

# Heart Failure With Normal Ejection Fraction: Consideration of Mechanisms Other Than Diastolic Dysfunction

*Travis Bench, MD, Daniel Burkhoff, MD, PhD, John B. O'Connell, MD, Maria Rosa Costanzo, MD, William T. Abraham, MD, Martin St. John Sutton, MD, and Mathew S. Maurer, MD*

---

## Corresponding author

Daniel Burkhoff, MD, PhD  
Division of Cardiology, Columbia University,  
177 Fort Washington Avenue, New York, NY 10032, USA.  
E-mail: db59@columbia.edu

Current Heart Failure Reports 2009, 6:57–64  
Current Medicine Group LLC ISSN 1546-9530  
Copyright © 2009 by Current Medicine Group LLC

More than half of patients with heart failure (HF) have a normal ejection fraction (EF). These patients are typically elderly, are predominantly female, and have a high incidence of multiple comorbid conditions associated with development of ventricular hypertrophy and/or interstitial fibrosis. Thus, the cause of HF has been attributed to diastolic dysfunction. However, the same comorbidities may also impact myocardial systolic, ventricular, vascular, renal, and extracardiovascular properties in ways that can also contribute to symptoms of HF by way of mechanisms not related to diastolic dysfunction. Accordingly, the descriptive term *HF with normal EF* has been suggested as an alternative to the mechanistic term *diastolic HF*. In this article, we review the current understanding of nondiastolic mechanisms that may contribute to the HF with normal EF syndrome to highlight potential pathways for research that may lead to new targets for therapy.

## Introduction

The incidence and prevalence of heart failure (HF) continue to increase and represent a growing public health problem. Epidemiologic studies have demonstrated that more than half of patients with HF have a preserved or normal ejection fraction (EF) [1,2]. These patients are typically elderly, are predominantly female, and have a high incidence of multiple comorbid conditions, including hypertension, dia-

betes, coronary artery disease, obesity, renal dysfunction, and anemia. These factors are frequently associated with the development of ventricular hypertrophy and/or interstitial fibrosis. The cause of HF in these patients has generally been attributed to impaired myocardial relaxation and has traditionally been described as *diastolic HF* [3–5]. However, this designation implies that a single pathophysiologic pathway explains what has become increasingly recognized as a syndrome comprising a heterogeneous group of patients. The comorbidities previously mentioned may also impact myocardial systolic, ventricular, vascular, renal, and extracardiovascular properties in ways that can also contribute to symptoms of HF by way of mechanisms not related to diastolic ventricular properties. Accordingly, the descriptive term *HF with normal EF* (HFNEF) has been suggested as an alternative to the mechanistic term *diastolic HF* [6,7]. Recognizing the success achieved in the treatment of systolic HF (SHF) by addressing neurohormonal and renal mechanisms, new therapies for HFNEF may be achieved by a similar shift in attention away from the heart. It is plausible that addressing nondiastolic mechanisms of HFNEF may provide further answers and, more importantly, lead to more therapeutic advances. This article reviews the current understanding of nondiastolic mechanisms that may contribute to the HFNEF syndrome to highlight potential avenues of research that may lead to new targets for therapy.

## Current Paradigms and Clinical Perspective HFNEF: a distinct clinical syndrome

Although many aspects of the initial clinical presentation of patients with HFNEF may be similar to those with SHF [8], it is recognized that these are different populations in terms of epidemiologic features and echocardiographic characteristics. For example, among outpatient populations, both groups exhibit markedly reduced exercise capacity, neuroendocrine activation, and poor quality of

life. However, it was shown in the ADHERE database [1•] that among 52,187 patients admitted to the hospital for acute decompensated HF, those with a normal EF ( $n = 26,322$ ) were more likely to be older ( $73.9 \pm 13.2$  years vs  $69.8 \pm 14.4$  years;  $P < 0.0001$ ), female (62% vs 40%;  $P < 0.0001$ ), and were less likely to have coronary artery disease (50% vs 59%;  $P < 0.0001$ ) or a previous myocardial infarction (24% vs 36%;  $P < 0.0001$ ). The normal EF group was more likely to have comorbid conditions, most notably hypertension (77% vs 69%;  $P < 0.0001$ ) and diabetes (45% vs 40%;  $P < 0.0001$ ) [1•]. The ADHERE registry [1•] (consistent with results of prior studies) also revealed a lower overall mortality in HFNEF patients compared with SHF patients (2.8% vs 3.9%; odds ratio [OR], 0.86;  $P = 0.005$ ), whereas symptom burden, duration of intensive care unit stay, overall length of hospital stay, and long-term mortality were similar between the two groups. Additionally, although similar data in a separate cohort of patients admitted for exacerbation of HF revealed lower longer-term mortality in HFNEF compared with SHF patients (29% vs 32% at 1 year and 65% vs 68% at 5 years; unadjusted hazard ratio [HR], 0.96; 95% CI, 0.93–1.00), secular trends revealed little improvement in clinical outcome compared with those seen in patients with SHF [9•]. Collectively, these studies highlight the changing epidemiology of HF occurring with increasing age of the population and the inadequacy of current therapeutic options for HFNEF. Thus, although this clinical syndrome is recognized as an increasingly common problem, recent therapeutic advances made in the treatment of SHF have not translated into improved overall morbidity or improved survival for those found to have a normal EF. Furthermore, until recently, this subgroup of patients had been excluded from nearly all large clinical trials of HF.

### Limited pathophysiologic understanding

One factor contributing to the lack of progress in improving outcomes is the limited understanding of the pathophysiology of HFNEF. Initial mechanistic studies concentrated on the role of ischemia and hypertrophy in decreasing left ventricular (LV) compliance and elevating LV end-diastolic pressure, which suggested a prominent role for abnormal calcium handling [10]. Subsequently, focus on other myocardial mechanisms predominated, including investigations into cardiomyocyte abnormalities (ie, calcium homeostasis, cytoskeletal components, and cellular energetics) and the role of the extracellular matrix [11].

Led by these early basic studies, much attention has been placed on studying features of the end-diastolic pressure-volume relationship (EDPVR), which provides a direct measure of ventricular compliance and capacitance. Although several well-studied cohorts have delineated the existence of abnormalities in the EDPVR [4,12], other studies have not confirmed these findings for all patient subgroups [13,14•].

In the clinical arena, recent efforts have focused on Doppler echocardiographic techniques, which provide a

noninvasive method of characterizing certain aspects of the dynamics of ventricular relaxation to aid in identifying patients with HFNEF and for suggesting mechanisms of disease. Studies of this type have promulgated the view that because these patients have clinical evidence of HF without measurable systolic dysfunction but do have measurable abnormalities of relaxation, the etiologic problem must be diastolic in nature. Indeed, newer criteria have been proposed for defining HFNEF, which are heavily reliant upon abnormalities in the patterns of blood flow and tissue velocities measured by Doppler echocardiography [15]. However, such abnormalities measured during diastole are not well linked to the underlying pathophysiologic processes [16] and are not specific to individuals with HFNEF; they are frequently found in patients with SHF and patients without HF. Despite increasing reliance on these measures, several investigators have argued that demonstration of echocardiographic Doppler evidence of diastolic dysfunction should not be required to diagnose HFNEF [16,17].

In contrast to the standard dichotomized view of HF in which the cause is a predominant abnormality of either systolic or diastolic function, some have suggested that the phenotypic expression of HF occurs on a continuum, with underlying myocardial dysfunction present in the early stages of the syndrome when diastolic abnormalities predominate [18,19]. Supporting data come from several studies showing that impaired regional systolic velocities—as assessed by tissue Doppler study of myocardial velocities and depressed systolic mitral annular amplitudes—are apparent in patients with HFNEF compared with normal controls [20]. Notably, these changes are not as pronounced as those seen in patients with a reduced EF. It is proposed that these initial abnormalities are compensated for by ventricular hypertrophy and neurohormonal activation, creating a hypercontractile LV state with abnormal relaxation, which causes resistance to LV filling. Over time, these initial compensatory reactions progress, resulting in a phenotype characteristic of SHF. Accordingly, in this paradigm, initial preservation of left ventricular ejection fraction (LVEF) reflects compensation on a hemodynamic level for underlying myocardial dysfunction. This concept is supported by the results of at least one animal study in which HFNEF was induced by small amounts of myocardial infarction [21]. Compensatory neurohormonal activation and ventricular hypertrophy are proposed to lead to maladaptive remodeling, and early changes in LV compliance are followed by late hemodynamic pump failure, resulting in classic SHF [19]. However, data on the progression of HFNEF to overt SHF are lacking and have been shown to occur rarely over the course of time subject to investigation [22]. Thus, many abnormalities can be identified in myocardial and ventricular properties of patients with HFNEF, and, despite several proposed theories of disease, there is no clear, widely accepted, unifying theory explaining the pathophysiology of HFNEF in all patients presenting with this syndrome.

## Available Clinical Data on Therapeutics

Successes achieved in therapeutics for SHF have not translated into improved outcomes for those with HFNEF. To date, only a few studies have been published in which HFNEF patients have been included, and these primarily have employed the standard therapies shown to be beneficial for patients with SHF, including  $\beta$ -blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, diuretics, vasodilators, digoxin, and aldosterone antagonists.

Investigators in the SENIORS study looked at the effect of nebivolol on mortality and hospitalization in elderly patients with HF [23]. More than 2000 patients (35% of the study cohort who had EF > 35%) with a history of HF were randomly assigned to nebivolol or placebo. The primary outcome (all-cause mortality or cardiovascular hospital admission) occurred in 31% of those on nebivolol compared with 35% on placebo (HR, 0.86; 95% CI, 0.74–0.99;  $P = 0.039$ ). Interestingly, this effect was shown to be independent of EF.

The PEP-CHF Investigators sought to determine the effect of the angiotensin-converting enzyme inhibitor perindopril on all-cause mortality and HF-related hospitalization in elderly patients with diastolic dysfunction [24]. Although underpowered, reductions in the primary outcome (HR, 0.692; 95% CI, 0.474–1.010;  $P = 0.055$ ) and hospitalization for HF (HR, 0.628; 95% CI, 0.408–0.966;  $P = 0.033$ ) were observed in those assigned to perindopril. The CHARM-Preserved trial [25] looked at patients with chronic HF (CHF) and a preserved LVEF to study the effects of angiotensin receptor blockade (candesartan) on cardiovascular death or hospital admission for CHF. The results suggest that although cardiovascular death did not differ between the two groups, candesartan had a moderate impact compared with placebo (230 vs 279;  $P = 0.017$ ) in preventing admissions for CHF among patients who had HF and LVEF of more than 40%. Of note, a recently completed small clinical trial of 150 patients with HFNEF (LVEF > 45%) randomly assigned to diuretics alone, diuretics plus irbesartan, or diuretics plus ramipril failed to demonstrate any additional benefit of angiotensin-converting enzyme/angiotensin receptor blocker when added to diuretics in terms of quality of life, recurrent hospitalizations, or ventricular structure [26].

The Digitalis Investigation Group evaluated the effects of digoxin on all-cause mortality and HF hospitalization in patients with HF regardless of EF. Those with LVEF of more than 45% ( $n = 988$ ) were enrolled in an ancillary study conducted parallel to the main trial. During follow-up, digoxin had no effect on all-cause mortality or cardiovascular hospitalization (HR, 0.82; 95% CI, 0.63–1.07;  $P = 0.136$ ). Although the use of digoxin was associated with a trend toward a reduction in HF-related hospitalizations (HR, 0.79; 95% CI, 0.59–1.04;  $P = 0.094$ ), there was a trend toward an increase in hospitalizations for unstable angina (HR, 1.37; 95% CI, 0.99–1.91;  $P = 0.061$ ). It was concluded that digoxin had

no effect on cardiovascular mortality or cardiovascular hospitalizations in ambulatory patients with CHF (mild to moderate) and an LVEF of more than 45% [27].

Ongoing studies include the TOPCAT trial [28], which is evaluating the aldosterone antagonist spironolactone in 4500 adults with HF and LVEF  $\geq 45\%$ , and the I-PRESERVE trial [29], which is evaluating the benefits of the angiotensin receptor blocker irbesartan in reducing mortality and cardiovascular hospitalization. These trials will test whether segregation of patients with HF based on EF (at least in terms of treatment) is warranted. Standard HF therapeutics have not yet demonstrated dramatic benefits for the population with HFNEF, suggesting that alternative targets for treatment need to be identified. In addition, information obtained from these studies and others shows that although it is clear that patient comorbid conditions need to be aggressively treated [30•], it needs to be clarified whether such treatment improves symptoms or outcomes related to HF. Importantly, it is recognized that many patients with HFNEF do not die directly from HF but from other cardiovascular and noncardiovascular causes.

## Nondiastolic Mechanisms

Controversy exists regarding the mechanisms of disease, and it has been suggested that diastolic dysfunction is not the underlying cause in all patients with HFNEF. It has also been suggested that (in contrast to SHF, in which a common underlying pathophysiology applies to most patients) HFNEF may result from different underlying pathophysiologic mechanisms [31]. Therefore, it is pertinent to review factors other than diastolic dysfunction that may contribute to the development of an HF state in the setting of normal LV pump function. In particular, the important clinical findings that need to be explained in this patient population include high resting pulmonary capillary pressures, effort intolerance, and a propensity for development of pulmonary edema.

### Volume overload

HF with either reduced or normal EF is a sodium-sensitive condition in which expansion of both intravascular (eg, plasma volume) and extravascular fluid volume is a hallmark. It is well documented that patients with HFNEF are more likely to have multiple comorbidities that may contribute to volume overload, including renovascular disease, obesity, sleep apnea, and anemia. Specific insights into the role of volume overload have been obtained through animal models of HFNEF [32], particularly those that employ the Dahl salt-sensitive rat, which develop severe hypertension and HF with a normal or preserved EF. In this model, the development of HF is accompanied not by an upward shifted EDPVR but by a worsening of renal function and evidence of volume expansion.

Several lines of evidence point to a chronic volume-loaded state in HFNEF patients. We originally identified that in a group of HFNEF patients with long-standing

hypertension, heart size was mildly increased compared with normal subjects without HF [13,14,33]. This contrasted with the subgroup of HFNEF patients who had idiopathic hypertrophic cardiomyopathies or infiltrative myocardial diseases and in whom heart size was smaller than normal. In this same study [13] it was shown that plasma volumes of hypertensive HFNEF patients were increased by an average of 16% compared with normal controls despite daily diuretic use. Similarly, core laboratory echocardiographic data from a recent phase 2 drug study confirmed that patients with HFNEF have markedly elevated end-diastolic volumes ( $145 \pm 40$  mL) compared with values of normal subjects from the same control laboratory ( $67 \pm 12$  mL) [34].

The primary role of volume expansion is further highlighted by data obtained from chronic indwelling intracardiac pressure sensors, such as the Chronicle device (Medtronic, Inc., Minneapolis, MN). Data obtained from patients with HFNEF have demonstrated that peak right ventricular pressure and estimated pulmonary diastolic pressures slowly increase in the days to weeks preceding an acute HF decompensation episode, suggesting a central role of gradually increasing plasma volume [35]. Complementary findings are derived from the UNLOAD trial [36] of ultrafiltration for inpatient treatment of HF exacerbation. Of the 186 patients enrolled in the study, 45 (24%) had a normal EF. Half of these patients received ultrafiltration, whereas the other half received standard care with intravenous diuretics. In the HFNEF patients, the amount of fluid removed within 48 hours was similar for ultrafiltration and diuretic groups, amounting to approximately 5 L. There were significant improvements in both groups in patient grading of the severity of dyspnea, and B-type natriuretic peptide decreased in the ultrafiltration group. No patients in the ultrafiltration arm experienced hypotension during this treatment compared with 16% in the standard care arm. Most importantly, such changes were not associated with evidence of worsening end-organ perfusion, particularly renal dysfunction. Thus, volume expansion precedes symptoms, volume removal alleviates symptoms without inducing hypotension or end-organ dysfunction, and it is not necessary to invoke changes in diastolic function to explain any of these findings.

At 90 days, HFNEF patients treated with ultrafiltration had hospitalization rates similar to those of patients given intravenous diuretics and higher than those of ultrafiltration-treated patients with systolic dysfunction. These findings suggest that patients with HFNEF are at a higher risk of recurrence of fluid overload, regardless of the modality employed to treat congestion. It can be hypothesized that HFNEF patients have higher central venous pressures, which, over time, are associated with a greater reduction of glomerular filtration rate and greater neuroendocrine activation.

Acute pulmonary edema is one of the most common clinical manifestations of HFNEF, and diuretics remain the mainstay of therapy for such patients to affect a

therapeutic reduction in preload volume. In the setting of HFNEF, it is believed that these patients are vulnerable to the hypotensive effects of diuretics and other preload-reducing agents because, with the presumed reduced diastolic compliance, patients are highly preload sensitive. However, available data do not support this premise. During aggressive treatment of acute pulmonary edema in HFNEF patients [37], blood pressure declines, but generally not to systolic blood pressures of less than 100 mm Hg [38]. This is consistent with the data presented from the UNLOAD trial.

Given the primary role of plasma volume expansion in contributing to the clinical manifestations of HFNEF, it is reasonable as in SHF that appropriate attention to diuretic therapy and dietary salt restrictions is paramount to the care of HFNEF patients. Aggressive approaches to monitoring fluid status with indwelling pressure sensors may be warranted in some patients with disease that is difficult to manage. Additionally, given the renin-angiotensin-aldosterone system activation that occurs with chronic diuretic therapy and its potentially deleterious effects on glomerular filtration, exploration of novel approaches, such as adenosine receptor antagonists [39] to achieve and maintain a euvolemic state while preserving renal function could provide important benefits to this population.

#### **Venoconstriction/volume redistribution**

Approximately 85% of blood volume resides in the venous side of the circulation. Classic Guytonian physiology has demonstrated that small alterations in venous tone and capacitance (particularly in the splanchnic bed) significantly impact the distribution of intravascular volume. Such alterations have been shown to be an important determinant of LV end-diastolic filling pressures. In SHF, pharmacologic venodilation and preload reduction have been shown to create greater declines in LV end-diastolic pressure than are achieved with arterial dilation. Although data regarding the role of venous tone and volume distribution are currently lacking for patients with HFNEF, the most important drugs used when these patients present with acute pulmonary edema are venodilators and diuretics, indicating that directly addressing total volume status and venous tone address important pathophysiologic mechanisms, at least in the acute setting. Indeed, one seminal article [37] demonstrated significant reductions in blood pressure after treatment for acute pulmonary edema in HFNEF without concomitant changes in ventricular volume or EF; we speculate that improvements relate at least partly to reductions in autonomic tone and the resulting increase in venous capacitance.

#### **Ventricular vascular coupling abnormalities**

Normal human aging is characterized by increased conduit artery stiffening with concomitant ventricular stiffening, which has been proposed as an underlying substrate for the development of HFNEF. Kawaguchi et al. [40] were the first to demonstrate that patients with HFNEF

had alterations of ventricular vascular coupling beyond age-matched hypertensive patients and such abnormalities could explain the lability of systolic blood pressure observed in these patients [41]. Exercise intolerance also has been associated with increased aortic stiffness and reduced aortic distensibility in HFNEF patients [42]; however, a mechanistic link has not been established. Supporting data from an animal model employing renal artery banding led to hypertension, decreased arterial elastance, and increased LV mass and interstitial fibrosis [43]. These changes tend to exacerbate load-dependent impairment of relaxation and are hypothesized to contribute to increased filling pressures with hypertensive episodes. In patients with isolated systolic hypertension [44], the use of alagebrium chloride to degrade end products of advanced glycation resulted in enhanced peripheral artery endothelial function as assessed by flow-mediated arterial dilatation (FMAD) in the superficial femoral artery ( $4.64\% \pm 1.07\%$  vs  $7.10\% \pm 1.13\%$ ;  $P = 0.047$ ). This was observed and associated with significantly improved central arterial impedance, reflected by a 37% decrease in the augmentation index ( $0.20\% \pm 0.05\%$  after treatment vs  $0.31\% \pm 0.04\%$  at baseline;  $P < 0.007$ ) and a 42% reduction in augmentation pressures ( $9.6 \pm 2.6$  mm Hg vs  $16.5 \pm 2.8$  mm Hg;  $P < 0.0008$ ) measured in the carotid artery. Through recently validated single-beat measures estimating EDPVR and ventricular capacitance and arterial elastance, Redfield et al. [45] showed that advancing age and female gender were associated with increases in vascular and ventricular systolic and diastolic stiffness. As a result, there has been renewed interest in the development and evaluation of new and existing therapies that can target these mechanisms.

### Chronotropic incompetence

Peak oxygen consumption ( $\text{Vo}_2$ ) depends on arteriovenous oxygen difference and cardiac output, with the latter determined by stroke volume and heart rate. Impaired stroke volume and heart rate responses have been noted to contribute to effort intolerance in patients with HF. Reduced heart rate responsiveness or chronotropic incompetence is associated with ischemic heart disease, LV dilatation, myocardial hypertrophy, and chronic HF (primarily SHF). Chronotropic incompetence has also been shown to be a predictor of mortality. However, the role of  $\text{Vo}_2$  measurements in HFNEF has only recently been characterized. Brubaker et al. [46] reported an increased prevalence of chronotropic incompetence in elderly HF patients compared with normal older controls without significant differences between HFNEF and SHF patients. Among patients with chronotropic incompetence, peak work load ( $40.9 \pm 5.0$  W vs  $61.3 \pm 2.7$  W;  $P < 0.05$ ) and peak  $\text{Vo}_2$  ( $12.4 \pm 0.8$  mL/kg<sup>1</sup>/min<sup>1</sup> vs  $14.6 \pm 0.4$  mL/kg<sup>1</sup>/min<sup>1</sup>;  $P = 0.01$ ) were lower than in patients without chronotropic incompetence, suggesting that chronotropic incompetence may have a significant impact on exercise tolerance in these patients. A recent

study demonstrated that chronotropic incompetence in HFNEF patients may be attributable to autonomic dysfunction [47]. Borlaug et al. [47] compared 17 HFNEF patients with 19 matched control patients without HF who underwent maximal-effort upright cycle ergometry with radionuclide ventriculography to determine rest and exercise cardiovascular function. They observed a blunted increase in heart rate in HFNEF patients ( $14.1 \pm 10.3$  bpm vs  $24.9 \pm 12.6$  bpm;  $P = 0.015$ ; 20.5% vs 36.3% increase;  $P = 0.007$ ). Moreover, the rate of heart rate decline after exercise was substantially slower in HFNEF patients than in controls. Because postexercise heart rate deceleration is thought to be a measure of autonomic function, these authors further studied patient heart rate responses to an increase in blood pressure during phase IV of a Valsalva maneuver. In response to an approximately 30 mm Hg rise in blood pressure, heart rate decline was impaired in HFNEF patients ( $3.7 \pm 2.8$  ms/mm Hg vs  $6.5 \pm 3.6$  ms/mm Hg;  $P < 0.05$ ), which supported a role of autonomic dysfunction. These data raised concerns about the use of  $\beta$ -blockers as a treatment option in HFNEF patients with impaired chronotropic and/or vasodilatory responses. Confirmation of these findings in larger prospectively collected series would be a logical next step. If chronotropic incompetence is shown to be prevalent, identifiable, reproducible, and associated with significant impairment in functional capacity in HFNEF, it has been proposed that cardiac pacing may have therapeutic benefits. However, the potential benefits of pacing must be balanced by the potential effect of higher heart rates to increase filling pressures because of incomplete ventricular relaxation [48]. Clearly, careful mechanistic studies that attempt to tease out beneficial and potential detrimental hemodynamic effects are necessary.

### Endothelial dysfunction

The vascular endothelium is considered the key regulator of vascular tone, inflammation processes, and thrombotic mechanisms. Impaired endothelial function is recognized as a first step in the atherogenic process and is associated with hypertension and HF. Studies have suggested that attenuated endothelial function can be seen early in the course of HF and leads to decreased organ perfusion, impaired exercise tolerance, and disease progression. Although endothelial dysfunction is known to be associated with disease severity, functional incapacity, and decompensation in patients with SHF, data relating to this mechanism as an etiologic factor in HFNEF are only beginning to emerge. Hundley et al. [49] conducted a study in 30 patients (11 normal, 9 with HFNEF, and 10 with SHF) who underwent a cardiovascular magnetic resonance assessment of FMAD followed by symptom-limited exercise testing with expired gas analysis. Severe reductions in exercise capacity and peak  $\text{Vo}_2$  were observed in patients with SHF ( $12 \pm 2$  mL/kg/min) and HFNEF ( $13 \pm 1$  mL/kg/min) when compared with normal controls ( $20 \pm 3$  mL/kg/min), but when compared with baseline, changes in leg FMAD were sub-

stantially reduced in patients with SHF ( $0.9 \pm 0.1 \text{ mm}^2$ ) but not in those with HFNEF ( $3.1 \pm 0.4 \text{ mm}^2$ ) or normal controls ( $3.9 \pm 0.5 \text{ mm}^2$ ). After adjusting for a wide range of variables, differences in FMAD between SHF and HFNEF patients widened ( $P < 0.05$ ), whereas values for those with HFNEF remained similar to normal controls. Although not suggesting a major role for endothelial dysfunction as a contributor to exercise intolerance in patients with HFNEF, other studies propose that the increased proximal aortic stiffness previously associated with reduced exercise capacity in HFNEF patients [42] may be pathophysiologically associated with impaired nitric oxide release from dysfunctional endothelium.

## Conclusions

A broad summary of disease mechanisms and associated factors that can lead to HF in the setting of normal EF has been provided above and also in a prior report [31]. It is evident that in patients with certain forms of intrinsic myocardial disease that diastolic dysfunction is the primary factor leading to HF, and the term *diastolic HF* is fully appropriate. However, there are many extracardiac pathophysiologic abnormalities identified in patients without such myocardial disease that may contribute to the development of HFNEF. Whether the degree to which such factors are primary mechanisms of disease or simply secondary changes in response to the HF state have not been clarified. In view of the diverse and heterogeneous makeup of the HFNEF population, we have proposed that HFNEF is not necessarily a single pathophysiologic clinical entity [6,13,14,31].

With the lack of randomized clinical studies showing benefit from any particular therapy to guide clinical decision making, there is an urgent need for new clinical investigations in this population [50]. Indeed, several clinical trials of pharmacologic agents that have become the standard of care for patients with SHF have been completed or are underway. We propose that if the broad HFNEF population is composed of patients with different underlying diseases, results of such clinical trials could be confounded by the heterogeneous nature of the patients enrolled. Therefore, identification of potentially pathophysiologically distinct subgroups of HFNEF patients could advance clinical research by suggesting rational bases for selecting new interventions.

## Clinical Trial Acronyms

ADHERE—Acute Decompensated Heart Failure National Registry; CHARM-Preserved—Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; I-PRESERVE—Irbesartan in Heart Failure With Preserved Ejection Fraction; PEP-CHF—Perindopril for Elderly People With Chronic Heart Failure; SENIORS—Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors; TOPCAT—Treatment of

Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist; UNLOAD—Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure.

## Disclosures

No conflicts of interest relevant to this article were reported.

## References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Yancy CW, Lopatin M, Stevenson LW, et al.: **Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database.** *J Am Coll Cardiol* 2006, 47:76–84. [Published erratum appears in *J Am Coll Cardiol* 2006, 47:1502.]

This is a subgroup analysis of patients enrolled in the ADHERE study who had preserved LV function. Clinical characteristics of these patients were compared with those of patients with low EF, and it was shown that the HFNEF patients represent a distinct patient population in whom clinical outcomes are particularly worrisome.

2. Kitzman DW, Daniel KR: **Diastolic heart failure in the elderly.** *Clin Geriatr Med* 2007, 23:83–106.
3. Aurigemma GP: **Diastolic heart failure—a common and lethal condition by any name.** *N Engl J Med* 2006, 355:308–310.
4. Zile MR, Baicu CF, Gaasch WH: **Diastolic heart failure—abnormalities in active relaxation and passive stiffness of the left ventricle.** *N Engl J Med* 2004, 350:1953–1959.
5. Redfield MM: **Understanding “diastolic” heart failure.** *N Engl J Med* 2004, 350:1930–1931.
6. Burkhoff D, Maurer MS, Packer M: **Heart failure with a normal ejection fraction: is it really a disorder of diastolic function?** *Circulation* 2003, 107:656–658.
7. **HFSA 2006 comprehensive heart failure practice guidelines: evaluation and management of patients with heart failure and preserved left ventricular ejection fraction** [no authors listed]. *J Card Fail* 2007, 12:e80–e85.
8. Kitzman DW, Little WC, Brubaker PH, et al.: **Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure.** *JAMA* 2002, 288:2144–2150.
9. Owan TE, Hodge DO, Herges RM, et al.: **Trends in prevalence and outcome of heart failure with preserved ejection fraction.** *N Engl J Med* 2006, 355:251–259.

This study provided a comprehensive analysis of characteristics and prognoses in HFNEF and its trends over time. Compared with patients with low-EF HF, HFNEF is accounting for a greater proportion of all cases of HF. Additionally, although prognosis has improved for low-EF HF, prognosis has not improved over the past decades for HFNEF.

10. Grossman W: **Diastolic dysfunction in congestive heart failure.** *N Engl J Med* 1991, 325:1557–1564.
11. Zile MR, Brutsaert DL: **New concepts in diastolic dysfunction and diastolic heart failure: Part II: causal mechanisms and treatment.** *Circulation* 2002, 105:1503–1508.
12. Lam CS, Roger VL, Rodeheffer RJ, et al.: **Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota.** *Circulation* 2007, 115:1982–1990. [Published erratum appears in *Circulation* 2007, 115:e535.]

13. Maurer MS, King DL, El-Khoury RL, et al.: Left heart failure with a normal ejection fraction: identification of different pathophysiologic mechanisms. *J Card Fail* 2005, 11:177–187.
  14. Maurer MS, Burkhoff D, Fried LP, et al.: Ventricular structure and function in hypertensive participants with heart failure and a normal ejection fraction: the Cardiovascular Health Study. *J Am Coll Cardiol* 2007, 49:972–981.
- This study provided confirmatory data for the observations of Maurer et al. [13] showing that heart size is not small in all patients with HFNEF, suggesting that diastolic dysfunction is not the mechanism in all patients. This study drew from a relatively large number of patients enrolled in a National Institutes of Health (NIH)–sponsored Cardiovascular Health Study with echocardiograms analyzed in a core laboratory.
15. Paulus WJ, Tschope C, Sanderson JE, et al.: How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007, 28:2539–2550.
  16. Maurer MS, Spevack D, Burkhoff D, Kronzon I: Diastolic dysfunction: can it be diagnosed by Doppler echocardiography? *J Am Coll Cardiol* 2004, 44:1543–1549.
  17. Zile MR, Gaasch WH, Carroll JD, et al.: Heart failure with a normal ejection fraction: is measurement of diastolic function necessary to make the diagnosis of diastolic heart failure? *Circulation* 2001, 104:779–782.
  18. De Keulenaer GW, Brutsaert DL: Diastolic heart failure: a separate disease or selection bias? *Prog Cardiovasc Dis* 2007, 49:275–283.
  19. De Keulenaer GW, Brutsaert DL: Systolic and diastolic heart failure: different phenotypes of the same disease? *Eur J Heart Fail* 2007, 9:136–143.
  20. Yu CM, Sanderson JE, Marwick TH, Oh JK: Tissue Doppler imaging a new prognosticator for cardiovascular diseases. *J Am Coll Cardiol* 2007, 49:1903–1914.
  21. He KL, Dickstein M, Sabbah HN, et al.: Mechanisms of heart failure with well preserved ejection fraction in dogs following limited coronary microembolization. *Cardiovasc Res* 2004, 64:72–83.
  22. Berenji K, Drazner MH, Rothermel BA, Hill JA: Does load-induced ventricular hypertrophy progress to systolic heart failure? *Am J Physiol Heart Circ Physiol* 2005, 289:H8–H16.
  23. McMurray J: Making sense of SENIORS. *Eur Heart J* 2005, 26:203–206.
  24. Cleland JG, Tendera M, Adamus J, et al.: The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006, 27:2338–2345.
  25. Yusuf S, Pfeffer MA, Swedberg K, et al.: Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003, 362:777–781.
  26. Yip GW, Wang M, Wang T, et al.: The Hong Kong diastolic heart failure study: a randomised controlled trial of diuretics, irbesartan and ramipril on quality of life, exercise capacity, left ventricular global and regional function in heart failure with a normal ejection fraction. *Heart* 2008, 94:573–580.
  27. Ahmed A, Rich MW, Fleg JL, et al.: Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. *Circulation* 2006, 114:397–403.
  28. ClinicalTrials.gov: Aldosterone antagonist therapy for adults with heart failure and preserved systolic function (TOPCAT). Available at <http://www.clinicaltrials.gov/ct2/show/NCT00094302?term=NCT00094302&rank=1>. Accessed January 2009.
  29. McMurray JJ, Carson PE, Komajda M, et al.: Heart failure with preserved ejection fraction: clinical characteristics of 4133 patients enrolled in the I-PRESERVE trial. *Eur J Heart Fail* 2008, 10:149–156.
  30. Shah SJ, Gheorghiadu M: Heart failure with preserved ejection fraction: treat now by treating comorbidities. *JAMA* 2008, 300:431–433.
- A comprehensive overview of prior studies of patients with HFNEF. The case is made that most patients with HFNEF die from non-HF-related problems, and the focus should be on treating comorbid conditions.
31. Maurer MS, Kronzon I, Burkhoff D: Ventricular pump function in heart failure with normal ejection fraction: insights from pressure-volume measurements. *Prog Cardiovasc Dis* 2006, 49:182–195.
  32. Klotz S, Hay I, Zhang G, et al.: Development of heart failure in chronic hypertensive Dahl rats: focus on heart failure with preserved ejection fraction. *Hypertension* 2006, 47:901–911.
  33. Maurer MS, El Khoury Rumbarger L, King DL: Ventricular volume and length in hypertensive diastolic heart failure. *J Am Soc Echocardiogr* 2005, 18:1051–1057.
  34. Farr MJ, Lang CC, Lamanca JJ, et al.: Cardiopulmonary exercise variables in diastolic versus systolic heart failure. *Am J Cardiol* 2008, 102:203–206.
  35. Zile MR, Bennett TD, St John Sutton M, et al.: Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights obtained from continuous monitoring of intracardiac pressures. *Circulation* 2008, 118:1433–1441.
- A subgroup analysis of patients with HF monitored continually with an indwelling right ventricular pressure monitor. The data show that right-sided pressures rise gradually in the days prior to the clinical presentation of an HF exacerbation requiring hospitalization; thus, gradual volume overload is an important component of the pathogenesis of the HF state.
36. Costanzo MR, Guglin ME, Saltzberg MT, et al.: Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol* 2007, 49:675–683. [Published erratum appears in *J Am Coll Cardiol* 2007, 49:1136.]
  37. Gandhi SK, Powers JC, Nomeir AM, et al.: The pathogenesis of acute pulmonary edema associated with hypertension. *N Engl J Med* 2001, 344:17–22.
  38. Little WC: Hypertensive pulmonary oedema is due to diastolic dysfunction. *Eur Heart J* 2001, 22:1961–1964.
  39. Gottlieb SS: Adenosine A1 antagonists and the cardiorenal syndrome. *Curr Heart Fail Rep* 2008, 5:105–109.
  40. Kawaguchi M, Hay I, Fetics B, Kass DA: Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. *Circulation* 2003, 107:714–720.
  41. Chen CH, Nakayama M, Nevo E, et al.: Coupled systolic-ventricular and vascular stiffening with age: implications for pressure regulation and cardiac reserve in the elderly. *J Am Coll Cardiol* 1998, 32:1221–1227.
  42. Hundley WG, Kitzman DW, Morgan TM, et al.: Cardiac cycle-dependent changes in aortic area and distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance. *J Am Coll Cardiol* 2001, 38:796–802.
  43. Munagala VK, Hart CY, Burnett JC Jr, et al.: Ventricular structure and function in aged dogs with renal hypertension: a model of experimental diastolic heart failure. *Circulation* 2005, 111:1128–1135.
  44. Zieman SJ, Melenovsky V, Clattenburg L, et al.: Advanced glycation endproduct crosslink breaker (alagebrium) improves endothelial function in patients with isolated systolic hypertension. *J Hypertens* 2007, 25:577–583.
  45. Redfield MM, Jacobsen SJ, Borlaug BA, et al.: Age- and gender-related ventricular-vascular stiffening: a community-based study. *Circulation* 2005, 112:2254–2262.
  46. Brubaker PH, Joo KC, Stewart KP, et al.: Chronotropic incompetence and its contribution to exercise intolerance in older heart failure patients. *J Cardiopulm Rehabil* 2006, 26:86–89.

47. Borlaug BA, Melenovsky V, Russell SD, et al.: **Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction.** *Circulation* 2006, 114:2138–2147.
48. Hay I, Rich J, Ferber P, et al.: **Role of impaired myocardial relaxation in the production of elevated left ventricular filling pressure.** *Am J Physiol Heart Circ Physiol* 2005, 288:H1203–H1208.
49. Hundley WG, Bayram E, Hamilton CA, et al.: **Leg flow-mediated arterial dilation in elderly patients with heart failure and normal left ventricular ejection fraction.** *Am J Physiol Heart Circ Physiol* 2007, 292:H1427–H1434.
50. Chatterjee K, Massie B: **Systolic and diastolic heart failure: differences and similarities.** *J Card Fail* 2007, 13:569–576.