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Background—Increased left ventricular stiffness is a distinct finding in patients who have heart failure with normal ejection fraction (HFNEF). To elucidate how diastolic dysfunction contributes to heart failure symptomatology during exercise, we conducted a study using an invasive pressure-volume loop approach and measured cardiac function at rest and during atrial pacing and handgrip exercise.

Methods and Results—Patients with HFNEF (n=70) and patients without heart failure symptoms (n=20) were enrolled. Pressure-volume loops were measured with a conductance catheter during basal conditions, handgrip exercise, and atrial pacing with 120 bpm to analyze diastolic and systolic left ventricular function. During transient preload reduction, the diastolic stiffness constant was measured directly. Diastolic function with increased stiffness was significantly impaired in patients with HFNEF during basal conditions. This was associated with increased end-diastolic pressures during handgrip exercise and with decreased stroke volume and a leftward shift of pressure-volume loops during atrial pacing.

Conclusions—Increased left ventricular stiffness contributed to increased end-diastolic pressure during handgrip exercise and decreased stroke volume during atrial pacing in patients with HFNEF. These data suggest that left ventricular stiffness modulates cardiac function in HFNEF patients and suggests that diastolic dysfunction with increased stiffness is a target for treating HFNEF. (***Circulation*. 2008;117:2051-2060.)**

Key Words: cardiac output ■ cardiomyopathy ■ diastole ■ heart failure ■ hemodynamics

Patients who have heart failure present with dyspnea and exercise intolerance, regardless of a preserved or an impaired ejection fraction (EF). Up to 50% of patients with heart failure have preserved EF (typically described as EF >50%),[1] and most of them show evidence of diastolic dysfunction.[2,3] Therefore, the term heart failure with normal EF (HFNEF) has emerged. The underlying hemodynamic mechanisms leading to clinical symptoms in HFNEF are still under debate. Thus, it is important to improve the knowledge in this field and to investigate the underlying hemodynamic pathophysiology because the number of patients with a diagnosis of HFNEF is growing continuously and studies providing reliable data for evidence-based medical strategies are limited. Recent studies especially have revealed the relevance of HFNEF: Patients with HFNEF have survival rates that are similar to or only slightly better than those of patients with impaired EF.[2,3]

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Under physiological conditions, left ventricular (LV) pressure rapidly decays after systole, allowing low filling pressures and adequate diastolic filling. In HFNEF, diastolic filling is thought to be compromised as a result of aggravation in active and/or passive relaxation. Elevated filling pressure will increase pressure in the pulmonary system and eventually lead to pulmonary edema. It has been proposed that increased diastolic LV stiffness modulates cardiac function, but only a few studies measuring invasive LV diastolic function in patients with HFNEF appear to be available to further clarify this issue today. Moreover, these studies produced conflicting results focusing on the exact pathophysiological changes in diastolic function and its main factor, the end-diastolic pressure-volume (PV) relationship.[4,5] Recently, a large population-based noninvasive study has focused on patients with HFNEF. The results of this study showed that increased diastolic stiffness is a distinct finding in this patient collective.[6] Nevertheless, how this pathophysiological parameter translates into heart failure symptomatology with dyspnea and exercise intolerance with signs of output failure is still a subject of discussion because systolic function is deemed to be rather normal. Therefore, the question of how

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differential responses to exercise and other stressors may contribute to the pathophysiology of HFNEF was addressed.[6]

We hypothesized that diastolic stiffness modulates cardiac function in HFNEF during exercise. To test this hypothesis, we conducted the first prospective conductance PV loop study to investigate systolic and diastolic LV function in patients with HFNEF not only at rest but also during handgrip exercise and atrial pacing to examine any possible impact of diastolic dysfunction on the clinical symptoms in patients with HFNEF.

Methods

HFNEF Group

Patients were considered eligible for this study if they presented with heart failure symptoms and had an EF >50% while being hospitalized for heart failure. All patients suffered from symptoms of dyspnea, paroxysmal nocturnal dyspnea, and/or exercise intolerance, and they had at least 2 episodes of heart failure–related hospitalization in the past year. All eligible patients were carefully screened for noncardiac causes of heart failure symptoms. In particular, lung diseases such as chronic obstructive lung disease were ruled out by chest radiography and lung function tests. Patients were tested for atrial fibrillation, heart valve disease, hypertrophic cardiomyopathy, and significant coronary artery disease by means of ECG, laboratory values, angiography, and/or echocardiography, and they were excluded from the study if positively diagnosed for any of these conditions. None of the patients had a history of acute coronary syndrome or significant obstruction of any coronary vessel, and none of them had had coronary stents implanted previously. Invasive diagnostics were performed between January 2004 and May 2007. Heart failure clinical status was quantified with the New York Heart Association (NYHA) classification. Exercise tolerance was assessed by a 6-minute walking distance test[7] and by bicycle ergometry as previously described.[8] In addition, N-terminal pro-brain natriuretic peptide (NT-proBNP) plasma levels were determined (Elecsys 2010, Roche Diagnostics GmbH, Mannheim, Germany), and the glomerular filtration rate was calculated with the Cockcroft-Gault formula. A total of 70 patients met the inclusion criteria and were enrolled in this study as the HFNEF group.

Control Group

Twenty patients who were referred for evaluation of repeated chest discomfort but had no symptoms of heart failure were scheduled for diagnostic coronary angiography to exclude coronary artery disease. They underwent the same protocol, including a 6-minute walking test, bicycle ergometry, lung function test, and chest x-ray.

Cardiac conditions were stable before catheterization in all patients, and all medication was withheld before invasive examination for 24 hours. All participants provided informed written consent. Data on the basal LV function in 28 patients have been reported previously.[9]

Echocardiography

Doppler echocardiography was performed with a Vingmed System Five operated at 2.5 to 3.5 MHz by experienced observers blinded to all invasive hemodynamic data. Mitral flow was recorded in the apical 4-chamber view, and the E/A ratio was determined.[10] The data were adjusted for age and heart rate.[11] Chamber dimensions, including LV end-diastolic diameter, septal and posterior wall thicknesses, and left atrial size, were evaluated with standard procedures. LV mass index was calculated according to Devereux's formula divided by body surface area.[12] End-diastolic meridional wall stress was calculated from hemodynamic parameters (LV end-diastolic pressure [LVEDP]) and echocardiographic parameters (posterior wall thickness and LV end-diastolic diameter) as described previously.[13]

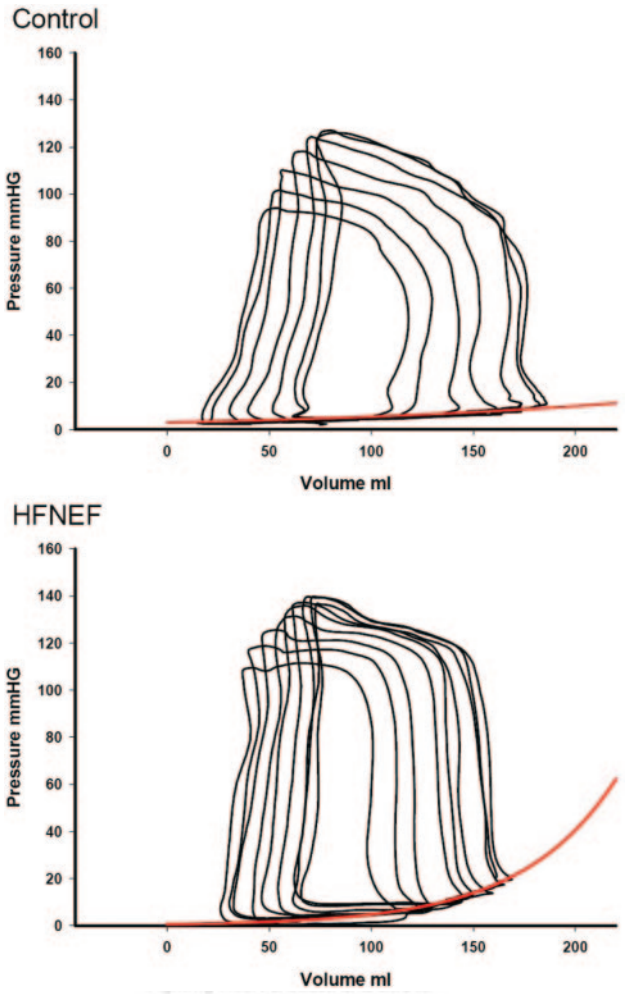

Figure 1. Representative PV loops during a preload reduction at sinus rhythm to obtain the end-diastolic PV relationship for a control subject and a patient with HFNEF. Red lines indicate the resulting end-diastolic PV relationship.

PV Measurements

The conductance catheter provides continuous online measurements of LV pressure and volume.[14] A total LV volume signal is calculated from a maximum of 7 segmental volume signals, representing short-axis slices of the ventricle. The present study used 7F combined pressure conductance catheters with 1-cm interelectrode spacing (CD Leycom, Zoetermeer, the Netherlands) introduced retrogradely by standard methods into the LV via the aortic valve. The catheter was connected to a Cardiac Function Laboratory (CD Leycom) for acquisition (250-Hz sample frequency) of LV volume, LV pressure, and ECG. The total LV volume was calibrated with thermodilution and hypertonic saline dilution as previously described and validated.[14,15] A temporary pacemaker lead was introduced into the right atrium. The systolic and diastolic LV function was obtained at normal sinus rhythm and during atrial pacing at 120 bpm for at least 5 minutes each. Hemodynamic indexes were obtained from steady-state PV loops. PV relationships were derived from PV loops recorded during preload reduction by balloon obstruction (NuMED, Hopkinton, NY) of the inferior vena cava for several beats (Figure 1). Cardiac performance was assessed by heart rate, stroke volume, end-diastolic volume, end-systolic volume, and cardiac output. Systolic preload-dependent LV function was assessed by EF, end-systolic pressure, and maximal rate of the LV pressure change (dP/dtmax). The systolic preload-independent LV function was assessed by the end-systolic PV relationship.[16,17] The end-systolic PV relationship was characterized by its linear slope, by the

Table 1. Patient Characteristics for the Control Group and HFNEF Group

Patient Characteristics	Control (n=20)	HFNEF (n=70)	*P*
Age, y	55 (46 to 60)	58 (52 to 64)	0.21*
White, n (%)	20 (100)	70 (100)	1†
Female/male, n (%)	11 (55)/9 (45)	40 (57.1)/30 (42.9)	1†
Body mass index, kg/m^2	25.5 (22.6 to 28.1)	27.8 (22.8 to 32.1)	0.193‡
Glomerular filtration rate, mL/min	87 (78 to 89)	83 (69 to 92)	0.165‡
NYHA class II to III, n (%)	0 (0)/0 (0)	43 (61.4)/27 (38.6)	<0.001‡
NT-proBNP, pg/mL	38 (22 to 46)	204 (113 to 374)	<0.001‡
Medications, n (%)			
β-Blocker	3 (15)	34 (48.6)	0.0092†
ACE inhibitors/ARBs	3 (15)	37 (52.9)	0.0042†
Ca^{2+} channel blocker	0 (0)	13 (18.6)	0.0644†
Diuretics	0 (0)	19 (27.1)	0.0054†
Concomitant diseases, n (%)			
Arterial hypertension			
Grade 1/2	4 (20)/0 (0)	11 (15.7)/15 (21.4)	0.053†
Diabetes mellitus	2 (10)	12 (17.1)	0.72†
Hyperlipoproteinemia	5 (25)	23 (32.8)	0.59†
Smoker	6 (30)	11 (15.7)	0.19†
Exercise testing			
6-min walking distance, m	514 (459 to 589)	286 (201 to 365)	<0.001‡
Bicycle ergometry, W	185 (170 to 200)	128 (102 to 140)	<0.001‡

ACE indicates angiotensin-converting enzyme; ARBs, angiotensin receptor blockers.
*Unpaired *t* test.
†Fisher's exact test.
‡Mann–Whitney *U* test.

end-systolic elastance (E_{ES}),[16] and the ratio of the afterload to the E_{ES}.[5] Diastolic load-dependent LV function was quantified by LVEDP, isovolumetric relaxation (relaxation time constant, τ), and the minimal rate of LV pressure change (dP/dtmin). The end-diastolic PV relationship (dP/dV) was calculated to determine LV functional chamber stiffness (LV stiffness, b). Furthermore, the load-independent diastolic function was derived from the end-diastolic PV relationship with exponential fitting to obtain the chamber stiffness constant (LV stiffness constant, β). Additionally, in a subset of patients (12 control subjects, 25 HFNEF patients) handgrip exercise was performed as a further study of LV function. To increase volume load and afterload, patients were asked to perform handgrip exercise with raised arms as long as possible, and PV data were acquired as described above before patients discontinued exercise.

Statistical Analysis

All continuous variables are reported as median values with the first and third quartiles. Group comparisons of normally distributed variables were tested by nonpaired *t* test (HFNEF group versus control group) and paired *t* test (sinus versus pacing). The nonparametric Mann–Whitney *U* test was used for comparisons of nonnormally distributed variables for the HFNEF and control groups. Paired comparisons of nonnormally distributed variables were analyzed by the Wilcoxon signed-rank test. Fisher's exact test was used to analyze categorical variables. Values of $P<0.05$ were considered statistically significant. The data were analyzed with SPSS version 12.0 (SPSS Inc, Chicago, Ill).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Study Groups

Patient characteristics are presented in Table 1. There were no significant differences between HFNEF patients and control subjects with respect to age, gender, race, and body mass index. All enrolled HFNEF patients had an NYHA class of II or III, whereas control patients had no heart failure symptoms. Consistent with the NYHA classifications, NT-proBNP was significantly increased in HFNEF patients compared with control subjects, and HFNEF patients showed significantly decreased exercise tolerance on both the 6-minute walk test and the bicycle ergometry.

Echocardiography

The results for echocardiography are presented in Table 2. All of the patients investigated showed cardiac dimensions within normal limits. The LV mass index as a sign of concentric hypertrophy was significantly higher in HFNEF patients. Patients with HFNEF had increased atrial size, which has been considered a predictor of cardiovascular mortality in HFNEF.[18] Mitral flow showed a significantly decreased E/A ratio. No patient showed pseudonormal or restrictive filling patterns. The end-diastolic wall stress was significantly increased in the HFNEF group as a result of the increased LVEDP yet unchanged LV chamber dimensions and increased wall thickness.

Table 2. Echocardiographic Characteristics

	Control (n=20)	HFNEF (n=70)	*P*
Chamber dimensions			
LVEDD, mm	47 (42 to 49)	46 (40 to 50)	0.573*
Septum, mm	9.8 (8.3 to 10.2)	11.4 (10.5 to 12.6)	<0.001*
Posterior wall, mm	9.4 (8.6 to 9.5)	11.2 (10.2 to 12.9)	<0.001*
LA, parasternal, mm	34 (31 to 36)	39 (35 to 42)	0.042*
LVMI, g/m^2	95 (81 to 99)	128 (109 to 135)	<0.001*
Diastolic wall stress, kdyne/cm^2	10.6 (9.4 to 11.2)	18.8 (16.1 to 20.5)	<0.001*
Mitral flow E/A	1.3 (1.1 to 1.5)	0.92 (0.8 to 1.15)	0.021†

LVEDD indicates LV end-diastolic diameter; LA, left atrium; LVMI, left ventricular mass index; E/A, ratio of peak early and late mitral flow.

*Unpaired *t* test.

†Mann–Whitney *U* test.

PV Measurements of Diastolic Function

The PV measurements of diastolic function are presented in Table 3. At baseline (ie, during normal sinus rhythm), patients with HFNEF showed prolonged τ, increased EDPs, and increased diastolic stiffness (b) and stiffness constant (β) compared with controls (Figure 1). In the control group, pacing with 120 bpm led to a shortening of active relaxation, as shown by a significantly reduced τ and improved dP/dtmin, as well as a decrease in the EDP. In contrast, b and β remained unchanged compared with basal conditions. In the HFNEF group, τ and dP/dtmin also improved significantly during pacing with 120 bpm compared with baseline. As in the control group, LVEDP dropped significantly, and b and β did not change significantly at 120 bpm.

PV Measurements of Systolic Function and Global Cardiac Function

The PV measurements of systolic function are presented in Table 4. Under basal conditions, there appeared to be no significant differences between HFNEF patients and control subjects for any systolic function index except end-systolic pressure. The role of systolic function in HFNEF is still a matter of discussion.[19] In our study, systolic function did not differ between the 2 groups under baseline conditions. In the

Table 3. Hemodynamic PV Measurements: Diastolic Function

	Control (n=20)	HFNEF (n=70)	*P*, Control vs HFNEF
EDP, mm Hg			
SR	5.6 (5.0 to 7.1)	16.1 (11.9 to 21.9)	<0.001*
120 bpm	4.5 (3.4 to 6)	7.7 (4.8 to 13.3)	0.002*
P, SR vs 120 bpm	0.009†	<0.001†	
dP/dtmin, mm Hg/s			
SR	−1857 (−1955 to −1773)	−1715 (−1914 to −1575)	0.132*
120 bpm	−2171 (−2223 to −1949)	−1889 (−2046 to −1627)	0.065*
P, SR vs 120 bpm	<0.001†	<0.001†	
τ, ms			
SR	41 (38 to 42)	54 (47 to 62)	<0.001*
120 bpm	36 (32 to 38)	43 (36 to 52)	<0.001*
P, SR vs 120 bpm	<0.001†	<0.001†	
β			
SR	0.0098 (0.009 to 0.011)	0.028 (0.022 to 0.038)	<0.001*
120 bpm	0.0089 (0.005 to 0.011)	0.03 (0.016 to 0.041)	0.0027*
P, SR vs 120 bpm	0.615†	0.938†	
Stiffness b, mm Hg/mL			
SR	0.09 (0.07 to 0.12)	0.24 (0.16 to 0.37)	<0.001*
120 bpm	0.07 (0.05 to 0.11)	0.19 (0.11 to 0.39)	0.0033*
P, SR vs 120 bpm	0.142†	0.664†	

EDP indicates end-diastolic pressure; SR, sinus rhythm; and 120 bpm, atrial pacing with 120 bpm. Probability values were not adjusted for multiple comparisons.

*Mann–Whitney *U* test.

†Wilcoxon signed-rank test.

Table 4. Hemodynamic PV Measurements: Systolic Function

	Control (n=20)	HFNEF (n=70)	*P*, Control vs HFNEF
ESP, mm Hg			
SR	115 (111 to 122)	136 (116 to 155)	0.016*
120 bpm	113 (100 to 127)	123 (108 to 137)	0.046*
P, SR vs 120 bpm	0.501†	<0.001†	
dP/dtmax, mm Hg/s			
SR	1682 (1546 to 1773)	1638 (1467 to 1829)	0.465‡
120 bpm	1994 (1867 to 2281)	1892 (1615 to 2146)	0.062‡
P, SR vs 120 bpm	0.002§	<0.001§	
EF, %			
SR	65 (62 to 75)	65 (59 to 73)	0.317*
120 bpm	70 (68 to 77)	66 (54 to 78)	0.127*
P, SR vs 120 bpm	0.039†	0.362†	
E_{ES}, mm Hg/mL			
SR	0.95 (0.8 to 1.1)	1.1 (0.95 to 1.25)	0.237‡
120 bpm	1.25 (1 to 1.5)	1.6 (1.1 to 2.0)	0.116‡
P, SR vs 120 bpm	0.043§	0.014§	
E_a/E_{ES}			
SR	1.3 (0.8 to 1.7)	1.3 (1 to 1.7)	0.323‡
120 bpm	1.2 (0.9 to 1.3)	1.2 (0.8 to 1.6)	0.665‡
P, SR vs 120 bpm	0.187§	0.078§	

Abbreviations as in Table 3, plus ESP indicates end-systolic pressure; E_{ES}, end-systolic elastance; and E_a/E_{ES}, ratio of E_a and E_{ES} indicating ventricular vascular coupling. Probability values were not adjusted for multiple comparisons.
*Unpaired *t* test.
†Paired *t* test.
‡Mann–Whitney *U* test.
§Wilcoxon signed-rank test.

control group, pacing with 120 bpm significantly increased dP/dtmax and E_{ES}. Likewise, in the HFNEF group, dP/dtmax and E_{ES} increased as a result of pacing.

Table 5 presents data on global cardiac function during sinus rhythm (baseline) and pacing at 120 bpm for HFNEF patients. Under basal conditions, there were no significant differences between groups in heart rate, end-diastolic volume, end-systolic volume, stroke volume, or cardiac output. No differences were detected in the ratio of afterload to E_{ES}. During pacing with 120 bpm, control patients showed a physiological response, evidenced by significantly increased cardiac output, with maintained end-systolic and increased end-diastolic volumes. In contrast, pacing with 120 bpm in HFNEF patients showed significantly reduced end-diastolic volume and stroke volume. These changes are evidenced by a smaller and leftward-shifted PV loop during pacing in the HFNEF group (Figure 2). Consequently, comparisons of the HFNEF and control patients during pacing showed significantly lower cardiac output, stroke volume, and end-diastolic volume for the HFNEF group.

Cardiac Function After Handgrip Exercise

The PV measurements of LV function before and after handgrip exercise are presented in Table 6. The heart rate increase was more pronounced in control subjects than in HFNEF patients. Exercise time was decreased in HFNEF patients compared with control patients: 1.4 minutes (1 to 1.9 minutes) versus 2.5 minutes (2.1 to 3.1 minutes); $P=0.017$, Mann–Whitney *U* test. End-diastolic volume was not significantly different before and after the handgrip test. EDP increased significantly in HFNEF patients, whereas EDP in control subjects did not change (Figure 3). In both groups, systolic pressure was found to increase after handgrip exercise. Cardiac stiffness was increased in HFNEF patients compared with control subjects. Nevertheless, cardiac stiffness was unchanged compared with its baseline value in the same group.

Discussion

The present study is the largest to date to investigate cardiac function in patients with HFNEF with an invasive PV loop approach. We found significant diastolic abnormalities in relatively young patients with HFNEF who were stable at rest but suffered from heart failure symptoms during exercise. These diastolic abnormalities were demonstrated by prolonged relaxation and increased diastolic stiffness, both analyzed by invasive measurements of PV loops. Increased LV stiffness contributed to increased EDPs during handgrip exercise and decreased stroke volume during atrial pacing. We therefore propose that diastolic stiffness is to be credited as one of the targets for treating HFNEF.

HFNEF is diagnosed predominantly in elderly patients, but recent community cohort studies have demonstrated that this disease begins to occur in patients during their 40s and 50s.[2,3]

Table 5. Hemodynamic PV Measurements: Global Cardiac Function

	Control (n=20)	HFNEF (n=70)	*P*, Control vs HFNEF
HR, bpm			
SR	76 (65 to 85)	71 (65 to 82)	0.468*
120 bpm	121 (118 to 122)	120 (119 to 122)	0.372*
P, SR vs 120 bpm	<0.001§	<0.001§	
SV, mL			
SR	109 (77 to 118)	94 (80 to 111)	0.084†
120 bpm	122 (115 to 139)	72 (51 to 85)	<0.001†
P, SR vs 120 bpm	0.013‡	<0.001‡	
CO, L/min			
SR	7.3 (5.8 to 9.8)	6.8 (5.5 to 8.0)	0.054†
120 bpm	14.5 (14.2 to 16.7)	8.2 (5.9 to 10.8)	<0.001†
P, SR vs 120 bpm	<0.001‡	<0.001‡	
ESV, mL			
SR	65 (50 to 69)	59 (36 to 66)	0.553‡
120 bpm	56 (33 to 66)	52 (35 to 61)	0.712‡
P, SR vs 120 bpm	0.252§	0.004§	
EDV, mL			
SR	158 (153 to 168)	151 (118 to 170)	0.746*
120/bpm	169 (161 to 199)	109 (90 to 128)	<0.001*
p values	0.046§	<0.001§	
P, SR vs 120 bpm			

Abbreviations as in Table 3, plus HR indicates heart rate; SV, stroke volume; CO, cardiac output; ESV, end-systolic volume; and EDV, end-diastolic volume. Probability values were not adjusted for multiple comparisons.

*Mann–Whitney *U* test.

†Unpaired *t* test.

‡Paired *t* test.

§Wilcoxon signed-rank test.

The present study investigated patients with HFNEF who were younger than the epidemiological mean. However, all patients had the definite diastolic dysfunction that recent guidelines required to be present for an HFNEF diagnosis.[20] Furthermore, because LV stiffness is known to increase with age,[21] we suggest that HFNEF not only is a disease of the elderly but might start earlier in life and become more frequent with increasing age and concomitant disease.

The role of systolic function in HFNEF is still a matter of discussion.[19] In our study, systolic function did not differ between the 2 groups under baseline conditions. Thus, our data show that systolic function was not significantly impaired in our study population. This concurs with several previous studies that view HFNEF as a diastolic dysfunction with normal or only mildly reduced EF.[21–23]

We found significant evidence of diastolic dysfunction in this HFNEF study population on the basis of echocardiographic and PV-derived parameters. The clinical status (NYHA) was further verified by more objective tests, including a reduced 6-minute walking distance, ergometry results, and increased NT-proBNP levels. Characterization by echocardiography revealed increased left atrial dimensions, which have already been reported to be a predictor of cardiovascular mortality in HFNEF.[18] This enlargement might result from the chronically increased workload required to fill the stiff LV. The present study, using the direct methodology with PV loops acquired during a loading intervention,[16] demonstrated increased LV stiffness as the main abnormality in HFNEF. This is in agreement with the results of Zile et al,[4] who demonstrated that patients with more severe heart failure symptoms (compared with the patients in the present study) have significant abnormalities in active relaxation and increased passive cardiac stiffness, supported by large population-based studies carried out using a noninvasive approach to measure diastolic stiffness.[6,21] In contrast, Kawaguchi et al[5] demonstrated high filling pressures resulting from a parallel upward shift in the PV relationship without increased LV stiffness. Furthermore, these authors demonstrated that the ventricular-arterial stiffening contributes to heart failure symptoms, an effect not seen in our collective. It therefore remains unclear which of these mechanisms leads to heart failure symptoms during exercise in HFNEF patients. To further clarify this issue, we evaluated diastolic and systolic LV function in HFNEF patients under basal and stress conditions during handgrip exercise and atrial pacing-induced tachycardia.

It has been considered that a stiff ventricle may possess only limited ability to use the Frank-Starling mechanism to increase stroke volume during exercise with increased heart rates.[24] For this reason, we performed atrial pacing to mimic

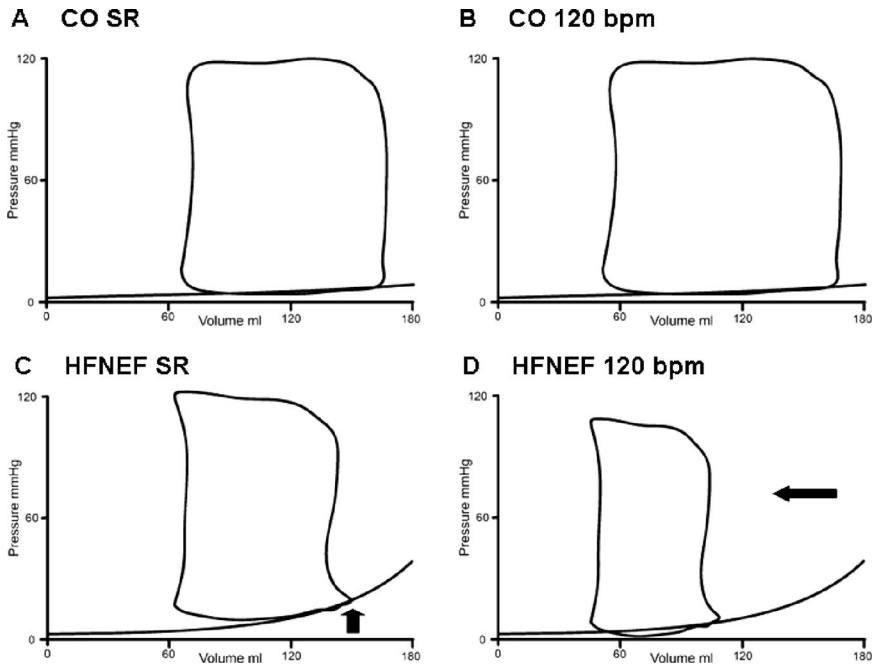

Figure 2. A, Schematic PV loop and β for a control subject. B, PV loop and β from the same control subject during atrial pacing–induced enhanced demand (heart rate, 120 bpm). C, Schematic PV loop and β from a patient with HFNEF under basal conditions (sinus rhythm [SR]) showing increased β and LVEDP (black arrow). D, PV loop and β from the same HFNEF patient during atrial pacing (heart rate, 120 bpm) showing a decreased stroke volume and decreased end-diastolic volumes (black arrow). CO indicates cardiac output.

increased cardiac demand during higher heart rates; we also performed handgrip exercise in a subset of patients. In the control group, increased heart rates by pacing resulted, as expected, in shortened isovolumetric relaxation time without any significant changes in the diastolic stiffness constant.[25,26] Similarly, HFNEF patients showed a pacing-induced shortening in τ and no change in the diastolic stiffness constant. In contrast to the control group, however, the HFNEF patients showed a reduction in LVEDP and LV end-diastolic volumes during pacing (Figure 1). This effect results from the abnormal diastolic stiffness becoming manifest during rapid pacing when the filling time is substantially reduced. As a result, diastolic filling was limited during pacing. This led to reduced end-diastolic volumes and consequently to reduced stroke volumes, as indicated by the shift to the left and narrowing of the PV loops (Figure 1), which also is in agreement with the findings of others.[27] This blunted cardiac output response resulting from stroke volume limitation may contribute to the development of heart failure symptoms in HFNEF patients because it was also shown in patients with hypertrophic cardiomyopathy.[28] Nevertheless, the exact mechanisms leading to exercise intolerance are still a matter of discussion, and further studies should investigate the influence of LVEDP and stiffness on exercise tolerance in patients with HFNEF. It is noteworthy that PV data during handgrip exercise and atrial pacing were positioned on the diastolic stiffness curve (which remained unchanged). Therefore, its steep exponential increase may explain the increase of the LVEDP during handgrip exercise in patients with HFNEF (Figure 2) and the reduced stroke volume during pacing.

It has been debated whether diastolic dysfunction or nondiastolic disturbances of the cardiovascular system can indeed limit exercise capacity in HFNEF patients. Borlaug et al[29] showed recently that nondiastolic limitations of the cardiovascular function may be predominant over diastolic dysfunction. They showed that reduced chronotropic reserve contributes to dyspnea and exercise intolerance in patients with HFNEF, as has also been documented in other studies.[30] Coherently and in agreement with Borlaug et al[29] and Kitzman et al,[30] we document that during handgrip exercise, heart rates in HFNEF patients did not rise adequately. Therefore, Borlaug and colleagues concluded that a possible strategy to treat HFNEF might be to increase heart rates.[29] In the present study, atrial pacing resulted in a frequency-dependent reduction in stroke volumes resulting from a shift to the left of the PV loops with a decrease in end-diastolic volumes. Pacing-induced tachycardia is a distinct form of stress and cannot be compared directly with physiological changes during exercise with altered afterloads. This has been documented by our data during handgrip in a supine position (when end-diastolic volumes were not changed significantly in the HFNEF group) and by further data of Borlaug et al[29] showing an increase in end-diastolic volume during treadmill exercise. Nevertheless, the changes observed in stroke volumes during atrial pacing (which resulted in higher heart rates compared with handgrip exercise) in the present study were compared with control subjects, in whom we did not observe this effect under the same conditions; therefore, decreased stroke volume during pacing-induced tachycardia may represent one pathophysiological limitation in HFNEF. The discrepancies noted here might be explained by the different forms of stress applied and by differences in the study population. Borlaug et al[29] recruited predominantly obese dark-skinned females, whereas our population consisted of nonobese white-skinned recruits. These differences, as well as the more severe limitation of exercise capacity in the former study[29] compared with the current collective, might explain the differences in study findings. Taken together, we conclude from the current data that diastolic dysfunction with increased stiffness contributes to cardiovascular abnormalities in HFNEF and that highly increased heart rates may limit

Table 6. Hemodynamic PV Measurements: Handgrip Exercise

	Control (n=12)	HFNEF (n=25)	*P*, Control vs HFNEF
HR, bpm			
SR	69 (61 to 75)	71 (65 to 79)	0.469*
Exercise	121 (108 to 139)	103 (90 to 120)	<0.001*
P, SR vs exercise	<0.001†	<0.001†	
Systolic BP, mm Hg			
SR	122 (110 to 129)	136 (121 to 155)	0.188‡
Exercise	163 (148 to 173)	179 (118 to 181)	0.036‡
P, SR vs exercise	<0.001§	<0.001§	
ESP, mm Hg			
SR	118 (107 to 125)	134 (112 to 152)	0.211*
Exercise	155 (141 to 167)	175 (156 to 188)	0.036*
P, SR vs exercise	<0.001†	<0.001†	
ESP, mm Hg			
SR	6.2 (5.5 to 7.4)	15.4 (11.3 to 19.6)	<0.001‡
Exercise	6.9 (4.6 to 7.9)	23.7 (15.8 to 28.5)	<0.001‡
P, SR vs exercise	0.212§	<0.001§	
EDV, mL			
SR	154 (145 to 160)	148 (126 to 169)	0.766*
Exercise	159 (145 to 181)	152 (131 to 172)	0.204*
P, SR vs exercise	0.072†	0.176†	
β			
SR	0.0093 (0.009 to 0.011)	0.029 (0.024 to 0.037)	<0.001‡
exercise	0.001 (0.008 to 0.012)	0.03 (0.016 to 0.041)	<0.001‡
P, SR vs exercise	0.635§	0.947§	

Abbreviations as in Tables 3 through 5. Probability values were not adjusted for multiple comparisons.
*Unpaired *t* test.
†Paired *t* test.
‡Mann–Whitney *U* test.
§Wilcoxon signed-rank test.

diastolic filling because of the decreased compliance of the LV and may contribute to the heart failure symptomatology in patients with HFNEF and diastolic dysfunction.

Besides the role of chronotropic incompetence, Maurer et al[31,32] discuss the role of fluid overload[31] and increased ventricular volume[32] as important pathological mediators of HFNEF. However, this increase, documented in patients from the Cardiovascular Health Study, which was apparent in only a subpopulation of their HFNEF patients,[33] was not observed in other community cohort studies.[6] It was therefore suggested that end-diastolic volume is rather normal in patients with HFNEF,[33] which is supported by our data measured by the invasive conductance technique. Furthermore, we show increased LVEDP during basal conditions at similar end-di-

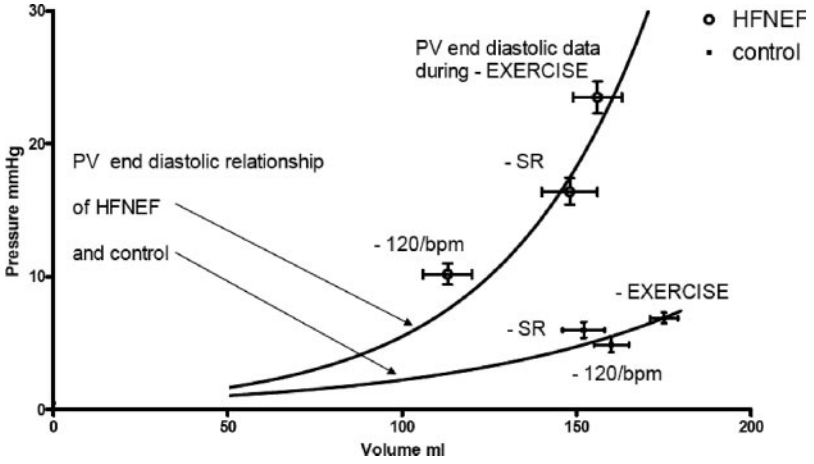

Figure 3. Black curves representing the end-diastolic PV relationships from the HFNEF and control groups (arrows indicate curve for HFNEF and control subjects, respectively). ○ Indicates the mean end-diastolic volume (with horizontal error bars indicating the SEM) and pressure (vertical error bars indicating SEM) during sinus rhythm (SR), during pacing with 120 bpm, or during exercise of the HFNEF group. ■ Indicates the mean end-diastolic volume and pressure (with vertical and horizontal error bars indicating SEM) of control subjects.

astolic volumes compared with control subjects, a finding that we suggest is mediated by the increased LV stiffness. Therefore, our data show that increased filling pressures occur in patients with HFNEF without volume overload and subsequent enlargement of the LV, although we did not measure intravascular volume directly in this study. This discrepancy might be explained by the normal renal function of our HFNEF patients compared with the renal dysfunction shown in the study population investigated by Maurer et al.[32] Renal dysfunction with volume overload might alter and aggravate the pathophysiology of HFNEF, especially when the exponential rise of the LV stiffness is taken into account, and this would lead to even higher filling pressures in relatively small LVs.

The cause of HFNEF might include a panel of heterogenic pathomechanisms, including volume overload, ventricular-vascular stiffening, chronotropic incompetence, and diastolic dysfunction with increased stiffness. This might explain some of the difficulties encountered in developing successful evidence-based therapies and why there might appear to be a difference in quality and quantity of the different pathologies in each individual patient.

Conclusions

Using direct invasive measurements, we have shown that diastolic abnormalities with increased diastolic stiffness lead to a reduced stroke volume during pacing-induced tachycardia and an increase in EDP during handgrip exercise. We therefore propose that increased diastolic stiffness significantly modulates the clinical symptoms in patients with HFNEF. A reduction in diastolic stiffness is one of the targets for treating HFNEF.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Heart failure with normal ejection fraction (HFNEF) is an increasing problem; today, ≈50% of all heart failure patients have a normal ejection fraction. The mortality rate seems to be similar to that of patients with reduced ejection fraction, but our knowledge about the underlying hemodynamic pathology is limited. We performed a study investigating the diastolic function of patients with HFNEF invasively using pressure-volume loops to obtain the diastolic stiffness of the left ventricle. The highly increased diastolic stiffness in the HFNEF group, the key finding of the present study, shows that diastolic dysfunction can be demonstrated in HFNEF patients. It may further explain their main clinical symptomatology: exercise intolerance. Artificial pacing to mimic tachycardia during exercise reduced the stroke volume resulting from a leftward shift of the pressure-volume loops and therefore blunted the increase in the cardiac output, which is needed to comply with increased oxygen demand during exercise in patients with HFNEF. This was associated with a limitation of workload during exercise. Although it was shown recently that nondiastolic abnormalities also occur in patients with HFNEF, we suggest that diastolic stiffness is another important feature of HFNEF that might trigger heart rate–dependent changes in the global cardiac function and therefore contribute to heart failure symptomatology. These data further suggest that destiffening therapies might be a future goal for treating HFNEF.