

Exercise Hemodynamics Enhance Diagnosis of Early Heart Failure With Preserved Ejection Fraction

Barry A. Borlaug, MD; Rick A. Nishimura, MD; Paul Sorajja, MD;
Carolyn S.P. Lam, MBBS; Margaret M. Redfield, MD

Background—When advanced, heart failure with preserved ejection fraction (HFpEF) is readily apparent. However, diagnosis of earlier disease may be challenging because exertional dyspnea is not specific for heart failure, and biomarkers and hemodynamic indicators of volume overload may be absent at rest.

Methods and Results—Patients with exertional dyspnea and ejection fraction >50% were referred for hemodynamic catheterization. Those with no significant coronary disease, normal brain natriuretic peptide assay, and normal resting hemodynamics (mean pulmonary artery pressure <25 mm Hg and pulmonary capillary wedge pressure [PCWP] <15 mm Hg) (n=55) underwent exercise study. The exercise PCWP was used to classify patients as having HFpEF (PCWP ≥25 mm Hg) (n=32) or noncardiac dyspnea (PCWP <25 mm Hg) (n=23). At rest, patients with HFpEF had higher resting pulmonary artery pressure and PCWP, although all values fell within normal limits. Exercise-induced elevation in PCWP in HFpEF was confirmed by greater increases in left ventricular end-diastolic pressure and was associated with blunted increases in heart rate, systemic vasodilation, and cardiac output. Exercise-induced pulmonary hypertension was present in 88% of patients with HFpEF and was related principally to elevated PCWP, as pulmonary vascular resistances dropped similarly in both groups. Exercise PCWP and pulmonary artery systolic pressure were highly correlated. An exercise pulmonary artery systolic pressure ≥45 mm Hg identified HFpEF with 96% sensitivity and 95% specificity.

Conclusions—Euvolemic patients with exertional dyspnea, normal brain natriuretic peptide, and normal cardiac filling pressures at rest may have markedly abnormal hemodynamic responses during exercise, suggesting that chronic symptoms are related to heart failure. Earlier and more accurate diagnosis using exercise hemodynamics may allow better targeting of interventions to treat and prevent HFpEF progression. (*Circ Heart Fail.* 2010;3:588-595.)

Key Words: heart failure ■ exercise ■ hemodynamics ■ diastole ■ diagnosis

Approximately one half of patients with heart failure (HF) have HF with preserved ejection fraction (HFpEF).¹⁻³ The natural history of HFpEF is not comprehensively defined because most previous studies have focused on progression of disease after an index event, typically a hospitalization for acutely decompensated HF with volume overload.¹⁻⁴ Many patients with decompensated incident HFpEF relate a history of chronic exertional dyspnea or exercise intolerance,⁴ yet this earlier phase of HFpEF remains poorly characterized. Symptoms of exertional dyspnea and intolerance are highly sensitive for HF,⁵ but they are nonspecific and widely prevalent, particularly in elderly patients in whom a number of conditions other than HF may cause or contribute to impaired functional capacity.⁶⁻⁹

Clinical Perspective on p 595

Diagnosis of HFpEF is based on current guidelines and requires objective evidence of elevated filling pressures either

at catheterization, by echocardiography, or by brain natriuretic peptide (BNP) assays.¹⁰ The potential for overdiagnosis of HFpEF, particularly when relying on surrogate markers of elevated filling pressures, has been appropriately emphasized by a number of investigators.⁶⁻¹¹ However, less is known regarding the potential for underdiagnosis of HFpEF in patients with lifestyle-limiting symptoms but no clinical evidence of hypervolemia.

We hypothesized that patients with HFpEF may present in a milder or “early” phase of disease characterized by exertional symptoms in the absence of volume overload. This group may not meet current diagnostic criteria based on resting hemodynamics alone, developing hemodynamic derangements characteristic of HF only during the stress of exercise. To test this hypothesis, we studied consecutive patients referred to a cardiac catheterization laboratory for diagnostic evaluation of unexplained exertional dyspnea who had normal BNP levels and normal resting hemodynamics. In

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From the Division of Cardiovascular Diseases, Department of Medicine, Mayo Clinic, Rochester, Minn.

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Correspondence to Barry A. Borlaug, MD, Mayo Clinic and Foundation, 200 First St SW, Rochester, MN 55905. E-mail borlaug.barry@mayo.edu
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such patients, we examined the hemodynamic responses to exercise to determine whether a subset of these patients displayed hemodynamic evidence of HF during exercise.

Methods

Study Population

We retrospectively examined consecutive patients referred to the Mayo Clinic cardiac catheterization laboratory between August 2005 and August 2009 for right heart catheterization (with or without left heart catheterization) for the clinical assessment of exertional dyspnea and fatigue. The study population included 55 consecutive patients with normal EF ($\geq 50\%$) and normal resting hemodynamics (defined later). Patients with elevated BNP or N-terminal pro-hormone BNP (>200 pg/mL or >220 pg/mL¹⁰), significant coronary artery disease (stenosis $\geq 50\%$), valvular heart disease (any stenosis, more than mild regurgitation), hypertrophic or infiltrative cardiomyopathy, constrictive pericarditis, exercise-induced pulmonary hypertension (PH) due to vascular disease (mean exercise pulmonary artery pressure [PAP] >30 mm Hg with pulmonary capillary wedge pressure [PCWP] <15 mm Hg¹²), or radiographic pulmonary congestion were excluded. The study was approved by the Mayo Clinic Institutional Review Board. The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Catheterization Protocol

Patients were studied on chronic medications in the fasted state after minimal sedation in the supine position. Standard right heart catheterization was performed through a 7- to 9-F sheath inserted through the internal jugular or femoral vein. Left heart catheterization was performed through the radial or femoral artery (6 F). High-fidelity right- and left-sided pressure measurements were obtained in most patients using 2-F micromanometer-tipped catheters advanced through the lumen of the corresponding fluid-filled catheter. Mean micromanometer pressures were calibrated to mean fluid-filled pressures at the beginning and throughout each case. Transducers were zeroed at midaxilla as measured by calipers in each patient.

Right atrium (RA) pressure, PAP, PCWP, and left ventricular (LV) end-diastole pressure (LVEDP) were measured at end-expiration and represent the mean of ≥ 3 beats. Because intrathoracic pressure swings are enhanced with the increased work of breathing during exercise, exercise pressures also are reported as the mean of inspiration and expiration. PCWP was verified based on characteristic waveforms, appearance on fluoroscopy, and oxygen saturation. LVEDP was determined following the atrial systolic deflection before the onset of isovolumic contraction. Systolic blood pressure (BP) was measured in the LV, or by arm cuff if left heart catheterization was not performed. Mean brachial BP was obtained from an oscillometric arm cuff sphygmomanometer.

Cardiac output was determined by the Fick method using directly measured saturations and oxygen consumption or by thermodilution and indexed to body surface area (cardiac index [CI]). Pulmonary vascular resistance index [PVRI=(mean PAP–PCWP)/CI] and total systemic vascular resistance index (SVRI=mean arterial BP/CI) were determined. Baseline oximetry run was performed to rule out left-to-right shunting.

Exercise Protocol

After assessment of resting hemodynamics, patients exercised by supine cycle ergometry or outstretched arm adduction lifting of 4-lb weights (if femoral access had been obtained). Patients performing the leg exercise cycled at 60 rpm starting at a 20-W workload and increasing by 10-W increments in 3-minute stages to maximum tolerated levels. For the arm exercise, repetition frequency was gradually increased to subjective fatigue. PCWP was determined at baseline, before exercise with passive leg elevation (if applicable), after 1.5 minutes at low-level (20-W) exercise, at peak, and during 1-minute recovery (legs still elevated for ergometry). Peak exercise CI was determined by the Fick method (direct oxygen consumption

Table 1. Baseline Characteristics

Characteristic	NCD (n=23)	HFpEF (n=32)	P
Age, y	47 \pm 17	65 \pm 13	<0.001
Female sex, %	65	72	0.6
White race, %	100	91	0.3
Body mass index, kg/m ²	27.3 \pm 5.5	32.0 \pm 5.9	0.004
Obesity, %	40	56	0.2
Hypertension, %	57	72	0.2
Diabetes, %	22	16	0.6
Atrial fibrillation, %	9	6	0.7
NYHA class II/III	20/3	27/5	0.8
Glomerular filtration rate, mL/min	95 \pm 36	86 \pm 31	0.3
BNP, pg/mL	49 \pm 54	71 \pm 49	0.3
NT-proBNP, pg/mL	38 \pm 22*	104 \pm 62†	0.07
Hemoglobin, g/dL	13.2 \pm 1.5	13.6 \pm 1.2	0.3
β -blockers, %	35	44	0.5
ACEI or ARB, %	30	38	0.6
Diuretic, %	35	53	0.18

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NT-proBNP, N-terminal prohormone BNP.

*n=4.

†n=7.

measurements) or thermodilution. Exercise cardiac output was not determined in the majority of patients (11/13) performing arm exercise.

Case Definitions

Prior studies in normal controls have shown that peak PCWP and LVEDP during supine exercise are <20 to 23 mm Hg^{13,14} and <25 mm Hg,^{15,16} respectively. For this analysis, patients with peak exercise PCWP ≥ 25 mm Hg were classified as having HFpEF, and those with values <25 mm Hg were classified as having noncardiac dyspnea (NCD). Exercise-induced PH was defined as mean PAP >30 mm Hg.¹²

Statistical Analysis

Results are reported as mean \pm SD. Between-group differences were compared by ANOVA or χ^2 test. Bivariate (Pearson coefficient) analysis was used to examine correlations between exercise measures. Multivariate linear regression was performed to adjust for group differences in baseline characteristics (age and body mass index), heart rate, BP, exercise protocol, peak exercise workload, and cardiac output measurement method. Regression analyses assumed that distributions were Gaussian, relationships between dependent and independent variables were linear, and errors were homoscedastic. These assumptions were tested by visual inspection of the distributions and of the standardized residual plots. Logistic regression with receiver operating characteristic analysis was used to identify clinical testing results associated with invasively confirmed HFpEF.

Results

Subject Characteristics

The sample population consisted predominantly of middle-aged to elderly women with hypertension (New York Heart Association [NYHA] class II) (Table 1). Patients with HFpEF were older and had higher body mass than patients with NCD. Sex, race, medical comorbidities, symptoms, laboratory results, and medication use were similar.

Clinical Evaluation Before Catheterization

Chest radiographs of patients with HFpEF were more likely to show cardiomegaly, with trends toward more LV hyper-

Table 2. Clinical Evaluation Before Hemodynamic Assessment

Evaluation	NCD (n=23)	HFpEF (n=32)	P
Radiographic			
Cardiomegaly, %	4	25	0.04
Echocardiographic			
LVEF, %	61±6	62±7	0.4
LV mass, g/m ²	84±22	92±20	0.16
LV hypertrophy, %	17	34	0.06
LA enlargement, %	38	65	0.06
E-wave, cm/s	80±20	80±20	0.8
A-wave, cm/s	60±30	80±30	0.08
E/A ratio	1.3±0.5	1.1±0.5	0.10
Medial E', cm/s	10±3	9±3	0.02
E/E' ratio	8±3	10±3	0.04
E/E' ratio >15, %	5	9	0.5
Estimated PASP, mm Hg	31±6	33±8	0.4
PASP >35 mm Hg, %	28	26	0.9
ESC HFpEF diagnosis, %	24	34	0.4

ESC indicates European Society of Cardiology; LA, left atrial.

trophy and left atrial enlargement (Table 2). Mean tissue-Doppler medial E' velocities were lower and E/e' ratios higher in HFpEF compared with NCD, but there was substantial overlap, and only 9% of patients with HFpEF had elevated E/e' ratios. Echo-estimated pulmonary artery systolic pressures (PAPs) and EF were similar in HFpEF and NCD. Applying contemporary diagnostic guidelines,¹⁰ 34% of patients with HFpEF and 24% with NCD would have been diagnosed as having HFpEF before catheterization ($P=0.4$).

Resting Hemodynamics

Resting heart rate, BP, and LVEDP were similar in the NCD and HFpEF patient groups (Table 3). PAPs and PCWP were higher in HFpEF at rest, although all values fell within normal limits. PVRI and SVRI were higher in HFpEF compared with NCD, whereas resting CI was lower.

Exercise Hemodynamics

The majority (76%) of patients performed leg exercise (Table 4). Increases in heart rate and cardiac output were lower with arm

Table 3. Resting Hemodynamics

Hemodynamics	NCD (n=23)	HFpEF (n=32)	P
Heart rate, bpm	72±12	70±9	0.5
Arterial systolic pressure, mm Hg	131±19	137±23	0.3
Arterial mean pressure, mm Hg	88±12	94±14	0.4
RA pressure, mm Hg	4±2	5±2	0.04
PASP, mm Hg	24±6	31±7	0.0003
Mean PAP, mm Hg	15±4	19±4	0.001
End-expiration PCWP, mm Hg	9±3	11±2	0.002
Average PCWP, mm Hg	9±3	11±2	0.003
LVEDP, mm Hg	12±3	13±2	0.13
CI, L/min per m ²	3.2±0.8	2.8±0.6	0.04
PVRI, Wood unit×m ²	2.1±1.0	3.2±1.5	0.006
SVRI, DSC×m ²	2300±700	2800±600	0.02

DSC indicates dynes second/cm⁵.

Table 4. Exercise Hemodynamics

Hemodynamics	NCD (n=23)	HFpEF (n=32)	P*
Arm/leg exercise	3/20	10/22	0.11
Peak leg ergometry workload, Watts	64±36	47±19	0.06
Heart rate, bpm	122±24	104±21	0.004
Arterial systolic pressure, mm Hg	153±26	182±34	0.002
Arterial mean pressure, mm Hg	101±15	125±20	0.0001
RA pressure, mm Hg	6±3†	14±4‡	0.0004
PASP, mm Hg	35±7	59±11	<0.00001
Mean PAP, mm Hg	23±5	43±7	<0.00001
End-expiration PCWP, mm Hg	13±5	32±6	<0.00001
Average PCWP, mm Hg	11±5	28±7	<0.00001
LVEDP, mm Hg	14±4	34±6	<0.00001
CI, L/min per m ²	6.7±1.4	4.9±1.0	<0.0001
PVRI, Wood unit×m ²	1.9±0.9	2.4±1.2	0.17
Exercise-induced PH, %	...	88	...
SVRI, DSC×m ²	1300±400	1900±400	0.0007

DSC indicates dynes second/cm⁵.

* $P<0.0001$ for all paired changes (within groups) compared with rest.

†n=11.

‡n=6.

exercise compared with leg ergometry, although changes in BP and filling pressures were similar (online-only Data Supplemental table I). Importantly, all within- and between-group comparisons of hemodynamic responses with exercise were similar when examining leg or arm exercise responses separately (data not shown). Exercise RA pressure was measured in 17 of 55 patients (NCD, 11/23; HFpEF, 6/32), and exercise LVEDP was measured in 25 of 55 (NCD, 7/23; HFpEF, 18/32).

The changes in PCWP by group throughout the exercise study are shown in Figure 1A. Passive elevation of the legs (before cycle exercise) was associated with an increase in PCWP in both groups, but the increase was much more prominent in HFpEF compared with NCD (7±3 mm Hg versus 2±3 mm Hg, respectively; $P<0.0001$) (Figure 1A). By case definition, the increase in PCWP during peak exercise was greater in HFpEF than in NCD (Figure 1A, Table 4). Intriguingly, most of the change in PCWP occurred within the first 1.5 minutes of exercise at a low-level (20-W) workload (NCD, 5±3 mm Hg [89% of peak]; HFpEF, 16±6 mm Hg [80% of peak]; $P<0.0001$). Higher left-sided heart filling pressures were confirmed by greater exercise increases in LVEDP in HFpEF (Figure 1B, Table 4). Each difference remained significant after adjusting for age and body mass index. In the immediate recovery phase (1 minute postexercise), PCWP returned to baseline leg up (leg exercise) or supine rest (arm) values in both groups (Figure 1A). PCWP averaged over the respiratory cycle tended to be lower compared with end-expiration values (Table 4), but this difference was not significant ($P=0.2$) and the 2 values were highly correlated ($R^2=0.89$; $P<0.0001$). PCWP averaged over the respiratory cycle was ≥ 20 mm Hg in all patients with HFpEF and ≤ 18 mm Hg in 22 of the 23 patients with NCD.

Similar to PCWP, increases in PAPs were markedly greater in HFpEF (Figure 1C, Table 4), with 88% of patients meeting criteria for exercise-induced PH.¹² This finding was related exclusively to pulmonary venous hypertension, as PVRI

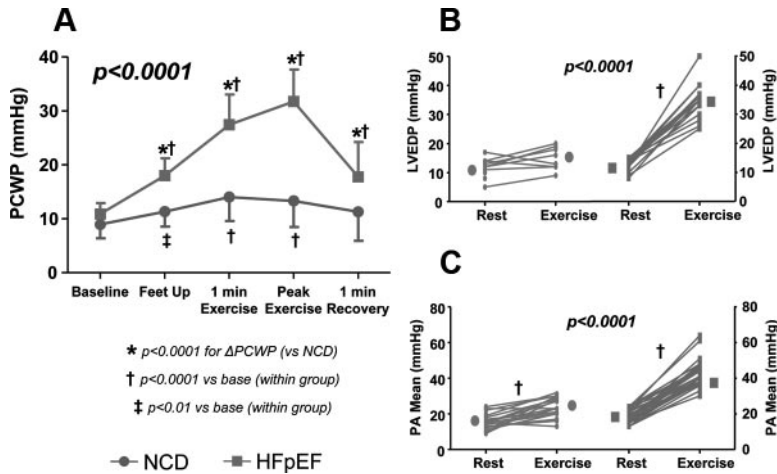


Figure 1. PCWP increased to a greater extent in HFpEF compared with NCD with leg elevation and during exercise (A). PCWP returned to baseline almost immediately in recovery. LVEDP (B) and mean PAP (C) also rose with exercise more dramatically in the HFpEF group (P for exercise change between groups).

dropped similarly in the HFpEF and NCD patient groups (Figure 2). Exercise-induced augmentation in heart rate and CI were blunted in HFpEF compared with NCD, whereas patients with HFpEF had a greater hypertensive response and less systemic vasodilation (Figure 2). Exercise changes and peak exercise PCWP, LVEDP, and PAP all remained significantly higher in the HFpEF patient group after adjusting for age, body mass index, heart rate, BP, exercise type, peak workload, and method of cardiac output determination (all $P \leq 0.0002$), whereas cardiac output response remained lower ($P = 0.02$). Heart rate responses were no longer different in patients with HFpEF versus NCD after adjusting for age, although prior studies have confirmed chronotropic incompetence in patients with HFpEF even when compared to age-matched controls.^{17–20}

Exercise change in PCWP was highly correlated with change in RA pressure (Figure 3A), with an intercept near 0 and slope of 0.44 ($R^2 = 0.84$; $P < 0.00001$) (Figure 3A). Peak exercise PCWP and PASP also were highly correlated, as were exercise changes in each pressure (Figure 3B to 3C). Receiver operating characteristic analysis showed that none of the clinical, radiographic, or echocardiographic parameters identified in Table 2 adequately identified catheterization-verified HFpEF (all areas under the curve, < 0.70) (Figure 3D). In contrast, leg-elevation and exercise PASP were highly predictive of HFpEF (area under the curve, 0.94 and 0.99, respectively). An exercise PASP ≥ 45 mm Hg identified HFpEF with 96% sensitivity and 95% specificity.

Sensitivity Analysis

Because the partition values for exercise PCWP that define abnormality are not well established, we repeated analyses defining HFpEF by an exercise PCWP > 15 mm Hg, > 18 mm Hg, and > 20 mm Hg. Each analysis produced similar results, with all differences in resting and exercise hemodynamic responses as depicted in Figures 1 to 2 and Tables 3 to 4 persisting (data not shown). Four patients would be reclassified as having HFpEF based on the most liberal partition value (15 mm Hg). Receiver operating characteristic analysis using PCWP > 15 mm Hg to define HFpEF shows similar results as PCWP ≥ 25 mm Hg (Figure 3), where leg-elevation PCWP and exercise PASP are most predictive of HFpEF.

Discussion

This study examined hemodynamic responses to exercise measured invasively in consecutive patients with preserved EF who were referred for catheterization to evaluate the cause of exertional dyspnea. Of 55 patients with normal BNP and normal resting pressures, 58% had an abnormal increase in left-sided heart filling pressures, with symptoms of exercise tolerance consistent with HFpEF. This finding was coupled with additional hemodynamic derangements characteristic of HF, including secondary PH and impairments in heart rate, vasodilation, and cardiac output reserve. Noninvasive diagnostic testing, including radiography, BNP, and echocardiography, did not distinguish HFpEF from NCD. Invasively measured exercise PAPs were highly correlated with left-sided heart pressures,

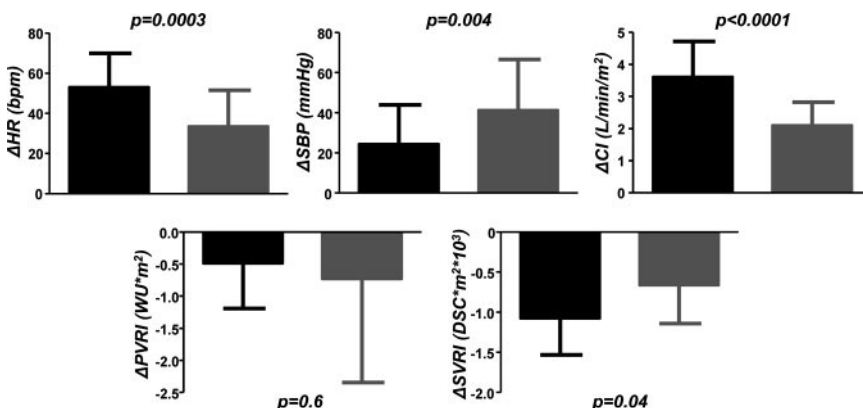


Figure 2. Increases in heart rate, CI, and systemic arterial vasodilation with exercise were impaired in HFpEF (gray) compared with NCD (black). Systolic BP increased to a greater extent in HFpEF, whereas pulmonary vasodilation was similar. Δ CI indicates change in CI; Δ HR, change in heart rate; Δ PVRI, change in PVRI; Δ SBP, change in systolic BP; Δ SVRI, change in SVRI.

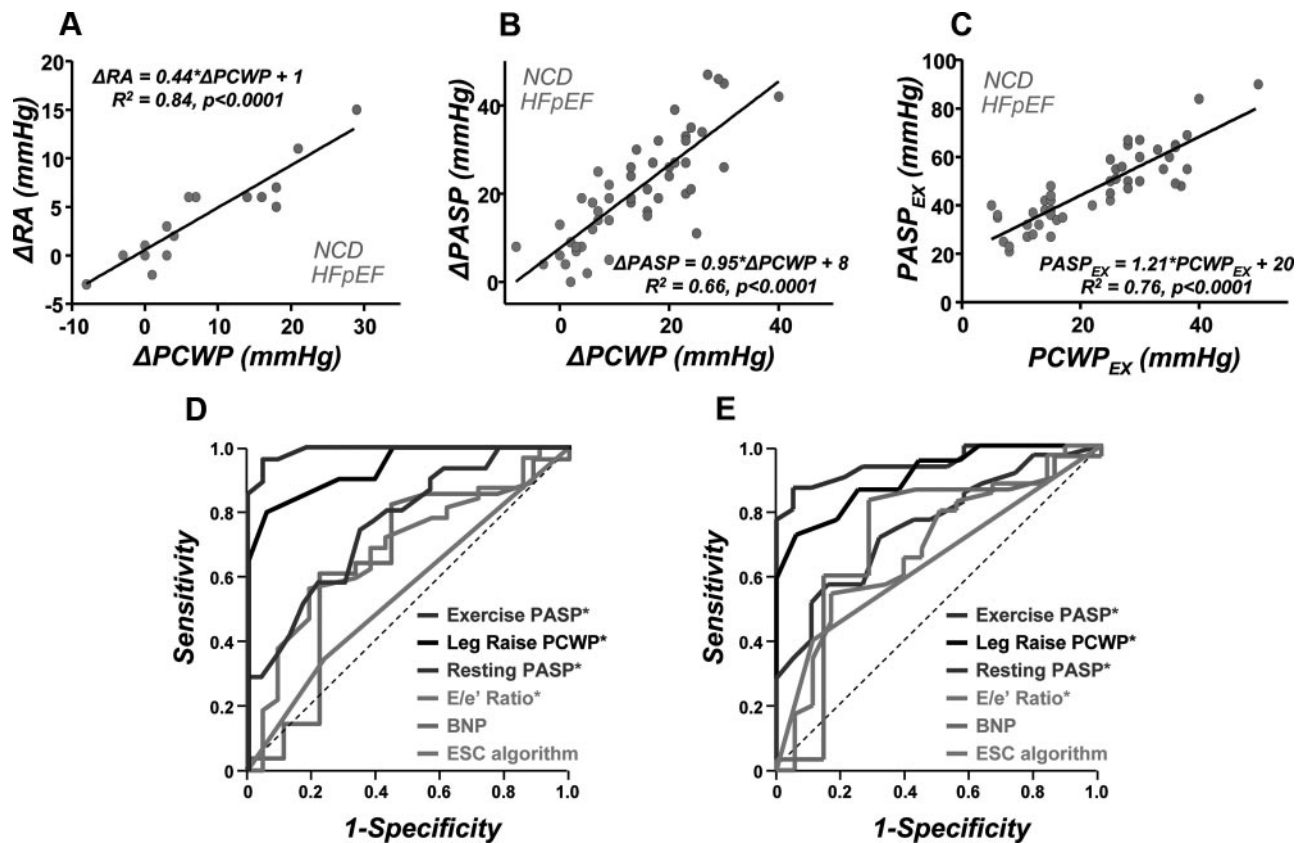


Figure 3. A and B, Exercise PCWP were highly correlated with the corresponding RA pressure and PASP. C, Peak exercise PCWP and PASP were strongly associated. D, Clinical measures (BNP, E/e' ratio) and diagnostic algorithms (European Society of Cardiology) did not robustly distinguish HFpEF from NCD. In contrast, PCWP with leg raise and peak exercise PASP showed excellent discrimination between HFpEF and NCD. E, Receiver operating characteristic curves using $PCWP > 15$ mm Hg to define HFpEF. See text for details. $\Delta PASP$, indicates change in PASP; $PASP_{EX}$, peak exercise PASP; $\Delta PCWP$, change in PCWP; $PCWP_{EX}$, peak exercise PCWP; ΔRA , change in RA pressure.

suggesting the potential for use of Doppler-estimated exercise PAPs in noninvasive screening. These findings support the hypothesis that an earlier or milder stage of HFpEF characterized by normal resting but abnormal exercise hemodynamics exists. These data also suggest the utility of hemodynamic exercise testing to identify this population of patients with less-advanced HFpEF. Further study is warranted to describe the prevalence and natural history of this early stage of disease; determine sensitive and specific, but simple approaches to diagnosis; and explore whether interventions in this population may prevent progression to more-advanced stages of HFpEF.

Clinical Diagnosis of HFpEF

Exertional dyspnea and fatigue are hallmark symptoms of HF,^{5,10,21} but they also are reported in a variety of noncardiac conditions, including obesity, pulmonary disease, anemia, deconditioning, and pulmonary vascular disease.^{6,8,11,22,23} Symptoms of exercise intolerance may even be regarded as inevitable by-products of normal aging, particularly if there is no clear evidence for LV dysfunction or pulmonary disease. Although population-based studies have reported that approximately half of patients with HF in the community have preserved EF,¹⁻³ it has been questioned whether many of these patients truly have HF.^{7,9} Plausible alternative sources of dyspnea may be present, such as spirometric abnormalities or obesity,⁶ although cardiac

and pulmonary disease may coexist within a given patient,²⁴ and obesity is a commonly observed comorbidity and risk factor in HFpEF.^{1-3,23}

A recent study found that although patients with clinically diagnosed HFpEF had severe subjective and objective exercise intolerance, mean N-terminal prohormone BNP levels were similar to healthy controls, leading the authors to question the diagnosis of HF.¹¹ However, BNP levels more accurately reflect wall stress than filling pressures, and both wall stress and BNP levels are known to be lower in HFpEF compared to HF with reduced EF.²⁵ Echo-Doppler and tissue-Doppler measures, such as E/e' ratio, have been shown to serve as reasonable noninvasive measures of LV filling pressures and diastolic dysfunction.²⁶ Indeed, the E/e' ratio served as a key decision point in a recent diagnostic algorithm proposed for HFpEF.¹⁰ Similarly, Tschope and colleagues²⁷ found that N-terminal prohormone BNP levels accurately identify the presence of diastolic dysfunction in patients with normal EF. However, in each of these studies, measurements were performed only at rest, and if filling pressures (and hence wall stress) are only intermittently elevated (eg, during exercise), it follows that these noninvasive markers of congestion may appear normal or near normal when measured in the clinic.

This study indicates that currently used diagnostic criteria may not accurately distinguish euvoletic patients with less-

advanced HFpEF from those with NCD. Identification of HFpEF should not rely on a diagnosis of exclusion, as recently suggested,⁹ but should be based on positive identification of objective measurable criteria. Our data suggest that exercise hemodynamics may provide such criteria. Exercise testing is not likely to be needed in patients with congestion where the diagnosis of HFpEF is obvious, but it may play an important role in identifying patients with intermediate probability, serving as an extension rather than as a replacement of current guidelines.¹⁰ Exercise testing will be important for clinical care and to identify patients more accurately for enrollment in future clinical trials. Indeed, one of the concerns raised regarding the negative results in prior trials in HFpEF has been that some of the subjects enrolled may not truly have had HF.^{9,23}

“Early” HFpEF

The American College of Cardiology/American Heart Association HF staging system complements the NYHA functional class designation by emphasizing the progressive nature of HF from risk (stage A and B) to overt symptoms (stage C) to preterminal (stage D) disease.²¹ The current data suggest that patients with HFpEF may present with overt (stage C) but primarily exertional (NYHA class II to III) symptoms without clinical volume overload at rest. This group is not well characterized because prior studies have focused largely on patients hospitalized for HFpEF.^{1–4} Our patients predominantly complained of NYHA class II symptoms and had not been given a formal diagnosis of HF. Intriguingly, commonly observed phenotypic markers of HFpEF, such as diastolic dysfunction, left atrial enlargement, LV hypertrophy, and atrial fibrillation were present but were not as severely abnormal as found in previous studies examining more-advanced HFpEF.^{28–30} The patients in the current study also had a number of impairments in cardiovascular reserve function with exercise that are increasingly recognized in patients with advanced HFpEF^{17–20,31–33}; collectively, these observations are consistent with the notion that this represents an early form of disease. The natural history of early HFpEF remains unclear, but we speculate that it may represent an important group in which interventions may be targeted with higher yield to prevent or delay the transition to advanced HFpEF where changes in the material properties of the ventricle and vasculature may be irreversible.

Mechanisms of Exercise-Induced Pulmonary Venous Hypertension

Diastolic dysfunction is considered a cornerstone in the pathophysiology of HFpEF,^{28,30,34} and the observed increases in PCWP with exertion in the current study are likely related in large part to abnormalities in diastolic reserve. Kitzman and colleagues³¹ first showed that normal exercise increases in LV preload volume are blunted in HFpEF, despite marked increases in PCWP. Similar to the current study, Kitzman et al also studied compensated outpatients and found that resting PCWP was not elevated, despite marked elevations during stress, which emphasizes that congestion may only be an intermittent phenomenon in HFpEF. Other groups have recently corroborated these findings, showing exaggerated increases in LV diastolic pressures during handgrip exercise.³⁴ In the current study, passive elevation of the legs before cycle ergometry (which increases venous return¹⁶)

was associated with a larger increase in PCWP in HFpEF compared to NCD. This finding is consistent with an inability to use the Frank-Starling mechanism in that the increase in venous return with passive leg raise could not be accommodated without raising filling pressures. Disparities in PCWP became even more pronounced during low-level and peak exercise. Pressures promptly returned toward baseline within 1 minute of recovery, emphasizing that these patients were not hypervolemic per se but that increases in venous return acutely raised ventricular and atrial pressures, which were transmitted to the pulmonary venous bed during exercise.

Increases in BP were greater and reductions in vascular resistance lower in HFpEF, and because high afterload impairs diastolic function,³⁵ these disparities in vasorelaxation may have contributed to the observed increases in PCWP in HFpEF. Because LV relaxation kinetics and end-diastolic pressure-volume relationships were not measured, we cannot discern to what extent changes in diastolic relaxation, compliance, or extrinsic forces might have contributed. Dauterman and colleagues³⁶ showed that approximately 40% of measured LV diastolic pressure is related to forces external to the LV, mediated by right heart–left heart interaction and pericardial restraint. We found that RA pressure rose in tandem with PCWP during exercise in the HFpEF and NCD patient groups, and intriguingly, the slope of this relationship was remarkably close to the 40% external contribution reported by Dauterman et al³⁶ and others.³⁷

PH and HFpEF

It has increasingly become appreciated that PH is a common finding in HFpEF.^{38,39} Pulmonary pressures increase with aging and vascular stiffening,⁴⁰ processes strongly implicated in the pathogenesis of HFpEF.^{23,35} Tolle and colleagues¹² recently reported that ≈50% of patients referred for invasive exercise hemodynamic testing have exercise-induced PH due to pulmonary venous hypertension. Elderly patients with PH are more likely to have elevated PCWP,³⁹ and 83% of patients with HFpEF have PH.³⁸ The presence of PH predicts increased mortality in HFpEF, and elevated PASP has been shown to be a more powerful predictor of HFpEF than other noninvasive measures of diastolic dysfunction.³⁸ The current results, coupled with these previous studies, reinforce the notion that PH noted at rest or with exercise may be more of an indication of elevated left-sided heart pressures than pulmonary vascular disease in many patients, particularly among the elderly.³⁹

The current results suggest a potential role for exercise PASP to noninvasively screen for HFpEF in patients with exertional dyspnea. In this study, commonly used radiographic, laboratory, and echocardiographic variables did not distinguish HFpEF from NCD (all areas under the curve, <0.70). Resting PASP at catheterization was slightly more robust (area under the curve, 0.75), but exercise PASP showed superior discriminative ability (area under the curve, 0.99; $P < 0.0001$). Because exercise PH also may be due to pulmonary vascular disease, invasive study may still be required, but if echo-Doppler-derived PASP is validated during exercise, it may serve as a useful screen in patients with exertional dyspnea of uncertain etiology.

Study Limitations

The study population included patients referred for cardiac catheterization and was not randomly selected; thus, there is referral bias that may limit generalizability of the findings. Because of the retrospective nature of this study, there also may be greater inaccuracy in the assessment of subjective findings, such as NYHA class or volume status. The type of exercise performed (arm or leg), the method of cardiac output assessment (Fick or thermodilution), and the measurement of RA and LV pressures with exercise were not uniform in all patients because their performance was based on catheterization indications, operator preference, and vascular access. Again, the study was retrospective in nature, with the intent to simply examine patients who showed an abnormal response to an exercise stressor (exercise PCWP ≥ 25 mm Hg), regardless of type. Importantly, stratified analysis comparing only patients who performed the leg or arm exercise separately showed similar differences within and between groups for all hemodynamic responses. As in community-based studies,²⁸ the HFpEF group was older and had higher body mass, but PAP and PCWP differences with exercise persisted after adjusting for age and body mass index. Because testing was while supine, these results may not apply to upright exercise. Objective exercise effort was not quantified, but prior studies have shown that maximal increases in PAP and PCWP occur early on during submaximal supine exercise,¹⁵ and our data similarly showed that 80% to 90% of the peak increase in PCWP was apparent during the first stage. Indeed, the observation that abnormalities are detectable at low workload is notable and enhances feasibility for application in laboratories not equipped for time-consuming exercise studies. The study population excluded patients with PH due to pulmonary vascular disease and patients with HFpEF and congestion apparent at rest, and the results may not apply to these populations. It is not established what a normal exercise PCWP in the supine position is or whether this differs with age, sex, or body size.^{12–16} Contractile function, which has been shown to be mildly impaired at rest and with exercise in HFpEF,^{18,41} was not assessed in this study and may have contributed to the observed differences in cardiac output reserve. We chose a more rigid partition value (≥ 25 mm Hg at end-expiration corresponding to ≥ 20 mm Hg averaged throughout respiration) to identify HFpEF, but it is very possible that many of the patients with less dramatic increases in PCWP also have or will develop HFpEF. Importantly, each of the hemodynamic differences observed between groups persisted in sensitivity analyses examining different exercise PCWP partition values to define HF. Finally, although all patients developed dyspnea during testing, the onset or severity of dyspnea was not determined or correlated with PCWP elevation, and factors other than pulmonary venous hypertension, such as ergoreflex activation or ventilation abnormalities, also may contribute to dyspnea in this population.^{18,42}

Conclusions

Symptoms of dyspnea and fatigue with exertion are common in practice and may be due to a wide variety of cardiac and noncardiac diseases. Despite clinical euolemia, normal BNP levels, echocardiography, and normal resting filling pressures, patients may show a number of hemodynamic changes characteristic of HFpEF during exercise stress. Invasive exercise

hemodynamic testing may enhance diagnosis of HFpEF in this expanding population of patients with exertional dyspnea of unknown etiology. Future research is required to better define and phenotype the clinical behavior, optimal treatment strategies for, and natural history of this early form of HFpEF, and future trials may examine whether progression to more advanced HFpEF can be delayed or prevented through interventions targeted to this group of patients.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Exertional dyspnea is a common complaint that may be due to cardiac or noncardiac etiologies. When the ejection fraction is depressed in a patient with exertional dyspnea, the diagnosis of heart failure typically is made. However, in patients with normal ejection fraction, it often is challenging to determine whether symptoms are due to heart failure with preserved ejection fraction (HFpEF) or noncardiac dyspnea, particularly when patients appear euvoletic. Clinical indicators of volume overload, such as examination findings, echocardiography, and brain natriuretic peptide levels, are commonly used to distinguish these groups, but it remains unknown whether the absence of volume overload as detected by these resting markers effectively rules out HFpEF. In this study, we demonstrate that in patients with “early” stage HFpEF, hemodynamic evidence of volume overload and diastolic dysfunction may be present only during the stress of exercise, and as such, the diagnosis of HFpEF may only be made by assessing hemodynamic responses during exercise. The increase in pulmonary wedge pressure with leg raise and submaximal exercise along with the increase in pulmonary artery systolic pressure with peak exercise each identified HFpEF with greater accuracy compared to conventional testing used to diagnose heart failure. These results show that the diagnosis of HFpEF may be missed if one relies exclusively on measures of ventricular function and filling pressures obtained at rest. Invasive exercise hemodynamics allow for more accurate and specific diagnosis of early HFpEF among patients complaining of exertional dyspnea.