JACC: HEART FAILURE VOL. ■, NO. ■, 2019

PUBLISHED BY ELSEVIER

Central and Peripheral Determinants of Exercise Capacity in Heart Failure Patients With Preserved Ejection Fraction

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ABSTRACT

OBJECTIVES This study sought to discern which central (e.g., heart rate, stroke volume [SV], filling pressure) and peripheral factors (e.g., oxygen use by skeletal muscle, body mass index [BMI]) during exercise were most strongly associated with the presence of heart failure and preserved ejection fraction (HFpEF) as compared with healthy control subjects exercising at the same workload.

BACKGROUND The underlying mechanisms limiting exercise capacity in patients with HFpEF are not fully understood.

METHODS In patients with HFpEF (n = 108), the hemodynamic response at peak exercise was measured using right-sided heart catheterization and was compared with that in healthy control subjects (n = 42) at matched workloads to reveal hemodynamic differences that were not attributable to the workload performed. The patients studied were prospectively included in the REDUCE-LAP HF (Reduce Elevated Left Atrial Pressure in Patients With Heart Failure) trials and HemReX (Effect of Age on the Hemodynamic Response During Rest and Exercise in Healthy Humans) study. Univariable and multivariable logistic regression models were used to analyze variables associated with HFpEF versus control subjects.

RESULTS Compared with healthy control subjects, pulmonary capillary wedge pressure (PCWP) and SV were the only independent hemodynamic variables that were associated with HFpEF, a finding explaining 66% ($p < 0.0001$) of the difference between the groups. When relevant baseline characteristics were added to the base model, only BMI emerged as an additional independent variable, in total explaining of 90% of the differences between groups ($p < 0.0001$): PCWP (47%), BMI (31%), and SV (12%).

CONCLUSIONS The study identified 3 key variables (PCWP, BMI, and SV) that independently correlate with the presence of patients with HFpEF compared with healthy control subjects exercising at the same workload. Therapies that decrease left-sided heart filling pressures could improve exercise capacity and possibly prognosis. (J Am Coll Cardiol HF 2019;■:■–■) © 2019 by the American College of Cardiology Foundation.

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ISSN 2213-1779/$36.00 https://doi.org/10.1016/j.jchf.2019.01.006

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

Ca-vo$_2$ = arteriovenous oxygen difference

CO = cardiac output

CVP = central venous pressure

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

IASD = interatrial shunt device

LV = left ventricular

LVEF = left ventricular ejection fraction

mPAP = mean pulmonary artery pressure

NT-proBNP = N-terminal pro-B-type natriuretic peptide

PCWP = pulmonary capillary wedge pressure

PVR = pulmonary vascular resistance

SV = stroke volume

SVR = systemic vascular resistance

Vo$_2$ max = maximal oxygen consumption

A hallmark of heart failure (HF) with preserved ejection fraction (HFpEF) is severely impaired exercise capacity. Exercise intolerance, manifested by symptoms of exertional dyspnea and fatigue, impairs quality of life and is therefore a key patient-centered outcome in HFpEF. In addition, reduced exercise capacity in HFpEF is associated with worse clinical outcomes (1,2). However, the underlying mechanisms limiting exercise capacity in patients with HFpEF remain incompletely understood (3). The studies performed to date have used a variety of techniques to examine mechanisms of exercise intolerance in HFpEF and have variably reported contributions of *central* factors (e.g., heart rate, stroke volume [SV], filling pressures) and *peripheral* factors (e.g., oxygen use by skeletal muscle, body mass index [BMI], renal function). However, only a few studies have directly analyzed the relationships between symptoms and aerobic capacity by using gold standard invasive measures (4–6). Importantly, no study to date has included a control group exercising at the matched workload to the peak level of HFpEF.

To fill this critical knowledge gap, we performed a study with invasive exercise tests, using data from 3 of the largest prospective trials of patients with HFpEF and healthy participants (n = 150) (7–9). The healthy control subjects were prospectively enrolled and rigorously screened to verify the absence of cardiac disease. To discern which central and peripheral factors were independently associated with patients with HFpEF compared with healthy control subjects, we performed 2 complementary analyses: we compared the hemodynamic response of patients with HFpEF at their peak exercise workload capacity with that of control subjects exercising at the same workload to reveal hemodynamic differences that were not attributable to the workload performed. In a supplemental analysis, the hemodynamic responses during peak exercise in both patients with HFpEF and control subjects were compared relative to the individual workloads achieved.

METHODS

This study used baseline data from 2 trials and 1 population study: the REDUCE LAP-HF (Reduce Elevated Left Atrial Pressure in Patients With Heart Failure) trial; the REDUCE LAP-HF I trial and the HemReX (Effect of Age on the Hemodynamic Response During Rest and Exercise in Healthy Humans) study. Patients and healthy participants were recruited from 2013 to 2016. All participants provided oral and written informed consent before enrollment. All studies were approved by relevant ethical committees and respected the Helsinki Declaration. The primary findings of the studies have been published (7–9). All measurements from patients with HFpEF were obtained before interatrial shunt device (IASD) implantation.

PATIENTS WITH HFpEF. Patients with elevated pulmonary capillary wedge pressure (PCWP) either at

and has received National Institutes of Health grants R01 HL127028, R01 HL140731, and R01 HL107577. Dr. Borlaug has received research funding from the National Heart, Lung, and Blood Institute (grants RO1 HL128526 and U10 HL110262), Mast Therapeutics, Medtronic, GlaxoSmithKline, and Teva; and has consulted and served on advisory boards for Actelion, Amgen, AstraZeneca, Merck, and MyoKardia. Dr. Burkhoff has been a consultant for and is the director of Hemodynamic Core Laboratory for Corvia Medical; and is the founder of PVLoops, LLC. Dr. Kitzman has received consulting fees from Corvia Medical, Medtronic, Bayer, Merck, Relypsa, and Abbvie; research funding from Novartis and Bayer; and owns stock in Gilead. Dr. Lam has received research support from Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, and Vifor Pharma; has consulted for Corvia, AstraZeneca, Bayer, Novartis, Amgen, Merck, Janssen Research & Development LLC, Menarini, Boehringer-Ingelheim, Abbott Diagnostics, Stealth BioTherapeutics, and Takeda; and is on the advisory board, steering committee, and/or executive committee for Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, Vifor Pharma, Novartis, Amgen, Merck, Janssen Research & Development LLC, Menarini, Boehringer-Ingelheim, Abbott Diagnostics, Corvia Medical, Stealth BioTherapeutics, JanaCare, Biofourmis, and Darma. Dr. Veldhuisen member of the steering committee of the REDUCE-LAP trial; and has received travel expenses from Corvia Medical. Dr. Ponikowski has received unrestricted research grants from Corvia Medical; and is an unpaid member of the Corvia Medical Scientific Advisory Group. Dr. Petrie has received speaker fees or consulting honoraria from Takeda, Novartis, AstraZeneca, Maquet, Boehringer-Ingelheim, Pfizer, Daiichi Sankyo, Servier, and Eli Lilly; has served on clinical events committees for Roche, Bayer, Stealth BioTherapeutics, AstraZeneca, GlaxoSmithKline, Novo Nordisk, Astellas, Cardiorentis, Reservlogix, and Boehringer-Ingelheim; and is an unpaid member of the Corvia Medical Scientific Advisory Group. Dr. Møller has received a research grant and speaker fees from Abiomed. Dr. Gustafsson has received unrestricted research grants from Corvia Medical; is an unpaid member of the Corvia Medical Scientific Advisory Group; has received speaker fees from Carmat, Abbott, and Orion; and has received a consultant fees from Bayer. Dr. Hassager has reported that he has no relationships relevant to the contents of this paper to disclose.

Manuscript received November 17, 2018; revised manuscript received December 30, 2018, accepted January 4, 2019.

rest or during exercise and with signs and symptoms of HF were included in 2 studies evaluating an IASD (IASD system II, Corvia Medical, Inc., Tewksbury, Massachusetts): REDUCE LAP-HF, which had a nonrandomized, open-label design; and REDUCE LAP-HF I, which had a randomized, double-blind design. The primary objective of the trials was to assess the safety and efficacy of IASD implantation. Key inclusion criteria were as follows: informed consent; New York Heart Association functional class II to IV; left ventricular ejection fraction (LVEF) ≥40% determined by echocardiography; ≥1 HF hospitalization within last 12 months before screening and/or elevated natriuretic peptides; age ≥40 years; elevated LV filling pressures with a gradient compared with central venous pressure (CVP) documented by ≥1 of the following; end-expiratory PCWP or LV end-diastolic pressure at rest ≥15 mm Hg and greater than CVP; and/or PCWP during supine bicycle exercise ≥25 mm Hg. Key exclusion criteria were cardiac index ≤2.0 l/min/m^2, obstructive or restrictive cardiomyopathy, moderate to severe heart valve disease, atrial fibrillation with resting heart rate >100 beats/min, and dialysis or estimated glomerular filtration rate <25 ml/min/1.73 m^2. Because the inclusion criteria and the invasive protocol were similar, data were pooled from the 2 studies. Additional details of the trial designs have been published (10,11).

HEALTHY SUBJECTS. A total of 62 healthy subjects 20 to 80 years of age were enrolled in the primary prospective study; however, only patients ≥40 years of age were included in the present study (n = 42) because this cutoff corresponded to the age inclusion criteria for the HFpEF studies. Healthy subjects were deemed eligible if they fulfilled inclusion criteria; were free of a history of any acute or chronic cardiac or pulmonary disease; had echocardiography without signs of chamber hypertrophy, reduced LVEF, or significant valvular disease; had normal spirometry for their age; had routine blood chemistry testing with normal values (including N-terminal pro-B-type natriuretic peptide [NT-proBNP]); had a BMI of 20 to 30 kg/m^2; and had an exercise test with electrocardiogram without any pathological findings. Additional details of the study design have been published (9).

The protocols of all 3 trials were published on ClinicalTrials.gov (NCT01913613, NCT02600234, NCT01974557) before subject enrollment.

BASELINE DATA. Each subject underwent transthoracic echocardiography performed according to echocardiographic and core laboratory standards at baseline. Blood samples were collected and analyzed according to standards used at each participating site.

HEMODYNAMIC PARAMETERS. Hemodynamic variables were measured at rest and during ergometer exercise with subjects in the supine position in both patients with HFpEF and healthy participants. Ergometer resistance was increased every 3 to 4 min with increments of either 20 W (patients with HFpEF) or 25 W (control subjects) until maximal effort was achieved. In patients with HFpEF, maximal effort or peak exercise was judged by patients and physicians, when patients were not able to maintain 60 revolutions/min on the ergometer at a given workload. In healthy participants, maximal effort was defined as 4 min of exercise in a supine ergometer with lactate buildup and objective signs of severe exertion at a workload corresponding to 75% of maximal oxygen consumption (Vo_2 max) identified during a previous test on an upright ergometer, in accordance with the lower Vo_2 max achievable in a supine compared with an upright position (4). A Swan-Ganz catheter was positioned in the pulmonary artery through the internal jugular or brachial vein. For all signals, 10-s segments were recorded. Signals were quantified by visual estimation of values at end-expiration. At rest, multiple beats (>3) were typically available, but often this was not the case during exercise with higher-ventilatory frequency.

The following hemodynamic data were collected: CVP, mean pulmonary artery pressure (mPAP), PCWP, cardiac output using thermodilution technique (CO), noninvasive systolic blood pressure, noninvasive diastolic blood pressure, noninvasive peripheral oxygen saturation (Sao_2), and heart rate. In addition, mixed venous oxygen (Svo_2) was sampled from the pulmonary artery.

DERIVED VARIABLES. Systemic vascular resistance (SVR) was calculated as: 80 × (mean arterial pressure − CVP) / CO. Pulmonary vascular resistance (PVR) in Wood units was calculated as (mPAP − PCWP) / CO. Transmural pressure gradient (TMG) was calculated as: PCWP − RAP. Transpulmonary pressure gradient (TPG) was calculated as mPAP − PCWP. Cardiac index was calculated as CO / body surface area. SV indexed, was calculated as cardiac index / heart rate. The venous blood oxygen content (Cvo_2) was calculated using the formula (6): Cvo_2 = hemoglobin $\left(\frac{g}{dl}\right)$ 1.39 × Svo_2. Arterial oxygen content was calculated similarly using either noninvasively measured arterial saturation or imputed on the basis the median value if missing (46%). We did not account for plasma-bound oxygen because we did not have data on partial pressures. However, this

TABLE 1 Patients' Characteristics

	Control Subjects (n = 42)	HFpEF (n = 108)	p Value
Age	59 ± 11	70 ± 8	<0.0001
Sex (female)	22/20 (52% female)	64/44 (59% female)	0.44
Weight (kg)	76 ± 11	94 ± 22	<0.0001
BMI (kg/m^2)	25 ± 3	34 ± 7	<0.0001
BSA (m^2)	1.90 ± 0.17	2.01 ± 0.25	0.01
Medical history			
Atrial fibrillation	0	45 (42)	<0.0001
COPD	0	16 (15)	<0.0001
Diabetes	0	46 (43)	<0.0001
NYHA functional class			<0.0001
II	N/A	18 (17)	
III	N/A	89 (82)	
IV	N/A	1 (1)	
Systolic BP	138 ± 16	138 ± 23	0.97
Diastolic BP	79 ± 9	71 ± 14	0.003
Vo_2 max (ml/min)	2,436 ± 661	1,381 ± 509	<0.0001
Vo_2 max (ml/kg/min)	32 ± 7	16 ± 4	<0.0001
RER (Vo_2:Vco_2)	1.10 ± 0.06	1.04 ± 0.09	0.01
eGFR (ml/min/1.73 m^2)	76 ± 13	57 ± 21	<0.0001
Hemoglobin (g/dl)	14 ± 1	13 ± 2	<0.0001
NT-proBNP (pg/ml)	59 [50-120]	390 [218-941]	<0.0001
Echocardiography			
LVEF (%)	62 ± 7	52 ± 10	<0.0001
LVEDVi (ml/m^2)	70 ± 16	69 ± 21	0.72
LAi (ml/m^2)	23 ± 8	39 ± 22	<0.0001
EA	1.2 ± 0.4	1.5 ± 1.2	0.11
E/e'	9 ± 3	15 ± 6	<0.0001
TAPSE (cm)	2.6 ± 0.4	2.0 ± 0.5	<0.0001
Medication			
Beta-blocker use	0	81 (84)	<0.0001
ACE inhibitors/angiotensin II receptor inhibitors	0	68 (76)	<0.0001

Values are mean ± SD, median [IQR], or n (%), unless otherwise indicated.

ACE = angiotensin-converting enzyme; BMI = body mass index; BP = blood pressure; BSA = body surface area; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HFpEF = heart failure with preserved ejection fraction; LAi = indexed left atrium; LVEDVi = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; N/A = not applicable; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; RER = respiratory exchange ratio; TAPSE = tricuspid annular plane systolic excursion; Vo_2 max = maximal oxygen consumption.

component contributes very little to oxygen content given that measurements are made close to sea level, and patients do not have grave anemia. Peripheral arteriovenous oxygen difference (Ca-vo_2) was calculated as the difference in blood oxygen content: Ca-vo_2 = Cao_2 − Cvo_2.

STATISTICAL ANALYSIS. Data were summarized using mean ± SD, except NT-proBNP, which was summarized as median [interquartile range]. Student's *t*-test and Wilcoxon rank sum test was used to test for differences between groups. A sensitivity analysis excluding patients with BMI >30 kg/m^2 and adjustments for BMI (and age) were performed because this was a pre-defined exclusion criterion for the control group. Because hemodynamic measurements were obtained at several submaximal exercise workloads in healthy control subjects compared with peak exercise only in patients with HFpEF, data obtained at various workloads from a single control patient could be included more than once in the matched workload analysis (72 workload entries from 42 patients). Hemodynamic data from the control group obtained at workloads higher than maximally achieved by the patients with HFpEF were omitted in the matched workload analysis. In the relative workload analysis, peak workloads were used in both groups.

Univariable and multivariable logistic regression models were used to analyze variables associated with HFpEF versus control subjects (i.e., the dichotomous dependent variable was the HFpEF). Because individual patients could contribute with data from more than 1 workload, SEs were estimated using patient-level clustering in regression models (matched workload analysis). Significant independent variables were identified using stepwise selection ($p < 0.05$). To minimize collinearity issues, no derived variables or indexed variables were included in the models. mPAP and PCWP were collinear, and only PCWP was used for modeling. Both hemodynamic measures and clinical variables listed in Table 1 were included in the models except Vo_2 max and NT-proBNP because of collinearity and missing data, respectively. Furthermore, New York Heart Association functional class, echocardiographic abnormalities, and medications were omitted because these measures were not present in the healthy control subjects by definition.

Dominance analysis was used to obtain the proportion of fit metric that was attributable to each independent variable as described by Azen and Budescu (12) (STATA package domin, StataCorp, College Station, Texas). This analysis aggregates results across multiple models, whereby the cumulative contributions of independent variables may differ slightly from the r^2 values. A p value of 0.05 was considered statistically significant. All analyses were conducted using STATA version 14.

RESULTS

Patients with HFpEF from the REDUCE-LAP HF (Reduce Elevated Left Atrial Pressure in Patients With Heart Failure) (7) (n = 64) and REDUCE-LAP HF I (8) (n = 44) trials were included and compared with healthy control subjects from the HemReX study (9) (n = 42). Baseline characteristics and hemodynamic variables at rest are summarized in Tables 1 and 2. All variables were significantly different between control

TABLE 2 Hemodynamic Variables at Rest and During Exercise at Matched Workloads*

	Baseline (Rest)			Exercise (Matched Workloads)			
	Control Subjects (n = 42)	HFpEF (n = 108)	p Value	Control Subjects (n = 72)	HFpEF (n = 107)	p Value	Adjusted p Value†
Workload (W)	0	0	–	45 ± 22	43 ± 18	0.41	0.57
Heart rate (beats/min)	63 ± 9	70 ± 14	0.005	93 ± 18	99 ± 20	0.04	0.03
MAP (mm Hg)	93 ± 9	93 ± 14	0.96	99 ± 14	111 ± 23	0.0007	0.17
SV (ml)	83 ± 21	82 ± 30	0.85	115 ± 31	90 ± 29	<0.0001	<0.0001
SVi (ml/m^2)	43 ± 8	41 ± 13	0.24	60 ± 13	44 ± 12	<0.0001	N/A
CO (l/min)	5.1 ± 1.0	5.6 ± 2.0	0.12	10.5 ± 2.3	8.7 ± 3.0	<0.0001	<0.0001
Cardiac index (l/min/m^2)	2.7 ± 0.4	2.8 ± 0.8	0.48	5.6 ± 1.1	4.3 ± 1.2	<0.0001	N/A
RAP (mm Hg)	5 ± 2	9 ± 3	<0.0001	10 ± 4	19 ± 6	<0.0001	<0.0001
mPAP (mm Hg)	15 ± 3	26 ± 8	<0.0001	30 ± 8	46 ± 11	<0.0001	<0.0001
PCWP (mm Hg)	9 ± 3	19 ± 6	<0.0001	19 ± 7	35 ± 7	<0.0001	<0.0001
SVR (dyne x s/cm^5)	1,437 ± 281	1,329 ± 415	0.13	712 ± 182	941 ± 355	<0.0001	<0.0001
PVR (Wood)	1.2 ± 0.5	1.5 ± 0.9	0.08	1.1 ± 0.5	1.4 ± 1.2	0.05	0.77
TPG (mm Hg)	6 ± 2	8 ± 4	0.02	11 ± 4	11 ± 8	0.52	0.005
TMG (mm Hg)	3 ± 2	9 ± 5	<0.0001	9 ± 4	16 ± 7	<0.0001	<0.0001
Cao_2 (ml/dl)	19.6 ± 1.7	17.1 ± 2.6	<0.0001	19.2 ± 1.5	16.7 ± 2.7	<0.0001	0.56
Cvo_2 (ml/dl)	14.9 ± 1.7	12.1 ± 2.2	<0.0001	9.6 ± 2.0	8.1 ± 2.8	0.0001	0.004
Ca-vo_2 (ml/dl)	4.8 ± 0.8	5.1 ± 1.3	0.19	9.6 ± 1.6	8.6 ± 2.8	0.01	0.02

Values are mean ± SD. *Data obtained at various workloads from a single control patient could be included more than once in the matched workload analysis accounting for the difference in n in the control group (n = 42 vs. 72). One patient with HFpEF did not manage to perform exercise, thus accounting for the difference in (n = 108 vs. 107). †Adjusted for age and body mass index (except indexed variables).

Cao_2 = arterial oxygen content; Ca-vo_2 = arteriovenous oxygen difference; CO = cardiac output; Cvo_2 = venous oxygen content; HFpEF = heart failure with preserved ejection fraction; MAP = mean arterial pressure; mPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SV = stroke volume; SVi = indexed stroke volume; SVR = systemic vascular resistance; TMG = transmural pressure gradient; TPG = transpulmonary pressure gradient.

subjects and patients with HFpEF at rest, except sex, systolic blood pressure, LV end-diastolic volume, EA ratio, mean arterial pressure, SV, indexed SV, CO, cardiac index, SVR, PVR, and Ca-vo_2. Limiting comparisons to patients (n = 33) and control subjects (n = 42) with BMI ≤30 kg/m^2, the same differences between groups were noted, except for BMI, body surface area, SV, indexed SV, and heart rate, which were statistically similar between groups, whereas EA ratio and PVR were higher and CO was lower in HFpEF compared with control subjects (Online Tables 1 and 2). Patients grouped according to LVEF above or below 50% had comparable baseline characteristics (Online Table 3).

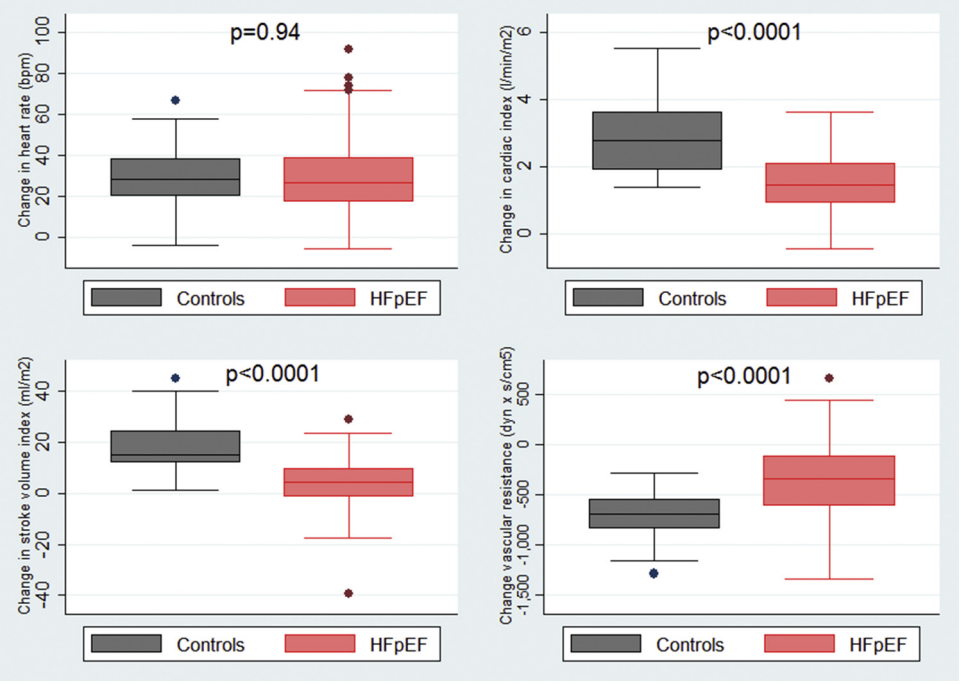
CENTRAL AND PERIPHERAL EXERCISE FACTORS AT MATCHED WORKLOADS. The maximal workload achieved by patients with HFpEF was 43 ± 18 W. The matched mean workload of the control group was 45 ± 22 W (p = 0.41 for difference between HFpEF [n = 107] vs. control subjects [n = 72]). See **Table 2** for hemodynamic data at matched workloads. The following changes from baseline to matched workload in HFpEF versus control subjects were observed: heart rate (+29 ± 19 beats/min vs. +29 ± 16 beats/min; p = 0.94); CO (+3.1 ± 1.9 l/min vs. +5.4 ± 2.0 l/min; p < 0.0001); cardiac index (+1.5 ± 0.9 l/min/m^2 vs. +2.9 ± 1.1 l/min/m^2; p < 0.0001); SV (+8 ± 21 ml vs. +35 ± 20 ml; p < 0.0001); SV [indexed] (+4 ± 10 ml/m^2 vs. +19 ± 10 ml/m^2; p < 0.0001); Ca-vo_2 (+3.7 ± 2.5 ml/dl vs. +4.9 ± 1.5 ml/dl; p = 0.0004); and SVR (−367 ± 365 dyne × s/cm^5 vs. −716 ± 234 dyne × s/cm^5; p < 0.0001) (**Figure 1**).

VARIABLES ASSOCIATED WITH HFpEF DURING EXERCISE AT MATCHED WORKLOADS. Hemodynamic variables associated with HFpEF during matched workloads are shown in **Table 3**. When relevant baseline variables from **Table 1** were added to the base model of hemodynamic variables during matched exercise, BMI was the only additional independent variable. BMI increased the r^2 value of the model from 0.66 to 0.90. The individual contributions of each independent variable are shown in **Figure 2**.

In a sensitivity analysis limited to control subjects and patients with BMI ≤30 kg/m^2, the results were similar with regard to both the independent hemodynamic variables identified (PCWP and SV) and the coefficients (Online Table 4).

CENTRAL AND PERIPHERAL EXERCISE FACTORS AT PEAK EXERCISE. The mean peak workload achieved was 45 ± 13 W versus 137 ± 35 W (p < 0.0001) for HFpEF versus control subjects.

FIGURE 1 Changes in Hemodynamic Variables From Baseline to Peak Exercise in HFpEF Compared With Control Subjects at Matched Workloads



bpm = beats per minute; HFpEF = heart failure with preserved ejection fraction.

Heart rate increased from baseline to peak exercise +29 ± 19 beats/min versus +64 ± 19 beats/min ($p < 0.0001$) for HFpEF versus control subjects. In the HFpEF group, there was no effect of beta-blocker use ($p = 0.14$) or atrial fibrillation ($p = 0.88$) on peak exercise heart rate, but progressive age was associated with lower heart rate at peak exercise ($p = 0.01$).

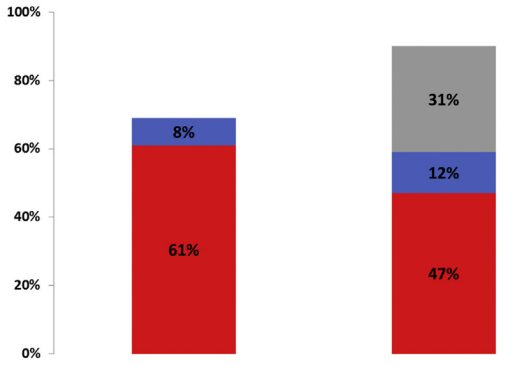
TABLE 3 Hemodynamic Variables Associated With HFpEF at Matched Workloads

	Univariable		Multivariable Model 1* ($R^2 = 0.66$; $p < 0.001$)		Multivariable Model 2† ($R^2 = 0.92$; $p = 0.15$)	
	Coefficient	p Value	Coefficient	p Value	Coefficient	p Value
Age (yrs)	0.1 (0.1, 0.1)	<0.001	–	–	0.1 (−0.0, 0.3)	0.14
BMI (kg/m^2)	0.4 (0.3, 0.5)	<0.001	–	–	2.3 (0.3, 4.2)	0.02
Heart rate (beats/min)	0.02 (0.00, 0.03)	0.04	–	–	–	–
MAP (mm Hg)	0.03 (0.01, 0.05)	0.001	–	–	–	–
SV (ml)	−0.03 (−0.04, −0.01)	<0.0001	−0.04 (−0.06, −0.01)	0.001	−0.24 (−0.44, −0.04)	0.02
RAP (mm Hg)	0.4 (0.3, 0.5)	<0.0001	–	–	–	–
PCWP (mm Hg)	0.4 (0.3, 0.5)	<0.0001	0.4 (0.2, 0.6)	<0.0001	0.9 (0.2, 1.5)	0.01
Ca-vo$_2$ (ml/dl)	−0.2 (−0.3, −0.0)	0.01	–	–	–	–
SVi (ml/m^2)	−0.11 (−0.14, −0.07)	<0.0001	–	–	–	–
CO (l/min)	−0.23 (−0.36, −0.10)	0.001	–	–	–	–
Cardiac index (l/min/m^2)	−0.90 (−1.19, −0.62)	<0.0001	–	–	–	–
mPAP (mm Hg)	0.2 (0.1, 0.3)	<0.0001	–	–	–	–
SVR (dyne × s/cm^5)	0.003 (0.001, 0.004)	<0.0001	–	–	–	–
PVR (Wood)	0.4 (−0.0, 0.7)	0.06	–	–	–	–

Values are mean (95% CI). *Model 1: heart rate, MAP, SV, RAP, PCWP, and Ca-vo$_2$ were included in the model. †Model 2: heart rate, MAP, SV, RAP, PCWP, and Ca-vo$_2$ (Model 1), adjusted for BMI and age.

Abbreviations as in Tables 1 and 2.

FIGURE 2 Contribution of Independent Variables Associated With HFpEF During Exercise at Matched Workloads



The contribution of each independent variable to the difference between heart failure with preserved ejection fraction (HFpEF) and control subjects at matched exercise is shown. The **first column** depicts the contribution of hemodynamic variables only. The **second column** depicts the contribution of hemodynamic and other independent variables identified. **Red** = PCWP, **blue** = SV, and **gray** = BMI. BMI = body mass index; PCWP = pulmonary capillary wedge pressure; SV = stroke volume.

TABLE 4 Hemodynamic Variables at Peak Exercise

	Control Subjects (n = 42)	HFpEF (n = 107)	p Value
Workload (W)	137 ± 35	43 ± 18	<0.001
Heart rate (beats/min)	127 ± 18	99 ± 20	<0.001
MAP (mm Hg)	111 ± 16	111 ± 23	0.96
SV (ml)	129 ± 33	90 ± 29	<0.001
SVi (ml/m^2)	68 ± 15	44 ± 12	<0.001
CO (l/min)	16 ± 3	9 ± 3	<0.001
Cardiac index (l/min/m^2)	8.4 ± 1.3	4.3 ± 1.2	<0.001
RAP (mm Hg)	10 ± 5	19 ± 5.5	<0.001
mPAP (mm Hg)	36 ± 10	46 ± 11	<0.001
PCWP (mm Hg)	21 ± 8	35 ± 7	<0.001
TMG (mm Hg)	11 ± 5	16 ± 7	<0.001
TPG (mm Hg)	15 ± 5	11 ± 8	0.001
SVR (dyne × s/cm^5)	535 ± 142	941 ± 355	<0.001
PVR (Wood)	0.96 ± 0.44	1.44 ± 1.23	0.022
Cao_2 (ml/dl)	19.48 ± 1.68	16.74 ± 2.72	>0.0001
Cvo_2 (ml/dl)	6.61 ± 1.46	8.06 ± 2.81	0.002
Ca-vo_2 (ml/dl)	12.87 ± 1.32	8.63 ± 2.82	<0.0001

Values are mean ± SD.
TMG = transmural pressure gradient; other abbreviations as in Table 2.

Cardiac index increased +1.5 ± 0.9 l/min/m^2 versus +5.8 ± 1.4 l/min/m^2 ($p < 0.0001$), and SV (indexed) increased +4 ± 10 ml/m^2 versus +26 ± 16 ml/m^2 ($p < 0.0001$) for patients with HFpEF versus control subjects.

At peak exercise, Ca-vo_2 was significantly lower in patients with HFpEF (9.1 ± 2.9 ml/dl) versus control subjects (12.8 ± 1.3 ml/dl) ($p < 0.0001$). SVR decreased −359 ± 371 dyne × s/cm^2 versus −904 ± 280 dyne × s/cm^5 ($p < 0.0001$) for patients with HFpEF versus control subjects.

Comparison of Central and Peripheral Exercise Factors Relative to Workload. All hemodynamic variables examined differed significantly between control subjects and patients with HFpEF at peak exercise, except mean arterial pressure (Table 4). In univariable analyses, all workload-corrected hemodynamic variables were individually associated with the HFpEF phenotype (Table 5). When multivariable analysis was performed with hemodynamic variables, only workload-corrected PCWP was independently associated with the presence of HFpEF, thus explaining 87% of the variability ($p < 0.0001$). A supplementary multivariable analysis using workload-corrected heart rate reserve (baseline to peak exercise in both groups) did not show that heart rate was significant ($p = 0.17$; data not shown).

When the model was adjusted for BMI and age, workload-corrected PCWP was still the largest contributor to the HFpEF phenotype: PCWP/workload (64%), BMI (21%), age (10%).

DISCUSSION

Our objective was to determine the factors that contribute most strongly to the presence of HFpEF, a cohort with profoundly impaired exercise capacity. Our study is the first to compare hemodynamic responses in patients with HFpEF during their peak levels of exercise with those of healthy control subjects at the same matched workload, thereby enabling determination of which hemodynamic differences were specific to the HFpEF phenotype, rather than being attributable to differences in workload achieved at peak exercise. A supplemental analysis of hemodynamic responses relative to workload at peak exercise for both groups was also performed.

At matched workloads, we identified 2 hemodynamic variables—PCWP and SV—and 1 anthropometric variable—BMI—that independently contributed to the HFpEF phenotype. Among these factors, the strongest was increased PCWP (47%). Together these variables accounted for 66% (without BMI) and 90% (with BMI) of the difference between patients with HFpEF and control subjects. These findings were supported by analysis of hemodynamic changes relative to workload during peak exercise.

EXERCISE-LIMITING FACTORS IN HFpEF AT MATCHED WORKLOADS. The patients with HFpEF had a similar absolute increase in heart rate compared

TABLE 5 Workload-Corrected Hemodynamic Variables Associated With HFpEF During Peak Exercise

	Univariable		Multivariable Model 1* ($R^2 = 0.87$; $p < 0.0001$)		Multivariable Model 2† ($R^2 = 0.94$; $p < 0.0001$)	
	Coefficient	p Value	Coefficient	p Value	Coefficient	p Value
Age (yrs)	0.11 (0.07, 0.15)	<0.0001	–	–	0.03 (−0.17, 0.22)	0.78
BMI (kg/m^2)	0.37 (0.24, 0.50)	<0.0001	–	–	0.52 (0.02, 1.03)	0.04
Heart rate/wl (beats/min/W)	6.7 (3.9, 9.5)	<0.0001	–	–	–	–
MAP/wl (mm Hg/W)	5.6 (3.3, 7.8)	<0.0001	–	–	–	–
SV/wl (ml/m^2/W)	4.8 (2.9, 6.8)	<0.0001	–	–	–	–
RAP/wl (mm Hg/W)	35.2 (20.2, 50.3)	<0.0001	–	–	–	–
PCWP/wl (mm Hg/W)	29.9 (11.3, 48.4)	0.002	28.0 (10.1, 45.8)	0.002	49.5 (0.2, 98.7)	0.049
Ca-vo$_2$/wl (ml/dl/W)	36.9 (22.9, 50.9)	<0.0001	–	–	–	–
SVi/wl (ml/m^2/W)	9.0 (5.5, 12.5)	<0.0001	–		–	–
CO/wl (l/min/W)	33.5 (19.3, 47.8)	<0.0001	–		–	–
Cardiac index/wl (l/min/m^2/W)	52.0 (29.5, 74.4)	<0.0001	–	–	–	–
mPAP/wl (mm Hg/W)	15.6 (8.5, 22.7)	<0.0001		–	–	–
TMP/wl (mm Hg/W)	28.6 (17.4, 39.8)	<0.0001	–	–	–	–
TPG/wl (mm Hg/W)	7.5 (3.6, 11.4)	<0.0001	–	–	–	–
SVR/wl (dyne x s/cm^5/W)	0.60 (0.36, 0.83)	<0.0001	–	–	–	–
PVR/wl (Wood/W)	110.4 (58.3, 162.4)	<0.0001	–	–	–	–

Values are mean (95% CI). *Model 1: heart rate, MAP, SV, RAP, PCWP, and Ca-vo$_2$ were included in the model (all corrected for workload). †Model 2: heart rate, MAP, SV, RAP, PCWP, and Ca-vo$_2$ (Model 1), adjusted for BMI and age.

wl = workload; other abbreviations as in Tables 1 and 2.

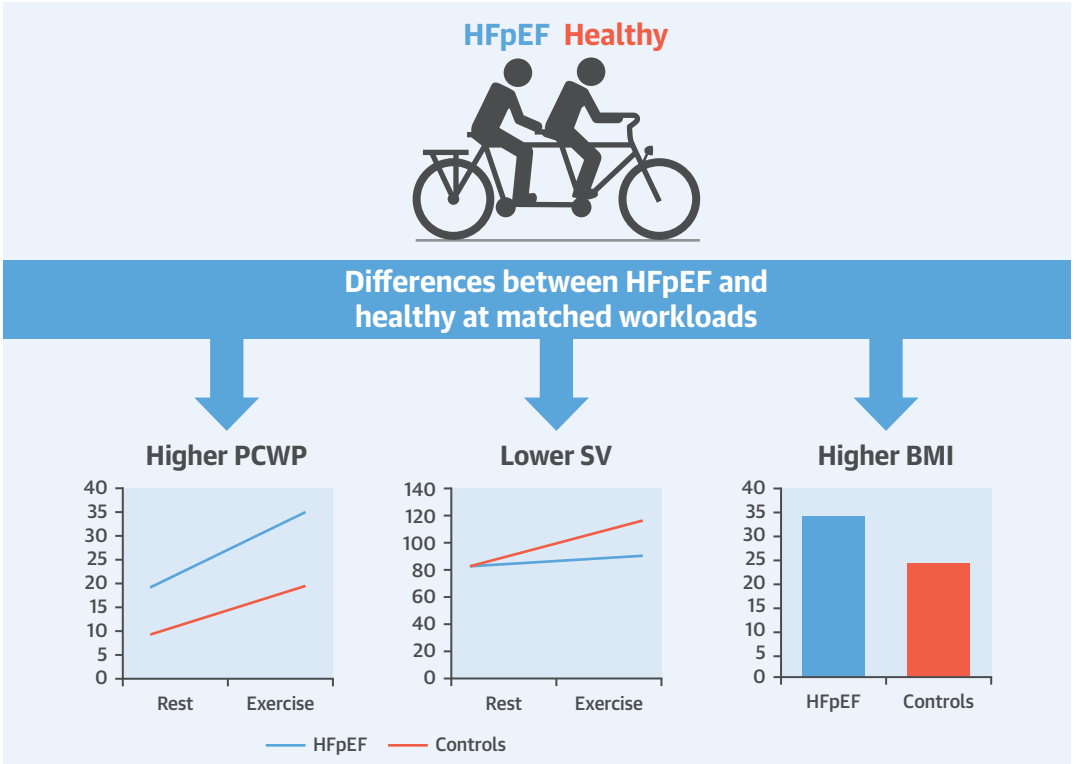
with control subjects, but modestly higher peak heart rate at similar workloads. Our finding that heart rate response did not appear abnormal in HFpEF is at variance with some prior studies, particularly those where exercise was performed in the upright position (13,14), but it is in agreement with others (15-17). Although our analyses did not show any association between the presence of HFpEF and heart rate at matched workload, this does not mean that modulating heart rate will not increase exercise capacity. In this study heart rate was markedly lower at peak exercise in patients with HFpEF compared with healthy subjects. This is a consistent finding in other HFpEF studies (18), and it has led to studies investigating whether atrial pacing improves exercise capacity in this cohort (RAPID-HF [Rate-Adaptive Atrial Pacing In Diastolic Heart Failure]; NCT02145351) (19).

At matched workloads, cardiac index was lower in HFpEF compared with control subjects because of an inability to increase SV during exercise, even though both groups had comparable SVs at rest. This observation is similar to findings at a matched lower-level workload (20 W) observed in prior studies (17,20). Importantly, whereas the limitation in exercise capacity in healthy persons is primarily governed by highest CO achievable (9), the limiting factor(s) in patients with HFpEF may be multifactorial and not necessarily limited by CO. Hence, in these patients, maximal exertion may be reached before their maximal uptake in oxygen.

PCWP showed dramatic increases during exercise, thus leading to a high PCWP/CO ratio in patients with HFpEF. The current data confirm and expand on prior studies showing that higher PCWP at peak exercise is associated with more impaired myocardial function (17), greater symptom severity (5), and worse aerobic capacity (4,5) in HFpEF. We also observed that Ca-vo$_2$ was significantly reduced in patients with HFpEF compared with control subjects, as previously reported by some groups (6,21,22). The current data are unique in that Ca-vo$_2$ was impaired in patients with HFpEF compared with control subjects even at submaximal workload, a finding that differs from 2 other studies that showed higher Ca-vo$_2$ during lower workloads in HFpEF (17,23). These data provide further support for the hypothesis that reduced oxygen extraction and use in skeletal muscle may be important determinants of functional limitation in HFpEF (6,24). However, our study design did not allow us to describe the mechanisms of peripheral oxygen use further.

When assessing which hemodynamic variables were *independently* associated with HFpEF, only 2 central factors were statistically significant: PCWP (61%), and SV (8%). This finding suggests that high left-sided heart filling pressure is a key contributor to exercise intolerance in HFpEF, in agreement with other studies (4,5,17). When baseline characteristics were added to the model, BMI was also a significant independent contributor. Thus just 3 variables

CENTRAL ILLUSTRATION Exercise-Related Variables Different Between Study Groups



Wolsk, E. et al. J Am Coll Cardiol HF. 2019;■(■):■–■.

Patients with heart failure with preserved ejection fraction exercising at their peak workload displayed significant higher left-sided heart filling pressures (pulmonary capillary wedge pressure) and body mass index and lower stroke volume compared with healthy control subjects exercising at matched workloads.

(PCWP, BMI, and SV) explained 90% of the variability between the HFpEF and control group designations (**Central Illustration**). In a sensitivity analysis limited to patients with BMI ≤30 kg/m^2 (where BMI was similar between groups), PCWP and SV remained the sole independent variables associated with the exercise limitation in HFpEF (Online Table 3).

Previous studies have shown hemodynamic impairments in HFpEF relative to control subjects at lower matched submaximal workloads (17,20,25), but this is the first study to show hemodynamic deficits in HFpEF at their individual peak workload when matched to the same workload as control subjects. This finding provides compelling evidence supporting the importance of abnormal hemodynamics, in particular left-sided heart filling pressures, in the pathophysiology of exercise intolerance in HFpEF.

Our finding of a strong association with BMI and reduced exercise capacity in HFpEF is in accord with other recent reports (26,27), including a recent study showing that BMI was strongly associated with New York Heart Association functional class in patients with HFpEF (28). Excess adipose tissue can contribute to HFpEF pathophysiology by a range of adverse effects, including systemic inflammation, capillary rarefaction in cardiac and skeletal muscle, and impaired skeletal muscle perfusion and mitochondrial function (26,29,30). The causal association between excess adipose tissue and exercise capacity in patients with HFpEF is further supported by data from Kitzman et al. (30), who demonstrated that caloric restriction in overweight patients with HFpEF significantly increased their exercise capacity (Vo_2 max) in proportion to reduced fat mass and increased percentage of lean mass. Importantly, in our study PCWP was associated with HFpEF independent of BMI. This finding is in agreement with recent data showing that ventilatory abnormalities and dyspnea in patients with HFpEF are related to PCWP even after accounting for the effects of BMI (5).

TABLE 6 Comparison of the Study Design and Findings in Selected Studies Investigating Exercise Limitation and HFpEF

	Wolsk et al. (Current Study)	Reddy et al. (4) (2018)	Obokata et al. (5) (2018)	Abudiab et al. (23) (2013)	Haykowsky et al. (21) (2011)	Borlaug et al. (14) (2006)
Year of inclusion	2013–2016	2000–2014	2011–2013	2002–2011	1998	2003–2005
Enrollment	Prospective	Retrospective	Retrospective	Retrospective	Retrospective	Prospective
HFpEF diagnosis established	Invasive	Invasive	Invasive	Clinical assessment	Clinical assessment	Invasive
HFpEF patients (n)	108	134	50	109	59	17
Healthy control subjects (n)	42	–	–	–	28	–
Exercise protocol (HFpEF vs. control subjects)	Peak vs. matched/peak vs. peak	Peak vs. peak	Peak vs. peak/submax. vs. submax.	Peak vs. peak	Peak vs. peak	Peak vs. peak/submax vs. submax.
Invasive measurements	Yes	Yes	Yes	65% of cases	No	No
Vo_2 max test performed	+	+	+	+	+	+
Primary novel findings	Differences in PCWP and SV explain majority of difference between HFpEF and healthy control subjects at same workload (peak vs. matched)	PCWP was independently correlated with exercise capacity within HFpEF patients	Dynamic changes in PCWP and pulmonary function were interrelated and associated with symptoms of dyspnea in HFpEF patients	Cardiac output relative to Vo_2 was lower in HFpEF patients compared with patient with non-cardiac dyspnea	Both cardiac output and arteriovenous oxygen content differences contribute to the exercise intolerance in HFpEF patients	HFpEF patients have reduced chronotropic, vasodilator, and cardiac output reserve during exercise compared with matched subjects

submax. = submaximal; other abbreviations as in Tables 1 and 2.

EXERCISE-LIMITING FACTORS IN HFpEF AT RELATIVE WORKLOADS. As expected, the healthy control group was able to work at considerably higher workloads compared with the patients with HFpEF. Because changes in hemodynamics are not necessarily proportional to the workload performed (9,17), this could potentially introduce a bias in the matched workload analyses given that the 2 groups had different relative workloads (maximal vs. submaximal workload). Hence, we performed a complementary analysis using changes relative to the workload performed at peak exercise for both groups.

Although all workload-corrected hemodynamic variables were individually associated with the HFpEF phenotype during exercise, the only independent variable was PCWP/workload ($r^2 = 0.87$). BMI was also significantly associated with the difference between patients with HFpEF and control subjects, thus increasing the r^2 modestly to 0.94. This analysis further supports that increased left-sided heart filling pressures comprise a major determinant of the exercise-associated limitation experienced by patients with HFpEF. Our study included a large number of well-characterized HFpEF patients and healthy control subjects enrolled across 3 continents, with comprehensive invasive hemodynamic measurements performed at rest and during exercise. We uniquely compared the hemodynamic response at peak exertion in patients with HFpEF with healthy control subjects at a similar workload, thereby elucidating the most significant differences between these groups. Furthermore, we prospectively included both patients with HFpEF and actively screened control subjects, thus ensuring healthy individuals (see Table 6 for a comparison with earlier studies).

STUDY LIMITATIONS. First, peak exercise was determined differently between patients and control subjects. However, this would not have affected the results of the matched workload analysis. Second, our healthy control subjects were selected to have a BMI between 20 and 30 kg/m^2, whereas no BMI limit was imposed on the patients with HFpEF because multiple population studies have shown patients with HFpEF in general tend to be overweight or obese (26). To account for this potential bias, we adjusted for BMI and performed a sensitivity analysis restricted to patients with BMI ≤30 kg/m^2, which confirmed the primary study findings. Third, some features of our study design may have minimized the potential contribution of heart rate to reduced exercise capacity. Because heart rate is linearly and tightly related to workload, matching workloads tend to minimize heart rate differences. However, our relative workload analysis likely decreased this potential bias. Fourth, activities of daily living during which patients experience their exertional symptoms are usually performed in the upright position, but we performed

exercise testing in the supine position because it facilitated use of invasive measurements, which was critical to assess the role of hemodynamic measures. Nevertheless, because patients and control subjects performed protocols in a similar position, this should not have substantial effects on intergroup differences. Fifth, as in other studies, our conclusions are based on group averages. However, as shown recently by Houstis et al. (22), mechanisms of exercise intolerance in HFpEF are likely multifactorial and may vary significantly among patients.

Finally, our HFpEF inclusion criteria were based on invasive measurements, not least PCWP. These criteria differ from HF guidelines, which use surrogate markers for increased left-sided heart filling pressure (e.g., increased left atrium, elevated natriuretic peptides), and hence our cohort studied may differ from study groups with HFpEF diagnosed using current guidelines. This issue may also have confounded the findings toward hemodynamic measures.

CONCLUSIONS

In this large group of patients and healthy control subjects who underwent invasive exercise testing, we identified 3 key variables (PCWP, BMI, and SV) that independently contributed to the reduced exercise capacity in patients with HFpEF compared with healthy control subjects during supine exercise at matched workloads. Together, these variables explained 90% of the difference between patients with HFpEF and control subjects, and among these, PCWP was the strongest contributor. These findings suggest the potential for interventions that alleviate high left-sided heart filling pressure during exercise to improve the key outcome of exercise intolerance in patients with HFpEF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with HFpEF have limited functional capacity, high left-sided heart filling pressures, and generally many comorbid conditions. The most significant differences between patients with HFpEF and healthy control subjects performing the same workload are increased PCWP, lower SV, and higher BMI.

TRANSLATIONAL OUTLOOK: Increased left-sided heart filling pressures are especially associated with differences between patients with HFpEF and healthy persons, a finding indicating that therapies aimed at reducing PCWP could result in improved exercise capacity for patients with HFpEF.

REFERENCES

1. Hegde SM, Claggett B, Shah AM, et al. Physical activity and prognosis in the TOPCAT trial (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist). Circulation 2017;136:982–92.

2. Nadruz W, West E, Sengeløv M, et al. Prognostic value of cardiopulmonary exercise testing in heart failure with reduced, midrange, and preserved ejection fraction. J Am Heart Assoc 2017;6:e006000.

3. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129–200.

4. Reddy YNV, Olson TP, Obokata M, Melenovsky V, Borlaug BA. Hemodynamic correlates and diagnostic role of cardiopulmonary exercise testing in heart failure with preserved ejection fraction. J Am Coll Cardiol HF 2018.

5. Obokata M, Olson TP, Reddy YNV, Melenovsky V, Kane GC, Borlaug BA. Haemodynamics, dyspnoea, and pulmonary reserve in heart failure with preserved ejection fraction. Eur Heart J 2018;39:2810–21.

6. Dhakal BP, Malhotra R, Murphy RM, et al. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction: the role of abnormal peripheral oxygen extraction. Circ Heart Fail 2015;8:286–94.

7. Hasenfuß G, Hayward C, Burkhoff D, et al. A transcatheter intracardiac shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF): a multicentre, open-label, single-arm, phase 1 trial. Lancet 2016;387:1298–304.

8. Feldman T, Mauri L, Kahwash R, et al. A transcatheter interatrial shunt device for the treatment of heart failure with preserved ejection fraction (REDUCE LAP-HF I): a phase 2, randomized, sham-controlled trial. Circulation 2018;137:364–75.

9. Wolsk E, Bakkestrøm R, Thomsen JH, et al. The influence of age on hemodynamic parameters during rest and exercise in healthy individuals. J Am Coll Cardiol HF 2017;5:337–46.

10. Hasenfuss G, Gustafsson F, Kaye D, et al. Rationale and design of the Reduce Elevated Left Atrial Pressure in Patients With Heart Failure (Reduce LAP-HF) Trial. J Card Fail 2015;21:594–600.

11. Feldman T, Komtebedde J, Burkhoff D, et al. Transcatheter interatrial shunt device for the treatment of heart failure: rationale and design of the randomized trial to REDUCE Elevated Left Atrial Pressure in Heart Failure (REDUCE LAP-HF I). Circ Heart Fail 2016;9:e003025.

12. Azen R, Budescu DV. The dominance analysis approach for comparing predictors in multiple regression. Psychol Methods 2003;8:129–48.

13. Phan TT, Shivu GN, Abozguia K, et al. Impaired heart rate recovery and chronotropic incompetence in patients with heart failure with preserved ejection fraction. Circ Heart Fail 2010;3:29–34.

14. Borlaug BA, Melenovsky V, Russell SD, et al. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. Circulation 2006;114:2138–47.

15. Maeder MT, Thompson BR, Brunner-La Rocca H-P, Kaye DM. Hemodynamic basis of exercise limitation in patients with heart failure and

normal ejection fraction. J Am Coll Cardiol 2010; 56:855–63.

16. Kitzman DW, Higginbotham MB, Cobb FR, Sheikh KH, Sullivan MJ. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. J Am Coll Cardiol 1991;17: 1065–72.

17. Borlaug BA, Kane GC, Melenovsky V, Olson TP. Abnormal right ventricular-pulmonary artery coupling with exercise in heart failure with preserved ejection fraction. Eur Heart J 2016;37: 3293–302.

18. Brubaker PH, Kitzman DW. Chronotropy: the Cinderella of heart failure pathophysiology and management. J Am Coll Cardiol HF 2013;1:267–9.

19. Kass DA, Kitzman DW, Alvarez GE. The restoration of chronotropic competence in heart failure patients with normal ejection fraction (RESET) study: rationale and design. J Card Fail 2010;16: 17–24.

20. Reddy YNV, Andersen MJ, Obokata M, et al. Arterial stiffening with exercise in patients with heart failure and preserved ejection fraction. J Am Coll Cardiol 2017;70:136–48.

21. Haykowsky MJ, Brubaker PH, John JM, Stewart KP, Morgan TM, Kitzman DW. Determinants of exercise intolerance in elderly heart failure patients with preserved ejection fraction. J Am Coll Cardiol 2011;58:265–74.

22. Houstis NE, Eisman AS, Pappagianopoulos PP, et al. Exercise intolerance in heart failure with preserved ejection fraction: diagnosing and ranking its causes using personalized O2 pathway analysis. Circulation 2018;137:148–61.

23. Abudiab MM, Redfield MM, Melenovsky V, et al. Cardiac output response to exercise in relation to metabolic demand in heart failure with preserved ejection fraction. Eur J Heart Fail 2013; 15:776–85.

24. Pandey A, Khera R, Park B, et al. Relative impairments in hemodynamic exercise reserve parameters in heart failure with preserved ejection fraction: a study-level pooled analysis. J Am Coll Cardiol HF 2018;6:117–26.

25. Borlaug BA, Olson TP, Lam CSP, et al. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. J Am Coll Cardiol 2010;56:845–54.

26. Kitzman DW, Shah SJ. The HFpEF obesity phenotype: the elephant in the room. J Am Coll Cardiol 2016;68:200–3.

27. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. Circulation 2017;136:6–19.

28. Dalos D, Mascherbauer J, Zotter-Tufaro C, et al. Functional status, pulmonary artery pressure, and clinical outcomes in heart failure with preserved ejection fraction. J Am Coll Cardiol 2016;68:189–99.

29. Haykowsky MJ, Kouba EJ, Brubaker PH, Nicklas BJ, Eggebeen J, Kitzman DW. Skeletal muscle composition and its relation to exercise intolerance in older patients with heart failure and preserved ejection fraction. Am J Cardiol 2014;113: 1211–6.

30. Kitzman DW, Brubaker P, Morgan T, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. JAMA 2016;315:36–46.

KEY WORDS body mass index, healthy, invasive exercise testing, heart failure with preserved ejection fraction, pulmonary capillary wedge pressure

APPENDIX For supplemental tables, please see the online version of this paper.