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Hemodynamic Basis of Exercise Limitation in Patients With Heart Failure and Normal Ejection Fraction

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Objectives The purpose of this study was to invasively investigate the hemodynamic response to exercise in patients with heart failure with normal ejection fraction (HFNEF) and to evaluate the ability of the peak early diastolic transmitral velocity to peak early diastolic annular velocity ratio (E/e′) to reflect exercise hemodynamics.

Background There is little information regarding the hemodynamic response to exercise in HFNEF.

Methods Patients with HFNEF (n = 14) and asymptomatic controls (n = 8) underwent right-side heart catheterization at rest and during supine cycle ergometer exercise and echocardiography with measurement of resting and peak exercise E/e′.

Results Resting pulmonary capillary wedge pressure (PCWP) (10 ± 4 mm Hg vs. 10 ± 4 mm Hg; p = 0.94) was similar in HFNEF patients and controls, but stroke volume index (SVI) (p = 0.02) was lower, and systemic vascular resistance index (SVRI) (p = 0.01) was higher in patients. Patients stopped exercise at lower work rate (0.63 ± 0.29 W/kg vs. 1.13 ± 0.49 W/kg; p = 0.006). Although peak exercise PCWP was similar in both groups (23 ± 6 mm Hg vs. 20 ± 7 mm Hg; p = 0.31), the peak PCWP/work rate ratio was higher in patients compared with controls (46 ± 31 mm Hg/W/kg vs. 20 ± 9 mm Hg/W/kg; p = 0.03). Peak exercise SVI (p = 0.001) was lower and SVRI was higher (p = 0.01) in patients. Resting E/e′ was modestly elevated in patients (13.2 ± 4.1 vs. 9.5 ± 3.4; p = 0.04). Peak exercise E/e′ did not differ between the groups (11.1 ± 3.4 vs. 9.4 ± 3.4; p = 0.28).

Conclusions The HFNEF patients achieved a similar peak exercise PCWP to that of asymptomatic controls, at a much lower workload. This occurs at a lower SVI and in the setting of higher SVRI. The E/e′ does not reflect the hemodynamic changes during exercise in HFNEF patients. (J Am Coll Cardiol 2010;56:855–63) © 2010 by the American College of Cardiology Foundation

The diagnosis of heart failure is essentially made on the basis of both the presence of a constellation of symptoms in which exercise intolerance due to dyspnea is a key feature, and the demonstration of impaired left ventricular (LV) function (1). A large body of evidence now indicates that in approximately 50% of patients with heart failure the left ventricular ejection fraction (LVEF) is normal, termed heart failure with normal ejection fraction (HFNEF) (2). HFNEF patients may be as symptomatically limited as are heart failure patients with reduced LVEF (3), and their survival is reduced in comparison with age-matched controls (4).

To date, little progress has been made with regard to the development of specific treatments for HFNEF (5–7). Accordingly, a major imperative exists for the detailed characterization of the key causes of symptoms in HFNEF.

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Although the majority of patients with HFNEF have symptoms only on exertion, very little detailed data exists regarding the hemodynamic response to exercise in these patients. Whereas recent noninvasive studies have shed more light on LV mechanics during exercise (8,9), fundamental questions on the exercise response in HFNEF remain unanswered. Sophisticated studies using LV conductance catheters and right atrial pacing to mimic exercise demonstrated a decrease in LV

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Abbreviations and Acronyms

E = peak early diastolic transmitral velocity

$e'_{septal/lateral/av}$ = peak early diastolic mitral annular velocities at septal and lateral annulus and averaged value

HFNEF = heart failure with normal ejection fraction

LV = left ventricular

LVEF = left ventricular ejection fraction

NYHA = New York Heart Association

PCWP = pulmonary capillary wedge pressure

$s'_{septal/lateral/av}$ = peak systolic mitral annular velocities at the septal and lateral annulus and the averaged value

SVI = stroke volume index

SVRI = systemic vascular resistance index

VO_2 = oxygen uptake

end-diastolic pressure and stroke volume at higher heart rates (10,11), whereas noninvasive studies revealed varying stroke volume responses to exercise (8,9,12). A wide range of causative mechanisms for HFNEF have been proposed, including altered diastolic performance (13), LV systolic dysfunction (9,14), altered ventriculovascular coupling (15), impaired vasodilator reserve (12), chronotropic incompetence (12), and increased pulmonary vascular reactivity (16).

Given the ongoing uncertainty about the pathophysiology of HFNEF, we aimed to invasively investigate the hemodynamic response to cycle ergometer exercise in patients with suspected HFNEF in comparison with asymptomatic control subjects. In conjunction, we evaluated the ability of noninvasive measures to accurately reflect the hemodynamic profile during exercise.

Methods

Patients and protocol. Between September 2008 and August 2009, we studied 14 patients with suspected HFNEF and 8 control subjects. Patients with HFNEF underwent right-side heart catheterization for evaluation of exercise intolerance corresponding to a New York Heart Association (NYHA) functional class II or III as well as objective evidence of impaired exercise capacity as assessed by cardiopulmonary exercise testing, treadmill exercise tests, or 6-min walking tests. None of the patients reported angina, and all participants either had a negative stress echocardiogram, a negative myocardial perfusion scan, or a negative exercise electrocardiogram. Patients without sinus rhythm and patients with left bundle branch block, cardiomyopathies, more than mild valvular heart disease, LVEF <50%, and a forced expiratory volume within 1 s less than the lower limit of normal were excluded. These criteria are in accordance with those from recently published mechanistic studies on HFNEF (8,9,11). Similar to these studies, the presence of LV diastolic dysfunction as defined by recent recommendations (17) was not an inclusion criterion. Control subjects matched for age, sex, and blood pressure with subjectively normal exercise tolerance were recruited by advertisement and from outpatient clinics.

All studies were performed in the nonfasting state and under full medication if applicable. All participants underwent transthoracic echocardiography at rest (full study) and during exercise (measurement of the peak early diastolic transmitral velocity [E] to peak early diastolic annular velocity [e′] ratio [E/e′] simultaneously with invasive hemodynamic measurements), and resting and exercise right-side heart catheterization. Ten HFNEF patients and all controls also underwent maximal cardiopulmonary exercise testing on a separate day. The study was approved by the ethics committee of the Alfred Hospital, and all participants provided written informed consent.

Echocardiography. Echocardiograms were obtained by 1 single experienced echocardiographer, using standard views in accordance with current guidelines (18,19). Measurements were performed off-line by a single reader. All reported measurements were averaged from 3 cycles. Pulsed-wave Doppler recordings of transmitral inflow were obtained between the mitral leaflet tips from the apical 4-chamber view to assess E and the peak late diastolic transmitral velocity and deceleration time. Peak systolic and peak early diastolic mitral annular velocities were measured by pulsed wave tissue Doppler at the septal and lateral annulus, and averaged values were also calculated ($s'_{septal/lateral/av}$ and $e'_{septal/lateral/av}$) (19). The E/e′ ratio was calculated for the septal (E/e'_{septal}) and the lateral ($E/e'_{lateral}$) annulus as well as based on e'_{av} (E/e'_{av}).

Cardiac catheterization. Cardiac catheterization was performed immediately after the resting echocardiogram. A 3-F arterial line was placed in a radial or brachial artery for blood pressure measurement and blood sampling. A balloon-tipped pulmonary artery catheter (7-F) was inserted through an introducer sheath placed in the right internal jugular or a brachial vein for measurement of right atrial pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure (PCWP). The wedge position was confirmed by fluoroscopy and pressure wave form, and the mean PCWP was measured at end expiration. Cardiac output was measured using thermodilution with measurements taken in triplicate. Measurements were indexed to body surface area, as appropriate. Data on stroke volume index (SVI) refer to thermodilution-derived values throughout the paper.

Subjects then started to exercise in the supine position on a cycle ergometer mounted to the catheter table at a work rate of 0.3 ± 0.1 W/kg body weight. Where this was the maximal symptom-limited work rate (8 HFNEF patients), hemodynamics were measured 3 min after the commencement of exercise. For the remaining patients, the work rate was increased to a second stage that corresponded at least to submaximal exercise (1.0 ± 0.2 W/kg in 6 HFNEF patients and 7 controls, and 1.5 W/kg in 1 control) with hemodynamic measures obtained after 3 min. Measurements of exercise E and e'_{septal} were obtained simultaneously with invasive measurements. Arterial and mixed venous blood samples were obtained at rest and peak exercise for blood gas analysis. Arteriovenous differences in oxygen content and oxygen uptake (VO_2) at rest and peak exercise were calculated according to the Fick principle from thermodilution-derived cardiac

Table 1 Clinical Characteristics of Patients With HFNEF and Controls

	HFNEF (n = 14)	Controls (n = 8)	p Value
Age, yrs	69 ± 10	61 ± 12	0.12
Sex, male/female	9 (64%)/5 (36%)	5 (63%)/3 (37%)	0.93
Body mass index, kg/m^2	29.6 ± 4.6	25.0 ± 5.1	0.046
Diabetes mellitus	2 (14%)	0	
Medication			
Aspirin	3 (21%)	0	
Warfarin	2 (14%)	0	
Statin	3 (21%)	0	
ACEI/ARB	8 (57%)	0	
Beta-blocker	5 (36%)	0	
Ca^{2+} blocker	8 (57%)	0	
Diuretic	4 (29%)	0	
Symptoms			<0.001
NYHA functional class II	6 (43%)	0	
NYHA functional class III	8 (57%)	0	
B-type natriuretic peptide, ng/l	40 (10–428)	60 (13–79)	0.65
N-terminal pro–B-type natriuretic peptide, ng/l	95 (13–1,018)	61 (12–141)	0.27
eGFR, ml/min/1.73 m^2	87 ± 33	96 ± 17	0.48
Hemoglobin, g/l	137 ± 10	146 ± 14	0.08

Data are given as mean ± SD, counts and percentages, or median (range).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; eGFR = estimated glomerular filtration rate; HFNEF = heart failure and normal ejection fraction; NYHA = New York Heart Association.

output, arterial and mixed venous oxygen saturations, and hemoglobin.

Cardiopulmonary exercise testing. On a separate day, subjects underwent maximal upright cardiopulmonary exercise testing on an electronically braked cycle ergometer using step protocols with 5- to 15-W increments every minute. Minute ventilation, VO_2, and carbon dioxide output were obtained breath by breath and averaged at 30-s intervals (SensorMedics, Yorba Linda, California). Peak VO_2 was defined as the maximum 30 s VO_2 average. The slope of the ventilation to carbon dioxide output relationship was calculated from all data points from the beginning to the end of exercise.

Natriuretic peptides. The B-type natriuretic peptide (ARCHITECT BNP assay, Abbott, Abbott Park, Illinois) and the N-terminal pro–B-type natriuretic peptide (Roche Elecsys proBNP assay on the E170 analyzer, Roche, Basel, Switzerland) were measured using commercially available assays.

Statistical analysis. Categorical data are given as counts and percentages, and comparisons between groups were performed using chi-square tests. Continuous data are presented as mean ± SD or median (range), as appropriate. Comparisons between groups were performed using unpaired *t* tests and Mann-Whitney *U* tests, respectively, and resting and peak exercise measurements were compared using paired t tests. To assess the impact of exercise on heart rate and the VO_2/work rate relationship at matched work rates, analysis of variance for repeated measures (mixed between-within subjects analysis of variance) was performed. Pearson or Spearman correlation coefficients between parameters of interest were calculated as appropriate. A p value <0.05 was considered statistically significant. Analysis was performed using a commercially available software package (SPSS version 15.0, SPSS, Inc., Chicago, Illinois).

Results

Patient characteristics. We studied an HFNEF population with demographic features similar to those described in other studies and controls of similar age and sex (Table 1). Patients with HFNEF had higher body mass index and were more likely to be receiving antihypertensive and heart failure medications than were controls. The groups did not significantly differ with regard to natriuretic peptide concentrations.

LV structure and function. As shown in Table 2, and in accordance with previous studies, patients with HFNEF had smaller LV dimensions, more concentric LV geometry, larger left atrial dimensions, lower systolic (except s'_{septal}) and early diastolic mitral annular velocities, and higher E/e′ compared with controls.

Resting and exercise hemodynamics and gas exchange. At rest (Table 3), heart rate, mean arterial pressure, right atrial pressure, mean pulmonary pressure, and PCWP did not differ between HFNEF patients and controls. However, cardiac index and SVI were lower, systemic vascular resistance index (SVRI) was higher, and pulmonary vascular resistance index tended to be higher in patients. The partial

Table 2 Echocardiographic Characteristics of Patients With HFNEF and Controls

	HFNEF (n = 14)	Controls (n = 8)	p Value
LV end-diastolic volume index, ml/m^2	46 ± 8	58 ± 20	0.05
LV end-systolic volume index, ml/m^2	17 ± 3	22 ± 8	0.03
Relative wall thickness	0.41 ± 0.08	0.33 ± 0.06	0.03
LV ejection fraction, %	63 ± 6	62 ± 5	0.62
LV mass index, g/m^2	83 ± 16	95 ± 29	0.28
Left atrial volume index, ml/m^2	21.3 ± 7.0	18.9 ± 5.9	0.41
E/A ratio	0.95 ± 0.37	1.26 ± 0.55	0.13
Deceleration time, ms	224 ± 63	226 ± 80	0.94
s'_{septal}, cm/s	7.0 ± 1.2	7.8 ± 1.8	0.20
$s'_{lateral}$, cm/s	6.9 ± 1.7	8.8 ± 2.1	0.03
s'_{av}, cm/s	6.9 ± 1.2	8.3 ± 1.5	0.03
e'_{septal}, cm/s	6.1 ± 1.5	9.0 ± 3.1	0.007
$e'_{lateral}$, cm/s	7.7 ± 2.1	11.8 ± 4.5	0.008
e'_{av}, cm/s	6.9 ± 1.6	10.4 ± 3.7	0.005
E/e'_{septal}	13.2 ± 4.1	9.5 ± 3.4	0.04
$E/e'_{lateral}$	10.6 ± 3.4	7.2 ± 2.2	0.02
E/e'_{av}	11.6 ± 3.3	8.1 ± 2.5	0.02

Data are given as mean ± SD.

E/A ratio = ratio of the peak early (E) to peak late (A) diastolic transmitral velocities; $e'_{septal/lateral/av}$ = peak early diastolic annular velocity measured at the septal/lateral mitral annulus and the average of both; $E/_{e'septal/lateral/av}$ = ratio of E to $e'_{septal/lateral/av}$; HFNEF = heart failure and normal ejection fraction; LV = left ventricular; $s'_{septal/lateral/av}$ = peak systolic annular velocity measured at the septal/lateral mitral annulus and the average of both.

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Table 3 Hemodynamics at Rest and Peak Exercise in Patients With HFNEF and Controls

	HFNEF (n = 14)	Controls (n = 8)	p Value
Rest			
Heart rate, beats/min	66 ± 10	66 ± 20	0.97
Right atrial pressure, mm Hg	5 ± 3	5 ± 3	0.80
Mean arterial pressure, mm Hg	100 ± 7	101 ± 17	0.90
Mean pulmonary artery pressure, mm Hg	18 ± 5	16 ± 4	0.31
PCWP, mm Hg	10 ± 4	10 ± 4	0.94
Pulmonary vascular resistance index, dyne·s/cm^5/m^2	274 ± 176	155 ± 63	0.08
Systemic vascular resistance index, dyne·s/cm^5/m^2	3,029 ± 737	2,241 ± 388	0.01
Cardiac index, l/min/m^2	2.6 ± 0.5	3.5 ± 1.0	0.01
Stroke volume index, ml/m^2	41 ± 9	51 ± 10	0.02
Peak exercise			
Heart rate, beats/min	102 ± 22	112 ± 20	0.33
Percent predicted heart rate, %	67 ± 14	70 ± 14	0.63
Mean arterial pressure, mm Hg	120 ± 14	124 ± 11	0.41
Mean pulmonary artery pressure, mm Hg	37 ± 10	32 ± 8	0.22
PCWP, mm Hg	23 ± 6	20 ± 7	0.31
PCWP/work rate ratio, mm Hg/W/kg	46 ± 31	20 ± 9	0.03
Pulmonary vascular resistance index, dyne·s/cm^5/m^2	257 ± 135	119 ± 53	0.01
Systemic vascular resistance index, dyne·s/cm^5/m^2	2,251 ± 879	1,331 ± 272	0.01
Cardiac index, l/min/m^2	4.6 ± 1.6	7.4 ± 1.4	0.001
Stroke volume index, ml/m^2	45 ± 10	68 ± 15	0.001

Data are given as mean ± SD.
HFNEF = heart failure and normal ejection fraction; PCWP = pulmonary capillary wedge pressure.

pressure of arterial oxygen (82 ± 16 mm Hg vs. 100 ± 23 mm Hg; p = 0.046) and arterial (96 ± 2% vs. 97 ± 1%; p = 0.04) and mixed venous (71 ± 4% vs. 74 ± 4%; p = 0.02) oxygen saturations were slightly lower in HFNEF patients compared with controls. The partial pressure of arterial carbon dioxide (38 ± 5 vs. 41 ± 5; p = 0.19) did not significantly differ between the groups.

Patients with HFNEF stopped exercise earlier (5.5 ± 2.4 min vs. 9.4 ± 1.9 min; p = 0.001), and at a significantly lower work rate (0.63 ± 0.29 W/kg vs. 1.13 ± 0.49 W/kg; p = 0.006) because of breathlessness and/or fatigue. Peak heart rate, mean arterial pressure, mean pulmonary arterial pressure, and PCWP at peak exercise were similar in patients with HFNEF and controls (Table 3). Thus, the PCWP/peak work rate ratio was markedly higher in HFNEF compared with controls. Patients with NYHA functional class II and III had similar PCWP at rest (10 ± 4 mm Hg vs. 10 ± 4 mm Hg; p = 0.90) and peak exercise (24 ± 4 mm Hg vs. 22 ± 7 mm Hg; p = 0.67), but patients with functional class III symptoms achieved a significantly lower peak work rate (0.45 ± 0.18 W/kg vs. 0.87 ± 0.23 W/kg; p = 0.002), and tended to have a higher PCWP/peak work rate ratio (59 ± 35 mm Hg/W/kg vs. 30 ± 13 mm Hg/W/kg; p = 0.08).

Peak exercise pulmonary vascular resistance index was also higher in patients compared with controls (Table 3). Notably, the partial pressure of arterial oxygen (88 ± 19 mm Hg vs. 87 ± 13 mm Hg; p = 0.90) and arterial (96 ± 2% vs. 97 ± 2%; p = 0.80), and mixed venous (51 ± 11% vs. 45 ± 6%; p = 0.23) oxygen saturation at peak exercise did not differ between the groups. There was a trend toward a lower partial pressure of arterial carbon dioxide (36 ± 4 mm Hg vs. 40 ± 3 mm Hg; p = 0.06) in patients compared with controls.

Determinants of exercise capacity. Calculated VO_2, arteriovenous differences in oxygen content, and cardiac index increased during exercise in both HFNEF patients and controls (Fig. 1). As shown in Figure 1A, VO_2 was slightly lower at rest but markedly lower at peak exercise in patients compared with controls. This difference in peak VO_2 between the groups was predominantly due to a lower peak exercise cardiac index in HFNEF patients, and only to a minor degree was it due to a nonsignificantly lower arteriovenous difference in oxygen content at peak exercise (Figs. 1B and 1C).

The difference in peak exercise cardiac index between patients and controls was mainly driven by a markedly lower peak exercise SVI in patients (Fig. 2A), whereas peak heart rate did not differ between the groups (Fig, 2B). The significantly lower SVI response in patients occurred at similar PCWP levels (Fig. 2C). The SVRI decreased during exercise in both groups but remained significantly higher in patients than controls at peak exercise (Fig. 2D). The SVI at peak exercise was closely and inversely related to SVRI at rest (r = −0.64; p < 0.001) and particularly SVRI peak exercise (r = −0.84; p < 0.001).

Upright noninvasive cardiopulmonary exercise testing. Data from maximal upright exercise tests are presented in Table 4. As expected for a heart failure population, peak work rate and peak VO_2 were lower, and the slope of the ventilation to carbon dioxide output relationship was higher

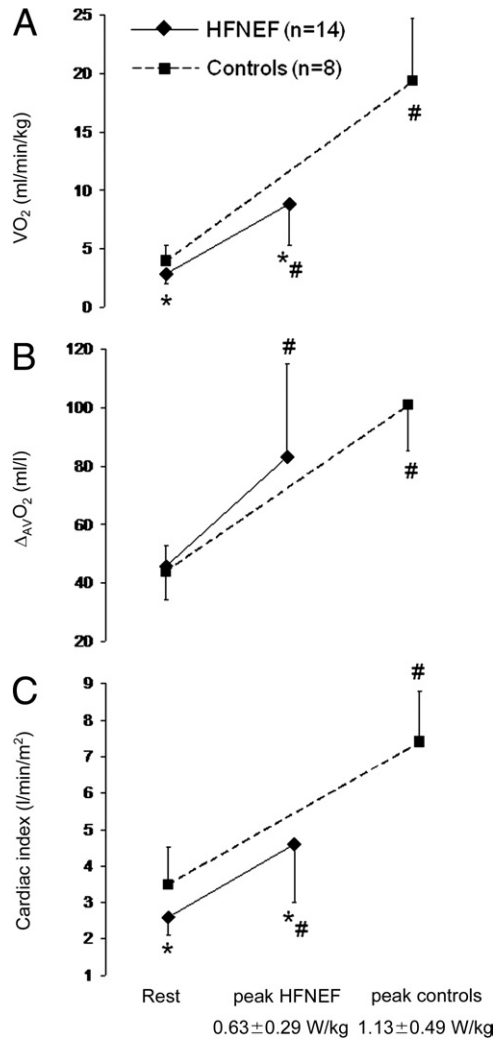

Figure 1 **Determinants of VO_2**

Changes in **(A)** oxygen uptake (VO_2), **(B)** arteriovenous difference in oxygen content ($\Delta_{AV}O_2$), and **(C)** cardiac index from rest to peak exercise in patients with heart failure and normal ejection fraction (HFNEF **[diamonds]**) and controls **(squares)**. **Error bars** represent mean and SD. *p < 0.05 versus controls; #p < 0.05 versus rest.

in HFNEF patients compared with controls. In contrast to supine exercise, which was submaximal in some subjects, peak heart rate was significantly lower in HFNEF patients compared with controls. However, the heart rate response at matched work rates did not significantly differ between patients and controls (Fig. 3A), and the VO_2/work rate relationship at similar work rates did not differ between the groups either (Fig. 3B).

E/e′ for the prediction of the exercise response. At rest, there was no correlation between PCWP and E/e'_{septal} ($r = 0.19$; $p = 0.39$), $E/e'_{lateral}$ ($r = 0.04$; $p = 0.87$), or E/e'_{av} ($r = 0.12$; $p = 0.59$). During exercise, there was a similar increase in both E and e'_{septal} in both HFNEF patients and controls (Figs. 4A and 4B); however, E/e'_{septal} did not significantly increase in either group, and peak exercise E/e'_{septal} did not significantly differ between patients and controls (Fig. 4C). Individual data for patients and controls are shown in Figure 5. There was no significant correlation between peak exercise E/e'_{septal} and peak exercise PCWP ($r = 0.22$; $p = 0.33$) or the peak exercise PCWP/work rate ratio ($r = 0.12$; $p = 0.61$).

Discussion

In the present study, HFNEF patients were characterized by a significantly reduced exercise capacity. However, the cardiac output response to exercise was parallel in HFNEF patients and control subjects at similar work rates, and the arteriovenous difference in oxygen content at peak exercise and the ΔVO_2/work rate relationship at matched work rates did not significantly differ between the groups, indicating that oxygen delivery was appropriate at the time at which HFNEF patients stopped exercise. Moreover, there was no evidence of a ventilatory limitation or arterial desaturation. The heart rate response during cardiopulmonary exercise testing was also similar, or perhaps even exaggerated at low workloads, and during assessment of invasive exercise, hemodynamics heart rates were similar in both groups.

Thus, the difference in peak exercise cardiac index was mainly due to a difference in SVI. In accordance with previous studies, HFNEF patients were characterized by a small LV cavity and a concentric remodeling, and SVI was lower already at rest. We did not measure LV volumes during exercise, but given the consistent observation that during exercise, LVEF in HFNEF either does not substantially change or increases slightly but less than in controls (8,12,20), this also indicates a lower exercise LV end-diastolic volume in HFNEF compared with controls. However, in contrast to recent studies using right atrial pacing (10,11) we saw no decrease in SVI.

The PCWP at rest was not different between patients and controls, a finding that is in contrast to a previous study (20), which, however, included patients with features that would not be consistent with a contemporary diagnosis of HFNEF (2), namely, patients with an underlying cardiomyopathy (cardiac amyloid or hypertrophic cardiomyopathy) (20). We found that HFNEF patients showed a rapid increase in PCWP at low SVI and at a low work rates, and this was accompanied by an early cessation of exercise. Thus, we found that the peak PCWP to peak work rate ratio, rather than the peak PCWP, was a suitable parameter to distinguish HFNEF patients and controls. However, in contrast to the general belief that an increase in LV filling pressures is not observed in normal physiology, we observed a similar rise in PCWP in controls, albeit at a much higher workload and cardiac output. Notably, this is a normal PCWP response during supine cycle exercise in this age group (21); and also, during upright exercise, PCWP increases substan-

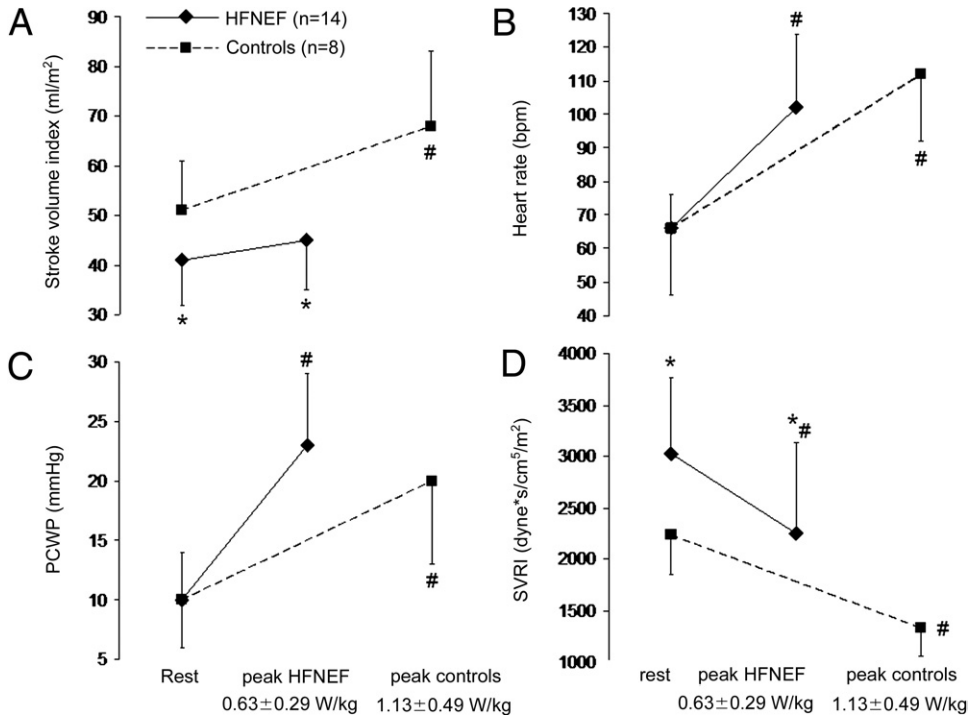

Figure 2 Hemodynamic Response to Exercise

Changes in **(A)** stroke volume index, **(B)** heart rate, **(C)** pulmonary capillary wedge pressure (PCWP), and **(D)** systemic vascular resistance index (SVRI) from rest to peak exercise in patients with heart failure and normal ejection fraction (HFNEF **[diamonds]**) and controls **(squares)**. **Error bars** represent mean and SD. *p < 0.05 versus controls; #p < 0.05 versus rest.

tially in healthy people, although the absolute peak exercise PCWP is lower than during supine exercise (22).

Our finding that HFNEF patients showed a higher slope of the ventilation to carbon dioxide output relationship is also consistent with a rapid, early symptom-producing rise in PCWP, although other mechanisms may contribute to ventilator inefficiency in these patients. Borlaug et al. (12) also proposed that pulmonary congestion was a major contributory factor to exercise intolerance in HFNEF patients. However, unlike our study, they did not measure invasive hemodynamics; rather, lung blood volume was taken as an index of pulmonary congestion, although there was no evidence that this method could detect pulmonary interstitial congestion (12).

Table 4 Cardiopulmonary Exercise Testing Data in Patients With HFNEF and Controls

	HFNEF (n = 10)	Controls (n = 8)	p Value
FEV_1, l	2.97 ± 0.67	3.35 ± 1.09	0.38
Percent predicted FEV_1, %	96 ± 10	108 ± 22	0.15
Exercise time, min	9.5 ± 2.2	11.8 ± 2.3	0.048
Peak heart rate, beats/min	124 ± 23	155 ± 19	0.007
Percent predicted heart rate, %	82 ± 14	98 ± 11	0.02
Peak work rate, W/kg	1.02 ± 0.43	2.24 ± 1.28	0.01
Percent predicted peak VO_2, %	67 ± 19	99 ± 38	0.03
Indexed peak VO_2, ml/min/kg	15.1 ± 4.9	26.6 ± 12.5	0.02
VE/VCO_2 slope	34.3 ± 5.4	28.4 ± 3.4	0.02
Breathing reserve, l	45 ± 29	42 ± 28	0.81
Peak exercise respiratory exchange ratio	1.28 ± 0.16	1.42 ± 0.09	0.06

Data are mean ± SD.

FEV_1 = forced expiratory volume in 1 s; HFNEF = heart failure and normal ejection fraction; VE/VCO_2 slope = slope of the relationship between minute ventilation and carbon dioxide output; VO_2 = oxygen uptake.

Our finding that HFNEF patients showed a higher slope of the ventilation to carbon dioxide output relationship is also consistent with a rapid, early symptom-producing rise in PCWP, although other mechanisms may contribute to ventilator inefficiency in these patients. Borlaug et al. (12) also proposed that pulmonary congestion was a major contributory factor to exercise intolerance in HFNEF patients. However, unlike our study, they did not measure invasive hemodynamics; rather, lung blood volume was taken as an index of pulmonary congestion, although there was no evidence that this method could detect pulmonary interstitial congestion (12).

Noninvasive studies have suggested that increased arterial load in HFNEF patients is not matched by increased myocardial contractility (14), and that the reduction in SVRI during exercise is lower compared with controls (12). In the present invasive study, we have demonstrated a higher SVRI in patients at rest and peak exercise and a very close inverse correlation between SVI and SVRI during exercise. Given that HFNEF has been shown to be characterized by complex abnormalities in LV systolic and diastolic function as well as torsion and untwisting (9), and given that at least LV longitudinal myocardial velocities (s′ and e′) are afterload dependent (23), it is possible that afterload even has a direct impact on LV function in HFNEF.

Taken together, our data clearly support the concept that a small noncompliant left ventricle and a stiff arterial system are the key mechanisms underlying the symptoms in pa-

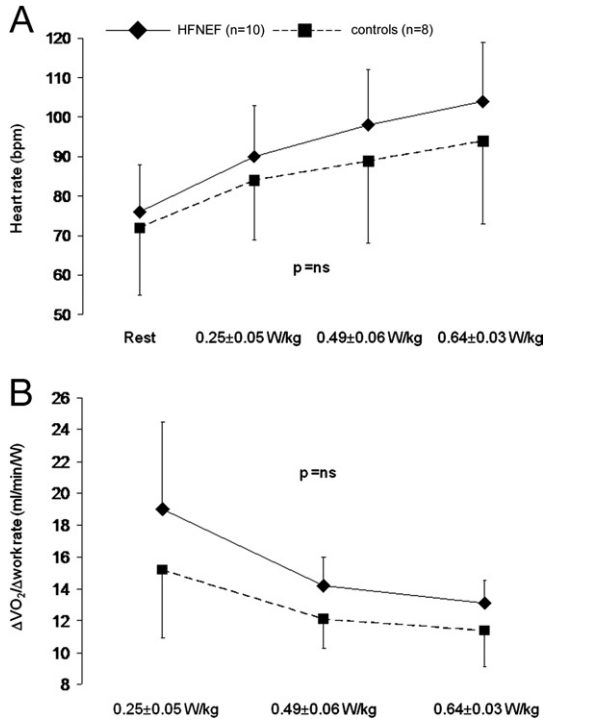

Figure 3 Heart Rate and Oxygen Uptake to Work Rate Response

(A) Heart rate response and **(B)** relationship between oxygen uptake and work rate ($\Delta VO_2/\Delta$work rate) for matched work rates in patients with heart failure and normal ejection fraction (HFNEF **[diamonds]**) and controls **(squares)**. Data are shown until the time point when the first patient stopped exercise. **Error bars** represent mean and SD. The p value for the interaction group *work rate is given. ns = nonsignificant.

tients with HFNEF. In contrast, there was no evidence for chronotropic incompetence.

Our study also provides clinically important and novel information on the utility of noninvasive markers proposed for the diagnosis of HFNEF (17,24). We confirmed that E/e′ at rest was higher in HFNEF patients than in controls, but this difference in E/e′ did not reflect a difference in PCWP, which is in accordance with recent studies in patients with hypertrophic cardiomyopathy and decompensated heart failure with reduced LVEF (25). Thus, while a high E/e′ appears to be a good marker of HFNEF, this is not because it reflects increased filling pressures at rest, but more likely because it indicates a low e′ and, presumably, also more complex abnormalities of LV function (9). We also found that E/e'_{septal} at peak exercise did not adequately represent changes in PCWP. A previous study had shown that E/e'_{septal} during exercise identified patients with an increase in LV end-diastolic pressure during exercise (26). However, that study included younger and unselected patients undergoing left-side heart catheterization, and as was evident from the mild increase in heart rate, low level exercise was used (26), which may explain the discrepant findings. Natriuretic peptide concentrations did not significantly differ between patients and controls, and that may be related to the small number of patients, to the typically skewed distribution of natriuretic peptide concentrations, and to a higher body mass index being associated with lower plasma concentrations.

Study limitations. We studied a small number of participants. However, this was a comprehensive, and to the best of our knowledge, the largest study investigating exercise hemodynamics in a typical elderly HFNEF population. In addition, we did not measure LV pressures directly. However, this would have required a femoral access in most patients, and would have made exercise involving a large part of the musculature impossible.

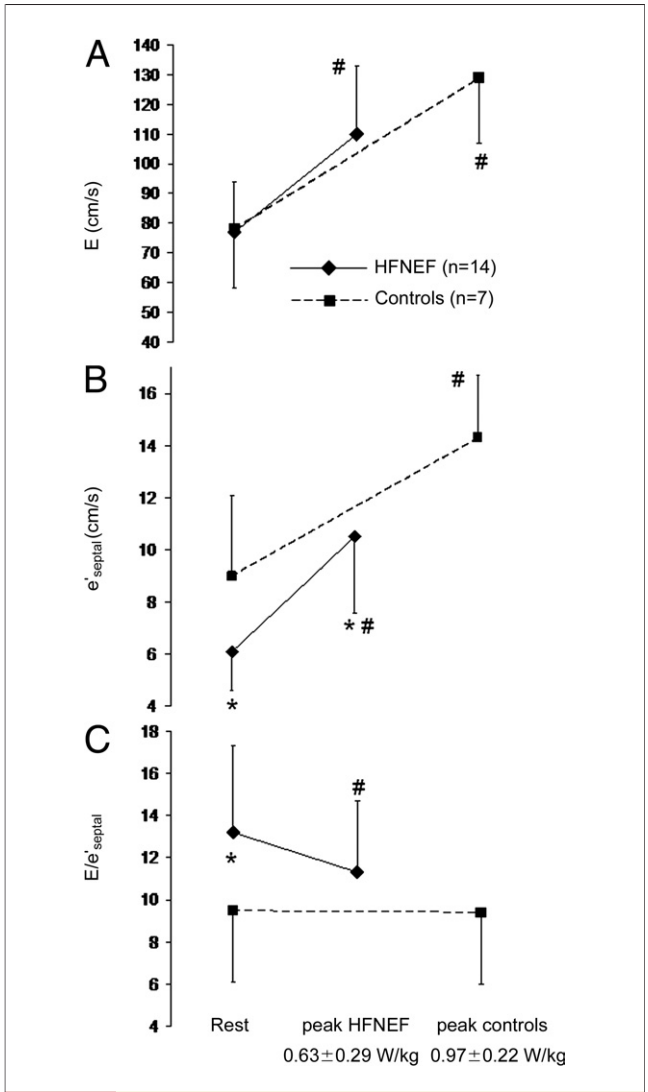

Figure 4 E/e'_{septal} and Filling Pressures

Changes in **(A)** the peak early diastolic transmitral velocity (E), and **(B)** the peak early diastolic annular velocity at the septal annulus (e'_{septal}) and **(C)** E/e'_{septal} from rest to peak exercise in patients with heart failure and normal ejection fraction (HFNEF **[diamonds]**) and controls **(squares)**. **Error bars** represent mean and SD. *$p < 0.05$ versus controls; #$p < 0.05$ versus rest.

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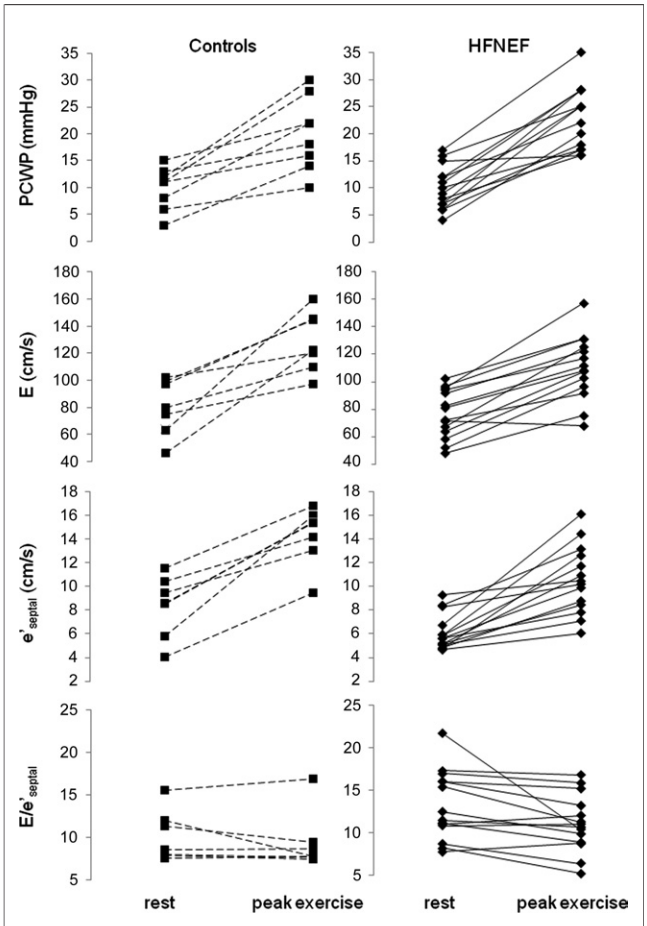

Figure 5 **Individual PCWP and Tissue Doppler Data**

Individual data for changes in peak early diastolic transmitral velocity (E), the peak early diastolic annular velocity at the septal annulus (e'_{septal}), E/e'_{septal}, and pulmonary capillary wedge pressure (PCWP) from rest to peak exercise in patients with heart failure and normal ejection fraction (HFNEF **[diamonds]**) and controls **(squares)**.

Conclusions

We propose that HFNEF patients exhibit a rapid rise in PCWP at a much lower workload than that of age-matched controls. Moreover, this occurs at a lower SVI and in the setting of higher SVRI. The E/e'_{septal} ratio does not accurately reflect the hemodynamic changes occurring during exercise in HFNEF patients, and we suggest, therefore, that invasive hemodynamic studies with exercise are required to formally establish the pathophysiologic profile in patients with suspected HFNEF and to evaluate the effects of novel therapies.

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Key Words: echocardiography ■ ejection fraction ■ exercise ■ heart failure ■ hemodynamics.