

STATE-OF-THE-ART PAPER

# Heart Failure With Normal Left Ventricular Ejection Fraction

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It is estimated that approximately 50% of the heart failure population has a normal left ventricular ejection fraction, a complex broadly referred to as heart failure with normal left ventricular ejection fraction (HFNEF). While these patients have been considered in epidemiologic studies and clinical trials to represent a single pool of patients, limited more detailed studies indicate that HFNEF patients are a very heterogeneous group, with a number of key pathophysiologic mechanisms. This review summarizes and critically analyzes available data on the pathophysiology of HFNEF, placing it into context with a recently developed diagnostic algorithm. We evaluate the utility of commonly applied echocardiographic measures and biomarkers and integrate mechanistic observations into potential future therapeutic directions. (J Am Coll Cardiol 2009;53:905-18) © 2009 by the American College of Cardiology Foundation

It is now widely acknowledged that the clinical features of heart failure (HF) can occur in patients with normal left ventricular ejection fraction (LVEF) (1-3), currently referred to as heart failure with normal ejection fraction (HFNEF). In some cases the presentation can be as dramatic as that in patients with low LVEF, for example in patients admitted with acute pulmonary edema (2). In conjunction with their clinical profile, stable HFNEF patients have been shown to display a similar physiologic and neurohormonal phenotype to patients with HF and reduced LVEF, including impaired peak oxygen consumption, and elevated circulating neurohormones, including B-type natriuretic peptide (BNP) and norepinephrine (4). Taken together, it is now generally accepted that an entity such as HFNEF exists (5). However, there is still much controversy (6-8) about the underlying pathophysiology. This high level of uncertainty is best reflected in the recent retreat from physiologic descriptors such as "diastolic HF" (9) to the much more descriptive term "HFNEF" (10). The aim of this review is to integrate clinical and pathophysiologic aspects of HFNEF, with a view to providing guidance in relation to the diagnosis and management of HFNEF.

## Epidemiology

Data from the Mayo Clinic registry (11) and other studies (12) indicate that approximately 50% of patients with HF have a normal or near normal LVEF or fractional shorten-

ing, although a variety of cutoffs for normal values have been applied (12). Compared with patients with HF and reduced LVEF, individuals with HFNEF are typically older and more likely to be women, together with a higher likelihood of hypertension (prevalence up to 88% [13]), obesity (prevalence of body mass index  $>30$  kg/m<sup>2</sup> typically approximately 40% [11,13]), renal failure, anemia, and atrial fibrillation (11). In conjunction, the prevalence of diabetes (approximately 30% [11,13]) and coronary artery disease (approximately 40% to 50% [11-13]) are substantial, being similar to that in HF patients with impaired LVEF (11). Consistent with the considerable symptomatic burden associated with HFNEF, the prognosis of patients with HFNEF also appears to be only marginally better than that of patients with HF and reduced LVEF (11,14).

Interestingly, it has been consistently found that the prevalence of HFNEF is higher in community patients than in referral patients with HF (45% vs. 55% [11,12]). Why might this be the case? Symptoms and signs of HF have limited sensitivity and specificity, and while the inclusion of echocardiographic and biomarker features may assist, considerable scope remains for underdiagnosis or overdiagnosis. Furthermore, comorbidities including advanced age, pulmonary disease, and obesity confound the diagnosis further (15). More broadly, the ability to extrapolate data generated from pathophysiologic studies to epidemiological studies is confounded by the application of various definitions. Specifically, for the latter type of studies, simply all patients with the clinical diagnosis of HF (e.g., Framingham criteria [11]) and an LVEF higher than the cutoff in the specific study (typically 50% [11]) were included, while cross-sectional mechanistic studies applied much more rigorous criteria. These studies typically excluded patients with "significant"

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**Abbreviations  
and Acronyms**

- ATP** = adenosine triphosphate
- $\beta$**  = left ventricular passive stiffness constant
- BNP** = B-type natriuretic peptide
- E'** = early diastolic peak mitral annulus velocity assessed by pulse-waved tissue Doppler
- E/E'** = transmitral peak velocity during early relaxation to early diastolic peak mitral annulus velocity
- HF** = heart failure
- HFNEF** = heart failure with normal left ventricular ejection fraction
- LV** = left ventricle/ventricular
- LVEDP** = left ventricular end-diastolic pressure
- LVEF** = left ventricular ejection fraction
- NT-proBNP** = N-terminal pro-B-type natriuretic peptide
- NYHA** = New York Heart Association
- $\tau$**  = time constant of the isovolemic left ventricular pressure decline

coronary artery disease (most often clinically assessed, however [1,4, 16–19]; see discussion in the following text), hypertrophic cardiomyopathy (4,16–19), and valvular heart disease (1,4,16–19), in an attempt to concentrate on a subgroup of patients with “true” HFNEF and similar pathophysiology. On this basis, it is probable that HFNEF patients represent a heterogeneous population, which is characterized only by the absence of an impaired LVEF, whereas the group of patients with “true” HFNEF is much smaller than generally believed (Fig. 1). Diabetic cardiomyopathy (20), although also reported in conjunction with a dilated phenotype and impaired LVEF (21) and perhaps obesity cardiomyopathy (22), would also be incorporated within many of the epidemiologic studies of HFNEF, given the high prevalence of diabetes and obesity in the populations examined.

**Morphologic Features  
and Function of the Left  
Ventricle (LV) in HFNEF**

In contrast to patients with HF and impaired LVEF (typically with LV dilation, eccentric LV hypertrophy, and low relative wall thickness), patients with HFNEF are characterized more often with a nondilated LV, concentric LV hypertrophy or at least concentric LV remodeling, and normal LVEF (Fig. 2) (23). A comparison of endomyocardial biopsies revealed higher cardiomyocyte diameter and higher myofibrillar density in patients with HFNEF compared with those with HF and impaired LVEF, whereas collagen volume fraction was similar (24).

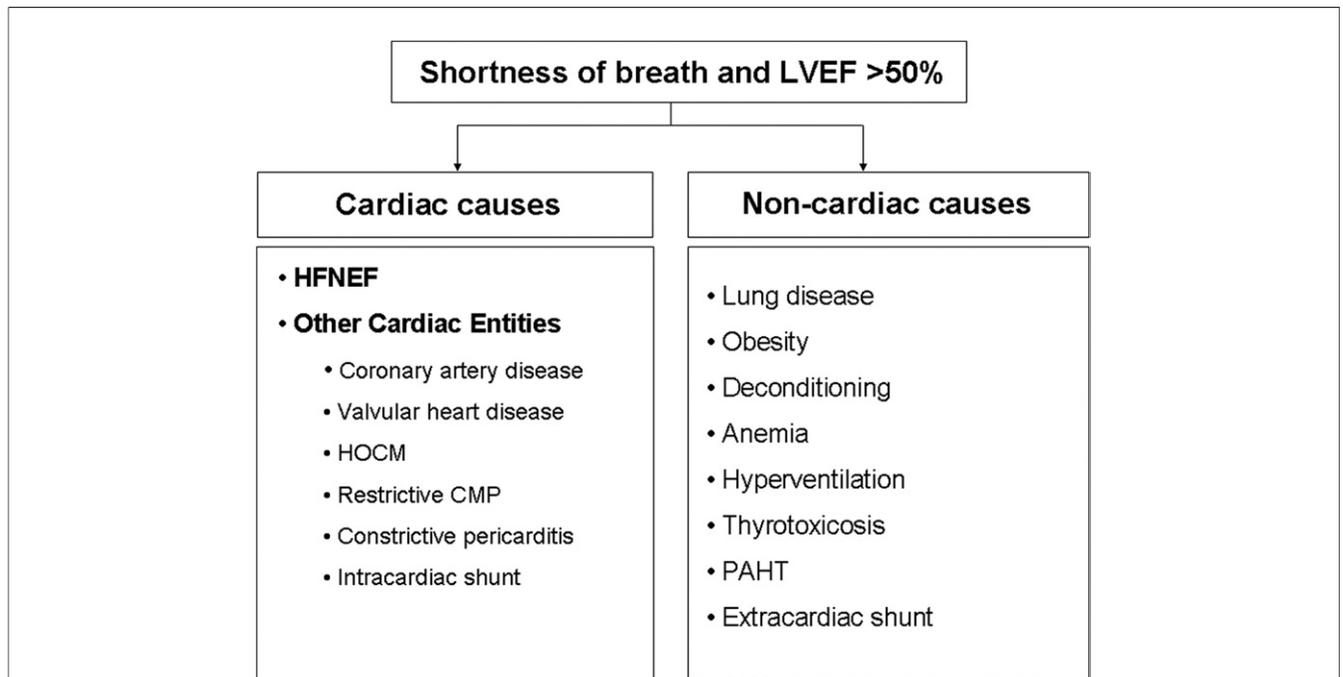
**Diastolic function.** The traditional concept of HFNEF is based on sophisticated conductance catheter studies (16,25). In contrast to patients with HF and impaired LVEF, where LV pressure–volume analysis typically reveals a less steep slope of end-systolic LV pressure–volume relationship than in subjects without HF, patients with HFNEF exhibit an upward and leftward shifted end-diastolic pressure–volume relationship, whereas the end-systolic pressure–volume relationship (end-systolic elastance) is unaltered or even steeper than in subjects without HF (26,27) (Fig. 2). In their landmark study, Zile et al. (16) have shown that patients with HFNEF (defined as symptoms of HF, LVEF

>50%, and concentric LV hypertrophy or concentric LV remodeling [25]) have abnormalities in both active LV relaxation, as marked by a prolonged time constant of the isovolemic pressure decline ( $\tau$ ), and LV stiffness, as reflected by an increased LV passive stiffness constant  $\beta$  (Fig. 2, Table 1). It is proposed that the increased LV stiffness in HFNEF patients is associated with a marked increase in left ventricular end-diastolic pressure (LVEDP) and pulmonary venous pressure after very small changes in LV end-diastolic volumes, which leads to dyspnea during exercise and even pulmonary edema (16,28). Exercise intolerance in these patients is thought to be due to failure to increase cardiac output sufficiently during exercise due to impaired LV filling and an inability to use the Frank-Starling mechanism (1,16,28).

**Is diastolic dysfunction the only explanation?** LV diastolic dysfunction is a common finding in the elderly, in particular among patients with hypertension (20). For example, in a cross-sectional study among 2,042 participants (29), the incidence of moderate-to-severe LV diastolic dysfunction in the presence of an LVEF >50% was 5.6%. However, only approximately 1% of the study population had symptoms of HF and an LVEF >50%. Although asymptomatic advanced LV diastolic dysfunction also is predictive of the future occurrence of HF (30), it is not clear why some patients with LV diastolic dysfunction have HFNEF and others are asymptomatic. Several studies have, therefore, tried to identify echocardiographic features distinguishing patients with LV hypertrophy and/or LV diastolic dysfunction from those with LV hypertrophy/LV diastolic dysfunction and HFNEF (Table 1).

Melenovsky et al. (19) compared 37 patients with HFNEF (previous hospitalization for pulmonary edema, LVEF >50%) with 40 patients with hypertensive LV hypertrophy without HF and 56 control subjects (Table 1). HFNEF patients had a higher LV mass index, more concentric LV geometry, higher transmitral peak velocity during early relaxation to early diastolic peak mitral annulus velocity (E/E') ratio, and larger left atrial volume than patients with hypertensive LV hypertrophy and control subjects. Most of these measurements distinguished HFNEF patients very well from control subjects but not from those with asymptomatic hypertensive LV hypertrophy (19). The product of LV mass index and left atrial volume had the highest accuracy for the prediction of HFNEF, perhaps highlighting the proposition that left atrial size reflects an integrative measure of the severity and chronicity of LV diastolic dysfunction (31).

Lam et al. (32) (Table 1) have shown that despite similar LV mass index, HFNEF patients had more impaired LV diastolic function (E/E' ratio), smaller LV end-diastolic volume index, and smaller stroke volume index compared with patients with hypertension but without HF. Conversely, others have found that HFNEF patients had a larger LV end-diastolic volume index and larger stroke volume index than patients with hypertension but without HF (Table 1) (33). In this and other studies, HFNEF



**Figure 1** Scheme Illustrating the Differential Diagnoses to the Syndrome of HFNEF

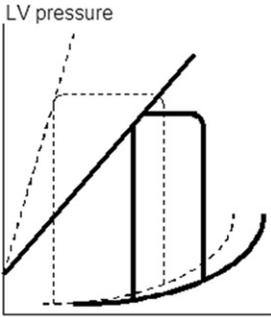
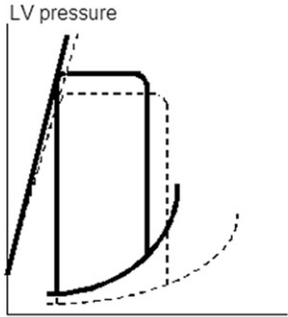
It is suggested that a certain proportion of patients given the clinical diagnosis of heart failure in the presence of a left ventricular ejection fraction (LVEF) >50% likely do not have symptoms arising from primary ventricular dysfunction. Within the group of patients with heart failure and LVEF >50%, only a subgroup has heart failure with normal left ventricular ejection fraction (HFNEF) in the sense that the term has been defined by pathophysiology studies (Tables 1 and 2) and the recently proposed diagnostic criteria (Fig. 3) (10). CMP = cardiomyopathy; HOCM = hypertrophic obstructive cardiomyopathy; PAHT = pulmonary arterial hypertension.

patients also had more comorbidities including anemia and renal dysfunction, leading to the suggestion that volume overload rather than an intrinsic abnormality of LV diastolic function may contribute to the pathophysiology of HFNEF (33).

**LV systolic function.** Historically, the description of HFNEF patients has been confused by the use of various terms including “diastolic HF” and “HF with preserved systolic function,” the latter term giving rise to considerable debate. By definition, the LVEF in patients with HFNEF is considered “normal,” although the distinction between normal and abnormal has varied considerably from 40% to 50% (28). However, the value of LVEF as a measure of LV systolic function in the predominantly elderly HFNEF population has been questioned (34), given, among other limitations, its considerable load dependence. The recognition that LVEF is an imprecise measure of LV systolic function has led to a range of more sensitive tools being applied in patients with HFNEF. Studies using invasive conductance catheterization to derive pressure-volume loops have tended to suggest that LV end-systolic elastance is normal or slightly increased, often in the setting of increased arterial elastance suggesting ultimately that “contractility” is normal (26,27). Recently developed echocardiographic measures of systolic function have also provided additional information while introducing further complexity. Several studies have shown that the annular peak systolic velocity assessed by tissue Doppler imaging is reduced in HFNEF

patients (35,36), while one more recent study suggested that LV twist is preserved in HFNEF patients albeit in the presence of reduced longitudinal and radial strain (37). One confounding issue in the application of “single point” echocardiographic measures such as strain is their load dependence, which is not accounted for in the presence of potential alterations in both pre-load and afterload in HFNEF. Thus, it is still controversial whether LV systolic function is normal in HFNEF. More importantly, however, the simple separation of the cardiac cycle into systolic and diastolic phases is not well justified (38,39), given various inter-related processes including the influence of systole on subsequent filling and the influence of passive ventricular properties on systolic function.

**Ventriculovascular coupling in HFNEF.** Although much of the recent emphasis in research has aimed at determining the mechanisms that contribute to *ventricular* dysfunction in HFNEF, it is increasingly evident that concomitant abnormalities in arterial mechanics play a major role (40). One integrated measure of arterial stiffness, the effective arterial elastance, is a global measure of arterial stiffness, which can relatively simply be determined as the ratio of LV end-systolic pressure/stroke volume (40) and is typically elevated in HFNEF patients. However, both end-systolic elastance and arterial elastance are typically elevated in HFNEF, leading to only a modest reduction in the ratio of arterial elastance/end-systolic elastance, similar to that observed in age-matched hypertensives (27). While this observation

	HF with impaired LVEF	HFNEF
LV morphology		
Pressure-volume loop		
LVEDV	↑	normal
LV mass	eccentric LV hypertrophy	concentric LV hypertrophy or concentric LV remodeling
Left atrium	dilated	dilated
LVEF	↓	normal
dp/dt	↓	normal
LVEDP	↑	↑
$\beta$	normal	↑
E/E'	↑	↑
BNP/NT-proBNP	↑	↑

**Figure 2 Comparison of the Characteristics of LV Morphology and Function in Patients With HF and Reduced LVEF and HFNEF**

The pressure-volume loops highlight that in patients with heart failure (HF) and impaired LVEF, the slope of the end-systolic pressure–volume relationship (end-systolic elastance), which is obtained by recording pressure-volume loops at different pre-load levels, is typically less steep (**solid lines**) than in people with normal hearts (**dashed lines**), and the loops are shifted toward larger volumes. In contrast, the end-systolic pressure–volume relationship is steeper or normal in HFNEF. However, HFNEF patients typically exhibit an end-diastolic pressure–volume relationship that is shifted upwards and to the left (**solid lines**) (**dashed lines** = normal).  $\beta$  = stiffness constant; BNP = B-type natriuretic peptide; dp/dt = rate of isovolemic increase in left ventricular pressure; E/E' = transmitral peak velocity during early relaxation to early diastolic peak mitral annulus velocity; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume; NT-proBNP = N-terminal pro-B-type natriuretic peptide; other abbreviations as in Figure 1.

may seem counterintuitive, it has been suggested that combined ventricular-arterial stiffening contributes to the syndrome of HFNEF by a number of mechanisms, as recently extensively reviewed elsewhere (40,41): 1) exaggerated increase in systolic blood pressure after small increases in LV end-diastolic volume; 2) a marked increase in systolic blood pressure after a further increase in arterial elastance in the presence of a high end-systolic elastance; 3) limited systolic reserve due to high baseline end-systolic elastance; 4) increased cardiac work to deliver a given cardiac output;

and 5) a direct influence of high arterial elastance on LV diastolic function (impaired relaxation). The first 2 mechanisms would also explain the sensitivity of these patients to overdiuresis and aggressive vasodilator therapy.

### Role of Atrial Fibrillation

The prevalence of atrial fibrillation is considerable in both epidemiological studies (30% to 40% [11,12]) and randomized controlled trials of HF with normal LVEF (20% to

**Table 1 Selected Studies Investigating Mechanisms Underlying HFNEF: Studies at Rest**

Mechanism	Study Group	Age (yrs)	Race	BMI <sub>2</sub> (kg/m <sup>2</sup> )	Diabetes (%)	CAD (%)	LVMI	LVEF (%)	E/E'	Key Data: Cases vs. Control Subjects
LV relaxation ↓ LV stiffness ↑ (16)	HFNEF (n = 47)	59 ± 12	NA	NA	NA	Excluded	Concentric LVH/ LV remodeling	>50%	NA	LVEDP higher in HFNEF: 25 ± 6 mm Hg vs. 8 ± 2 mm Hg
	Control subjects (chest pain, n = 10)	58 ± 16	NA	NA	NA	Excluded (angiography)	NA	>50%	NA	LVEDV smaller in HFNEF: 103 ± 22 ml vs. 115 ± 9 ml τ longer in HFNEF: 59 ± 14 ms vs. 35 ± 10 ms β higher in HFNEF: 0.03 ± 0.01 vs. 0.01 ± 0.01
LVH ↑/LA dilation ↑ (19)	HFNEF (n = 37)	65 ± 10	76% African American	37 ± 8	60	42	81 ± 23 g/m <sup>2.7</sup>	65 ± 10	15 ± 5	Maximal LA volume higher in HFNEF: 84 ± 26 ml vs. 60 ± 16 ml
	Control subjects (LVH, n = 40)	67 ± 10	73% African American	31 ± 6	35	10	58 ± 12 g/m <sup>2.7</sup>	67 ± 10	11 ± 5	Maximal LA volume × LVMI higher in HFNEF: 6,989 ± 2,974 ml × g/m <sup>2.7</sup> vs. 3,516 ± 1,367 ml × g/m <sup>2.7</sup>
LV volume ↓ (32)	HFNEF (n = 244)	76 (22-99)	NA	32 ± 20	37	53	102 ± 29 g/m <sup>2</sup>	62 ± 6	18 ± 10	LVEDVI lower in HFNEF: 61 ± 16 ml/m <sup>2</sup> vs. 65 ± 14 ml/m <sup>2</sup>
	Control subjects (HTN, n = 719)	66 (46-91)	NA	30 ± 6	11	16	100 ± 23 g/m <sup>2</sup>	65 ± 6	9 ± 3	SVI lower in HFNEF: 42 ± 10 ml/m <sup>2</sup> vs. 46 ± 10 ml/m <sup>2</sup> LV relaxation (E') slower in HFNEF: 6.0 ± 2.1 cm/s vs. 7.7 ± 3.9 cm/s
Volume overload (33)	HFNEF (n = 167)	76 ± 7	65% Caucasian	27 ± 6	30	58	98 ± 34 g/m <sup>2</sup>	72 ± 7	NA	LVEDVI higher in HFNEF: 69 ± 22 ml/m <sup>2</sup> vs. 62 ± 14 ml/m <sup>2</sup>
	Control subjects (HTN, n = 2,184)	73 ± 6	78% Caucasian	27 ± 5	20	20	87 ± 24 g/m <sup>2</sup>	74 ± 7	NA	SVI higher in HFNEF: 50 ± 14 ml/m <sup>2</sup> vs. 46 ± 11 ml/m <sup>2</sup> eGFR lower in HFNEF: 56 ± 22 ml/min vs. 61 ± 20 ml/min Anemia* more prevalent in HFNEF: 19% vs. 8%

Data are given as mean ± SD or median (range). \*Hemoglobin <12 g/dl in women and <13 g/dl in men.

β = left ventricular passive stiffness constant; BMI = body mass index; CAD = coronary artery disease; E' = early diastolic peak mitral annulus velocity; E/E' = transmitral peak velocity during early relaxation to early diastolic peak mitral annulus velocity; eGFR = estimated glomerular filtration rate; HFNEF = heart failure with normal ejection fraction; HTN = hypertension; LA = left atrial; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; LVEDV(I) = left ventricular end-diastolic volume (index); LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index; NA = not available; SVI = stroke volume index; τ = time constant of the left ventricular isovolumic pressure decline.

30% [13,42,43]). Fung et al. (44) reported that HFNEF patients (LVEF  $\geq 50\%$ ) with atrial fibrillation (29%) had worse functional class and quality of life, lower 6-min walking distance, and larger left atrial diameter than those without atrial fibrillation. In the CHARM (Candesartan in Heart Failure) study, atrial fibrillation was associated with adverse cardiovascular outcomes irrespective of baseline LVEF (45). High heart rate, loss of atrial systole, irregular cycle length with implications of the Frank-Starling mechanism, and its episodic nature in many patients have been discussed as a mechanism by which atrial fibrillation confers a worsened clinical status in HFNEF (44).

Given that echocardiographic assessment of LV diastolic function is extremely challenging in atrial fibrillation (46), these patients have been excluded from many recent pathophysiology studies on HFNEF (16–19). Interestingly, Fung et al. (44) found similar E/E' ratios in HFNEF patients with and without atrial fibrillation (21.4 vs. 20.2) but larger left atrial size in those with atrial fibrillation. In the study by Melenovsky et al. (19), left atrial emptying fraction was lower in HFNEF patients than in control subjects (patients with hypertensive LV hypertrophy), and during handgrip exercise, late diastolic annular tissue velocity remained virtually unchanged in HFNEF patients but increased in control subjects (5% vs. 35% change). Thus, HFNEF patients with left atrial enlargement may be particularly symptom prone on the basis of reduced atrial emptying and an increased risk of paroxysmal atrial fibrillation (47).

### Role of Coronary Artery Disease

In patients with coronary artery disease, provocation of myocardial ischemia by rapid atrial pacing results in an upward shift of the diastolic LV pressure–volume relationship (48). Ischemia affects early diastole by prolongation of  $\tau$  (48–50), which is reversed after removal of the ischemic burden by coronary bypass grafting (50), whereas the effects on passive stiffness are less clear. Given the high risk profile for, or high prevalence of, documented coronary artery disease, and the fact that in none of the epidemiological studies and randomized controlled trials evaluating treatment for HFNEF have attempts been made to exclude myocardial ischemia with a sensitive method, it is tempting to speculate that a considerable number of patients with atypical presentation of myocardial ischemia (silent or dyspnea) has been labeled as HFNEF. This suspicion is supported by a study reporting a 15% incidence of hospital admission due to unstable angina in patients previously diagnosed with HFNEF during a median follow-up of 38 months (51).

### Response to Exercise

Peak oxygen consumption in HFNEF patients is significantly reduced if compared with healthy control subjects

(4,52) or asymptomatic patients with hypertensive LV hypertrophy (18). Kitzman et al. (4) found a similarly impaired peak oxygen consumption in patients with HFNEF and those with HF and impaired LVEF (14.2 ml/kg/min vs. 13.1 ml/kg/min), although the higher proportion of women in the HFNEF (86% vs. 35%) group makes interpretation of absolute values for peak oxygen consumption difficult.

Comparatively few studies have evaluated the hemodynamic response to aerobic exercise. In a comprehensive study using upright bicycle exercise testing with simultaneous right heart catheterization and serial radionuclide ventriculography (1), cardiac index, stroke volume index, and LV end-diastolic volume index at rest did not differ between HFNEF patients and control subjects but were lower in patients with HFNEF at peak exercise, resulting in a markedly lower peak oxygen consumption (Table 2). Pulmonary capillary wedge pressure at rest was somewhat higher in HFNEF patients compared with control subjects but much higher at peak exercise (Table 2). These findings were interpreted as impaired LV filling on the one hand and failure to use the Frank-Starling mechanism properly on the other hand (1). The HFNEF group also had a diminished arteriovenous oxygen difference, which led to the suggestion that “peripheral factors” such as the leg vasculature or the musculature might contribute to exercise intolerance in HFNEF (1).

In a study by Borlaug et al. (18), HFNEF patients (with a history of pulmonary edema and LVEF  $>50\%$ ) showed a lower increase in heart rate, a lower decrease in systemic vascular resistance index, and a lower increase in cardiac index during exercise when compared with the control group (Table 2). Notably, LV end-diastolic volume index did not decrease in either group during exercise but increased to a similar degree. This observation led to the suggestion that the chronotropic and vasodilatory reserve in HFNEF patients is diminished (18). Notably, an impaired chronotropic response in patients with HFNEF had also been reported by others (1,17).

Westermann et al. (17) compared hemodynamics at rest, during right ventricular pacing at 120 beats/min, and during handgrip exercise in 70 comparatively young HFNEF patients and 20 control subjects (Table 2). At rest, LVEDP,  $\tau$ , and  $\beta$  were higher in HFNEF patients as compared with that in control subjects. During pacing,  $\tau$  and LVEDP decreased in both groups, and the median LVEDP in the HFNEF group even became normal (8 mm Hg), whereas  $\beta$  remained unchanged in both groups. However, in contrast to control subjects, LV end-diastolic volume and stroke volume in HFNEF patients decreased during pacing, which was interpreted as the manifestation of increased stiffness during high heart rates. However, handgrip exercise was associated with a marked increase in LVEDP in HFNEF patients but not in control subjects, and LV end-diastolic volumes did not

**Table 2 Selected Studies Investigating Mechanisms Underlying HFNEF: Studies Including Exercise**

Mechanism	Study Group	Age (yrs)	Race	BMI (kg/m <sup>2</sup> )	Diabetes (%)	CAD	LVMI	LVEF (%)	Peak VO <sub>2</sub> (ml/kg/min)	Key Data: Cases vs. Control Subjects
LV filling ↓, failure of Frank-Starling mechanism, chronotropic incompetence (1)	HFNEF (n = 7)	65 ± 12	NA	NA	29	Excluded (angiography)	107 ± 27 g/m <sup>2</sup>	58	11.6 ± 4.0	Lower peak heart rate in HFNEF: 126 ± 27 beats/min vs. 154 ± 11 beats/min
	Healthy control subjects (n = 10)	61 ± 8	NA	NA	0	Excluded (exercise test)	NA	≥50	22.7 ± 6.1	Lower peak exercise LVEDVI in HFNEF: 56 ± 14 ml/m <sup>2</sup> vs. 68 ± 12 ml/m <sup>2</sup> Lower peak exercise SVI in HFNEF: 34 ± 9 ml/m <sup>2</sup> vs. 46 ± 7 ml/m <sup>2</sup> Higher peak exercise PCWP in HFNEF: 25.7 ± 9.1 mm Hg vs. 7.1 ± 4.4 mm Hg
Chronotropic incompetence, vasodilatory reserve ↓ (18)	HFNEF (n = 17)	65 ± 9	71% African American	37 ± 8	"Most"	NA	75 ± 24 g/m <sup>2.7</sup>	73 ± 7	9.0 ± 3.4	Lower increase in heart rate in HFNEF: peak exercise: ≈18 beats/min vs. ≈48 beats/min*
	Control subjects (LVH, n = 19)	65 ± 9	78% African American	31 ± 6	"Most"	NA	60 ± 16 g/m <sup>2.7</sup>	70 ± 8	14.4 ± 3.4	Smaller reduction in SVRI in HFNEF: peak exercise: ≈600 dyne × s × cm <sup>5</sup> × m <sup>2</sup> vs. ≈1,100 dyne × s × cm <sup>5</sup> × m <sup>2</sup> *
LV stiffness ↑ (17)	HFNEF (n = 70)	58 (52–64)	100% Caucasian	28 (23–32)	17	Excluded (history)	128 (109–135) g/m <sup>2</sup>	65 (59–73)	NA; 128 W	Rest → pacing 120 beats/min LVEDP ↓ in HFNEF and control subjects: 16.1→7.7 mm Hg vs. 5.6→4.5 mm Hg τ ↓ in HFNEF and control subjects: 54→43 ms vs. 41→36 ms LVEDV ↓ in HFNEF: 151→109 ml vs. 158→169 ml SV ↓ in HFNEF: 94→72 ml vs. 109→122 ml Rest → handgrip exercise Lower increase in heart rate in HFNEF: 71→103 beats/min vs. 69→121 beats/min LVEDP ↑ only in HFNEF: 15→23 mm Hg vs. 6→7 mm Hg LVEDV unchanged in HFNEF/control subjects: 148→152 ml vs. 154→159 ml
	Control subjects (chest pain, n = 20)	55 (46–60)	100% Caucasian	26 (23–28)	10	Excluded (angiography)	95 (81–99) g/m <sup>2</sup>	65 (62–75)	NA; 184 W	

Data are given as mean ± SD or median (interquartile range). \*Exact data not given in the study; they were estimated from the figure.  
 PCWP = pulmonary capillary wedge pressure; SVRI = systemic vascular resistance index; VO<sub>2</sub> = oxygen consumption; other abbreviations as in Table 1.

decrease in either group. Notably,  $\beta$  was unaffected in both groups (17).

It has been criticized (8) that the hemodynamic response to pacing in control subjects in this study did not correspond to more typical physiologic responses. Pacing in healthy humans has been reported to result in a decrease in LV end-diastolic volume and stroke volume and thereby a blunted cardiac output response (53), which is interpreted as a physiologic response in an attempt to minimize the increase in myocardial oxygen demand resulting from the increase in heart rate (8). Thus, the decrease in LV end-diastolic volume and stroke volume in HFNEF patients during pacing is difficult to interpret, particularly in the context of a normal LVEDP (8). Importantly, during the more physiologic form of exercise (handgrip), there was no change in LV end-diastolic volume. Thus, we are faced with conflicting data from small studies concerning the hemodynamic response to exercise in HFNEF, which in part might be explained by differences in study methodology and populations studied (Table 2).

### Diagnosis of HFNEF

**Principle of the diagnosis of HFNEF.** In 2000, Vasan and Levy (9) suggested the following criteria for the diagnosis of HFNEF or “diastolic HF,” respectively. A patient could be definitely diagnosed with “diastolic HF” if the following 3 criteria were fulfilled: 1) symptoms and signs of HF; 2) LVEF  $\geq 50\%$  within 72 h of the HF event; and 3) evidence of LV diastolic dysfunction by abnormal LV relaxation/filling/distensibility indexes on cardiac catheterization. A probable diagnosis could be obtained if the former 2 criteria were fulfilled but if there was no information on LV diastolic function, and the diagnosis was still possible in a patient with symptoms and signs of HF, LVEF  $\geq 50\%$  but not within 72 h of the HF event, and lack of information on LV diastolic function. This approach was based on the assumption that echocardiography was not a reliable tool to assess LV diastolic function (9).

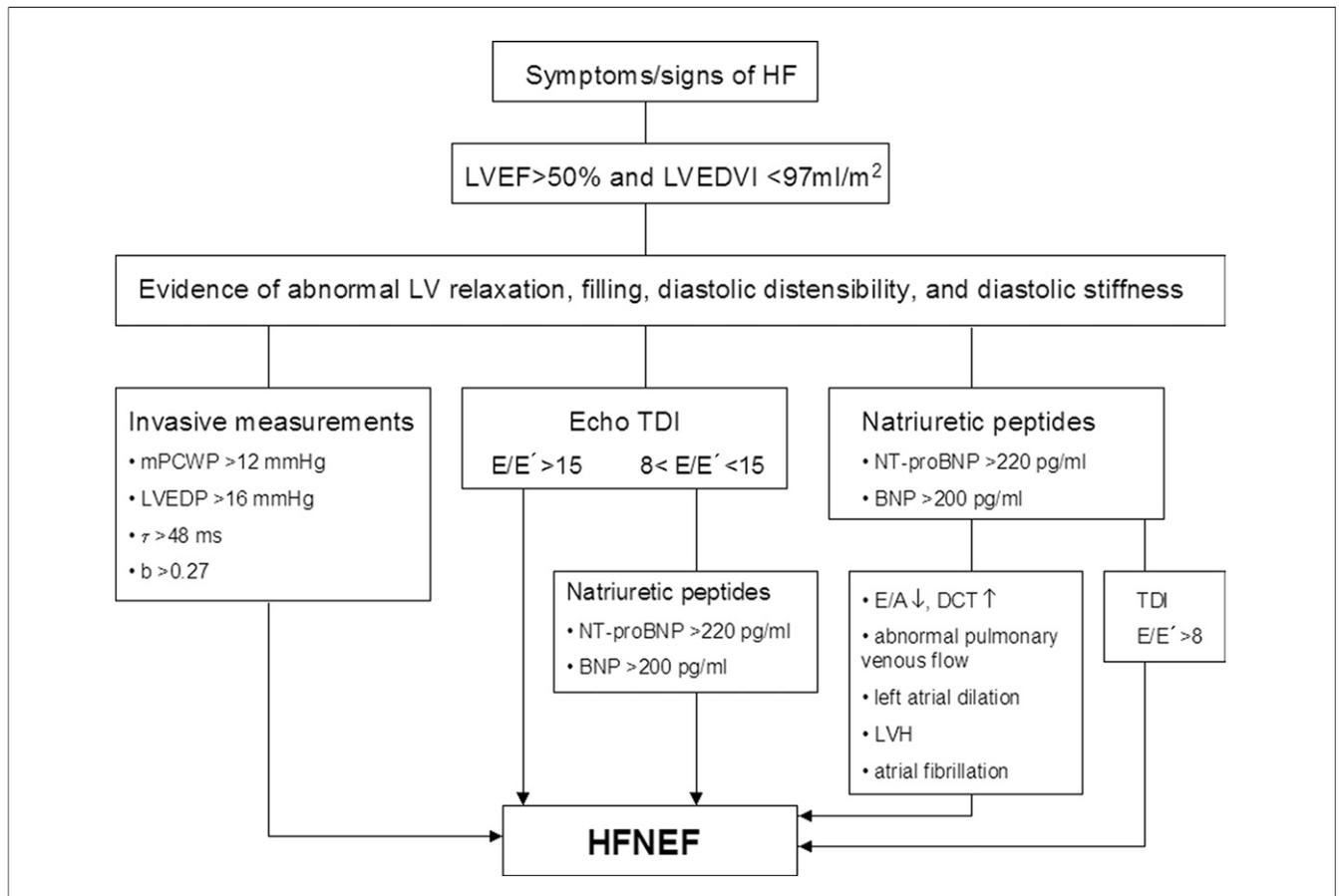
In 2007, the European Working Group on HFNEF proposed a new diagnostic algorithm (10), which is based on the concept of Vasan and Levy (9) but includes new insights into the utility of noninvasive tools to estimate LV filling pressures. The principle of this algorithm is displayed in Figure 3. Three conditions must be fulfilled for the diagnosis of HFNEF: 1) symptoms and signs of HF; 2) LVEF  $\geq 50\%$  in a nondilated LV (LV end-diastolic volume  $< 97$  ml/m<sup>2</sup>, which is the cutoff between a moderately and severely abnormal LV volume index according to the American Society of Echocardiography recommendations for chamber quantification [54]); and 3) evidence of elevated LV filling pressures. Three ways to diagnose elevated LV filling pressures have been proposed: first, invasive measurements; second, unequivocal tissue Doppler imaging findings; and third, a combination of elevated natriuretic pep-

tides and echocardiographic indexes of LV diastolic function/LV filling pressures (10). The utility of these tools will be discussed in the following paragraphs.

**Invasive diagnostics.** Apart from prolonged  $\tau$  and increased  $\beta$ , which require sophisticated measurement (not usually performed in routine clinical practice), elevated LVEDP or pulmonary capillary wedge pressure are also suggested to be appropriate for the diagnosis of HFNEF in the presence of HF symptoms and an LVEF  $> 50\%$  (10). It should be noted that both HFNEF and a constrictive physiology (which should be differentiated from HFNEF [10]) may present with the latter constellation. This differentiation would be possible using tissue Doppler imaging as  $E'$  is typically low in HFNEF but normal in constriction (55).

**Echocardiography.** Conventional Doppler echocardiography using mitral inflow and pulmonary venous flow patterns clearly has limitations with respect to the assessment of LV diastolic function, which is best illustrated by the data from the echocardiography substudy of the CHARM-PRESERVED (Candesartan in Heart Failure—Preserved) trial (56), where those reading the echocardiograms were able to differentiate a normal from a pseudonormal mitral inflow pattern in only 14% of patients. In the other 86% of cases, a pseudonormal pattern was diagnosed based on an elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) level (56), which relies on the optimistic assumption that NT-proBNP can accurately differentiate a normal from a pseudonormal inflow pattern. Therefore, a diagnosis of HFNEF based on Doppler echocardiography alone is not possible according to the new algorithm (10). Currently, the most sensitive and widely available echocardiographic technique for the assessment of LV diastolic function is that of tissue Doppler imaging. Whereas the ratio of early to late diastolic peak mitral inflow velocities exhibits a J-shaped relationship with LVEDP, tissue Doppler-derived intramyocardial velocities continuously decline from normal to advanced LV diastolic dysfunction. As a consequence,  $E'$  decreases and the  $E/E'$  ratio continuously increases with advanced LV diastolic dysfunction.

Nonetheless, the limitations to this technique in the context of HFNEF should be noted. In the original study by Ommen et al. (57), the correlation quotient between the  $E/E'$  ratio ( $E'$  measured at the medial mitral annulus) and the mean LV diastolic pressure was 0.60 for patients with LVEF  $< 50\%$  but only 0.47 for those with LVEF  $> 50\%$ . However, all patients with an  $E/E'$  ratio  $> 15$  had a mean diastolic LV pressure  $> 12$  mm Hg. Thus, the new algorithm suggests an  $E/E'$  ratio  $> 15$  for the diagnosis of elevated LV filling pressure and thus HFNEF in a patient with typical symptoms and signs of HF and LVEF  $> 50\%$ . An  $E/E'$  ratio between 8 and 15, however, was associated with a very wide range of mean LV diastolic pressures in the study by Ommen et al. (57), and, thus, further measurements are suggested in a patient with suspected HFNEF and an  $E/E'$  ratio between 8 and 15 (10).



**Figure 3** Principles of the Algorithm Proposed for the Diagnosis of HFNEF by the Working Group of the European Society of Cardiology

b = left ventricular passive stiffness; DCT = deceleration time; E/A = ratio of early to late diastolic peak mitral inflow velocities; LVEDVI = left ventricular end-diastolic volume index; LVH = left ventricular hypertrophy; mPCWP = mean pulmonary capillary wedge pressure; τ = time constant of the isovolumic pressure decline; TDI = tissue Doppler imaging; other abbreviations as in Figures 1 and 2. Adapted from Paulus et al. (10), with permission from Oxford press.

Data supporting this approach in the setting of possible HFNEF are very sparse and basically rely on 1 study (58). Among 43 patients with HFNEF and 12 control subjects without cardiac disease, Kasner et al. (58) found a strong correlation between E/E' and LVEDP ( $r = 0.71$ ) but only moderate correlations between E/E' and  $\tau$  ( $r = 0.34$ ), and  $\beta$  ( $r = 0.53$ ). The area under the receiver-operator characteristic curve for the invasive diagnosis of HFNEF using pressure-volume loop analysis was reported as 0.91. Of note, this applied only for E/E' assessed at the lateral annulus, and E/E' values measured at the medial annulus did not differentiate HFNEF patients from control subjects (58). In the previously mentioned study by Melenovsky et al. (19), however, the area under the receiver-operator characteristic curve for the E/E' ratio (averaged from medial and lateral annulus) for the prediction of HFNEF (defined as a history of pulmonary edema and LVEF > 50%) was only 0.69. Values for E' at the lateral annulus are generally higher than at the medial annulus, resulting in lower E/E' ratios at the lateral annulus (59). Thus, E/E' cutoffs derived from studies using the medial or the lateral annulus are not directly comparable.

The E/E' ratio also seems to reflect LV filling pressure during exercise. A study among 37 unselected patients (the majority with preserved LV systolic function) undergoing both left heart catheterization with measurement of LVEDP and simultaneous echocardiography revealed that E/E' measured at the medial annulus was related to LVEDP both at rest and during exercise. However, the correlation between E/E' and LVEDP directly after exercise was somewhat worse ( $r = 0.59$ ) than at rest ( $r = 0.67$ ) (60).

**Natriuretic peptides.** BNP and the N-terminal part of its precursor peptide, NT-proBNP, are established tools for the exclusion of possible HF in patients presenting to the emergency room with dyspnea of unclear origin (61,62), and although data are more sparse, also in outpatients presenting with symptoms possibly attributable to HF (63,64). Notably, the majority of data about BNP and NT-proBNP for the evaluation of patients with possible HF was derived from studies with patients with HF and impaired LVEF. Among patients with preserved LVEF but not necessarily HF, BNP and NT-proBNP levels were found to be related to the severity of LV diastolic dysfunction (61,65), and

based on these data, NT-proBNP has even been used to distinguish a normal from a “pseudonormal” (LVEDP elevated) LV filling pattern (56).

The working group has proposed a BNP level >200 pg/ml or an NT-proBNP level >220 pg/ml to confirm the diagnosis of HFNEF in patients with symptoms of HF, LVEF >50%, and an ambiguous E/E' value between 8 and 15 (10). This NT-proBNP cutoff was derived from a carefully combined echocardiography and invasive study among patients with both LV diastolic dysfunction as assessed by Doppler echocardiography and symptoms of HF and a control group without LV diastolic dysfunction or symptoms (65). The area under the receiver-operator characteristic curve for NT-proBNP to predict HFNEF was 0.83. However, the study group was significantly younger (age  $51 \pm 19$  years), and the proportion of women was lower (46%) than in other typical HFNEF populations. Given that female sex and older age are associated with higher NT-proBNP levels (66), the proposed cutoffs might be too low and thus too unspecific to differentiate elderly patients with and without HFNEF. Second, the BNP cutoff of >200 pg/ml was derived from a study in emergency department patients (67) and may, therefore, not be more broadly representative. These limitations were also acknowledged by the working group, who recommended that BNP and NT-proBNP should be mainly used for the exclusion of HFNEF, with upper limits for exclusion of 100 and 120 pg/ml, respectively (10).

## Treatment

Given that the mechanisms underlying HFNEF are still under debate, it is not surprising that there is no evidence-based treatment for patients with HFNEF. However, LV hypertrophy seems to be an important target for *prevention of HF*. A recent analysis of a subgroup from the Cardiovascular Healthy Study without a history of previous myocardial infarction identified LV hypertrophy as a predictor for the future development of HF independent of age, sex, obesity, diabetes, and hypertension (68). In addition, regression of the Cornell product under antihypertensive therapy has been found to be associated with less hospitalization for HF in hypertensive patients (69). Aggressive treatment of hypertension and diabetes is recommended to prevent HF by guidelines (5), and it may also reduce the incidence of HFNEF.

For the *treatment* of HFNEF, guidelines recommend blood pressure control (class I, level A) (5). All other recommendations are evidence level C. Given the high prevalence of diabetes and LV hypertrophy, there is a compelling indication for angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in many patients. However, the 3 trials evaluating the angiotensin receptor blockers candesartan (the CHARM-PRESERVED trial [42]) and irbesartan (the I-PRESERVED [Irbesartan in Heart Failure With Preserved Ejection Fraction Study] trial

[70]) and the angiotensin-converting enzyme inhibitor perindopril (the PEP-CHF [Perindopril for Elderly People With Chronic Heart Failure] trial [43]) in patients with HFNEF did not reveal a survival benefit when compared with that seen in placebo. This might, however, have been at least in part due to patient selection: the CHARM-PRESERVED study included patients with the clinical diagnosis of HF and an LVEF  $\geq 40\%$ . Notably, in the echocardiographic substudy, only 67% had evidence of LV diastolic dysfunction (56). In the PEP-CHF study (43), an LVEF of more than approximately 40% (defined by wall motion score), evidence of LV diastolic dysfunction based on Doppler echocardiography (not tissue Doppler), and clinical criteria had to be fulfilled. Very recently, the I-PRESERVED trial (70) evaluated the use of irbesartan in patients age  $\geq 60$  years with an LVEF  $\geq 45\%$  and symptoms of HF (New York Heart Association [NYHA] functional class II to IV with prior hospitalization) or NYHA functional class III or IV symptoms in the absence of prior hospitalization. Furthermore, 1 of the following features was also required for inclusion: pulmonary congestion in chest X-ray, LV hypertrophy (electrocardiogram or echocardiogram), left bundle branch block, or left atrial enlargement (echocardiography) in absence of atrial fibrillation (70). Patients were overall very symptomatic (almost 80% in NYHA functional class III or IV) and had a high event rate. However, despite a more pronounced reduction in systolic (3.6 mm Hg vs. 0.2 mm Hg) and diastolic (2.1 mm Hg vs. 0.2 mm Hg) blood pressure, there were no differences in the primary end point (death from any cause or hospitalization for cardiovascular causes) between the irbesartan and placebo groups (70). Detailed tissue Doppler studies of diastolic function were not included in the I-PRESERVED study. A number of reasons may have contributed to the negative study result, including multifactorial dyspnea (41% with body mass index  $\geq 30$  kg/m<sup>2</sup>) and even the absence of HF (25th percentiles for NT-proBNP 139 and 131 pg/ml in the irbesartan and placebo groups, respectively), comparatively well-controlled hypertension at study inclusion (systolic blood pressure 137 mm Hg vs. 136 mm Hg), a high rate of study drug discontinuation (33%), a very high proportion of patients on baseline loop or thiazide diuretics (82% vs. 84%), and a high proportion of patients on other inhibitors of the renin-angiotensin-aldosterone system (baseline treatment and post-randomization initiation). In another recent study (the VALIDD [VALsartan In Diastolic Dysfunction] study), it was shown that blood pressure lowering in patients with hypertension and LV diastolic dysfunction, either with a valsartan-based regimen or a regimen not including inhibitors of the renin-angiotensin-aldosterone system, elicited a similar reduction in blood pressure and an improvement in diastolic relaxation in both groups (71). Of note, the degree of blood pressure lowering was much greater than that in the I-PRESERVED trial, and this, therefore, suggests that blood pressure control may be a key factor in determining the response to treatment.

However, it is possible that impaired LV relaxation was not the main pathophysiologic factor underlying the symptoms of the patients in the I-PRESERVED trial.

### HFNEF—the Future?

**Trial design.** Given the symptomatic and prognostic profile of HFNEF and the lack of effective therapy, a clear imperative remains to elucidate the mechanisms responsible for HFNEF. To identify the mechanisms that underlie HFNEF, it is more appropriate that patients with HFNEF are not compared with healthy control subjects, but with patients with LV hypertrophy/LV diastolic dysfunction without HF. In the design of clinical trials, the role of contributing factors such as ischemia, uncontrolled hypertension, and atrial fibrillation must be clearly defined, which is critical in order to provide a homogeneous cohort in which to investigate the effect of specific interventions. In particular, inducible ischemia must be searched actively with a sensitive method, and the ischemic burden must be removed before a patient can be diagnosed with HFNEF. Although associated with some limitations, the diagnostic algorithm (10) discussed would be a way for a standardized and more specific inclusion process.

**Possible therapeutic strategies for the treatment of patients with HFNEF.** Assuming that impaired relaxation and increased stiffness are major mechanisms underlying HFNEF, it is appropriate that the development of therapeutic tools that specifically address these abnormalities should be a priority, as recently reviewed (72–74). The molecular basis of myocardial relaxation has been extensively investigated in both isolated cardiomyocyte and intact heart preparations (72–74). Active relaxation depends upon the integrated process of the regulation of diastolic intracellular calcium levels and the uncoupling of the myofilament proteins responsible for cellular contraction. Intracellular calcium control during diastole is critically dependent upon calcium uptake into the sarcoplasmic reticulum, mediated by the sarcoplasmic/endoplasmic reticulum

calcium adenosine triphosphate (ATP)ase type 2. There is evidence that low sarcoplasmic/endoplasmic reticulum calcium ATPase type 2 activity is related to impaired relaxation (75), and gene transfer has been suggested as a possible strategy (72,73). Activity of sarcoplasmic/endoplasmic reticulum calcium ATPase type 2 is closely regulated by the interacting protein, phospholamban, which is subject to further control by phosphorylation. Recent studies showed that percutaneous delivery of a modified phospholamban encoded in an adenovirus favorably affected LV function in a large animal model of HF (76). Interventions that specifically target the myofilament proteins have not been extensively evaluated, although it is noteworthy that a recent study of levosimendan, a myofilament calcium-sensitizing agent, suggested that it may improve LV diastolic function (77).

Apart from active relaxation, passive LV stiffness, at least in part due to myocardial fibrosis, is also a key target not only in HF with impaired LVEF but also in HFNEF. There are a number of substances currently evaluated in clinical trials (78) (Table 3) that are thought to favorably influence the disease process of HFNEF by reduction of LV hypertrophy and myocardial fibrosis and LV diastolic function. Many of these substances have been successfully used in other settings. An innovative approach is the use of the advanced glycation end products cross-links breaker alagebrium, which in a pilot study in 23 HFNEF patients resulted in a reduction in LV mass and an increase in E' (79) and which is currently evaluated in a multicenter study (78). There is intense research on the antifibrotic effects of inhibitors of growth factors, cytokines, and other signaling molecules involved in cardiac remodeling in the context of HF with impaired LVEF, some of which have shown promising results in experimental studies (80). Such strategies might be applicable to HFNEF as well.

The role of the sympathetic nervous system and the renin-angiotensin-aldosterone system in HFNEF is largely unknown. However, given that LV hypertrophy is associ-

**Table 3** Substances Evaluated for the Treatment of Patients With HFNEF in Completed but Unpublished or Ongoing Clinical Studies (According to NIH Clinical Trials Registry\*)

Substance	Drug Class	Postulated Targets
Valsartan	Angiotensin-receptor blocker	RAAS, blood pressure, LVH, LV relaxation
Aliskiren	Selective renin inhibitor	RAAS, blood pressure, LVH, LV relaxation
Spironolactone	Aldosterone antagonist	Collagen turnover, LV relaxation and stiffness
Eplerenone	Aldosterone antagonist	Collagen turnover, LV relaxation and stiffness, endothelial dysfunction
Sitaxsentan	Endothelin receptor A antagonist	Blood pressure, LVH
Alagebrium	Advanced glycation end products cross-links breaker	Advanced glycation end products, LV relaxation and stiffness
Atorvastatin	Statin	Collagen turnover, LV relaxation and stiffness, vascular function
Sildenafil	Phosphodiesterase-5 inhibitor	LVH, LV stiffness, vascular stiffness
Exenatide	Glucagon-like peptide-1 receptor antagonist	Aortic stiffness, LV stiffness
Ranolazine	Inhibitor of the slowly inactivating component of the cardiac Sodium current (late I <sub>Na</sub> channel)	Intracellular calcium, LV relaxation
Ivabradine	Inhibitor of the “funny” channel (I <sub>f</sub> channel)	Heart rate, duration of diastole

\*National Institutes of Health (NIH) Clinical Trials Registry (78).

RAAS = renin-angiotensin-aldosterone system; other abbreviations as in Table 1.

ated with increased sympathetic activity (81), and more severe LV hypertrophy seems to be associated with higher likelihood of HFNEF (19), the sympathetic nervous system may play a role in the pathogenesis of HFNEF as well. Candesartan has been shown to reduce the sympathetic activity measured by iodine-123-meta-iodobenzylguanidine scintigraphy in patients with HFNEF (defined as LVEF >40%) (82). It remains to be tested whether angiotensin receptor blocker therapy improves outcome in carefully selected HFNEF patients.

Although not explicitly stated in guidelines (5), beta-blockers and negatively chronotropic calcium-channel blockers are often proposed for the treatment of HFNEF based on the assumption that rate lowering and prolongation of diastole results in better LV filling and output (28), and a study evaluating the purely heart rate-lowering agent ivabradine in HFNEF is currently ongoing (78). This concept has been challenged by the previously mentioned studies suggesting that chronotropic incompetence may be an important mechanism contributing to exercise intolerance in HFNEF (1,18). However, the increase in LVEDP during exercise (1,17) with associated dyspnea rather than chronotropic incompetence may be the reason to cease exercise at comparatively low heart rates. One might also argue that chronotropic incompetence due to beta receptor desensitization is a feature of HF with impaired LVEF as well (83), and these patients benefit from beta-blocker therapy. Thus, the role of beta-blocker therapy for the treatment of HFNEF remains to be established. In addition, the optimal management of atrial fibrillation in HFNEF is not clear either.

In addition, less recognized factors may play a role in the pathophysiology of HFNEF. HFNEF is associated with obesity (11), which may, in part, be explained by the fact that obesity is a surrogate for obstructive sleep apnea. Obstructive sleep apnea is associated with a variety of cardiovascular abnormalities (84), including increased sympathetic nerve activity, hypertension, LV hypertrophy, LV diastolic dysfunction, and paroxysmal atrial fibrillation. Many of the latter abnormalities can be reduced or even reversed with continuous positive airway pressure ventilation (84), and there is even some evidence that treatment of severe obstructive sleep apnea with continuous positive airway pressure ventilation reduces cardiovascular mortality (85). Data on the effects of continuous positive airway pressure ventilation on peak oxygen consumption in patients with HF and impaired LVEF and concomitant obstructive sleep apnea are conflicting (84). However, due to the association with hypertension, LV hypertrophy, and atrial fibrillation, the role of obstructive sleep apnea in HFNEF may be even more important than in HF with impaired LVEF, and treatment may be more effective.

## Conclusions

HFNEF, used as a term to describe a condition associated with HF symptoms and normal LVEF, and without obvi-

ous explanation for the symptoms (e.g., coronary artery disease, valvular heart disease), is typically associated with concentric LV hypertrophy or concentric LV remodeling, increased left atrial size, and LV diastolic dysfunction. Given that the latter conditions are much more prevalent than HFNEF, symptoms of HF may be due to the contribution of additional mechanisms, including unrecognized ischemia, paroxysmal atrial fibrillation, altered left atrial function, chronotropic incompetence, vascular stiffness, peripheral factors, and others. Further research to unravel the pathophysiology of HFNEF in very well characterized patients and appropriate control subjects with a focus on the exercise response and the neurohumoral axis is needed to establish therapeutic strategies.

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**Key Words:** heart failure ■ normal ejection fraction ■ diastolic function ■ pathophysiology ■ diagnosis.