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Determinants of Exercise Intolerance in Elderly Heart Failure Patients with Preserved Ejection Fraction

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Abstract

Objectives—To determine the mechanisms responsible for reduced aerobic capacity (peak VO_2) in heart failure patients with preserved ejection fraction (HFPEF).

Background—HFPEF is the predominant form of HF in older persons. Exercise intolerance is the primary symptom among patients with HFPEF and a major determinant of reduced quality of life. In contrast to patients with HF and reduced EF, the mechanism of exercise intolerance in HFPEF is less well understood.

Methods—Left ventricular volumes (2D echocardiography), cardiac output (CO), VO_2 and calculated arterial-venous oxygen content difference (A-VO_2 Diff) were measured at rest and during incremental, exhaustive upright cycle exercise in 48 HFPEF patients (age 69±6 years) and 25 healthy age-matched controls (HC).

Results—In HFPEF compared to HC, VO_2 was reduced at peak exercise (mean±SE: 14.3±0.5 vs. 20.4±0.6 mL·kg min^{-1}; p<0.0001) and was associated with a reduced peak CO (6.3±0.2 vs. 7.6±0.2 L·min^{-1}, p<0.0001) and A-VO_2 Diff (17±0.4 vs. 19±0.4 ml·dl^{-1}, p<0.0007). The strongest independent predictor of peak VO_2 was the change in A-VO_2 Diff from rest to peak exercise (A-VO_2 Diff reserve) for both HFPEF (partial correlant 0.58, standardized β coefficient 0.66; p=0.0002) and HC (partial correlant 0.61, standardized β coefficient 0.41; p=0.005)

Conclusions—Both reduced CO and A-VO_2 Diff contribute significantly to the severe exercise intolerance in elderly HFPEF patients. The finding that A-VO_2 Diff reserve is an independent

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predictor of peak exercise VO_2 suggests that peripheral, 'non-cardiac' factors are important contributors to exercise intolerance in these patients.

Keywords

Exercise; Heart Failure; Aging

Introduction

Heart failure with preserved ejection fraction (HFPEF) constitutes 50% or more of elderly patients presenting with heart failure.(1–3) A cardinal feature of HFPEF is reduced exercise tolerance which correlates with symptoms as well as reduced quality of life (4). Although numerous studies have investigated the physiological mechanisms for reduced aerobic capacity (peak VO_2) in HF patients with reduced EF (5–7), much less is known regarding its mechanisms in patients with HFPEF.

Kitzman et al.(8) suggested that the reduced peak VO_2 in HFPEF patients was primarily due to reduced cardiac output (CO) secondary to an inability to increase end-diastolic (EDV) and stroke volume (SV) via the Frank-Starling mechanism. In contrast, other investigators found that the blunted CO was secondary to impaired heart rate (HR)(9–10), contractile (9–11), and vasodilator reserve (9–11) as EDV reserve was preserved.

Several investigators have shown that peripheral factors, including impaired vascular reserve (10), abnormal blood flow distribution (7) and skeletal muscle dysfunction (5), are important contributors to exercise intolerance in patients with HF and reduced EF. However, no study has focused on the potentially important role that peripheral 'non-cardiac' factors may play in limiting exercise performance in HFPEF. Thus, uncertainty remains regarding the mechanisms of the key symptom of chronic HFPEF, exercise intolerance, including the relative roles of reduced CO, and its key components, and arterial-venous oxygen content difference (A-VO_2 Diff). Therefore, the purpose of the present study was to measure VO_2, left ventricular (LV) volumes, CO, and calculated A-VO_2 Diff during cycle exercise in elderly patients with HFPEF and healthy age-matched controls (HC). We tested the hypothesis, based on our prior observation in a small number of patients (8), that the reduced peak VO_2 in patients with HFPEF is due primarily to a blunted EDV response which limits exercise SV and CO.

Methods

Subjects

As previously described (4,12–14), HFPEF patients had clinical signs and symptoms of HF as defined by an NHANES HF clinical score ≥3 and the criteria of Rich et al.(15–16) with normal resting systolic function (LVEF ≥50%, and no segmental wall motion abnormalities at rest or during exercise) and no evidence of significant anemia; coronary artery, valvular, infiltrative, pericardial, pulmonary, or renal disease. Patients were recruited by retrospective review of clinic visits and hospital discharge records at the Wake Forest University Medical Center, Winston-Salem, NC. Cases of HF were ascertained by retrospective review of clinic visits and hospital discharge records from the Wake Forest University Medical Center, Winston-Salem, NC, that appeared to potentially fulfill inclusion/exclusion criteria. Of the resultant 573 participants who were then contacted for a screening visit, 59 met criteria for HPEF and were enrolled into the study. The subjects in this report are a subset of those from a previous study from our laboratory who had adequate echo images during exercise.(4) They did not differ significantly from the overall group in age, gender, body size, NYHA class, or peak VO_2.

Healthy controls (n=28) were recruited from the community and excluded if they had any chronic medical illness; were on any daily prescription medications; had current medical complaints; had an abnormal physical examination (including blood pressure ≥140/90 mmHg); had abnormal results on screening tests (rest and exercise ECG, and spirometry); or were exercising on a regular basis.(4,12)

Protocol Overview

The study protocol was approved by the Wake Forest University Institutional Review Board and written consent was obtained from all participants. Participants reported to the laboratory in the morning and evaluated in the post-absorptive state having all cardio-active medications, caffeine and nicotine withheld since the evening prior as previously described. (4) Both testing and analysis were performed by individuals blinded to participant groups and clinical information.

Cardiopulmonary exercise testing

Exercise testing was performed on an upright cycle ergometer. The initial power output was set at 12.5 watts (W), increased to 25W for 3 minutes, and followed thereafter by 25W increments every 3 minutes.(13–14,17) Expired gas analysis was performed using a commercially available metabolic measurement system (Medgraphics CPX) with the highest values obtained during the final 30 seconds used as the peak score. Ventilation threshold and VO_2-work rate relationship were calculated using standard methods.(18–19)

Rest and exercise echocardiography

Echocardiograms were performed using a Hewlett-Packard model Sonos 5500 ultrasound imaging system with a multiple frequency transducer as previously described (4,20). Adequate acoustic windows were available in 48 of 59 HFPEF participants and 25 of 28 HC. Standard two-dimensional images were obtained in the parasternal long and short axes, and apical four and two chamber views. Pulsed-wave Doppler tracings of mitral valve inflow velocity were recorded at the leaflet tips.(21–22) During exercise, the sonographer focused soley on capture of optimal apical 4-chamber views for LV volume assessment.

An experienced echosonographer trained in quantitative analyses who was unaware of participant group or condition analyzed all images by tracing the endocardial borders during diastolic and systolic frames from 3 digital cineloops and the results were averaged as previously described (4,20). The EDV and end systolic volume (ESV) were calculated using the single plane ellipsoid apical four-chamber area-length method (23). Stroke volume, CO and EF were derived from standard equations while A-VO_2 Diff was calculated as $VO_2 \div$ CO.

We have validated 2-D resting echocardiographic volume measurements of EDV against EDV derived from radionuclide angiography (Fick equation derived SV/radionuclide angiography EF) in 14 healthy subjects between 22 to 73 years. Image analysis was blinded to identity of the subject. Mean EDV by echocardiography was 105.9±5.9 ml and 114.9±7.6 by the Fick/radionuclide angiography. Individual patient data were highly correlated (r=0.82). In addition, echocardiography showed an excellent day-to-day reproducibility (r=0.88) and intra-and inter-observer variability (r = 0.96 and 0.94, respectively).(24–25)

Statistical Analysis

Comparison between groups for continuous variables was assessed using student's t tests and a Chi-square test for categorical variables. Outcome variables were adjusted for sex while LV volumes were additionally adjusted for body surface area. General linear models were used to compare variables adjusted for covariates. The relationship between LV

volumes/hemodynamics and increasing workload were assessed by repeated measures analysis of covariance using general linear and polynomial mixed models (26). Given that some individuals with HFPEF (n=14) could not exercise beyond 25 watts, repeated measures between groups were limited to rest, 12.5W, 25 watts, and peak exercise workloads. No value was used twice. Multivariable linear regression models were used to estimate the relative contributions of independent variables to exercise capacity (peak VO_2). (27) Variables were selected *a priori* based on prior studies and literature relevant to the study population.(8–10;12;22) A two-sided p-value of < 0.05 was determined as significant. All statistical analysis was performed with SAS version 9.1 (Cary, NC) utilizing PROC MIXED for analysis of repeated measures.

Results

Baseline demographics, ventricular morphology and function

HFPEF subjects were predominantly older, white women with a history of hypertension and NYHA class II symptoms (Table 1). Body mass, systolic, mean and pulse pressures were significantly higher in HFPEF than HC (Table 1).

LV wall thickness, LV mass/EDV ratio, EF and atrial filling velocity were significantly higher while the E/A ratio was lower in HFPEF versus HC indicative of abnormal LV diastolic filling (Table 2). No difference was found between groups for deceleration time or isovolumic relaxation time.

Cardiac output, arterial-venous oxygen content difference and oxygen consumption during peak cycle exercise

Exercise time, peak power output, HR, CO, A-VO_2 Diff and peak VO_2 were significantly reduced in HFPEF versus HC (Table 3, Figure 1). The results for these major outcomes remained unchanged when adjusting for peak power output and respiratory exchange ratio. VO_2 at the ventilation threshold and VO_2-work rate relationship were significantly reduced in HFPEF versus HC (Table 3).

Mean arterial pressure was increased during submaximal exercise at 25 watts in HFPEF compared to HC (116+2.0 vs. 107+2.1 mmHg; p=0.002) and was not significantly different at peak exercise (122+2.1 vs. 118+2.5 mmHg; p=0.17), showing a pattern similar to that of systolic blood pressure (Figure 1F).

Left ventricular volumes and ejection fraction during sub-maximal and peak exercise

Peak exercise SV and EF were not different between groups (Figure 2A and B); however, at 25W HFPEF had a lower SV than HC (Figure 2A). The significantly lower baseline EDV, in HFPEF versus HC persisted to a similar degree during exercise (Figure 2C). Baseline ESV was significantly higher in HC and successively decreased during exercise such that no difference was found between groups at peak exercise (Figure 2D).

The absolute and percent change in EDV was not significantly different between groups during low-level exercise where most of the change in EDV occurred (Figure 3, Panels A1 and A2). The percent change in EDV from rest to peak exercise was greater in HFPEF than HC (10.3±2.0 versus 2.9±2.1%, p=0.03, Figure 3, Panel A2). The absolute or percent change in ESV was not different between groups during sub-maximal exercise but the reduction in ESV at peak exercise was blunted in HFPEF (Figure 3, Panel B1 and B2). The absolute or percent change in SV was not different between groups during sub-maximal or peak exercise (Figure 3, Panel C1 and C2). The change in HR was significantly reduced in HFPEF at peak exercise (Figure 3, Panel D1and D2). A similar pattern was seen for CO,

whereby CO response was not different between groups at low-level exercise but was decreased in HFPEF at peak exercise (Panel E1and E2). The absolute change in EF and SBP was not different between groups (p=0.11 and p=0.19, respectively); however, the percent change for both measures was lower in HFPEF compared to HC (p=0.04 and p=0.02, respectively). The absolute and percent change in A-VO_2 diff was lower in HFPEF versus HC (p=0.008 and p=0.002, respectively). Finally, overall results remained unchanged when additional analyses were performed where 25- watt values from subjects whose peak power output was 25 watts were included for submaximal analyses.

Determinants of peak VO_2

The change in A-VO_2 Diff from rest to peak exercise was the strongest independent predictor of peak VO_2 for both HC (partial correlant 0.61, standardized β coefficient 0.41; p=0.005) and HFPEF participants (partial correlant 0.58, standardized β coefficient 0.66; p=0.0002, Table 4). Among HC, the change in SV (partial correlant 0.47, standardized β coefficient 0.39; p=0.04) was more highly correlated with peak VO_2 than the change in HR (partial correlant 0.41, standardized β coefficient 0.27; p=0.07). In HFPEF the reverse was observed in that the change in HR (partial correlant 0.53, standardized β coefficient 0.43; p=0.0007) was more highly correlated with peak VO_2 than the change in SV (partial correlant 0.35, standardized β coefficient 0.32; p=0.04).

The cardiac contribution to peak exercise VO_2 was also analyzed as cardiac output rather than its factors (heart rate and stroke volume). Among the HFPEF patients, in univariate analysis, the correlation with peak VO_2 of rest to peak exercise change in cardiac output (0.31; p=0.04) was significant but somewhat weaker than that for the rest to peak exercise change in A-VO_2 diff (0.45; p=0.004). In multivariate analysis, the partial correlant with peak VO_2 of the rest to peak exercise change in CO (0.71; p<0.0001) was relatively similar to the rest to peak exercise change in A-VO_2 diff (0.72; p<0.0001)

These overall results were not significantly changed after adjustment for beta-blocker therapy or calcium channel blockers. Overall results were also unchanged if LV volume data were analyzed by indexing to body surface area.

Discussion

In this study, we sought to understand the mechanisms of the severe exercise intolerance observed in elderly patients with HFPEF by measuring LV volumes/hemodynamics and expired gasses in a group of well characterized patients with HFPEF compared to HC subjects. The major new finding of this study was that the reduced peak VO_2 in HFPEF compared to HC was the result of both reduced peak CO and A-VO_2 Diff. In turn, the reduced peak CO was due primarily to reduced peak and reserve heart rate; however, contrary to our hypothesis, the reduced peak VO_2 was not attributable to failure of the LV to dilate as the absolute change in EDV from rest to peak exercise was not significantly different between HFPEF than HC. Finally, our finding that the change in A-VO_2 Diff from rest to peak exercise was a strong, independent predictor of peak VO_2 in HFPEF patients suggests that, as has been found in patients with HF and reduced EF, (5,7,28) ‘non-cardiac’, peripheral factors play an important role in limiting their exercise capacity.

Cardiac output, arterial-venous oxygen content difference and oxygen consumption during sub-maximal exercise

Few studies have examined peak VO_2 in HFPEF (4,8–9,29) and even fewer have made the measurements required to calculate A-VO_2 Diff (4,8). We did this by simultaneously measuring VO_2 and CO, a method that has been used in studies evaluating mechanisms of

exercise intolerance in HF patients with reduced EF.(6,30) Although submaximal CO, A-VO_2 Diff and VO_2 were similar between groups, different physiologic mechanisms were employed by HFPEF and HC to increase CO (Figure 1). The smaller SV in HFPEF was associated with a higher HR while the opposite responses were found for HC. Further, the blunted sub-maximal SV reserve is likely due to decreased contractility as the change in EDV and SVR were similar between groups. Despite these differences, our finding of a plateau in SV during sub-maximal exercise is consistent with prior studies in healthy older sedentary individuals (31–32) and HF patients with reduced EF.(5–6)

Cardiac output, arterial-venous oxygen content difference and oxygen consumption during peak exercise

Unlike sub-maximal exercise, and partly in contrast to our hypothesis, the marked reduction in peak VO_2 in HFPEF was due to both decreased peak CO and A-VO_2 diff. In turn, the lower peak CO was secondary to the blunted peak (and reserve) HR as SV was similar for HFPEF and HC. These results are consistent with Brubaker et al.(12) and others (9–10,33–35) who demonstrated that chronotropic incompetence contributes to exercise intolerance in HFPEF.

Despite peak SV being similar between the groups, the mechanisms that underlie the SV response differed between groups. Specifically, HFPEF patients relied to a greater extent on LV filling (EDV reserve) while HC relied on increased LV emptying (ESV reserve) to increase SV from rest to peak exercise.(36) These divergent responses did not appear to be related to differences in afterload as exercise SVR was not different between groups; however, it may be the result of reduced contractile reserve as peak power index, single-beat end-systolic elastance and preload-recruitable stroke work are reduced during sub-maximal and peak exercise in HFPEF.(10)

To date, five studies have examined the physiologic mechanisms of exercise intolerance in HFPEF patients (Table 5).(8–11,37) Kitzman et al.(8) compared LV volume/hemodynamic responses to upright cycle exercise in 7 HFPEF patients (1 amyloid, 2 hypertrophic cardiomyopathy, and 4 with hypertension) and 10 age-matched controls. The novel finding was that the lower peak VO_2 in HFPEF versus HC was due to reduced peak CO and A-VO_2 Diff, findings consistent with our results (Figure 1). Contrary to our present data in a larger, more uniform and better characterized cohort of HFPEF patients, the blunted peak SV was attributed to an inability to utilize the Frank-Starling mechanism as 2.5-fold rise in LV filling pressure from rest to peak exercise was not associated with a concomitant increase in EDV. The divergent EDV response between studies may be due to the type of HF patients studied. Specifically, Kitzman et al.(8) included HF patients (i.e. hypertrophic cardiomyopathy and amyloid) who have limited use of the Frank-Starling mechanism during exercise (38) while in the present study these patients were excluded. Importantly however, in our prior study peak exercise A-VO_2 diff, which at that time was measured invasively by direct oximetry, was reduced compared to controls, supporting the findings of our present study.

Mader et al.(37), using right heart catheterization and expired gas analysis during supine exercise, in 14 HFPEF patients (mean age: 69 years) and 8 age and gender- matched controls. The reduced peak VO_2, in HFPEF versus controls was primarily due to a lower peak cardiac and to a lesser extent to reduced peak A-VO_2 Diff. In turn, the lower peak cardiac output was secondary to a lower peak stroke volume as peak heart rate was similar between groups. Our finding of a lower stroke volume, CO and A-VO_2Diff during upright peak cycle exercise confirms and extend the above findings obtained during supine exercise.

Borlaug et al.(9) compared the cardiovascular responses during upright cycle exercise in 17 HFPEF patients (predominantly older, obese, diabetic and hypertensive black women with LV hypertrophy) and 19 age, sex, and co-morbidity matched controls without HF. The main finding was that the reduced peak VO_2 in HFPEF compared to controls was due to impaired chronotropic, vasodilator, and CO reserve. In a follow-up study, Borlaug et al. (10) confirmed that the reduced exercise capacity in HFPEF patients (mean 67 years) versus age-matched hypertensive controls (n=19) without HF and healthy controls (n=10) was secondary to reduced chronotropic, inotropic and vasodilator reserve.

Lastly, Ennezat et al.(11) assessed ventricular-vascular function during semi-recumbent cycle exercise in 25 white HFPEF patients (predominantly older women with hypertension) and 25 age, sex and co-morbidity matched controls. These investigators reported that the blunted CO reserve was the result of decreased contractile and vasodilator reserve as chronotropic and EDV reserve were similar between groups.

While the differences between the findings of these studies may not be explainable by any single factor, there were multiple differences in patient populations (racial composition, sex, and co-morbidites) of both the patients and controls as well as in methods and study design that make them difficult to directly compare. For instance, nearly all of the controls included in Borlaug et al.(9) and Ennezat et al.(11) studies were female and hypertensive. In contrast, 52% of our controls were female and all were healthy and free from chronic medical conditions, particularly hypertension.

Determinants of peak exercise VO_2

In the report by Borlaug et al.(9), HR, CO and SVR reserve were significantly related to peak VO_2 in HFPEF and controls who had similar demographic and clinical features but without HF. In the present study, we found that in addition to cardiac output, the change in A-VO_2 Diff from rest to peak exercise a strong, independent predictor of peak VO_2 in HFPEF patients and HC. This suggested that peripheral ‘non-cardiac’ factors may contribute to limiting exercise performance in elderly HFPEF patients as well as in healthy older sedentary individuals. This finding is not surprising given that capacity for both oxygen delivery and utilization play important roles in limiting exercise performance in healthy older individuals as well as diseased populations.(4–7,28,39)

Limitations

Although we screened participants with HFPEF in order to reduce the confounding effects of medical co-morbidities, this strategy had the potential to introduce selection bias; however, the demographics and the anthropometric measurements of the HFPEF group closely matched those of population-based studies.(1–3)

Our peak SV and CO may be underestimated due to the technical challenge of acquiring echocardiographic images during peak exercise. Only patients with adequate acoustic windows were able to be included. However, this technique has been used successfully in previous publications by investigators in our group and others.(40–42)

A-VO_2 diff was not independently measured, but was calculated via the Fick equation as VO_2/CO. The calculated peak A-VO_2 Diff in our HF and HFPEF subjects is somewhat higher than that previously reported by others.(6,8,31) However, the pattern of our results are relatively similar to those reported previously in which A-VO_2 diff was measured directly using invasively obtained systemic and pulmonary arterial blood samples.(6,8,39) Moreover, the key finding that A-VO_2 Diff is reduced and contributes to reduced peak exercise VO_2 in HFPEF patients is not surprising, given that A-VO_2 Diff is known to be an important contributor to peak exercise VO_2 in healthy persons and in HF patients with

reduced EF.(4–7,28) Finally, as each group was measured using similar methods, comparisons between groups is meaningful.

We and others have previously reported that peak HR is blunted in HFPEF patients,(9–10) however, it is not possible to excluded the possibility that the effects of beta blocker medications in some of the HFPEF patients may have persisted beyond the 24-hour washout period and likewise alterations in the beta receptor due to chronic exposure may be present, either of which may predispose to a blunted HR response. However, the results were unchanged when adjustments were performed for chronic beta blocker usage.

Although the Doppler indexes at supine rest indicated the presence of abnormal LV diastolic filling, due to technical limitations including merging of the E and A wave, these were not measured during upright exercise. Furthermore, tissue Doppler was not performed. Thus, the present study was unable to evaluate the contribution(s) abnormal LV diastolic filling or regional systolic function to the patients exercise intolerance. Finally, although all HFPEF patients had normal mitral valve morphology and function at rest, it is possible that mitral regurgitation during exercise may have contributed to the lower peak exercise SV in this group.

By study design, participants were ambulatory outpatients who were stable, well compensated, had no recent acute exacerbation, and were physically able to participate in exhaustive exercise testing. As a result, the study population was predominantly NYHA class II, and not all patients required daily diuretics. The prevalence of diuretics (58%) was similar to that recently reported by Borlaug et al (58%) and only slightly less (65%) than that reported in stable HF patients undergoing exercise testing who had mean EF of 30% and similar age and NYHA class.(35,43)

Future directions

The mechanisms responsible for the lower peak A-VO_2 Diff in HFPEF were not assessed in this study; however, they may be due to impaired peripheral vascular function (endothelial dysfunction, abnormal vasodilation, reduced muscle blood flow, muscle oxygen diffusional conductance) and/or musculoskeletal function (skeletal muscle atrophy, reduced mitochondrial and capillary density).(7,10,28,44) Accordingly, future studies are required to determine if interventions, such as regular exercise training, that improve peripheral vascular and skeletal muscle function result in increased exercise A-VO_2 Diff and VO_{2peak} in HFPEF patients.

Summary

The reduced peak VO_2 in clinically stable elderly HFPEF patients is secondary to decreased peak HR, CO and A-VO_2 Diff. Moreover, peripheral ‘non-cardiac’ factors play a prominent role in limiting exercise performance in HFPEF, since the change in A-VO_2 Differences from rest to peak exercise was a strong independent predictor of peak VO_2. This suggests that interventions that increase HR, skeletal muscle perfusion or oxygen extraction by the active muscles may also improve peak exercise performance in elderly HFPEF patients.

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Abbreviations

A-VO_2 Diff	arterial-venous oxygen difference
CO	cardiac output
EDV	End-diastolic volume
EF	Ejection fraction
ESV	End-systolic volume
HC	Healthy controls
HFPEF	Heart failure and preserved ejection fraction
Peak VO_2	Peak exercise oxygen consumption (aerobic capacity)

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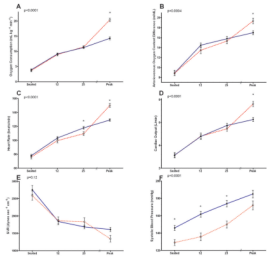

Figure 1. Comparison at seated rest, 12 watts, 25 watts, and peak exercise between HFPEF (—) and HC (--)

All variables adjusted for sex. (* $p<0.05$). The p-value at the upper left of each panel represents the group-by-intensity interaction.

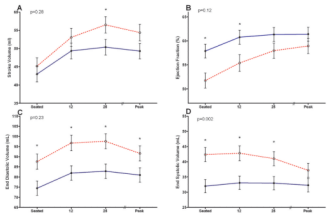

Figure 2. Comparison at seated rest, 12 watts, 25 watts, and peak exercise between HFPEF (—) and HC (--)

LV volumes adjusted for sex and BSA. EF adjusted for sex. (* $p<0.05$). The p-value at the upper left of each panel represents the group-by-intensity interaction.

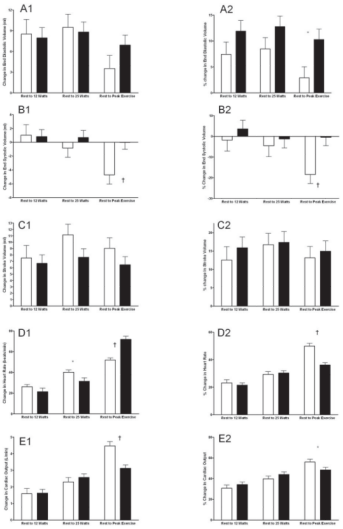

Figure 3. Comparison of change and percent change from rest to 12 watts, rest to 25 watts, and rest to peak exercise in HFPEF (■) and HC (□)

End diastolic volume (A1 and A2), end systolic volume (B1 and B2), stroke volume (C1 and C2), and cardiac output (E1 and E2) adjusted for sex and BSA. Heart rate (D1 and D2) adjusted for sex. (* $p<0.05$, † $p<0.01$)

Table 1

Participant Characteristics

Characteristic	HFPEF (n=48)	HC (n=25)	p-value
Age (years)	69 (6)	68 (5)	0.68
Female, number (%)	41 (85)	13 (52)	0.01
White, number (%)	39 (81)	25 (100)	0.01
Weight (kg)	81 (16)	72 (12)	0.02
Body mass index (kg/m^2)	30.6 (6.0)	25.0 (3.6)	<0.0001
Body surface area (m^2)	1.85 (0.2)	1.81 (0.2)	0.46
Systolic blood pressure (mmHg)	146 (19)	130 (10)	<0.0001
Diastolic blood pressure (mmHg)	82 (8)	80 (7)	0.19
Mean blood pressure (mmHg)	103 (10)	97 (6)	0.001
Pulse pressure (mmHg)	63 (17)	50 (12)	0.001
Brain Natriuretic Peptide	55 (98)	10 (11)	0.02
Doppler Diastolic Function			
Normal	7 (15)	19 (76)	<0.0001
Abnormal relaxation	33 (70)	6 (24)	0.0002
Pseudonormal	7 (15)	0 (0)	0.09
Diabetes mellitus	8 (17)	-- --	--
History of hypertension	39 (81)	-- --	--
NYHA class			
II	31 (65)	-- --	--
III	17 (35)	-- --	--
Medications			
ACE-inhibitors	14 (29)	-- --	--
Digoxin	10 (21)	-- --	--
Diuretics	28 (58)	-- --	--
Beta-blockers	11 (23)	-- --	--
Calcium channel blockers	18 (38)	-- --	--
Nitrates	4 (8)	-- --	--

Values are mean (SD), except for Female sex and White race which are number (%).

NYHA = New York Heart Association; ACE = angiotensin converting enzyme

Table 2

Supine Resting Echocardiographic and Doppler Measures

Characteristic	HFPEF (n=48)	HC (n=25)	p-value
Ejection fraction (%)	59 (1.1)	53 (1.3)	<0.0001
Septal wall thickness (cm)	1.23 (0.05)	0.84 (0.05)	<0.0001
Posterior wall thickness (cm)	1.11 (0.03)	0.92 (0.04)	<0.0001
LV mass (g)	161 (7)	142 (8)	0.06
LV mass ($g/m^{2.7}$)	41 (2)	34 (2)	0.03
LV mass/EDV ratio	2.2 (0.1)	1.5 (0.1)	0.02
E-wave velocity (cm/s)	55 (3)	54 (3)	0.88
A-wave velocity (cm/s)	81 (5)	58 (5)	0.001
E/A ratio	0.76 (0.04)	0.93 (0.04)	0.002
Deceleration time (ms)	260 (10)	254 (9)	0.65
Isovolumic relaxation time (ms)	122 (4)	117 (4)	0.42

Values are mean (SE). All comparisons adjusted for sex.

LV = left verntricular; E = early mitral inflow Doppler; A = atrial mitral inflow Doppler

Table 3

Cardiopulmonary Exercise Performance

Parameter	HFPEF (n=48)	HC (n=25)	p-value
Exercise time (min)	8.2 (0.4)	10.6 (0.4)	<0.0001
Peak power output (W)	58 (3.1)	83 (3.6)	<0.0001
Peak oxygen consumption ($mL \cdot min^{-1}$)	1206 (38)	1463 (45)	<0.0001
Peak oxygen consumption ($mL \cdot kg \cdot min^{-1}$)	14.3 (0.5)	20.4 (0.6)	<0.0001
Respiratory exchange ratio	1.10 (0.01)	1.17 (0.02)	0.008
Oxygen consumption at ventilation threshold ($mL \cdot min^{-1}$)	793 (27)	838 (30)	0.30
Oxygen consumption at ventilation threshold ($mL \cdot kg \cdot min^{-1}$)	9.4 (0.3)	11.5 (0.4)	0.001
Ventilation threshold (% peak oxygen consumption)	67 (2)	58 (2)	0.001
Ventilation/carbon dioxide slope	34.7 (1.0)	32.2 (1.1)	0.08
Oxygen uptake-work rate relationship	7.0 (0.3)	9.7 (0.6)	<0.0001

Values are mean (SE). All comparisons adjusted for sex except for respiratory exchange ratio and the oxygen uptake-work relationship

Table 4

Predictors of Peak Oxygen Consumption

	Univariate Predictor		Multivariable Predictor				
Variable	**Simple Correlation**	**P Value**	**Partial Correlant**	**Unstandardized Coefficient (B)**	**Standardized Coefficient**	**t Statistic**	**P Value**
HC							
Age	0.18	0.35	−0.20	−9.28	−0.10	−0.89	0.39
Gender	0.80	<0.0001	0.69	437.83	0.56	3.99	0.001
SBP	0.08	0.70	−0.15	−1.98	−0.07	−0.66	0.51
Δ HR	0.23	0.24	0.41	5.35	0.27	1.90	0.07
Δ SV	0.37	0.06	0.47	13.79	0.39	2.27	0.04
Δ A-VO2 Diff	0.10	0.65	0.61	3226.31	0.41	3.25	0.005
HFPEF							
Age	−0.48	<0.0001	−0.29	−7.67	−0.19	−1.77	0.08
Gender	0.52	<0.0001	0.60	310.30	0.48	4.49	<0.0001
SBP	0.07	0.607	−0.03	−0.21	−0.02	−0.17	0.87
Δ HR	0.39	0.003	0.53	5.05	0.43	3.72	0.0007
Δ SV	0.14	0.354	0.35	11.25	0.32	2.18	0.04
Δ A-VO2 Diff	0.45	0.004	0.58	3627.31	0.66	4.25	0.0002

Δ change from rest to peak exercise

SBP= systolic blood pressure; HR= heart rate; SV= stroke volume; A-VO2 Diff= arterial-venous oxygen content difference

Table 5

Studies of Determinants of Exercise Intolerance in Heart Failure with Preserved Ejection Fraction

	Kitzman[8]	Borlaug[9]	Ennezat[10]	Borlaug[11]		Maeder[38]	Current study
	HFPEF vs. AMC	**HFPEF vs. AGCC**	**HFPEF vs. HYPER**	**HFPEF vs. AMC**	**HFPEF vs. HYPER**	**HFPEF vs. AMC**	**HFPEF vs. AMC**
Peak VO_2	↓	↓	NR	↓	↓	↓	↓
Δ CO	↓	↓	↓	↓	↓	↓	↓
Δ A-VO_2diff	↓	NR	NR	NR	NR	↔	↓
Δ HR	↓	↓	↔	↓	↓	↔ supine, ↓ upright	↓
Δ EDV	↓	↔	↔	↔	↔	NR	↔
Δ ESV	↔	NR	↓	↓	↓	NR	↓
Δ SV	↓	↔	↓	NR	NR	↓	↔
Δ EF	↓	↓	↓	↓	↓	NR	↓
Δ SVR	NR	↓	↓	↓	↓	↓	↔

(Δ, peak exercise minus rest change; HFPEF, Heart failure preserve ejection fraction; AMC, age-matched control; AGCC, age-gender and co-morbidity matched controls; HYPER, hypertensive age-matched controls; VO_2, oxygen uptake; CO, cardiac output; A-VO_2 diff, arterial-venous oxygen content difference; HR, heart rate; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction; SVR, systemic vascular resistance; NR, not reported; ↓, lower in HFPEF vs. comparison group; ↑, higher in HFPEF vs. comparison group, ↔, no difference between HFPEF and comparison group)