

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

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Objectives	The purpose of this study was to determine the mechanisms responsible for reduced aerobic capacity (peak $\dot{V}O_2$) in patients with heart failure with preserved ejection fraction (HFPEF).
Background	HFPEF is the predominant form of heart failure 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 heart failure and reduced ejection fraction, the mechanism of exercise intolerance in HFPEF is less well understood.
Methods	Left ventricular volumes (2-dimensional echocardiography), cardiac output, $\dot{V}O_2$, and calculated arterial-venous oxygen content difference (A- $\dot{V}O_2$ 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.
Results	In HFPEF patients compared with healthy controls, $\dot{V}O_2$ was reduced at peak exercise (14.3 ± 0.5 ml·kg·min ⁻¹ vs. 20.4 ± 0.6 ml·kg·min ⁻¹ ; $p < 0.0001$) and was associated with a reduced peak cardiac output (6.3 ± 0.2 l·min ⁻¹ vs. 7.6 ± 0.2 l·min ⁻¹ ; $p < 0.0001$) and A- $\dot{V}O_2$ Diff (17 ± 0.4 ml·dl ⁻¹ vs. 19 ± 0.4 ml·dl ⁻¹ , $p < 0.0007$). The strongest independent predictor of peak $\dot{V}O_2$ was the change in A- $\dot{V}O_2$ Diff from rest to peak exercise (A- $\dot{V}O_2$ Diff reserve) for both HFPEF patients (partial correlate, 0.58; standardized β coefficient, 0.66; $p = 0.0002$) and healthy controls (partial correlate, 0.61; standardized β coefficient, 0.41; $p = 0.005$).
Conclusions	Both reduced cardiac output and A- $\dot{V}O_2$ Diff contribute significantly to the severe exercise intolerance in elderly HFPEF patients. The finding that A- $\dot{V}O_2$ Diff reserve is an independent predictor of peak $\dot{V}O_2$ suggests that peripheral, noncardiac factors are important contributors to exercise intolerance in these patients. (J Am Coll Cardiol 2011;58:265–74) © 2011 by the American College of Cardiology Foundation

Heart failure with preserved ejection fraction (HFPEF) constitutes 50% or more of elderly patients presenting with heart failure (HF) (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 $\dot{V}O_2$) in HF patients with reduced ejection fraction (EF) (5–7), much less is known regarding its mechanisms in patients with HFPEF.

See page 275

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Kitzman et al. (8) suggested that the reduced peak $\dot{V}O_2$ 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) and contractile (9–11) and vasodilator (9–11) reserve 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 noncar-

**Abbreviations
and Acronyms****A-VO₂ Diff** = arterial-venous oxygen difference**CO** = cardiac output**EDV** = end-diastolic volume**EF** = ejection fraction**ESV** = end-systolic volume**HC** = healthy control**HF** = heart failure**HFPEF** = heart failure with preserved ejection fraction**NYHA** = New York Heart Association**peak VO₂** = peak exercise oxygen consumption (aerobic capacity)**SV** = stroke volume

diac 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-VO₂ Diff). Therefore, the purpose of the present study was to measure VO₂, left ventricular (LV) volumes, CO, and calculated A-VO₂ Diff during cycle exercise in elderly patients with HFPEF and age-matched healthy controls (HCs). We tested the hypothesis, based on our previous observation in a small number of patients (8) that the reduced peak VO₂ in patients with HFPEF is due primarily to a blunted EDV response, which limits exercise SV and CO.

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Methods

Subjects. As previously described (4,12–14), HFPEF patients had clinical signs and symptoms of HF as defined by an National Health and Nutrition Examination Survey HF clinical score of ≥ 3 and the criteria of Rich et al. (15,16) with normal resting systolic function (LVEF $\geq 50\%$, and no segmental wall motion abnormalities at rest or during exercise) and no evidence of significant anemia or 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, North Carolina. Cases of HF were ascertained by retrospective review of clinic visits and hospital discharge records from the Wake Forest University Medical Center that appeared to potentially fulfill inclusion/exclusion criteria. Of the resultant 573 participants who were then contacted for a screening visit, 59 met the criteria for HFPEF and were enrolled in the study. The subjects in this report are a subset of those from a previous study from our laboratory who had adequate echocardiographic images during exercise (4). They did not differ significantly from the overall group in age, sex, body size, New York Heart Association (NYHA) functional class, or peak VO₂.

The HCs ($n = 28$) were recruited from the community and excluded if they had any chronic medical illness, were taking any daily prescription medications, had current medical symptoms, had abnormal findings on physical examination (including blood pressure $\geq 140/90$ mm Hg), had abnormal results on screening tests (rest and exercise electrocardiogram 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 were evaluated in the post-absorptive state having all cardioactive medications, caffeine, and nicotine withheld since the evening before 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 W, increased to 25 W for 3 min, and followed thereafter by 25-W increments every 3 min (13,14,17). Expired gas analysis was performed using a commercially available metabolic measurement system (Medgraphics CPX, Medical Graphics Corp., St. Paul, Minnesota), with the highest values obtained during the final 30 s used as the peak score. Ventilation threshold and VO₂ work rate relationship was calculated using standard methods (18,19).

Rest and exercise echocardiography. Echocardiograms were obtained using a Sonos 5500 ultrasound imaging system (Hewlett-Packard, Palo Alto, California) 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 HCs. Standard 2-dimensional images were obtained in the parasternal long and short axes, and apical 4- and 2-chamber views. Pulsed-wave Doppler tracings of mitral valve inflow velocity were recorded at the leaflet tips (21,22). During exercise, the sonographer focused solely on capturing 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 cine loops, 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 4-chamber area-length method (23). The SV, CO, and EF were derived from standard equations, whereas A-VO₂ Diff was calculated as: $VO_2 \div CO$.

We validated 2-dimensional 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 and 73 years of age. Image analysis was blinded to the identity of the subject. Mean EDV by echocardiography was 105.9 ± 5.9 ml and 114.9 ± 7.6 ml 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 intraobserver and interobserver variability ($r = 0.96$ and 0.94 , respectively) (24,25).

Statistical analysis. Comparison between groups for continuous variables was assessed using the Student *t* test and a chi-square test for categorical variables. Outcome variables were adjusted for sex, whereas LV volumes were addition-

Table 1 Participant Characteristics

Characteristic	HFPEF Patients (n = 48)	HCs (n = 25)	p Value
Age, yrs	69 ± 6	68 ± 5	0.68
Female	41 (85)	13 (52)	0.01
White	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, mm Hg	146 ± 19	130 ± 10	<0.0001
Diastolic blood pressure, mm Hg	82 ± 8	80 ± 7	0.19
Mean blood pressure, mm Hg	103 ± 10	97 ± 6	0.001
Pulse pressure, mm Hg	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	0.09
Diabetes mellitus	8 (17)	—	—
History of hypertension	39 (81)	—	—
NYHA functional 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 or n (%).

ACE = angiotensin-converting enzyme; HC = healthy control; HFPEF = heart failure with preserved ejection fraction; NYHA = New York Heart Association.

ally 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 was 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 W, repeated measures between groups were limited to rest and 12.5-W, 25-W, 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 VO₂) (27). Variables were selected a priori based on previous studies and literature relevant to the study population (8-10,12,22). A 2-sided p value <0.05 was determined as significant. All statistical analyses were performed with SAS version 9.1 (SAS Institute, Cary, North Carolina) using 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 functional class II symptoms (Table 1). Body mass, systolic, mean, and pulse

pressures were significantly higher in HFPEF patients than in HCs (Table 1).

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

CO, A-VO₂ Diff, and peak VO₂. Exercise time, peak power output, HR, CO, A-VO₂ Diff, and peak VO₂ were significantly reduced in HFPEF patients compared with HCs (Table 3, Fig. 1). The results for these major outcomes remained unchanged when adjusting for peak power output and respiratory exchange ratio. VO₂ at the ventilation threshold and the VO₂-work rate relationship were significantly reduced in HFPEF patients compared with HCs (Table 3).

Mean arterial pressure was increased during submaximal exercise at 25 W in HFPEF patients compared with HCs (116 ± 2.0 mm Hg vs. 107 ± 2.1 mm Hg; p = 0.002) and was not significantly different at peak exercise (122 ± 2.1 mm Hg vs. 118 ± 2.5 mm Hg; p = 0.17), showing a pattern similar to that of systolic blood pressure (Fig. 1F).

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

The absolute change and percentage of change in EDV were not significantly different between groups during low-level exercise where most of the change in EDV occurred (Figs. 3A1 and 3A2). The percentage of change in EDV from rest to peak exercise was greater in HFPEF patients than HCs (10.3 ± 2.0% vs. 2.9 ± 2.1%, p = 0.03)

Table 2 Supine Resting Echocardiographic and Doppler Measures

Characteristic	HFPEF Patients (n = 48)	HCs (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.

A = atrial mitral inflow Doppler; E = early mitral inflow Doppler; EDV = end-diastolic volume; LV = left ventricular; other abbreviations as in Table 1.

Table 3 Cardiopulmonary Exercise Performance

Parameter	HFPEF Patients (n = 48)	HCs (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·min ⁻¹	1,206 ± 38	1,463 ± 45	<0.0001
Peak oxygen consumption, ml·kg·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·min ⁻¹	793 ± 27	838 ± 30	0.30
Oxygen consumption at ventilation threshold, ml·kg·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. Abbreviations as in Table 1.

(Fig. 3A2). The absolute or percentage of change in ESV was not different between groups during submaximal exercise, but the reduction in ESV at peak exercise was blunted in HFPEF patients (Figs. 3B1 and 3B2). The absolute or percentage of change in SV was not different between groups during submaximal or peak exercise (Figs. 3C1 and 3C2). The change in HR was significantly reduced in HFPEF patients at peak exercise (Figs. 3D1 and 3D2). A similar pattern was seen for CO, in which CO response was not different between groups at low-level exercise but was decreased in HFPEF patients at peak exercise (Figs. 3E1 and 3E2). The absolute changes in EF and systolic blood pressure were not different between groups ($p = 0.11$ and $p = 0.19$, respectively); however, the percentage of change for both measures was lower in HFPEF patients compared with HCs ($p = 0.04$ and $p = 0.02$, respectively). The absolute change and percentage of change in A-VO₂ Diff were lower in HFPEF patients compared with HCs ($p = 0.008$ and $p = 0.002$, respectively). Finally, overall results remained unchanged when additional analyses were performed when 25-W values from subjects whose peak power output was 25 W were included for submaximal analyses.

Determinants of peak VO₂. The change in A-VO₂ Diff from rest to peak exercise was the strongest independent predictor of peak VO₂ for both HC (partial correlate, 0.61; standardized β coefficient, 0.41; $p = 0.005$) and HFPEF patients (partial correlate, 0.58; standardized β coefficient, 0.66; $p = 0.0002$) (Table 4). Among HCs, the change in SV (partial correlate, 0.47; standardized β coefficient, 0.39; $p = 0.04$) was more highly correlated with peak VO₂ than the change in HR (partial correlate, 0.41; standardized β coefficient, 0.27; $p = 0.07$). In HFPEF patients, the reverse was observed in that the change in HR (partial correlate, 0.53; standardized β coefficient, 0.43; $p = 0.0007$) was more highly correlated with peak VO₂ than the change in SV (partial correlate, 0.35; standardized β coefficient, 0.32; $p = 0.04$).

The cardiac contribution to peak VO₂ was also analyzed as CO rather than its factors (HR and SV). Among the HFPEF patients, in univariate analysis, the correlation with

peak VO₂ of rest to peak exercise change in CO (0.31; $p = 0.04$) was significant but somewhat weaker than that for the rest to peak exercise change in A-VO₂ Diff (0.45; $p = 0.004$). In multivariate analysis, the partial correlate with peak VO₂ 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-VO₂ Diff (0.72; $p < 0.0001$).

These overall results were not significantly changed after adjustment for beta-blocker or calcium-channel blocker therapy. 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 gases in a group of well-characterized patients with HFPEF compared with HCs. The major new finding of this study was that the reduced peak VO₂ in HFPEF patients compared with HCs was the result of both reduced peak CO and A-VO₂ Diff. In turn, the reduced peak CO was due primarily to reduced peak and reserve HR; however, contrary to our hypothesis, the reduced peak VO₂ was not attributable to failure of the left ventricle to dilate as the absolute change in EDV from rest to peak exercise was not significantly different between HFPEF patients and HCs. Finally, our finding that the change in A-VO₂ Diff from rest to peak exercise was a strong, independent predictor of peak VO₂ in HFPEF patients suggests that, as has been found in patients with HF and reduced EF (5,7,28), noncardiac peripheral factors play an important role in limiting their exercise capacity.

CO, A-VO₂ Diff, and VO₂. Few studies have examined peak VO₂ in HFPEF patients (4,8,9,29), and even fewer have made the measurements required to calculate A-VO₂ Diff (4,8). We did this by simultaneously measuring VO₂ 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-VO₂ Diff,

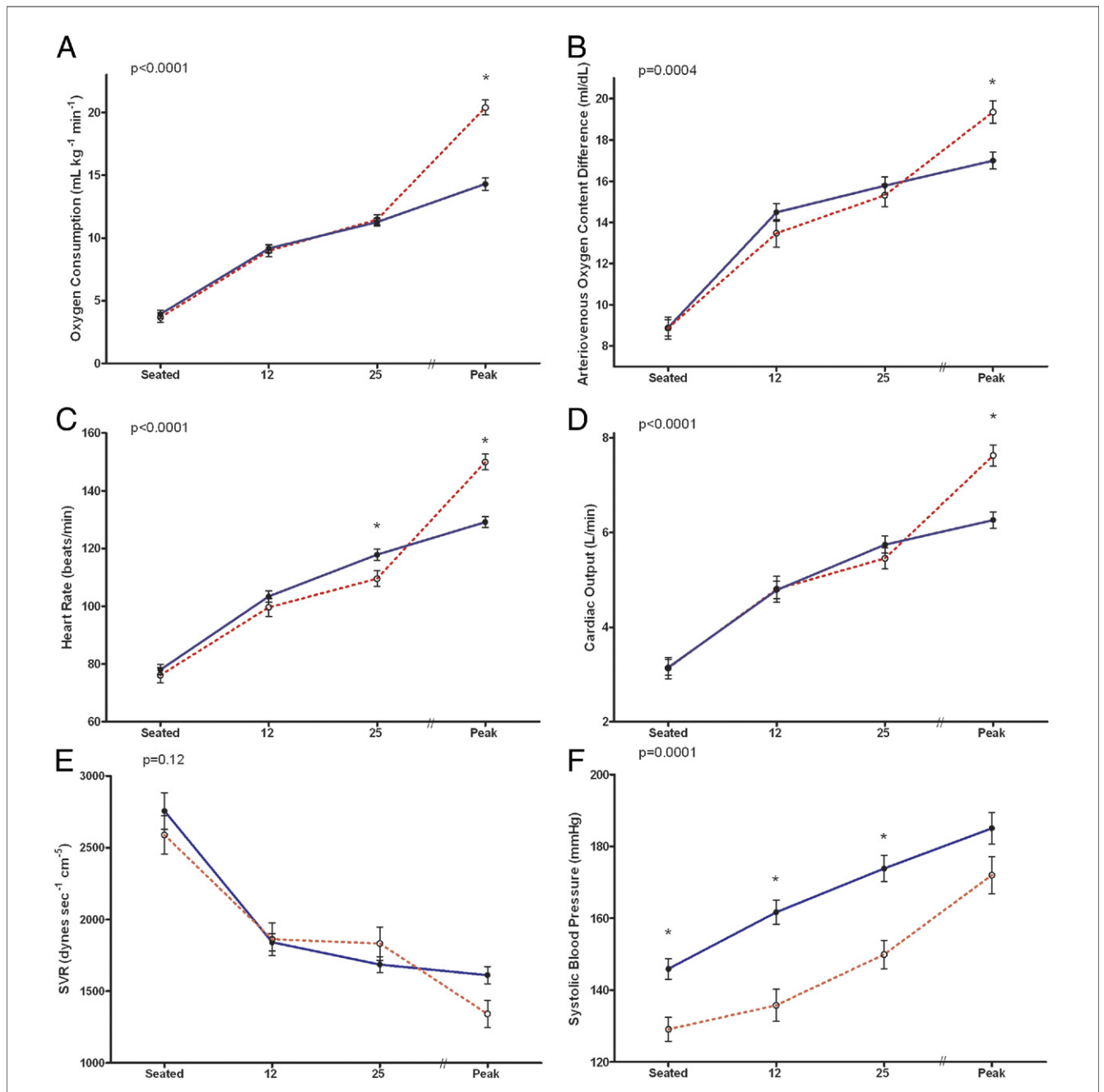


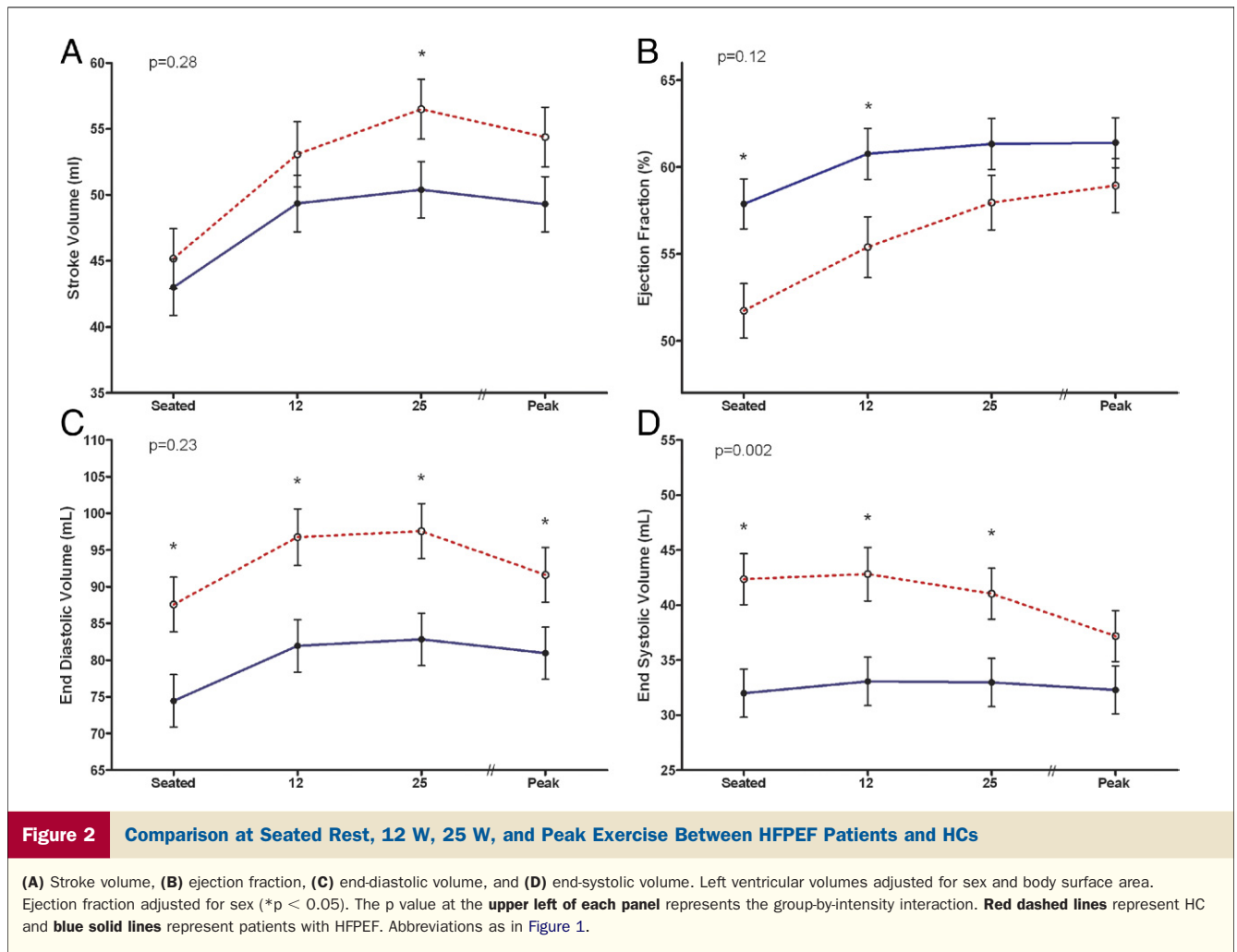
Figure 1 Comparison at Seated Rest, 12 W, 25 W, and Peak Exercise Between HFPEF Patients and HCs

(A) Oxygen consumption, (B) arteriovenous oxygen content difference, (C) heart rate, (D) cardiac output, (E) systemic vascular resistance (SVR), and (F) systolic blood pressure. All variables adjusted for sex (* $p < 0.05$). The p value at the upper left of each panel represents the group-by-intensity interaction. Red dashed lines represent healthy controls (HC) and blue solid lines represent patients with heart failure with preserved ejection fraction (HFPEF).

and VO_2 were similar between groups, different physiological mechanisms were used by HFPEF patients and HCs to increase CO (Fig. 1). The smaller SV in HFPEF patients was associated with a higher HR, whereas the opposite responses were found for HCs. Furthermore, the blunted submaximal SV reserve is likely due to decreased contractility as the changes in EDV and systemic vascular resistance (SVR) were similar between groups. Despite these differ-

ences, our finding of a plateau in SV during submaximal exercise is consistent with findings of previous studies in healthy older sedentary individuals (31,32) and HF patients with reduced EF (5,6).

CO, A- VO_2 Diff, and peak VO_2 . Unlike submaximal exercise, and partly in contrast to our hypothesis, the marked reduction in peak VO_2 in HFPEF patients 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 the SV was similar for HFPEF patients and HCs. These results are consistent with those of Brubaker et al. (12) and others (9,10,33–35) who demonstrated that chronotropic incompetence contributes to exercise intolerance in HFPEF patients.

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), whereas HCs relied on increased LV emptying (ESV reserve) to increase the SV from rest to peak exercise (36). These divergent responses did not appear to be related to differences in afterload because 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 submaximal and peak exercise in HFPEF patients (10).

To date, 5 studies have examined the physiological 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 cardiomyop-

athy, and 4 with hypertension) and 10 age-matched controls. The novel finding was that the lower peak VO_2 in HFPEF patients versus HCs was due to reduced peak CO and A-VO_2 Diff, findings consistent with our results (Fig. 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 use the Frank-Starling mechanism because a 2.5-fold increase 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), whereas in the present study, these patients were excluded. Importantly, however, in our previous study, peak exercise A-VO_2 Diff, which at that time was measured invasively by direct oximetry, was reduced compared with controls, supporting the findings of our present study.

Mader et al. (37) used right heart catheterization and expired gas analysis during supine exercise in 14 HFPEF patients (mean age 69 years) and 8 age- and sex-matched

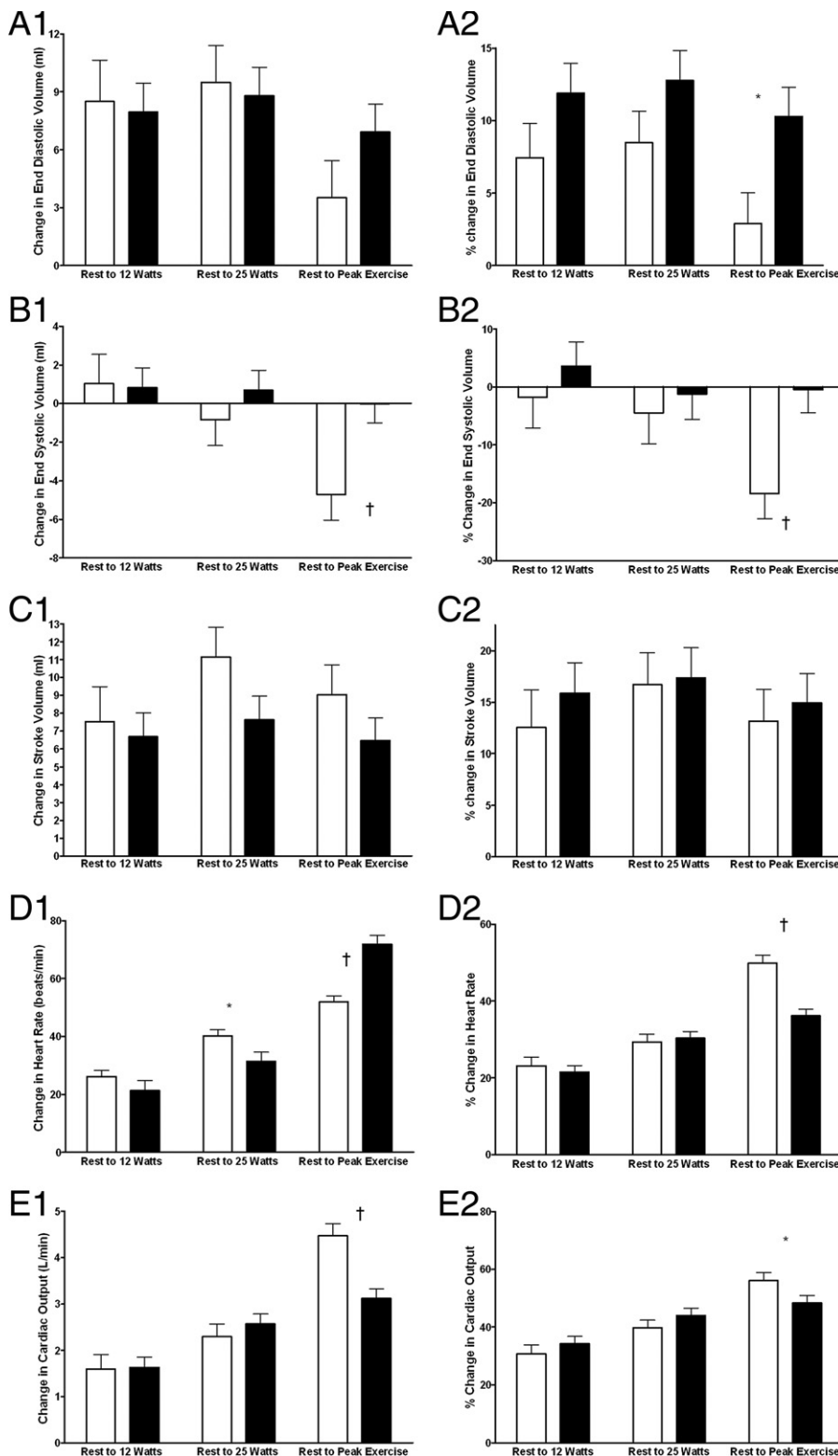


Figure 3

Comparison of Change and Percentage of Change From Rest to 12 W, Rest to 25 W, and Rest to Peak Exercise in HFPEF Patients and HCs

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 body surface area. Heart rate (**D1** and **D2**) adjusted for sex (* $p < 0.05$, † $p < 0.01$). **Solid bars** = HFPEF patients; **open bars** = HCs. Abbreviations as in Figure 1.

Table 4 Predictors of Peak Oxygen Consumption

Variable	Univariate Predictor		Multivariable Predictor				
	Simple Correlation	p Value	Partial Correlate	Unstandardized Coefficient (B)	Standardized Coefficient	t Statistic	p Value
HCs							
Age	0.18	0.35	-0.20	-9.28	-0.10	-0.89	0.39
Sex	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
ΔHR	0.23	0.24	0.41	5.35	0.27	1.90	0.07
ΔSV	0.37	0.06	0.47	13.79	0.39	2.27	0.04
ΔA-Vo ₂ Diff	0.10	0.65	0.61	3,226.31	0.41	3.25	0.005
HFPEF patients							
Age	-0.48	<0.0001	-0.29	-7.67	-0.19	-1.77	0.08
Sex	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
ΔHR	0.39	0.003	0.53	5.05	0.43	3.72	0.0007
ΔSV	0.14	0.354	0.35	11.25	0.32	2.18	0.04
ΔA-Vo Diff	0.45	0.004	0.58	3,627.31	0.66	4.25	0.0002

Δ = change from rest to peak exercise; A-Vo₂ Diff = arterial-venous oxygen content difference; HR = heart rate; SBP = systolic blood pressure; SV = stroke volume; other abbreviations as in Table 1.

controls. The reduced peak V_{O₂}, in HFPEF patients versus controls was primarily due to a lower peak cardiac and to a lesser extent to reduced peak A-Vo₂ Diff. In turn, the lower peak CO was secondary to a lower peak SV because the peak HR was similar between groups. Our finding of lower SV, CO, and A-Vo₂ Diff during upright peak cycle exercise confirms and extends the 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 comorbidity-matched control subjects without HF. The main finding was that the reduced peak V_{O₂} in HFPEF patients compared with 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 age 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.

Last, Ennezat et al. (11) assessed ventricular-vascular function during semirecumbent cycle exercise in 25 white HFPEF patients (predominantly older women with hypertension) and 25 age-, sex-, and comorbidity-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.

Although 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 comorbidities) 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 the 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 of chronic medical conditions, particularly hypertension.

Determinants of peak V_{O₂}. In the study by Borlaug et al. (9), HR, CO, and SVR were significantly related to peak V_{O₂} in HFPEF patients and controls who had similar

Table 5 Studies of Determinants of Exercise Intolerance in HFPEF

	Kitzman et al. (8) HFPEF vs. AMC	Borlaug et al. (9) HFPEF vs. ASCC	Ennezat et al. (11) HFPEF vs. HYPER	Borlaug et al. (10)		Maeder et al. (37) HFPEF vs. AMC	Current Study HFPEF vs. AMC
				HFPEF vs. AMC	HFPEF vs. HYPER		
Peak V _{O₂}	↓	↓	NR	↓	↓	↓	↓
ΔCO	↓	↓	↓	↓	↓	↓	↓
ΔA-Vo ₂ Diff	↓	NR	NR	NR	NR	↔	↓
ΔHR	↓	↓	↔	↓	↓	↔ supine, ↓ upright	↓
ΔEDV	↓	↔	↔	↔	↔	NR	↔
ΔESV	↔	NR	↓	↓	↓	NR	↓
ΔSV	↓	↔	↓	NR	NR	↓	↔
ΔEF	↓	↓	↓	↓	↓	NR	↓
ΔSVR	NR	↓	↓	↓	↓	↓	↔

Δ = peak exercise minus rest change; AMC = age-matched controls; ASCC = age-, sex-, and comorbidity-matched controls; CO = cardiac output; EF = ejection fraction; ESV = end-systolic volume; HYPER = hypertensive age-matched controls; NR = not reported; SVR = systemic vascular resistance; V_{O₂} = oxygen uptake; ↓ = lower in HFPEF vs. comparison group; ↑ = higher in HFPEF vs. comparison group; ↔ = no difference between HFPEF and comparison group; other abbreviations as in Tables 1, 2, and 4.

demographic and clinical features but without HF. In the present study, we found that in addition to CO, the change in A-VO₂ Diff from rest to peak exercise was a strong, independent predictor of peak VO₂ in HFPEF patients and HCs. This suggested that peripheral noncardiac 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 use plays an important role in limiting exercise performance in healthy older individuals as well as diseased populations (4-7,28,39).

Study limitations. Although we screened participants with HFPEF to reduce the confounding effects of medical comorbidities, 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-VO₂ Diff was not independently measured, but was calculated using the Fick equation as VO₂/CO. The calculated peak A-VO₂ 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 is relatively similar to those reported previously in which A-VO₂ Diff was measured directly using invasively obtained systemic and pulmonary arterial blood samples (6,8,39). Moreover, the key finding that A-VO₂ Diff is reduced and contributes to reduced peak O₂ in HFPEF patients is not surprising, given that A-VO₂ Diff is known to be an important contributor to peak VO₂ in healthy persons and in HF patients with reduced EF (4-7,28). Finally, because each group was measured using similar methods, comparisons between groups are meaningful.

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

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 waves, these were not measured during upright exercise. Furthermore, tissue Doppler imaging 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, al-

though 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 and 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 functional 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%) (35) and only slightly less (65%) than that reported in stable HF patients undergoing exercise testing who had a mean EF of 30% and were of similar age and NYHA functional class (43).

Future directions. The mechanisms responsible for the lower peak A-VO₂ Diff in HFPEF patients 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 whether interventions, such as regular exercise training, that improve peripheral vascular and skeletal muscle function result in increased exercise A-VO₂ Diff and peak VO₂ in HFPEF patients.

Conclusions

The reduced peak VO₂ in clinically stable elderly HFPEF patients is secondary to decreased peak HR, CO, and A-VO₂ Diff. Moreover, peripheral noncardiac factors play a prominent role in limiting exercise performance in HFPEF patients because the change in A-VO₂ Diff from rest to peak exercise was a strong independent predictor of peak VO₂. 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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REFERENCES

1. Senni M, Tribouilloy CM, Rodeheffer RJ, et al. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. *Circulation* 1998;98:2282-9.
2. Kitzman DW, Gardin JM, Gottdiener JS, et al., for the CHS Research Group. Importance of heart failure with preserved systolic function in patients > or = 65 years of age. *Cardiovascular Health Study*. *Am J Cardiol* 2001;87:413-9.
3. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *J Am Coll Cardiol* 1999;33:1948-55.

4. Kitzman DW, Little WC, Brubaker PH, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. *JAMA* 2002;288:2144–50.
5. Wilson JR, Mancini DM, Dunkman WB. Exertional fatigue due to skeletal muscle dysfunction in patients with heart failure. *Circulation* 1993;87:470–5.
6. Sullivan MJ, Knight JD, Higginbotham MB, Cobb FR. Relation between central and peripheral hemodynamics during exercise in patients with chronic heart failure. Muscle blood flow is reduced with maintenance of arterial perfusion pressure. *Circulation* 1989;80:769–81.
7. Esposito F, Mathieu-Costello O, Shabetai R, Wagner PD, Richardson RS. Limited maximal exercise capacity in patients with chronic heart failure: partitioning the contributors. *J Am Coll Cardiol* 2010;55:1945–54.
8. 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.
9. 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.
10. Borlaug BA, Olson TP, Lam CS, et al. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2010;56:845–54.
11. Ennezat PV, Lefetz Y, Marechaux S, et al. Left ventricular abnormal response during dynamic exercise in patients with heart failure and preserved left ventricular ejection fraction at rest. *J Card Fail* 2008;14:475–80.
12. Brubaker PH, Joo KC, Stewart KP, Fray B, Moore B, Kitzman DW. Chronotropic incompetence and its contribution to exercise intolerance in older heart failure patients. *J Cardiopulm Rehabil* 2006;26:86–9.
13. Hundley WG, Kitzman DW, Morgan TM, et al. Cardiac cycle-dependent changes in aortic area and distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance. *J Am Coll Cardiol* 2001;38:796–802.
14. Marburger CT, Brubaker PH, Pollock WE, Morgan TM, Kitzman DW. Reproducibility of cardiopulmonary exercise testing in elderly patients with congestive heart failure. *Am J Cardiol* 1998;82:905–9.
15. Rich MW, Beckham V, Wittenberg C, Leven CL, Freedland KE, Carney RM. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. *N Engl J Med* 1995;333:1190–5.
16. Schocken DD, Arrieta MI, Leaverton PE, Ross EA. Prevalence and mortality rate of congestive heart failure in the United States. *J Am Coll Cardiol* 1992;20:301–6.
17. Kaminsky LA, Brubaker PH, Peaker B, Kitzman DW. Prediction of peak oxygen uptake from cycle exercise test work level in heart failure patients ≥ 65 years of age. *Am J Cardiol* 2000;85:1385–7.
18. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* 1986;60:2020–7.
19. Hansen JE, Sue DY, Oren A, Wasserman K. Relation of oxygen uptake to work rate in normal men and men with circulatory disorders. *Am J Cardiol* 1987;59:669–74.
20. Gandhi SK, Powers JC, Nomeir AM, et al. The pathogenesis of acute pulmonary edema associated with hypertension. *N Engl J Med* 2001;344:17–22.
21. Kitzman DW, Sheikh KH, Beere PA, Philips JL, Higginbotham MB. Age-related alterations of Doppler left ventricular filling indexes in normal subjects are independent of left ventricular mass, heart rate, contractility and loading conditions. *J Am Coll Cardiol* 1991;18:1243–50.
22. Warner JG Jr., Metzger DC, Kitzman DW, Wesley DJ, Little WC. Losartan improves exercise tolerance in patients with diastolic dysfunction and a hypertensive response to exercise. *J Am Coll Cardiol* 1999;33:1567–72.
23. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989;2:358–67.
24. Kitzman DW, Brubaker PH, Millsaps P, Craven T, Little WC. Left ventricular end-diastolic volume (EDV) responses in normal elderly: comparison of orthostatic change and upright bicycle exercise. *Circulation* 1995;92:1468.
25. Kitzman DW, Stewart KP, Brubaker PH. The magnitude and time course of the left ventricular end-diastolic volume (EDV) response during upright exercise in normal elderly men and women (abstr). *Circulation* 1995;92:1468.
26. Searle SR, Casella G, McCulloch CE. *Variance Components*. New York, NY: John Wiley & Sons, 1992.
27. Harrell FE Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15:361–87.
28. Warburton DE, Taylor A, Bredin SS, Esch BT, Scott JM, Haykowsky MJ. Central haemodynamics and peripheral muscle function during exercise in patients with chronic heart failure. *Appl Physiol Nutr Metab* 2007;32:318–31.
29. Tan YT, Wenzelburger F, Lee E, et al. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. *J Am Coll Cardiol* 2009;54:36–46.
30. Dubach P, Myers J, Dziekan G, et al. Effect of high intensity exercise training on central hemodynamic responses to exercise in men with reduced left ventricular function. *J Am Coll Cardiol* 1997;29:1591–8.
31. Ogawa T, Spina RJ, Martin WH 3rd, et al. Effects of aging, sex, and physical training on cardiovascular responses to exercise. *Circulation* 1992;86:494–503.
32. Chantler PD, Melenovsky V, Schulman SP, et al. The sex-specific impact of systolic hypertension and systolic blood pressure on arterial-ventricular coupling at rest and during exercise. *Am J Physiol Heart Circ Physiol* 2008;295:H145–53.
33. Phan TT, Abozguia K, Nallur Shivu G, et al. Heart failure with preserved ejection fraction is characterized by dynamic impairment of active relaxation and contraction of the left ventricle on exercise and associated with myocardial energy deficiency. *J Am Coll Cardiol* 2009;54:402–9.
34. 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.
35. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail* 2010;3:588–95.
36. Higginbotham MB, Morris KG, Williams RS, McHale PA, Coleman RE, Cobb FR. Regulation of stroke volume during submaximal and maximal upright exercise in normal man. *Circ Res* 1986;58:281–91.
37. Maeder MT, Thompson BR, Brunner-La Rocca HP, Kaye DM. Hemodynamic basis of exercise limitation in patients with heart failure and normal ejection fraction. *J Am Coll Cardiol* 2010;56:855–63.
38. Lele SS, Thomson HL, Seo H, Belenkie I, McKenna WJ, Frenneaux MP. Exercise capacity in hypertrophic cardiomyopathy. Role of stroke volume limitation, heart rate, and diastolic filling characteristics. *Circulation* 1995;92:2886–94.
39. Beere PA, Russell SD, Morey MC, Kitzman DW, Higginbotham MB. Aerobic exercise training can reverse age-related peripheral circulatory changes in healthy older men. *Circulation* 1999;100:1085–94.
40. Scott JM, Esch BT, Haykowsky MJ, et al. Cardiovascular responses to incremental and sustained submaximal exercise in heart transplant recipients. *Am J Physiol Heart Circ Physiol* 2009;296:H350–8.
41. Stickland MK, Welsh RC, Petersen SR, et al. Does fitness level modulate the cardiovascular hemodynamic response to exercise? *J Appl Physiol* 2006;100:1895–901.
42. Tischler MD, Plehn JF. Applications of stress echocardiography: beyond coronary disease. *J Am Soc Echocardiogr* 1995;8:185–97.
43. Brubaker PH, Moore JB, Stewart KP, Wesley DJ, Kitzman DW. Endurance exercise training in older patients with heart failure: results from a randomized, controlled, single-blind trial. *J Am Geriatr Soc* 2009;57:1982–9.
44. Katz SD, Maskin C, Jondeau G, Cocke T, Berkowitz R, LeJemtel T. Near maximal fractional oxygen extraction by active skeletal muscle in patients with heart failure. *J Appl Physiol* 2000;88:2138–42.

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