Circulation: Heart Failure Editors' Picks

Most Important Articles in Interventions and Devices for Advanced Heart Failure

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The following are highlights from *Circulation: Heart Failure* Topic Review. This series summarizes the most important articles, as selected by the editors, that have been published in the *Circulation* portfolio. The objective of this series is to provide our readership with a timely comprehensive selection of important articles that are relevant to the heart failure audience. The studies included in this article represent the most noteworthy research in the area of interventions and devices for advanced heart failure. (*Circ Heart Fail*. 2012; 5:e83–e90.)

Incomplete Recovery of Myocyte Contractile Function Despite Improvement of Myocardial Architecture With Left Ventricular Assist Device Support

Summary: Sustained recovery of the failing left ventricle (LV) during pressure-volume unloading with an LV assist device (LVAD) is rare and may be related to incomplete recovery of sarcomeric contractility. In this study, the authors evaluated contractility and biochemistry at the most fundamental contractile level of the heart: the sarcomere. Force development in muscle is the result of actin and myosin interactions and cross-bridge cycling, processes regulated by modifications of the sarcomeric contractile proteins. Sarcomeric contractility was assessed by measuring isometric forces on skinned LV myocytes from patients with nonischemic cardiomyopathy before and after LVAD placement. The authors found that contractile dysfunction at the level of the sarcomere was present in failing hearts and paralleled organ-level contractile dysfunction as assessed by ejection fraction. Furthermore, there were improvements in LV and myocyte size with partial recovery of sarcomeric force after LVAD placement, but LVAD-supported myocyte forces were still half of that seen in nonfailing hearts. The persistence of sarcomeric contractile dysfunction may be one of the reasons most LVADs cannot be explanted in clinical practice. In assessing for biochemical alterations of sarcomeric proteins after LVAD implantation, there were changes in troponin-I phosphorylation, which may account for some of the improvement in sarcomeric force, but the other sarcomeric contractile proteins revealed minimal biochemical changes, suggesting that other interventions (in addition to mechanical unloading with an LVAD) may be needed to optimize troponin-I phosphorylation, modify other sarcomeric protein biochemistry, or both to further enhance sarcomeric and organ-level recovery.

Conclusions: There is significant improvement in LV and myocyte size with LVAD, but there is only partial recovery of ejection fraction and myocyte contractility. LVAD support was only associated with biochemical changes in troponin I, suggesting that alternate mechanisms might contribute to contractile changes after LVAD and that additional interventions may be needed to alter biochemical remodeling of the sarcomere to further enhance myofilament and organ-level recovery.[1]

Drug and Device Effects on Peak Oxygen Consumption, 6-Minute Walk Distance, and Natriuretic Peptides as Predictors of Therapeutic Effects on Mortality in Patients With Heart Failure and Reduced Ejection Fraction

Summary: Although peak oxygen consumption, 6-minute walk distance, and natriuretic peptides (B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide) are predictors of mortality in patients with heart failure, it is not known whether therapy-induced changes in these measures can predict therapeutic effect on mortality. This report quantitatively assesses the relationship between therapeutic effects on these short-term markers and therapeutic effects on long-term outcome in patients with heart failure and left ventricular dysfunction. For each intervention, the authors calculated the odds ratio for mortality, as well as the trial-level average drug or device-induced change in the markers. They assessed the correlation between the odds ratio for death with the placebo-corrected change in the functional parameter or biomarker across the interventions. This analysis, limited to trial-level data from different therapeutic eras, suggests that drug- or device-induced effects on peak oxygen consumption, 6-minute walk distance, and natriuretic peptides found in short-term trials do not predict the corresponding average long-term therapeutic effects on mortality for patients with heart failure and left ventricular dysfunction. Although these markers may be useful in assessing therapeutic effects on functional capacity or pathophysiology, these data suggest that they are not good surrogates for therapeutic effects on longer-term outcomes.

Conclusions: This analysis, limited to trial-level data from different therapeutic eras, suggests that drug- or device-induced effects on peak oxygen consumption, 6-minute walk, and natriuretic peptides found in short-term trials do not predict the corresponding average long-term therapeutic effects on mortality for patients with heart failure and left ventricular dysfunction.[2]

Effects of Continuous-Flow Versus Pulsatile-Flow Left Ventricular Assist Devices on Myocardial Unloading and Remodeling

Summary: Continuous-flow left ventricular assist devices (LVADs) are increasingly used for patients with end-stage heart failure.

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Continuous-flow devices have the advantage of smaller size, longer durability, higher energy efficiency, less thrombogenicity, and less surgical trauma compared with the previously used pulsatile-flow LVADs. The authors investigated the effects of ventricular unloading using continuous-flow versus pulsatile-flow LVADs on myocardial structure and function. They analyzed 31 patients with a pulsatile-flow LVAD and 30 patients with a continuous-flow LVAD. Echocardiographic parameters of systolic and diastolic functions improved more in patients with pulsatile-flow LVADs compared with those with continuous-flow LVADs. Myocardial gene expression of extracellular matrix markers and brain natriuretic peptide, as well as serum levels of brain natriuretic peptide, metalloproteinase-9, and tissue inhibitor of metalloproteinase-4, was more significantly reduced in patients with pulsatile-flow LVADs than those with continuous-flow LVADs. This study is the first systematic assessment comparing pulsatile and nonpulsatile VADs in relation to these markers of myocardial reverse remodeling and extracellular matrix turnover. These observations demonstrate a more profound unloading of the failing myocardium by pulsatile-flow devices than by the continuous-flow devices currently used. These differences may be important if assist devices are implanted with the hope of supporting cardiac recovery.

Conclusions: Mechanical unloading of the failing myocardium using pulsatile devices is more effective as indicated by echocardiographic parameters of systolic and diastolic left ventricular functions, as well as dynamics of B-type natriuretic peptide and extracellular matrix markers. Therefore, specific effects of pulsatile mechanical unloading on the failing myocardium may have important implications for device selection, especially for the purpose of bridge to recovery in patients with advanced heart failure.[3]

Patient-Reported Outcomes in Left Ventricular Assist Device Therapy: A Systematic Review and Recommendations for Clinical Research and Practice

Summary: Evidence suggests that patients receiving left ventricular assist device (LVAD) therapy experience an improvement in health status over time, independent of device type and setting. However, although their physical disability becomes less prominent after implantation, many patients experience difficulties with psychological adjustment, especially early after implantation, which is associated with worrying about LVAD malfunction, complications, waiting for a donor heart, and being away from family. Furthermore, overall functioning of LVAD patients is still more impaired compared with transplant recipients on physical, social, and emotional functioning. Extensive information on patient-reported outcomes in LVAD patients is limited, with many of the existing studies having methodological shortcomings. To advance the field of LVAD research and to optimize the care of an increasingly growing population of LVAD patients, more well-designed large-scale studies are needed to further elucidate the impact of LVAD therapy on patient-reported outcomes.

Conclusions: There is a paucity of studies on the patient perspective of LVAD therapy. To advance the field of LVAD research and to optimize the care of an increasingly growing population of patients receiving LVAD therapy, more well-designed large-scale studies are needed to further elucidate the impact of LVAD therapy on patient-reported outcomes.[4]

Efficacy and Safety of Carvedilol in Treatment of Heart Failure with Chronic Kidney Disease: A Meta-Analysis of Randomized Trials

Summary: Chronic heart failure is a clinical syndrome associated with increased rates of morbidity, frequent hospitalizations, and increased utilization of healthcare costs, as well as all-cause mortality. Similarly, chronic kidney disease (CKD) increases the risk for adverse cardiovascular outcomes in the general population, as well as in those with underlying heart failure. There is a paucity of evidence whether therapeutic interventions that are effective for the treatment of heart failure in the general population are also effective in those patients with heart failure with concomitant CKD. Consequently, clinicians may be reluctant to use these evidence-based therapies in the presence of CKD. The authors performed a post hoc meta-analysis of individual patient-level data from 2 large, randomized, controlled trials [CAPRICORN (Carvedilol Postinfarct Survival Control in Left Ventricular Dysfunction Study) and COPERNICUS (Carvedilol Prospective Randomized, Cumulative Survival study)] of carvedilol in patients with ischemic or nonischemic left ventricular dysfunction. The data were categorized for the presence or absence of CKD, based on the estimated glomerular filtration rate (<60 or ≥60 mL/min per 1.73 m^2, respectively), using the Modified Diet Renal Disease equation from the serum creatinine values obtained at the time of enrollment. This study demonstrates that carvedilol therapy leads to similar benefits in the presence of CKD as in those patients with heart failure without CKD. However, the effect of carvedilol therapy in patients with heart failure with advanced CKD (estimated glomerular filtration rate <45 mL/min per 1.73 m^2) was not different from placebo. This hypothesis-generating finding that carvedilol may not be efficacious in very advanced stages of CKD must be confirmed by future studies. The authors also observed that the use of carvedilol therapy in the presence of CKD can lead to transient fluctuations in renal function and increases the risk for orthostatic hypotension and other electrolyte abnormalities. Hence, patients with heart failure with concomitant CKD should have careful dose titration, as well as judicious monitoring of kidney function, blood pressure, and electrolytes when treated with carvedilol.

Conclusions: This analysis suggests that the benefits of carvedilol therapy in patients with systolic left ventricular dysfunction with or without symptoms of heart failure are consistent even in the presence of mild-to-moderate CKD. Whether carvedilol therapy is similarly efficacious in patients with heart failure with more advanced kidney disease requires further study.[5]

PDE5 Inhibition With Sildenafil Improves Left Ventricular Diastolic Function, Cardiac Geometry, and Clinical Status in Patients With Stable Systolic Heart Failure: Results of a 1-Year, Prospective, Randomized, Placebo-Controlled Study

Summary: In 45 optimally treated patients with systolic heart failure, the authors tested the hypothesis that NO pathway oversignaling through chronic phosphodiesterase 5 inhibition (sildenafil 50 mg 3 times per day) may be beneficial on left ventricular (LV) diastolic function, cardiac remodeling, and functional and clinical status. Patients were randomly assigned to placebo or sildenafil for 1 year, with assessment of LV diastolic function, cardiac geometry, LV ejection fraction, cardiopulmonary exercise performance, and quality of life at 6 months and 1 year. In the sildenafil group, at 6 months and 1 year, diastolic relaxation indexes and LV filling pressure improved compared with placebo, as suggested by a significant increase in early diastolic tissue Doppler velocities (E′) at the mitral lateral and septal annuli and by a significant reduction in the ratio of early transmitral (E) to E′, respectively. Changes were accompanied by reverse remodeling as documented by a significant reduction in left atrial volume index and LV mass index compared with placebo. Furthermore, sildenafil improved exercise performance (peak oxygen consumption), ventilation efficiency (ventilation to Co_2 production slope), and quality of life. The drug was well tolerated, and minor adverse effects were noted. The present findings suggest, as first evidence reported in human beings, that chronic phosphodiesterase 5 inhibition promotes a sustained significant improvement in LV diastolic function properties, cardiac geometry, and clinical status in patients with systolic heart failure.

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Conclusions: Findings confirm that in heart failure sildenafil improves functional capacity and clinical status and provides the first human evidence that LV diastolic function and cardiac geometry are additional targets of benefits related to chronic phosphodiesterase 5 inhibition.[6]

Acquired von Willebrand Syndrome in Patients With an Axial-Flow Left Ventricular Assist Device

Summary: Rotary blood pumps replaced pulsatile displacement pumps in long-term left ventricular support. Their mechanical stability, combined with miniaturization of the pump, was favorable compared with the first-generation pulsatile devices. However, with prolongation of support times, bleeding episodes became a limitation of this therapy. In addition to epistaxis, gastrointestinal bleeding from the small bowel was seen in these patients at an incidence not known in patients with pulsatile devices. The finding of acquired von Willebrand syndrome (vWS) in all our patients being supported with the HeartMate II axial flow device may contribute to the pathophysiological understanding of this clinical problem. In addition to intended anticoagulation and platelet inhibition, primary hemostasis is impaired by acquired vWS. Although there is no consensus yet on how to treat patients with bleeding episodes, it is helpful to know that in the case of gastrointestinal bleeding the source is likely to be found in the small intestine and that treatment of acquired vWS may be required. Recommendations for anticoagulation for patients with the HeartMate II device were revised several times in the past to lower international normalized ratio levels to prevent bleeding. Patients should be advised that epistaxis and potential gastrointestinal bleeding are associated with long-term ventricular support. Physicians are encouraged to check for vWS also in patients with implanted rotary blood pumps other than the HeartMate II.

Conclusions: A diagnosis of vWS type 2 was established in all patients after left ventricular assist device implantation, and bleeding events confirmed this finding. Reversibility of this condition was found after removal of the device.[7]

The Development of Aortic Insufficiency in Left Ventricular Assist Device–Supported Patients

Summary: Severe aortic insufficiency (AI) after left ventricular assist device (LVAD) implantation can lead to ineffective cardiac output and heart failure symptomatology. In this analysis, echocardiograms (n=315) from 78 subjects supported with a HeartMate-XVE (n=25) or HeartMate-II (n=53) LVAD were reviewed, and AI severity was quantified at baseline and postoperatively. AI was noted to progress with the duration of LVAD support. Correlates of worsening AI post-LVAD were female sex, smaller body surface area, and HeartMate-II model. AI was also worse in subjects with increasing aortic sinus diameters postoperatively or an aortic valve that did not fully open on systole. Further studies are needed to determine whether progressive AI has a clinical impact on long-term LVAD support and whether interventions may be undertaken to retard its development.

Conclusions: AI progresses over time in LVAD-supported patients. As we move toward an era of long-term cardiac support, more studies are needed to determine the clinical significance of these findings.[8]

Application of the Seattle Heart Failure Model in Ambulatory Patients Presented to an Advanced Heart Failure Therapeutics Committee

Summary: Identification of individuals with advanced heart failure who are at high risk for poor outcomes is important for assessment of urgency and candidacy for heart transplantation and mechanical circulatory support. The Seattle Heart Failure Model (SHFM) is a multivariable risk model that predicts event-free survival of patients with heart failure. The authors applied SHFM to ambulatory patients with advanced heart failure who were presented to the advanced heart failure therapeutics committee at our institution. The authors found that SHFM offered modest discrimination of risk for the primary composite outcome of mortality, ventricular assist device, or urgent transplantation, with underestimation of risk in those patients listed for nonurgent transplantation. Clinicians can use SHFM for patients being evaluated for advanced therapies but should interpret risk prediction with caution.

Conclusions: In ambulatory patients presented to an advanced heart failure therapeutics committee for evaluation of heart transplantation, SHFM offers modest discrimination of risk for the primary composite outcome of mortality, ventricular assist device, or urgent transplantation, with underestimation of risk in those patients listed for nonurgent transplantation. Interpretation of risk prediction by SHFM in this patient population must be done with caution.[9]

Right Ventricular Response to Intensive Medical Therapy in Advanced Decompensated Heart Failure

Summary: Right ventricular (RV) systolic function is generally recognized as an important determinant of outcome in patients with heart failure, but its quantitative assessment is limited by the complex RV geometry. This study sought to evaluate the effect of intensive medical therapy on RV performance in patients admitted to the hospital with advanced decompensated heart failure, using both conventional RV echocardiographic indices and 2-dimensional strain analysis of the RV free wall. RV peak systolic strain was measured as the average peak longitudinal strain of the basal, mid, and apical segment of the RV free wall shortly after admission and 48 to 72 hours later. Not baseline RV function but rather a dynamic improvement in RV mechanics (defined as an absolute increase in RV peak systolic strain after 48 to 72 hours) in response to intensive medical therapy was found to be associated with lower long-term adverse events in this study population. These results suggest that in the setting of acute heart failure, it may be important to see the return to a more normal hemodynamic profile also reflected by an improvement in RV mechanics. Future research should determine whether an acute response of RV function to intensive medical therapy is eventually sustained at a much longer follow-up.

Conclusions: Dynamic improvement in RV mechanics in response to intensive medical therapy was associated with lower long-term adverse events in patients with acute decompensated heart failure than in patients not showing improvement.[10]

Continuous Monitoring of Intrathoracic Impedance and Right Ventricular Pressures in Patients With Heart Failure

Summary: This study prospectively compared intrathoracic impedance and continuous right ventricular pressure measurements in patients with heart failure. It demonstrated that decompensated heart failure develops based on medium-term hemodynamic derangements and is preceded by significant changes in intrathoracic impedance and right ventricular pressures during the month before a major clinical heart failure event. In general, intrathoracic impedance and pressure changes are moderately correlated, but the correlation increases within the month before a major and minor heart failure event. Whether patient management strategies that incorporate device-based hemodynamic sensors have a beneficial impact on morbidity and mortality outcomes and whether the diagnostic accuracy of proactive fluid detection can be increased by a combined use of impedance

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and right ventricular pressure monitoring remain to be investigated in large clinical randomized trials.

Conclusions: Decompensated heart failure develops based on hemodynamic derangements and is preceded by significant changes in intrathoracic impedance and right ventricular pressures during the month before a major clinical event. Impedance and pressure changes are moderately correlated. Future research may establish the complementary contribution of both parameters to guide diagnosis and management of patients with heart failure by implantable devices.[11]

Survival After Cardiac Transplantation in Patients With Hypertrophic Cardiomyopathy

Summary: Heart transplantation is a treatment option for a select subset of patients with hypertrophic cardiomyopathy (HCM). However, the prevalence of and outcome for HCM patients who undergo transplantation in the United States are unknown. The authors acquired demographic, clinical, and survival outcome data for heart-only transplant recipients from the United Network of Organ Sharing Registry for a retrospective 15-year period. Patients with HCM composed 1% of patients transplanted during this time, with the remainder comprising 3 non-HCM patient subgroups, including ischemic cardiomyopathy (54%), dilated cardiomyopathy (44%), and restrictive cardiomyopathy (1%). The 1-, 5-, and 10-year overall transplant survival for patients with HCM was 85%, 75%, and 61%, respectively, with a trend toward greater survival over time compared with non-HCM transplant patients (P=0.05). Compared with patients transplanted for ischemic cardiomyopathy, patients with HCM had more favorable survival (P=0.02) but no difference compared with patients transplanted for restrictive (P=0.08) or dilated (P=0.25) cardiomyopathy. Patients with HCM compose a small portion of the US heart transplant population (1%) but have a trend toward better survival over time after transplantation, compared with that of patients transplanted for non-HCM cardiovascular diseases.

Conclusions: Patients with HCM compose a small subset (1%) of the overall population of patients who undergo heart transplantation in the United States. Nonetheless, survival after transplant among patients with HCM is comparable with that of patients transplanted for non-HCM cardiovascular diseases, with possible enhanced survival over time.[12]

Exercise Training in Patients With Advanced Chronic Heart Failure (NYHA Class IIIb) Promotes Restoration of Peripheral Vasomotor Function, Induction of Endogenous Regeneration, and Improvement of Left Ventricular Function

Summary: Limitation of exercise capacity in patients with chronic heart failure is as a result of not only impairment of left ventricular function but also a result of peripheral maladaptations, involving a blunted peripheral perfusion and intrinsic alterations of skeletal muscle. In patients with stable, moderate heart failure, exercise training has been shown to enhance exercise capacity and to partially reverse intrinsic alterations of skeletal muscle in the absence of harmful side effects on central hemodynamics. The present study demonstrates that in patients with advanced heart failure (New York Heart Association class IIIb), aerobic endurance training for a period of 12 weeks leads to an increase in exercise capacity. This was associated with a decline in left ventricular end-diastolic and end-systolic dimensions and an augmentation in ejection fraction. Exercise training resulted in an improvement in peripheral vasomotion and enhanced capillary density in the skeletal muscle as a sign of skeletal muscle regeneration. Correction of endothelial dysfunction and enhanced neovascularization in the skeletal muscle might be at least partially the result of an increase in number and improvement in the function of endogenous progenitor cells. In summary, improvement in endothelial and cardiac functions and augmentation in capillary density of the skeletal muscle associated with regular physical activity suggest that exercise training is not only an intervention to improve exercise capacity and clinical symptoms but may also induce endogenous vascular repair and cardiac remodeling in patients with advanced heart failure.

Conclusions: Twelve weeks of exercise training in patients with advanced chronic heart failure is associated with augmented regenerative capacity of circulating progenitor cells, enhanced flow-mediated dilation suggestive of improvement in endothelial function, skeletal muscle neovascularization, and improved left ventricular function.[13]

A Simultaneous X-Ray/MRI and Noncontact Mapping Study of the Acute Hemodynamic Effect of Left Ventricular Endocardial and Epicardial Cardiac Resynchronization Therapy in Humans

Summary: The absence of clinical response in 30% to 40% of patients receiving cardiac resynchronization therapy poses a great challenge to heart failure clinicians and device implanters. It is well documented that positioning of the left ventricular (LV) lead in areas of myocardial scar in patients with ischemic cardiomyopathy is associated with a diminished response to cardiac resynchronization therapy (CRT). Regions of slow conduction exist in both nonischemic and ischemic cardiomyopathy, which can be delineated using noncontact mapping, whereby the electrophysiological properties of a chamber can be characterized using a multielectrode array. Using this technique, the authors evaluated the effect of pacing inside and outside regions of slow conduction on acute hemodynamic response to CRT. Procedures were performed in a combined x-ray and magnetic resonance imaging environment so that tissue characterization by delayed-enhancement cardiac magnetic resonance imaging could be correlated with electrophysiological assessment. Both endocardial and transvenous epicardial LV pacing were performed with the hypothesis that endocardial pacing may be more effective as a result of reproducing the physiological pattern of activation of the LV myocardium, as well as lack of constraint by the coronary venous anatomy. The authors found that zones of slow conduction could be identified using delayed-enhancement cardiac magnetic resonance in patients with an ischemic heart failure cause but not in nonischemic cardiomyopathy. The acute effect of CRT was superior in response to endocardial compared with epicardial pacing. Stimulation within zones of slow conduction was associated with a diminished response to CRT. This is a potential explanation for lack of response to CRT and reinforces the need for positioning the LV lead on an individual basis.

Conclusions: Endocardial LV pacing seems superior to conventional CRT, although the optimal site varies between subjects and is influenced by pacing within areas of slow conduction. Delayed-enhancement cardiac magnetic resonance was a poor predictor of zones of slow conduction in nonischemic patients.[14]

Effect of Flow-Triggered Adaptive Servo-Ventilation Compared With Continuous Positive Airway Pressure in Patients With Chronic Heart Failure With Coexisting Obstructive Sleep Apnea and Cheyne-Stokes Respiration

Summary: In patients with chronic heart failure (CHF), the presence of sleep-disordered breathing, including either obstructive sleep apnea

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or Cheyne-Stokes respiration-central sleep apnea, is associated with a poor prognosis. A large-scale clinical trial showed that continuous positive airway pressure (CPAP) did not improve the prognosis of such patients with CHF, probably because of insufficient sleep-disordered breathing suppression. Recently, it was reported that adaptive servo-ventilation (ASV) can effectively treat sleep-disordered breathing. However, there are no specific data about the efficacy of flow-triggered ASV for cardiac function in patients with CHF with sleep-disordered breathing. The aim of this study was to compare the efficacy of flow-triggered ASV with CPAP in patients with CHF with coexisting obstructive sleep apnea and Cheyne-Stokes respiration-central sleep apnea. Thirty-one patients with CHF, defined as left ventricular ejection fraction <50% and New York Heart Association class ≥II, with coexisting obstructive sleep apnea and Cheyne-Stokes respiration-central sleep apnea, were randomly assigned to either CPAP or flow-triggered ASV. The suppression of respiratory events, changes in cardiac function, and compliance with the devices during the 3-month study period were compared. Although both devices decreased respiratory events, ASV more effectively suppressed respiratory events (ΔAHI [apnea-hypopnea index]: −35.4±19.5 with ASV; −23.2±12.0 with CPAP; $P<0.05$). Compliance was significantly greater with ASV than with CPAP (5.2±0.9 versus 4.4±1.1 hours/night; $P<0.05$). The improvements in quality-of-life and LVEF were greater in the ASV group (ΔLVEF: +9.1±4.7% versus +1.9±10.9%). These results suggest that patients with coexisting obstructive sleep apnea and Cheyne-Stokes respiration-central sleep apnea may receive greater benefit from treatment with ASV than with CPAP.

Conclusions: These results suggest that patients with coexisting obstructive sleep apnea and Cheyne-Stokes respiration-central sleep apnea may receive greater benefit from treatment with ASV than with CPAP.[15]

Reversal of Severe Heart Failure With a Continuous-Flow Left Ventricular Assist Device and Pharmacological Therapy: A Prospective Study

Summary: Myocardial recovery sufficient to allow pump removal is thought to be rare after left ventricular assist device support. The authors have previously shown that a specific combination of drug therapy and left ventricular assist device unloading results in recovery in two thirds of patients with dilated cardiomyopathy receiving a pulsatile device. However, there has been a transition to rotary devices, and this protocol has not been previously used with non-pulsatile devices. The authors report the results of a prospective study of 20 Heartmate II bridge-to-transplantation patients receiving a specific drug regimen consisting of a combination of angiotensin-converting enzymes, β-blockers, angiotensin II inhibitors, and aldosterone antagonists to maximize reverse remodeling, followed by the β_2-agonist clenbuterol to promote physiological hypertrophy to maximize the incidence and durability of recovery. Patients were regularly tested (echocardiograms, exercise tests, catheterizations) with the pump at low speed. One patient was lost to follow-up and died. Of the remaining 19, 12 (63.2%) were explanted. Before explantation at low flow, echocardiographic, exercise test, and hemodynamic data were excellent. Actuarial survival without recurrence of heart failure was 83.3% at 1 and 3 years. Hence, a high rate of reversal of end-stage heart failure secondary to nonischemic cardiomyopathy can be achieved with nonpulsatile flow with mechanical and pharmacological therapy. An increasing number of patients in the future are likely to have these devices implanted as an alternative to transplantation, and, of these, all with nonischemic dilated cardiomyopathy are candidates for recovery. These data suggest that using ventricular assist devices as a platform could result in myocardial recovery in a significant number of these patients.

Conclusions: Reversal of end-stage heart failure secondary to nonischemic cardiomyopathy can be achieved in a substantial proportion of patients with nonpulsatile flow through the use of a combination of mechanical and pharmacological therapy.[16]

Incidence and Predictors of Early and Late Mortality After Transcatheter Aortic Valve Implantation in 663 Patients With Severe Aortic Stenosis

Summary: Transcatheter aortic valve implantation using the self-expandable CoreValve prosthesis was performed in 663 patients with severe aortic stenosis and high surgical risk in 14 Italian centers. Procedural success was 98%, and intraprocedural mortality was 0.9%. The mortality rates at 30 days and 1 year were 5.4% and 15.0%, respectively. Early mortality was acceptably low compared with the anticipated risk calculated by means of the EuroSCORE and was strongly associated with the occurrence of procedural complications. Late mortality continued to occur from 30 days to 1 year after transcatheter aortic valve implantation, primarily as the effect of postprocedural paravalvular aortic regurgitation ≥2+ and nonvalve-related comorbidities, such as cerebrovascular disease, chronic kidney disease, and heart failure. Clinical and hemodynamic benefits observed acutely after transcatheter aortic valve implantation were sustained at 1 year.

Conclusions: Benefit of transcatheter aortic valve implantation with the CoreValve Revalving System is maintained over time up to 1 year, with acceptable mortality rates at various time points. Although procedural complications are strongly associated with early mortality at 30 days, comorbidities and postprocedural paravalvular aortic regurgitation ≥2+ mainly impact late outcomes between 30 days and 1 year.[17]

Left Ventricular Lead Position and Clinical Outcome in the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) Trial

Summary: Although cardiac resynchronization therapy is an accepted therapeutic modality for patients with heart failure and conduction disturbances, a significant proportion of patients remain nonresponsive to this treatment. An important determinant of successful cardiac resynchronization therapy for heart failure is the position of the left ventricular (LV) pacing lead. The aim of this study was to analyze the impact of the LV lead position on outcome in patients randomized to cardiac resynchronization therapy defibrillator in the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) study. The LV lead position was assessed in 799 patients by means of coronary venograms and chest x-rays recorded at the time of device implantation. The LV lead location was classified along the short axis into an anterior, lateral, or posterior position and along the long axis into a basal, midventricular, or apical region. The results demonstrate that LV lead location along the short axis (ie, anterior, lateral, or posterior walls) does not influence the primary end points of heart failure hospitalization and all-cause mortality. A midventricular (lateral, anterior, or posterior) position was found in 506 (63%), a basal position in 183 (23%), and an apical position in 110 (14%) patients. The apical lead location compared with leads located in the nonapical position (basal or midventricular region) was associated with a significantly increased risk for heart failure and death (hazard ratio, 1.72; 95% CI, 1.09–2.71; $P=0.019$) after adjustment for the clinical covariates.

Conclusions: LV leads positioned in the apical region were associated with an unfavorable outcome, suggesting that this lead location should be avoided in cardiac resynchronization therapy.[18]

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Effectiveness of Cardiac Resynchronization Therapy by QRS Morphology in the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT)

Summary: There is an increasing interest and need to identify patients with heart failure who benefit from cardiac resynchronization therapy (CRT), as well as those who do not. In patients with a wide QRS complex who qualify for CRT, QRS morphology indicates different conduction delays, represented on the ECG as left bundle branch block (LBBB), right bundle branch block, or nonspecific intraventricular conduction disturbances. The Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) demonstrated that in patients with mild-to-moderate heart failure, CRT with defibrillator implantation significantly reduced the risk of heart failure events or death compared with treatment with only an implantable cardioverter-defibrillator. This analysis of the MADIT-CRT trial data demonstrated that compared with non-LBBB patients (those with right bundle branch block or nonspecific intraventricular conduction disturbances), patients with LBBB QRS morphology showed significant clinical benefit from CRT with defibrillator therapy, as measured by reduced risk of heart failure event or death and risk of ventricular tachycardia/fibrillation or death. Non-LBBB patients did not benefit clinically, despite a significant reduction in left ventricular volumes. These findings formed the basis for recent Food and Drug Administration approval of new broadened indications for CRT in mild or asymptomatic heart failure patients with LBBB. There is still a question as to whether CRT therapy should be used in non-LBBB patients even when advanced heart failure is present and which non-LBBB patients might still benefit clinically from CRT. Further research investigating the rationale, mechanisms, and clinical benefit is needed to determine whether CRT therapy should be pursued in non-LBBB patients.

Conclusions: Heart failure patients with New York Heart Association class I or II and ejection fraction ≤30% and LBBB derive substantial clinical benefit from CRT with defibrillator: a reduction in heart failure progression and a reduction in the risk of ventricular tachyarrhythmias. No clinical benefit was observed in patients with a non-LBBB QRS pattern (right bundle branch block or intraventricular conduction disturbances).[19]

Efficacy and Safety of Celivarone, With Amiodarone as Calibrator, in Patients With an Implantable Cardioverter-Defibrillator for Prevention of Implantable Cardioverter-Defibrillator Interventions or Death: The ALPHEE Study

Summary: Sudden cardiac death is preventable with implantable cardioverter-defibrillators. These devices can now be placed not only in patients who have had a sustained arrhythmia but also in those deemed high risk for whom a mortality benefit can also be derived. Unfortunately, a sizable percentage of patients who receive these devices may have frequent or inappropriate shock therapy. It has been discovered that these events are psychologically devastating, cause frequent hospitalizations, and predispose to morbid and mortal events. Although antiarrhythmic drugs are frequently used to prevent frequent device discharges, no drug has gained US regulatory approval for this indication. On the basis of favorable data obtained in a small phase IIA trial, the authors studied the efficacy and safety of celivarone, a novel benzofuran derivative and congener of amiodarone and dronedarone, for the prevention of device activation and sudden death. In a multinational, multicenter, prospective, double-blind, randomized parallel-group trial, the authors compared 3 doses of celivarone with placebo and included an amiodarone calibrator arm to confirm the adequacy of the design and the study population. Although it proved to be well tolerated and safe, the authors found no significant benefit for celivarone for this indication at any dose. Amiodarone, as expected, reduced device activations, including shocks, but was associated with a higher mortality than placebo, whereas celivarone was mortality neutral. The search for drugs to prevent device activation and death in implantable cardioverter-defibrillator patients will continue. The Dose Ranging Study of Celivarone with Amiodarone as Calibrator for the Prevention of Implantable Cardioverter Defibrillator Interventions or Death (ALPHEE), although a negative trial, provides a precedent for the study of new drugs for ventricular indications.

Conclusions: Celivarone was not effective for the prevention of implantable cardioverter-defibrillator interventions or sudden death.[20]

Combined Atrial and Ventricular Antitachycardia Pacing as a Novel Method of Rhythm Discrimination: The Dynamic Discrimination Download Study

Summary: The authors describe the dynamic discrimination pacing algorithm in dual-chamber defibrillators that can terminate arrhythmias or discriminate between 1:1 supraventricular tachycardias and ventricular tachycardias if the arrhythmia persists. This novel algorithm considers the rhythm ventricular in origin if the first sensed event after simultaneous atrial and ventricular antitachycardia pacing is on the ventricular channel and supraventricular in origin otherwise. The authors tested this algorithm in 62 dual-chamber defibrillator recipients who were followed up for 9.6±3.3 months. The dynamic discrimination algorithm terminated or correctly classified 1379 of 1381 supraventricular tachycardia sequences for an overall specificity of 99.9% (generalized estimating equation adjusted, 99.8%) and 23 of 26 ventricular tachycardia for an overall sensitivity of 88.5% (generalized estimating equation adjusted, 82.1%). Testing this new algorithm in larger patient populations is warranted.

Conclusions: The authors describe a new pacing algorithm in dual-chamber defibrillators that can terminate arrhythmias or discriminate between 1:1 supraventricular tachycardia and ventricular tachycardia if the arrhythmia persists.[21]

Preoperative Factors Associated With Adverse Outcome After Tricuspid Valve Replacement

Summary: Patients with severe tricuspid regurgitation may develop progressive biventricular dysfunction and have increased mortality. Referral for surgical correction is often delayed until patients develop significant heart failure. Appropriate patient selection and optimal timing for tricuspid valve replacement are crucial for optimal outcome, but there is a lack of objective criteria to guide clinicians. In the present study, the authors retrospectively analyzed preoperative clinical and echocardiographic parameters associated with operative and long-term mortality after tricuspid valve replacement surgery. One third of the authors' patients had preoperative New York Heart Association functional class IV, which suggests that surgical timing was late in many patients. Their main finding is that good outcomes for tricuspid valve replacement are achievable in properly selected patients. Operative mortality is reduced to around 6% when patients are operated on in an earlier symptomatic state (New York Heart Association <IV) or when hemodynamically stable (no need for intra-aortic balloon pumps). Furthermore, if operated on before echocardiographic evidence of increased right ventricular filling pressure, survival may be improved even further. Therefore, establishment of guidelines using clinical and echocardiographic parameters is critically important. On the basis of the authors' observations, they propose that surgical correction of severe tricuspid regurgitation should be considered before the development of advanced heart failure (New

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York Heart Association functional class IV) or evidence of increased right ventricular filling pressure as shown by pseudonormalization of right index myocardial performance ratio.

Conclusions: Tricuspid valve replacement for severe tricuspid regurgitation can be performed with an acceptable operative mortality if patients undergo surgery before the onset of advanced heart failure symptoms. Late mortality is associated with a high preoperative Charlson index, short right index of myocardial performance ratio, and advanced New York Heart Association class.[22]

Intrathoracic Impedance Monitoring, Audible Patient Alerts, and Outcome in Patients With Heart Failure

Summary: Heart failure is associated with frequent hospitalizations, often because of volume overload. It is difficult, however, to identify patients at risk for hospitalization, and signs and symptoms are often unspecific. Measurement of intrathoracic impedance with an implanted device with an audible patient alert may detect increases in pulmonary fluid retention early. In the Diagnostic Outcome Trial in Heart Failure (DOT-HF), the authors studied patients with chronic heart failure who had undergone implantation of an implantable cardioverter-defibrillator alone or with cardiac resynchronization therapy. All devices featured a monitoring tool to track changes in intrathoracic impedance (OptiVol) and other diagnostic parameters. Patients were randomized to have information available to physicians and patients as an audible alert in case of preset threshold crossings (access arm) or not (control arm). The primary end point was a composite of all-cause mortality and heart failure hospitalizations. The study showed that the use of an implantable diagnostic tool to measure intrathoracic impedance with an audible patient alert did not improve outcome and in fact increased outpatient visits and heart failure hospitalizations in this population. These findings may have important implications. Although changes in intrathoracic impedance have been associated in a large number of studies with an increased risk for cardiovascular events in patients with heart failure, questions remain about its clinical use, sensitivity, and specificity. Furthermore, the audible alert, in particular, seems to have played a role in the increased number of outpatient visits and heart failure hospitalizations.

Conclusions: Use of an implantable diagnostic tool to measure intrathoracic impedance with an audible patient alert did not improve outcome and increased heart failure hospitalizations and outpatient visits in patients with heart failure.[23]

Gender Bias in Studies for Food and Drug Administration Premarket Approval of Cardiovascular Devices

Summary: The safety and effectiveness of cardiovascular devices may differ by sex. Several national initiatives and guidelines during the past 2 decades have attempted to increase the amount of available sex-specific data for drugs and devices. Despite Food and Drug Administration policy to analyze sex bias in all device applications, the majority of high-risk cardiovascular devices approved by the administration still do not contain such information. Policy changes are necessary to ensure analysis of sex-specific data during device evaluation to optimize safety and effectiveness data.

Conclusions: There is a lack of sex-specific safety and effectiveness data for high-risk cardiovascular devices before Food and Drug Administration approval. The justifications for this lack of evidence may perpetuate the status quo. More rigorous Food and Drug Administration requirements for sex-specific data before device approval could present an opportunity to improve cardiovascular outcomes.[24]

Elevated B-Type Natriuretic Peptide Is Associated With Increased In-Hospital Mortality or Cardiac Arrest in Patients Undergoing Implantable Cardioverter-Defibrillator Implantation

Summary: Elevated B-type natriuretic peptide (BNP) is associated with increased perioperative mortality. Implantable cardioverter-defibrillator implantation is usually well tolerated but occasionally results in death or postimplant cardiac arrest. Markedly elevated BNP before implantable cardioverter-defibrillator implant is associated with a significantly higher risk of death or cardiac arrest. Preoperative BNP ≥1000 pg/mL and biventricular implantable cardioverter-defibrillator implantation are associated with 2.16% mortality in real-world practice. Preimplantation risk assessment should include measurement of BNP.

Conclusions: Elevated BNP level was significantly associated with increased risk of in-hospital mortality or cardiac arrest in patients undergoing implantable cardioverter-defibrillator implant. Strategies aimed at reducing preprocedural BNP or creating systems to manage procedural risk merit further investigation.[25]

Transcoronary Ethanol Ablation for Recurrent Ventricular Tachycardia After Failed Catheter Ablation: An Update

Summary: Catheter ablation of scar-related ventricular tachycardias (VTs) still fails in some patients, usually because of an inability to reach the arrhythmia substrate. Transcoronary ethanol ablation (TCEA) offers an alternative for these patients. The authors began offering TCEA routinely at their institution when endocardial and epicardial ablation fail or when a deep intramural substrate, such as in the septum, is anticipated. To the authors' knowledge, this update provides the largest reported experience of TCEA for VT and further clarifies its limitations with present techniques. In 19% of patients, TCEA was considered but not performed because of unsuitable coronary anatomy. Of the 22 patients who received TCEA, VT recurrences were completely prevented in 36%, and arrhythmia control was improved in an additional 27%. Complete heart block occurred in 5 patients, and 1 patient with advanced heart failure died 5 days after the procedure. Thus, TCEA is a useful treatment option when catheter ablation fails but has significant limitations.

Conclusions: In patients with difficult-to-control VT in whom radiofrequency catheter ablation fails, TCEA prevents all VT recurrences in 36% and improves arrhythmia control in an additional 27%. Inadequate target vessels, collaterals, and recurrence of modified VTs limit efficacy, but TCEA continues to play an important role for difficult VTs in these high-risk patients.[26]

Effect of Right Ventricular Versus Biventricular Pacing on Electric Remodeling in the Normal Heart

Summary: Biventricular pacing (BIV) has been shown to have beneficial effects in a subset of patients with systolic heart failure and to prevent the deleterious effects of high-burden right ventricular (RV) pacing in patients with preserved left ventricular function. The mechanisms of these salutary effects are not fully elucidated. In this study, the authors examined the effect of BIV versus RV pacing on the normal heart in a rabbit model of epicardial pacing. After 4 weeks of pacing, the QT interval was significantly shorter in the BIV group compared with the RV or sham-operated (nonpaced) groups. Also, compared with rabbits in the RV group, rabbits in the BIV group had shorter RV effective refractory period and shorter left ventricular paced QT interval during the drive train of stimuli and close to

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refractoriness. Also, protein expression of KVLQT1 was significantly increased in the BIV group compared with the RV and control groups, whereas protein expression of SCN5A and connexin43 was significantly decreased in the RV compared with the other study groups. ERG protein expression was significantly increased in both pacing groups compared with controls.

Conclusions: In this rabbit model, the authors demonstrate a direct effect of BIV but not RV pacing on shortening the native QT interval, as well as the paced QT interval during burst pacing and close to the ventricular effective refractory period. These findings underscore the fact that the effect of BIV pacing is partially mediated through direct electric remodeling and may have implications as to the effect of BIV pacing on arrhythmia incidence and burden.[27]

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