

## Recent Diagnostic and Therapeutic Innovations in Heart Failure Management

ANIL K. GEHI, M.D., SEAN P. PINNEY, M.D., AND ALAN GASS, M.D.

### Abstract

Although there has been substantial progress in the treatment of congestive heart failure over the last several decades, it is clear that heart failure continues to burden our aging population. As the epidemic of heart failure grows, there remains an unmistakable need for novel diagnostic and therapeutic options in its management. In this article, we review recent innovations in the management of congestive heart failure, highlighting several recent clinical trials.

**Key Words:** Heart failure, diagnosis, therapy, innovations, review.

### Introduction

ACCORDING TO THE NATIONAL HEART, Lung and Blood Institute (NHLBI), approximately 5 million people in the United States have been diagnosed as having congestive heart failure (CHF) (1). Each year approximately 550,000 people are diagnosed with CHF, with the incidence approaching 1% after age 65. For those diagnosed with CHF, the annual mortality is approximately 45%, and 80% will die within 5 years, a prognosis worse than that of the majority of cancers (2).

Hospital admissions for CHF account for \$3.6 billion in Medicare expenditures for 990,000 admissions each year (2). The total annual cost to the health care system approaches \$25 billion. And 20% of all hospital admissions are for CHF. Among persons older than 65, the rate of CHF hospitalization increased by 159% in the last decade (1). The number of hospitalizations of patients with a principal diagnosis of CHF has increased

steadily over the past 2 decades and is expected to double during the next 40 years as the result of the progressive aging of the Western population (3). Given this growing epidemic, considerable effort continues to be made to reduce the number of hospitalizations, decrease the morbidity and mortality, and improve the quality of life of those suffering from heart failure.

### Current Therapies

In the past two decades, there has been substantial progress in the treatment of heart failure. A multitude of clinical trials have demonstrated the benefits of angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor antagonists, beta-blockers, aldosterone antagonists, biventricular pacing, and the use of multidisciplinary teams to treat failure (1, 4, 5). These interventions have clearly been shown to reduce morbidity and mortality, reduce the rate of hospitalizations, and improve the overall functional status of patients with systolic congestive heart failure.

However, it is important to realize the limitations of these advances. Despite the results of clinical trials, large epidemiologic surveys fail to show any meaningful change in overall death rates. Rather, death from CHF seems only to have been delayed after the initial diagnosis (1). Furthermore, the actual prescribing of medications with proven benefit in systolic congestive heart failure contin-

---

The Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Anil Gehi, M.D., Box 1030, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029; email: anil.gehi@msnyuhealth.org

Adapted from a Cardiology Grand Rounds presentation to the Department of Medicine, Mount Sinai School of Medicine, New York, NY on November 17, 2003, and updated as of November 2004.

ues to be woefully inadequate. A recent survey of more than 33,000 outpatient visits for CHF showed that ACE inhibitors are still used by only 39% of patients (6) and beta-blockers by only 30–40% of eligible patients (7). Before considering novel approaches, we must first make considerable effort to remedy this deficiency.

Many new and exciting diagnostic and therapeutic innovations have recently been developed. This review will highlight the hypotheses and important evidence for many of these innovations.

## Diagnostic Innovations

### B-Type Natriuretic Peptide

An important recent advance in evaluating the patient with congestive heart failure is the use of B-type natriuretic peptide. To provide rapid and effective treatment for patients with heart failure, accurate differentiation of heart failure from other causes of dyspnea must be established. In chronic heart failure, a reliance on physical signs to assess ventricular filling pressures may be misleading (8). An objective, easily available assessment of the severity of heart failure may help direct aggressive therapy for those patients with the worst prognoses.

B-type natriuretic peptide (BNP) is a neurohormone released from the cardiac ventricles in response to increased wall tension (9). The “BNP” (Breathing Not Properly) study evaluated BNP levels using a rapid, bedside assay of 1,586 patients who presented to the emergency department with acute dyspnea. When compared with the clinical diagnosis of congestive heart failure by two independent, blinded cardiologists, the diagnostic accuracy of BNP at a cutoff of 100 pg/mL was 83.4%. The negative predictive value at levels less than 50 pg/mL was 96% (9).

In a second study, 250 predominantly male patients presented with dyspnea at an academic Veteran’s Affairs hospital. At a blood concentration of 80 pg/mL, BNP was an accurate predictor of the presence of CHF (95%) when compared with a consensus of two cardiologists. A concentration less than 80 pg/mL had an excellent negative predictive value (98%) (10).

In a prospective study of 1,050 patients with or without CHF, BNP levels increased with CHF severity as determined by New York Heart Association (NYHA) class, but were only statistically significant when comparing individuals with and without CHF, using a cutoff of 100 pg/ml (11). Individuals without CHF had a median BNP of 9.29 pg/mL. Median BNPs among patients with NYHA classes I–IV were 83.1, 235, 459, and 1,119 pg/mL, respectively.

In a randomized study of 69 patients with CHF, therapy was guided by BNP or standard clinical assessment. At 6 months’ follow-up, BNP-guided therapy reduced total cardiovascular events and delayed time to a first event, compared with clinically guided therapy (12).

Additionally, BNP levels have been found to correlate with the risk of death, heart failure, and myocardial infarction (MI) in patients presenting with acute coronary syndrome (ACS). A baseline level of BNP at presentation with an ACS correlates with outcomes at 30 days and 10 months in a stepwise fashion, in increasing quartiles of BNP levels (13). BNP levels may also enable risk stratification to predict sudden cardiac death in patients with heart failure. In a study of 452 patients with heart failure and an EF < 35%, using a cutoff of 130 pg/mL, sudden-death-free survival was significantly higher in patients below (99%) compared with patients above (81%) this cutoff (14).

In summary, the BNP assay has clearly been shown to be beneficial in ruling out heart failure as a cause of dyspnea when an upper limit of 80–100 pg/mL is used. At values greater than 300 pg/mL, the BNP assay points to cardiac disease as a contributing factor to dyspnea, although the BNP assay does not distinguish between different etiologies of heart failure. However, an elevated BNP level, regardless of etiology, portends a worsened prognosis for a number of outcomes, including risk of death, heart failure, MI, and sudden cardiac death. The utility of the BNP assay for an individual patient, as a means of following the progression of heart failure and response to treatment has not yet been established, but is presently being evaluated.

### C-Reactive Protein

As the inflammatory model of atherosclerotic disease has emerged, C-reactive protein (CRP) has been studied as a marker of systemic inflammation. In the last several years, an elevated CRP has been shown to be an independent predictor of the development of atherosclerosis, and prognostic of future cardiovascular events (15).

In this context, recent studies have found an elevated CRP to be a predictor of the development of both heart failure and heart failure admission. CRP levels were measured in a cohort of 732 elderly Framingham Study subjects free of prior MI or heart failure. After a mean follow-up of 5.2 years, a serum CRP level  $\geq 5$  mg/dL was found to be associated with a 2.8-fold increased risk of CHF (16). In the ABC (Health, Aging, and Body Composition) study, incident coronary heart disease,

stroke and CHF events as well as blood levels of IL-6, CRP, and tumor necrosis factor (TNF)-alpha were assessed during a mean follow-up of 3.6 years among 2,225 elderly patients without baseline cardiovascular disease. CRP was found to be significantly associated with CHF events (17).

In a prospective study of 76 patients with heart failure admitted to the hospital, CRP levels, NYHA class, and ejection fraction (EF) were assessed. CRP levels were found to trend higher in relation to EF and NYHA class at discharge. At 18 months of follow-up, patients with CRP levels > 0.9 mg/dL were more likely to be readmitted for heart failure. In multivariate analysis, CRP level remained predictive of readmission, independent of NYHA class and EF (18).

## Therapeutic Innovations

### Neurohormonal Agents

As the neurohormonal model of heart failure has become more accepted, several new neurohormonal agents have emerged as potential therapies in heart failure. These agents antagonize the neurohormonal reflexes that have detrimental effects on the heart or augment the reflexes that may be beneficial in maintaining organ perfusion.

### Nesiritide

Therapeutic options for patients hospitalized with acute exacerbations of chronic heart failure are limited. Inotropes such as dobutamine and milrinone achieve short-term hemodynamic improvement and symptomatic relief; however, they consistently fail to show improvements in mortality or length of hospital stay (19). Nesiritide is a recombinant human BNP, an important counter-regulatory neurohormone in the pathogenesis of heart failure, recently approved for the treatment of patients hospitalized with decompensated heart failure (20).

In an initial efficacy trial of 127 patients, intravenous nesiritide had beneficial hemodynamic effects on patients with decompensated CHF, decreasing pulmonary capillary wedge pressure (PCWP) by 9.6 mm Hg at 6 hours (21). Other hemodynamic trials have shown nesiritide to be effective in also reducing mean right atrial pressure and systemic vascular resistance, while being accompanied by a significant increase in cardiac index, without a significant effect on heart rate (20). Additionally, nesiritide has been found to have a vasodilatory effect on coronary arteries, augmenting coronary artery blood flow (22).

The VMAC (Vasodilation in the Management of Acute Congestive Heart Failure) trial was a multicenter, randomized, double-blind trial of 489 inpatients with dyspnea and decompensated CHF. It randomized intravenous nesiritide to nitroglycerin in addition to standard medications for 24 hours. At 3 hours and 24 hours, there was an increased reduction in PCWP in the nesiritide group compared with the nitroglycerin group, but no significant difference in dyspnea (23).

The PRECEDENT (Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Nesiritide Therapy) trial randomized 255 patients with decompensated CHF to nesiritide or dobutamine. At 24 hours, dobutamine significantly increased the number of ventricular tachycardia (VT) events, PVCs, and heart rate (HR) compared with nesiritide, while both drugs were similarly effective in improving the signs and symptoms of CHF (24).

Recently, the FUSION-1 (Follow-Up Serial Infusions of Natreacor) trial demonstrated that three months of weekly infusions of nesiritide could be safely administered to recently hospitalized outpatients. Subset analyses suggested reduced mortality or hospitalization for selected high-risk patients (25). The larger, multicenter FUSION-2 trial will investigate whether the benefit of weekly nesiritide infusions persists once the infusions are stopped.

To date, however, there are no long-term data showing decrease in length of hospitalization, readmission rate, or mortality, with nesiritide.

### Omapatrilat

Atrial and brain (B-type) natriuretic peptides (ANP and BNP) as well as adrenomedullin and bradykinin are metabolized by neutral endopeptidase (NEP). NEP inhibitors increase plasma concentrations of these counter-regulatory neurohormones. Omapatrilat, an orally active, long-acting inhibitor of NEP and ACE, is the most prominent of a class of agents known as vasopeptidase inhibitors. Initial efficacy trials, including a randomized, double-blind hemodynamic study of 369 patients with symptomatic heart failure treated with omapatrilat, demonstrated an acute reduction in PCWP, systolic blood pressure, and systemic vascular resistance that was maintained after 12 weeks (26).

The IMPRESS (Inhibition of Metalloprotease by Omapatrilat in a Randomized Exercise and Symptoms Study of Heart Failure) trial of 573 patients with NYHA Class II–IV heart failure randomly assigned patients to omapatrilat, an inhibitor of neutral endopeptidase and ACE or lisino-

pril. After 24 weeks, there was a trend towards benefit in the combined endpoint of death and admission for worsening heart failure (27). Omapatrilat improved heart failure class among those patients with more severe (NYHA III–IV) symptoms when compared with lisinopril (27).

The larger OVERTURE (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events) trial was powered for morbidity and mortality endpoints to assess long-term efficacy in heart failure. In this randomized trial of 5,770 patients with NYHA Class II–IV heart failure, which compared enalapril to omapatrilat, there was no difference in the primary combined endpoints of all-cause mortality and heart failure hospitalizations (28). Furthermore, the 2.17% incidence of angioedema found in the OCTAVE (Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril) trial, studying the efficacy of omapatrilat in hypertension, has led to further concerns about this novel agent (29).

### Vasopressin Receptor Antagonists

Arginine vasopressin (AVP) is a powerful vasoconstrictor and antidiuretic agent present at increased levels in heart failure. In addition to having deleterious effects on body fluid regulation and hemodynamics, accumulating evidence suggests that AVP can cause structural changes in the myocardium (30). AVP acts via V1 receptors found on the blood vessel and in the myocardium as well as V2 receptors found on the renal tubule.

A double-blinded trial of 143 patients with symptomatic NYHA Class III or IV heart failure randomized patients to short-term treatment with intravenous conivaptan, a dual V1a/V2 AVP receptor antagonist or placebo. At 6 hours after infusion, those on conivaptan had increased urine output and a significantly reduced PCWP and right atrial (RA) pressure compared with placebo, although there were no significant changes in cardiac index, systemic or pulmonary vascular resistance, blood pressure, or heart rate (31).

A trial of 254 patients with heart failure randomly assigned patients to oral tolvaptan, a selective V2 AVP receptor antagonist, or placebo. After 25 days, the patients randomized to tolvaptan had reduced body weight, edema, and normalized serum sodium, with no significant change in heart rate, blood pressure, renal function, or quality of life (32).

Results from the ACTIV in CHF (Acute and Chronic Therapeutic Impact of a Vasopressin 2 Antagonist in Congestive Heart Failure) trial were recently reported (33). The study randomized 319

patients hospitalized with heart failure to tolvaptan or placebo within 72 hours of admission, for up to 60 days. The patients taking tolvaptan had a major reduction in body weight and a normalization of serum sodium within 24 hours, which was sustained at discharge. There were no differences between the groups in coronary heart failure at 60 days.

A long-term clinical efficacy study in progress known as EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure), similar in design to ACTIV, will enroll 3,600 patients. This trial is expected to be completed in 2005.

### Thromboxane Inhibitors

The decline in renal plasma flow in heart failure leads to the renal production of such vasoconstrictor neurohormones as prostaglandin F<sub>2</sub> (PGF<sub>2</sub>) and thromboxane A<sub>2</sub> (TxA<sub>2</sub>) to preserve glomerular filtration. Persistently increased TxA<sub>2</sub> levels such as exist in heart failure can worsen renal function (34).

Picotamide, an oral renal TxA<sub>2</sub> / PGH<sub>2</sub> receptor inhibitor was administered in a study of 14 patients with NYHA Class IV heart failure in an 8-day, randomized, double-blind cross-over study. Compared with placebo, effective renal plasma flow and glomerular filtration rate increased. After 8 days of treatment, picotamide was associated with an increase in diuresis, an improvement in serum creatinine, a decrease in pulmonary artery and right atrial pressure, a decrease in body weight, and a corresponding reduction in dyspnea (34).

### Endothelin Antagonists

Endothelin is a potent vasoconstrictor with remodeling effects similar to those of angiotensin II. Plasma endothelin levels are elevated in patients with heart failure and increase with worsened hemodynamics and symptoms (35). Several selective and non-selective endothelin receptor antagonists are under investigation, although for the most part results have been discouraging.

Bosentan is an oral, non-selective endothelin receptor antagonist, currently approved for use in patients with pulmonary hypertension; it has not yet shown efficacy in heart failure. Though early trials were encouraging, the ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure) trial, which randomized 1,613 patients with NYHA Class III–IV heart failure to bosentan or placebo, failed to show benefit in morbidity or mortality at 1-year follow-up (36).

Darusentan, an oral, selective endothelin A receptor antagonist, was studied in the EARTH (En-

dothelin Antagonist Receptor Trial in Heart Failure) trial (37). This trial, which randomized 642 patients to darusentan or placebo, found no benefit in clinical or physiological outcomes.

Tezosentan is an encouraging intravenous dual endothelin A/B receptor antagonist. In an efficacy, dose-finding trial, 292 patients admitted to the hospital with an exacerbation of heart failure were randomized to tezosentan or placebo. After 6 hours of therapy, patients treated with tezosentan had decreased PCWP and increased cardiac index compared with those on placebo (38–40).

### Other Neurohormonal Agents

Several other neurohormonal agents undergoing investigation have as yet failed to show efficacy in heart failure. Moxonidine is a centrally acting sympathetic outflow inhibitor with encouraging hemodynamic actions. Early trials involving patients with Class II–III heart failure demonstrated neurohormonal benefit (41). However, the larger MOXCON (Sustained Release Moxonidine for Congestive Heart Failure) mortality trial was stopped prematurely due to an excess of adverse events (42). Nolomirole, an inhibitor of dopaminergic and adrenergic outflow, which has shown promise in animal studies (43), is currently undergoing further investigation in the ECHOS (Echo Cardiography and Heart Outcome Study) trial.

### Statins

Even though statins are of proven benefit to patients with ischemic heart disease, their potential use by patients with non-ischemic heart failure has been suggested, given their anti-inflammatory and vascular protective effects (44). In a study of 63 patients with symptomatic, non-ischemic, dilated cardiomyopathy, patients were randomized to receive simvastatin 10 mg/day or placebo. After 14 weeks, those on simvastatin, while demonstrating only a modest reduction in serum cholesterol, had a significantly lower NYHA functional class and an improved EF when compared with those taking placebo. This benefit corresponded to lower concentrations of TNF-alpha, IL-6, and BNP (44). Two large prospective trials of rosuvastatin use in heart failure (GISSI-HF and CORONA) will attempt to resolve this matter.

### Immunomodulators

Congestive heart failure is associated with elevated levels of TNF-alpha. Several experimental

studies have suggested involvement of TNF-alpha in the pathogenesis of heart failure (45).

In a small trial, 47 patients with NYHA Class III or IV heart failure were randomized to etanercept, a TNF-alpha inhibitor, or placebo. After 3 months of therapy, patients on etanercept showed an improvement in LV function and a trend towards improvement in functional status (46). However, in the RENEWAL trial, a combination of the RENAISSANCE (Randomized Etanercept North American Strategy to Study Antagonism of Cytokines) trial and the RECOVER (Research into Etanercept: Cytokine Antagonism in Ventricular Dysfunction) trial, which randomized a total of 1,800 patients to etanercept or placebo—there was no benefit in the combined endpoints of death and CHF hospitalization after 12 months' follow-up (47). In the ATTACH (TNF Therapy against Congestive Heart Failure) trial, a study which randomized 150 patients with NYHA Class III or IV heart failure to infliximab (another TNF-alpha inhibitor) or placebo, there was actually an increase in the combined endpoints of death and hospitalization for heart failure at 28 weeks' follow-up (48). However, the effects of TNF-alpha inhibition in patients with NYHA Class I or II are unknown.

Another form of immune modulation therapy recently reported supports the role of immune activation in the pathogenesis of heart failure. Weekly injections of autologous blood exposed to oxidative stress, which previously were shown experimentally to reduce inflammatory cytokines and increase anti-inflammatory cytokines, were studied in a phase II trial (49). Among 75 patients randomized to immunomodulatory therapy, at six months' follow-up, there was a significantly reduced risk of death and hospitalization and a trend towards improved quality of life. A phase III trial of this encouraging therapy, known as ACCLAIM (Advanced Chronic Heart Failure Clinical Assessment of Immune Modulation Therapy), is currently underway.

### Matrix Metalloproteinases

The cardiac extracellular matrix is composed of an extensive network of collagens. Collagen cross-linking is an important factor in the systolic and diastolic function of the heart. In response to myocyte damage, hemodynamic load, or neurohormonal factors, the extracellular matrix of the heart undergoes remodeling. This remodeling is controlled by the interplay of matrix metalloproteinases (MMPs) that degrade collagens and inhibitors of metalloproteinases (TIMPs). Various cytokines (such as TNF-alpha and IL-6) and neurohormones (such as norepinephrine, angiotensin

II, and endothelin) upregulate MMP expression. Several animal studies have suggested that modulation of MMPs and TIMPs may be an exciting new direction in the prevention and treatment of heart failure, although there remain many concerns of potential adverse consequences of therapy (50, 51)

### Anticoagulation

The relative risk of stroke associated with heart failure varies from as much as 4.1 among those aged 50–59 to 1.5 by age 80–89, reflecting the greater proportion of strokes resulting from other causes (52). Retrospective analyses of the SAVE (Survival and Ventricular Enlargement) and the SOLVD (Studies of Left Ventricular Dysfunction) trials have shown that the rate of stroke is inversely proportional to EF. Furthermore, retrospective analyses of the SOLVD data demonstrated a highly significant reduction in mortality for those patients with ischemic or non-ischemic left ventricular dysfunction treated with warfarin (52). Several large prospective randomized trials have sought to answer this question.

The WATCH (Warfarin and Antiplatelet Therapy in Chronic Heart Failure) trial of patients with heart failure and an EF  $\leq$  35 was designed to enroll 4,500 patients with 5-year follow-up and a primary outcome of death, stroke, or myocardial infarction. WATCH was to include a third treatment arm randomizing patients to clopidogrel (52). Recently reported at the 2004 American College of Cardiology Scientific Sessions, WATCH was halted prematurely due to a lack of patient enrollment. With only 1,587 patients, there was no difference in death, MI, and stroke between aspirin and warfarin at 23 months' follow-up.

The WASH (Warfarin / Aspirin Study in Heart Failure) trial, also limited by poor patient enrollment, randomized 279 patients to no antithrombotic therapy, aspirin, or warfarin. Again no difference was found in clinical outcomes at 27 months (53).

The WARCEF (Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction) trial is an ongoing study randomizing patients with heart failure and an EF  $\leq$  30% to warfarin (target INR 2.5–3.0) or aspirin. The trial of 2,860 patients will accumulate 5-year follow-up data with the primary outcome being all-cause mortality and stroke. Perhaps when outcomes of this trial are combined with those of WATCH and WASH, a clearer answer to the question of antithrombotic therapy will be available. However, with available data, long-term warfarin therapy cannot be recommended.

### Anemia

Approximately half of all patients with heart failure are anemic (hemoglobin  $<$  12g%) (54). The prevalence and severity of this anemia appear to increase with increasing severity of CHF. In a study of 142 patients at an outpatient CHF clinic, the mean Hb concentration decreased from 13.7% in mild CHF (NYHA class I) to 10.9% in severe CHF (NYHA class IV). There was an associated increase in the prevalence of Hb  $<$  12% from 9.1% of patients in NYHA class I to 79.1% in NYHA class IV (55). This anemia is believed to be caused by a number of factors, including poor nutrition, associated renal insufficiency causing inappropriately low erythropoietin levels, bone marrow depression, erythropoietin resistance caused by excessive TNF-alpha, gastrointestinal blood loss from various antiplatelets and anticoagulants, and hemodilution caused by the excessive plasma volume (54). An analysis of the SOLVD trial showed that the level of hematocrit (Hct) was an independent risk factor for mortality. During a mean follow-up of 33 months, the mortality was 22%, 27%, and 34% for those with a Hct  $>$  40%, 35–40%, and  $<$  35%, respectively (56).

A randomized controlled trial of 32 patients with moderate-to-severe CHF (NYHA III–IV), whose Hb levels were persistently between 10.0 and 11.5%, addressed the question of whether treating the anemia improved outcomes. Silverberg et al. treated patients with subcutaneous erythropoietin (EPO) and IV iron to increase the level of Hb to at least 12.5%. After an average follow-up of 8.2 months, the mean NYHA class improved (42.1% vs. 11.4%), the left ventricular ejection fraction increased (+5.5% vs. –5.4%), the need for furosemide decreased, and the number of days spent in the hospital decreased, for those patients treated with EPO and IV iron (57). Additionally, in a randomized trial of 26 anemic patients with CHF, Mancini et al. found that those randomized to EPO had significant improvement in exercise capacity after a follow-up of 3 months (58).

### Sinus Rhythm

The prevalence of atrial fibrillation increases as the severity of heart failure increases, ranging from 4% in those with minimally symptomatic CHF (NYHA Class I–II) to approximately 50% in those with severe symptoms (NYHA Class IV) (59). Patients with atrial fibrillation have a worse prognosis than those without it. In the SOLVD-Prevention trial, atrial fibrillation was independently associated with an increased all-cause mor-

tality at 3 years, from 23% to 34%. The DIG trial similarly demonstrated a relative risk (RR) of mortality of 2.45 and RR of hospitalization of 3.0 at a mean follow-up of 38 months for those in atrial fibrillation (59).

The onset of atrial fibrillation may be associated with a decrease in cardiac output and a worsening of heart failure that is multifactorial. Loss of atrioventricular synchrony can result in impaired diastolic filling, reduced stroke volume and an approximately 20% reduction in cardiac output. An irregular ventricular response elevates right atrial and pulmonary capillary wedge pressure, worsening many of the symptoms of CHF. Cellular and extracellular remodeling occurs as a result of atrial fibrillation. Patients with atrial fibrillation have higher levels of atrial natriuretic peptide and endothelin. Tachycardia in patients with a rapid ventricular response can lead to a reduction in ventricular function (59).

Subset analyses of two randomized trials have demonstrated improved survival among patients with heart failure and atrial fibrillation who reverted to sinus rhythm. The CHF-STAT trial randomized 674 patients with ischemic and non-ischemic NYHA Class III–IV heart failure to amiodarone or placebo. Among those patients who at baseline were in atrial fibrillation, those who converted to sinus rhythm on amiodarone, compared to those who did not, were found to have a significantly lower mortality (60, 61). The DIAMOND (The Danish Investigators of Arrhythmia and Mortality on Dofetilide Study Group) trial randomized 1,518 patients with CHF and atrial fibrillation to dofetilide or placebo. At one-year follow-up, 61% of patients treated with dofetilide vs. 33% on placebo had reverted to sinus rhythm. While overall mortality in the dofetilide group was not significantly different from that of the placebo group, for those patients with restoration of sinus rhythm, there was a significant reduction in mortality (RR=0.44) (62).

Even though these trials did not show an overall improvement in outcomes with antiarrhythmic therapy, there appeared to be a benefit in patients who converted to sinus rhythm. As newer, more effective techniques for the maintenance of sinus rhythm emerge, this issue should be readdressed.

### **Non-pharmacologic Options: Exercise**

Until the early 1980s, it was thought that significant left ventricular systolic dysfunction was a contraindication to exercise (63). However, following early reports of enhanced exercise capacity and enhanced ventricular reserve with exercise

training, a number of small trials demonstrated physiologic benefits from exercise training, including increased peak oxygen consumption, increased peak cardiac output, reduction in sympathetic nervous system activity, improved endothelial function, and decreased insulin resistance (63).

More recently, larger randomized trials have called attention to the importance of exercise training. A 1999 study of exercise training in heart failure randomized 110 patients with stable CHF to an exercise regimen of exercise training 2–3 times per week or no exercise. At one-year follow-up, exercise training was associated with improved quality of life, decreased mortality (RR=0.37), and decreased hospital readmission for heart failure (RR=0.29) (64). The ELVD-CHF (Exercise in Left Ventricular Dysfunction and Chronic Heart Failure) trial, reported in 2003, randomized 90 patients with stable chronic heart failure to a 6-month exercise training program or no exercise. At 6 months, LV volumes diminished and EF improved for the exercise group, with a corresponding improvement in walking distance and quality of life. There was also a trend towards fewer hospital admissions for patients randomized to exercise (65).

Given the available evidence supporting exercise training for patients with heart failure, the Committee on Exercise, Rehabilitation, and Prevention of the American Heart Association Council on Clinical Cardiology has concluded that exercise training is safe and beneficial in improving exercise capacity and quality of life. The committee advocates exercise training programs for patients with chronic heart failure (66).

### **Conclusion**

As the epidemic of heart failure continues to grow, medical science continues to make enormous gains in the management of the disease. Our understanding of the mechanism of disease progression has led to a shift in drug development from that of enhancing cardiac function to that of inhibiting the detrimental effects of the neurohormonal axis. As this review demonstrates, considerable effort in the development of novel therapies is underway. Very soon our options for treatment will expand greatly. We can only hope that these novel approaches continue to extend survival and enhance quality of life among those suffering from heart failure.

### **References**

1. Jessup M, Brozena S. Heart failure. *N Engl J Med* 2003; 348(20):2007–2018.

2. Anonymous. 2003 Heart and stroke statistical update: American Heart Association. 2003.
3. Malinin AI, O'Connor CM, Dzhanashvili AI, et al. Platelet activation in patients with congestive heart failure: do we have enough evidence to consider clopidogrel? *Am Heart J* 2003; 145:397–403.
4. Konstam MA. Improving clinical outcomes with drug treatment in heart failure: what have trials taught? *Am J Cardiol* 2003; 91(6A):9D–14D.
5. McAlister FA, Lawson FM, Teo KK, Armstrong PW. A systematic review of randomized trials of disease management programs in heart failure. *Am J Med* 2001; 110(5):378–384.
6. Stafford RS, Radley DC. The underutilization of cardiac medications of proven benefit, 1990 to 2002. *J Am Coll Cardiol* 2003; 41(1):56–61.
7. Gheorghide M, Gattis WA, Lukas MA, O'Connor CM. Rationale and design of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy for Heart Failure (IMPACT-HF) study. *Am Heart J* 2003; 145:S60–S61.
8. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. *JAMA* 1989; 261:884–888.
9. Maisel AS, Krishnaswamy P, Nowak RM, et al.; Breathing Not Properly Multinational Study Investigators. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002; 347(3):161–167.
10. Dao Q, Krishnaswamy P, Kazanegra R, et al. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. *J Am Coll Cardiol* 2001; 37:379–385.
11. Wieczorek SJ, Wu AH, Christenson R, et al. A rapid B-type natriuretic peptide assay accurately diagnoses left ventricular dysfunction and heart failure: a multicenter evaluation. *Am Heart J* 2002; 144:834–839.
12. Troughton RW, Frampton CM, Yandle TG, et al. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. *Lancet* 2000; 355:1126–1130.
13. de Lemos JA, Morrow DA, Bentley JH, et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *N Engl J Med* 2001; 345:1014–1021.
14. Berger R, Huelsman M, Strecker K, et al. B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. *Circulation* 2002; 105(20):2392–2397.
15. Shah SH, Newby LK. C-reactive protein: a novel marker of cardiovascular risk. *Cardiol Rev* 2003; 11:169–179.
16. Vasan RS, Sullivan LM, Roubenoff R, et al. Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. *Circulation* 2003; 107:1486–1491.
17. Cesari M, Penninx BW, Newman AB, et al. Inflammatory markers and onset of cardiovascular events: results from the health ABC study. *Circulation* 2003; 108(19):2317–2322.
18. Alonso-Martinez JL, Llorente-Diez B, Echegaray-Agara M, et al. C-reactive protein as a predictor of improvement and readmission in heart failure. *Eur J Heart Fail* 2002; 4(3):331–336.
19. Gheorghide M, Gattis WA, Adams KF Jr, et al. Rationale and design of the pilot randomized study of nesiritide versus dobutamine in heart failure (PRESERVD-HF). *Am Heart J* 2003; 145(2 Suppl):S55–S57.
20. Adams KF, Jr., Mathur VS, Gheorghide M. B-type natriuretic peptide: from bench to bedside. *Am Heart J* 2003; 145:S34–S46.
21. Colucci WS, Elkayam U, Horton DP, et al. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. Nesiritide Study Group. *N Engl J Med* 2000; 343(4):246–253. Errata in: *N Engl J Med* 2000; 343(20):1504 and *N Engl J Med* 2000; 343(12):896.
22. Michaels AD, Klein A, Madden JA, Chatterjee K. Effects of intravenous nesiritide on human coronary vasomotor regulation and myocardial oxygen uptake. *Circulation* 2003; 107:2697–2701.
23. Publication Committee for the VMAC Investigators (Vasodilation in the Management of Acute CHF). Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. *JAMA* 2002; 287(12):1531–1540. Erratum in *JAMA* 2002; 288(5):577.
24. Burger AJ, Horton DP, LeJemtel T, et al. Effect of nesiritide (B-type natriuretic peptide) and dobutamine on ventricular arrhythmias in the treatment of patients with acutely decompensated congestive heart failure: the PRECEDENT study. *Am Heart J* 2002; 144:1102–1108.
25. Yancy CW, Saltzberg MT, Berkowitz RL, et al. Safety and feasibility of using serial infusions of nesiritide for heart failure in an outpatient setting (from the FUSION I trial). *Am J Cardiol* 2004; 94:595–601.
26. McClean DR, Ikram H, Mehta S, et al. Vasopeptidase inhibition with omapatrilat in chronic heart failure: acute and long-term hemodynamic and neurohumoral effects. *J Am Coll Cardiol* 2002; 39:2034–2041.
27. Rouleau JL, Pfeffer MA, Stewart DJ, et al. Comparison of vasopeptidase inhibitor, omapatrilat, and lisinopril on exercise tolerance and morbidity in patients with heart failure: IMPRESS randomised trial. *Lancet* 2000; 356:615–620.
28. Packer M, Califf RM, Konstam MA, et al. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). *Circulation* 2002; 106:920–926.
29. Ochiai Y, McCarthy PM, Smedira NG, et al. Predictors of severe right ventricular failure after implantable left ventricular assist device insertion: analysis of 245 patients. *Circulation* 2002; 106:1198–1202.
30. Lee CR, Watkins ML, Patterson JH, et al. Vasopressin: a new target for the treatment of heart failure. *Am Heart J* 2003; 146(1):9–18.
31. Udelson JE, Smith WB, Hendrix GH, et al. Acute hemodynamic effects of conivaptan, a dual V(1A) and V(2) vasopressin receptor antagonist, in patients with advanced heart failure. *Circulation* 2001; 104:2417–2423.
32. Gheorghide M, Niazi I, Ouyang J, et al. Vasopressin V2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. *Circulation* 2003; 107(21):2690–2696.
33. Gheorghide M, Gattis WA, O'Connor CM, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. *JAMA* 2004; 291:1963–1971.
34. Castellani S, Panizza R, Di Serio C, et al. Thromboxane inhibition improves renal perfusion and excretory function in severe congestive heart failure. *J Am Coll Cardiol* 2003; 42:133–139.
35. McMurray J, Pfeffer MA. New therapeutic options in congestive heart failure: Part I. *Circulation* 2002; 105:2099–2106.
36. Kalra PR, Moon JC, Coats AJ. Do results of the ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure) study spell the end for non-selective endothelin antagonism in heart failure? *Int J Cardiol* 2002; 85:195–197.
37. Anand I, McMurray J, Cohn JN, et al. Long-term effects of darusentan on left-ventricular remodelling and clinical outcomes in the EndothelinA Receptor Antagonist Trial in Heart Failure (EARTH): randomised, double-blind, placebo-controlled trial. *Lancet* 2004; 364(9431):347–354.

38. Kaluski E, Kobrin I, Zimlichman R, et al. RITZ-5: randomized intravenous Tezosentan (an endothelin-A/B antagonist) for the treatment of pulmonary edema: a prospective, multicenter, double-blind, placebo-controlled study. *J Am Coll Cardiol* 2003; 41:204–210.
39. O'Connor CM, Gattis WA, Adams KF Jr, et al. Tezosentan in patients with acute heart failure and acute coronary syndromes: results of the Randomized Intravenous Tezosentan Study (RITZ-4). *J Am Coll Cardiol* 2003; 41:1452–1457.
40. Torre-Amione G, Young JB, Colucci WS, et al. Hemodynamic and clinical effects of tezosentan, an intravenous dual endothelin receptor antagonist, in patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol* 2003; 42:140–147.
41. Swedberg K, Bristow MR, Cohn JN, et al. Effects of sustained-release moxonidine, an imidazoline agonist, on plasma norepinephrine in patients with chronic heart failure. *Circulation* 2002; 105:1797–1803.
42. Cohn JN, Pfeffer MA, Rouleau J, et al. Adverse mortality effect of central sympathetic inhibition with sustained-release moxonidine in patients with heart failure (MOXCON). *Eur J Heart Fail* 2003; 5:659–667.
43. Evasio P, Anna C, Fiorella P, et al. Effect of nolomirole on monocrotaline-induced heart failure. *Pharmacol Res* 2004; 49:1–5.
44. Node K, Fujita M, Kitakaze M, et al. Short-term statin therapy improves cardiac function and symptoms in patients with idiopathic dilated cardiomyopathy. *Circulation* 2003; 108:839–843.
45. Fichtlscherer S, Rossig L, Breuer S, et al. Tumor necrosis factor antagonism with etanercept improves systemic endothelial vasoreactivity in patients with advanced heart failure. *Circulation* 2001; 104:3023–3025.
46. Bozkurt B, Torre-Amione G, Warren MS, et al. Results of targeted anti-tumor necrosis factor therapy with etanercept (ENBREL) in patients with advanced heart failure. *Circulation* 2001; 103:1044–1047.
47. Mann DL, McMurray JJ, Packer M, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). *Circulation* 2004; 109(13):1594–1602.
48. Chung ES, Packer M, Lo KH, et al. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor- $\alpha$ , in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. *Circulation* 2003; 107:3133–3140.
49. Torre-Amione G, Sestier F, Radovancevic B, Young J. Effects of a novel immune modulation therapy in patients with advanced chronic heart failure: results of a randomized, controlled, phase II trial. *J Am Coll Cardiol* 2004; 44:1181–1186.
50. Creemers EE, Cleutjens JP, Smits JF, Daemen MJ. Matrix metalloproteinase inhibition after myocardial infarction: a new approach to prevent heart failure? *Circ Res* 2001; 89:201–210.
51. Feldman AM, Li YY, McTiernan CF. Matrix metalloproteinases in pathophysiology and treatment of heart failure. *Lancet* 2001; 357:654–655.
52. Pullicino PM, Halperin JL, Thompson JL. Stroke in patients with heart failure and reduced left ventricular ejection fraction. *Neurology* 2000; 54:288–294.
53. Cleland JG, Findlay I, Jafri S, et al. The Warfarin/Aspirin Study in Heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. *Am Heart J* 2004; 148:157–164.
54. Silverberg DS, Wexler D, Iaina A. The importance of anemia and its correction in the management of severe congestive heart failure. *Eur J Heart Fail* 2002; 4:681–686.
55. Silverberg DS, Wexler D, Blum M, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. *J Am Coll Cardiol* 2000; 35:1737–1744.
56. Al-Ahmad A, Rand WM, Manjunath G, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2001; 38:955–962.
57. Silverberg DS, Wexler D, Sheps D, et al. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. *J Am Coll Cardiol* 2001; 37:1775–1780.
58. Mancini DM, Katz SD, Lang CC, et al. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. *Circulation* 2003; 107:294–299.
59. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. *Am J Cardiol* 2003; 91(6A):2D–8D.
60. Deedwania PC, Singh BN, Ellenbogen K, et al. Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation: observations from the veterans affairs congestive heart failure survival trial of antiarrhythmic therapy (CHF-STAT). The Department of Veterans Affairs CHF-STAT Investigators. *Circulation* 1998; 98(23):2574–2579.
61. Massie BM, Fisher SG, Radford M, et al. Effect of amiodarone on clinical status and left ventricular function in patients with congestive heart failure. CHF-STAT Investigators. *Circulation* 1996; 93:2128–2134.
62. Moller M, Torp-Pedersen CT, Kober L. Dofetilide in patients with congestive heart failure and left ventricular dysfunction: safety aspects and effect on atrial fibrillation. The Danish Investigators of Arrhythmia and Mortality on Dofetilide (DIAMOND) Study Group. *Congest Heart Fail* 2001; 7:146–150.
63. Coats AJ. Exercise training for heart failure: coming of age. *Circulation* 1999; 99:1138–1140.
64. Belardinelli R, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. *Circulation* 1999; 99:1173–1182.
65. Giannuzzi P, Temporelli PL, Corra U, Tavazzi L. Antiremodeling effect of long-term exercise training in patients with stable chronic heart failure: results of the Exercise in Left Ventricular Dysfunction and Chronic Heart Failure (ELVD-CHF) Trial. *Circulation* 2003; 108:554–559.
66. Pina IL, Apstein CS, Balady GJ, et al. Exercise and heart failure: A statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. *Circulation* 2003; 107:1210–1225.