chosen for implantation in short lesions of the common iliac artery because these allow precise placement and have the potential for further expansion with larger balloons if necessary. Self-expanding stents may be considered for long, less calcified, non-ostial lesions in the external iliac artery.

Antegrade iliac approach

In total occlusions, antegrade recanalization is recommended. Particularly in occlusions of the common iliac artery, retrograde recanalization can lead to dissection of the distal abdominal aorta, making stent implantation far above the aortic bifurcation necessary. This scenario can be avoided using a cross-over approach. After retrograde puncture of the contralateral common femoral artery (CFA), a suitably shaped 5F guiding catheter (Hook or Shepherd–Hook) is positioned at the aortic bifurcation. The occlusion is initially passed with a stiff 0.89-mm (0.035-inch) hydrophilic guidewire, which is finally placed into the ipsilateral CFA. Using this wire as a marker, the artery is punctured and a second 8F sheath is inserted.

An angled shaped wire loop, introduced through the ipsilateral sheath, is used for snaring and retrieving the hydrophilic wire from the 8F sheath. After this step the wire in the cross-over position is exchanged for an ipsilateral guidewire and the dilatation and stenting process is performed in a retrograde fashion (Fig. 35.8).

Transbrachial approach

In some cases of chronic total occlusion of the common iliac artery, the cross-over approach may not offer enough support for successful recanalization. In these cases or in bilateral iliac obstructions, transbrachial access is an important alternative. The left brachial approach should be preferred whenever possible in order to avoid passage of the aortic arch, with subsequent risk of cranial embolization. By advancing a 90-cm shuttle introducer to the aortic bifurcation, the iliac arteries are directly accessible.

Periprocedural treatment

During intervention 5000 units of heparin is the standard dose. All patients should receive acetylsalicylic acid 100 mg/day, and in cases where stenting is used clopidogrel 75 mg daily for 4 weeks may be given additionally.

Summary of outcome results

Iliac artery stenoses

Technical success rates of more than 95% and 5-year patency rates of 80–90% have been reported for balloon angioplasty of short-segment stenosis of the iliac arteries. Whether iliac stenoses should undergo direct stent implantation has been addressed in the Dutch Iliac Stent Trial [85]. A total of 279 patients with short iliac artery stenoses were randomly assigned to receive direct stent placement or primary angioplasty with subsequent stent placement in case of a residual mean pressure gradient > 10 mmHg across the treated site (stent frequency in this group, 43%). As there were no substantial differences in technical results and clinical outcomes between the two treatment strategies at short-term and long-term follow-up, provisional stenting in the case of an insufficient angioplasty result can be considered state-of-the-art treatment for focal iliac artery stenoses.

Iliac artery occlusions

STENT-SUPPORTED RECONSTRUCTION OF THE AORTO-ILIAC BIFURCATION

According to the TASC recommendations, complex iliac artery obstructions, particularly bilateral stenoses or total occlusions, are usually treated with aorto-femoral or aorto-bifemoral graft surgery. Although highly effective, these surgical interventions are associated with a substantial procedure-related risk. Further development of percutaneous techniques, particularly the introduction of the 'kissing stent' procedure, has minimized PTA-related complications. This technique minimizes the risk of contralateral embolism or contralateral iliac artery occlusion due to dislodgement of atherosclerotic or thrombotic material during unilateral PTA (Fig. 35.8). In a series of 48 patients with obstructions of the aorto-iliac segments who underwent kissing stent implantation, primary technical success was 100%. A clinical improvement of +2 to +3 grading according to the AHA criteria was observed in 41 and 7 patients respectively. The primary angiographic patency rate at 2 years was 87%. In three cases significant restenoses were detected, which could be successfully treated by PTA. No relevant complications, particularly no embolic events or thrombotic occlusions, occurred in this series [86]. Two recently published studies, with a technical success rate of 100% in 106 and 50 patients respectively, have confirmed these results (Table 35.5). In addition, the low restenosis and reocclusion rates of these studies are corresponding [87,88].

Table 35.5 Interventional therapy of obstructions of the aortic bifurcation with the 'kissing stent' technique: technical success, complications and follow-up

Reference	*N*	Technical success	Complications*	Primary patency†	Follow-up (months)
Scheinert *et al.* [86]	48	48 (100%)	0	86.8%	24
Haulon *et al.* [87]	106	106 (100%)	0	81.1%	24
				79.4%	36
Mouanoutoua *et al.* [88]	50	50 (100%)	2 (4%)‡	92%	20

*Embolization, dissection, vessel rupture, death.
†Cumulative patency rates (Kaplan–Meier life-table method).
‡Distal embolization after recanalization of acute thrombotic occlusion.

RECANALIZATION OF CHRONIC ILIAC ARTERY OCCLUSIONS

Long-term patency after 3 years for PTA of complete iliac occlusions is reported to be 20% lower than that for iliac stenosis [89,90]. However, using an appropriate approach such as the cross-over or transbrachial technique and new stent devices, long-term results might be more favourable. In a study with 212 patients with unilateral chronic iliac artery occlusions, recanalization by excimer laser-

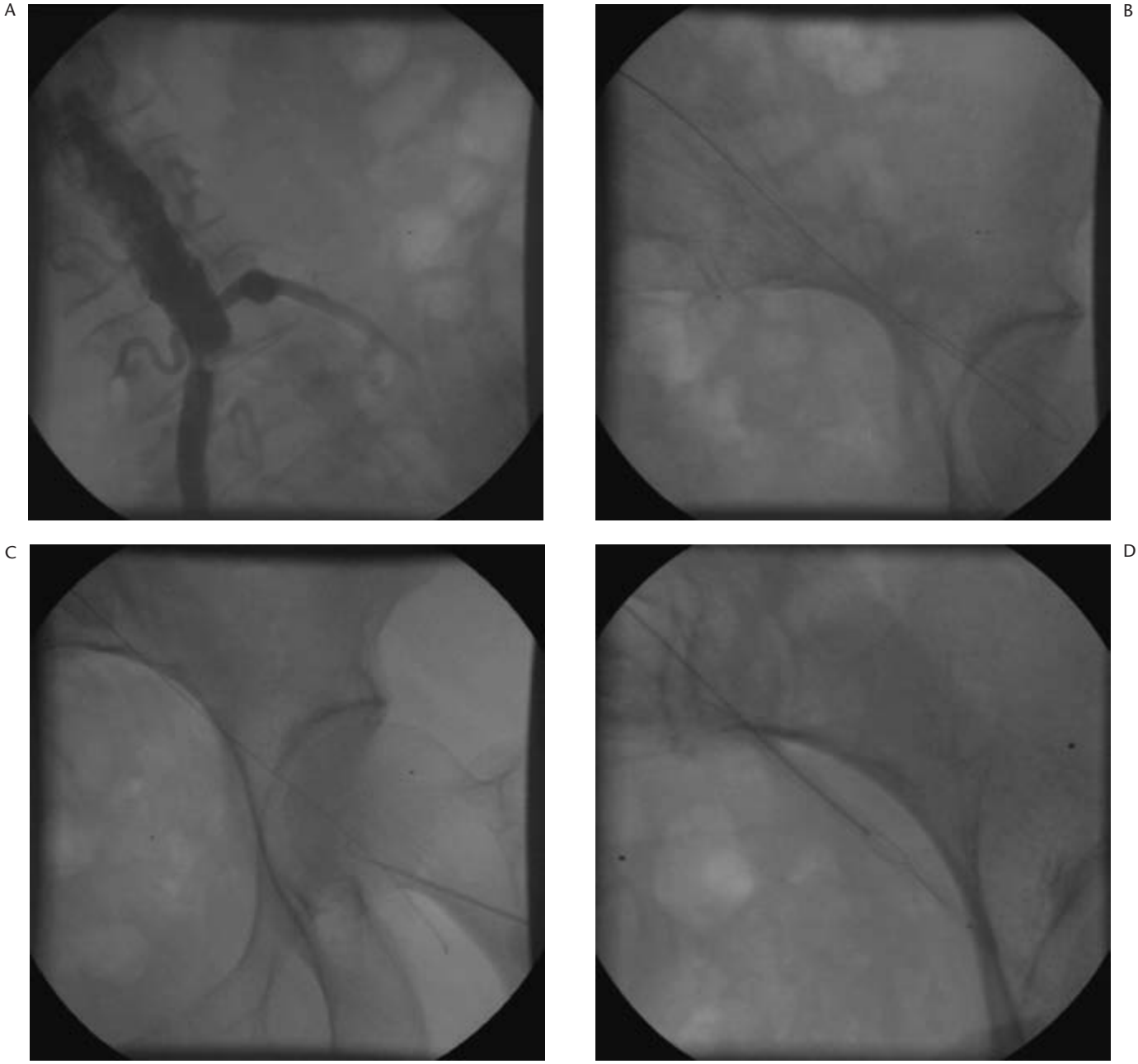
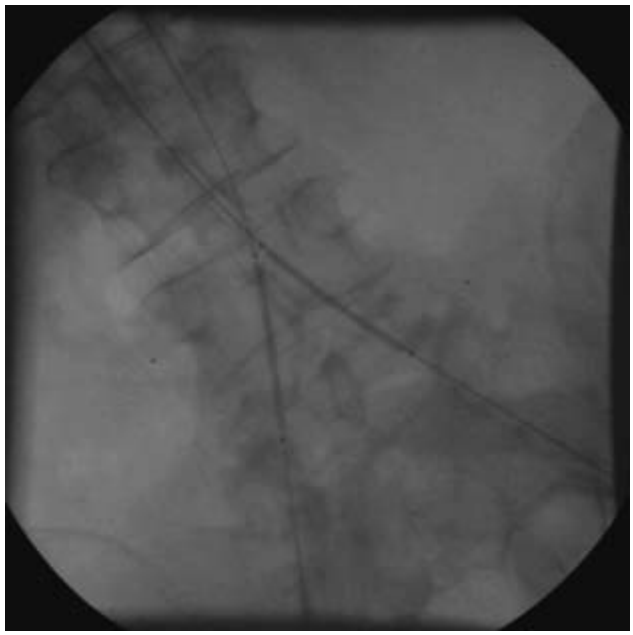
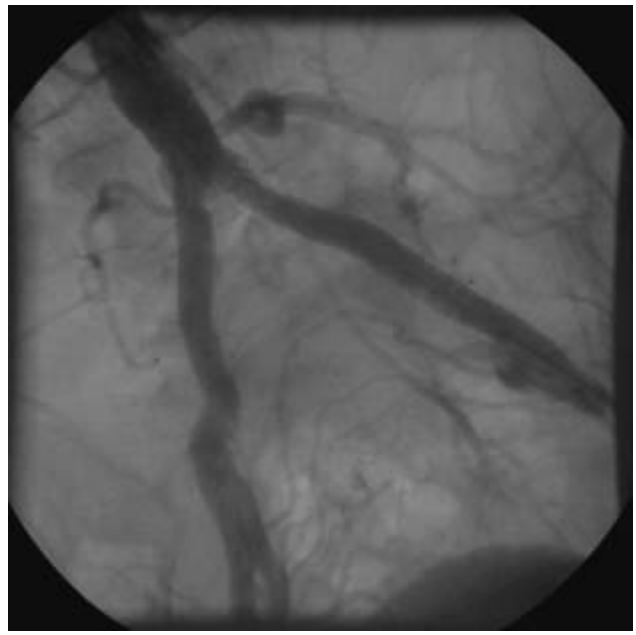


Figure 35.8 Cross-over recanalization of a chronic total iliac occlusion. (A) Occlusion of left common and high-grade stenosis of right common iliac artery. (B) Initial passing of the occlusion with a stiff hydrophilic guidewire, which is finally placed in the common femoral artery. (C) Puncture of the ipsilateral common femoral artery under fluoroscopic control using the guidewire as a marker. (D) Snaring of the cross-over wire with an angled wire loop or a snaring kit and retrieval of the guidewire from the ipsilateral sheath, using this as retrograde approach.

E





F

Figure 35.8 (*Cont'd*) (E) 'Kissing stent' technique is the implantation of two stents simultaneously. (F) Final result.

Table 35.6 Stent–supported reconstruction of the aorto-iliac bifurcation: cumulative patency rates

	Follow-up (months)	No. of patients	Lost to follow-up	Local events	Patency (%)	SD
Primary clinical patency	0	48	–	–	100	–
	6	48	–	–	100	–
	12	40	7	1	97.8	2.1
	18	29	8	3	89.6	4.9
	24	21	7	1	85.3	6.3
Primary angiographic patency	0	43	–	–	100	–
	6	43	–	–	100	–
	12	28	14	1	97.2	2.7
	18	19	8	1	93.2	5.6
	24	13	5	1	86.8	7.4

assisted angioplasty and primary stent implantation was performed [91]. Technical success was achieved in 190 of 212 patients (89.6%), associated with a marked clinical improvement (+3 or +2 grades according to AHA guidelines) in 112 (52.8%) and 67 (31.6%) cases respectively. The major complication rate in this series was 1.4%. Primary patency rates of 81.2% at 2 and 75.7% at 4 years demonstrate that this technique is a safe and effective treatment for patients with chronic iliac artery occlusions (Fig. 35.7 and Table 35.6). A summary of our results with transbrachial recanalization of chronic iliac occlusions is given in Table 35.7.

Recanalization of the femoro-popliteal tract

More than 50% of all lesions in PAOD are localized in the femoro-popliteal tract. Occlusions predominate over stenoses in this arterial segment. Furthermore, most femoro-popliteal lesions/obstructions are extensive and there is often coexistent multilevel atherosclerotic disease.

In this region, endovascular treatment is recommended by the TASC consensus paper for short stenoses and occlusions (Table 35.8). In contrast, long chronic occlusions

Pre-interventional and peri-interventional data
Number of patients: 45 (primary brachial approach, 32; secondary approach after failed femoral access, 13)
Unilateral occlusion: 36
Unilateral occlusion + contralateral stenosis: 5
Bilateral occlusion: 4
Median occlusion length: 10.2 cm
Number of implanted stents: 74
Primary technical success: 98% ($n = 44$)

Results
Clinical improvement*: +3 grades in 41% ($n = 18$) and +2 grades in 50% ($n = 22$)
Mean clinical follow-up: 17 months
Primary patency†: 97% at 9 months and 92% at 12 months
Secondary patency†: 100% at 12 months and 88% at 24 months

*Rutherford classification.
†Cumulative patency rates (Kaplan–Meier life-table method).

Table 35.7 Summary of results for transbrachial recanalization of chronic total iliac artery occlusions

Lesion type		Recommendation
TASC A	Single stenosis < 3 cm	Endovascular treatment
TASC B	Single stenoses 3–5 cm Heavily calcified stenoses < 3 cm Multiple lesions, each < 3 cm	More evidence is needed to make firm recommendations about best treatment
TASC C	Single stenosis or occlusion < 5 cm Multiple lesions, each 3–5 cm	More evidence is needed to make firm recommendations about best treatment
TASC D	Complete occlusion of the superficial femoral artery	Bypass surgery

Table 35.8 TASC recommendations for the treatment of lesions of the superficial femoral artery

of the SFA are predominantly considered for vascular surgery [7]. However, because of the related morbidity and mortality, surgical interventions are reserved for patients with ischaemic rest pain or advanced claudication. In contrast, percutaneous revascularization techniques permit a lower threshold for interventions, particularly considering new techniques for endovascular recanalization.

Access methods for infra-inguinal interventions

A key issue in the successful completion of an endovascular intervention is selection of the appropriate vascular access. Two standard approaches are available for femoral, popliteal and tibial artery interventions: the cross-over and the antegrade approach. A third possibility is the transpopliteal approach, although this technique should be used by expert interventionalists in exceptional cases only.

Cross-over access

In order to provide optimal support for the recanalization procedure, the use of a cross-over sheath is recommended. After an arterial sheath has been placed in the CFA in a standard retrograde fashion, the contralateral ilio-femoral system is reached by placing a 5F diagnostic catheter (Cobra, Hook, Shepherd–Hook, IMA, Simmons I–II or a diagnostic right coronary catheter) at the aortic bifurcation. The catheter is manipulated so that its tip 'engages' the ostium of the contralateral common iliac artery. A soft, hydrophilic, 0.89-mm (0.035-inch) guidewire is navigated through the guide catheter and advanced into the femoral artery. The diagnostic catheter is then advanced using a 'push-and-pull' technique. The soft guidewire is then exchanged for a stiff guidewire. The stiff guidewire opens the angle of the aortic bifurcation and facilitates placement of the appropriate cross-over sheath.

Nowadays, the cross-over approach from the CFA is considered in many centres the standard access technique for femoro-popliteal interventions. Compared with the antegrade approach, the technically easy cross-over approach is thought to be associated with a markedly lower complication rate.

Antegrade access

The antegrade approach can be applied in cases where cross-over access is not possible because of difficult anatomy of the pelvic vessels (e.g. previous aorto-bifemoral bypass, stents in the region of the aortic bifurcation). Some interventionalists prefer the antegrade approach because it provides more direct access to many lesions in the medial and distal femoro-popliteal segment and the infrageniculate arteries. Furthermore, it may be helpful for crossing very calcified lesions.

However, compared with the cross-over approach, antegrade puncture is technically more challenging, particularly in obese patients. Furthermore, a high puncture of the CFA is usually required to provide sufficient space for navigation of the guidewire into the SFA. Supra-inguinal puncture should be avoided due to the high risk of retroperitoneal haemorrhage. Injection of contrast media through the needle may help to identify the anatomy of the femoral bifurcation. In order to facilitate this, a slightly lateral projection (25°) should be used to open up the angle of the bifurcation.

Transpopliteal access

Transpopliteal access can be considered a salvage technique after a failed attempt to recanalize the lesion with a cross-over or antegrade approach. A patent distal femoral and proximal popliteal artery, as well as sufficient peripheral run-off, are essential for this approach. After retrograde placement of a 4F sheath into the ipsilateral CFA and after placing the patient in the prone position, the popliteal puncture is performed using 'roadmap' fluoroscopy by injection of contrast media through the 4F sheath. After puncturing the popliteal artery at a steep angle (70–80°) and insertion of a guidewire, a 4–6F sheath is introduced. This approach is complex but is successful in nearly 80% of patients where there has been failure of antegrade recanalization of SFA occlusions.

Lesion crossing

Routinely, femoro-popliteal stenoses and occlusions are passed using a 0.46-mm (0.018-inch) guidewire. In case of failure, an angled-tip 0.89-mm (0.035-inch) stiff hydrophilic guidewire is recommended. A multipurpose catheter (4F or 5F) may be helpful in providing additional support and also improves the steerability of the guidewire. For long or uncrossable lesions, the use of the excimer laser catheter is recommended [92].

Alternatively, using the so-called percutaneous intended extraluminal (subintimal) recanalization (PIER) technique, the J-tipped wire is directed subintimally at the very beginning of the occlusion by using an angulated support catheter [93]. To achieve re-entry into the true lumen distal to the occlusion, cautious probing with the wire tip is recommended in order to avoid further dissection of the artery into the healthy segment. Inability to re-enter the true lumen must be expected in up to 20% of total occlusions. Our experience shows that the only predictor of failure is the degree of calcification. A transpopliteal approach can be an option in this situation.

Percutaneous transluminal balloon angioplasty

In most cases, PTA has to be considered the treatment of choice for short focal femoro-popliteal lesions. The dimensions of the balloon should be chosen according to the length of the lesion (20–80 mm) and the diameter proximal and distal to the lesion (4–6 mm). Over-sized balloons may cause dissections. With the exception of severely calcified lesions, balloon inflation should not exceed 8–10 atm. Inflation time should last at least 30 s and up to 2 min. In the case of an unsatisfactory result, a second prolonged balloon inflation should be attempted before stenting.

Patency after balloon angioplasty

Guidelines for the management of PAOD published by TASC [7] recommend PTA as first-choice therapy in lesions up to 3 cm in length, whereas occlusions more than 5 cm in length should undergo bypass operation (Table 35.8). In fact, the reported long-term patencies after balloon angioplasty of SFA lesions are inconsistent, varying from 73% after 4 years to 23% after only 6 months for long lesions [94]. Besides the length of the lesion, other factors may also have an influence on long-term outcome, such as lesion type (stenosis vs. occlusion), clinical stage (claudication vs. critical ischaemia) or outflow [95].

In the case of long lesions, we recommend the use of excimer laser technology for recanalization. Using this technology [92] successful recanalization is achieved in more than 90% of total occlusions of the SFA. With debulking of obstructive material it is possible to transform an occlusion into a stenosis. Subsequently, balloon dilatation can be performed with lower pressure, which may reduce arterial wall stress and the rate of subsequent dissections. This may lead to a reduced need for stenting and reduced stimulation of the mechanism that causes restenosis [96] (Fig. 35.9).

According to an early publication, the PIER technique has a long-term patency rate of up to 71% after 12 months [97]. However, the latest study shows considerably inferior results, with a primary assisted patency rate of only 37% after 12 months and even worse results for patients

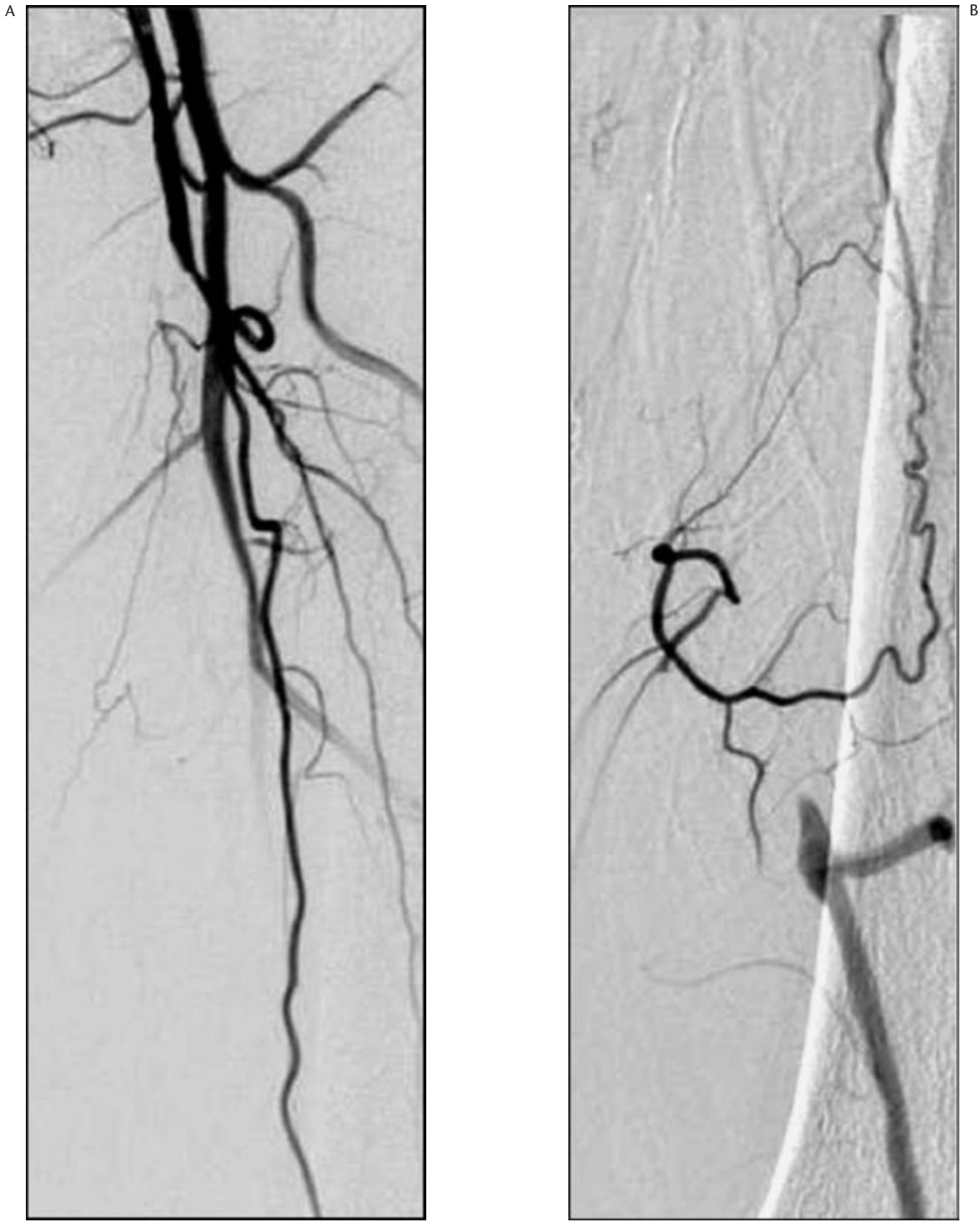


Figure 35.9 (A,B) Long occlusion of the left superficial femoral artery. (C–E) Result after laser recanalization and additional balloon angioplasty.

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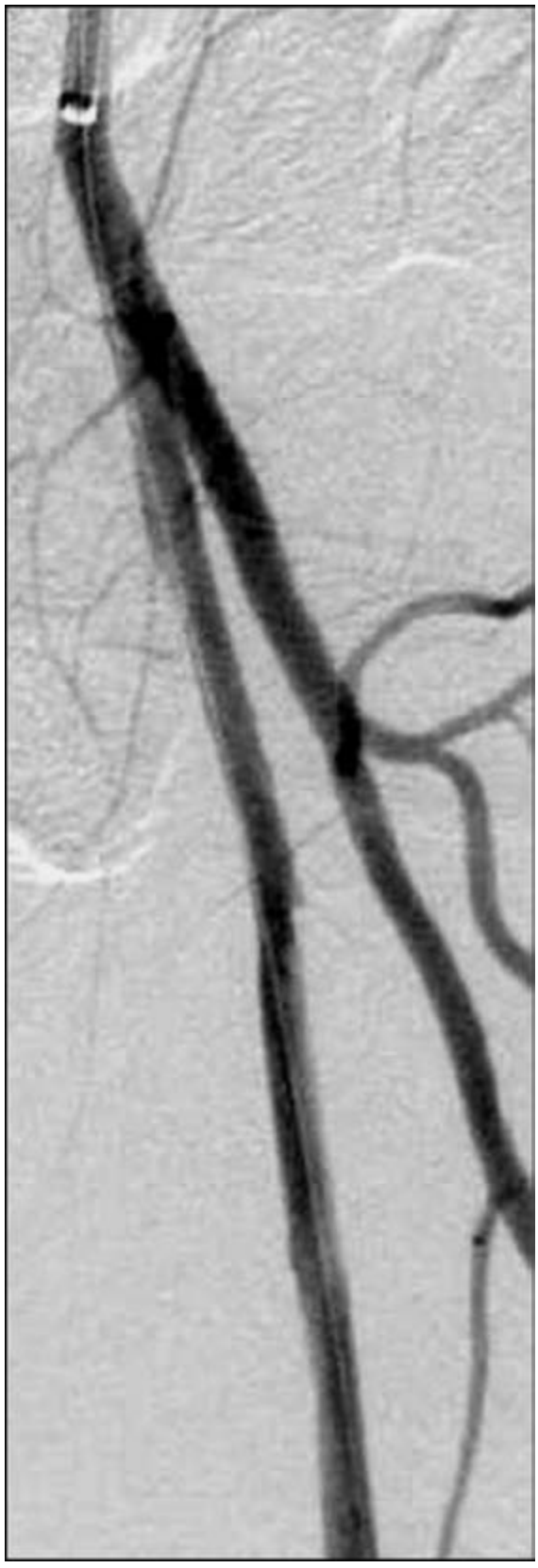

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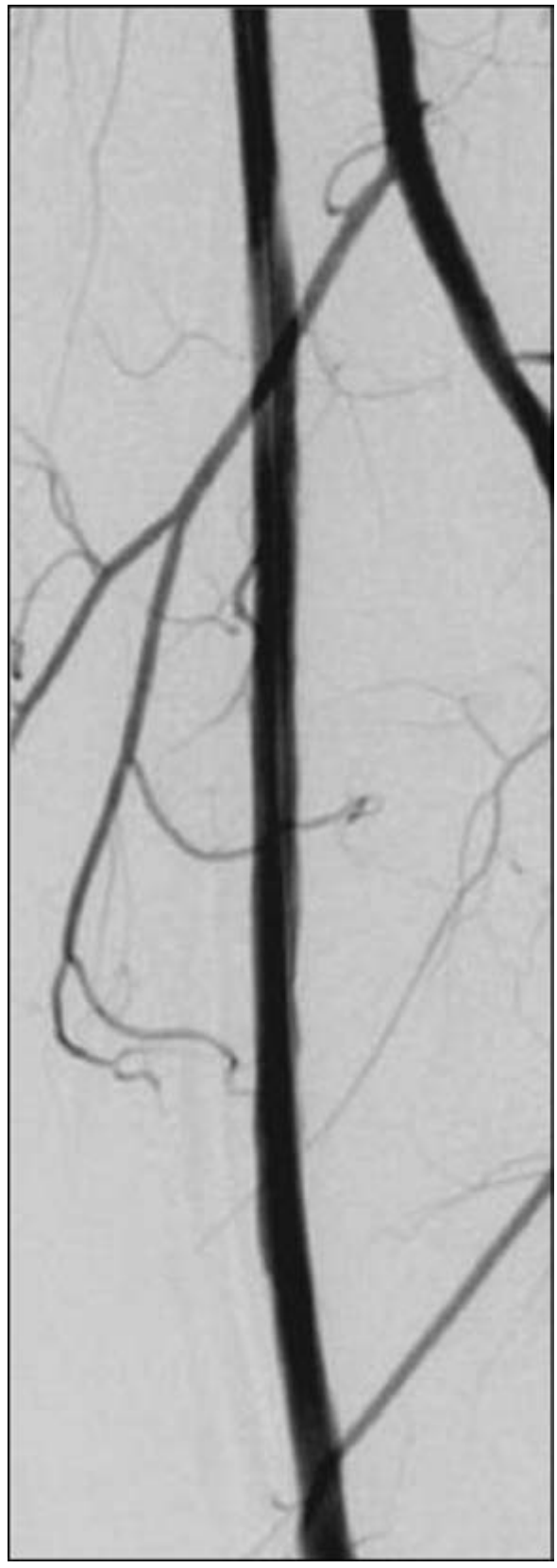

Figure 35.9 (*Cont'd*)

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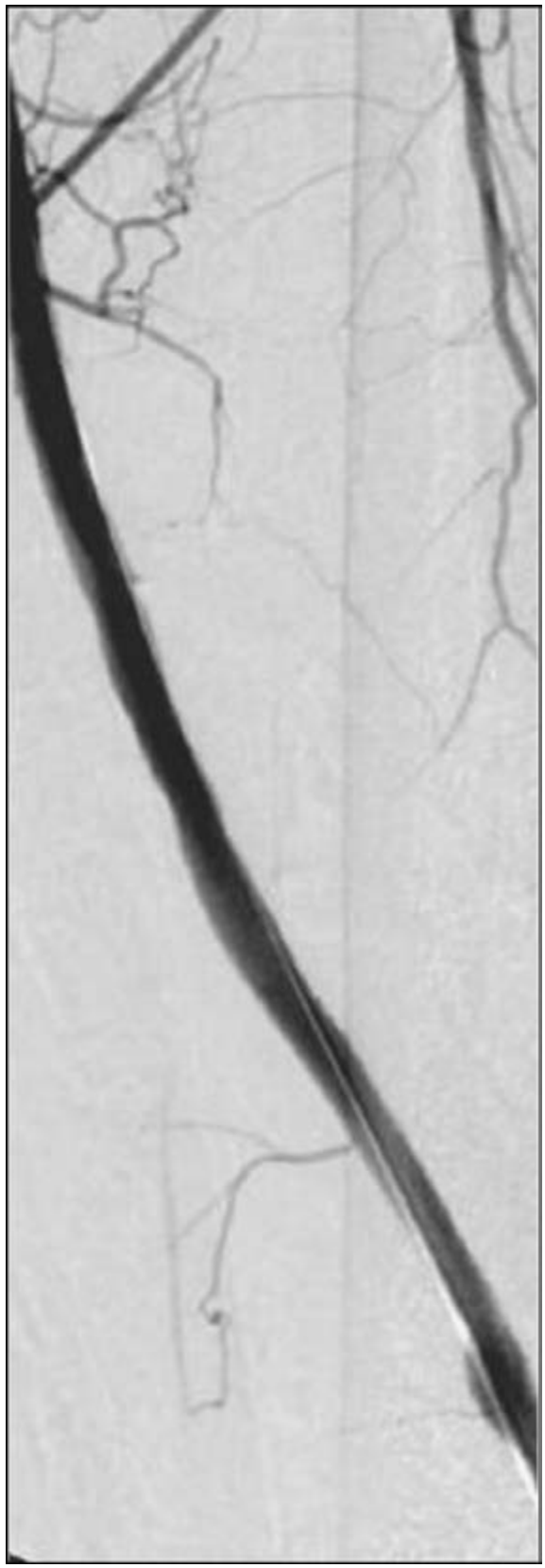


Figure 35.9 (*Cont'd*)

with critical ischaemia, with a 6-month patency rate of only 24% [93].

Stenting of the SFA

The primary success rate for recanalization of even chronic long occlusions of the SFA is very high (80%). The most challenging aspect of endovascular therapy is to maintain patency. Stents have been advocated for improving patency of the femoro-popliteal tract but the published results do not yet meet expectations. Gray *et al*. [98] observed a primary patency rate of 22% after stenting long occlusions of the SFA (mean lesion length 16.5 cm) at 1-year follow-up.

The use of balloon-expandable stents in the SFA should be completely abandoned. Only self-expanding stents should be used in the SFA, an artery that is subject to compression, elongation, shortening and distortion over its whole length. Stainless steel stents were the first self-expanding stent used in the SFA. A relevant disadvantage of this type of stent is its extensive and unpredictable foreshortening of up to one-third of its unconstrained state, making exact placement difficult. Furthermore, the radial force, which is still effective after deployment, may provoke further enlargement, with consequent ongoing foreshortening and potential development of gaps between initially overlapping stents.

Another concept of self-expansion uses the thermal memory characteristics of nitinol, an elastic intermetallic alloy of nickel and titanium. Preshaped at high temperature to its nominal dimension, the stent is soft and deformable after cooling. When exposed to body temperature during deployment, the stent tends to expand rapidly to its nominal diameter. Its negligible foreshortening (5%) makes implantation more precise.

The results of a multicentre study comparing the long-term patency of nitinol stents and stainless steel stents in the treatment of long diffuse SFA lesions showed encouraging results [99]. In a sample of 329 procedures on the SFA, stainless steel Wallstents were used in 166 interventions and nitinol stents in 163 interventions. Mean lesion length was 20 cm and 80% of these lesions were total occlusions. The 1-year primary, assisted primary and secondary patency rates were 61%, 75% and 79% for nitinol stents compared with 30%, 53% and 64% for Wallstents respectively (Fig. 35.10). The long-term secondary patency of about 80% achieved using nitinol stents in long lesions demonstrates that this technology is safe and clinically very effective.

Indications for stenting the femoro-popliteal artery

Primary stenting of the SFA remains controversial. Pub-

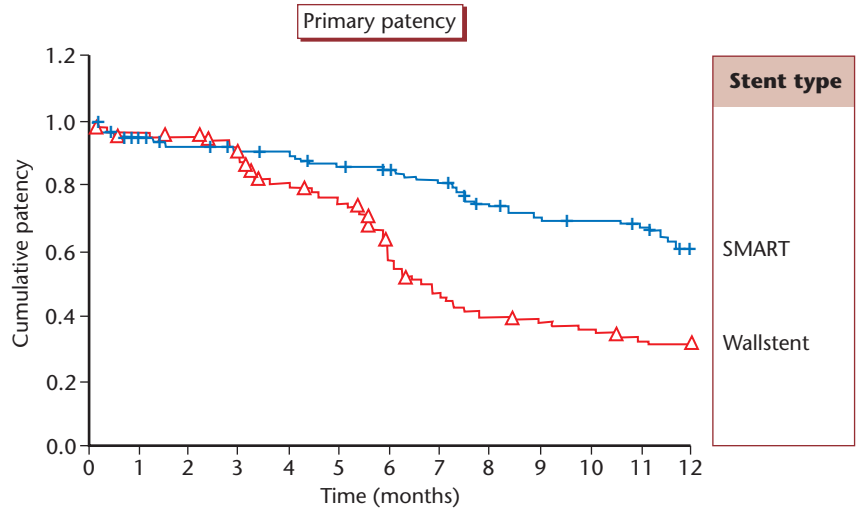


Figure 35.10 The 12-month primary patency of nitinol stents compared with stainless steel Wallstents in long lesions of the superficial femoral artery.

lished randomized trials have not demonstrated the superiority of systematic over selective stenting after balloon angioplasty for lesions of the SFA. However, only shorter lesions were included and only balloon-expandable stents were used in these trials [100]. Comparative data using nitinol stents in longer lesions might lead to different results. The accepted indications for stenting are flow-limiting dissections after PTA, a residual pressure gradient > 15 mmHg or a remaining stenosis > 30%, elastic recoil, as well as failure to maintain initial patency.

In a recent meta-analysis of long-term results after angioplasty of femoro-popliteal arterial lesions collected from 19 studies, outcomes of 923 balloon dilatations and 473 stent implantations were compared [95]. The 3-year patency rate after balloon angioplasty was 61% for stenoses and claudication, 43% for stenoses and CLI, and 30% for occlusions and CLI. The 3-year patency rates after stent implantation were 63–66% and were independent of the clinical state and type of lesion.

Technique of stent implantation

The stent should always cover the whole lesion, and preferably extend for a few millimetres into the healthy vessel. The occlusion of side branches after stenting is rare. The diameter of self-expanding nitinol stents should be 1–2 mm larger than the reference vessel (5–7 mm). Postdilation for adaptation of the stent is necessary in the majority of cases.

Surveillance after SFA stenting

Acute reocclusion of a stented SFA is a rare complication, particularly using the cross-over approach for implantation of a nitinol stent and with administration of low-molecular-weight heparin. In our experience, a post-intervention anticoagulation regimen including acetylsalicylic acid (100 mg/day), clopidogrel (75 mg/day) and low-molecular-weight heparin for several days or weeks has nearly eliminated the problem of acute reocclusions.

Late restenosis or reocclusion by intimal hyperplasia or progressive arteriosclerosis remain relevant problems in this arterial segment. In contrast to other regions, restenosis can emerge after many years. Therefore follow-up examinations are extremely important. DUS is the method of choice.

Stent fracture

The SIROCCO I trial [101], a randomized comparison of drug-eluting versus bare stents in SFA lesions, revealed that fracture can occur in self-expanding nitinol stents in this arterial segment. Triggered by this observation, we investigated the occurrence and clinical impact of stent fracture in a cohort of 93 patients (121 legs) treated by implantation with different types of self-expanding nitinol stent. Systematic radiographic screening was performed 10.7 months (mean) after implantation. The mean length of the stented segment was 15.7 cm. Stent fractures were detected in 37.2% of the treated legs. Fractures could be classified as minor, single-strut fracture (48.4%), moderate with fracture of more than one strut (26.6%), and severe with complete separation of the segments (25%). The rate of stent fracture depended on the length of the stented vessel and was highest in lesions > 16 cm in length. The primary patency rate at 12 months was significantly lower for patients with stent fractures (41.1% vs. 84.3%, $P < 0.0001$) [102]. Differences

in fracture rates and impact on patency of different stent designs needs to be clarified in further studies. The treatment of restenoses or reocclusions in cases of stent fracture can make in-stent stenting necessary, at least for severe stent fractures.

Treatment of in-stent restenosis

Excimer laser is a very successful technique for the treatment of in-stent restenosis or reocclusion. Simple balloon angioplasty remains another option. Endovascular atherectomy has been used but published results are discouraging: a randomized study demonstrated a tendency towards poorer results in comparison with balloon angioplasty [103]. This, along with the technically demanding procedure, has led to atherectomy not being established as a routine treatment method. However, recently introduced technical improvements of the atherectomy system, including a complete redesign of the previous device, have shown promising acute results in single-centre reports of the treatment of long femoropopliteal lesions [104].

Treatment of acute and subacute occlusions of the SFA

An embolic or thrombotic occlusion of the femoropopliteal tract often leads to an acute onset of severe symptoms. Surgical removal of the thrombotic material using a Fogarty catheter is still considered the therapy of choice in many centres. Endovascular techniques such as thrombus aspiration, thrombolysis, mechanical thrombectomy and conventional balloon angioplasty and stenting, or a combination of techniques, are effective alternatives [19].

In longer acute occlusions of the SFA, the use of a thrombectomy device can be recommended as first choice. Various mechanical thrombectomy catheters have been developed, using either the vortex principle or the Bernoulli and Venturi effect, for removing the thrombus. Many of these devices are successful only in acute thrombotic occlusions and need additional application of thrombolytic agents in a considerable number of cases. Local intra-arterial infusion or infiltration of the thrombus using specially designed infusion catheters with side holes can be performed; preferably, thrombolytic agents should be infused over hours or even days using different infusion regimens until control angiography is performed.

Comparison of the efficacy of thrombolytic agents is difficult because of the different techniques used in local application of the drugs and different dosages; however, recent trends favour recombinant tissue plasminogen activator (rt-PA) over streptokinase and urokinase. Direct thrombus infiltration by end-hole catheters or perforated balloons is time-saving and has proved to be highly successful, with a low complication rate especially in combination with PTA and thrombus aspiration [105]. Another approach may be local thrombolysis using a regimen of 5 mg rt-PA as a bolus followed by continuous infusion of either 1 mg rt-PA plus 750 units heparin per hour or 2 mg rt-PA plus 500 units heparin per hour over a period of 12 and maximally 24–36 h [106].

Complications of SFA recanalization

Complications after angioplasty of SFA stenoses are reported to occur in 0–5% and are nearly exclusively limited to the entry site. The risk of perforation is minimal if balloons are chosen according to the reference vessel size, which rarely exceeds 5 mm. In cases of perforation and persistent bleeding, prolonged blockage with a balloon or stenting often leads to sealing. Nevertheless, a covered stent should be available at all times. The possibility of peripheral embolization with consequent occlusion of the trifurcation during angioplasty of acute or subacute SFA occlusions has always to be taken into account. Solid scientific data on the incidence of relevant complications after SFA interventions are not available.

New techniques for endoluminal therapy of femoro-popliteal lesions

New strategies for lowering the risk of restenosis, including brachytherapy, stentgrafts and drug-eluting stents, are the subject of ongoing trials. First results from randomized trials on brachytherapy after angioplasty of femoro-popliteal lesions with [107] or without [108] stenting have shown a significant effect on intimal hyperplasia. The need for a special room for the procedure because of the use of gamma radiation is a limitation and makes other techniques for prevention of restenosis more attractive than brachytherapy.

Endoluminal stentgrafts were introduced to prevent hypertrophic neointima formation in the SFA after angioplasty but led to high early and late restenosis rates, with a considerable complication rate [109].

Drug-eluting stents are the most attractive alternative to conventional stent implantation. In a small pilot study (SIROCCO), 36 patients with symptomatic SFA lesions with a mean length of 8.5 cm were randomized to a non-coated or sirolimus-coated SMART nitinol stent. Angiographic follow-up at 6 months revealed no restenosis in the sirolimus-treated group. However, an unexpected low rate of restenosis of 23.5% in the control

group with the uncoated nitinol stent led to a non-significant difference between the two groups in terms of restenosis of 50% or more [101]. Therefore, an increased number of patients ($n = 57$) were enrolled (SIROCCO II). However, after 6 months of follow-up the data of the SIROCCO I trial were confirmed, showing no restenosis for the drug-eluting stents and only a 7.7% restenosis rate for the bare stents. With regard to the primary endpoint, mean stent diameter, pooled data from the two trials showed a significant difference in favour of drug-eluting stents, even with the exceptional outcomes for the bare SMART stent [110]. Further analysis will reveal whether these encouraging results are maintained during the long-term follow-up.

Interventions below the knee

Despite recent reports showing primary success rates of greater than 80–90%, the validity of transcutaneous techniques (PTA) in patients with stenoses or occlusions in popliteal or infrageniculate arteries is still controversial. In fact early reported experiences met with limited success [111,112]. The weakness of recent non-randomized studies is, in many cases, due to lack of a clear protocol, poorly defined follow-up that does not differentiate between primary, primary assisted and secondary patency rates, and poor documentation of clinical improvement, which is not strictly related to the patency of the treated vessel.

Isolated lesions below the knee are present in only 15% of cases. Approximately 30% of symptomatic patients with PAOD have diffuse arterial disease affecting the femoro-popliteal tract and the tibial arteries. The majority of patients with CLI, many of whom are diabetics, have distal arterial disease with occlusions in the tibial arteries. Despite the presence of combined lesions in the SFA and infrapopliteal arteries, it is routine in many interventional centres to treat only the obstructions in the SFA, hoping for improved run-off through the collateral system. This attitude reflects several factors, including technical requirements and limited data on the effectiveness of these procedures in category 3 patients (Rutherford classification) as well as in patients with chronic or subacute critical leg ischaemia with or without tissue loss (category 4 to 6) normally considered for surgical bypass or amputation. The complexity of the problems related to the optimal treatment modality for this patient cohort has to be reviewed in light of advances in interventional tools and techniques and with the therapy goals in mind.

Revascularization strategies

Primary lesion crossing

In most cases, below-the-knee stenoses or occlusions can be treated using an ipsilateral antegrade approach; alternatively, the intervention can be performed using the cross-over technique. Both approaches have advantages and disadvantages. With the cross-over approach, by using long introducers or placing guiding catheters (e.g. 6F multipurpose) through the cross-over sheath with the tip in the distal superficial femoral or popliteal artery, support for subsequent lesion crossing with the balloon catheter is enhanced and, furthermore, potential delivery of stents to the infrapopliteal arteries is protected.

Once the sheath is placed, the target lesion is crossed with a guidewire. Below the knee, only atraumatic 0.46-mm (0.018-inch) or 0.36-mm (0.014-inch) guidewires should be used for this purpose. The high steerability and torqueability of the new guidewires permit occlusions to be passed in the majority of cases. In some cases showing calcified total occlusions, the use of a 0.89-mm (0.035-inch) hydrophilic guidewire may be necessary; however, after initial passage of the occlusion, this guidewire should be exchanged for a less traumatic wire.

Dilatation process

Only low-profile balloons should be used to dilate infrapopliteal vessels, which are similar in diameter to coronary arteries. Dimensions of the PTA balloon should be chosen according to the proximal and distal reference segment. Balloon over-sizing should be avoided in order to reduce the risk of relevant dissections in these fragile vessels. In cases of long occlusions or multiple-vessel stenoses, long balloons up to 120 mm should be used (Fig. 35.11); alternatively coronary balloons can be used. Faglia *et al*. [37] evaluated the feasibility, technical effectiveness and limb salvage potential of PTA, particularly infrapopliteal, in diabetic subjects with ischaemic foot ulcer. PTA was performed in 191 (85.3%) of 219 subjects with stenoses > 50%, even when the lesions were longer than 10 cm or multiple and calcified. The ABI improved significantly after PTA. Clinical recurrence occurred in 14 subjects, 10 of whom underwent a second successful PTA. Of the 191 patients who underwent PTA, only 10 (5.2%) underwent an above-the-ankle amputation. These data show that PTA of infrapopliteal arteries is feasible in most diabetic subjects with ischaemic foot ulcer and is effective for foot revascularization. Clinical recurrence was infrequent and the procedure could be successfully repeated in most cases.

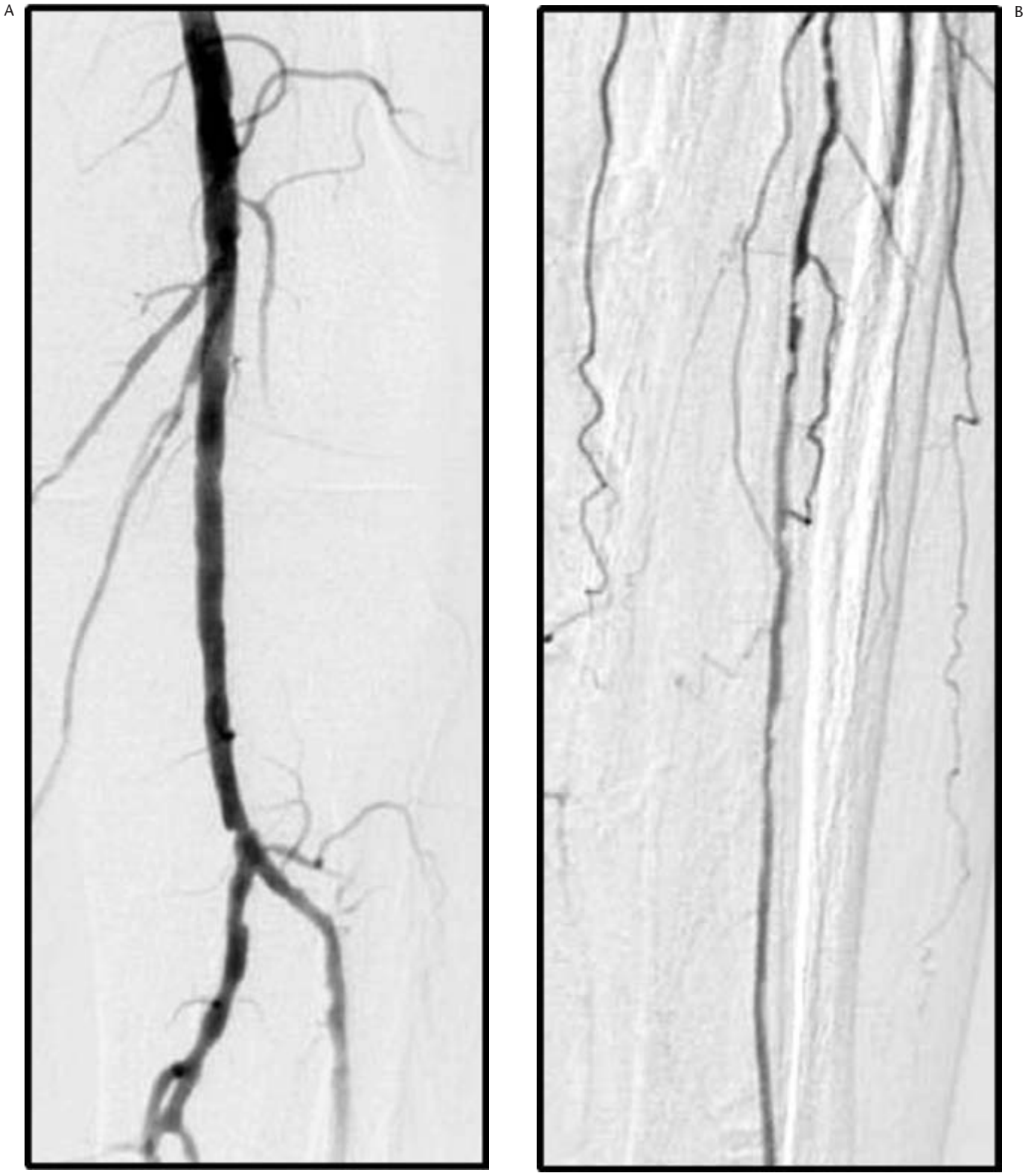
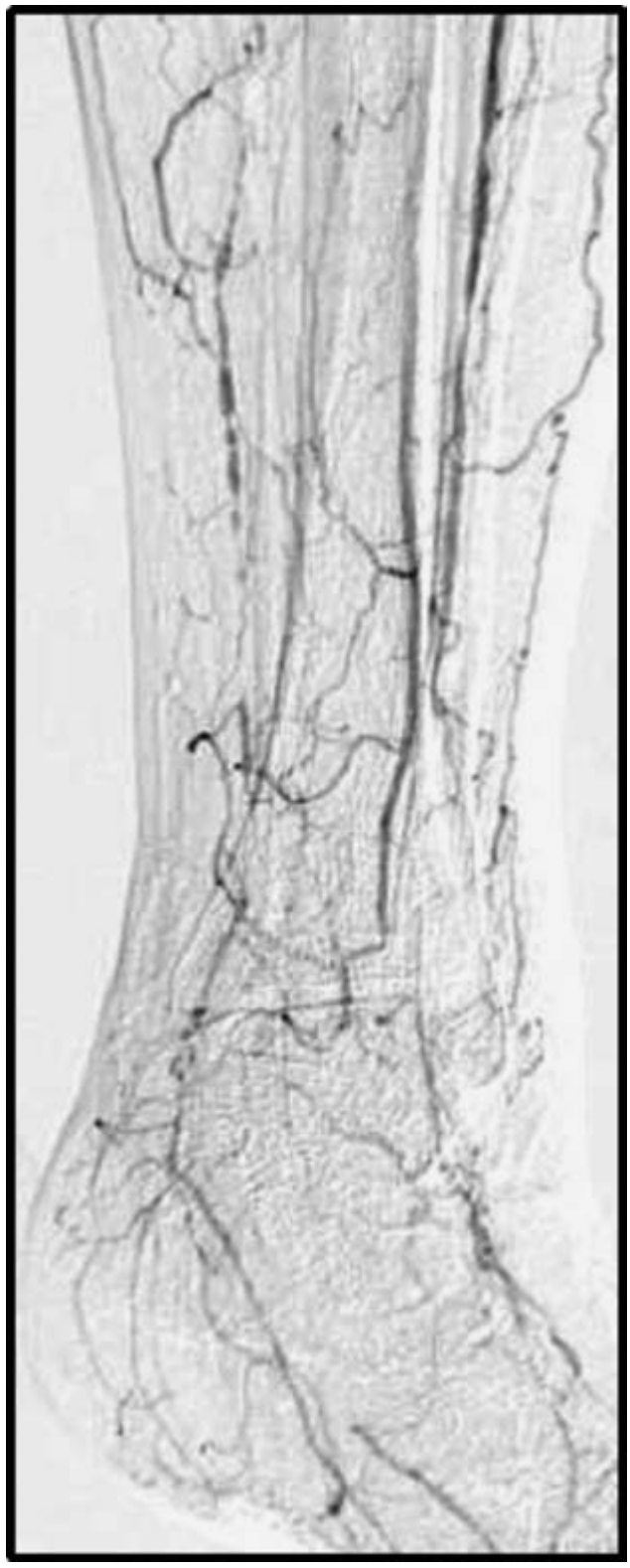


Figure 35.11 Diabetic patient with Rutherford class 5 peripheral arterial occlusive disease and gangrene of left forefoot. (A–C) Occlusion of the posterior and anterior tibial artery, high-grade stenoses of the fibular artery. (D) Dilatation of the occluded posterior tibial artery with a 2/120-mm balloon. (E–F) Final result after recanalization of all below-the-knee arteries.

C



D

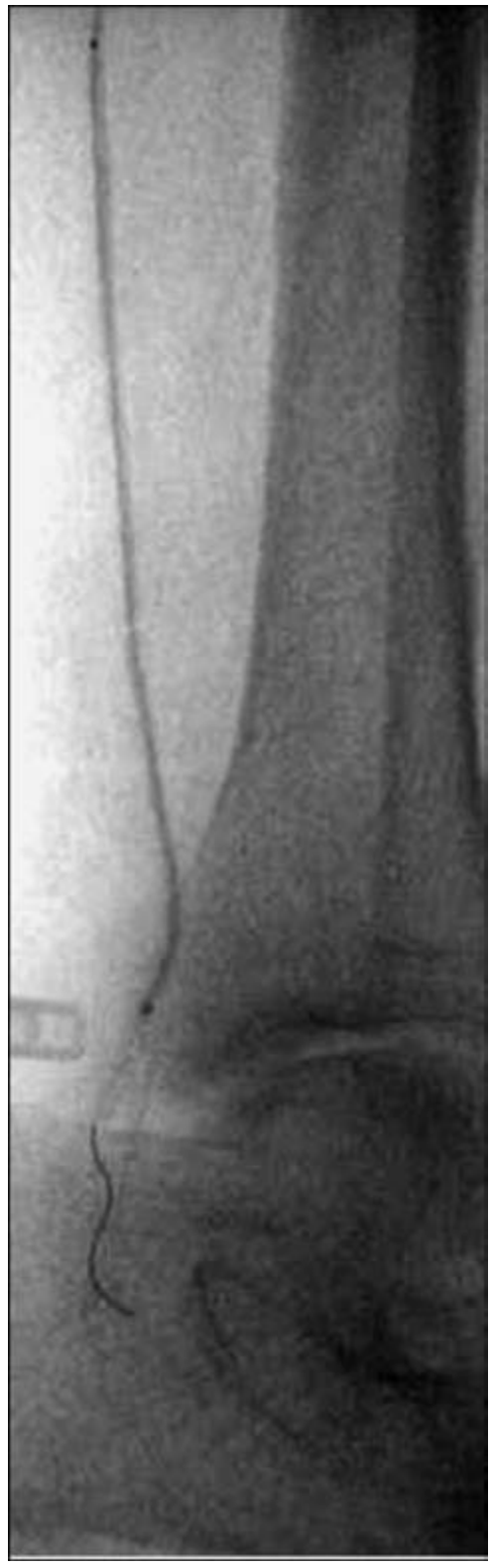


Figure 35.11 (*Cont'd*)

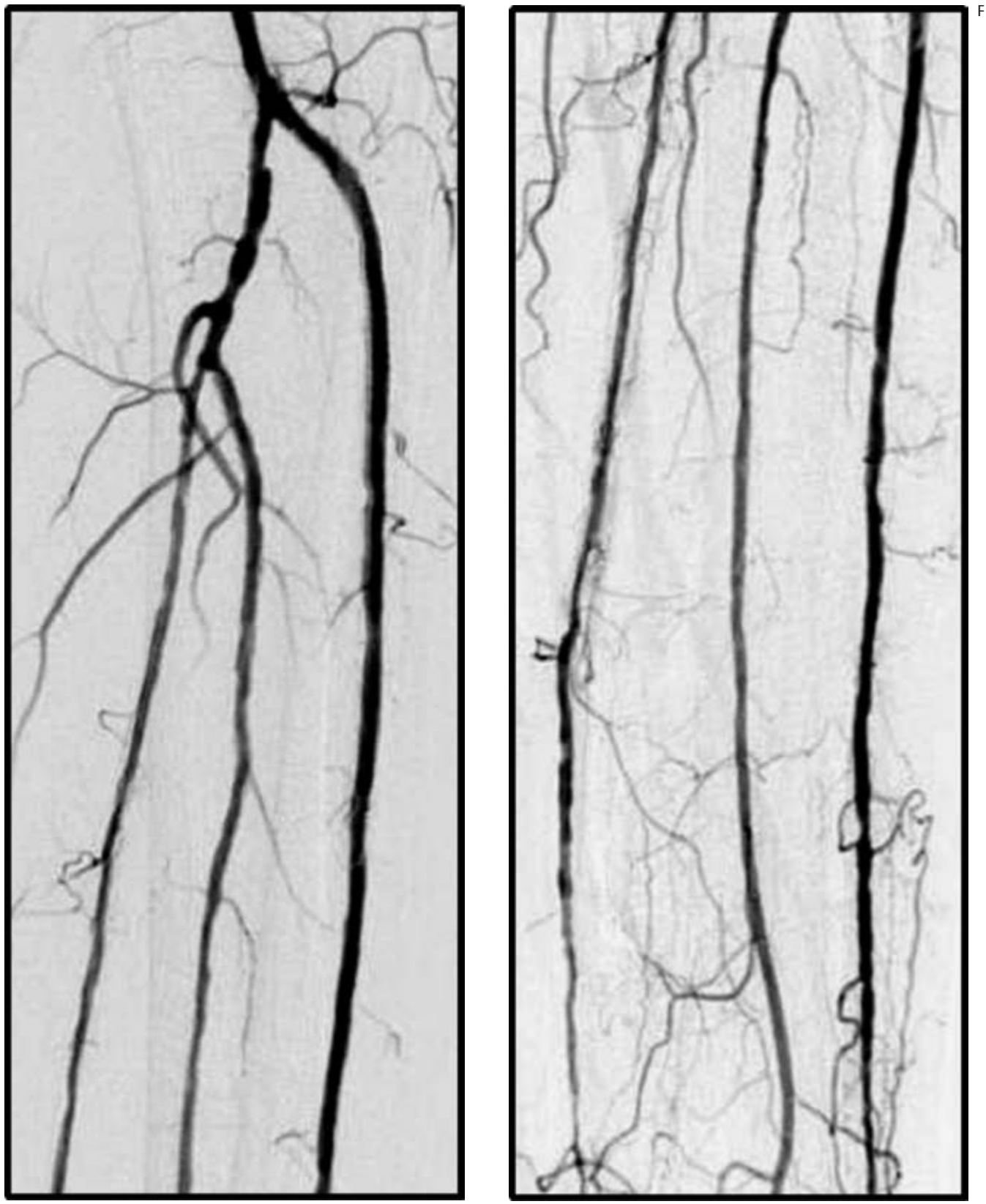


Figure 35.11 (*Cont'd*)

Excimer laser debulking technique

One limitation of conventional recanalization techniques remains the partial inability to cross total occlusions. As an alternative, laser ablation can be used in a step-by-step manner where the guidewire and then a laser catheter are sequentially advanced and activated (millimetre by millimetre) until the occlusion or stenosis is crossed. After the wire has crossed the lesion, with or without the aid of the excimer laser step-by-step technique, recanalization of the atheroma and/or the thrombus is achieved with multiple passes of an appropriately sized laser catheter. To improve the effectiveness of ablation, saline or lactated Ringer's solution should be infused locally while the laser catheter is activated. The excimer laser's ability to remove atheroma and thrombus provides progressive simplification of a complex diffuse lesion or occlusion into a focal stenosis that is easily treated by balloon angioplasty.

In contrast to published single-centre retrospective angioplasty registries [112–115], the multicentre laser studies prospectively enrolled patients who were poor surgical candidates and who presented with multilevel obstructive disease not amenable to standard angioplasty techniques. The LACI trial [116,117], the CIS series [118], LACI Belgium trial [119] and the LACI-RTO series all resulted in excellent limb salvage rates in a patient population with a high percentage of diabetes and other comorbidities, poor distal run-off, and diffuse multilevel disease. The LACI registries demonstrated that a combined therapeutic strategy of excimer laser atherectomy, balloon angioplasty and optional stenting can be successfully applied to virtually all vascular disease states commonly found in patients with CLI, not just to the simplest disease patterns. Pretreatment with laser-facilitated guidewire placement in chronic total occlusions removed the thrombus burden and provided luminal gain, thereby simplifying the vascular milieu and reducing the chance of balloon-induced distal embolization and dissection.

Stenting below the knee

At present, there are few evidence-based results indicating the effectiveness and durability of stents for infrageniculate application. Feiring *et al*. [120] treated 82 patients (92 limbs) with CLI and/or severe lifestyle-limiting claudication (LLC) with primary stent-supported angioplasty. The results indicate that the use of stents below the knee is effective and safe. Below-knee stent-supported angioplasty for CLI and LLC improves ABI comparable to tibial bypass, heals amputations and ulcerations, relieves rest pain and improves ambulation. Because below-knee stent-supported angioplasty is associated with minimal major adverse events, it may hold promise as an alternative therapy for patients with CLI and LLC. However, data concerning the long-term patency rate of stents in this region are not yet available. Therefore, stent implantation in below-the-knee arteries should be limited to restenosis, to cases with very calcified lesions and to bail-out situations.

Dedicated development of stent devices suitable for popliteal, and particularly tibial, arteries is urgently expected. Well-designed trials demonstrating the validity of stents in tibial arteries are mandatory before guidelines for their use may be defined. Finally, it is uncertain if, when and where drug-eluting stents may bring a breakthrough similar to coronary interventions.

Postprocedural treatment

During the intervention, 5000–10 000 units of heparin should be administered intra-arterially. Heparin anticoagulation may be continued for 24 h (1000–1200 units/h i.v.), maintaining an activated partial thromboplastin time of 60–80 s. In the case of recanalization of total occlusions or stent implantation, we recommend prolonging anticoagulation with weight-adjusted low-molecular-weight heparin for 3 weeks. Acetylsalicylic acid (100 mg/day) is given to all patients. Clopidogrel (75 mg/day) is prescribed for at least 6 weeks. In selected cases, a longer duration of clopidogrel administration may be considered. We have to stress that these are personal recommendations not supported by scientific data but only by daily clinical experience, and by analogy to coronary interventions.

Managing procedural complications

Although infrequent, procedural complications do occur in complex infrapopliteal or tibio-peroneal interventions. Spasms may be managed with intra-arterial injection of 0.2–0.6 mg nitroglycerine. In some cases, prolonged balloon inflation with low pressure may solve the problem. Major dissections may be 'sealed' with prolonged balloon inflations. In many cases, stent implantation will be necessary.

Local thrombi are rare. We primarily recommend direct catheter thrombus aspiration, perhaps combined with local administration of 3–8 mg rt-PA before using mechanical aspiration techniques. The application of abciximab in combination with catheter manipulation has shown promising results in preliminary trials [121].

Distal embolization, particularly in below-the-knee interventions, has to be considered a serious adverse event with potentially deleterious consequences. There are no definitive data that universally support one treatment strategy over the others. We normally prefer local lytic

therapy in combination with mechanical thrombolysis. Others recommend direct catheter aspiration, preferably using a tracker 0.97-mm (0.038-inch) catheter in crural arteries. This approach has the advantage of being quick and cheap but requires ipsilateral access.

Perforation with clinical sequelae is rare. Prolonged balloon inflation or stent implantation can normally solve the problem. The use of endovascular prostheses is very limited.

Comparative summary of treatment options for CLI

The primary goal of successful revascularization in the CLI patient population is not necessarily long-term patency but restoration of direct blood flow to the foot in order to induce healing of skin lesions, relieve pain and avoid major amputation.

The LACI study showed that laser-assisted PTA provided a limb salvage rate as high as the reference values observed for a best-case treatment strategy for patients who were good bypass candidates, while not affecting patient mortality. LACI achieved limb salvage rates comparable to the 'gold standard' of bypass surgery, without higher serious adverse events. The clinical advantage of the laser-assisted strategy is that a single intravascular regimen achieves a lower rate of major amputation in a more extensively diseased population than PTA does in simpler disease patterns. No other interventional technique has been supported with such a large patient population treated in multiple centres. Plain balloon angioplasty is also highly successful in patients with CLI due to infrapopliteal lesions, although the data are from single centres and should be compared with laser-assisted recanalization techniques in multicentre studies.

Using new advances, endovascular techniques show technical success rates in excess of 82% and as high as 98% with limb salvage rates exceeding 85% in single-centre and multicentre reports published since 1999. These results are equal to or better than individual surgical reports. The primary reason for the widespread adoption of endovascular intervention in CLI is based on the concept of repeatable recanalization with low complication rates and on the fact that the surgical option remains open in the majority of the cases after PTA procedures.

Personal perspective

The rapidly evolving technical improvements over the last few years have produced not only dramatic changes in the treatment of PAOD but also substantial shifts in the perception and socio-political evaluation of the disease. A few years ago, and in many countries still today, PAOD was considered a more-or-less fatal illness without real prospects of medical treatment, the only alternative being vascular surgery in selected cases. Nowadays, using sophisticated non-invasive techniques, it is possible to determine the extent and severity of the disease without any serious risk to the patient. This should permit a more detailed analysis of the individual clinical situation, enabling consideration of risks and benefits in a considerably ageing population, who have the right to receive optimal medical care that should include improvements in quality of life. What will be 'best treatment' of POAD in the near future? One thing should be absolutely clear: medical inactivity is the most costly and definitely the most inadequate attitude. Although prevention remains the best solution, we have to deal with the reality of an increasing incidence of atherosclerosis, amounting to at least 2500 cases per million inhabitants over 65 years old.

With regard to the different forms of POAD, it is our opinion that in the treatment of carotid stenoses in high-risk patients the endovascular techniques of stenting with neuroprotection are not inferior to vascular surgery. It is likely that carotid stenting will also be an alternative in asymptomatic patients with high-degree stenoses. In the near future, the biggest problem with the treatment of carotid artery stenoses will not be the techniques themselves but the lack of adequately trained interventionalists. Intensive education and strict guidelines for certification are mandatory. We also believe that the endovascular treatment of nearly all other obstructive lesions of the supra-aortic arch and the intracranial vessels will soon dominate the field.

It is generally accepted that the treatment of choice for sclerotic renal artery stenoses is PTA plus stenting; however, we have to deal with an important non-technical problem: the clinical indication. The interventional community has to generate solid scientific data indicating the clinical effectiveness of the intervention, not just the primary success rate and long-term patency. It will be hard to generate such data because financial support for adequately planned randomized studies on stenotic lesions of the renal arteries will remain very limited.

With regard to the pelvic region, we are convinced that nearly everyone considers the TASC recommendations an important step but now out of

date. The new recanalization techniques, in combination with excellent balloon-expandable and self-expandable stents with or without the support of lytic therapy, guarantee extremely high success rates with long-term results comparable with surgical series, so that the number of inaccessible iliac lesions is no higher than 10%.

The situation is completely different in the infra-inguinal region. Recanalization techniques are highly effective with primary success rates in excess of 90%, including for very long and calcified lesions. However, the long-term results are still not satisfactory in this extremely complex conduit that is subject to the continuously changing forces of compression, distortion and elongation. The improvements achieved with nitinol stents in stabilizing the primary intervention are overshadowed by the next nightmare—stent fracture. Improvements in the mechanical properties of the stent, particularly for the treatment of long lesions, are absolutely mandatory before there is serious discussion on the application of drug-eluting stents in the femoro-popliteal tract. One of the biggest challenges for the interventionalist in the near future will be the tibial vessels, considered for two decades an almost untouchable zone. The use of coronary material in combination with new debulking techniques has changed the scenario completely, permitting unexpected results.

It is unacceptable to regard CLI as an untreatable end-stage disease. On the contrary, CLI is a reason to act. Amputation, with its associated enormous costs, is no longer satisfactory when limb salvage rates of 85–90% can be achieved. Intensive collaboration with the industry will be necessary in order to develop more effective dedicated tools. Encouraging animal and preliminary clinical results indicate that gene therapy could be a valuable adjunctive treatment, particularly in CLI.

Finally, it is our opinion that a prerequisite for optimal care of this often polymorbid cohort of patients is collaboration of the different disciplines. Involvement of the vascular surgeon is mandatory, and centres dedicated to the treatment of the vascular patient should be intensively supported. It is hard to believe that the seminal work of Andreas Grüntzig on peripheral vessels provoked the formation of innumerable coronary centres, whereas 30 years after the publication of his dissertation on peripheral interventions we are still fighting in some fields for the right to exist.

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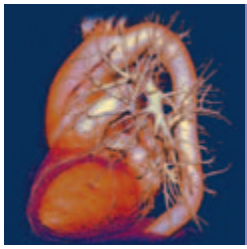


36 Venous Thromboembolism

Sebastian M. Schellong, Henri Bounameaux and Harry R. Büller

Summary

In this chapter, deep vein thrombosis and pulmonary embolism are discussed as manifestations of the same disease process. Despite the steadily growing use of medical thromboprophylaxis, pulmonary embolism remains the third most frequent cause of cardiovascular mortality.

The current concept of venous thromboembolism is that of a multifactorial disease. Besides age, several transient and permanent risk factors have been recognized. The strongest in the former group are surgery and trauma, whereas the latter is dominated by active cancer and thrombophilia. However, a substantial proportion of cases present without an identifiable risk factor and are therefore classified as 'idiopathic' or 'unprovoked' episodes. In those patients, or in the presence of a permanent risk factor, venous thromboembolism is a chronic relapsing disease.

The diagnosis of a current episode has to be based on the result of an imaging procedure. During the last 10 years, compression ultrasound and helical computerized tomography have turned out to be the most powerful diagnostic tools. However, strategies have been developed to safely exclude the disease on the basis of clinical pre-test probability and D-dimer testing alone in one-third of all suspected cases.

For most patients anticoagulation is the only acute treatment modality. Low-molecular-weight heparins represent the current standard of care. The post-thrombotic syndrome as the long-term sequela of deep vein thrombosis can be effectively prevented by compression therapy. Haemodynamic instability in pulmonary embolism requires systemic thrombolysis according to the risk of fatal right heart failure. Vitamin K antagonists remain the standard treatment for maintenance therapy, the duration of which has to be balanced between the risk of recurrence and the potential for major bleeding.

Natural history

Venous thrombosis results from the presence of a clot in the venous circulation. Signs and symptoms of the disease are caused by obstruction of the respective vein(s) and/or by embolization of parts of the clot into the pulmonary circulation. This definition applies only for lower and upper extremity veins. Thrombosis of cerebral and visceral veins is beyond the scope of this chapter.

Pulmonary embolism is not a rare complication but occurs regularly in patients with deep vein thrombosis (DVT). For this reason, DVT and pulmonary embolism are considered as two manifestations of the same disease: venous thromboembolic disease or venous thromboembolism (VTE). As they share most aspects of natural history, diagnosis and treatment, DVT and pulmonary embolism will be discussed together.

Aetiology

Venous thrombus formation is due to an imbalance between local and systemic procoagulant – anticoagulant and profibrinolytic – antifibrinolytic activity. According to Virchow, all pathogenic factors responsible for this imbalance can be classified into three categories: disturbances of venous flow, disturbances of vessel wall and disturbances of blood components. Table 36.1 gives a sample of pathogenic factors of the respective categories.

Table 36.1 Pathophysiological mechanisms underlying venous thromboembolism, according to Virchow's triad

Impairment of blood flow (venous stasis)	Vessel wall impairment	Impairment of blood constituents
External compression of proximal veins	Malignant infiltration	Dehydration
Solid tumour	Inflammatory infiltration	Polyglobulinaemia
Arterial aneurysm	Surgery	Polycytosis
Tourniquet	Venous puncture	Hyperfibrinogenaemia
(Lympho)coele	Other trauma	Inherited thrombophilia
Baker's cyst	Hyperhomocysteinaemia	Antiphospholipid antibodies/lupus-like anticoagulant
Pregnancy	Antiphospholipid antibodies/lupus-like anticoagulant	Heparin-induced thrombocytopenia
Internal obstruction	Heparin-induced thrombocytopenia	Tumour procoagulant
Residual thrombus from previous DVT	Residual thrombus from previous DVT	Pregnancy, puerperium
Catheter		Drugs
Immobilization		Hypofibrinolysis
Impaired respiratory movements		Alien body (catheter, pacemaker cable, caval filter)
Obesity		
Congestive heart failure		
Varicose veins		

There are distinct subject-related or circumstantial constellations placing a patient at risk for venous thromboembolism. Almost all of them involve more than one pathogenic factor. The constellations with the biggest impact are age, cancer and surgery. Table 36.2 gives the most frequent constellations, listing the mechanisms involved and the magnitude of risk [1]. With regard to prognostic and therapeutic implications, risk factors are classified as transient or permanent. In most cases of VTE, more than one risk factor can be identified. According to the presence or absence of an identifiable transient risk factor, the actual episode of VTE is referred to as 'provoked' ('triggered') or 'unprovoked' ('idiopathic').

Epidemiology

Combining the results of incidence studies from different countries with different methodologies, the annual incidence of VTE, if standardized for age and sex distribution in the USA, is 71–117 cases per 100 000 population [2]. On clinical grounds, the ratio between pulmonary embolism and DVT is 1:3 to 2:3; if the information is mainly autopsy based the ratio is 0.5:0.5. The largest impact on VTE incidence is age (Fig. 36.1), with incidences of < 5/100 000 in childhood to > 500/100 000 in persons above 80 years of age. Between males and females there seems to be no clear difference in VTE incidences. For aetiological constellations, approximately

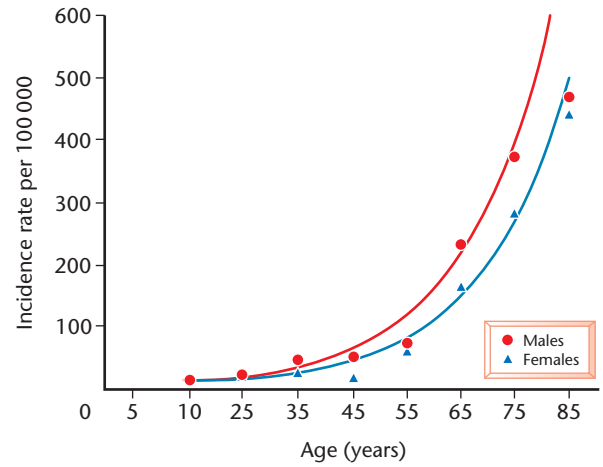


Figure 36.1 Age dependency of VTE incidence [2].

20% of cases are due to cancer, and surgery, trauma and immobilization account for around 50% of cases. The remaining 30% (ranging from 26% to 47% in different studies) have to be classified as 'idiopathic' or 'unprovoked'. When tested systematically for thrombophilia, a large proportion (25–50%) of patients with VTE will show one or more of the established conditions, such as factor V Leiden mutation, prothrombin 20210 mutation, deficiency of antithrombin, of protein C or S, or antiphospholipid syndrome [3].

Table 36.2 Clinical risk factors for venous thromboembolism

Clinical risk factor	Category
Surgery	
Fracture (hip or leg)	Strong
Hip or knee replacement	Strong
Major general surgery	Strong
Arthroscopic knee surgery	Moderate
Laparoscopic surgery	Weak
Trauma	
Major trauma	Strong
Spinal cord injury	Strong
Medical illness	
Malignancy	Moderate
Congestive heart or respiratory failure	Moderate
Paralytic stroke	Moderate
Previous venous thromboembolism	Moderate
Bed rest > 3 days	Weak
Iatrogenic factors other than surgery	
Central venous line	Moderate
Chemotherapy	Moderate
Oral contraceptive therapy	Moderate
Hormone replacement therapy	Moderate
Non-disease-related conditions	
Pregnancy/postpartum	Moderate
Pregnancy/antepartum	Moderate
Increasing age/decennium	Weak
Varicose veins	Weak
Prolonged sitting (air or car travel)	Weak
Obesity	Weak
Thrombophilia	
Antiphospholipid syndrome	Strong
Severe antithrombin deficiency	Strong
Severe protein C deficiency with family history	Strong
Severe protein S deficiency with family history	Strong
Factor V Leiden mutation, homozygous	Strong
Factor V Leiden mutation, heterozygous	Moderate
Prothrombin 20210 mutation	Moderate
Elevated factor VIII and IX levels	Moderate
Hyperhomocysteinaemia	Moderate

Categories: Strong = odds ratio > 10; moderate = odds ratio 2–9; weak = odds ratio < 2.
Risk factors are weighted within each section and within each category.
Adapted from ref. [1].

Types of acute deep vein thrombosis (Fig. 36.2)

By far the most common type of deep vein thrombosis is ascending leg DVT. It originates in calf muscle veins or in the paired calf veins. Owing to a persisting thrombogenic stimulus, and precipitated by the presence of the thrombus itself, the clot grows from distal to proximal by apposition of new thrombotic material. In every stage of thrombus propagation the process can be aborted by a change of balance between thrombogenic and antithrombotic mechanisms. If not, the clot may grow from calf muscles to iliac veins within days or even hours. In other cases propagation to femoral or iliac veins may take weeks.

With actively propagating thrombus proximal parts of the clot may break off and move via the right heart to the lungs. As long as the thrombus is confined to the paired calf veins, the risk for embolization is low. If the thrombus extends beyond the paired calf veins into popliteal veins or above, and in particular in the case of a fast-growing thrombus, the risk for pulmonary embolism

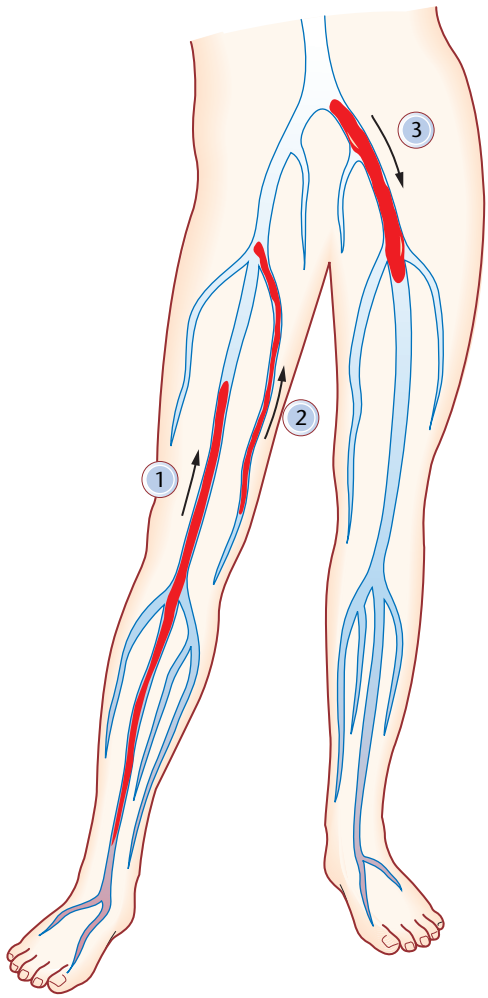


Figure 36.2 Types of deep vein thrombosis. 1, ascending DVT; 2, transfascial DVT; 3, descending iliofemoral DVT.

becomes high. The length of the embolus may vary from millimetres to dozens of centimetres.

Less frequent but clinically more impressive is the descending type of leg DVT. It originates from the iliac veins. In 90% of cases the left iliac vein is primarily involved. The reason for this uneven side distribution is the so-called venous spur, named after May and Thurner. It is a fibrous obstructive lesion within the left common iliac vein as a response to the chronic microtraumatization of this venous segment by the pulse movements of the right common iliac artery crossing the left iliac vein. Among the trigger factors for left-sided iliac vein thrombosis are pregnancy and recent onset of oral contraceptive use. Thrombotic obstruction of the iliac vein by thrombus can develop within hours, leading to rapid and massive leg swelling, pain and discoloration.

There are rare patients in whom the venous return of the leg is completely blocked due to an overwhelming thrombotic obstruction of the entire venous circulation. Oedema may increase to an extent that tissue pressure compromises arterial inflow and fully obstructs microcirculation (phlegmasia coerulea dolens). Viability of the leg is threatened as long as revascularization of at least the iliac veins cannot be accomplished [4].

The third type of leg DVT is transfascial thrombosis. The site of origin is the greater or lesser saphenous vein. Superficial phlebitis with thrombosis in varicose as well as in non-varicose veins has the potential to propagate proximally. Once approaching the inflow segment into the deep venous system it crosses the fascia at the inguinal (greater saphenous vein) or popliteal level (lesser saphenous vein), thereby turning from superficial into deep vein thrombosis. The deep vein part of the clot is prone to embolization.

Upper extremity DVT usually is segmental subclavian and/or axillary vein thrombosis. Trigger factors are either a central venous line or heavy shoulder/arm muscular exercise ('thrombose par effort', Paget–von Schrötter syndrome). In some cases thrombosis is precipitated by an anatomic narrowing formed by the clavicle and the first rib or a neck rib ('thoracic inlet syndrome'). Also, upper extremity DVT is the first sign of mediastinal malignancy, mostly lymphoma or bronchus carcinoma. Pulmonary embolism from upper extremity DVT has been documented [5].

Without pulmonary embolism, DVT alone does not have a mortality of itself. However, 10–20% of patients will die in the first year owing to underlying diseases, mostly cancer.

Pulmonary embolism

Every clot in the venous circulation has a tendency to grow. Speed and extent of thrombus growth are defined by the presence and the strength of the underlying risk factor(s). Fresh appositional thrombus is prone to be dislodged from its original site. From there it will be transported by the venous blood flow and, after having passed the right heart, it will embolize into the pulmonary circulation. The impact of this event on the clinical condition of the patient depends exclusively on the size of the embolus. Millimetre-sized emboli will go entirely asymptomatic, whereas large thrombotic masses corresponding to the volume of the iliofemoral veins may result in shock or sudden death.

In the case of a patent foramen ovale and increased pulmonary artery pressure (e.g. previous pulmonary embolism or Valsalva manoeuvre), small clots may be pushed across to the left atrium and cause central or peripheral arterial occlusion (paradoxical embolization); larger clots may stick within the foramen ovale (transit thrombus or straddling thrombus). Sometimes the

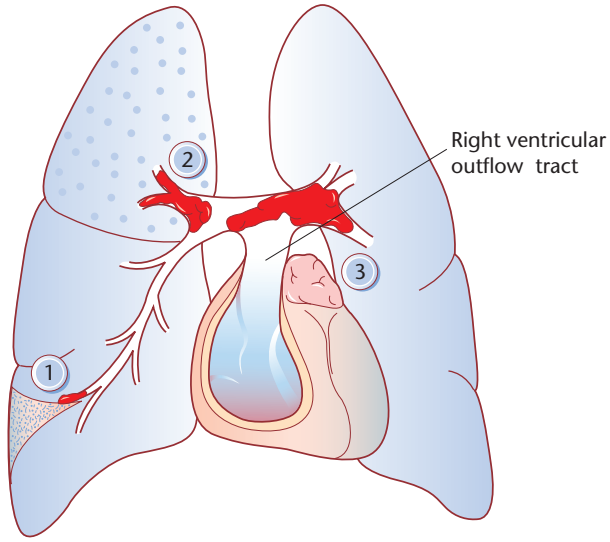


Figure 36.3 Elements of pathophysiology in pulmonary embolism. 1, Haemorrhagic pulmonary infarction with or without pneumonia in subsegmental pulmonary embolism; 2, significant perfusion/ventilation mismatch in segmental or lobar pulmonary embolism; 3, massive pulmonary artery obstruction of > 50% with right heart failure.

embolus or parts of it will be caught by the tricuspid valve. At this site it may cause further thrombus accumulation with relapsing embolization.

Three categories of sequelae of pulmonary embolization have to be considered (Fig. 36.3): local alterations of lung and pleural tissue, functional impairment of respiration and impairment of cardiac function; the first will occur preferably with subsegmental and segmental emboli (peripheral pulmonary embolism), the last two in lobar or main stem pulmonary artery occlusion (central pulmonary embolism). Subsegmental and segmental emboli cause a local imbalance between pulmonary arterial blood flow for gas exchange and systemic arterial nutritional blood flow in subpleural areas of the lung. Lung infarction results in pleural irritation with pleuritic chest pain, alveolar haemorrhage and infarction pneumonia. As long as VTE is untreated, relapses may occur, producing a changing pattern of multiple peripheral pulmonary infiltrates.

Larger emboli exclude a number of segments or even lobes of the lung from perfusion, although ventilation of these parts is preserved. The resulting perfusion–ventilation mismatch impairs gas exchange significantly, leading to hypoxia, which may be mild or life threatening. Mismatch and hypoxia lead to vasoconstriction of the pulmonary circulation, thereby contributing to an increase in pulmonary artery pressure. More importantly, however, right ventricular afterload is increased by massive thromboembolic obstruction of the pulmonary vessels itself [6]. As the right heart of a previously healthy person is only adapted to an invariably low mean pulmonary artery pressure of about 25 mmHg, the sharp increase in afterload is a critical challenge. An increase to more than 40 mmHg will lead to right ventricular dysfunction, right heart failure or sudden death due to irreversible right ventricular dilatation. In many cases, the first arrival of a large embolus in the main stem of the pulmonary artery causes right heart failure, which resolves several heart beats later when the embolus is fragmented and pushed to more peripheral parts of the pulmonary circulation. As left ventricular load depends on right ventricular output, this sequence of events will clinically manifest as syncope.

Early mortality of pulmonary embolism is a direct function of right ventricular performance. Without right ventricular dysfunction (RVD) as assessed by echocardiography, in-hospital mortality does not exceed 1%. In patients with significant RVD, but stable systemic haemodynamics, mortality rises to approximately 16%. If systemic circulation is affected, which is caused by frank right heart failure, short-term mortality approaches 60% [7,8].

A particular type of pulmonary embolism is chronic relapsing embolization of small clots from persisting DVT. Both every single pulmonary event and the underlying—often limited—DVT remain clinically silent for months or years. Fresh emboli will steadily add to older ones and to fibrous scarring of pulmonary arteries. In this case the right ventricle is able to adapt to the slowly increasing afterload. Patients will be diagnosed only late in the course of the disease, with fixed pulmonary artery pressures of 60–80 mmHg or higher. In NYHA classes III and IV of chronic thromboembolic pulmonary hypertension (CTPH) intermediate-term prognosis is poor [9].

Chronic sequelae of venous thromboembolism

Once the acute VTE has been overcome, endogenous repair mechanisms will be activated. Fibrinolysis will dissolve fresh thrombus material, whereas occlusive peripheral thrombi will be organized by granulation tissue and will be recanalized during the following weeks and months. Although patency can be restored, venous function may remain impaired due to destruction of the venous valves. Reflux causes chronic venous hypertension of the leg, leading to secondary varices with venous volume overload, which further enhances venous hypertension. Corresponding clinical symptoms are pain and swelling with leg dependency. Mediated by backwards damage of the microcirculation, venous hypertension leads to trophic disturbance of the skin with the extreme of venous ulcer. Without any measure to counteract venous hypertension about 50% of

patients with DVT will suffer from some degree of the post-thrombotic syndrome (PTS), 20% having severe signs or symptoms. Venous ulcer will occur in less than 10%. With every relapse of ipsilateral DVT the risk of severe PTS increases [10].

Iliac DVT of the descending type will resolve completely without PTS in most patients owing to either endogenous recanalization or, more frequently, collateralization. However, venous claudication will develop in some of them. This may be caused by insufficient transport capacity of collaterals or by spinal irritation, in the case when lumbar collaterals within the vertebral canal are used.

Upper extremity DVT is collateralized within days or weeks. However, some patients will persistently suffer from exertion-driven symptoms such as pain, swelling and discoloration.

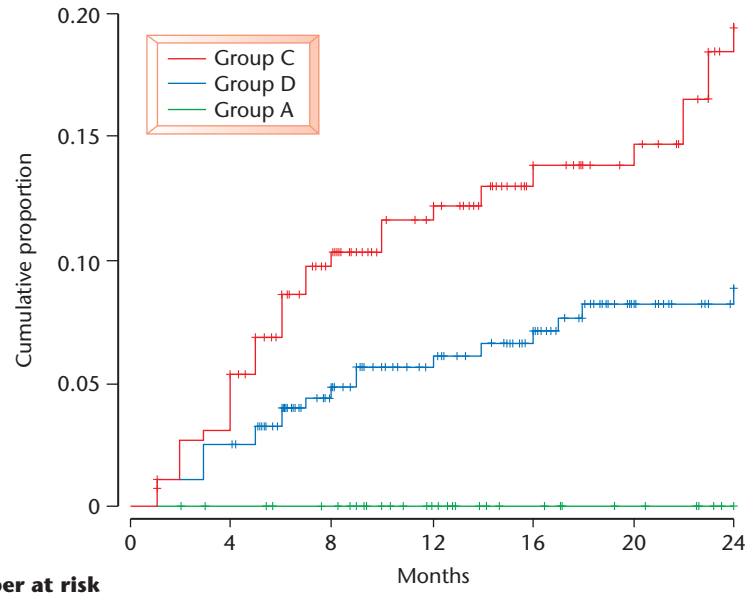
Owing to the significantly more powerful fibrinolytic capacity of the pulmonary circulation, pulmonary hypertension is rare after a single episode of pulmonary embolism and is seen in not more than 4% of cases [11].

Venous thromboembolism as a chronic relapsing disease

Even in adequately treated patients with acute VTE, relapses will occur. For DVT it has been established that after having received 3 months of anticoagulation the cumulative incidence of recurrent VTE is 5% after 3 months, 18% after 2 years and 30% after 8 years. Of these recurrences, 45% were ipsilateral, 36% contralateral and 19% were pulmonary embolism. Factors that increase the risk of recurrence are age and body mass index [12]. Recurrence rates for pulmonary embolism are at least as high as for DVT. Interestingly, 80% of recurrences of DVT will again be a DVT, and 80% of the recurrency in patients with pulmonary embolism will again be a pulmonary embolism. Mortality of both types of recurrence differs largely, being 5% in DVT and 25% in pulmonary embolism.

The most important determinant of recurrence is the presence or absence of a transient risk factor as the trigger factor for the index event [13]. In general, with a transient risk factor present the risk of recurrence is as low as 0–4% in the first 2 years. If no transient risk factor can be identified ('idiopathic' or 'unprovoked' VTE) or if the identified risk factor is permanent (cancer, thrombophilia), the risk of recurrence is as high as 20% or more (Fig. 36.4).

For thrombophilia an overall hazard ratio of 1.44 for the risk of recurrence has been established. However, considerable differences exist within the group of thrombophilias. On the one hand, it has become clear that the heterozygous factor V Leiden mutation as well as the heterozygous prothrombin 20210 mutation do not increase or minimally increase the risk of recurrence. On the other hand, individuals with a severe antithrombin deficiency or those from VTE families with severe protein C or protein S deficiencies have such a high risk for a



Number at risk

Group C	193	184	153	133	110	98	81
Group D	279	269	235	209	185	155	139
Group A	86	82	79	71	61	58	53

Figure 36.4 Risk of recurrence in venous thromboembolism according to precipitating factor [13]. Group A, recent surgery; group C, idiopathic VTE; group D, non-surgical trigger factors.

first event that, only under the assumption of the persistence of this predisposition, their risk of recurrence may be considered to be much higher than for most of all other patients with idiopathic VTE, even though solid data are lacking. The same high level of risk has to be anticipated in patients with a lupus-like anticoagulant and/or with antibodies against cardiolipin. In between these two groups, various thrombophilic conditions may be rated, such as: a persistent elevation of factor VIII or factor IX; hyperhomocysteinaemia and combined thrombophilias, such as factor V Leiden mutation plus factor II mutation or the homozygous form of factor V Leiden.

A 'thrombophilic' condition *per se* is present if the index event is already the recurrence of a previous episode of VTE. Prandoni and colleagues [12] found that the hazard ratio for recurrence after a second episode was 1.7; accordingly, the Austrian AUREC cohort [14] showed 22% recurrences 2 years after a second episode compared with 10.5% after a first one.

With these data in mind, a dichotomy has to be introduced into the disease concept of VTE. An acute VTE episode as a response to a transient thrombogenic stimulus such as surgery or trauma will very likely remain the only episode during life. On the other hand, in the absence of such a stimulus, or with an identifiable permanent risk factor present, VTE becomes a lifelong chronic relapsing disease.

Recently, two markers that may help to identify individual patients with increased risk of recurrence have been validated. Persistent residual vein thrombosis, as detected by serial compression ultrasound of the common femoral and popliteal veins, defines a likelihood of recurrent VTE events with a factor between 2 and 3 compared with those without residual vein thrombosis [15]. Similarly, a low D-dimer level 1 month after cessation of at least 3 months' anticoagulation after a first VTE event has a 60% risk reduction for VTE recurrences in the following 2 years [16,17].

Diagnosis

Venous thromboembolic disease places a person at risk for an acute life-threatening illness or even death, and for a chronic disabling condition in the long term. For this reason, a reliable and quick diagnosis is warranted in every clinical suspicion. As the disease is common, and signs and symptoms are equivocal, suspicion should be raised frequently in daily practice. Under these circumstances a cohort of patients with suspicion of VTE will contain around 20% of positive cases. This, in turn, means that the diagnostic work-up has to be as non-invasive and as cost-effective as possible in order not to harm the subjects without the disease, and not to inappropriately increase the burden for the health system.

History, signs and symptoms

Suspicion of DVT may be founded on every one-sided leg symptom such as discomfort, pain, oedema, discoloration and warmth. According to pathophysiology, suspicion of pulmonary embolism should be raised in every patient with pleuritic chest pain, with dyspnoea, with syncope and with sudden haemodynamic instability. As in all clinical reasoning, the possibility of VTE has to be weighed against alternative diagnoses according to the individual risk profile and medical history. VTE is more likely in patients with recent surgery or trauma, with recent immobilization, with cancer, with a previous episode of VTE and with a positive family history.

Once suspicion of VTE has been raised a diagnostic work-up has to be performed, which should lead to a clear-cut 'yes' or 'no' answer. Physical examination is unable to provide enough evidence against or in favour of the diagnosis to dispense from objective testing. The same is true for the basic diagnostics of pulmonary embolism, for example ECG, chest radiograph or arterial blood gases analysis. However, all of these diagnostic elements may contribute to a categorization of the patient regarding his probability of having the disease. This probability definitely helps to guide the diagnostic work-up (see below).

Today, a broad variety of diagnostic tools for VTE are available. The following paragraphs will discuss them separately. In a second step they will be combined into diagnostic pathways (algorithms) that have been proven to be safe and resource saving.

Diagnostic tools

Assessment of clinical (pre-test) probability

The most quick and simple way to categorize patients with suspected VTE is to add up basic clinical information into a qualitative assessment of probability for either DVT or pulmonary embolism. This can be done by a formal scoring system that ascribes a certain number of points to predefined clinical features, and which defines thresholds for different categories of probability. Alternatively, the evaluation can be undertaken by an experienced physician who integrates the clinical information intuitively. In any case, the result of clinical or pre-test probability assessment has to be given in two or three categories (high vs. intermediate vs. low; high vs. non-high; high vs.

Table 36.3 Clinical pre-test probability in DVT according to Wells

Criterion	Score
Active cancer (patient receiving treatment for cancer within the previous 6 months or currently receiving palliative treatment)	1
Paralysis, paresis or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks, requiring general or regional anaesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented deep vein thrombosis	1
Alternative diagnosis at least as likely as deep vein thrombosis	–2

A score of 2 or higher indicates that the probability of deep vein thrombosis is likely; a score of < 2 indicates that the probability of deep vein thrombosis is unlikely. In patients with symptoms in both legs, the more symptomatic leg is used for scoring.

Table 36.4 Clinical pre-test probability in pulmonary embolism according to Wicki

Criterion	Score
History	
Previous pulmonary embolism or DVT	2
Recent surgery	3
Clinical findings	
Age 60–79 years	1
Age ≥ 80 years	2
Pulse rate > 100 beats/min	1
Arterial blood gases	
P_aCO_2 < 4.8 kPa	2
P_aCO_2 4.8–5.2 kPa	1
P_aO_2 < 6.5 kPa	4
P_aO_2 6.5–7.99 kPa	3
P_aO_2 8.0–9.49 kPa	2
P_aO_2 9.5–11 kPa	1
Chest radiograph	
Plate-like atelectasis	1
Elevation of hemidiaphragm	1

Note: ≤ 4 points indicates a low probability of pulmonary embolism; 5–8 points indicates a moderate probability; ≥ 9 points indicate a high probability of pulmonary embolism.

low), and it has to be documented explicitly as with any result of other diagnostic tests. Table 36.3 , and Tables 36.4 and 36.5, present scores for DVT and pulmonary embolism, respectively [18–20]. Validation of scores demonstrated that they discriminate reliably between groups with low (2–5%), intermediate (10–20%) and high (more than 40%) prevalence of the disease.

D-Dimer testing

D-Dimers are degradation products of cross-linked fibrin. They are generated by the action of the fibrinolytic enzyme plasmin. As any thrombotic process in the circulation is accompanied by increased endogenous fibrinolysis, a rise in plasma D-dimer levels indicates some kind of thrombotic activity. The more extensive the thrombotic process, the higher plasma D-dimer levels can be measured. For technical as well for practical reasons, the result of D-dimer testing is given as 'positive' vs. 'negative' by defining a threshold plasma level. The threshold is chosen according to sensitivity and specificity of the test, and to its purpose. In general, specificity of D-dimer testing for VTE is low, as many other conditions and disorders (e.g. infection, inflammatory disease, trauma, surgery, pregnancy) may be accompanied by fibrin generation and lysis. Therefore, thresholds have been chosen to allow for excluding VTE in case of a concentration below the threshold (so-called negative results).

Different test systems are being used at present. Latex-enhanced ELISA systems require full laboratory equipment and provide continuous values for plasma D-dimer levels. Card ELISA tests are able to present results in categories of plasma levels. Bedside test systems give only the positive/negative type of result and have the lowest sensitivity of the available systems. On the other hand, only bedside tests and rapid ELISA test systems are suitable for a quick work-up (within 1 h) of patients in an ambulance or in the emergency ward.

For DVT there is a sensitivity gap of different extent with all available test systems. This means that the combination with other diagnostic tools is required to safely

Table 36.5 Clinical pre-test probability in pulmonary embolism according to Wells

Criterion	Score
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3.0
An alternative diagnosis is less likely than pulmonary embolism	3.0
Heart rate greater than 100 beats/min	1.5
Immobilization or surgery in the previous 4 weeks	1.5
Previous DVT/pulmonary embolism	1.5
Haemoptysis	1.0
Malignancy (at treatment, treated in the last 6 months or palliative)	1.0

Note: ≤ 2.0 points indicates a low probability of pulmonary embolism; 2.0–5.5 points indicates a moderate probability; and ≥ 6.0 points indicates a high probability.

exclude the disease. For pulmonary embolism there is evidence that the disease can safely be excluded by means of D-dimer testing alone, except perhaps in the patients categorized as having high clinical probability. D-Dimer test systems should only be used in clinical practice if they have been validated in methodologically sound studies with sufficient patient samples [21].

Venous ultrasound

Venous ultrasound is able to detect deep venous thrombosis by means of different diagnostic criteria: direct visualization of intravascular thrombus using B-mode, or alteration or lack of the flow signal using pulsed wave (PW) or colour Doppler. The most simple and unequivocal modality, however, is compression ultrasound (CUS) using the B-mode technique. Since the 1980s, venous ultrasound has been tested against venography in numerous studies with differing protocols. In 1998, a meta-analysis showed that sensitivity is high enough to exclude the disease in US-negative patients in symptomatic proximal DVT. However, sensitivity was much lower in symptomatic distal DVT and did not allow ruling out of the diagnosis. This led to the conclusion that CUS should be performed only on proximal veins. As virtually all symptomatic proximal DVTs are detectable either in the groin or in the popliteal region, examination of these two regions should suffice [22]. Because of the low emboligenic potential of isolated calf DVT, it has been demonstrated that it is safe to withhold anticoagulation in patients with a negative CUS for proximal veins, which remains negative when repeated after 1 week [23]. However, this approach is not cost effective as 80% of patients require a repeat CUS.

Alternatively, more thorough CUS protocols have been developed which systematically examine all veins of the leg including the calf veins (complete compression ultrasound, CCUS, Fig. 36.5). It has been demonstrated that a single CCUS examination of all leg veins is safe in excluding DVT when used as the only diagnostic test in all patients [24,25]. Such a protocol is not time consuming but requires in-depth training of sonographers. Theoretically, using CCUS for diagnosis of DVT might lead to overtreatment: first, the rate of false-positive distal DVT findings generated by CCUS is not known, even though the magnitude of this problem seems to be limited. Second, as distal DVT in many cases has a self-limited course it might not be indicated to treat every distal DVT detected by CCUS. Data to solve the latter problem are not available yet. *Thus, some experts argue that a single negative proximal CUS might also rule out the diagnosis of DVT in these patients, as the 3-month thromboembolic risk is similar to the risk observed in patients with a negative venogram.*

Venous ultrasound is not only useful for diagnosing patients with symptoms of DVT but also for the work-up of patients with clinically suspected pulmonary embolism. If a DVT can be demonstrated by ultrasound in a patient with signs and symptoms suggestive of pulmonary embolism, the diagnostic process can be stopped, as treatment of the—proven—DVT is almost equal to that of the—yet unproven—pulmonary embolism. A considerable number of diagnostic algorithms have incorporated this consideration (see below).

Venography

It is the historic privilege of venography to set the gold standard for the diagnosis of DVT. As a matter of fact, a negative venography reliably excludes DVT [26]. However, there are clear drawbacks of this method: radiation burden, adverse effects of contrast media such as allergic reactions or hyperthyroidism, and discomfort for the patient. A widely under-recognized problem is that—similar to the situation with venous ultrasound—different venography protocols may yield different quality levels of results, as has been demonstrated by a comparison of the elaborate long leg method with the standard ascending

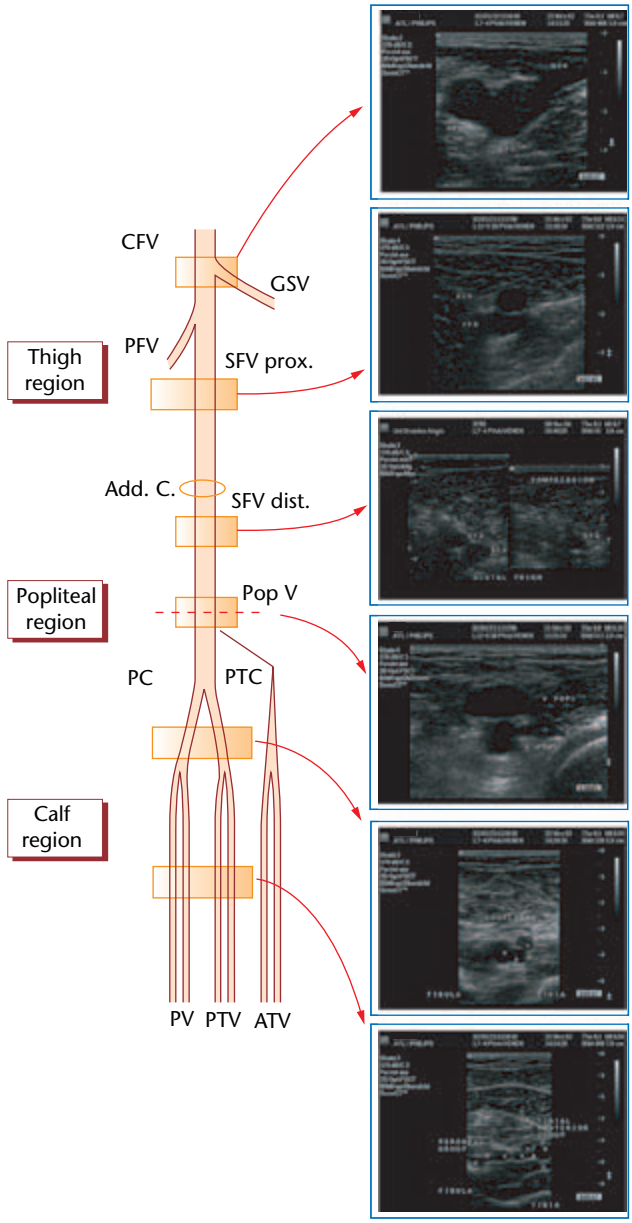


Figure 36.5 Visualization of all regions of the leg veins in transverse planes for complete compression ultrasound (CCUS). CFV, common femoral vein; GSV, greater saphenous vein; PFV, profound femoral vein; SFV, superficial femoral vein; prox., proximal; dist., distal; Add. C., adductor canal; Pop V, popliteal vein; PC, peroneal confluens; PTC, posterior tibial confluens; PV, peroneal veins; PTV, posterior tibial veins; ATV, anterior tibial veins.

venography by Paulin Rubinov [27]. Furthermore, with sharply declining numbers of venograms performed, experience of radiologists fades away, giving rise to an overall quality problem of the procedure. Thus, with the emergence of ultrasound venography has changed its role from gold standard to a back-up procedure.

Lung scan

From a pathophysiological point of view, lung scan provides the most direct information about a patient with suspected pulmonary embolism, i.e. a perfusion defect in an otherwise healthy part of the lung. The advantages of the method include the low radiation burden and the huge amount of scientific data having evaluated its diagnostic efficacy. A clear-cut positive examination has such a high specificity that further therapy can be based on this result. Furthermore, a definitely negative scan excludes pulmonary embolism. No further testing will be needed in order to withhold anticoagulation [28]. However, the problem with lung scan is the high proportion (50–60%) of indeterminate test results, i.e. results that do not allow for an unequivocal diagnosis [29]. The efficacy of the procedure can be enhanced by applying the SPECT technique instead of planar imaging [30]. Of utmost importance for appropriate utilization of the method is that the result of each individual examination is given in categories ('positive', 'negative' or 'indeterminate') rather than in great anatomic detail.

Spiral computerized tomography

Spiral CT offers a very elegant way to visualize clots in the pulmonary circulation. This may by achieved within body cross-sections only or by means of digital reconstruction of the pulmonary arterial tree (CT pulmonary angiography, CTPA) [31]. Specificity seems to be not a significant problem. However, sensitivity depends critically on the technical equipment. First-generation single-row detector CTs were able to reliably detect thrombi down to a size of segmental pulmonary arteries. The overall sensitivity of 70% compared with pulmonary angiography precluded this test from being used as the only test for exclusion of pulmonary embolism [32]. Sensitivity of CTPA has significantly increased with second- or third-generation scanners, i.e. 4-row or 16-row multislice detectors (Fig. 36.6) [33]. As of today, no formal accuracy data are available for the most advanced scanning technologies compared with pulmonary angiography. Neither are adequate management studies with, for example,16-row detector CTs [34]. Nevertheless, with increasing experience confidence is growing that a negative CTPA with a high-end machine safely excludes pulmonary embolism. Among the pros for CTPA are the increasing geographical availability and the short duration of the examination procedure, making it suitable even for patients with cardiorespiratory instability. Drawbacks of the method are the need for contrast media and the high radiation burden relatively exceeding that of lung scanning by four- to sixfold.

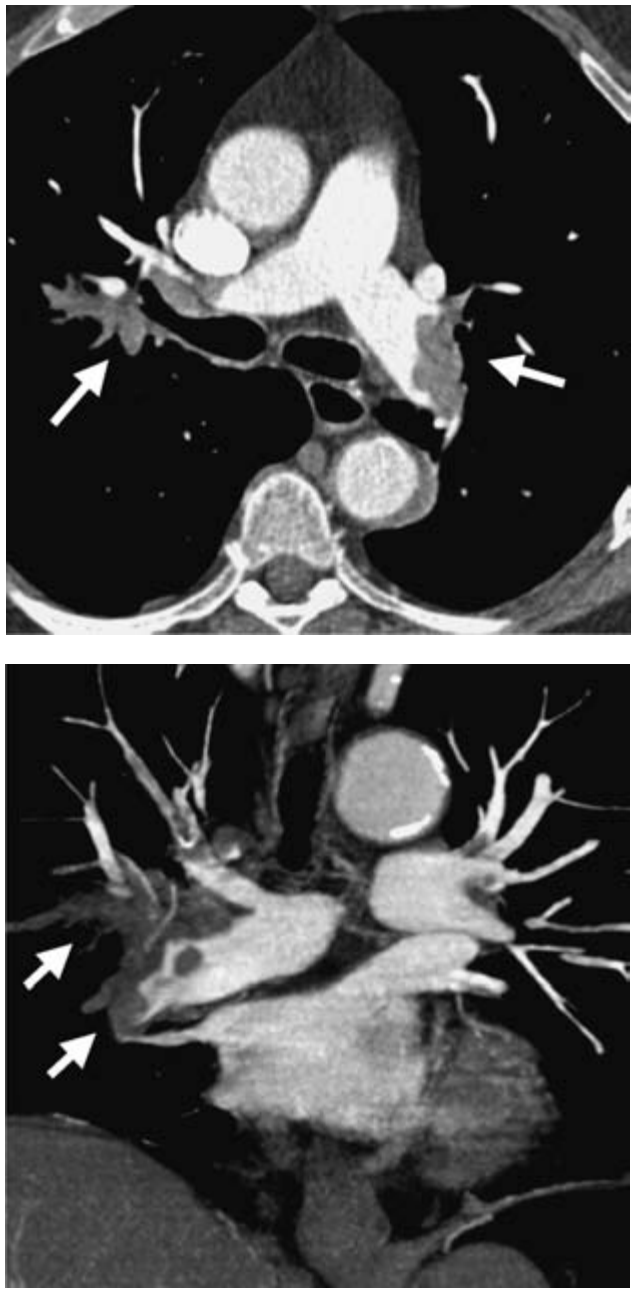


Figure 36.6 Helical computerized tomography for diagnosis of pulmonary embolism. (A) Transverse plane with massive bilateral embolization. (B) Coronal plane from CT pulmonary angiography with predominant right-sided embolization. (Courtesy of Dr J. Leonhard, Institute of Diagnostic and Interventional Radiology, University Hospital Dresden.)

It has been demonstrated that by means of CT angiography the peripheral venous circulation can be visualized as well. Even if the radiology literature reports almost ideal sensitivity and specificity figures for detection of DVT, the clinical need for this procedure is at least questionable. However, CT is a valuable method in detecting isolated iliac vein and inferior or superior caval thrombosis. The advantage is the exact visualization not only of its extent but also of possibly causal pathologies in the surrounding anatomic region (pelvic mass, retroperitoneal mass, mediastinal mass).

Pulmonary angiography

All that has been said about venography applies to pulmonary angiography as well. However, some issues make this procedure even more problematic. First, pulmonary angiography is an entirely invasive procedure that bears the highest procedural risk among all diagnostic tests for VTE. Second, imaging quality of pulmonary angiography has significantly been impaired by the almost complete transition from classic X-ray film angiography to the DSA technology. Third, even more than for venography, radiologists' personal experience and skills with this method have been reduced to very few centres, the number of which is declining steadily. Today, pulmonary angiography serves as a back-up procedure in clinical diagnostic studies rather than in real life.

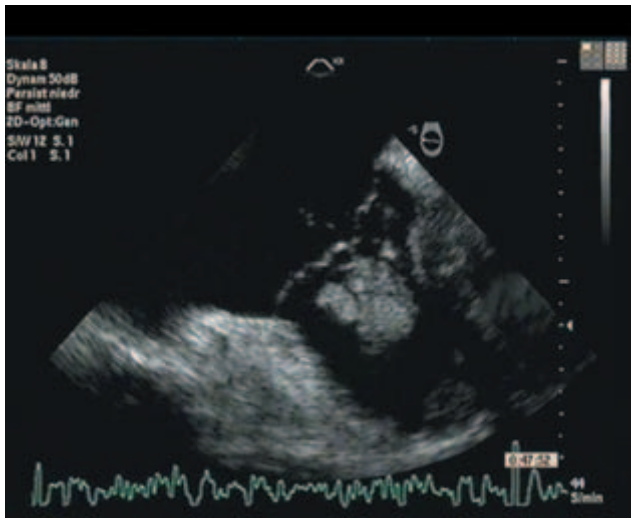
Magnetic resonance imaging

Different imaging modalities of MRI provide a clear visualization of clots in both the peripheral venous and the pulmonary artery circulation. The use of contrast agents enhances image quality and reduces examination time [35]. As for CT, radiologists report excellent accuracy data for MRI in comparison with standard diagnostic procedures [36]. However, availability of MRI, and in particular with VTE adopted protocols, is limited and resource utilization is high. In addition, the optimal place of MRI in the diagnostic work-up of a patient with suspicion of VTE has never been investigated consistently. At present, MRI is a promising imaging alternative for VTE, which may have advantages over standard tests in specific clinical situations, for example detection of isolated iliac or caval DVT in a patient with contraindications to X-ray contrast agents, or in pregnancy [37]. Nevertheless, the technique awaits validation in methodologically sound outcome studies with sufficient patient samples.

ECHOCARDIOGRAPHY

Echocardiography is able to directly visualize rare types of venous thromboemboli, i.e. a transit or straddling thrombus, a pulmonary artery main stem embolus or an embolus caught in the tricuspid valve (Fig. 36.7). The true value of echocardiography, however, lies in the assessment of right ventricular dysfunction as a consequence

A



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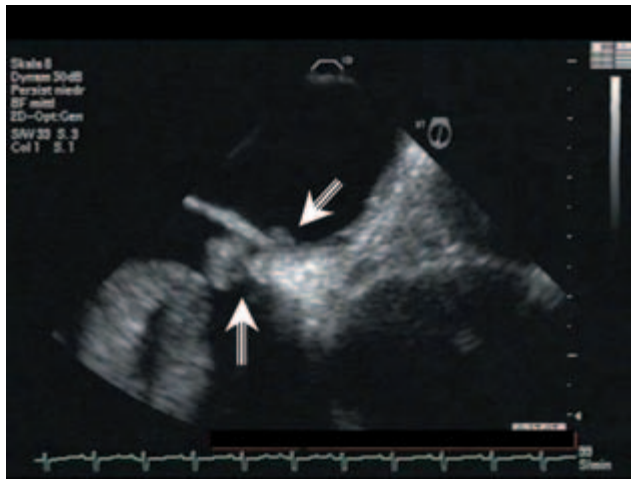

Figure 36.7 Thrombus visualization by echocardiography. (A) Large right atrial thrombus caught by the tricuspid valve. (B) Straddling thrombus in transit from the right to the left atrium (see arrows). (Courtesy of Dr M. Weise, Medical Clinic, University Hospital Dresden.)

of pulmonary artery obstruction [38]. Parameters for RVD include: (1) an end-diastolic diameter of the right ventricle of more than 30 mm; (2) the paradoxical, i.e. systolic outwards movement of the interventricular septum; and (3) a dys- or akinesia of the free right ventricular wall (Fig. 36.8). Pulmonary artery pressure may be assessed by systolic Doppler velocity measurement over the tricuspid valve. However, the PA pressure does not reflect the degree of right ventricular impairment. Obviously, the higher the PA pressure the better the right ventricular performance. As there is a strong correlation between RVD and in-hospital mortality, pulmonary embolism echocardiography provides a unique tool for risk stratification during the initial treatment phase and should be performed

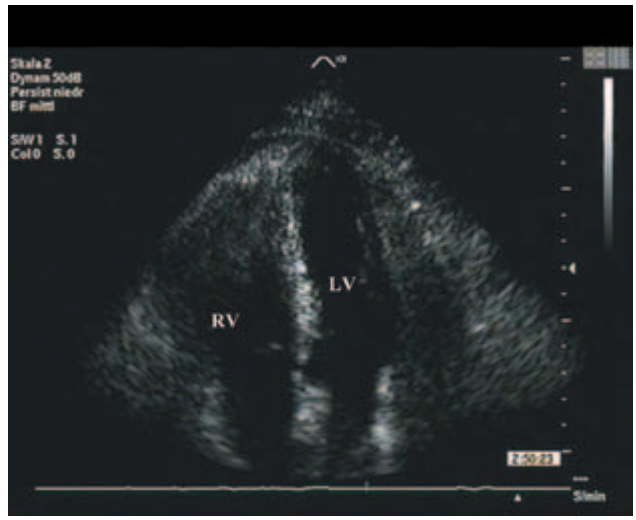

Figure 36.8 Acute right ventricular dysfunction: massive enlargement of the right ventricle with lack of filling of the left ventricle due to decreased preload. (Courtesy of Dr M. Weise, Medical Clinic, University Hospital Dresden.)

in every patient with an established diagnosis of pulmonary embolism. Additional echocardiographic criteria of increased mortality are a patent foramen ovale and a floating thrombus in the right atrium and/or ventricle.

Besides risk assessment, echocardiography may be a valuable tool for establishing the diagnosis of pulmonary embolism. A patient with haemodynamic instability (tachycardia with hypotension; syncope) due to pulmonary embolism does regularly have some degree of right ventricular dysfunction that can easily be detected by echocardiography. That means that the diagnosis of pulmonary embolism in a haemodynamically unstable patient may be indirectly established by echocardiography, as there is virtually no differential diagnosis for this combination of clinical presentation (instability) and objective test (right ventricular dysfunction). The only diagnostic confounder is chronic pulmonary disease with acute cardiac failure, which can easily be differentiated by history-taking. Thus, if a patient with suspected pulmonary embolism is in a critical haemodynamic condition, the diagnosis may be established by echocardiography in the intensive care unit. The certainty of the indirect echocardiographic diagnosis is sufficient to base even invasive therapeutic measures on it.

Diagnostic algorithms in venous thromboembolism

In order to enhance the diagnostic effectiveness and to reduce the burden for both patients and health-care resources, the diagnostic tools should be combined in a

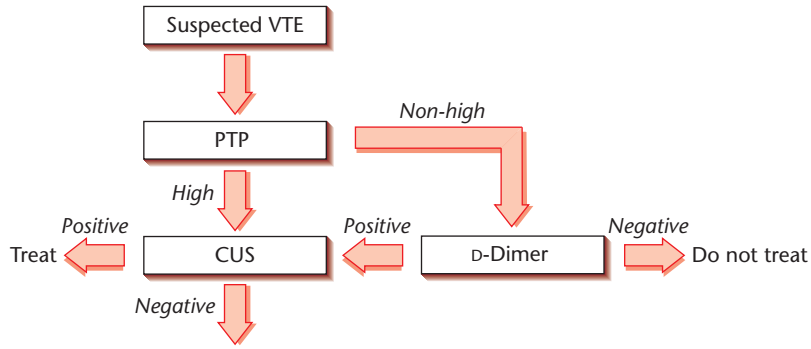

Figure 36.9 Diagnostic algorithm for the diagnosis of venous thromboembolism. For patients with suspicion of DVT the work-up may be finished after ultrasound. Patients with suspicion of pulmonary embolism who have been tested negative by ultrasound will undergo spiral CT or lung scan (see text). Abbreviations: VTE, venous thromboembolism; PTP, pre-test probability; CUS, compression ultrasound.

structured work-up of all patients under suspicion of VTE. The goal is to safely diagnose a maximum number of patients by simple and non-invasive tests.

In general, if there is suspicion of VTE, diagnostic work-up has to be carried out straight away without delay. If any of the tests or their results is not available, subcutaneous injections of low-molecular-weight heparin (LMWH) should be given in therapeutic dosages to minimize the risk of immediate pulmonary embolism. The period of 'blind' treatment should not exceed 24–36 h, i.e. two or three injections in order to minimize the risk of bleeding complications.

For both entities, DVT and pulmonary embolism, the first diagnostic step should be the combination of pre-test probability and D-dimer (Fig. 36.9). The combination of a non-high pre-test probability and a negative D-dimer reliably excludes VTE, so that the patient can be left without anticoagulant treatment [39]. This situation applies to approximately one-third of outpatients clinically suspected of DVT or pulmonary embolism, when using a rapid ELISA test. A positive D-dimer in a patient with a non-high pre-test probability will prompt further testing, as well as a high pre-test probability regardless of the D-dimer result.

For both entities, venous ultrasound will be the next logical step as it is entirely non-invasive, and patients with proven DVT are diagnosed as having VTE and can be treated appropriately regardless whether they are under suspicion of DVT or of pulmonary embolism [40]. The remaining task will be to safely exclude the disease in ultrasound negative patients with positive D-dimer or high pre-test clinical probability [41].

For patients with clinically suspected DVT, the need for further testing depends on the comprehensiveness of the ultrasound protocol. If the sonographer has been trained for a complete ultrasound protocol and states that he has imaged the entire leg vein system and that it was negative, the patient can be left untreated without further testing. If the proximal veins were negative and the examination of distal veins was equivocal or not examined at all then the patient should have a repeat ultrasound for proximal veins after 1 week or proceed to venography if the final diagnosis is warranted immediately.

Patients with suspected pulmonary embolism will proceed to either lung scan or spiral CT, depending on local availability and expertise. A positive as well as a negative lung scan make the final diagnosis. The same is true for a positive spiral CT. The traditional way to resolve the remaining uncertainties was to refer the patient to pulmonary angiography. However, albeit that confirming data are still lacking, most clinicians are convinced that a negative CTPA with a third-generation scanner is equal to a negative pulmonary angiography. Regardless of clinical trials, daily practice is irresistably moving in this direction. However, it has to be kept in mind that with first-generation scanners there remains a diagnostic gap and at least a negative CUS should be requested in addition to the negative monoslice CT scan result [42].

The haemodynamically unstable patient with suspected pulmonary embolism should be handled differently. Given the high diagnostic yield of echocardiography in this patient group the patient should be transferred to an intensive care unit first. Only if echocardiography in combination with the clinical information is not able to establish the diagnosis will the patient need to undergo alternative imaging procedures. For the unstable patient, CTPA will be the first choice.

Treatment

Treatment of VTE is composed of three periods: the acute phase (days), the intermediate (weeks to months) and the long-term period (months to years). According to the natural history of the disease treatment comprises three components (Fig. 36.10): (1) control of thrombus progression during acute disease in order to clear away the

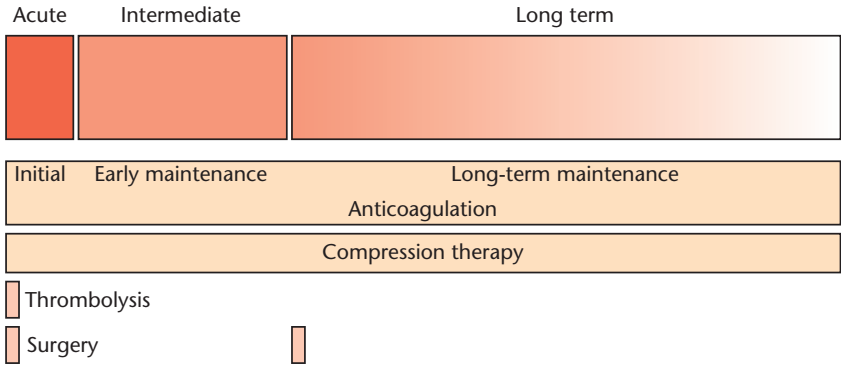

Figure 36.10 Treatment phases and treatment elements of venous thromboembolism.

risk of an immediate, possibly fatal pulmonary embolism; (2) control of acute and chronic pulmonary and peripheral venous hypertension; and (3) control of relapsing disease in the intermediate and long-term course. The pivotal measure for the first and the third component is anticoagulation. For the purpose of this chapter, therapeutic anticoagulation of VTE will be referred to as 'initial anticoagulation' (acute phase), 'early maintenance therapy' (intermediate) or 'long-term maintenance therapy'. The term 'maintenance therapy' corresponds to the concept of VTE as a chronic relapsing disease, and avoids an inaccurate use of the term 'secondary prevention'. All therapeutic aspects of VTE are covered by the 7th ACCP consensus of September 2004, which is based on the available evidence [43]. The present chapter follows the recommendations and suggestions of the ACCP consensus in all major topics. The very few deviations will be discussed.

Treatment modalities of the acute phase

More than 90% of patients with VTE will be treated by anticoagulation alone, for DVT in conjunction with compression therapy. Alternatives or add-ons out of the full spectrum of treatment options may be considered only in a few patients with specific conditions. Most of them are related to contraindications against anticoagulation, to haemodynamic instability, or to decompensation of the leg circulation.

Initial anticoagulation

At present, therapeutic dosages of heparins are the standard for initial anticoagulation. Almost all available LMWH preparations have been tested against unfractionated heparin (UFH). Several meta-analyses have pooled these trials, with the overall result that fixed-dose subcutaneous LMWHs without laboratory monitoring are at least as safe and efficacious as intravenous UFH with activated partial thromboplastin time (aPTT) monitoring [44]. One trial demonstrated this explicitly for pulmonary embolism [45]. Regarding major bleeding, some meta-analyses showed superiority of LMWHs. These results apply for patients with preserved renal function. Thus, LMWHs have to be considered as the actual standard for the initial anticoagulation of patients with VTE, i.e. both DVT and pulmonary embolism. The different preparations with their respective dose regimens are listed in Table 36.6. Patients with impaired renal function and patients with cutaneous allergy against LMWHs should be treated with intravenous UFH. Dose adjustments according to aPTT measurements should follow a nomogram to enhance performance of UFH administration. In order to facilitate the diagnosis in the case of heparin-induced thrombocytopenia (HIT), platelet counts have to be performed at day 1 of heparin treatment and should be repeated during administration beyond day 7, and at regular intervals thereafter.

The synthetic pentasaccharide fondaparinux has been

Table 36.6 LMWHs for treatment of acute DVT

Preparation	Brand name	Manufacturer	Dose	Regimen
Certoparin	MonoEmbolex	Novartis	8000 aXaU	b.d.
Dalteparin	Fragmin	Pfizer	100 aXaU/kg BW	b.d.
Enoxaparin	Lovenox/Clexane	Sanofi-Aventis	1.0 mg/kg BW	b.d.
Nadroparin	Fraxiparin	Glaxo SmithKline	85 aXaU/kg BW	b.d.
Nadroparin	Fraxiforte/Fraxodi	Glaxo SmithKline	171 aXaU/kg BW	o.d.
Tinzaparin	Innohep	Leo	175 aXaU/kg BW	o.d.

Note: aXaU, anti-factor Xa units; BW, body weight; o.d., once daily; b.d., twice daily.

Table 36.7 Treatment concept for pulmonary embolism stratified by the haemodynamic situation

Haemodynamic situation	Treatment modalities
Cardiac arrest	Cardiopulmonary resuscitation (even extended) Intubation, ventilation Immediate (bolus) systemic thrombolysis without regard to any bleeding risk Therapeutic anticoagulation (UFH)
Unstable systemic haemodynamics	Catecholamines Intubation, ventilation when needed Early systemic thrombolysis (2 h) with regard to only life-threatening bleeding risk Therapeutic anticoagulation (UFH)
Systemic haemodynamics stable; right ventricular dysfunction in echocardiography; positive cardiac troponins	Therapeutic anticoagulation (LMWH, fondaparinux) Consider elective systemic thrombolysis (2 h) in patients without any increased bleeding risk
Systemic haemodynamics stable; no right ventricular dysfunction in echocardiography	Therapeutic anticoagulation (LMWH, UFH, fondaparinux)

evaluated in two large trials for the initial anticoagulation of DVT and pulmonary embolism [46,47]. It showed non-inferiority compared with LMWH in patients with DVT, and in pulmonary embolism compared with UFH infusion. The drug is about to be approved in most European countries. A once-daily 7.5-mg subcutaneous injection is administered (5.0 mg for individuals < 50 kg body weight and 10 mg for those above 100 kg). As with LMWHs, the drug is excreted via the kidneys and may therefore not be given in renal insufficiency. However, it does not cross-react with LMWHs in cutaneous allergy and has no potential for induction of heparin-induced thrombocytopenia.

Initial anticoagulation with heparin or fondaparinux has to be administered for at least 5 days, awaiting full activity of the oral anticoagulant. After this period early maintenance therapy will follow. The present standard is to switch to therapy with vitamin K antagonists (VKAs). As it takes 5–7 days to accomplish therapeutic anticoagulation with VKAs, the first doses can be given simultaneously with the initial anticoagulation, in most patients on the day of diagnosis. The initial anticoagulant will be stopped when the intended stable therapeutic intensity of VKAs has been achieved.

Systemic thrombolysis

Systemic thrombolysis in VTE is able to reduce thrombus mass more rapidly and more comprehensively than anticoagulation alone. This holds true when given for pulmonary embolism as well as for DVT. On the other hand, bleeding complications will occur at a significantly increased frequency compared with anticoagulation alone. The figures for major haemorrhage, intracranial haemorrhage and fatal haemorrhage approximate 15%, 1.5% and 1% respectively [48].

In pulmonary embolism the goal of thrombolysis is short term. Reduction of thrombotic obstruction of the pulmonary artery bed enables the right ventricle to recover from severe dysfunction or frank failure. Obviously, the advantage is present only if right ventricular function is critically challenged. This is the case in patients under cardiopulmonary resuscitation (CPR) due to pulmonary embolism or in manifest shock. A recent meta-analysis of all randomized trials comparing thrombolytic therapy with heparin revealed that only in haemodynamically unstable patients was thrombolysis associated with a reduction of recurrence and death. If those patients were excluded, no benefit of thrombolysis could be found [49]. The preferable regimen is intravenous infusion of 100 mg of recombinant plasminogen activator (rtPA) within 2 h, starting with a loading dose of 10–20 mg. Under CPR, the 100 mg may be given as a single or a fractionated bolus injection. Possible alternatives are either high-dose urokinase or streptokinase. By contrast, there is definitely no indication for thrombolysis in patients who are haemodynamically stable. It is under debate whether patients with right ventricular dysfunction, as assessed by echocardiography and whose systemic circulation is (still) stable, will benefit from thrombolysis.

One randomized controlled trial demonstrated that the clinical course of the disease could indeed be improved [50]. However, there was no impact on mortality. In addition, the study population was highly selected regarding comorbidities and bleeding risk. Besides echocardiography, measurement of cardiac troponins and of pro-brain natriuretic peptide may help in identifying patients in whom thrombolysis should be considered [51,52]. A stratified treatment concept of systemic thrombolysis in pulmonary embolism is given in Table 36.7 [53].

In DVT the goal of thrombolysis is exclusively long term, i.e. reduction of frequency and severity of PTS. It is anticipated that removal of the clot decreases venous outflow resistance and prevents the venous valves from scarring; thereby, venous haemodynamics would be preserved. From retrospective and prospective cohorts there is some indication that this concept is durable; however, a prerequisite seems to be complete early lysis of the entire clot. This result will be achieved only in one-third of the patients at best. Given the low rate of clinically severe cases of PTS of approximately 10% under standard treatment and the potentially life-threatening complications of systemic thrombolysis. As a matter of fact, there has been no randomized controlled trial that has demonstrated that systemic thrombolysis is superior to standard therapy by anticoagulation and compression stockings [54]. The only indication might be the exceptionally rare condition of phlegmasia coerulea dolens, as even incomplete lysis with recanalization of the iliac veins could overcome the acute critical haemodynamics.

Catheter-based procedures

Several authors have convincingly demonstrated that pulmonary artery thrombus burden can be reduced by mechanical thrombus fragmentation, thereby allowing for rapid right ventricular recovery. Transfemoral, transjugular or transbrachial catheter devices with or without local thrombolysis are used [55]. There are no data as to whether this approach is more efficacious than systemic thrombolysis. However, it certainly requires more logistics, equipment and trained personnel. It seems very likely that no prospective study will systematically investigate the potential value of this regimen. Still, it may be argued that mechanical thrombus fragmentation can be beneficial in haemodynamically unstable patients with severe contraindications against systemic thrombolysis, such as early postoperative patients, particularly after brain surgery or in the immediate postpartum period.

Over the last years, there is increasing interest among interventionalists in applying catheter-based therapies to DVT. The most common procedure is distal cannulation of the vein with intra-thrombal administration of thrombolytic agents. If the clot is successfully removed, remaining stenoses, in particular in the iliac segments, are subjected to recanalization by balloon angioplasty, with or without stenting [56]. There is a registry with increasing numbers of treatment episodes. Most of the patients have the descending type of DVT [57]. However, the target criterion of success, i.e. frequency and severity of PTS in treated patients, is not consistently reported. Before acceptance of catheter-based methods in VTE, the long-term benefit has to be clearly established by appropriately designed randomized controlled trials [58].

Caval filters

Caval filters have widely been used in the past with a sharply declining frequency in the last decade. The rationale for caval filter insertion is to lower the chance of (recurrent) pulmonary embolism originating from a proven proximal DVT. Several types of filter devices have been developed. In addition to technical details of filter insertion and placement, the main differences are related to long-term durability and complications such as filter fragmentation, perforation, migration, embolization or filter thrombosis [59]. After decades of obvious overuse, a randomized controlled trial established that in proximal DVT the frequency of early pulmonary embolism could be lowered by insertion of a caval filter in addition to standard anticoagulation, even although mortality was not affected. However, in the long term, the caval filter group had significantly more episodes of recurring DVT than the standard treatment group [60]. Today, the only indications for insertion of a caval filter include early recurrence of pulmonary embolism despite appropriate anticoagulation, or absolute contraindications against any type and intensity of anticoagulation. However, these patients not only have a high risk of filter thrombosis and subsequent pulmonary embolism; most of them will turn out to have advanced cancer. Whatever rare reason for filter insertion is made plausible in a specific patient, temporary filters should be favoured over permanent filters.

Surgery

Emergency open-lung pulmonary thrombectomy, a procedure with a history of more than 150 years, is of no distinctive value in today's medicine. In a remarkable prospective comparison with systemic thrombolysis, no advantage of heart–lung machine-assisted thrombectomy could be found [61]. It requires even more logistics than mechanical thrombus fragmentation. Theoretically, it could be an option for a patient under CPR who cannot be stabilized by systemic thrombolysis; however, to substantiate this concept at least a couple of such cases resulting in full recovery should be reported [62].

In DVT, scientific support for the validity of the thrombectomy approach is even less than for thrombolysis. Only one randomized controlled trial including 30 patients with incomplete follow-up and non-standardized treatment in the control arm evaluated the target criterion, i.e. development of PTS [63]. The main consistent finding in larger cohort studies is a procedure-related mortality of approximately 3% [64]. An additional problem is the high rate of early and late re-occlusions. As with the catheter-guided approach, surgery is a treatment concept —if at all—for descending iliac DVT of recent onset in young and otherwise healthy individuals [65].

Logistics of initial treatment

By tradition in some European countries, bed rest was a treatment modality for DVT. Two randomized controlled trials, even though of limited sample size, demonstrated that under the condition of therapeutic anticoagulation, bed rest does not reduce the embolic potential of acute DVT [66,67]. In addition, immediate ambulation under graduated compression therapy offers a benefit regarding relief of symptoms.

The emergence of LMWHs has brought outpatient treatment of DVT into perspective. Two randomized controlled trials demonstrated that, at least in selected patients, home treatment with subcutaneous LMWH is as safe and effective as in-hospital treatment with intravenous UFH [68,69]. Subsequent feasibility studies revealed that several prerequisites have to be met for outpatient treatment of DVT. Patient-related factors are a low acute bleeding risk and full compliance. Institution-related factors are personnel capacity for individual patient education at diagnosis, 24-h accessibility and ability to provide or organize professional home care if needed. DVT characteristics and comorbidities seem to be less important [70]. With these requirements fulfilled, 80–90% of outpatients with acute proximal DVT can be treated primarily at home [71].

Maintenance therapy

Once the acute embolic risk has been tempered down by immediate and adequate anticoagulation, maintenance therapy is required to overcome the risk of recurrence. According to the natural history of VTE, early and long-term maintenance therapy have to be differentiated.

Early maintenance therapy

As early recurrences are triggered by the presence of the clot and its endogenous repair rather than by patient-related or circumstantial risk factors, the duration of early maintenance therapy should reflect the extent of the clot, i.e. thrombus mass. There is evidence that for isolated calf vein thrombosis a course of 6 weeks of therapy is sufficient, and that a 3-month course is appropriate for femoropopliteal DVT [72]. It seems plausible to assume this period to be 6 months for massive DVT involving iliac veins or the inferior caval vein. The standard therapy regimen for this period is VKA, with an intensity international normalized ratio (INR) of 2.0–3.0. Table 36.8 gives the main features of the most widely used vitamin K antagonists.

Given the high endogenous fibrinolytic potential of the pulmonary circulation, pulmonary emboli will subside within 3 months of maintenance therapy. Therefore, the presence or absence of pulmonary embolism gives no reason for prolonging the period of early maintenance therapy. Any additional consideration taking into account the higher case fatality rate of a pulmonary embolism recurrence has to be handled as part of the long-term maintenance therapy issue.

These durations are the minimal therapy of any VTE episode that may not be reduced. However, only patients with a first triggered episode of VTE will receive early maintenance therapy alone. Once this period is over, the actual VTE episode and the patient in whom it occurred have to be assessed with regard to whether to prolong maintenance therapy for a limited or an indefinite period of time. Making a decision about long-term maintenance therapy has to balance the risk of recurrence of VTE against the bleeding risk of the planned treatment regimen in the patient. Decision-making will also include the preferences of the informed patient.

Bleeding risk associated with standard vitamin K antagonist treatment

Determinants of haemorrhagic complications in patients

Table 36.8 Vitamin K antagonists

Generic name	Brand name	Half-life (S-/R-Enantiomer)	Average maintenance dose	Loading dose
Acenocoumarol	Sintrom	1–12 h	4 mg	No
Warfarin	Coumadin	25–47 h	5 mg	No
Phenprocoumon	Marcumar/Falithrom	125–160 h	3 mg	Yes

on VKA therapy are intensity of anticoagulation, patient characteristics, length of therapy and the use of concomitant drugs. Particularly for intracranial haemorrhage, the most important risk factor is the intensity of anticoagulation [73].

For secondary prophylaxis of VTE with the standard intensity INR of 2.0–3.0, there are two sources of data regarding the frequency of haemorrhagic complications. Data quality is high from randomized controlled trials. However, due to selection bias the frequencies of complications may be considerably lower than in registries of patients in standard care [74]. In randomized trials, the incidence of major bleeds within the first 3 months is about 1%. For prolonged anticoagulation, the annual frequencies are 0.2–0.6% for fatal bleeds, 2–3% for major bleeds and 5–15% for minor bleeds. A retrospective cohort of unselected patients on standard intensity VKA treatment in an outpatient setting reported a monthly incidence of major haemorrhage of 0.82% for the first 3 months decreasing to 0.36% for the months thereafter, amounting to an annual incidence of 4.3%. These figures may reflect the everyday standard of care situation more closely. By contrast, Prandoni and colleagues [75] reported an annual incidence for major bleeds of 0.5% for a cohort of well-selected patients on indefinite VKA treatment after a second VTE in an outpatient setting of a highly specialized institution.

Comorbid conditions have a strong impact on bleeding complications. The most common are history of gastrointestinal bleeding with a hazard ratio of 2.7, history of stroke (HR 2.6), and the presence of recent myocardial infarction, renal insufficiency, severe anaemia or diabetes (HR 2.2). Active cancer has a higher risk of bleeding as well.

Net clinical benefit

When comparing different regimens of secondary prophylaxis the criterion for a treatment decision should be the net clinical benefit of the available alternatives. This benefit is mostly considered to be the sum of recurrent VTE events prevented at the cost of all major bleeding episodes provoked by anticoagulation. In order to integrate both components, a given regimen can be characterized by its 'net clinical harm', i.e. the sum of VTE events plus major bleeds compared with the respective sum of the alternative regimen. However, it should be kept in mind that the nature of a VTE recurrence and a major bleed differ substantially. On the basis of all randomized controlled trials on VTE treatment between 1966 and 1997, Douketis and colleagues [76] established that the risk of fatal pulmonary embolism after start of treatment of a VTE episode was low, with incidences of 0.4% per year for DVT patients and 1.5% per year for patients with pulmonary embolism during the anticoagulation period. After anticoagulation, it was 0.3% per year in DVT patients; for patients with pulmonary embolism there was no such event. Based on substantially the same trial data, Linkins [77] and colleagues were able to define the clinical impact of major bleeding episodes in VTE patients. They found a case fatality rate of major bleedings of 13.4% for all patients and 9.1% for those receiving anticoagulation for more than 3 months. This rate is about twice as high as the case fatality rate of a recurrent VTE episode in DVT patients. Probably even more meaningful are the figures for intracranial haemorrhage. The overall rate of intracranial haemorrhage was 1.15% per year and 0.65% per year for those on long-term anticoagulation. This comparison indicates that assessment of the risk benefit ratio of long-term maintenance therapy has a component that is subjected to highly individual judgements and preferences.

Duration of long-term maintenance therapy with vitamin K antagonist

The basic fact in the search for optimal duration of maintenance therapy is that the recurrence rate for VTE is very low (< 1%) as long as VKA with a target INR of 2.0 to 3.0 is given [78]. A second fact that may safely guide the decision is that the risk of recurrence in secondary VTE, i.e. after an episode with a transient risk factor, is too low to justify anticoagulation beyond the required minimum duration of early maintenance therapy. Conversely, for all identifiable and strong permanent risk factors it is now generally accepted to prolong maintenance therapy indefinitely after a first VTE event. This is true for the antiphospholipid syndrome [79] and for active cancer [80], and it is common practice by tradition for inherited thrombophilias, such as severe symptomatic antithrombin deficiency or severe protein C or S deficiencies in patients with VTE and a positive family history.

For recurrent disease as well as for unprovoked episodes, randomized controlled trials were performed in order to establish an optimal duration of maintenance therapy [81,82]. However, these studies only confirmed the basic facts mentioned above: the rate of recurrence is very low during anticoagulation, and the number of bleeding episodes does increase steadily with prolongation of anticoagulation. However, subgroup analyses pointed to a relative additional benefit for patients with thrombophilias. In addition, two studies—one for DVT and another for pulmonary embolism—found consistently that there seems to be a kind of 'catch-up' phenomenon after cessation of prolonged maintenance therapy [83,84]. This observation supports the view that the period ideally

should be indefinite in a patient who needs prolonged therapy.

Based on these findings and considerations, the ACCP consensus made the following recommendations: patients with a first idiopathic episode of VTE with or without thrombophilia should receive maintenance therapy for 6–12 months. It is suggested to consider indefinite treatment in these patients. Patients with two documented VTE episodes should receive indefinite treatment. In all patients with indefinite treatment the risk–benefit ratio should be reassessed at periodic intervals. It was stated that these recommendations and suggestions ascribe a higher value to preventing recurrences than on bleeding and costs [43].

Intensity of long-term maintenance therapy with vitamin K antagonist

Recently, two trials tested the efficacy and safety of a low-intensity VKA regimen with a target INR of 1.5–2.0 as long-term maintenance therapy in patients with unprovoked or recurrent VTE. The PREVENT trial compared it to placebo [85], and the ELATE trial to the standard intensity of INR 2.0–3.0 [86]. The relative efficacy is shown in Fig. 36.11 [87]. The major advantage over placebo is achieved by the low-intensity regimen with a considerably smaller surplus benefit of the standard intensity regimen. Not surprisingly, major bleeding rates in the low-intensity arms of both studies (1% per year) were lower than those in standard intensity arms in previous studies (2–4% per year), even though neither study was powered to detect a significant difference in bleeding rates. However, in direct comparison with the ELATE study, the rate of major bleeds in the standard VKA arm was found to be as low as in the low-intensity arm. Thus, the recommendation for clinical practice now depends on how this low bleeding rate can be generalized. As long as the bleeding risk in a given patient is estimated to be as low as 1% per year, the higher efficacy of the standard intensity regimen should be offered.

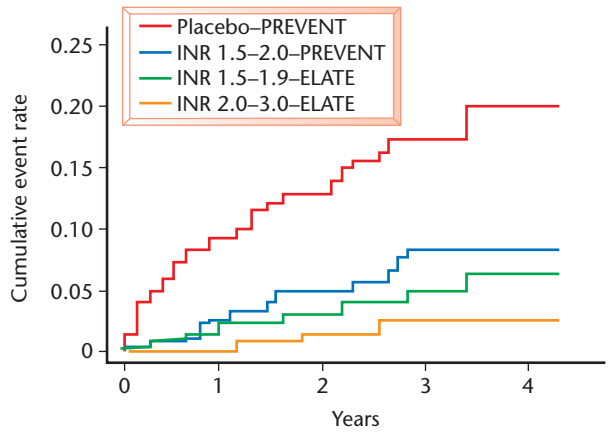

Figure 36.11 Combined results of the PREVENT and the ELATE trial showing the gain in prevention of recurrences achieved by three different regimens (placebo/no treatment vs. VKA INR 1.5–2.0 vs. VKA INR 2.0–3.0 (from [87]).

Alternatives to vitamin K antagonist in maintenance therapy

Since 1994, a couple of randomized controlled trials have been performed to evaluate the efficacy and safety of LMWHs compared with VKA in early maintenance therapy of DVT. The most recent meta-analysis of the published data identified seven studies including more than 1300 patients [88]. Regarding safety, there was an insignificant trend in favour of LMWHs; regarding safety, LMWHs showed a statistically significant reduction in major bleeds by 55%; with regard to total mortality no difference was found. Two additional trials are available as abstracts only, comparing tinzaparin with VKA for a duration of 12 weeks in more than 1200 patients with acute VTE [89]. The results are in line with the meta-analysis cited above, with equal efficacy and at least a trend towards superior safety regarding major and minor bleeds. Different dosages of LMWHs have been used as a substitute for standard intensity VKA treatment varying from high-dose prophylactic to full therapeutic dosages. No direct comparison is available. However, at least the half-therapeutic dose should be chosen. In cancer patients, a large randomized trial demonstrated superior efficacy of 75% of therapeutic dose LMWH over standard intensity VKA [90]. For this reason, cancer patients should receive LMWH instead of VKA for the first months of maintenance therapy.

Regarding practical issues, the cost of long-term LMWH use has to be considered. Given the relatively weak data basis for a real advantage of LMWHs—at least in the non-cancer population—standard VKA treatment remains the first choice for most patients after an acute episode of VTE. In patients with difficult access to laboratory monitoring or in those with poor compliance to VKA dose adjustments, LMWHs may be considered as a feasible, effective and safe alternative.

A large patient group that clearly benefits from this alternative consists of those patients who need to interrupt their VKA long-term maintenance therapy in order to undergo any kind of invasive or surgical procedure. For feasibility reasons, LMWHs may be considered as the first option for the bridging period between cessation and full re-institution of VKA medication [91]. There are no randomized controlled trials to establish the relative efficacy and safety of LMWH bridging regimens in

comparison with dose-adjusted UFH. Moreover, there are no consistent data allowing for an estimate of thrombotic and/or bleeding complications in bridging episodes with UFH. Thus, it is of great value that the number of prospective cohorts of bridging episodes with LMWH is growing, indicating that LMWHs—albeit not approved—are safe and effective in this indication [92].

New anticoagulants are being developed at present with the explicit goal to create an alternative to VKA for secondary as well as long-term maintenance therapy. Melagatran, with its orally administrable prodrug ximelagatran, is a small-molecule direct thrombin inhibitor that produces effective anticoagulation when given twice daily, without the need for dose adjustments or laboratory monitoring. The THRIVE DVT treatment study programme established that a dose of 36 mg ximelagatran twice daily is equally safe and effective compared with standard treatment with LMWH/VKA when given on the day of diagnosis for a duration of 6 months. In addition, in the THRIVE III study it was demonstrated that a dose of 24 mg twice daily given for 18 months after an initial 6-month course of standard intensity VKA reduces the rate of recurrences from 12.8% to 2.6% compared with placebo [93]. Surprisingly, there was no difference between placebo and active drug in the rates of both minor and major bleeds. This risk–benefit constellation makes ximelagatran a potentially very attractive alternative to VKA in this indication. However, the not yet fully understood problem of liver enzyme elevation in 6–10% of patients under long-term administration of ximelagatran, possibly indicating liver toxicity of the drug, has to be resolved in order to obtain approval by authorities.

Currently, a large phase III study programme is evaluating the safety and efficacy of the long-acting pentasaccharide idraparinux in initial anticoagulation and early and long-term maintenance therapy of VTE. The 5-day half-life of the parenteral compound allows for a once-weekly dosing schedule without laboratory monitoring [94].

Chronic sequelae of venous thromboembolism

These present as post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension, the details of which are given below.

Post-thrombotic syndrome

As chronic venous hypertension is the pivotal factor in the pathophysiology of this condition, compression therapy is the appropriate measure to counteract post-thrombotic syndrome. Randomized controlled trials demonstrated the effect of graduated elastic compression stockings compared with no treatment. When administered from the beginning of DVT treatment, compression therapy will almost halve the overall incidence of PTS. The effect is evenly distributed throughout the different degrees of severity of PTS [95]. Below-knee stockings will be appropriate for almost all patients. The pressure at ankle level has to be between 30 and 40 mmHg.

Only half of all patients with DVT will develop PTS. As these patients can reliably be identified only at 2 years after the index event, compression therapy must be recommended for all of them in the initial treatment phase. After 2 years the patient must be re-evaluated clinically. If he/she shows signs and symptoms of PTS when not using the stockings, he/she is likely to need them permanently for symptom control in order to avoid progression of PTS. If no symptoms occur he/she may discontinue their use later.

Once PTS has developed as a clinically relevant condition, again compression therapy is the mainstay of treatment. This is particularly true in patients with venous ulcer. The local and surgical measures to treat venous ulceration are not within the scope of this chapter.

Chronic thromboembolic pulmonary hypertension

At diagnosis, almost all patients with CTPH have had a period of months or years with clinically silent, repetitive pulmonary embolism from undetected DVT. Only a few patients will develop the condition as consequence of a single symptomatic pulmonary embolism episode. However, in order not to miss those cases, all patients with pulmonary embolism who have had any degree of right ventricular dysfunction during acute illness should undergo echocardiography 1 year after the acute event. If there is still some degree of pulmonary hypertension they must be subjected to close surveillance with control examinations at regular intervals. Deteriorating pulmonary hypertension should prompt a thorough re-evaluation for DVT and may require lifelong anticoagulation.

If CTPH clinically progresses to NYHA class III or IV, or if the patient has already reached this stage when being diagnosed for the first time, pulmonary thromboendarterectomy (PTEA) should be considered. The procedure itself is technically demanding. Even more taxing, however, is the immediate postoperative period, which can be managed only by a team of specialists dedicated to this specific problem. Thus, PTEA for CTPH is confined to a very few centres. Still, perioperative mortality has been reported to be in the range of 5–25%. Following PTEA, permanent anticoagulation is required. In addition, most surgeons will insert a permanent caval filter as part of the procedure.

Other manifestations of venous thromboembolism

Minimal disease

All therapeutic considerations so far are related to proximal DVT and to pulmonary embolism. There are only very few data that help to guide therapy of minimal thromboembolic disease, i.e. DVT confined to single segments of the calf veins or even isolated calf muscle vein thrombosis. Today, maintenance therapy for 3 months is the upper end of the spectrum of therapeutic recommendations. At the other end, several authors suggest not even looking for minimal disease as it does not require therapy at all. Given the undisputable potential of minimal disease to progress to proximal DVT and pulmonary embolism [96], there is a real gap in the present knowledge that has to be filled by reliable data. The most important issue is to identify in advance those patients in whom minimal disease will propagate. While awaiting these data, a reasonable compromise could be to administer anticoagulation, for example by LMWH, for a limited period of time (1–4 weeks) in conjunction with compression therapy for 3 months. Prolongation of these measures may be tailored according to the individual course of the disease. An alternative would be to not administer anticoagulants and to perform follow-up with repeated ultrasound.

Superficial thrombophlebitis

Unfortunately, knowledge of therapy is confounded by the fact that the two distinct entities headed under the term 'superficial thrombophlebitis' have not been consistently differentiated in current literature [97]. Based on natural history, circumscript phlebitis in varicose veins has to be discriminated from ascending saphenous phlebitis for the purpose of diagnosis as well as of therapy.

As long as superficial thrombophlebitis is locally confined to venous segments with varicosity, the risk of progression into the deep venous system via the inguinal or popliteal junctions of the greater or the lesser saphenous vein is low. Progression into the deep venous system via perforator veins at the level of the inflammatory lesion may occur in 10–20% of cases, but does not seem to place the patient at risk for clinical manifest DVT or pulmonary embolism [98]. Thus, in most cases of varicose vein thrombophlebitis, local measures such as percutaneous incision thrombectomy, cooling and compression therapy, in conjunction with systemic non-steroidal anti-inflammatory drugs (NSAIDs), are sufficient to control the actual episode. In the interval, varicophlebitis as a complication of varices should prompt the evaluation of the patient as a candidate for varicosectomy.

By contrast, with the ascending type of saphenous vein thrombosis there is a substantial probability of progression into the popliteal or the femoral vein, respectively, leading to DVT and even pulmonary embolism. Therapeutic anticoagulation for a minimum duration of 10–20 days, preferably with LMWH, is effective in preventing thrombus propagation into the deep venous system. Compression therapy may be added. Up until now, the question is unanswered as to whether maintenance therapy should be given in order to counteract the risk of recurrence [99].

Upper extremity deep vein thrombosis

As the upper extremity is a potential source of pulmonary embolism and has a high rate of symptoms seriously affecting activities of daily living, even in the long term the same sequence of therapeutic elements has to be applied as for DVT of the leg. No randomized controlled data about treatment modalities are available [5]. By analogy, initial anticoagulation, preferably with LMWHs in therapeutic dosage, will be followed by early maintenance therapy. Most authors suggest a duration of 3 months. Catheter-guided thrombolysis is technically feasible, with a low procedural complication rate. Successful recanalization has been documented in many cases. However, the effect on long-term course remains unclear. Given the high rate of temporary risk factors, long-term maintenance therapy plays no role in upper extremity DVT. However, in the rare case of thoracic inlet syndrome surgical decompression may be indicated.

Almost all patients with long-term symptoms have not received adequate compression therapy. Similar to stockings for the leg, DVT compression 'sleeves' are available and should be prescribed from the very beginning of therapy. They have to be fitted carefully to the individual patient and closely quality controlled.

Heparin-induced thrombocytopenia

The immunological type of heparin-induced thrombocytopenia (HIT) is a complication of heparin administration and in itself a cause of venous as well as arterial thromboembolism. All aspects of pathophysiology, clinical course, diagnosis and therapy have been reviewed extensively during the past 10 years and several comprehensive monographs are readily available [100]. Therefore, only a very few clinical considerations will be presented here.

Unlike in other diseases, diagnosis and therapy of HIT are simultaneous processes. The clinical suspicion is derived from the laboratory finding of thrombocytopenia fulfilling the diagnostic criterion of a rapid, more than

Table 36.9 Alternative anticoagulants in HIT

Generic name	Drug class	Route of administration	Half-life	Prophylactic dose regimen	Therapeutic dose regimen	Monitoring
Danaparoid	Heparinoid	i.v., s.c.	25 h (prolonged in renal impairment)	750 IU, b.d. or t.d.s.	2250 IU bolus; infusion of 400 to 150 U/h with dose adjustment	aXa activity; therapeutic level 0.5–0.8 U/ml
Lepirudin	Recombinant hirudin analogue (peptidic)	i.v., s.c.	1.3 h (~200 h in renal failure)	15 mg b.d.	0.40 mg/kg bolus; infusion of 0.15 mg/kg/h with dose adjustment	aPTT 1.5–2.5 fold [alternative: ECT]
Argatroban	Synthetic direct thrombin inhibitor (peptidomimetic)	i.v.	40–50 min (four- to fivefold in liver impairment)	Not tested	No bolus; infusion of 2 µg/kg/min with dose adjustment	aPTT 1.5–3.0 fold (< 100 s)

Note: ECT, ecarin clotting time; i.v., intravenous; s.c., subcutaneous; IU, international units. For special dose regimens, see [100].

50% drop compared with the baseline value. The absolute platelet count does not provide the same information. Thrombocytopenia may occur with or without symptomatic thromboembolic events. However, there must be ongoing heparin therapy for at least 5 to 7 days. In case of suspicion of HIT, heparin therapy has to be stopped and replaced with alternative anticoagulation. The two compounds with explicit approval in Europe are the high-sulphated heparinoid danaparoid and the recombinant hirudin analogue lepirudin. In the USA and Japan, the peptidomimetic direct thrombin inhibitor argatroban is approved as well (Table 36.9). The dosage has to be chosen according to the previous heparin dose (prophylactic vs. therapeutic). With a thromboembolic event present, therapeutic regimens have to be applied.

Having established alternative anticoagulation, the diagnosis has to be examined carefully in order to definitely confirm or refute it. Results of HIT antibody tests (ELISA or HIPA) will be available with a delay of only around 2 days. A negative result of both tests excludes the diagnosis. In this case, heparin can be restarted. A positive antibody test supports the diagnosis; however, it is far from proving it. In this case, the alternative anticoagulation has to be continued. For confirmation of the diagnosis, an increase of platelet count must occur after 4 days to 2 weeks. If thrombocytopenia persists, any differential diagnosis is more likely than HIT. In general, validation of the diagnosis is more difficult in thrombocytopenia alone than in an episode of arterial or venous thromboembolism with thrombocytopenia.

A firm diagnosis of HIT has to be discussed with the patient to enable him to avoid re-exposure to heparin in future treatment settings. Some sort of emergency document may be helpful. A patient with a history of confirmed HIT must not receive either UFH or LMWH, in particular during the period of elevated HIT antibody titres. Thromboprophylaxis as well as VTE treatment may be provided by danaparoid or—once registered—fondaparinux. Titres will return to normal within months after the acute illness. A patient with a history of HIT may safely undergo open-heart surgery with an UFH-anticoagulated heart–lung machine if the test is negative for HIT antibodies. Obviously, the short period of re-exposure to UFH is not sufficient to reactivate the immune mechanism.

Personal perspective

In the past decade, fundamental changes have occurred regarding both the conception and the management of VTE. The most challenging discovery was the elucidation of a broad variety of thrombophilic conditions, which formed the concept of a widespread genetic susceptibility for the disease. However, the translation of individual genetic findings into clinical practice turned out to be more difficult than anticipated in the enthusiasm of the first few years. By contrast, the identification of patients who suffer from VTE as a chronic relapsing disease by clinical evaluation only has been firmly established, confirming the unprovoked and the relapsing episode as strongest indicators for a high risk of recurrence.

Management of VTE switched from the hospital-only setting to a primarily out-patient-based patient care. The stimulus for this development was the proof that low-molecular-weight heparins in therapeutic dosage are at least as efficacious and safe as unfractionated heparin in the initial anticoagulation, thereby allowing for subcutaneous administration without laboratory monitoring.

The field is now moving to address one major unresolved issue, i.e. the individualization of the risk–benefit ratio of long-term maintenance therapy after initial- and intermediate-term anticoagulation. The determinants are not only the risk of disease recurrence, for which new markers are being assessed, but also the features of new anticoagulants that are currently under development. If new drugs turn out to be associated with a lower bleeding risk than vitamin K antagonists then the current trend towards longer periods of maintenance therapy will increase.

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