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Cardiac output response to exercise in relation to metabolic demand in heart failure with preserved ejection fraction

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Aims Exercise intolerance is a hallmark of heart failure with preserved ejection fraction (HFpEF), yet its mechanisms remain unclear. The current study sought to determine whether increases in cardiac output (CO) during exercise are appropriately matched to metabolic demands in HFpEF.

Methods and results Patients with HFpEF ($n = 109$) and controls ($n = 73$) exercised to volitional fatigue with simultaneous invasive ($n = 96$) or non-invasive ($n = 86$) haemodynamic assessment and expired gas analysis to determine oxygen consumption (VO_2) during upright or supine exercise. At rest, HFpEF patients had higher LV filling pressures but similar heart rate, stroke volume, EF, and CO. During supine and upright exercise, HFpEF patients displayed lower peak VO_2 coupled with blunted increases in heart rate, stroke volume, EF, and CO compared with controls. LV filling pressures increased dramatically in HFpEF patients, with secondary elevation in pulmonary artery pressures. Reduced peak VO_2 in HFpEF patients was predominantly attributable to CO limitation, as the slope of the increase in CO relative to VO_2 was 20% lower in HFpEF patients (5.9 ± 2.5 vs. 7.4 ± 2.6 L blood/L O_2, $P = 0.0005$). While absolute increases in arterial–venous O_2 difference with exercise were similar in HFpEF patients and controls, augmentation in arterial–venous O_2 difference relative to VO_2 was greater in HFpEF patients (8.9 ± 3.4 vs. 5.5 ± 2.0 min/dL, $P < 0.0001$). These differences were observed in the total cohort and when upright and supine exercise modalities were examined individually.

Conclusion While diastolic dysfunction promotes congestion and pulmonary hypertension with stress in HFpEF, reduction in exercise capacity is predominantly related to inadequate CO relative to metabolic needs.

Keywords Diastolic heart failure • Exercise • Oxygen consumption • Cardiac output • Stroke volume • Heart rate

Introduction

Heart failure (HF) has been defined as an inability of the heart to provide cardiac output (CO) to the body at a rate commensurate with its needs, or to do so only at the cost of elevated filling pressures.[1] Resting CO is generally preserved until the most advanced stages of disease, but CO reserve with exercise is impaired at earlier stages in HF with reduced ejection fraction (HFrEF).[2,3] In practice, CO reserve is estimated indirectly by measuring the peak oxygen consumption (peak VO_2) attained during exercise.[4] However, because increases in CO are tightly coupled to changes in VO_2,[5,6] simultaneous measurement of CO and VO_2 allows for more robust assessment of the adequacy of cardiac oxygen delivery relative to metabolic needs.[2,4] This relationship ($\Delta CO/\Delta VO_2$ slope) is characteristically depressed in HFrEF.[2]

Half of patients with HF have preserved EF (HFpEF).[7,8] Peak VO_2 is similarly depressed in HFpEF and HFrEF,[9] yet the nature of VO_2 impairment with exercise in HFpEF remains controversial.[10–22] Potential mechanisms include CO limitation, subjective dyspnoea, impaired vasodilation, skeletal muscle dysfunction,

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deranged pulmonary gas exchange or mechanics, patient motivation, fitness level, body habitus, and medical co-morbidities. It has recently been reported that exertional capacity in HFpEF is constrained predominantly by abnormalities in cardiac filling[13,22] or peripheral O_2 extraction,[18] rather than CO impairment. Distinguishing these possibilities is of fundamental importance when contemplating novel treatments for HFpEF, a disease with no proven therapy.[7,8]

The current study aimed to characterize the relationships between ventricular filling and ejection relative to metabolic demand, oxygen delivery, and extraction during exercise in patients with HFpEF. Because haemodynamics differ in the upright and supine positions, and because of potential for referral bias when exclusively studying a catheterization population, we include subjects studied using both invasive and non-invasive methods to measure CO in both the supine and upright positions. We hypothesized that CO reserve relative to VO_2 would be impaired in HFpEF patients compared with controls.

Methods

Study population

The total study population is compiled from three cohorts of patients with HFpEF and controls. Cohort 1 ($n = 112$) includes consecutive patients and controls who underwent invasive supine exercise ergometry studies with simultaneous expired gas analysis at the Mayo Clinic from 2002 to 2011. No data from the cohort 1 patients have been previously published. Cohort 2 ($n = 50$)[15] and cohort 3 ($n = 36$)[12] are from previously published prospective studies examining upright exercise haemodynamics. Some clinical characteristics, exercise capacity, and ventricular–vascular function data from cohorts 2 and 3 have been published,[12,15] but the cardiovascular responses as they relate to VO_2, the primary aim of the current study, have not been reported. This study complies with the Declaration of Helsinki and has been approved by Institutional Review Boards of the Mayo Clinic and Johns Hopkins Hospital.

Heart failure with preserved EF was defined by LVEF $\geq$ 50% and cardiologist-adjudicated diagnosis of HF (Framingham criteria).[12,15] Exclusion criteria were significant valvular disease (moderate or greater left-sided regurgitation, any stenosis), cor pulmonale, significant pulmonary disease, unstable coronary disease or coronary spasm, primary renal or hepatic disease, constrictive pericarditis, or infiltrative, restrictive, or hypertrophic cardiomyopathies. Controls in cohort 1 were referred to the cath lab for assessment of exertional dyspnoea and were found to display no cardiac pathology after thorough invasive and non-invasive evaluation. Controls in the non-invasive cohorts were recruited from the community.

Study measurements performed at rest and during exercise in cohorts 1–3 are shown in Supplementary material, *Table S1*. All patients were studied in the post-absorptive state. Baseline ventricular morphology and function, diastolic filling characteristics, and left atrial volume were measured by transthoracic echocardiography. Echocardiographic LV stroke volume (SV) was determined from LV outflow Doppler, EF was determined by Simpson's biplane method, and LV end-diastolic volume was determined by SV/EF.[15,19] Heart rate (HR) was continuously recorded by electrocardiography. Breath-by-breath expired gas analysis was performed at rest and during exercise in all studies (MedGraphics, St Paul, MN, USA) to measure oxygen consumption (VO_2).

Invasive haemodynamic exercise assessment (cohort 1)

Right heart catheterization was performed in the supine position through the internal jugular vein.[17] Right atrial (RAP), pulmonary artery (PAP), and pulmonary capillary wedge (PCWP) pressures were assessed at end-expiration at rest and after $\geq$ 2 min had elapsed at peak workload during supine cycle ergometry. Systemic blood pressure (BP) was measured by intra-arterial (radial) catheter ($n = 55$) or by cuff sphygmomanometry ($n = 41$).

Arterial–venous oxygen content difference (AVO_2diff) was measured directly as the difference between systemic and pulmonary arterial O_2 contents (=saturation $\times$ haemoglobin $\times$ 1.34). CO was determined by the direct Fick method (=VO_2/AVO_2diff). The SV was determined by CO/HR. Pulmonary vascular resistance [PVR = (mean PAP – PCWP)/CO] and effective arterial elastance (Ea = 0.9 $\times$ systolic BP/SV)[15,23] were determined as measures of pulmonary and systemic arterial afterload.

Non-invasive haemodynamic exercise assessment (cohorts 2 and 3)

Subjects in cohorts 2 and 3 underwent maximal-effort graded exercise testing on an upright cycle ergometer as previously described.[12,15] Cardiac volumes, SV, and EF were assessed at rest and during the final 2 min of exercise by echocardiography in cohort 2 and nuclear gated blood pool scan in cohort 3. CO was determined by SV $\times$ HR. AVO_2diff was determined by the Fick method (=VO_2/CO).[19] Ea was determined as in cohort 1.

Statistical analysis

Data are reported as mean $\pm$ standard deviation or median (25th, 75th interquartile range). Between-group differences were compared by *t*-test, Wilcoxon rank-sum test, or χ^2. Multivariable linear regression analysis was used to adjust for relevant baseline group differences and to examine differences with upright and supine exercise, in which the dependent variable was the normally distributed continuous outcome variable of interest, and factors entered into the model included age, gender, body mass, and history of hypertension, diabetes, creatinine, and medication use, or exercise posture. For non-normally distributed variables entered into regression models, the assumption of normally distributed residuals was verified by Quantile plots, and no violations were observed.

Results

Subject characteristics

Patients with HFpEF ($n = 109$) and controls ($n = 73$) were assembled from cohorts 1 (n = 71, 25), 2 (n = 21, 29), and 3 (n = 17, 19). The vast majority (n = 100) of patients met recently proposed diagnostic criteria for HFpEF.[24] In the remaining nine HFpEF subjects, there was incomplete echocardiographic data limiting classification, though each of these patients had been previously hospitalized for pulmonary oedema that improved with diuresis. Compared with controls, HFpEF patients were older, heavier, and more likely to display co-morbidities and receive treatment with antihypertensives and diuretics (*Table 1*). Levels of BNP were higher in HFpEF patients compared with controls, whereas haemoglobin and estimated glomerular filtration rate were lower. LV chamber size was similar in HFpEF patients and

Table 1 Baseline characteristics

	Control ($n = 73$)	HFpEF ($n = 109$)	*P*-value
Clinical characteristics			
Age (years)	59 ± 14	67 ± 11	<0.0001
Female (%)	75	72	0.6
Body mass index (kg/m^2)	29.1 ± 5.5	33.2 ± 7.0	<0.0001
Body surface area (m^2)	1.95 ± 0.26	2.08 ± 0.29	0.002
Hypertension (%)	64	82	0.009
Diabetes (%)	16	33	0.01
Beta-blockers (%)	33	61	0.0003
Diuretics (%)	18	69	<0.0001
Haemoglobin (g/dL)	13.1 ± 1.7	12.4 ± 1.5	0.006
Estimated GFR (mL/min/1.73 m^2)	67 ± 20	55 ± 18	0.0001
BNP (pg/mL)	36 (15, 71)	112 (49, 207)	<0.0001
LV morphology and function			
LV end-diastolic volume (mL)	117 ± 25	115 ± 33	0.6
LV end-systolic volume (mL)	41 ± 14	38 ± 15	0.3
LV mass (g/height$^{2.7}$)	45 ± 15	51 ± 18	0.015
Left atrial volume (mL)	59 ± 15	93 ± 29	<0.0001
Left atrial volume index (mL/m^2)	30 ± 7	45 ± 13	<0.0001
LVEF (%)	63 ± 8	65 ± 7	0.09
E/A ratio	1.0 ± 0.3	1.3 ± 0.8	0.006
E' (cm/s)	7 ± 4	7 ± 3	0.9
E/E' ratio	11 ± 5	14 ± 8	0.004
Resting haemodynamics			
Heart rate (b.p.m.)	71 ± 11	69 ± 10	0.4
Systolic blood pressure (mmHg)	138 ± 21	141 ± 24	0.5
Mean blood pressure (mmHg)	98 ± 15	95 ± 15	0.2
Pulse pressure (mmHg)	60 ± 14	70 ± 21	0.0009
Systemic O_2 content (mL/dL)[a]	16.4 ± 1.6	15.6 ± 2.1	0.11
PA O_2 content (mL/dL)[a]	12.6 ± 1.5	11.3 ± 1.7	0.001
Right atrial pressure (mmHg)[a]	4 ± 2	9 ± 4	<0.0001
PA systolic pressure (mmHg)[a]	26 ± 6	39 ± 11	<0.0001
Mean PA pressure (mmHg)[a]	16 ± 4	25 ± 7	<0.0001
PCWP (mmHg)[a]	9 ± 3	16 ± 6	<0.0001
Cardiac output (L/min)	5.4 ± 1.4	5.4 ± 1.7	0.9
Cardiac index (L/min/m^2)	2.8 ± 0.7	2.6 ± 0.8	0.2
PVR (mmHg/L/min)[a]	1.2 ± 0.7	2.0 ± 1.3	0.008
Ea (mmHg/mL)	1.7 ± 0.4	1.8 ± 0.6	0.4

Data are reported as mean ± standard deviation, percentage of population, or median (25th, 75th interquartile range where appropriate.
E', mitral valve inflow tissue velocity; E/A, early to late mitral valve inflow velocity; GFR, glomerular filtration rate (Modified Diet in Renal Disease equation); HFpEF, heart failure with preserved ejection fraction; PA, pulmonary artery; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.
[a]Data only available for Cohort 1 population ($n = 71$ HFpEF and 25 controls).

controls, while LV mass, left atrial volume, and E/e' ratio were greater in HFpEF patients.

Baseline haemodynamics

Resting HR, BP, CO, and Ea were similar in HFpEF patients and controls (*Table 1*). Pulmonary artery O_2 content was lower in those with HFpEF, suggesting relative inadequacy of O_2 delivery compared with controls. Pulse pressure was higher in HFpEF patients, consistent with greater systemic arterial stiffening. Right and left heart filling pressures, PAPs, and PVR were higher in HFpEF patients than in controls.

Exercise performance

Resting VO_2 was similar in HFpEF patients and controls, but when scaled to weight, resting VO_2 was lower in those with HFpEF (*Table 2*). Compared with controls, HFpEF patients achieved lower peak workload, reduced peak VO_2, and less increase in VO_2 during exercise. Each of these differences persisted after

Table 2 Exercise responses

	Control ($n = 73$)	HFpEF ($n = 109$)	*P*-value
Exercise performance			
Peak workload (W)	80 ± 30	40 ± 20	<0.0001
Resting VO_2 (mL/min)	261 ± 65	249 ± 78	0.3
Resting VO_2 (mL/kg/min)	3.26 ± 0.63	2.72 ± 0.68	<0.0001
Exercise VO_2 (mL/min)	1269 ± 395	899 ± 312	<0.0001
Exercise VO_2 (mL/kg/min)	15.7 ± 4.2	9.8 ± 3.0	<0.0001
ΔVO_2 (mL/min)	+1008 ± 354	+651 ± 272	<0.0001
ΔVO_2 (mL/kg/min)	+12.5 ± 3.9	+7.1 ± 2.8	<0.0001
Exercise systemic O_2 content (mL/dL)[a]	17.0 ± 1.6	16.2 ± 2.1	0.11
Exercise PA O_2 content (mL/dL)[a]	8.4 ± 1.9	6.9 ± 2.1	0.003
Resting AVO_2diff (mL/dL)	5.1 ± 1.8	4.8 ± 1.3	0.2
Exercise AVO_2diff (mL/dL)	10.1 ± 2.8	9.9 ± 3.2	0.7
ΔAVO_2diff (mL/dL)	+5.0 ± 1.8	+5.2 ± 2.5	0.6
Peak exercise haemodynamics			
Heart rate (b.p.m.)	128 ± 23	101 ± 20	<0.0001
Systolic BP (mmHg)	183 ± 34	166 ± 34	0.001
Mean BP (mmHg)	122 ± 22	112 ± 22	0.005
PA systolic pressure (mmHg)[a]	41 ± 9	68 ± 13	<0.0001
Mean PA pressure (mmHg)[a]	26 ± 6	46 ± 9	<0.0001
PCWP (mmHg)[a]	14 ± 4	33 ± 8	<0.0001
Cardiac output (L/min)	12.5 ± 2.8	9.2 ± 2.8	<0.0001
Cardiac index (L/min/m^2)	6.4 ± 1.3	4.4 ± 1.2	<0.0001
PVR (mmHg/L/min)[a]	1.0 ± 0.4	1.5 ± 1.1	<0.05
Ea (mmHg/mL)	1.7 ± 0.5	1.8 ± 0.7	0.8
Integrated changes with exercise			
ΔAVO_2diff/ΔVO_2 (min/dL)	+5.5 ± 2.0	+8.9 ± 3.4	<0.0001
$\Delta CO/\Delta VO_2$ (L blood/L O_2)	+7.4 ± 2.6	+5.9 ± 2.5	0.0005

Data are reported as mean ± standard deviation.
AVO_2diff, arterial–venous oxygen difference; BP, blood pressure; CO, cardiac output; Ea, arterial elastance; HFpEF, heart failure with preserved ejection fracttion; PA, pulmonary artery; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance, VO_2, volume of oxygen consumed.
[a]Data only available for Cohort 1 population ($n = 71$ HFpEF and 25 controls).

adjusting for age, body mass index (BMI), hypertension, diabetes, glomerular filtration rate, haemoglobin, vasodilator use, and beta-blocker use. Exercise systemic O_2 content was similar in HFpEF patients and controls, while pulmonary artery O_2 content was lower in those with HFpEF. No difference between the groups was observed in resting, peak exercise, or absolute exercise change in AVO_2diff.

Exercise haemodynamics

Compared with controls, HFpEF subjects demonstrated less increase in HR, BP, SV, EF, and CO with exercise (*Table 2*, *Figure 1*). Depressed EF reserve was due to lesser reduction in LV end-systolic volume in HFpEF patients, as changes in end-diastolic volume were similar in HFpEF patients and controls. Right and left heart filling pressures and PAPs with exercise were higher in those with HFpEF than in controls. Each of these differences persisted after adjusting for age, BMI, hypertension, diabetes, glomerular filtration rate, haemoglobin, vasodilator use, and beta-blocker use. Pulmonary hypertension in HFpEF patients was predominantly due to high PCWP, as PVR reductions with exercise were similar in HFpEF patients and controls (−0.5 ± 1.0 vs. −0.2 ± 0.7 mmHg/L/min, $P = 0.3$). Exercise Ea and changes in Ea were similar between HFpEF patients and controls.

Integrated responses

Depressed CO reserve in HFpEF patients could be caused by the lower absolute workload achieved or by cardiac limitation. To distinguish between these possibilities, the enhancement in CO relative to VO_2 was then analysed, identifying CO limitation as the primary culprit in HFpEF on average (*Figure 2A* and *B*). This is reflected by a significantly lower $\Delta CO/\Delta VO_2$ slope in HFpEF patients compared with controls (5.9 ± 2.5 vs. 7.4 ± 2.6, $P = 0.0005$; *Table 2*). Enhancement of CO with exercise was also reduced in HFpEF patients for any change in LV filling pressure (PCWP) or LV end-diastolic volume (*Figure 3A* and *B*). The $\Delta CO/\Delta VO_2$ relationships were similar in HFpEF subjects treated or not treated with beta-blockers (5.6 ± 2.4 vs. 6.3 ± 2.6, $P = 0.2$). In contrast to VO_2, scaling ΔCO to external work

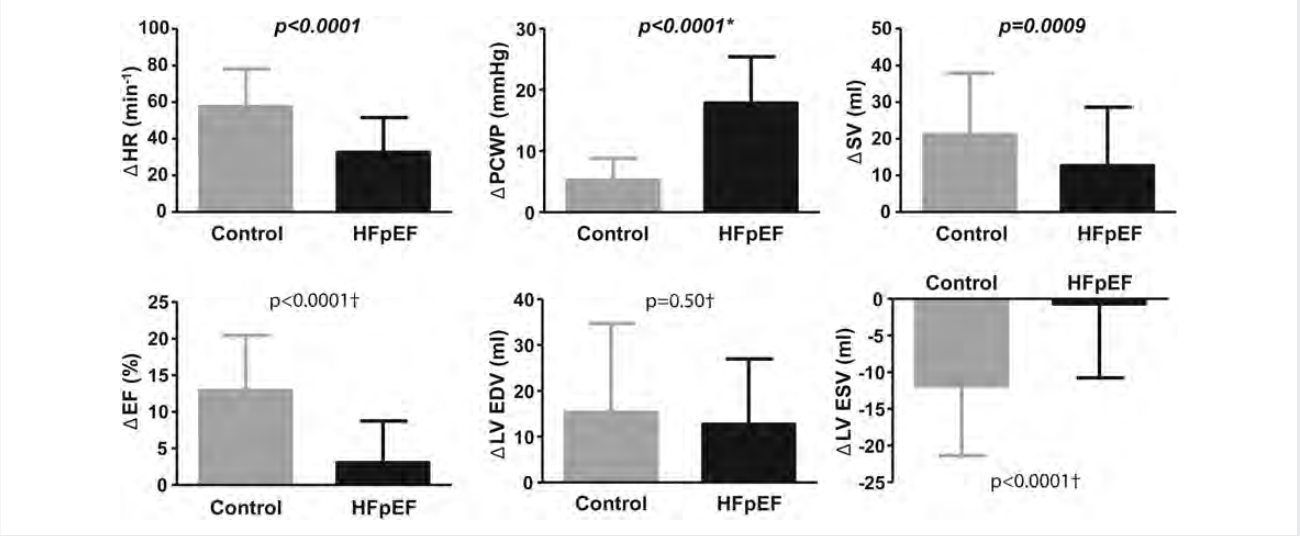

Figure 1 Haemodynamic changes with exercise in heart failure with preserved ejection fraction (HFpEF; black) compared with controls (grey). *Data available only for cohort 1 ($n = 71$ HFpEF and 25 controls); †Data available only for cohorts 2 and 3 ($n = 38$ HFpEF and 48 controls). EDV, end-diastolic volume; HR, heart rate; SV, stroke volume.

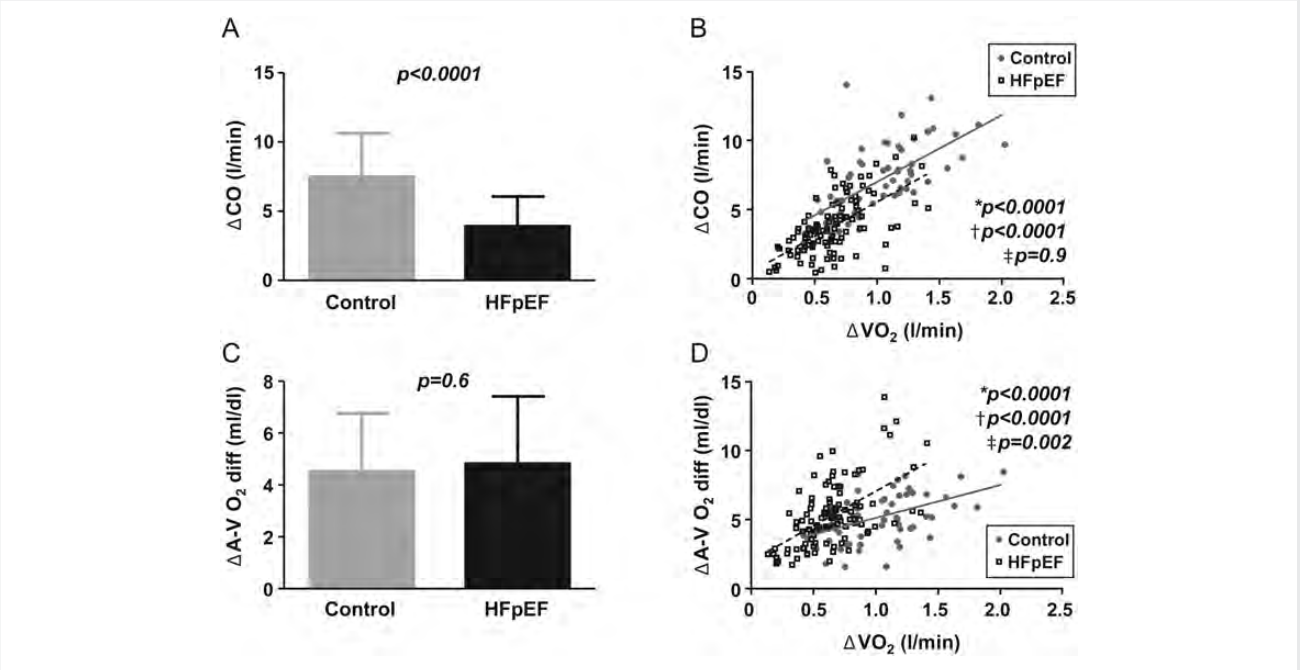

Figure 2 (*A* and *B*) Absolute increases in cardiac output (ΔCO) and ΔCO as a function of metabolic requirements (ΔVO_2) were impaired in heart failure with preserved ejection fraction (HFpEF; boxes–dashed line) compared with controls (circles–solid line). (*C*) Absolute increases in arterial–venous oxygen extraction (ΔAVO_2diff) were similar at peak exercise, although O_2 extraction relative to O_2 consumption was greater in HFpEF (*D*). *P*-values refer to *bivariate comparisons, †HFpEF vs. control, and ‡interaction terms.

performed (in Watts) did not reveal a difference in HFpEF patients and controls overall or when substratified into lower and higher VO_2 categories (Supplementary material, *Table S2*).

While absolute changes in oxygen extraction (AVO_2diff) at peak exercise were similar in HFpEF patients and controls (*Table 2*, *Figure 2C*), HFpEF subjects relied on a greater increase in AVO_2diff for any absolute change in VO_2 (*Figure 2D*). The increase in O_2 extraction relative to O_2 consumption (ΔAVO_2diff/ΔVO_2 slope) was thus greater in HFpEF patients compared with controls (8.9 ± 3.4 vs, 5.5 ± 2.0 min/dL, $P < 0.0001$). Diabetics had higher

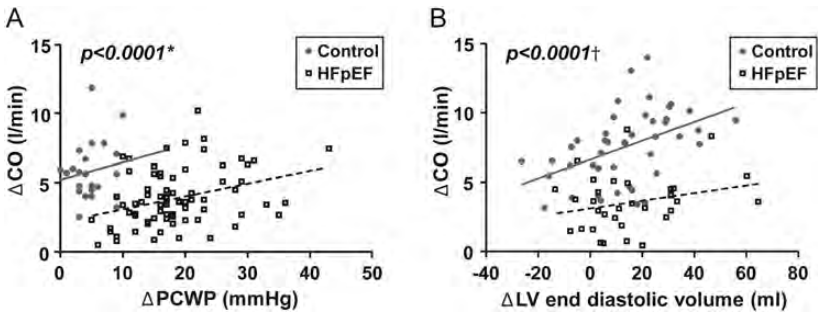

Figure 3 (*A*) Exercise increases in cardiac output (ΔCO) were impaired in heart failure with preserved ejection fraction (HFpEF; boxes–dashed line) compared with controls (circles–solid line) for any change in pulmonary capillary wedge pressure (ΔPCWP) or (*B*) LV end-diastolic volume. *Data available only for cohort 1 ($n = 71$ HFpEF and 25 controls); †Data available only for cohorts 2 and 3 ($n = 38$ HFpEF and 48 controls).

resting AVO_2diff ($P = 0.04$), but changes in AVO_2diff with exercise were not different from those of non-diabetics. There were no differences in AVO_2diff at rest or with exercise in the hypertensive and obese subgroups.

Importantly, these differences in $\Delta CO/\Delta VO_2$ and $\Delta AVO_2diff/\Delta VO_2$ in HFpEF patients and controls were consistently observed when cohorts 1–3 were analysed separately rather than together (*Table 3*). Thus, regardless of body position during exercise, or method used to measure CO, the increase in CO was on average consistently impaired in those eith HFpEF, relative to metabolic demand. These differences persisted after adjusting for age, BMI, hypertension, diabetes, glomerular filtration rate, haemoglobin, vasodilator use, and beta-blocker use.

Impact of body position

Compared with supine ergometry, upright exercise was associated with greater increases in VO_2, CO, AVO_2diff, HR, and BP (Supplementary material, *Table S3*). However, in multivariable regression analysis including exercise position in the model, HFpEF subjects continued to display highly significant impairments in the exercise augmentation in HR, SV, BP, CO, VO_2, and $\Delta CO/\Delta VO_2$, with greater $\Delta AVO_2diff/\Delta VO_2$ (Supplementary material, *Table S3*). Significant group × position interactions were observed for exercise increases in CO and BP, where HFpEF patients displayed the smallest increases compared with controls during upright exercise.

Discussion

This study assessed haemodynamic responses to exercise in order to determine how cardiac filling and ejection capacity affect oxygen delivery and extraction to mediate exercise limitation (reduced VO_2) in patients with HFpEF. We demonstrate that compared with controls, the increase in CO relative to metabolic requirements (VO_2) is fundamentally impaired in HFpEF. CO reserve limitation in HFpEF was coupled to impairments in LV contractile and chronotropic reserve. Increases in LV preload (end-diastolic volume) during exercise were similar in HFpEF patients and controls, but similar preload recruitment in those with HFpEF required three-fold greater increases in LV filling pressures (PCWP), causing secondary elevation in PAP, which may impair right ventricular ejection and further contribute to blunted CO reserve. Increases in AVO_2diff at peak exercise were similar in HFpEF patients and controls, but increases relative to absolute O_2 consumption were enhanced in those with HFpEF, suggesting peripheral adaptation to the impairment in O_2 delivery (CO reserve). These findings were consistently observed during both supine and upright exercise and employing both invasive and non-invasive modalities to assess CO, indicating that in addition to abnormalities in LV diastolic filling, impairments in CO reserve with stress contribute to the impairment in oxygen consumption in patients with HFpEF.

Cardiac output and peak VO_2 in heart failure with preserved ejection fraction

Functional capacity (peak VO_2) is similarly impaired in HFpEF and HFrEF.[9] Peak VO_2 is an integrated measure of cardiac reserve that is being used to diagnose HFpEF[25] and as an endpoint in clinical trials.[26–28] Thus, better characterization of the fundamental mechanisms underlying VO_2 limitation in HFpEF is essential for improved understanding of pathophysiological mechanisms and to better inform future trial design and identify therapeutic targets.

Most studies have reported that exercise VO_2 and CO are individually depressed in HFpEF.[10,12,15–20,23,29,30] However, VO_2 and CO at any time during exercise are largely determined by the intensity of work being performed.[4] Thus, group differences in CO might be caused by cardiac limitations or non-cardiovascular factors including patient motivation, peripheral limitations, fitness, or orthopaedic issues. Elevation in cardiac filling pressures (at rest or with stress) is the most conspicuous and consistently observed haemodynamic feature in HFpEF.[17] Non-diastolic limitations have been reported,[12,15,16,19,23,29,30] but their roles have been questioned.[22] Impaired exercise reserve responses in non-diastolic parameters (e.g. HR or contractile response) may not be causal of exercise intolerance, but rather consequence of premature cessation of exercise in response to dyspnoea from high filling pressures,[18] abnormal metabolic–neural signalling,[31,32] or non-cardiac factors such as deconditioning or obesity.[11,14] Indeed, textbooks

Table 3 Uniformity of results across cohorts

	Cohort 1 (n = 96)		Cohort 2 (n = 50)		Cohort 3 (n = 36)	
	Control (n = 25)	HFpEF (n = 71)	Control (n = 29)	HFpEF (n = 21)	Control (n = 19)	HFpEF (n = 17)
Peak VO_2 (mL/min)	996 ± 280	823 ± 268*	1492 ± 365	1168 ± 279*	1215 ± 352	863 ± 343*
ΔVO_2 (mL/min)	+781 ± 260	+596 ± 233*	+1203 ± 335	+867 ± 268*	+937 ± 304	+598 ± 299*
Peak CO (L/min)	11.5 ± 2.5	9.1 ± 2.8*	12.5 ± 3.1	9.1 ± 2.5*	13.4 ± 2.6	9.5 ± 2.9*
ΔCO (L/min)	+5.9 ± 2.2	+3.8 ± 2.1*	+8.1 ± 2.4	+4.3 ± 2.1*	+6.9 ± 2.9	+3.0 ± 1.8*
Peak CI (L/min/m^2)	6.0 ± 1.0	4.4 ± 1.1*	6.8 ± 1.5	4.5 ± 1.5*	6.3 ± 1.3	4.5 ± 1.2*
ΔCI (L/min/m^2)	+3.0 ± 1.0	+1.8 ± 0.9*	+3.5 ± 1.7	+1.4 ± 0.8*	+4.1 ± 1.0	+2.1 ± 1.0*
Peak AVO_2diff (mL/dL)	8.4 ± 1.8	9.1 ± 2.3	12.4 ± 2.2	13.2 ± 3.6	9.2 ± 2.4	9.6 ± 3.9
ΔAVO_2diff (mL/dL)	+4.6 ± 1.5	+4.7 ± 2.0	+5.5 ± 1.8	+6.9 ± 3.1	+4.8 ± 2.0	+5.4 ± 3.1
Δ$CO/\Delta VO_2$ (L blood/L O_2)	7.6 ± 1.8	6.3 ± 2.4*	6.6 ± 1.5	5.0 ± 1.9*	8.3 ± 4.3	5.3 ± 3.0*
Δ$AVO_2/\Delta VO_2$ (min/dL)	6.5 ± 1.8	8.9 ± 3.4*	4.7 ± 1.8	8.2 ± 2.7*	5.3 ± 2.2	9.4 ± 4.1*

AVO_2diff, arterial–venous oxygen difference; CI, cardiac index; CO, cardiac output; HFpEF, heart failure with preserved ejection fraction; VO_2, oxygen consumption.
*$P < 0.05$ vs control.
Cardiac output reserve impairment in HFpEF

of exercise physiology describe how patients with HFrEF are limited by inadequate CO reserve with exercise, whereas patients with HFpEF have normal CO responses but elevated filling pressures.[33] It has even been questioned whether HFpEF truly represents a form of cardiac failure, since patients are frequently elderly with co-morbidities that might in themselves produce symptoms of effort intolerance that are not directly attributable to cardiac dysfunction.[21]

The current data provide compelling evidence that the reduction in exercise capacity in HFpEF is determined largely by inadequate CO reserve, which, when combined with stress-induced elevations in cardiac filling pressures,[10,13,16,17,20] markedly limits exercise capacity. The strength of this experimental approach lies in the simultaneous assessment of both whole-body O_2 delivery (CO) and O_2 consumption (VO_2). Because increases in CO during exercise are ultimately driven by increases in VO_2,[5,6] this analysis allows for direct comparisons of exercise responses between patients with HFpEF and controls, without the need to adjust for measures of effort adequacy (such as the respiratory exchange ratio) that are necessary to gauge metabolic status when CO is not directly measured. Intriguingly, scaling CO reserve to external work failed to reveal the cardiac limitation in HFpEF, suggesting that this index is less sensitive to haemodynamic impairments in HFpEF.

The relationship between CO and VO_2 is typically depressed in patients with HFrEF,[2] in keeping with the definition of HF as an inability to pump blood adequately to the body at normal filling pressures.[1] However, only one previous study has examined the relationship between CO and VO_2 in HFpEF.[18] Bhella and colleagues found that peak VO_2 and CO were reduced in HFpEF, similar to the current data, but, when plotting CO relative to VO_2, the authors surprisingly found that the enhancement in CO was elevated in HFpEF. The authors speculated that abnormalities in skeletal muscle might generate metabolic signals that drive excessive increases in CO, leading to increased ventricular filling pressures during exercise in HFpEF.[18]

The current data argue against this hypothesis, showing that on average the increase in CO relative to VO_2 was impaired in HFpEF. The reasons for the discordant findings are not obvious, although it is notable that the SV enhancement during exercise in HFpEF patients noted by Bhella *et al.* (+74% increase) was remarkably high, and well in excess of the +16% increase noted in the current study and the −7 to +10% changes with exercise reported by other groups.[16,23,29,30] Secondly, Bhella and colleagues found that the resting VO_2 was elevated in the HFpEF patients—suggesting a hypermetabolic state. In contrast, in the current study, the resting O_2 consumption (scaled to body mass) was lower in HFpEF. These differences may relate to changes in metabolism reflecting variability in HF severity or chronicity between the two study populations.

Determinants of cardiac output limitation

Cardiac output reserve limitation in HFpEF was related to impaired SV and HR, similar to previous studies,[10,12,15–17,19,23,29,30] Inadequate SV (and EF) reserve was due to an inability to reduce LV end-systolic volume with exercise, since end-diastolic volume increased similarly in HFpEF patients and controls. Impaired

reduction in end-systolic volume could be caused by inadequate enhancement in contractility, blunted afterload reduction, or both. Previous studies have reported attenuated reductions in systemic vascular resistance (SVR) during exercise in HFpEF patients.[12,29,30] In this study, effective arterial elastance (Ea), which characterizes total (resistive and pulsatile) arterial afterload, changed similarly in HFpEF patients and controls. This finding may appear at odds with previous studies showing increased arterial stiffness and impaired flow-mediated dilation in HFpEF.[12,15,29] However, it is also known that Ea varies directly with HR, in addition to SVR.[3] Because HR was ~30% higher at peak exercise in controls, this would inflate the exercise Ea value in this group, even if other components of afterload were lower. The similar change in Ea observed during exercise in the current study suggests that the blunted SV and EF responses with exercise in HFpEF patients were caused primarily by limitations in contractile reserve.

Enhancement in LV end-diastolic volume was similar in HFpEF patients and controls, though diastolic reserve was clearly impaired, as evidenced by the three-fold greater elevation in PCWP in HFpEF patients. It is currently unknown if mitigation of PCWP elevation in HFpEF would directly improve aerobic capacity, though a recent trial found that exercise training was associated with a reduced resting E/e' ratio (a marker of PCWP), and the extent of resting E/e' improvement was correlated with the improvement in peak VO_2.[27] Elevation in LV diastolic pressure is often considered to limit exercise capacity by provoking dyspnoea, yet it is notable that PCWP increases during exercise in patients with HFpEF were associated with dramatic elevations in PAPs, increasing right ventricular afterload. Given the well-described impact of right ventricular dysfunction on exercise capacity in HFrEF,[35] the enhanced load sensitivity of the right ventricle,[36] and the deleterious impact of increased PCWP on pulsatile right ventricular load,[37] it is likely that PCWP elevation from diastolic dysfunction in HFpEF has additional implications for right ventricular reserve that may also limit CO responses to exercise.

Arterial–venous oxygen extraction reserve

The Fick equation dictates that VO_2 is equal to the product of CO and AVO_2diff, and patients with HF may display reduced peak VO_2 that is related to abnormalities in the latter, the former, or both.[18,19,38] We found that AVO_2diff at peak exercise was not different between HFpEF patients and controls, though the increase in AVO_2diff as a function of VO_2 (ΔAVO_2 difference/ΔVO_2 slope) was enhanced in those with HFpEF. We speculate that this functions to compensate partly for inadequate O_2 delivery from CO reserve impairment at submaximal workloads in HFpEF.

The similar increase in peak exercise AVO_2diff in cases and controls is similar to recent findings from Maeder and colleagues,[16] but differs from two recent reports showing reduced AVO_2diff at peak exercise in HFpEF patients.[18,19] These discrepancies may relate to the populations studied and different analytical approaches. The latter studies enrolled disease-free controls, as opposed to the current study that included controls with co-morbidities that might influence O_2 extraction. Haykowsky *et al.* performed comparisons of AVO_2diff relative to workload (Watts) as opposed to VO_2. They also found that the oxygen uptake/work slope was attenuated in HFpEF, meaning that VO_2 was lower for any workload in HFpEF. Thus, the ΔAVO_2diff/ΔVO_2 slope in their HFpEF group might be expected to have been steeper if their data were examined according to VO_2.

When CO is reduced, circulation time is increased, which may provide greater time for gas diffusion at the capillaries and greater O_2 extraction.[39] Thus, our findings should not be taken to indicate that patients with HFpEF are more 'adept' at peripheral O_2 extraction, or that abnormalities in the periphery do not play key roles in limiting exercise capacity in HFpEF, as indicated in multiple recent studies.[2,18,19,38] Indeed, even with limited CO reserve, improvements in peripheral function may be attainable with interventions such as exercise training, probably related to the greater plasticity in the vasculature and skeletal muscle.[26,27,40] Future research may clarify whether clinical evaluation of both VO_2 and CO reserve will allow for more refined insight as to whether limitations in a specific patient are due predominantly to cardiac or peripheral factors, possibly to better tailor therapy.[4]

Limitations

Patients with HFpEF and control subjects were drawn from three cohorts, two prospectively enrolled and one retrospective. Cohort 1 was a cath lab referral population, introducing potential bias. The protocols and methods to measure CO were different. However, all are well established, and the finding of impaired CO reserve relative to VO_2 was uniformly and consistently observed in both upright and supine exercise when analysed separately and taking into account body position (*Table 3*; Supplementary material, *Table S3*). Cardiac pressure and volume were not measured simultaneously during exercise and in the same patient, but pressure and volume data in the three cohorts were included to provide insight into the mechanisms for CO limitation in HFpEF. Importantly, the primary endpoints (CO and VO_2) were directly measured at rest and during exercise in all subjects. Baseline differences were present, including greater age, adiposity, beta-blocker use, and creatinine in those with HFpEF. However, all group differences remained highly significant after adjusting for each of these baseline differences. Subjective symptoms (dyspnoea, fatigue) were not quantified, and many subjects did not exercise to their ideal maximum capacity, particularly during supine ergometry, where peak HR and VO_2 were lower. However, attainment of true maximal objective exercise workload is not necessary in this analysis, because adequacy of CO reserve was evaluated by scaling it to the physiological variable that drives it (VO_2). This study did not assess for the development of mitral regurgitation during exercise, which may also contribute to impaired CO reserve and exertional pulmonary hypertension in HFpEF.[29] Not all HFpEF subjects were taking chronic diuretics (69%), but this prevalence is similar to other studies of compensated HFpEF outpatients.[19]

Conclusions

The reduction in oxygen consumption during exercise in patients with HFpEF is determined predominantly by inadequate CO to the body relative to metabolic requirements. These data suggest that in addition to therapies targeting elevation in cardiac filling

pressures, treatments designed to enhance CO responses with stress may prove beneficial to improve exercise capacity and outcomes in HFpEF.

Supplementary material

Supplementary material is available at *European Journal of Heart Failure* online.

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