Randomized, Double-Blind, Multicenter, Placebo-Controlled Study Evaluating the Effect of Aldosterone Antagonism With Eplerenone on Ventricular Remodeling in Patients With Mild-to-Moderate Heart Failure and Left Ventricular Systolic Dysfunction

Summary: Few data are available on effects of aldosterone antagonism in patients with mild-to-moderate heart failure (HF). In this multicenter, randomized, double-blind, placebo-controlled study, patients with mild-to-moderate HF and left ventricular (LV) systolic dysfunction were randomly assigned to receive eplerenone 50 mg/d versus placebo in addition to contemporary background therapy. The primary efficacy analysis was the between-group comparison of the change in LV end-diastolic volume index by quantitative radionuclide ventriculograms. During 36 weeks of treatment, there was no apparent between-group difference in the changes in end-diastolic volume index. There was a reduction in the collagen turnover marker procollagen type I N-terminal propeptide and plasma B-type natriuretic peptide in the eplerenone group when compared with placebo \( (P=0.01\) and \( P=0.04\), respectively). There was no change in symptom status or quality-of-life measures. In a clinically stable, well-treated population of patients with mild-to-moderate HF symptoms and LV dysfunction, 36 weeks of treatment of aldosterone antagonism with eplerenone at a dose of 50 mg/d daily had no detectable effect on parameters of LV remodeling. Thus, the role of aldosterone antagonism in this population of patients with HF remains uncertain.

Conclusions: In a clinically stable, well-treated population of patients with mild-to-moderate HF symptoms and LV dysfunction, 36 weeks of treatment of aldosterone antagonism with eplerenone at a dose of 50 mg/d daily had no detectable effect on parameters of LV remodeling.1

A Randomized Double-Blind Trial of Enalapril in Older Patients With Heart Failure and Preserved Ejection Fraction: Effects on Exercise Tolerance and Arterial Distensibility

Summary: Exercise intolerance is the primary symptom in patients with heart failure and preserved ejection fraction (HFPEF); however, little is known regarding its therapy. This randomized, double-blind, placebo-controlled study examined the effect of 12 months of treatment with the angiotensin-converting enzyme inhibitor enalapril on exercise tolerance and quality of life, as well as the alterations in left ventricular and arterial function that may contribute to HFPEF pathophysiology. Patients at baseline were stable and compensated and had controlled blood pressure. Contrary to the authors’ primary hypothesis, the angiotensin-converting enzyme inhibitor produced no differences in exercise performance, aortic distensibility, or left ventricle mass and volume. There was a trend toward improved quality of life, modest reductions in resting diastolic and peak exercise systolic blood pressures, and mild improvement in carotid arterial distensibility. Doppler measurements of left ventricular diastolic function were not significantly changed. Along with results of large clinical event trials, these findings suggest that using angiotensin II as a therapeutic target in patients with stable, compensated HFPEF and controlled blood pressure does not substantially improve key clinical outcomes; suggest that our understanding of HFPEF may be incomplete; and highlight the need for new treatment paradigms for this important and common disorder.

Conclusions: In stable, older patients with compensated HFPEF and controlled blood pressure, 12 months of enalapril did not improve exercise capacity or aortic distensibility. These data, combined with those from large clinical event trials, suggest that angiotensin inhibition does not substantially improve key long-term clinical outcomes in this group of patients. This finding contrasts sharply with observations in heart failure with reduced ejection fraction and highlights our incomplete understanding of this important and common disorder.2

Exercise Training in Older Patients With Heart Failure and Preserved Ejection Fraction: A Randomized, Controlled, Single-Blind Trial

Summary: Heart failure (HF) with preserved left ventricular ejection fraction (HFPEF) is the most common form of HF in the older population, and exercise intolerance is its primary chronic symptom and a strong determinant of reduced quality of life. In patients with HF with reduced ejection fraction, exercise training (ET) improves exercise intolerance and quality of life; however, little is known regarding the effect of ET in HFPEF. In this randomized, attention-controlled, single-blind study of elderly patients with isolated HFPEF, 16 weeks of medically supervised ET (3 days per week) was found to be safe and resulted in a 21% improvement in exercise capacity (peak exercise oxygen uptake) in the ET group compared with the control group \( (P=0.0002)\). There were also significant improvements in exercise time, 6-minute walk distance, and ventilatory anaerobic threshold (all \( P<0.002)\). There was improvement in the physical quality-of-life score \( (P=0.03)\) but not in the total score \( (P=0.11)\). Although the present results do not allow elucidation of the mechanism of improvement in
exercise capacity, there were no changes in resting left ventricular structure and function or neurohormone levels. These results indicate that ET is safe and can improve both peak and submaximal exercise performance in older patients with HFPEF. This finding is particularly relevant because large pharmacological intervention trials in HFPEF have thus far had neutral results and because exercise intolerance is an important determinant of quality of life in these patients. Therefore, this nonpharmacological intervention may be a worthwhile consideration for patients with this common and increasingly prevalent disorder.

**Conclusions:** ET improves peak and submaximal exercise capacity in older patients with HFPEF.

### 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 type 5 (PDE5) inhibition (sildenafil 50 mg 3× per day) may be beneficial to 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 transmitial (E) to E′, respectively. Changes were accompanied by a reverse remodeling as documented by a significant reduction of left atrial volume index and LV mass index compared with placebo. Furthermore, sildenafil improved exercise performance (peak VO₂), ventilation efficiency (ventilation to CO₂ 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 PDE5 inhibition promotes a sustained significant improvement in LV diastolic function properties, cardiac geometry, and clinical status in patients with systolic heart failure.

**Conclusions:** Findings confirm that in heart failure, sildenafil improves functional capacity and clinical status; these findings also provide the first human evidence that LV diastolic function and cardiac geometry are additional targets of benefits related to chronic PDE5 inhibition.

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

**Summary:** Chronic heart failure (HF) is a clinical syndrome associated with increased rates of morbidity, frequent hospitalizations, and increased use 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 HF. There is a paucity of evidence whether therapeutic interventions that are effective for the treatment of HF in the general population are also effective in those HF patients 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 m², respectively), using the Modified Diet Renal Disease equation from the serum creatinine values obtained at the time of enrollment. The present study demonstrated that carvedilol therapy leads to similar benefits in the presence of CKD as in those HF patients without CKD. However, the effect of carvedilol therapy in HF patients with advanced CKD (estimated glomerular filtration rate <45 mL/min per 1.73 m²) 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 HF 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 HF are consistent even in the presence of mild-to-moderate CKD. Whether carvedilol therapy is similarly efficacious in HF patients with more advanced kidney disease requires further study.

### Metformin Use and Mortality in Ambulatory Patients With Diabetes Mellitus and Heart Failure

**Summary:** Diabetes mellitus and heart failure (HF) commonly coexist in the same patient, and it is important to note that the presence of diabetes mellitus in HF patients is associated with increased morbidity and mortality. Therefore, efforts to adequately treat diabetes mellitus have become increasingly important. Historically, metformin has been contraindicated in HF patients because of concerns of lactic acidosis. Recent animal studies and retrospective studies of patients with diabetes mellitus and HF have suggested that metformin may in fact be beneficial. One important limitation of these previous human studies is the potential for selection bias, in that patients with more severe illness may be less likely to have been prescribed metformin. Propensity score methods are statistical techniques developed to balance covariates in 2 groups in observational studies and, therefore, reduce potential selection bias. In the present study of a national cohort of ambulatory patients with diabetes mellitus and established HF, the authors used propensity score-matched methods to assess the association between metformin and outcomes. Using these techniques, the authors demonstrated that metformin use was associated with lower rates of mortality at 2-year follow-up, without differences in HF hospitalizations or total hospitalizations between the 2 groups. Future prospective studies are needed to confirm the potential benefits and safety of metformin in diabetic patients with HF. Until these data are available, the present study adds to a growing body of literature suggesting that metformin may be beneficial in this population.

**Conclusions:** Metformin therapy was associated with lower rates of mortality in ambulatory patients with diabetes mellitus and HF. Future prospective studies are necessary to define the optimal therapy for diabetic patients with HF.
Ginseng Inhibits Cardiomyocyte Hypertrophy and Heart Failure via NHE-1 Inhibition and Attenuation of Calcineurin Activation

Summary: Heart failure is a major cause of hospitalization and is associated with high financial costs and societal burden. Cardiac hypertrophy and myocardial infarction are major risk factors for the development of heart failure. In recent years, there has been growing interest in botanicals as alternative medicines for cardiovascular disease. Ginseng is a popular, traditional herbal medicine and has been widely used to treat cardiovascular diseases for thousands of years in Asia. Despite increasing interest in ginseng in Western societies, its efficacy and mechanism of action are poorly understood. The authors sought to understand the effect of ginsenosides on cardiomyocyte hypertrophy and myocardial infarction-induced heart failure. In in vitro studies, the authors showed that ginsenosides were able to attenuate cardiomyocyte hypertrophy. Further studies revealed that the anti-hypertrophic effect of ginsenosides was mediated by inhibiting NHE-1 activity and blocking calcium-mediated signaling, which is evidenced by decreased intracellular calcium levels, calcineurin activity, and NFAT3 translocation. In support of in vitro findings, the authors’ in vivo studies demonstrated that oral administration of ginsenosides prevented the progression of heart failure by reducing postinfarction myocardial hypertrophy and improving hemodynamics. Although results from animal studies must be interpreted cautiously, these findings support the development of ginsenosides as potential therapeutics for the treatment of cardiac diseases, and demonstrate the cellular bases for these actions.

Conclusions: Taken together, these results demonstrate a robust anti-hypertrophic and antiremodeling effect of ginseng, which is mediated by inhibition of NHE-1-dependent calcineurin activation.7

A Prospective, Randomized Trial of Single-Drug Versus Dual-Drug Immunosuppression in Heart Transplantation: The Tacrolimus in Combination, Tacrolimus Alone Compared (TICTAC) Trial

Summary: Cardiac transplantation has become the definitive treatment for eligible patients with end-stage cardiovascular disease, with durable 10- and 20-year outcomes. However, the immunosuppressive regimen that facilitates long-term positive outcomes is also responsible for chronic ill effects, including hypertension, weight gain, and malignancies. In the Tacrolimus in Combination, Tacrolimus Alone Compared (TICTAC) trial, the authors report on the first prospective, randomized effort to compare conventional dual-drug immunosuppression with single-drug therapy. In both study groups, corticosteroids were discontinued within the first 2 months, which was well tolerated. The authors report excellent outcomes, with a median of 3 years (range, 1–5 years) of follow-up, although the trial was limited to 150 patients at 2 centers. The importance of this trial is that it shows that immunosuppression can be reduced in a prospective fashion, allowing some patients to take only single antirejection medication. In addition, the fact that corticosteroids were safely discontinued in all trial participants suggests that, potentially, this class of medication may be a less necessary part of the long-term treatment of these patients.

Conclusions: Addition of mycophenolate to single-agent immunosuppression did not provide an advantage over single-agent immunosuppression in terms of rejection, allograft vasculopathy, or 3-year survival. Corticosteroids, which have traditionally been a mainstay of therapy, were successfully discontinued in all patients. These conclusions are tempered by the limited statistical power associated with a sample size of only 150 patients.8

Usefulness of Carvedilol in the Treatment of Chronic Aortic Valve Regurgitation

Summary: The medical treatment of asymptomatic patients with severe aortic valve regurgitation (AR) remains controversial. No pharmacological treatment has been clearly shown to be effective to protect the myocardium against the deleterious effects of chronic volume overload. Despite the recent publication of promising human data, β-blockade in chronic AR remains controversial because of the deleterious effects of bradycardia. More data are needed to support this potentially new treatment strategy. The authors hypothesized that carvedilol might be a safe treatment option in chronic AR, considering its combined β-blocking and α-blocking effects and proven efficacy in patients with established heart failure. They designed a study in a rat model of chronic AR, testing the efficacy of carvedilol at maintaining cardiac function and slowing the development of eccentric left ventricular hypertrophy over 6 months, starting treatment 2 weeks after surgical AR induction. Carvedilol treatment resulted in less left ventricular dilatation. Ejection fraction was improved and filling pressures were reduced by carvedilol. β1-Adrenoreceptor expression was also improved. Those beneficial effects were noted, despite the presence of drug-induced bradycardia. The results of the present study revealed that carvedilol exerted protective effects against volume-overload cardiomyopathy in this model of AR with preserved ejection fraction. These results, in addition to those shown previously with metoprolol, suggest a protective class effect of β-blockers.

Conclusions: Carvedilol exerted protective effects against volume-overload cardiomyopathy in this model of AR with preserved ejection fraction. These results suggest a protective class effect of β-blockers. Combined with the recent publication of promising human data, the findings support the need to carefully design a prospective study in humans to evaluate the effects of β-blockers in chronic AR.9

Cardiac Resynchronization Therapy Reduces the Risk of Cardiac Events in Patients With Diabetes Mellitus Enrolled in the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT)

Summary: Cardiac resynchronization therapy has been shown to reduce the risk of death or heart failure (HF) in patients with New York Heart Association Class III or IV HF. The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) study extended these results to patients with class I and II HF. In this diabetes mellitus substudy of the MADIT-CRT, the authors observed that patients with diabetes mellitus exhibited more indexes of adverse prognosis and had significantly more endpoint events than those without diabetes mellitus. Patients with diabetes mellitus who received combined therapy with cardiac resynchronization and an implantable cardioverter defibrillator versus those receiving implantable cardioverter-defibrillator therapy only benefited from this intervention as much as patients without diabetes mellitus. Patients with diabetes mellitus did not have more arrhythmic or adverse events (including infection) compared with patients without diabetes mellitus, and they exhibited a similar degree of echocardiographic improvement reflective of beneficial left ventricular remodeling. The data indicate that patients with diabetes mellitus, mildly symptomatic HF, left ventricular systolic dysfunction, and QRS duration >130 ms should receive cardiac resynchronization defibrillator therapy.

Conclusions: Patients with diabetes mellitus, left ventricular dysfunction, mildly symptomatic HF, and wide QRS complex derive similar
benefit from cardiac resynchronization with defibrillator therapy compared with patients without diabetes mellitus.10

**Dyssynchrony, Contractile Function, and Response to Cardiac Resynchronization Therapy**

**Summary:** Although cardiac resynchronization therapy (CRT) has been shown to reduce cardiovascular outcomes in patients with heart failure and left ventricular dysfunction, almost one third of patients who receive CRT do not respond to treatment. Determining which patients are more or less likely to benefit from CRT remains a therapeutic challenge. Left ventricular mechanical dysynchrony has been suggested as a method for overcoming the limitations of estimating electric dyssynchrony. Echocardiographic assessments of both left ventricular mechanical dysynchrony and discrete contractile function, which can reflect the extent of myocardial viability and scar burden, can now be performed in a highly reproducible and angle-independent manner by using speckle-tracking analysis. Therefore, in a sample of 1077 patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial—Cardiac Resynchronization Therapy Trial, the authors used echocardiographic myocardial deformation analyses to investigate whether or not mechanical synchrony and contractility might predict response to CRT. The authors observed that the combination of mechanical dyssynchrony and preserved contractile function significantly predicted lower risk for recurrent heart failure or death after CRT, even after adjusting for factors conventionally associated with CRT response. The results indicate that the ventricle must be dyssynchronous but also viable, as reflected by contractile function, to benefit from CRT. These findings suggest that mechanical dyssynchrony and contractile function may be more directly related to clinical response and outcomes than conventionally measured electric dyssynchrony. The authors’ analyses were strengthened by the availability of a large sample size, data on long-term clinical outcomes, and the presence of a control group that allowed estimation of the treatment effect.

**Conclusions:** Both mechanical dyssynchrony and contractile function are important independent correlates of benefit from CRT.11

**Application of an Exercise Intervention on the Evolution of Diastolic Dysfunction in Patients With Diabetes Mellitus: Efficacy and Effectiveness**

**Summary:** Diastolic dysfunction (DD) is associated with adverse cardiovascular outcomes and is a common finding in patients with type 2 diabetes mellitus (T2DM). However, the evolution and potential therapies for DD are poorly understood, and pharmacological studies have been largely disappointing. Exercise has beneficial effects on glycemic control, lipid levels, weight loss, blood pressure, and other vascular parameters in T2DM. This prospective, randomized study describes the impact of an exercise and lifestyle intervention on DD at 3 years in a group of patients with T2DM. Although confirming that DD is common in patients with T2DM, the intervention program on an intention-to-treat basis did not significantly reduce the progression of subclinical DD. This finding may reflect the recognized difficulty of adherence to prolonged exercise intervention, which also was seen in this trial. These findings reinforce the importance of further investigations to identify potential treatment options for patients with T2DM who have evidence of myocardial dysfunction.

**Conclusions:** Despite being efficacious in the subgroup who completed 3 years of exercise-based lifestyle intervention, randomization to this program was not effective in reducing progression of subclinical DD in patients with T2DM, which may reflect the recognized difficulty of adherence to prolonged exercise intervention.12

**Prognostic Value of Baseline Plasma Amino-Terminal Pro-Brain Natriuretic Peptide and Its Interactions With Irbesartan Treatment Effects in Patients With Heart Failure and Preserved Ejection Fraction: Findings from the I-PRESERVE Trial**

**Summary:** Natriuretic peptides are independent predictors of adverse outcomes in patients with heart failure (HF) and reduced ejection fraction, but data to support their role in HF and preserved ejection fraction are limited. Several recent HF trials have excluded patients with low natriuretic peptide levels to increase the likelihood of including patients with more severe HF and to increase the number of outcome events. This approach also assumes that the study intervention will have a greater effect in higher-risk patients, but this presumption is not well established. The authors tested this hypothesis in a post hoc analysis of 3480 patients in the I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction Trial) who had a baseline measurement of N-terminal pro-brain natriuretic peptide. Baseline N-terminal pro-brain natriuretic peptide level was independently associated with an increased risk of all end points measured. Overall, irbesartan had no effect on any of the outcomes; however, its use was associated with improved outcomes in patients with N-terminal pro-brain natriuretic peptide levels below, but not above, the median. After adjusting for 20 baseline covariates, irbesartan still had a beneficial effect on the primary outcome (hazard ratio, 0.74; 95% CI, 0.60–0.90; P=0.003), all-cause mortality (hazard ratio, 0.75; 95% CI, 0.56–0.99; P=0.046), and HF composite outcome (hazard ratio, 0.57; 95% CI, 0.41–0.80; P=0.001) in patients with N-terminal pro-brain natriuretic peptide below the median. These findings may indicate a beneficial effect of irbesartan on early, but not later, high-risk stages of the disease and question the strategy of using elevated natriuretic peptide level as a patient selection criterion in HF with preserved ejection fraction trials.

**Conclusions:** The unexpected benefit of irbesartan in lower-risk patients with HF with preserved ejection fraction in this post hoc analysis may indicate effects on early, but not later, high-risk stages of the disease. These findings question the strategy of using elevated natriuretic peptide level as a patient selection criterion in HF with preserved ejection fraction trials. More studies are needed to support or contest this practice.13

**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 (peak VO₂), 6-minute walk distance, and natriuretic peptides (BNP and NT-proBNP) are predictors of mortality in heart failure patients, 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 $\text{VO}_2$, 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.14

Left Ventricular Assist Device Therapy in Patients With Restrictive and Hypertrophic Cardiomyopathy

Summary: Patients with end-stage restrictive cardiomyopathy (RCM) or hypertrophic cardiomyopathy (HCM) have a dismal prognosis. The only option that may increase survival in these patients is heart transplantation. However, because of continued donor shortages, a long transplant waiting time, and development of irreversible pulmonary hypertension, many of these patients die of irreversible heart failure and incur high mortality. Continuous-flow left ventricular assist devices (LVAD) have been recognized to improve outcomes in patients with advanced dilated or ischemic cardiomyopathy who are failing maximal medical treatment; however, patients with end-stage RCM or HCM were not represented in these LVAD trials. This is the first report to show the feasibility of continuous axial flow pumps in patients with end-stage RCM or HCM. However, these patients can incur more right heart failure and central venous catheter–related infections. There are also numerous technical challenges with implantation of LVAD that are unique to these patients, including the need for myomectomy to enable inflow cannula implantation and the increased risk for “suck-down” events. This single-center experience lacks the statistical power to make conclusions regarding survival, and this data cannot necessarily be extrapolated to other centers. This feasibility study should prompt prospective clinical trials or a national registry to assess whether LVAD therapy can be used routinely as destination therapy or bridge to transplantation in this challenging group of patients.

Conclusions: The preliminary data show that patients with end-stage heart failure caused by RCM or HCM may benefit from continuous axial flow LVAD therapy. This small study suggests that mortality is comparable with those patients who have dilated or ischemic cardiomyopathy, but right heart failure, prolonged inotropic use, and central venous catheter infections are more common in patients with RCM and HCM who are treated with LVAD. Because of the small numbers, the differences should be interpreted cautiously, and prospective clinical trials would be required to recommend this therapy for these patients as bridge to transplantation or destination treatment.15

Central and Peripheral Blood Flow During Exercise With a Continuous-Flow Left Ventricular Assist Device: Constant Versus Increasing Pump Speed: A Pilot Study

Summary: The present study shows that patients with end-stage heart failure provided with an axial-flow left ventricular assist device have significant increases in cardiac output and leg blood flow even during strenuous cycling, but that cerebral perfusion is compromised. In these patients, cerebral perfusion at rest is only 80% of what is seen in normal subjects. During exercise, cerebral perfusion decreases, whereas normal subjects show a substantial elevation in cerebral perfusion. In a randomized fashion, with patients being their own controls, the authors evaluated the effect of increasing left ventricular assist device (LVAD) pump speed in parallel with exercise and found that increased pump speed increased cardiac output during light exercise and improved cerebral perfusion. Although it did not achieve normalization of cerebral perfusion, the latter nonetheless increased during exercise, as seen in normal subjects. In light of these pilot results, the authors think that it might be advantageous during exercise to increase the pump speed of continuous-flow left ventricular assist devices.

Conclusions: With maximal exercise, the axial-flow LVAD supports near-normal increments in cardiac output and leg perfusion, but cerebral perfusion is poor. Increased pump speed augments cerebral perfusion during exercise.16

Pulmonary Hypertension in Heart Failure With Preserved Ejection Fraction: A Target of Phosphodiesterase-5 Inhibition in a 1-Year Study

Summary: Heart failure with left ventricular diastolic dysfunction and preserved ejection fraction is a considerable public health concern. Its prevalence is increasing rapidly, and the outcome is similar to that of systolic heart failure. Because of development of pulmonary vasoconstriction and hypertension, heart failure with preserved ejection fraction may turn into right ventricular (RV) failure, an event highly predictive of poor outcome. Thus, prevention and treatment of the unfavorable, backward hemodynamic and vascular effects are relevant clinical challenges. In heart failure, nitric oxide–dependent pulmonary vasodilatation is impaired. Because phosphodiesterase-5 is highly expressed in the lungs and its inhibition potentiates nitric oxide signaling by increasing cyclic guanosine monophosphate concentration, the authors tested whether sildenafil could benefit patients with heart failure with preserved ejection fraction. In this 1-year, placebo-controlled, randomized study, the authors found that at 6 and 12 months, sildenafil, and not placebo, improved life quality; reduced pulmonary artery, wedge, and right atrial pressures and RV end-diastolic pressure and dimension; shifted leftward the RV Frank-Starling relationship; increased cardiac output and contractile function in parallel with decrease of pulmonary artery elastance; and improved alveolar-capillary membrane gas conductance, whose changes inversely correlated with those in mean right atrial pressure. Thus, in heart failure with preserved ejection fraction, sildenafil modulates pulmonary vasoconstriction, improves RV function, and reduces RV dimensions. As a consequence, chronic phosphodiesterase-5 inhibition may facilitate left ventricular filling through ventricular interdependence. Alveolar-capillary membrane gas conductance improvement likely reflects lung interstitial water reabsorption, and its relationship with right atrial pressure suggests that pulmonary lymphatic drainage, a safety mechanism against interstitial edema, is at least partially restored by right atrial pressure reduction. Results may lead to promising prognostic insights.

Conclusions: The multifaceted response to phosphodiesterase-5 inhibition in heart failure with preserved ejection fraction includes improvement in pulmonary pressure and vasomotility, RV function and dimension, left ventricular relaxation and distensibility (structural changes and/or ventricular interdependence), and lung interstitial water metabolism (wedge pulmonary pressure decrease improving hydrostatic balance and right atrial pressure reduction facilitating lung lymphatic drainage). These results enhance our understanding of heart failure with preserved ejection fraction and offer new directions for therapy.17
References


Circulation: Heart Failure Editors' Picks: Most Important Articles in Heart Failure and Therapeutics
Robb D. Kociol

Circ Heart Fail. 2012;5:e73-e78
doi: 10.1161/CIRCHEARTFAILURE.112.969766
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/5/4/e73

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Heart Failure can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Heart Failure is online at:
http://circheartfailure.ahajournals.org//subscriptions/