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Hemodynamic Correlates and Diagnostic Role of Cardiopulmonary Exercise Testing in Heart Failure With Preserved Ejection Fraction

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ABSTRACT

OBJECTIVES This study sought to define the invasive hemodynamic correlates of peak oxygen consumption (Vo_2) in both supine and upright exercise in heart failure with preserved ejection fraction (HFpEF) and evaluate its diagnostic role as a method to discriminate HFpEF from noncardiac etiologies of dyspnea (NCD).

BACKGROUND Peak Vo_2 is depressed in patients with HFpEF. The hemodynamic correlates of reduced peak Vo_2 and its role in the clinical evaluation of HFpEF are unclear.

METHODS Consecutive patients with dyspnea and normal EF (N = 206) undergoing both noninvasive upright and invasive supine cardiopulmonary exercise testing were examined. Patients with invasively verified HFpEF were compared with those with NCD.

RESULTS Compared with NCD (n = 72), HFpEF patients (n = 134) displayed lower peak Vo_2 during upright and supine exercise. Left heart filling pressures during exercise were inversely correlated with peak Vo_2 in HFpEF, even after accounting for known determinants of O_2 transport according to the Fick principle. Very low upright peak Vo_2 (<14 ml/kg/min) discriminated HFpEF from NCD with excellent specificity (91%) but poor sensitivity (50%). Preserved peak Vo_2 (>20 ml/kg/min) excluded HFpEF with high sensitivity (90%) but had poor specificity (49%). Intermediate peak Vo_2 cutoff points were associated with substantial overlap between cases and NCD.

CONCLUSIONS Elevated cardiac filling pressure during exercise is independently correlated with reduced exercise capacity in HFpEF, irrespective of body position, emphasizing its importance as a novel therapeutic target. Noninvasive cardiopulmonary testing discriminates HFpEF and NCD at high and low values, but additional testing is required for patients with intermediate peak Vo_2. (J Am Coll Cardiol HF 2018;6:665–75) © 2018 by the American College of Cardiology Foundation.

Heart failure (HF) can be defined as an inability of the heart to pump blood to the body at a rate commensurate with its needs, or to do so only at the cost of elevated filling pressures (1). About one-half of patients with HF have a preserved ejection fraction (HFpEF) (2). High filling pressures during exercise are pathognomonic of HFpEF (1–5), but the relationships between hemodynamics and exercise capacity remain unclear. Indeed, although exertional dyspnea is often considered to be caused by left atrial hypertension in HF, studies in HF with reduced EF (HFrEF) have failed to detect any association between exercise filling pressures and aerobic capacity (6–8).

Peak oxygen consumption (Vo_2) as measured by cardiopulmonary exercise testing (CPET) is the gold standard assessment for aerobic capacity (9–11). Reduced peak Vo_2 in HFpEF is used as an endpoint for

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ABBREVIATIONS AND ACRONYMS

A Vo_2 = arteriovenous oxygen difference

CPET = cardiopulmonary exercise testing

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

HR = heart rate

NCD = noncardiac etiologies of dyspnea

PA = pulmonary artery

PCWP = pulmonary capillary wedge pressure

Vco_2 = CO_2 production

V_E = minute ventilation

Vo_2 = oxygen consumption

clinical trials (12,13) and is known to be prognostic (14–16). However, CPET is not currently incorporated into HFpEF diagnostic guidelines (17,18). Reductions in peak Vo_2 are often considered to reflect poor cardiac output reserve, but peripheral abnormalities also contribute in many patients with HFpEF (19,20). Invasive CPET, which combines expired gas analysis with direct measures of hemodynamics, has emerged as the gold standard test to identify or exclude HFpEF in patients with unexplained dyspnea (4,9,21,22).

SEE PAGE 676

Because few data are available relating filling pressures to aerobic capacity in people with HFpEF and because no study has directly evaluated the potential utility of noninvasive CPET in diagnosis, we performed a detailed evaluation of both noninvasive and invasive CPET in a large, consecutive series of patients with and without HFpEF.

TABLE 1 Baseline Characteristics

	Control (n = 72)	HFpEF (n = 134)	p Value
Anthropometrics			
Age, yrs	54 ± 16	67 ± 11	<0.0001
Female	58	60	0.8
Body mass index, kg/m^2	28.4 ± 5.8	32.7 ± 6.8	<0.0001
Comorbidities			
Diabetes	10	25	0.007
Angiographic CAD (n = 46/88)	28	31	0.8
Hypertension	84	96	0.007
Atrial fibrillation	6	20	0.004
Laboratories			
Hemoglobin, g/dl	12.7 ± 1.5	12.2 ± 1.4	0.005
eGFR, ml/min	92 ± 24	80 ± 25	0.0009
NT-proBNP, pg/ml	78 (29–187)	435 (107–1,134)	<0.0001
Medications			
ACE inhibitor/ARB	31	50	0.007
Beta-blocker	35	65	<0.0001
Diuretic	32	55	0.002
Echocardiography			
LVEDD, mm	48 ± 5	49 ± 6	0.5
EF, %	63 ± 5	62 ± 6	0.4
LAVI, ml/m^2	30 ± 12	40 ± 15	<0.0001
E/e′ ratio	10 ± 4	13 ± 6	<0.0001
RVSP, mm Hg	29 ± 5	37 ± 11	<0.0001

Values are mean ± SD, %, or median (interquartile range).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; e′ = early diastolic septal tissue Doppler velocity; E = early diastolic mitral inflow velocity; EF = ejection fraction; eGFR = estimated glomerular filtration rate; HFpEF = heart failure with preserved ejection fraction; LAVI = left atrial volume index; LVEDD = left ventricular end diastolic dimension; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RVSP = right ventricular systolic pressure.

METHODS

All consecutive patients undergoing invasive hemodynamic exercise testing for the evaluation of unexplained dyspnea over a 15-year period from January 2000 to January 2014 at the Mayo Clinic in Rochester, Minnesota, were identified. From this cohort, patients who had undergone both transthoracic echocardiography and CPET within 1 year of the date of invasive CPET were included. All patients were evaluated by a cardiologist at Mayo Clinic before and after testing. The study was reviewed and approved by the Mayo Clinic Institutional Review Board.

HFpEF patients were defined by typical symptoms of HF (dyspnea), normal EF (≥50%), and elevated pulmonary capillary wedge pressure (PCWP) at rest or exercise (rest ≥15 mm Hg, exercise ≥25 mm Hg) (1–4). Patients with significant valvular heart disease (> mild stenosis, > moderate regurgitation), pulmonary arterial hypertension, constrictive pericarditis, high output failure, unstable coronary disease, primary cardiomyopathies, history of low EF (<50%), significant pulmonary disease, and heart transplantation were excluded.

Control subjects with noncardiac causes of dyspnea (NCD) were required to display no evidence of cardiac etiology of dyspnea after exhaustive clinical evaluation, including a normal EF, normal pulmonary artery (PA) pressures (rest <25 mm Hg, exercise <40 mm Hg), and normal rest and exercise PCWP (criteria in the preceding text).

INVASIVE CPET. Right heart catheterization was performed via the right internal jugular vein in the fasted state and supine position after minimal sedation as previously described to measure hemodynamics at rest and peak exercise (3–5). Details of the invasive hemodynamic assessment are provided in the Online Appendix.

NONINVASIVE CPET. On a separate day from the invasive CPET, standard noninvasive upright treadmill or upright cycle ergometry exercise was performed using the same expired gas analysis technique as the invasive studies (MedGraphics, St. Paul, Minnesota) to measure breath-by-breath Vo_2 and CO_2 production (Vco_2), as well as respiratory exchange ratio (RER = Vco_2/ Vo_2), ventilatory efficiency (minute ventilation [V_E]/Vco_2 nadir), and O_2 pulse (Vo_2/heart rate [HR]) (9–11). Additional details are available in the Online Appendix.

Because peak Vo_2 varies with age, sex, and muscle mass, absolute measured values were converted to

TABLE 2 Invasive Hemodynamic and Cardiopulmonary Exercise Data

	Rest			Peak Exercise		
	Control (n = 72)	HFpEF (n = 134)	p Value	Control (n = 72)	HFpEF (n = 134)	p Value
Vital signs						
HR	67 ± 13	63 ± 13	0.02	109 ± 26	100 ± 22	0.005
SBP	139 ± 26	148 ± 30	0.10	168 ± 38	179 ± 35	0.20
MBP	95 ± 17	100 ± 17	0.10	106 ± 20	116 ± 20	0.02
Central hemodynamics						
Right atrial pressure mm Hg	5 ± 2	9 ± 3	<0.0001	7 ± 5	18 ± 6	<0.0001
PA mean pressure, mm Hg	16 ± 4	25 ± 8	<0.0001	25 ± 8	45 ± 10	<0.0001
PASP, mm Hg	28 ± 7	39 ± 11	<0.0001	41 ± 13	63 ± 14	<0.0001
PCWP, mm Hg	9 ± 4	16 ± 6	<0.0001	14 ± 5	31 ± 6	<0.0001
PCWP/watts, mm Hg/W	–	–	–	0.2 ± 0.2	0.9 ± 0.4	<0.0001
O_2 delivery and metabolism						
Peak watts achieved, W	–	–	–	67 ± 29	40 ± 18	<0.0001
O_2 consumption, ml/min	222 ± 60	225 ± 61	0.80	979 ± 350	812 ± 270	0.002
O_2 consumption, ml/kg/min	2.7 ± 0.6	2.5 ± 0.6	0.01	12.5 ± 4.7	9.1 ± 2.8	<0.0001
Cardiac output, l/min	5.4 ± 1.6	4.9 ± 1.4	0.04	10.4 ± 3.2	8.4 ± 3.0	<0.0001
Cardiac index, l/min/m^2	2.80 ± 0.72	2.49 ± 0.67	0.003	5.42 ± 1.54	4.21 ± 1.40	<0.0001
Stroke volume index, ml/m^2	43 ± 10	41 ± 12	0.30	50 ± 16	43 ± 17	0.02
A Vo_2, ml/dl	4.2 ± 0.8	4.7 ± 0.9	0.0001	9.6 ± 2.1	10.0 ± 2.2	0.20

Values are mean ± SD. Adjustment of multiple hypothesis testing was not performed.

A Vo_2 = arteriovenous O_2 content difference; HFpEF = heart failure with preserved ejection fraction; HR = heart rate; MBP = mean blood pressure; PA = pulmonary artery; PASP = pulmonary artery systolic pressure; PCWP = pulmonary capillary wedge pressure; SBP = systolic blood pressure.

relative values normalized to body weight (ml/kg/min), as well as percent predicted peak Vo_2 using both the Wasserman-Hansen equation (current recommendation) (11) and the Fletcher et al. (23,24) nomogram (Online Table 1).

STATISTICAL ANALYSIS. Data are reported as mean ± SD or median (interquartile range). Chi square, Wilcoxon rank sum, or Student's *t*-test were used as appropriate to compare HFpEF and controls. Logistic regression was used to evaluate whether CPET variables could discriminate patients with HFpEF from NCD. Receiver-operating curves were constructed to evaluate the diagnostic performance of each test by the Youden index and C-statistic. To apply clinically, noninvasive CPET variables were dichotomously classified as normal or abnormal based on standard partition values identifying low- and higher-risk patients according to Malhotra et al. (9) (>20 and <14 ml/kg/min). Linear regression was used to explore relationships between peak Vo_2 at the time of CPET and invasive central hemodynamics in univariate analysis and in multivariable analysis after adjusting (a priori) for known determinants of peak Vo_2 according to the Fick Principle (stroke volume, HR, A Vo_2 difference), as well as other previously established correlates including age and sex. Collinearity between exercise variables was assessed by variance inflation factors, with values >5 indicating significant collinearity in the model (25). Correction for multiple hypothesis testing was not performed. All tests were 2-sided, with a p value <0.05 considered significant. Analyses were performed using JMP 13.0.0 (SAS Institute, Cary, North Carolina).

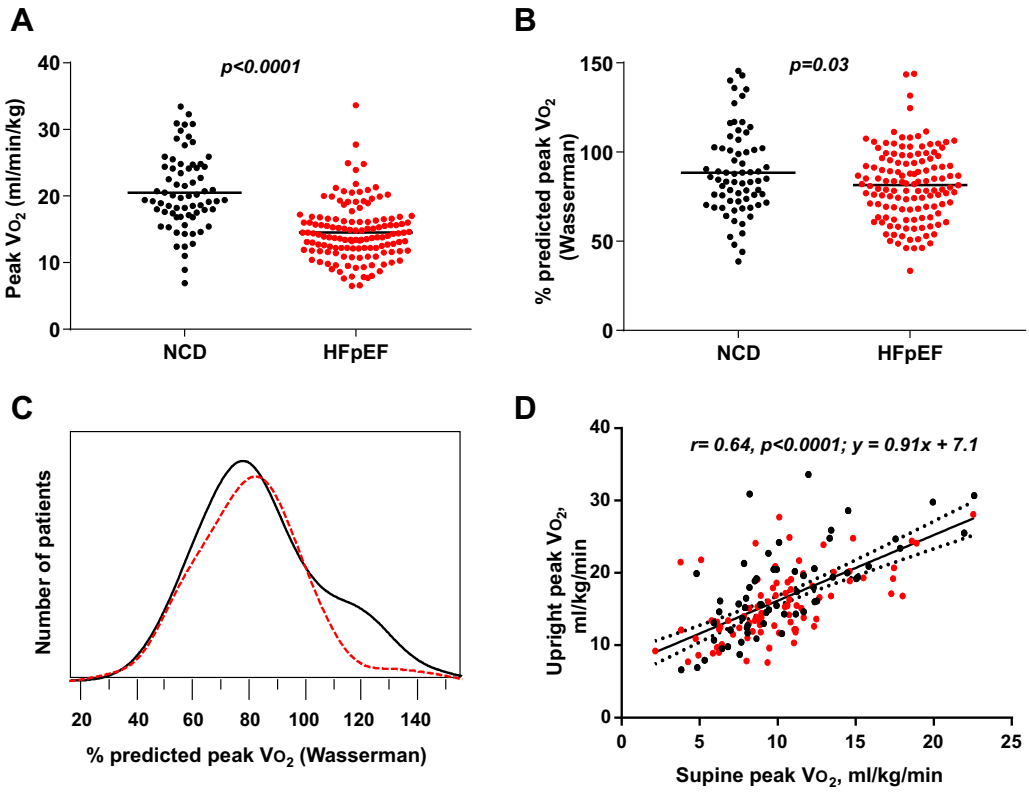
RESULTS

Patients with HFpEF (n = 134) were older and heavier than patients with NCD (n = 72), with a greater prevalence of comorbid conditions, including diabetes, hypertension, kidney disease, anemia, and atrial fibrillation (Table 1). As expected, HFpEF patients displayed more evidence of congestion, with higher N-terminal pro-B-type natriuretic peptide levels, E/e′, and estimated PA systolic pressure.

INVASIVE CPET. Right- and left-sided filling pressures and PA pressures were higher at rest and with peak exercise in the HFpEF group (Table 2). Peak Vo_2 and peak workload performed at invasive CPET were reduced in HFpEF as compared with NCD patients. This was explained principally by lower CO reserve, as A Vo_2 difference reserve was similar in HFpEF and NCD. All group differences remained significant after adjusting for age and body mass index.

NONINVASIVE CPET. Noninvasive CPET was obtained a median of 3 days (interquartile range: 1 to 20 days) before invasive CPET. As expected by the

FIGURE 1 Peak O_2 Consumption in Patients With HFpEF and Noncardiac Dyspnea



Peak O_2 consumption (Vo_2) in HFpEF **(red)** and NCD **(black)** indexed to body weight **(A)** and after converting to percent predicted peak Vo_2 by the Wasserman nomogram **(B and C)**. **(D)** Correlation between peak Vo_2 measured during invasive hemodynamic testing in the supine and upright position. HFpEF = heart failure with preserved ejection fraction; NCD = noncardiac etiologies of dyspnea.

greater muscle mass recruited in the upright position, peak Vo_2 attained during upright noninvasive CPET was ~60% higher than supine invasive CPET (16.6 vs. 10.2 ml/kg/min; $p < 0.0001$). However, the 2 tests were well correlated with one another ($r = 0.64$; $p < 0.0001$) (Figure 1).

As with invasive CPET, HFpEF patients displayed lower peak Vo_2 compared with NCD patients during noninvasive upright CPET, with similar peak RER (Table 3, Figure 1). The Vo_2 at tidal volume was lower in HFpEF patients, but O_2 pulse and V_E/Vco_2 nadir were similar in cases and control patients. Residual breathing reserve and peak arterial saturations were normal and similar between HFpEF and NCD at peak exercise, indicating that there was not a significant pulmonary limitation to exercise in either group.

RELATIONSHIPS BETWEEN HEMODYNAMICS AND EXERCISE CAPACITY. Peak Vo_2 measured at invasive CPET and noninvasive CPET decreased with increasing exercise PCWP as measured during peak supine exercise and also varied inversely with exercise PA pressure and PCWP indexed to workload (Figure 2). These relationships were stronger for upright exercise compared with supine exercise for PCWP and PA pressure (interaction $p \leq 0.003$). Peak Vo_2 correlated directly with exercise cardiac output (Figure 2).

To determine whether PCWP was an independent predictor of peak Vo_2, we performed multivariable linear regression modeling including known determinants of peak Vo_2: age, sex, and the components based on the Fick principle (HR, stroke volume, and A Vo_2 difference). After adjusting for these covariates, PCWP remained an independent correlate of peak Vo_2 in patients with HFpEF ($p = 0.0004$), but not in patients with NCD ($p = 0.50$) (Table 4).

One-half (50%) of HFpEF patients displayed peak Vo_2 in the range considered to reflect higher risk in HF (<14 ml/kg/min) (9). Compared with patients with peak Vo_2 ≥14 ml/kg/min, this group displayed more severe hemodynamic derangements during

exercise, with poorer cardiac output reserve and higher PCWP (Figure 3).

DIAGNOSIS OF HFpEF USING NONINVASIVE CPET. In addition to older age, multiple CPET variables were predictive of the presence of HFpEF, including chronotropic incompetence, abnormal HR recovery, reduced V_{O_2} at ventilatory threshold, and low O_2 pulse (Table 5). However, none of these variables clearly discriminated cases and control patients (all areas under the curve <0.73). Peak V_{O_2} <14 ml/kg/min displayed very high specificity for HFpEF (91%), but poor sensitivity (50%), whereas conversely peak V_{O_2} >20 ml/kg/min had high sensitivity (90%), but poor specificity (49%). Peak V_{O_2} <17 ml/kg/min displayed the highest Youden index to discriminate groups from our data, with an area under the curve of 0.78, indicating fair to good discrimination. V_E/V_{CO_2} nadir, which is roughly equivalent to V_E/V_{CO_2} slope, was not effective to discriminate HFpEF from NCD (Table 5).

Conversion of relative peak V_{O_2} (in ml/kg/min) to percent predicted peak V_{O_2} using the Wasserman-Hansen equation attenuated the separation between cases and control patients, with a substantial worsening of overlap (Figure 1, Table 3). Indeed, 52% of patients with invasively verified HFpEF displayed peak V_{O_2} ≥80% predicted using the Wasserman equation. By contrast, 97% of patients with invasively verified HFpEF displayed peak V_{O_2} <80% predicted according to the Fletcher scheme (Table 3). The Fletcher-based cutoffs for percent predicted peak V_{O_2} modestly discriminated cases from control patients, although the cutoffs were not superior to absolute peak V_{O_2} indexed to body weight (Table 5).

TABLE 3 Noninvasive Cardiopulmonary Exercise Data

	Control (n = 72)	HFpEF (n = 134)	p Value
Vital signs			
Baseline HR, min^{-1}	77 ± 14	73 ± 13	0.02
Peak HR, min^{-1}	142 ± 27	118 ± 20	<0.0001
HR recovery, min^{-1}	16 ± 11	10 ± 11	0.0003
Baseline systolic BP, mm Hg	119 ± 19	126 ± 21	0.02
Peak systolic BP, mm Hg	153 ± 31	149 ± 29	0.30
Peak exercise capacity			
Peak RER	1.14 ± 0.11	1.14 ± 0.13	0.70
Peak V_{O_2}, ml/min	1,659 ± 547	1,334 ± 479	<0.0001
Peak V_{O_2}, ml/kg/min	20.5 ± 5.6	14.5 ± 4.3	<0.0001
O_2 sat, %	96 ± 12	95 ± 11	0.80
Breathing reserve, %	46 ± 15	45 ± 15	0.60
Percent predicted peak V_{O_2} by Wasserman formula			
Peak V_{O_2}, % predicted	89 ± 24	81 ± 20	0.03
Peak V_{O_2}, <80% predicted, %	41	48	0.30
Peak V_{O_2}, <70% predicted, %	20	30	0.10
Peak V_{O_2}, <60% predicted, %	9	16	0.10
Peak V_{O_2}, <50% predicted, %	4	5	0.90
Percent predicted peak V_{O_2} by Fletcher formula			
Peak V_{O_2}, % predicted	64 ± 18	49 ± 13	<0.0001
Peak V_{O_2}, <80% predicted, %	80	97	<0.0001
Peak V_{O_2}, <70% predicted, %	71	92	0.0001
Peak V_{O_2}, <60% predicted, %	44	78	<0.0001
Peak V_{O_2}, <50% predicted, %	23	54	<0.0001
Other expired gas variables			
Peak O_2 pulse, ml/min/beat	12 ± 3	11 ± 3	0.40
V_{O_2} at VT, ml/min	1,205 ± 383	985 ± 361	<0.0001
V_{O_2} at VT, ml/kg/min	14.9 ± 4.0	10.8 ± 3.3	<0.0001
VT percent of peak V_{O_2}, %	74 ± 9	75 ± 13	0.40
V_E/V_{CO_2} nadir	30 ± 5	31 ± 5	0.20

Values are mean ± SD. Adjustment of multiple hypothesis testing was not performed.

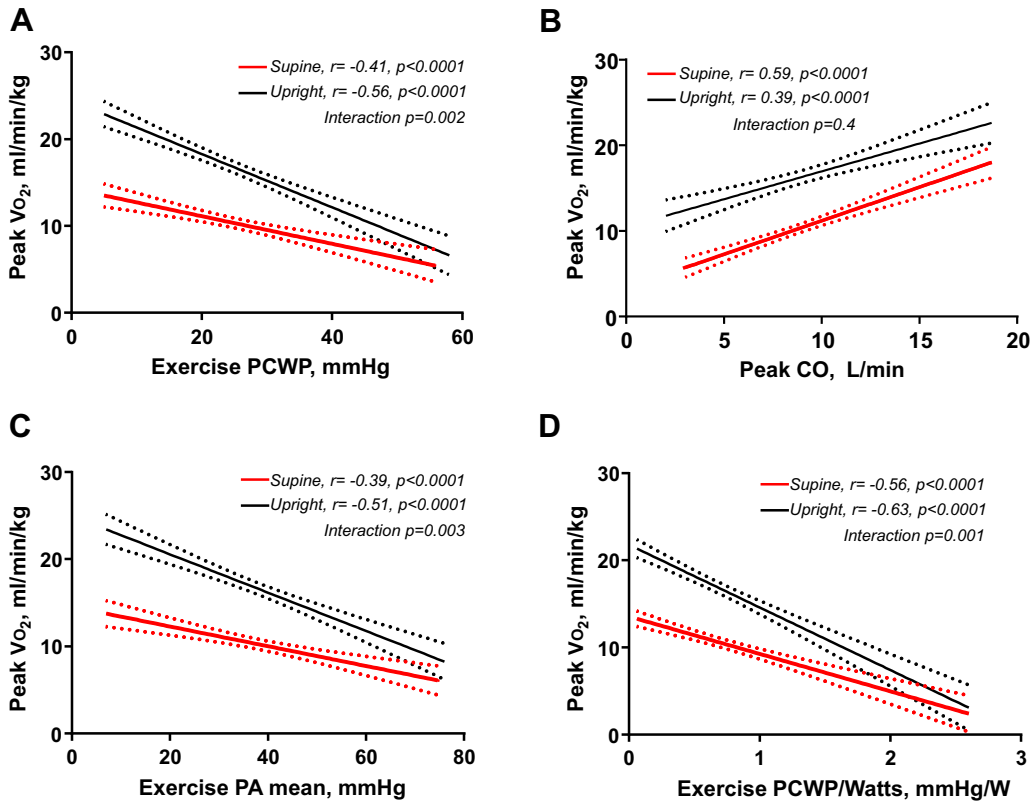
BP = blood pressure; RER = respiratory exchange ratio; RR = respiratory rate; V_{CO_2} = carbon dioxide production; V_E = minute ventilation; V_{O_2} = oxygen consumption; VT = tidal volume; other abbreviations as in Table 2.

DISCUSSION

This study examined the invasive hemodynamic correlates of exercise capacity in HFpEF and the utility of noninvasive CPET as a potential test to discriminate HFpEF from noncardiac causes of exertional dyspnea. There are 2 key findings that have far-reaching implications. First, we observed that elevation in cardiac filling pressures during supine exercise is an independent correlate of reduced exercise capacity in patients with HFpEF, regardless of body position, and even after accounting for other known determinants related to oxygen delivery, diffusion, utilization, and extraction according to the Fick principle. Second, we demonstrate that there is good discrimination of HFpEF from NCD using peak V_{O_2} values below and above currently suggested cutoffs (peak V_{O_2} values of <14 and >20 ml/min/kg) (9), but many patients lie within the intermediate gray zone between these boundaries where CPET may be less robust to distinguish HFpEF from NCD. In these patients, more definitive evaluation using exercise hemodynamic testing is required to establish the diagnosis (Figure 4).

EXERCISE HEMODYNAMICS AND EXERCISE CAPACITY. Elevation in left ventricular filling pressures increases the hydrostatic pressure in the pulmonary capillaries, altering Starling forces to favor fluid movement out of the vascular space and into the interstitium, which can alter lung compliance and promote dyspnea (26). Elevation in filling pressures during exercise in HFpEF is associated with increased risk of death, even when resting pressures are normal (27). Conversely, reduction in filling pressures improves dyspnea as well as morbidity and mortality, at least in patients with HFrEF (28–30). Although it would seem self-evident that increases in PCWP during exercise

FIGURE 2 Relationships Between Exercise Capacity and Supine Exercise Hemodynamics



Correlation between peak O_2 consumption (Vo_2) in both upright **(black)** and supine **(red)** positions, and exercise pulmonary capillary wedge pressure (PCWP), pulmonary artery (PA) pressure, cardiac output (CO), and PCWP indexed to work performed in watts (W).

should cause dyspnea and thus worsen exercise capacity, studies performed to date conducted in patients with HFrEF have failed to identify any correlation between cardiac filling pressures and peak Vo_2 (6–8).

By contrast, we observed a significant inverse relationship between exercise PCWP and peak Vo_2. Intracardiac pressures are lower in the upright position, leading some to question the relevance of hemodynamics measured in the supine position to activities of daily life, which are more likely to be performed in the upright position. In this regard, it is notable that we observed that the inverse relationships between elevated left ventricular filling pressures during supine exercise and peak Vo_2 were even more pronounced for upright exercise (**Figure 2**).

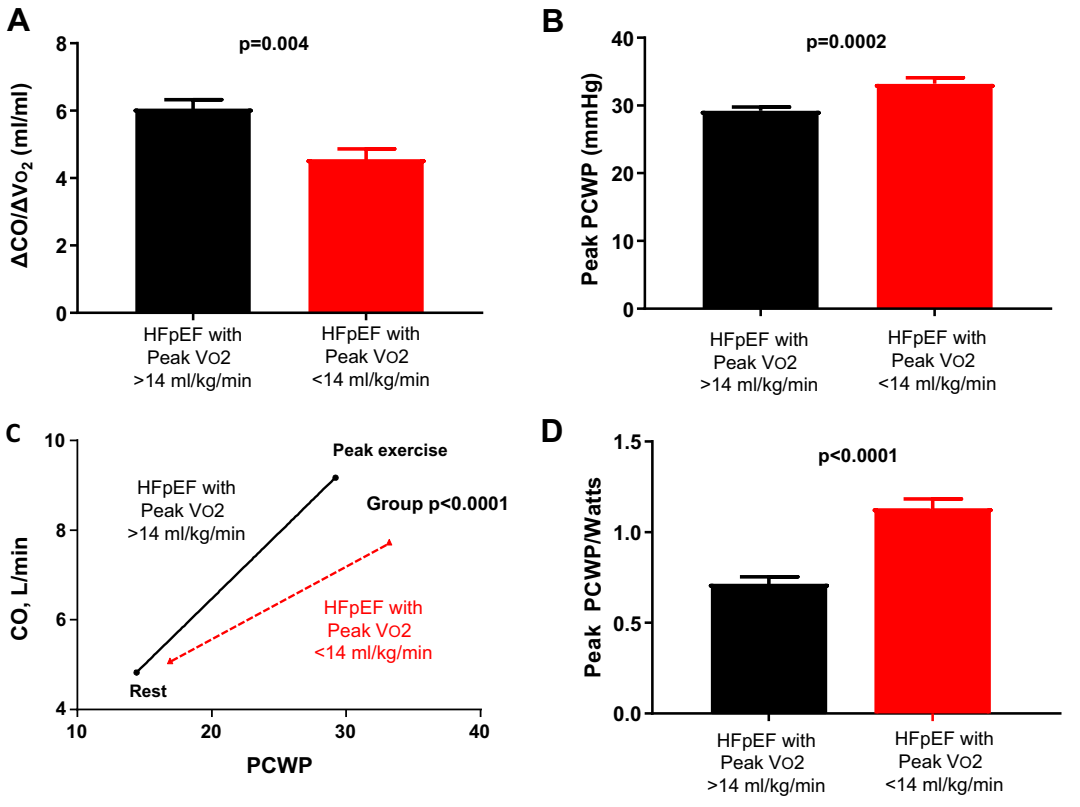
Importantly, these data show for the first time to our knowledge that elevated exercise PCWP is an

TABLE 4 Independent Correlates of Peak Vo_2

	Variance Inflation Factor	Standardized β Estimate	p Value
Noncardiac dyspnea			
Age, yrs	2.46	−0.15	0.40
Female	1.22	−0.07	0.60
Peak stroke volume, ml	1.57	0.35	0.03
Peak heart rate, min^{-1}	1.85	0.37	0.04
Peak A Vo_2, ml/dl	1.48	0.31	0.05
Peak PCWP, mm Hg	1.49	−0.10	0.50
HFpEF			
Age, yrs	1.29	−0.20	0.04
Female	1.15	−0.19	0.04
Peak stroke volume, ml	1.70	0.26	0.02
Peak heart rate, min^{-1}	1.42	0.27	0.007
Peak A Vo_2, ml/dl	1.22	0.15	0.10
Peak PCWP, mm Hg	1.01	−0.29	0.0006

Abbreviations as in Tables 2 and 3.

FIGURE 3 Characteristics of HFpEF Patients With Severely Depressed Aerobic Capacity



Compared with HFpEF patients with peak Vo_2 ≥14 ml/kg/min **(black)**, patients with severely decreased peak Vo_2 (<14 ml/kg/min) **(red)** display **(A)** worse CO response relative to metabolic demand ($\Delta CO/\Delta Vo_2$), **(B)** higher PCWP, **(C)** higher PCWP relative to cardiac output reserve, and **(D)** higher PCWP relative to ergometric work performed. Abbreviations as in Figures 1 and 2.

independent correlate of reduced peak Vo_2. According to the Fick principle, Vo_2 is equal to the product of cardiac output and A Vo_2 difference. Remarkably, exercise PCWP remained a significant correlate of peak Vo_2 even after accounting for these determinants, as well as other known correlates including age, sex, and body mass. These data emphasize the important role of elevated PCWP in the pathophysiology of exercise intolerance in HFpEF and support ongoing research into pharmacological and device-based interventions to reduce exercise PCWP in HFpEF (13,31-36).

The reasons for the variance between the current data in patients with HFpEF and prior studies performed in patients with HFrEF are unclear (6-8). Although HFpEF patients are limited in part by cardiac output reserve (1,5), this impairment may not be as profound as is observed in patients with HFrEF (20,37). It may be that in HFrEF, exercise capacity is more constrained by poor output, whereas HFpEF patients may be more likely to cease exercising because of dyspnea caused by high filling pressures, or other sequelae of high PCWP, such as inadequate right ventricular ejection in the setting of exercise-induced pulmonary hypertension (5).

NONINVASIVE CPET IN DIAGNOSIS. Studies to date have uniformly reported that peak Vo_2 is depressed in HFpEF (1,4,5,19,20,38-46). However, surprisingly little data exist on the diagnostic utility of CPET for HFpEF, with most prior studies focusing on its prognostic role (14-16). Current HF guidelines acknowledge the difficulty in establishing the diagnosis of HFpEF (17), but do not directly address the diagnostic potential of CPET for HFpEF (10,11,47). The 2016 HF guidelines from the European Society of Cardiology do give a Grade IIa recommendation for CPET in the evaluation of HF among patients with unexplained

TABLE 5 Noninvasive CPET Predictors of HFpEF

Univariate	OR (95% CI)	AUC	Sensitivity	Specificity	p Value
Age >60 yrs	7.5 (4.0–14.4)	0.7256	80	35	<0.0001
Chronotropic incompetence	2.2 (1.2–4.0)	0.5935	69	49	0.009
HR recovery <6 beats/min	4.2 (1.9–10.8)	0.6081	31	90	0.001
V_{O_2} at AT <9 ml/kg/min	6.1 (2.3–21.2)	0.6091	28	94	0.001
V_{O_2} at AT <11 ml/kg/min	6.8 (3.3–15.1)	0.6957	54	85	<0.0001
O_2 pulse <0.14 ml/beat/kg	3.2 (1.8–6.0)	0.6371	73	54	0.0001
V_E/V_{CO_2} >30	1.1 (0.6–2.0)	0.5112	48	50	0.80
V_E/V_{CO_2} >36	1.7 (0.7–4.4)	0.5284	16	90	0.30
Peak V_{O_2}/kg					
Peak V_{O_2} <14 ml/kg/min	10.7 (4.6–29.1)	0.7071	50	91	<0.0001
Peak V_{O_2} <20 ml/kg/min	8.1 (4.0–17.2)	0.6906	90	49	<0.0001
Peak V_{O_2} <17 ml/kg/min	12.4 (6.2–24.6)	0.7778	80	76	<0.0001
% Pred (Wasserman)					
Peak V_{O_2} <50% predicted	1.1 (0.3–5.1)	0.5012	5	96	0.90
Peak V_{O_2} <60% predicted	2.0 (0.8–5.7)	0.5367	16	91	0.10
Peak V_{O_2} <70% predicted	1.7 (0.8–3.4)	0.5474	30	80	0.10
Peak V_{O_2} <80% predicted	1.4 (0.8–2.5)	0.5376	48	59	0.30
% Pred (Fletcher)					
Peak V_{O_2} <50% predicted	3.9 (2.1–7.7)	0.6544	54	77	<0.0001
Peak V_{O_2} <60% predicted	4.6 (2.5–8.6)	0.6704	78	56	<0.0001
Peak V_{O_2} <70% predicted	4.5 (2.0–10.3)	0.6018	92	29	0.0002
Peak V_{O_2} <80% predicted	8.1 (2.8–29.7)	0.5851	97	20	<0.0001

AUC = area under the curve; CI = confidence interval; OR = odds ratio; Pred = predicted; V_E/V_{CO_2} = ventilatory efficiency; other abbreviations as in Tables 2 and 3.

dyspnea, but there is no evidence supporting this recommendation (Level of Evidence: C) (18).

The current data fill this knowledge gap, providing the first direct evidence on the ability of noninvasive CPET to distinguish HFpEF from NCD. Importantly, the diagnosis was determined in all participants using the gold standard of invasive CPET testing, allowing for the ability to definitively establish or refute the presence of HFpEF, rather than reaching a "diagnosis of exclusion," which is often used in clinical practice (17), or relying on echocardiography and natriuretic peptide testing, which are poorly sensitive (3,4). The inclusion of a comparator group of older patients with noncardiac dyspnea and a normal EF is a strength, because this reflects the sort of patients that are encountered in everyday practice.

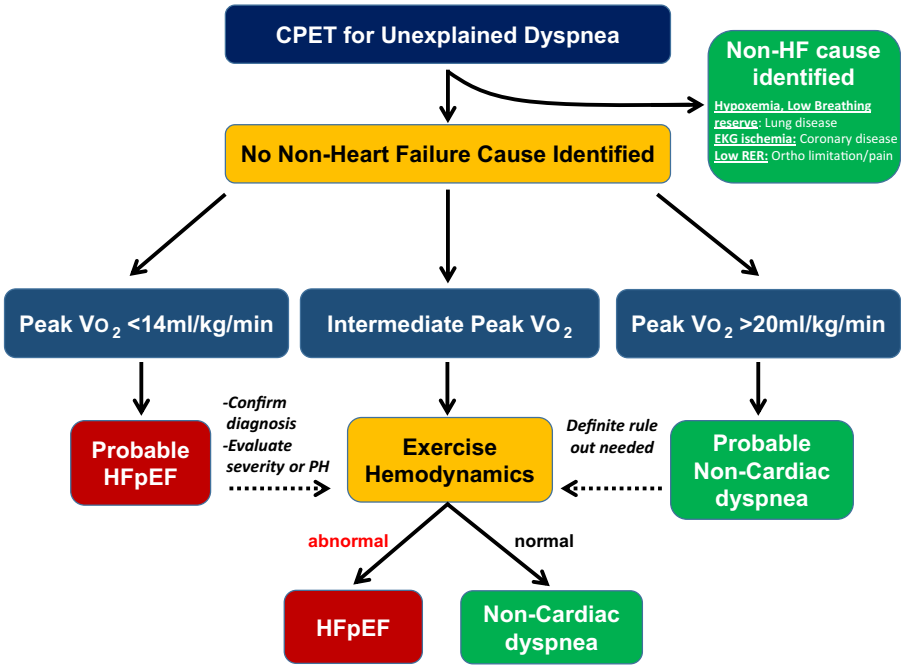
Peak V_{O_2} relative to body weight emerged as the most useful discriminatory noninvasive CPET variable to diagnose HFpEF among these patients with unexplained dyspnea, with very high sensitivity and specificity at extreme values (>20 or <14 ml/kg/min). However, there was a large intermediate zone (14 to 20 ml/kg/min) with substantial overlap. This appears to be related to the fact that many patients with noncardiac dyspnea display mild impairments in aerobic capacity beyond what would be seen in totally healthy volunteers. Because a large proportion of patients fall within this intermediate range, the current data suggest that CPET alone may not be best suited to serve as a key for noninvasive diagnosis of HFpEF, and invasive hemodynamic exercise testing, ideally with simultaneous CPET, should remain as the reference standard in the evaluation of possible HFpEF.

CONVERTING PEAK V_{O_2} TO PERCENT PREDICTED. Conversion of measured peak V_{O_2} to percent predicted peak V_{O_2} is currently recommended when evaluating patients with unexplained dyspnea using CPET (10,11). The Hansen-Wasserman formula (23), derived using data from 77 male shipyard workers, is the recommended method to make this determination. We observed that percent predicted peak V_{O_2} using this method only obscured differences between HFpEF and NCD (**Figure 1**). Importantly, a large proportion of patients with invasively proven HFpEF displayed percent predicted peak V_{O_2} that was minimally impaired according to the Wasserman formula: 52% of HFpEF patients displayed peak V_{O_2} ≥80% by the Wasserman equation, and 84% of HFpEF patients displayed peak V_{O_2} ≥60% by this method. These data raise serious questions regarding the use of this formula in the evaluation of patients with HFpEF.

A different nomogram from Fletcher et al. (24) performed better to discriminate the groups, but this was not superior to using measured peak V_{O_2} values adjusted for body weight, which is much easier to apply clinically and appears to discriminate HFpEF from NCD. Further study is required to identify the optimal metrics to normalize aerobic capacity for diagnostic purposes.

STUDY LIMITATIONS. There is selection bias in that patients were referred for an invasive procedure for unexplained dyspnea. However, invasive CPET testing is necessary to clearly establish or refute the presence of HFpEF, which is not possible with noninvasive studies, and this study would not have been possible without the gold standard assessment (3,4). Patients with significant pulmonary disease were excluded because this cohort is more readily identifiable using examination, imaging, and pulmonary function testing, and we can therefore make no conclusions regarding the ability of CPET testing to discriminate this group from patients with isolated HFpEF or NCD. Functional class was not ascertained in this study, and the specific causes of noncardiac dyspnea were rarely identified because the focus was on identifying or excluding HFpEF specifically.

FIGURE 4 Utilization of CPET in the Evaluation of Unexplained Dyspnea



Proposed diagnostic algorithm for cardiopulmonary exercise testing (CPET) for unexplained dyspnea. When obvious causes have been excluded, measurement of peak Vo_2 by CPET allows for discrimination of HFpEF from noncardiac dyspnea at very low (<14 ml/kg/min) or relatively peak Vo_2 (>20 ml/kg/min), respectively. However, given the substantial overlap in the intermediate range, additional testing, as with hemodynamic exercise testing, is required in patients with peak Vo_2 14 to 20 ml/kg/min. EKG = electrocardiogram; RER = respiratory exchange ratio; other abbreviations as in Figure 1.

Noninvasive CPET testing, echocardiography, and invasive CPET were not performed simultaneously, but because the median time between noninvasive CPET and invasive CPET was only 3 days, there is minimal risk of medication or other physiological changes that might have influenced test results. Exercise was performed in different positions, but the observation that upright exercise performance was even more tightly correlated with hemodynamics measured in the supine position is a strength of this study, particularly because cardiac catheterization is most commonly performed in the supine position. CPET with or without stress imaging is also valuable to detect ischemic disease and other NCD (Figure 4), and these were not evaluated in this study because patients with significant pulmonary disease were excluded. Furthermore, among patients with HFpEF, CPET can provide valuable information about pulmonary and chronotropic reserve and may also be used to longitudinally follow clinical course or gauge the efficacy of therapeutic interventions.

CONCLUSIONS

Elevation in left ventricular filling pressure with exercise is independently correlated with depressed exercise capacity, supporting its central role in the pathophysiology of HFpEF. Very low or relatively preserved peak Vo_2 measured noninvasively by CPET is useful to discriminate HFpEF from NCD, but people with exertional dyspnea and only mildly depressed peak Vo_2 require additional testing to clarify the diagnosis because NCD may also reduce peak Vo_2.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Although exercise capacity (peak oxygen consumption [Vo_2]) is depressed in HFpEF, its hemodynamic determinants and role in diagnosis remains unclear. We demonstrate that: 1) peak Vo_2 correlates with invasive cardiac output and biventricular filling pressures regardless of body position during exercise; 2) peak PCWP is an independent correlate of peak Vo_2 only in HFpEF; and 3) peak Vo_2 <14 ml/kg/min or >20 ml/kg/min was useful to rule-in and rule-out HFpEF, respectively, whereas intermediate values and currently used complex nomograms were less discriminatory.

TRANSLATIONAL OUTLOOK: Therapies targeting PCWP with exercise and its impact on exercise capacity require further study. Future research should seek to clarify role of additional testing to improve the ability of noninvasive CPET to discriminate HFpEF from NCD.

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APPENDIX For an expanded Methods section and references as well as a supplemental table, please see the online version of this paper.