Central and peripheral determinants of exercise capacity in heart failure patients with preserved ejection fraction

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Abstract

Background

The underlying mechanisms limiting exercise capacity in patients with heart failure and preserved ejection fraction (HFpEF) are not fully understood.

Objectives

We sought to discern which *central* (e.g. heart rate, stroke volume, filling pressure) and *peripheral* factors (e.g. O_2 utilization by skeletal muscle, BMI) during exercise were most strongly associated with the presence of HFpEF as compared to healthy controls exercising at the same workload.

Methods

In HFpEF (n=108) patients, we measured the hemodynamic response at peak exercise using right heart catheterization, and compared it with healthy controls (n=42) at matched workloads, to reveal hemodynamic differences that were not attributable to the workload performed. The populations studied were prospectively included in REDUCE-LAP HF trials and HemReX study. Univariable and multivariable logistic regression models were used to analyze variables associated with HFpEF vs. controls.

Results

Compared with healthy controls, pulmonary capillary wedge pressure (PCWP) and stroke volume (SV), were the only independent hemodynamic variables that were associated with HFpEF, explaining 66% ($p<0.0001$) of the difference between 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%), SV (12%).

Conclusion

We identified 3 key variables (PCWP, BMI, and SV, respectively) that independently correlate with the presence of HFpEF patients compared to healthy controls exercising at the same workload. Therapies that decrease left heart filling pressures could improve exercise capacity, and possibly prognosis.

Condensed abstract

Background and objectives

We sought to discern which factors during exercise that were associated with the presence of HFpEF as compared to healthy controls.

Methods

In HFpEF (n=108) patients, we measured the hemodynamic response at peak exercise and compared it with healthy controls (n=42) at matched workloads.

Results

Pulmonary capillary wedge pressure (PCWP), BMI, and stroke volume (SV), were the only independent hemodynamic variables that were associated with HFpEF, explaining 90% ($p<0.0001$) of the difference between groups.

Conclusion

Therapies that decrease left heart filling pressures could improve exercise capacity, and possibly prognosis.

Key words: HFpEF, invasive exercise testing, PCWP, BMI, healthy

Abreviations list
BMI – body mass index
Ca-vO_2 – arterio-venous oxygen difference
CVP – central venous pressure
CI – cardiac index
CO – cardiac output
HFpEF – heart failure with preserved ejection fraction
mPAP – mean pulmonary pressure
PCWP – pulmonary capillary wedge pressure
PVR – pulmonary vascular resistance
SVR – systemic vascular resistance
VO_2-max – maximal oxygen consumption

Introduction

A hallmark of heart failure 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 HFpEF patients 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, filling pressures) and *peripheral* factors (e.g. O_2 utilization by skeletal muscle, BMI, renal function), but only a few have directly analyzed the relationships between symptoms and aerobic capacity using gold-standard invasive measures(4–6). Importantly, no study to date has included a control population exercising at the matched workload to the peak level of HFpEF.

In order to fill this critical knowledge gap, we performed a study with invasive exercise tests, using data from 3 of the largest prospective trials of HFpEF patients and healthy participants (n=150)(7–9). Importantly, the healthy controls were prospectively enrolled and rigorously screened to verify

the absence of cardiac disease. To discern which central and peripheral factors that were independently associated with HFpEF patients compared to healthy controls, we performed two complementary analyses: we compared the hemodynamic response of HFpEF patients at their peak exercise workload capacity to that of controls exercising at the same workload to reveal hemodynamic differences, not attributable to the workload performed. In a supplemental analysis the hemodynamic response during peak exercise in both HFpEF patients and controls were compared relative to the individual workloads achieved.

Methods

This study used baseline data from 2 trials and one population study; Reduce Elevated Left Atrial Pressure in Patients With Heart Failure (REDUCE LAP-HF) trial, REDUCE LAP-HF I trial, and The Effect of Age on the Hemodynamic Response During Rest and Exercise in Healthy Humans (HemReX) study. Patients and healthy participants were recruited 2013-2016. All participants provided oral and written informed consent prior to 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 HFpEF patients were obtained prior to InterAtrial Shunt Device (IASD) implantation.

HFpEF population

In summary, patients with elevated pulmonary capillary wedge pressure (PCWP) either at rest or during exercise, and signs and symptoms of HF were included in two studies evaluating an IASD (IASD system II, Corvia Medical, Inc. [Tewksbury, MA, USA]) (REDUCE LAP-HF: nonrandomized, open-label design. REDUCE LAP-HF I: randomized, double-blinded design). The primary objective of the trials was to assess the safety and efficacy of IASD implantation. Key

inclusion criteria were: informed consent, NYHA class II-IV, LVEF≥40% determined by echocardiography, ≥ 1 HF hospitalization within last 12 months prior to screening and/or elevated natriuretic peptides, age ≥ 40 years, elevated left ventricular filling pressures with a gradient compared to central venous pressure (CVP) documented by ≥1 of the following [end-expiratory PCWP or LVEDP at rest ≥15 mmHg and greater than CVP] and/or PCWP during supine bike exercise ≥25 mmHg. Key exclusion criteria were: cardiac index ≤2.0 l/min/m^2, obstructive or restrictive cardiomyopathy, moderate-severe heart valve disease, atrial fibrillation with resting heart rate >100 beats/min and dialysis or eGFR <25 ml/min/1.73m^2. As the inclusion criteria and the invasive protocol were similar, data was pooled from the two studies. Additional details on the trial designs have been published(10, 11).

Healthy population

Sixty-two healthy subjects aged 20-80 were enrolled in the primary prospective study, however only patients aged ≥40 years were included in the present study (n=42), as this cutoff corresponded to the age inclusion criteria for the HFpEF studies. Healthy subjects were deemed eligible if they fulfilled inclusion criteria; free from history of any acute or chronic cardiac or pulmonary disease; echocardiography without signs of chamber hypertrophy, reduced left ventricular (LV) ejection fraction or significant valvular disease; normal spirometry for their age; routine blood chemistry test with normal values (including NT-proBNP); BMI 20-30 kg/m^2; and an exercise test with ECG without any pathological findings. Additional details on 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 (TTE) 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 in the supine position in both HFpEF patients and healthy participants. Ergometer resistance was increased every 3-4 minutes with increments of either 20 watt (HFpEF) or 25 watt (controls) until maximal effort was achieved. In HFpEF patients, maximal effort/peak exercise was judged by patients and physicians, when patients were not able to maintain 60 revolutions per minute on the ergometer at a given workload. In healthy participants, maximal effort was defined as 4 minutes of exercise in a supine ergometer with lactate buildup and objective signs of severe exertion at a workload corresponding to 75% of 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 to an upright position(4). A Swan-Ganz catheter was positioned in the pulmonary artery via the internal jugular or brachial vein. For all signals, 10 second 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), non-invasive systolic blood pressure (SBP), non-invasive diastolic blood pressure (DBP), non-invasive peripheral oxygen saturation (SaO_2), and heart rate (HR). In addition, mixed venous oxygen (SvO_2) was sampled from the pulmonary artery.

Derived variables

Systemic vascular resistance (SVR) was calculated as 80 x (MAP – CVP)/CO. Pulmonary vascular resistance (PVR) in Wood units was calculated as (mPAP - PCWP)/CO. Transmural pressure (TMP) was calculated as PCWP – RAP. Transpulmonary gradient (TPG) was calculated as mPAP-PCWP. Cardiac index (CI) was calculated as CO/body surface area (BSA). Stroke volume, indexed was calculated as CI/heart rate (HR). The venous blood oxygen content (CvO_2) was calculated using the formula(6): $CvO2 = hemoglobin\ \left(\frac{g}{dL}\right) \times 1.39 \times SvO2$. Arterial oxygen content was calculated likewise using either non-invasively measured arterial saturation or imputed based on the median value if missing (46%). We did not account for plasma-bound oxygen, as we did not have data on partial pressures. However, this component contributes very little to oxygen content given that measurements are made close to sea level, and that patients do not suffer from grave anemia. Peripheral arterio-venous difference was calculated as the difference in blood oxygen content; $Ca\text{-}vO_2 = CaO_2\text{-}CvO_2$.

Statistics

Data was summarized using mean±SD, except NT-proBNP which was summarized as median [IQR]. 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, as this was a pre-defined exclusion criterion for the control group. As hemodynamic measurements were obtained at several sub-maximal exercise workloads in healthy controls compared to peak exercise only in 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 HFpEF patients was 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 vs. controls, ie. the dichotomous dependent variable was the HFpEF. As individual patients could contribute with data from more than one workload, standard errors 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. Mean pulmonary pressure 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 due to collinearity and missing data, respectively. Furthermore, NYHA class, echocardiographic abnormalities, and medications were omitted, as these measures were not present in the healthy controls by definition.

Dominance analysis was used to obtain the proportion of fit metric which was attributable to each independent variable as described by Azen et al.(12) (STATA package *domin*). 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 (College Station, TX).

Results

Patients with HFpEF from the REDUCE-LAP HF(7) (n=64) and REDUCE-LAP HF I(8) (n=44) trials were included and compared with healthy controls from the HemReX study(9) (n=42).. Baseline characteristics and hemodynamic variables at rest are summarized in Tables 1 & 2. All variables were significantly different between controls and HFpEF at rest except; gender, SBP, left ventricular end-diastolic volume (LVEDVi), EA ratio, MAP, SV, SVi, CO, CI, SVR, PVR, and Ca-

vO_2. Limiting comparisons to patients (n=33) and controls (n=42) with BMI ≤ 30 kg/m^2, the same differences between groups were noted, except for BMI, BSA, SV, SVI, and HR which were statistically similar between groups, while EA ratio and PVR were higher and CO was lower in HFpEF compared to controls (see tables S1-2, Supplemental material). Patients grouped according to LVEF above or below 50%, had comparable baseline characteristics (see table S3).

Central and peripheral exercise factors at matched workloads

The maximal workload achieved by HFpEF patients 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. controls [n=72]). See Table 2 for hemodynamic data at matched workloads. The following changes from baseline to matched workload in HFpEF vs controls were observed; *Heart rate* (+29±19 vs. +29±16 bpm, p=0.94), *Cardiac output* (+3.1±1.9 vs. +5.4±2.0 l/min, p<0.0001), *Cardiac index* (+1.5±0.9 vs. +2.9±1.1 l/min/m^2, p<0.0001), *stroke volume* (+8±21 vs. +35±20 ml, p<0.0001), *stroke volume* [indexed] (+4±10 vs. +19±10 ml/m^2, p<0.0001), *arterio-venous oxygen difference* [Ca-vO_2] (+3.7±2.5 vs. +4.9±1.5 ml/dl, p=0.0004), and *systemic vascular resistance* (-367±365 vs. -716±234 dyne x 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 controls and patients with BMI ≤30 kg/m^2, the results were similar with regard to both the independent hemodynamic variables identified (PCWP and SV), as well as the coefficients (table S4, Supplemental material).

Central and peripheral exercise factors at peak exercise

The mean peak workload achieved was 45±13 vs. 137±35 W, p<0.0001 for HFpEF vs. controls.

Heart rate increased from baseline to peak exercise +29±19 vs. +64±19 bpm, p<0.0001 for HFpEF vs. controls. 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).

Cardiac index increased +1.5±0.9 vs. +5.8±1.4 l/min/m^2, p<0.0001, and *stroke volume* (indexed) increased +4±10 vs. +26±16 ml/m^2, p<0.0001 for HFpEF vs. controls.

At peak exercise, *arterio-venous oxygen difference* (Ca-vO_2) was significantly lower in HFpEF patients 9.1±2.9 vs. controls 12.8±1.3 ml/dl, p<0.0001. *Systemic vascular resistance* decreased -359±371 vs. -904±280 dyne x s/cm^5, p<0.0001 for HFpEF vs controls.

Comparison of central and peripheral exercise factors relative to workload

All hemodynamic variables examined differed significantly between controls and HFpEF patients 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, 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 biggest 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 for whom exercise capacity is profoundly impaired. Our study is the first to compare hemodynamic responses in HFpEF patients during their peak levels of exercise to those of healthy controls 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 hemodynamics 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 HFpEF and controls. These findings were supported by analysis of hemodynamic changes relative to workload during peak exercise.

Exercise-limiting factors in HFpEF at matched workloads

The HFpEF patients had a similar absolute increase in heart rate compared to controls, 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 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 HFpEF compared to healthy, which is a consistent finding in other HFpEF studies(18), and has led to studies investigating whether atrial pacing improves exercise capacity in this cohort [NCT02145351](19). At matched workloads, cardiac index was lower in HFpEF compared to controls, which was due to an inability to increase stroke volume during exercise, despite both groups having comparable stroke volumes at rest. This observation is similar to findings at matched lower-level workload (20W) observed in prior studies(17, 20). Importantly, whereas the limitation in exercise capacity in healthy persons is primarily governed by highest cardiac output achievable(9), the limiting factor(s) in HFpEF patients may be multifactorial, and not necessarily limited by cardiac output. Hence, in these patients, maximal exertion may be reached before their maximal uptake in oxygen.

PCWP showed dramatic increases during exercise leading to a high PCWP:CO ratio in HFpEF patients. The current data confirms and extends upon 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 arterio-venous oxygen difference ($Ca\text{-}vO_2$) was significantly reduced in HFpEF patients compared to controls, as previously reported by some groups(6, 21, 22). The current data are unique in that $Ca\text{-}vO_2$ was impaired in HFpEF compared to controls even at submaximal workload, which differs from 2 other studies that showed higher $Ca\text{-}vO_2$ during lower workloads in HFpEF(17, 23). These data provide further support for the hypothesis that reduced oxygen extraction and utilization in skeletal muscle may be an important determinant of functional limitation in HFpEF(6, 24), however our study design did not allow us to further describe the mechanisms of peripheral oxygen utilization

When assessing which hemodynamic variables were *independently* associated with HFpEF, only 2 central factors were statistically significant: PCWP (61%), and SV (8%). This suggests that high left 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 (PCWP, BMI, and SV) explained 90% of the variability between HFpEF and control group designation. In a sensitivity analyses limited to patients with BMI $\leq$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 (Table S3, Supplemental material).

Previous studies have shown hemodynamic impairments in HFpEF relative to controls 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 controls. This provides compelling evidence supporting the importance of abnormal hemodynamics, in particular left 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 to NYHA class in HFpEF patients(28). Excess adipose tissue can contribute to HFpEF pathophysiology via 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 HFpEF patients is further supported by data from Kitzman et al. who demonstrated that caloric restriction in overweight HFpEF patients significantly increased their exercise capacity (VO_2-max) in proportion to reduced fat mass and increased percent lean mass(30).

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 HFpEF patients are related to PCWP even after accounting for the effects of BMI(5).

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 HFpEF patients. As changes in hemodynamics are not necessarily proportional to the workload performed(9, 17), this could potentially introduce a bias in the matched workload analyses as the two groups performed different relative workloads (max vs. sub-max 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 HFpEF and controls, increasing the r^2 modestly to 0.94. This analysis further supports that increased left heart filling pressures is a major determinant of the exercise associated limitation experienced by HFpEF patients.

Strengths and Limitations

Our study included a large number of well-characterized HFpEF patients and healthy controls 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 HFpEF patients with healthy controls at a similar workload, thereby elucidating the most significant differences between these groups. Furthermore, we prospectively included both HFpEF patients and actively screened controls ensuring healthy individuals (see table 6 for a comparison with earlier

studies). However, there are limitations: 1) Peak exercise was determined differently between patients and controls. However, this would not have affected the results of the matched workload analysis. 2) Our healthy controls were selected to have a BMI between 20-30 kg/m^2, whereas no BMI limit was imposed on the HFpEF patients as multiple population studies have shown HFpEF patients in general tend to be overweight/obese(26). To account for this potential bias, we adjusted for BMI, and performed sensitivity analysis restricted to patients with BMI $\leq$30 kg/m^2, which confirmed the primary study findings 3) Some features of our study design may have minimized the potential contribution of heart rate to reduced exercise capacity. Since 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. 4) 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, since patients and controls performed protocols in similar position, this should not have substantial effects on intergroup differences. 5) As in other studies, our conclusions are based on group averages. However, as shown recently by Houstis et al., mechanisms of exercise intolerance in HFpEF are likely multi-factorial, and may vary significantly between patients(22). 6) Our HFpEF inclusion criteria were based on invasive measurements, not least PCWP. These criteria differ from HF guidelines, that use surrogate markers for increased left heart filling pressure (e.g. increased left atrium, elevated natriuretic peptides), and hence our cohort studied may differ from HFpEF populations diagnosed using current guidelines. This may also have confounded the findings towards hemodynamic measures.

Conclusion

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

Competency in Medical Knowledge

Patients with HFpEF experience limited functional capacity, high left heart filling pressures, and generally many comorbid conditions. The most significant differences between HFpEF patients and healthy controls performing the same workload are increased PCWP, lower SV, and a higher BMI.

Translational Outlook

Especially increased left heart filling pressures are associated with differences between HFpEF patients and healthy, indicating that therapies aimed at reducing PCWP could result in improved exercise capacity for HFpEF patients.

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Table 1. Patient characteristics.

	Controls (n=42)	HFpEF (n=108)	p-value
Age	59±11	70±8	<0.0001
Sex (females)	22/20 (52% females)	64/44 (59% females)	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 class			<0.0001
2	N/A	18 (17%)	
3	N/A	89 (82%)	
4	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)	2436±661	1381±509	<0.0001
VO_2-max (ml/kg/min)	32±7	16±4	<0.0001
RER (VO2:VCO2)	1.10±0.06	1.04±0.09	0.01
eGFR (ml/min/1.73m^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			
Betablocker use	0	81 (84%)	<0.0001
ACE/A2RA	0	68 (76%)	<0.0001

Table 2. Hemodynamic variables at rest and during exercise at matched workloads.

	Baseline (rest)			Exercise (matched workloads)			
	Controls (n=42)	HFpEF (n=108)	p-value	Controls (n=72)	HFpEF (n=107)	p-value	Adjusted p-value*
Workload (watt)	0	0	-	45±22	43±18	0.41	0.57
Heart rate (bpm)	63±9	70±14	0.005	93±18	99±20	0.04	0.03
MAP (mmHg)	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/m2)	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
CI (l/min/m2)	2.7±0.4	2.8±0.8	0.48	5.6±1.1	4.3±1.2	<0.0001	N/A
RAP (mmHg)	5±2	9±3	<0.0001	10±4	19±6	<0.0001	<0.0001
mPAP (mmHg)	15±3	26±8	<0.0001	30±8	46±11	<0.0001	<0.0001
PCWP (mmHg)	9±3	19±6	<0.0001	19±7	35±7	<0.0001	<0.0001
SVR (dyne x s/cm5)	1437±281	1329±415	0.13	712±182	941±355	<0.0001	<0.0001
PVR (Wood)	1.2±0.5	1.5±0.9	0.08	1.12±0.50	1.44±1.23	0.05	0.77
TPG (mmHg)	6±2	8±4	0.02	11±4	11±8	0.52	0.005
TMG (mmHg)	3±2	9±5	<0.0001	9±4	16±7	<0.0001	<0.0001
CaO2 (ml/dl)	19.6±1.7	17.1±2.6	<0.0001	19.2±1.5	16.7±2.7	<0.0001	0.56
CvO2 (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-vO2 (ml/dl)	4.8±0.8	5.1±1.3	0.19	9.6±1.6	8.6±2.8	0.01	0.02

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=43 vs. 72). One HFpEF patient did not manage to perform exercise, accounting for the difference in (n=108 vs. 107). *Adjusted for age and BMI (except indexed variables).

Table 3. Hemodynamic variables associated with HFpEF at matched workloads.

	Univariable		Multivariable Model 1 (R^2:0.66, p<0.001)		Multivariable Model 1 (R^2:0.92, p=0.15)	
	Coefficient	**p-value**	**Coefficient**	**p-value**	**Coefficient**	**p-value**
Age (Y)	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 (bpm)	0.02 (0.00, 0.03)	0.04				
MAP (mmHg)	0.03 (0.01, 0.05)	0.001				
SV (ml/m^2)	-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 (mmHg)	0.4 (0.3, 0.5)	<0.0001				
PCWP (mmHg)	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				
CI (l/min/m^2)	-0.90 (-1.19, -0.62)	<0.0001				
mPAP (mmHg)	0.2 (0.1, 0.3)	<0.0001				
SVR (dyne x s/cm^5)	0.003 (0.001, 0.004)	<0.0001				
PVR (Wood)	0.4 (-0.0, 0.7)	0.06				

Model 1: HR, MAP, SV, RAP, PCWP, and Ca-v02 were included in the model.

Model 2: HR, MAP, SV, RAP, PCWP, and Ca-v02 (Model 1), adjusted for BMI and age.

Table 4. Hemodynamic variables at peak exercise.

	Controls (n=42)	HFpEF (n=107)	p-value
Workload (watt)	137 ± 35	43 ± 18	<0.001
Heart rate (bpm)	127 ± 18	99 ± 20	<0.001
MAP (mmHg)	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
CI (l/min/m^2)	8.4 ± 1.3	4.3 ± 1.2	<0.001
RAP (mmHg)	10 ± 5	19 ± 5.5	<0.001
mPAP (mmHg)	36 ± 10	46 ± 11	<0.001
PCWP (mmHg)	21 ± 8	35 ± 7	<0.001
TMP (mmHg)	11 ± 5	16 ± 7	<0.001
TPG (mmHg)	15 ± 5	11 ± 8	0.001
SVR (dyne x s/cm^5)	12 ± 7	91 ± 51	<0.001
PVR (Wood)	535 ± 142	941 ± 355	<0.001
CaO_2 (ml/dl)	0.96 ± 0.44	1.44 ± 1.23	0.022
CvO_2 (ml/dl)	19.48 ± 1.68	16.74 ± 2.72	<0.001
Ca-vO_2 (ml/dl)	6.61 ± 1.46	8.06 ± 2.81	0.002

Table 5. Workload (wl) corrected hemodynamic variables associated with HFpEF during peak exercise.

	Univariable		Multivariable Model 1 (R^2:0.87, p<0.0001)		Multivariable Model 1 (R^2:0.94, p<0.0001)	
	Coefficient	**p-value**	**Coefficient**	**p-value**	**Coefficient**	**p-value**
Age (Y)	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 (bpm/watt)	6.7 (3.9, 9.5)	<0.0001				
MAP/wl (mmHg/watt)	5.6 (3.3, 7.8)	<0.0001				
SV/wl (ml/m^2/watt)	4.8 (2.9, 6.8)	<0.0001				
RAP/wl (mmHg/watt)	35.2 (20.2, 50.3)	<0.0001				
PCWP/wl (mmHg/watt)	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/watt)	36.9 (22.9, 50.9)	<0.0001				
SVi/wl (ml/m^2/watt)	9.0 (5.5, 12.5)	<0.0001				
CO/wl (l/min/watt)	33.5 (19.3, 47.8)	<0.0001				
CI/wl (l/min/m^2/watt)	52.0 (29.5, 74.4)	<0.0001				
mPAP/wl (mmHg/watt)	15.6 (8.5, 22.7)	<0.0001				
TMP/wl (mmHg/watt)	28.6 (17.4, 39.8)	<0.0001				
TPG/wl (mmHg/watt)	7.5 (3.6, 11.4)	<0.0001				
SVR/wl (dyne x s/cm^5/watt)	0.60 (0.36, 0.83)	<0.0001				
PVR/wl (Wood/watt)	110.4 (58.3, 162.4)	<0.0001				

Model 1: HR, MAP, SV, RAP, PCWP, and Ca-v02 were included in the model (all corrected for workload).

Model 2: HR, MAP, SV, RAP, PCWP, and Ca-v02 (Model 1), adjusted for BMI and age.

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) (JACC HF 2018)	Obokata et al.(5) (EHJ 2018)	Abudiab et al.(EJHF 2013)	Haykowsky et al. (JACC 2011)	Borlaug et al. (Circ 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 controls (n)	42	-	-	-	28	-
Exercise protocol (HFpEF vs. controls)	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
VO2 max test performed	+	+	+	+	+	+
Primary novel findings	Differences in PCWP and SV explain majority of difference between HFpEF and healthy controls 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 VO2 was lower in HFpEF patients compared to patient with non-cardiac dyspnea	Both cardiac output and arterial-venous 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

Figure 1. Changes in hemodynamic variables from baseline to peak exercise in HFpEF compared to controls at matched workloads.

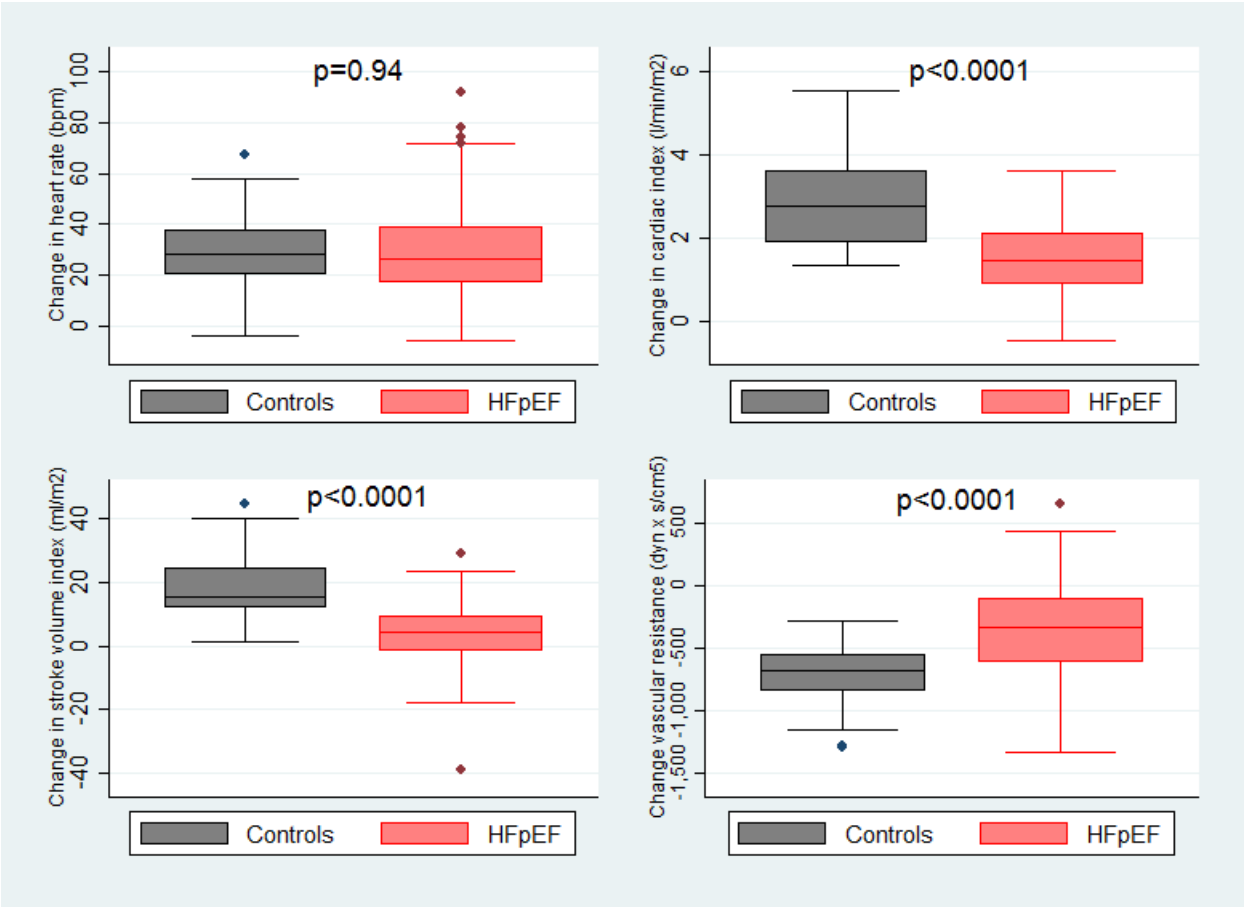
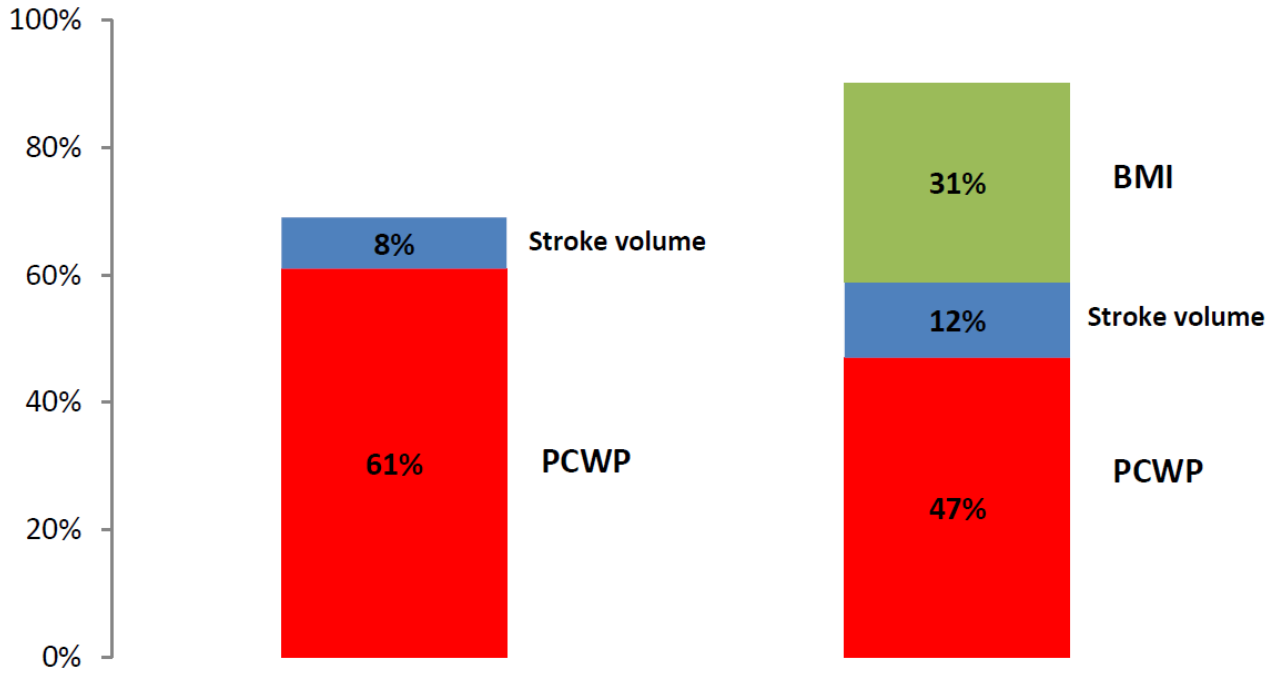


Figure 2. The contribution of independent variables associated with HFpEF during exercise at matched workloads



The contribution of each independent variable to the difference between HFpEF and controls at matched exercise is shown. The first column depicts the contribution of hemodynamic variables only. The second column depicts the contribution of hemodynamic + other independent variables identified.