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Global Cardiovascular Reserve Dysfunction in Heart Failure With Preserved Ejection Fraction

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Objectives The purpose of this study was to comprehensively examine cardiovascular reserve function with exercise in patients with heart failure and preserved ejection fraction (HFpEF).

Background Optimal exercise performance requires an integrated physiologic response, with coordinated increases in heart rate, contractility, lusitropy, arterial vasodilation, endothelial function, and venous return. Cardiac and vascular responses are coupled, and abnormalities in several components may interact to promote exertional intolerance in HFpEF.

Methods Subjects with HFpEF (n = 21), hypertension without heart failure (n = 19), and no cardiovascular disease (control, n = 10) were studied before and during exercise with characterization of cardiovascular reserve function by Doppler echocardiography, peripheral arterial tonometry, and gas exchange.

Results Exercise capacity and tolerance were reduced in HFpEF compared with hypertensive subjects and controls, with lower VO_2 and cardiac index at peak, and more severe dyspnea and fatigue at matched low-level workloads. Endothelial function was impaired in HFpEF and in hypertensive subjects as compared with controls. However, blunted exercise-induced increases in chronotropy, contractility, and vasodilation were unique to HFpEF and resulted in impaired dynamic ventricular-arterial coupling responses during exercise. Exercise capacity and symptoms of exertional intolerance were correlated with abnormalities in each component of cardiovascular reserve function, and HFpEF subjects were more likely to display multiple abnormalities in reserve.

Conclusions HFpEF is characterized by depressed reserve capacity involving multiple domains of cardiovascular function, which contribute in an integrated fashion to produce exercise limitation. Appreciation of the global nature of reserve dysfunction in HFpEF will better inform optimal design for future diagnostic and therapeutic strategies. (J Am Coll Cardiol 2010;56:845–54) © 2010 by the American College of Cardiology Foundation

Exercise intolerance is a defining symptom in patients with heart failure and preserved ejection fraction (HFpEF), yet its mechanisms remain poorly understood (1). Reductionist strategies to studying human disease are predicated on the concept that a single unifying process causes a specific disease phenotype. However, HFpEF is principally a disease of the elderly (2), and in geriatric medicine, it is more likely that multiple processes and age-related comorbidities coexist in the same patient (3). These processes interact synergistically to produce a clinical phenotype. Because exercise requires coordinated changes in ventricular function, arterial tone, endothelial function, venous return, and autonomic signaling, it would be expected that abnormalities in many such components exist and interact to promote subjective and objective exercise limitation in HFpEF (4,5).

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Accordingly, the present study sought to examine multiple components of exercise reserve responses in patients with HFpEF, including assessment of chronotropic, preload, contractile, endothelial and global vascular reserve functions, and importantly, ventricular-arterial coupling reserve responses. Because population-based studies have shown that patients with HFpEF are typically older, hypertensive, and female (2), and because each of these features may independently affect cardiovascular function, we compared reserve responses in HFpEF to a predominantly female, elderly hypertensive control group without HF, in addition to an apparently healthy control group free of cardiovascular disease.

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Abbreviations and Acronyms

BP = blood pressure
Ea = effective arterial elastance
Ees = end-systolic elastance
EF = ejection fraction
HFpEF = heart failure with preserved ejection fraction
HR = heart rate
HRR = heart rate reserve
LV = left ventricular
LVEDVI = left ventricular end-diastolic volume index
PAT = peripheral arterial tonometry
PRSW = pre-load recruitable stroke work
PWRI = peak left ventricular power index
RER = respiratory exchange ratio
RH = reactive hyperemia
RHI = reactive hyperemia index
SV = stroke volume
SVI = stroke volume index
SVRI = systemic vascular resistance index
VCO_2 = volume carbon dioxide produced
V_E = minute ventilation
VO_2 = volume oxygen consumption

Methods

Study population. Subjects with HFpEF (n = 21) confirmed by Framingham criteria (5) and EF >50% were studied in an outpatient, compensated state. Exclusion criteria included valvular or pericardial disease, infiltrative or hypertrophic cardiomyopathy, cor pulmonale, pulmonary disease, unstable coronary disease, atrial fibrillation, pregnancy, primary renal or hepatic disease, and inability to exercise or to suspend cardiovascular medicines. Hypertensive control subjects without HF (n = 19, defined by history of blood pressure >140/90 mm Hg and treatment with ≥1 antihypertensive medication) were identified from medical chart review and contacted for participation. Healthy controls without cardiovascular disease or diabetes mellitus (n = 10) were recruited by advertisement. Because population-based studies have shown that HFpEF patients are predominantly older and female (2), we sought to enroll controls with similar demographics during screening. The study was approved by the Mayo institutional review board. The authors had access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Study design. Cardiovascular medicines were withheld for 24 h before study. Subjects were studied in a compensated, fasting state in a quiet, temperature-controlled room (21°C). Transthoracic echo-Doppler/tissue Doppler study acquired at rest and during the final 1.5 min of each 3-min graded exercise stage (GE Vivid 7, GE Healthcare, Chalfont St. Giles, United Kingdom). Endothelial function was measured using peripheral arterial tonometry (PAT). All data were interpreted off-line in a blinded fashion. Heart failure symptoms were assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ). Levels of B-type natriuretic peptide were assessed by enzymatic immunoassay (Beckman Instruments, Chaska, Minnesota). Glomerular filtration rate was estimated by the modified Cockroft-Gault formula. Daily dose of beta-blocker was expressed as units of metoprolol (total daily milligrams of metoprolol = atenolol × 2 = carvedilol × 4) (5). Brachial blood pressure (BP) was obtained by auscultation by a single investigator during rest and each stage of exercise. Mean BP (diastolic pressure plus pulse pressure divided by 3) and end-systolic BP (0.9 × systolic BP) were calculated as previously described (6).

Exercise metabolic performance. Subjects underwent maximal-effort upright cycle exercise testing starting at 20 W workload, increasing by 20 W every 3 min until exhaustion. Oxygen consumed (VO_2), carbon dioxide produced (VCO_2), minute ventilation (V_E), and respiratory exchange ratio (RER = VCO_2/VO_2) were measured (MedGraphics, St. Paul, Minnesota) throughout exercise to quantify exercise performance (5). Subjective symptoms of fatigue and dyspnea were recorded at each workload by the Borg effort score (6 to 20) and dyspnea score (0 to 10), where higher values indicate more severe symptoms (7).

Cardiovascular function and reserve analysis. Echo-Doppler measurements represent the mean of ≥3 beats. The left ventricular (LV) mass was obtained from 2-dimensional measurements of wall thickness and chamber dimension (8). The EF was determined from Simpson's biplane method (8). Stroke volume (SV) was determined from the LV outflow dimension and pulse-wave Doppler and was indexed to body surface area (SVI). Cardiac index was determined from the product of heart rate (HR) and SVI.

CHRONOTROPIC RESERVE. Heart rate reserve (HRR) was determined from continuous 12-lead electrocardiogram using standard formulas, with chronotropic incompetence is defined as HRR <0.8, or HRR <0.62 in subjects receiving beta-adrenergic antagonists (9).

PRE-LOAD AND PRE-LOAD RESERVE. The left ventricular end-diastolic volume index (LVEDVI) was determined from the quotient of SVI/EF (8,10). Resting transmitral flow velocities (E and A) and mitral annular tissue-Doppler velocities (E′ and A′) were measured to assess diastolic function. The E/E′ ratio was used to estimate filling pressures at rest (8). Doppler estimation of filling pressures with exercise was not performed.

CONTRACTILE FUNCTION AND RESERVE. Load-independent contractility was determined using 3 separate indexes: 1) peak power index (PWRI [determined from product of peak volumetric ejection rate from LV outflow Doppler and systolic BP, divided by EDV]) (10,11); 2) single-beat end-systolic elastance (Ees [determined from BP, SV, EF, and pre-ejection and systolic ejection time intervals from LV outflow Doppler]) (12); and 3) single-beat pre-load recruitable stroke work (PRSW [determined from SV, mean BP, LV mass, and EDV]) (13). The change in each parameter was used to characterize contractile reserve.

VASCULAR FUNCTION AND RESERVE. Ventricular afterload was measured by systemic vascular resistance (mean BP × 80/CO) and effective arterial elastance (Ea = ESP/SV)

(6,8) at rest, with the change in each during exercise used to characterize global arterial reserve.

ENDOTHELIAL FUNCTION. The PAT was measured using the EndoPAT 2000 system (Itamar-Medical, Caesarea, Israel). Endothelial function was quantified by the reactive hyperemic (RH) change in digital blood flow after arm occlusion (14,15). After 5 min of baseline recording, a BP cuff was inflated to supra-systolic pressure in the test arm. After 5 min of occlusion, the cuff was rapidly deflated, with PAT tracings recorded. The RH-PAT response was determined as the ratio of PAT amplitude in the test arm to control arm, averaged in 30-s intervals after cuff deflation, divided by the average PAT ratio measured for the 140-s interval before cuff inflation. The reactive hyperemia index (RHI) was determined as the RH-PAT ratio measured between 60 s and 120 s after occlusion. Endothelial dysfunction was defined categorically by RHI <2.0. The RHI was log-transformed for subsequent analysis (14).

Dynamic peripheral vasodilation was further assessed by changes in PAT amplitude responses during exercise (16). Mean PAT amplitudes were determined from 3 min recordings obtained at rest and at peak exercise after manually deleting motion artifacts. Exercise PAT responses were normalized to baseline PAT amplitude to create a dimensionless unit, and represent the average of both arms.

VENTRICULAR-VASCULAR COUPLING AND COUPLING RESERVE. Ventricular-arterial interaction was assessed by the coupling ratio (Ea/Ees) of arterial to ventricular systolic elastance (6).

Statistical analysis. Continuous variables are reported as mean ± SD. Between-group differences were compared by chi square, 1-way analysis of variance, or Wilcoxon rank-sum/Kruskal-Wallis tests. Normality was evaluated by the Shapiro-Wilk W test. Bonferroni correction was applied for multiple comparisons. The hyperemic changes in PAT amplitude between groups were compared by repeated measures analysis of variance assuming a quadratic relationship of PAT ratio over time. Linear regression was performed to test associations between reserve function, symptoms and exercise performance.

Results

Subject characteristics. Age, sex, race (all but 2 Caucasian), and renal function were similar in all groups, with controls and HFpEF being more obese than hypertensive subjects (Table 1). Coronary disease and diabetes mellitus were more common in HFpEF subjects. The B-type natriuretic peptide levels were higher and KCCQ scores lower (more symptomatic) with HFpEF. The HFpEF subjects were more likely to be receiving loop diuretics and lipid-lowering therapy. Other medication use was similar in HFpEF subjects and hypertensive subjects, including beta-blockers and mean dose of beta-blockers (not shown).

Resting cardiovascular function. The HR, BP, LVEDVI, contractility, ventricular-arterial coupling, and cardiac index were similar across groups at rest (Table 1). The E/E′ was higher in HFpEF subjects, consistent with diastolic dysfunction. Global vascular function (Ea and SVRI) was not different between groups. However, the hyperemic increase in PAT amplitude after cuff occlusion was blunted in HFpEF and hypertensive subjects compared with controls, consistent with depressed endothelium-dependent vasodilation (Fig. 1). Mean RHI was lower in HFpEF and hypertensive subjects compared with controls, but similar in HFpEF and hypertensive subjects (Table 1). The prevalence of endothelial dysfunction was 42% in HFpEF subjects ($p < 0.05$ vs. control; p = NS vs. hypertension), 28% in hypertensive subjects ($p = 0.056$ vs. control), and 0% in controls.

Exercise performance. Exercise time, peak workload, VO_2 at ventilatory threshold, peak VO_2, and percent predicted peak VO_2 were all impaired in HFpEF subjects compared with control and hypertensive subjects, whereas the latter groups were similar (Table 2). Borg effort and dyspnea scores in HFpEF were higher at matched submaximal workload (20 W), indicating greater perceived difficulty with exercise. At peak, Borg scores were similar in HFpEF subjects, hypertensive subjects, and controls, consistent with maximal subjective effort in all groups. Peak RER tended to be lower in HFpEF subjects, though excluding the subjects who failed to attain a peak RER >1.0 did not affect the differences observed in any parameters (not shown).

Reserve responses at matched low-level (20 W) exercise.

CHRONOTROPIC RESERVE. HR increased in HFpEF subjects (+23 ± 6 beats/min, $p < 0.0001$), hypertensive subjects (+23 ± 10 beats/min, $p < 0.0001$), and controls (+26 ± 8 beats/min, $p < 0.0001$), with no between-group difference ($p > 0.2$).

PRE-LOAD RESERVE. The LVEDVI increased in HFpEF subjects (+6 ± 9 ml/m^2), hypertensive subjects (+5 ± 7 ml/m^2), and controls (+11 ± 9 ml/m^2; $p < 0.0001$ for all), with no between-group difference ($p > 0.2$).

CONTRACTILE RESERVE. The increase in contractility assessed by Ees, PRSW, and PWRI was 65% to 85% lower in HFpEF subjects compared with hypertensive and normal controls (Fig. 2). The LVESVI failed to drop in HFpEF subjects (+2 ± 7 ml/m^2) in comparison with hypertensive and healthy controls (−6 ± 5 ml/m^2 and −5 ± 5 ml/m^2, respectively; both $p < 0.05$ compared with HFpEF subjects).

VASCULAR FUNCTION AND RESERVE. Vasodilation was attenuated in HFpEF subjects, with less reduction in SVRI and Ea compared with hypertensive and normal controls (Fig. 2).

VENTRICULAR VASCULAR COUPLING RESERVE. The combination of blunted increases in contractility and impaired vasodilation in HFpEF patients was associated with impaired ventricular-arterial coupling, with less reduction in the Ea/Ees ratio (Fig. 2) and less increase EF (+0 ± 8%

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Table 1 Clinical Characteristics and Resting Cardiovascular Function

	Control (n = 10)	Hypertension (n = 19)	HFpEF (n = 21)	p Value
Clinical characteristics				
Age, yrs	62 ± 7	65 ± 11	67 ± 11	0.4
Sex, female	70	74	76	0.9
Body mass index, kg/m^2	31.2 ± 7.9	28.3 ± 3.0	34.3 ± 6.6*	0.004
KCCQ score	99 ± 4	94 ± 16	69 ± 18*†	<0.001
Hypertension	0	100†	86†	<0.001
Coronary artery disease	0	11	33†	0.02
Diabetes mellitus	0	5	43*†	0.003
Smoking	0	0	9	0.2
GFR, ml/min	87 ± 17	81 ± 20	81 ± 38	0.9
Plasma BNP, pg/ml	38 ± 40	60 ± 50	152 ± 106*†	0.001
Hemoglobin, g/dl	13.0 ± 2.2	14.2 ± 1.5	13.0 ± 1.3	0.06
Beta-blockers	0	42†	57†	<0.001
ACEI or ARB	0	53†	67†	<0.001
Loop diuretic	0	0	57*†	<0.001
Lipid lowering	40	63	90†	0.009
LV mass index, mg/m^2	68.2 ± 19.8	90.7 ± 21.8	88.0 ± 27.1	<0.05
Resting function				
Heart rate, beats/min	70 ± 8	71 ± 12	68 ± 12	0.9
Pre-load				
LVEDVI, ml/m^2	54 ± 8	59 ± 12	58 ± 19	0.6
E/E′ ratio	12 ± 4	12 ± 5	20 ± 7*†	0.003
Contractility				
PWRI, mm Hg/s	330 ± 80	348 ± 59	339 ± 69	0.8
PRSW, g/cm^2	79 ± 19	77 ± 19	81 ± 40	0.9
Ees, mm Hg/ml	1.48 ± 0.38	1.72 ± 0.38	1.79 ± 0.76	0.4
Vascular function				
Systolic BP, mm Hg	123 ± 16	136 ± 12	131 ± 21	0.2
Ea, mm Hg/ml	1.88 ± 0.40	1.97 ± 0.51	1.77 ± 0.62	0.3
SVRI, dyne·m^2/s·cm^{-5}	3,430 ± 920	3,430 ± 750	3,100 ± 880	0.4
Log RHI	1.33 ± 0.34	0.92 ± 0.38†	0.85 ± 0.42†	0.009
Endothelial dysfunction	0	28	42†	0.016
Ventricular arterial coupling				
Coupling ratio, Ea/Ees	1.32 ± 0.34	1.16 ± 0.24	1.08 ± 0.35	0.2
Ejection fraction, %	58 ± 7	58 ± 5	60 ± 6	0.5
Cardiac index, l/min·m^2	2.2 ± 0.5	2.4 ± 0.6	2.3 ± 0.6	0.7

Values are mean ± SD or %. Final column reflects overall group analysis of variance (ANOVA) or chi square. For between-group comparisons: *$p < 0.05$ versus hypertension; †$p < 0.05$ versus control (ANOVA after Bonferroni).

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin-receptor blockers; BNP = B-type natriuretic peptide; BP = blood pressure; Ea = arterial elastance; Ees = left ventricular end-systolic elastance; GFR = glomerular filtration rate; HFpEF = heart failure with preserved ejection fraction; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEDVI = left ventricular end-diastolic volume index; PRSW = left ventricular pre-load recruitable stroke work; PWRI = peak left ventricular power index; RHI = reactive hyperemia index; SVRI = systemic vascular resistance index.

in HFpEF vs. +14 ± 7% in controls and +13 ± 6% in hypertensive subjects, $p < 0.0001$). Augmentation in cardiac index at 20W was lower in HFpEF subjects (+1.1 ± 0.4 l/min × m^2) than in controls (+2.2 ± 0.9 l/min × m^2, $p < 0.001$) and hypertensive subjects (vs. +1.8 ± 0.7 l/min × m^2, $p = 0.002$).

Reserve responses at peak exercise. CHRONOTROPIC RESERVE. Peak HR was reduced in HFpEF subjects compared with both control and hypertensive subjects (Table 3). The HRR was lower in HFpEF subjects (56 ± 17%) compared with hypertensive subjects (79 ± 20%, $p < 0.001$) and controls (93 ± 17%, $p < 0.0001$), even after adjusting for chronic beta-blocker use. Among HFpEF subjects with peak RER >1.0, the prevalence of chronotropic incompetence was 57%.

PRE-LOAD RESERVE. The EDVI tended to increase more in controls, but this was not significant ($p = 0.2$).

CONTRACTILE RESERVE. Increases in contractility at peak exercise were ~65% lower in HFpEF subjects compared with hypertensive subjects and controls for each load-independent measure ($p < 0.001$). Peak exercise reduction in ESVI was impaired in HFpEF subjects.

VASCULAR RESERVE. Exercise reduction in SVRI and augmentation in peripheral blood flow (PAT amplitude) were both blunted in HFpEF subjects compared with hypertensive subjects and controls, although the changes in Ea were similar across groups at peak.

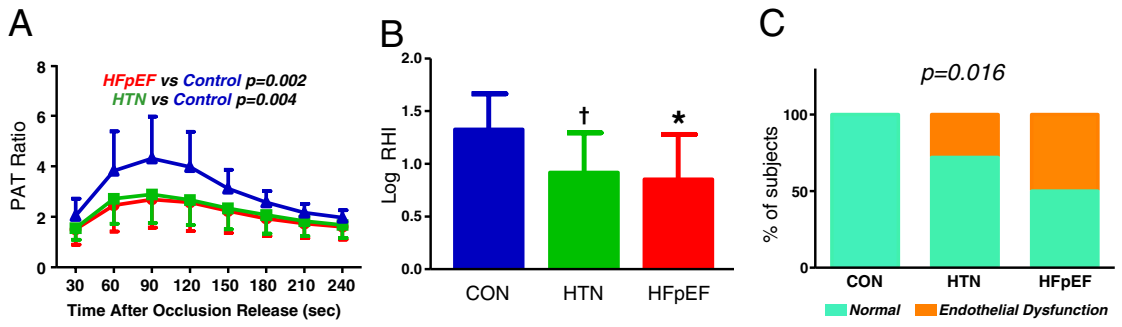

Figure 1 **Assessment of Endothelial Function**

(A) Increases in peripheral arterial tonometry (PAT) amplitude with reactive hyperemia are diminished in heart failure with preserved ejection fraction (HFpEF) patients **(red line)** and hypertensive subjects **(green line)** compared with control subjects **(blue line)**, consistent with endothelial dysfunction. **(B)** Mean reactive hyperemia index (log RHI) is reduced in HFpEF subjects **(red bar)** and hypertensive subjects **(green bar)** compared with control **(blue bar)**. **(C)** Compared with control, endothelial dysfunction **(orange area)** was more prevalent in HFpEF subjects (42%, $p < 0.05$) and tended to be more common in hypertensive subjects (28%, $p = 0.056$). **Green area of bars** indicates normal. *$p < 0.05$ HFpEF versus control; †$p < 0.05$ hypertension versus control. CON = control; HTN = hypertension.

VENTRICULAR VASCULAR COUPLING RESERVE. Contractile and vascular reserve impairments produced abnormal dynamic ventricular-arterial coupling responses at peak exercise in HFpEF subjects, with less reduction in the Ea/Ees ratio and less increase in EF and cardiac index. Reflecting the potent differences in contractile reserve function, systolic BP increased less in HFpEF subjects (34 ± 25 mm Hg) than in hypertensive subjects (56 ± 23 mm Hg, $p < 0.05$) or healthy controls (76 ± 28 mm Hg, $p < 0.05$).

Impact of coronary disease. No subject displayed ischemic electrocardiographic or wall motion changes during exercise. After adjusting for history of coronary disease, all differences in endothelial function and ventricular-vascular reserve remained significant (not shown). Subgroup analysis restricted to only subjects without history of coronary disease showed similar impairments in low-level and peak contractile reserve in HFpEF subjects, with the exception of the increase in Ees at 20 W, which was no longer significant (not shown). Among subjects without coronary disease, the prevalence of endothelial dysfunction was 0% in controls, 31% in HFpEF subjects, and 31% in hypertensive subjects (each $p = 0.02$ compared with control). In this subgroup, log RHI tended to be lower in HFpEF subjects compared with control (0.96 ± 0.42 vs. 1.33 ± 0.34), although this difference was no longer significant ($p = 0.09$ after Bonferroni).

Global reserve dysfunction and exercise intolerance in HFpEF. Several indexes of cardiovascular reserve function including chronotropic (ΔHR), contractile (ΔPWRI), vascular (ΔSVRI, ΔPAT), endothelial (log RHI), and ventricular-arterial (ΔEa/Ees) coupling responses were each significantly associated with peak VO_2 (Table 4). The number of individual reserve abnormalities (defined as <25th percentile values observed in the healthy controls) were tabulated for each subject. The HFpEF patients had the greatest number of abnormalities (Fig. 3A), and the presence of more reserve abnormalities was associated with

Table 2 **Exercise Performance**

	Control (n = 10)	Hypertension (n = 19)	HFpEF (n = 10)	p Value
Exercise time, s	831 ± 230	801 ± 314	497 ± 214*†	0.0005
Peak workload, W	96 ± 25	91 ± 27	55 ± 23*†	<0.0001
Respiratory exchange ratio	1.09 ± 0.07	1.09 ± 0.08	1.02 ± 0.09	0.02
VO_2 at VAT, cc/kg/min	14.6 ± 2.7	13.8 ± 2.6	10.4 ± 2.3*†	<0.0001
Peak VO_2, cc/kg/min	18.6 ± 3.3	18.1 ± 3.5	12.7 ± 3.1*†	<0.0001
Percent predicted peak VO_2, %	87 ± 22	93 ± 24	57 ± 18*†	<0.0001
V_E/VCO_2 slope	34.0 ± 2.9	34.1 ± 4.0	35.6 ± 5.0	0.7
20 W Borg effort, 6–20	8.6 ± 1.6	9.2 ± 1.7	11.1 ± 2.0*†	0.003
20 W Borg dyspnea, 0–10	0.9 ± 0.7	1.0 ± 0.9	2.6 ± 1.6*†	0.0009
Peak Borg effort, 6–20	16.4 ± 1.6	16.1 ± 1.8	15.7 ± 2.2	0.7
Peak Borg dyspnea, 0–10	5.4 ± 2.2	5.1 ± 1.8	4.5 ± 2.0	0.9

Final column reflects overall group ANOVA or chi square. For between-group comparisons: *$p < 0.05$ versus control; †$p < 0.05$ versus hypertension (ANOVA after Bonferroni).

VAT = ventilatory anaerobic threshold; VCO_2 = carbon dioxide production; V_E = minute ventilation; VO_2 = volume oxygen consumption; other abbreviations as in Table 1.

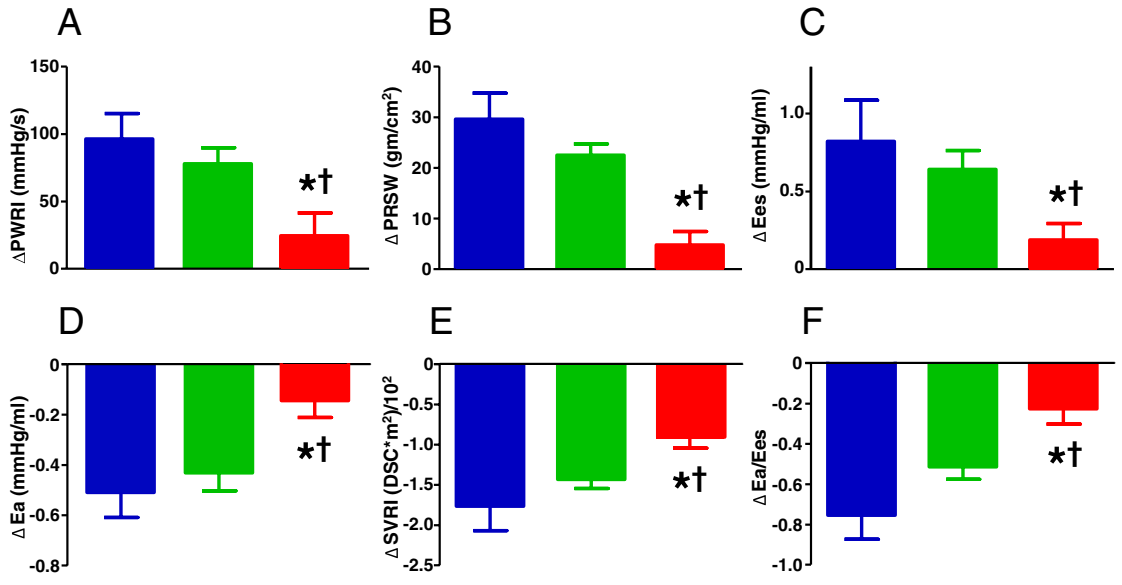

Figure 2 **Contractile, Vascular, and Coupling Reserve With Low-Level Exercise (20 W)**

(A to C) Compared with both control subjects **(blue bars)** and hypertensive subjects **(green bars)**, contractile reserve was blunted in heart failure with preserved ejection fraction (HFpEF) **(red bars)** at 20 W, evidenced by blunted increases in end-systolic elastance (Ees), pre-load recruitable stroke work (PRSW), and peak power index (PWRI). **(D, E)** Vasodilation (reduction in arterial elastance [Ea] and systemic vascular resistance index [SVRI]) was also impaired in HFpEF. **(F)** These deficits led to abnormal ventricular-arterial coupling responses (i.e., less reduction in Ea/Ees ratio) in HFpEF subjects compared with controls and hypertensive subjects. *$p < 0.05$ versus hypertension; †$p < 0.05$ versus control (analysis of variance after Bonferroni).

progressively more depressed exercise capacity (Fig. 3B). Of note, several indices of cardiovascular reserve function also correlated with subjective dyspnea and fatigue at matched low-level workload (Table 4).

Discussion

This study found evidence for global impairment in cardiovascular reserve function in HFpEF subjects compared with normal and hypertensive controls, including limitations in chronotropic, contractile, endothelial, and vascular reserve, resulting in markedly impaired ventricular-arterial coupling responses to exercise. Depressed reserve responses correlated with reduced exercise capacity and greater subjective symptoms at low-level workload, and the accumulation of more individual abnormalities was associated with progressively greater impairment in exercise capacity. These data confirm and extend upon a growing body of evidence demonstrating that the pathophysiology of HFpEF is complex and characterized by global impairment in multiple domains of cardiovascular reserve function.

Contractile reserve. Patients with HFpEF have a "normal" ejection fraction, but EF is a rather poor measure of contractility because of its sensitivity to load and chamber remodeling (17,18). To accurately assess contractility, preload and afterload must both be accounted for (19). Using load-independent measures, we observed that contractile reserve responses with exercise were blunted in HFpEF subjects at peak exercise. However, it is difficult to discern whether differences in peak contractility alone are meaningful, because HFpEF subjects reach lower peak workloads. In other words, are observed deficits in contractile reserve in HFpEF subjects a mechanism or consequence of exercise limitation?

The current study resolves this question by demonstrating that at matched, low-level workload (20 W), contractile reserve is impaired in HFpEF. In an earlier study, we found inotropic reserve impairments in HFpEF subjects compared with hypertensive subjects at peak but not at low-level exercise (5). However, the hypertensive control group in the latter study had more severe limitation (peak VO_2 70% predicted) and more abnormal ventricular remodeling (~90% with LV hypertrophy). The current findings are consistent with recent reports from other groups showing attenuated increases in EF with exercise (20,21) and reduced tissue-Doppler systolic shortening velocities and strain (22).

The mechanisms limiting contractile reserve in HFpEF remain speculative. While 1 prior study reported that resting contractility in HFpEF subjects is similar to normal subjects (19), a recent population-based study found that chamber and myocardial contractility are subtly but significantly impaired in HFpEF subjects (18). We speculate that these "mild" impairments in resting contractility become more limiting during the stress imposed by exercise. Abnormalities in calcium handling may contribute, as Liu et al. (23) demonstrated a blunted force-frequency relationship in

Table 3 Cardiovascular Reserve Responses at Peak Exercise

	Control (n = 10)	Hypertension (n = 19)	HFpEF (n = 21)	p Value
Chronotropic reserve				
ΔHR	+82 ± 21	+65 ± 15	+47 ± 17*†	<0.0001
Pre-load reserve				
ΔLV EDVI, ml/m^2	+13 ± 15	+7 ± 10	+5 ± 9	0.2
Contractile reserve				
ΔPWRI, mm Hg/s	+471 ± 179	+391 ± 119	+139 ± 103*†	<0.0001
ΔPRSW, g/cm^2	+112 ± 53	+93 ± 54	+27 ± 23*†	<0.0001
ΔEes, mm Hg/ml	+2.87 ± 1.52	+2.18 ± 0.94	+0.88 ± 0.82*†	0.0002
ΔLV ESVI, ml/m^2	−5 ± 7	−7 ± 6	+1 ± 9†	0.004
Vascular reserve				
ΔEa, mm Hg/ml	+0.19 ± 0.62	−0.07 ± 0.42	+0.22 ± 0.37	0.16
ΔSVRI, dyne·m^2/s·cm^{-5}	−2,070 ± 730	−1,890 ± 610	−1,110 ± 530*†	0.0006
Δdigital PAT amplitude	+2.52 ± 0.99	+2.33 ± 1.38	+1.46 ± 0.77*	0.027
Coupling reserve				
Δcoupling ratio, Ea/Ees	−0.93 ± 0.22	−0.67 ± 0.24	−0.21 ± 0.39*†	<0.0001
Δejection fraction, %	+16 ± 8	+16 ± 7	+3 ± 7*†	<0.0001
ΔCI, l/min·m^2	+5.1 ± 2.2	+4.1 ± 1.1	+2.2 ± 1.1*†	<0.0001

Final column reflects overall group ANOVA or chi square. For between-group comparisons: *p < 0.05 versus control; †p < 0.05 versus hypertension (ANOVA after Bonferroni).

CI = cardiac index; Δ = peak change; EDVI = end-diastolic volume index; HR = heart rate; PAT = peripheral arterial tonometry; other abbreviations as in Table 1.

human HFpEF. Finally, both systolic and diastolic reserve may be affected by abnormalities in energy substrate bioavailability, as has recently been demonstrated in HFpEF (21,24).

Endothelial function and vasodilator reserve. Investigators first noted endothelial dysfunction in patients with heart failure and reduced ejection fraction (HFrEF) in the early 1990s (25,26), and recent work has suggested that this may contribute to symptoms of breathlessness and fatigue by enhancing abnormal skeletal muscle signaling during exercise (27). However, few studies have examined endothelial function in HFpEF subjects.

Table 4 Relationships Between Reserve and Peak Exercise Capacity or Symptoms at Matched Low-Level Workload (20 W)

	Pearson r	p Value
Peak volume oxygen consumption		
Chronotropic reserve, ΔHR	0.70	<0.0001
Contractile reserve, ΔPWRI	0.73	<0.0001
Endothelial function, log RHI	0.43	0.003
Vascular reserve, ΔSVRI	−0.40	0.009
Vascular reserve, Δ log PAT	0.52	0.0007
Coupling reserve, ΔEa/Ees	−0.51	0.0006
20 W Borg fatigue		
Chronotropic reserve, ΔHR	−0.37	0.007
Contractile reserve, ΔPWRI	−0.44	0.004
Endothelial function, log RHI	−0.52	0.0002
Vascular reserve, ΔSVRI	0.37	0.02
Vascular reserve, Δ log PAT	−0.47	0.003
Coupling reserve, ΔEa/Ees	0.52	0.0006
20 W Borg dyspnea		
Chronotropic reserve, ΔHR	−0.48	0.0005
Contractile reserve, ΔPWRI	−0.61	<0.0001
Endothelial function, log RHI	−0.39	0.007
Vascular reserve, ΔSVRI	0.37	0.02
Vascular reserve, Δ log PAT	−0.32	0.052
Coupling reserve, ΔEa/Ees	0.49	0.001

Abbreviations as in Tables 1 and 3.

Hundley et al. (28) measured exercise capacity and flow-mediated arterial dilation in the femoral artery by magnetic resonance imaging in 9 subjects with HFpEF, comparing them to 11 normal controls and 10 HFrEF subjects. Exercise capacity was reduced in both HFrEF and HFpEF, but flow-mediated arterial dilation was impaired only in HFrEF. However, flow-mediated vasodilation in large conduit arteries (e.g., femoral) may differ from that observed in the microvasculature (as in the current study). We now show for the first time that endothelial function is impaired in HFpEF subjects compared with apparently healthy controls, assessed at the microvasculature. Part of this deficit may be related to atherosclerosis, though RHI remained lower in HFpEF subjects after adjusting for coronary disease, and mean RHI values were similar in HFpEF patients with or without coronary disease. Hypertensive subjects also displayed endothelial dysfunction, but had preserved exercise capacity, possibly related to preservation of other components of reserve function. Endothelial dysfunction correlated with reduced exercise capacity and greater symptoms, suggesting a role in contributing to objective and subjective exertional intolerance in HFpEF.

During normal exercise, arterial resistance decreases to accommodate large increases in flow with minimal increment in pressure (6). Prior studies have demonstrated using derived indices of arterial load, such as SVRI and Ea, that

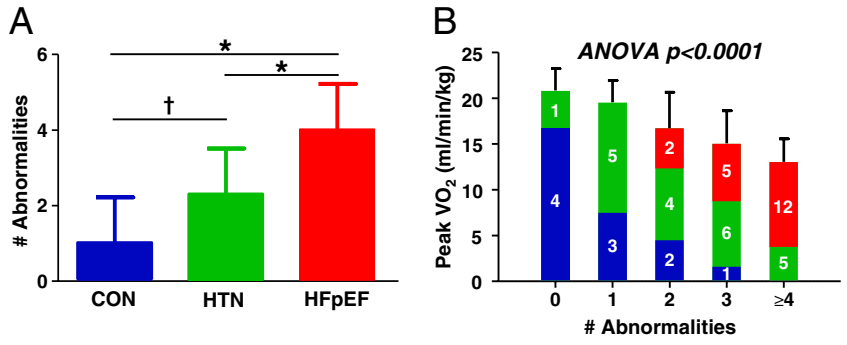

Figure 3 **Global Reserve Dysfunction**

(A) Heart failure with preserved ejection fraction (HFpEF) subjects displayed a greater number of abnormalities in cardiovascular reserve function than did hypertensive (HTN) subjects and normal controls (CON), and hypertensive subjects had more abnormalities than healthy controls. *p < 0.001; †p < 0.05. **(B)** The presence of a greater number of reserve abnormalities was associated with more severely depressed exercise capacity. **Numbered colored bars** indicate total number of subjects in each grouping for control subjects **(blue)**, hypertensive subjects **(green)**, and HFpEF subjects **(red)**. The p value reflects 1-way analysis of variance (ANOVA) testing the relationship of number of abnormalities versus peak VO_2.

exercise vasodilation is blunted in HFpEF (5,20,22). The current findings confirm these studies using the same derived vascular measures, and importantly, extend upon them by demonstrating for the first time that directly measured peripheral vasodilation (change in digital PAT amplitude with exercise) is also depressed in HFpEF.

Ventricular-arterial interaction with exercise. Abnormal vasorelaxation, combined with blunted contractile reserve, led to abnormal ventricular-arterial coupling in HFpEF. In the pressure-volume plane, contractility is expressed by end-systolic elastance (Ees), defined by the slope and intercept of the end systolic pressure-volume relationship, while afterload is defined by effective arterial elastance (Ea), a lumped parameter incorporating both mean and pulsatile vascular load (6). Ventricular-arterial interaction is described by the coupling ratio (Ea/Ees). Under normal circumstances, Ea/Ees drops with exercise, because the increase in Ees exceeds the change in Ea, leading to an increase in EF (6). The normal exercise drop in Ea/Ees becomes impaired with aging (29), and Phan et al. (21) recently found that the drop in the ratio of end-systolic volume to stroke volume (which is related to Ea/Ees) was impaired in HFpEF subjects compared with hypertensive subjects at 50% maximal effort (21). The current findings confirm and extend upon the latter, showing that abnormal ventricular-arterial coupling is present both at matched, objective low-level workload and throughout exercise in HFpEF subjects compared with hypertensive subjects and normal controls.

Chronotropic reserve. The current data confirm previously reported impairment in peak chronotropic reserve and its relationship to exercise limitation (5,21). Heart rate reserve was lower in the HFpEF patients, and more than half met criteria for chronotropic incompetence (9). In contrast to an earlier study (5) and to contractile and vascular reserves in this study, HR responses were not blunted at submaximal workload in HFpEF, making it difficult to discern whether chronotropic incompetence contributed to exercise limitation in HFpEF or was simply related to the lower peak workload achieved.

Pre-load reserve. While diastolic dysfunction was present at rest, exercise changes in diastolic compliance and relaxation were not assessed in this study. Kitzman et al. (30) found that EDVI failed to increase with exercise in HFpEF patients compared with controls, whereas in the current study and in an earlier report (5), EDVI increased by 5% to 10% in HFpEF subjects during exercise. However, nearly one-half of the patients in the Kitzman study had either infiltrative or hypertropic cardiomyopathy, diseases known to produce the most extreme forms of diastolic dysfunction. These patients were excluded from the latter analyses, and that may explain the apparent discrepancies in pre-load reserve. We observed a trend toward greater EDVI reserve in healthy controls at peak exercise compared with HFpEF subjects and hypertensive subjects, and the absence of a significant difference may be related to the small sample size in the healthy controls. Finally, changes in filling pressures with exercise, which are known to be abnormal in HFpEF subjects (30,31), were not assessed in this study, and therefore the current results should not be interpreted as minimizing the importance of diastolic reserve in HFpEF (30).

Clinical implications. Because diastolic dysfunction is readily detectable in most HFpEF patients and plausibly explains many symptoms, it has traditionally been conceptualized as the sole or predominant mechanism. This pathophysiologic model is similar to other disorders where a single lesion (e.g., cortisol excess) produces a wide variety of clinical sequelae (bone loss, hypertension, glucose intolerance). Our data show that rather than being a disease of diastolic dysfunction alone, HFpEF is characterized by a number of abnormalities in endothelial and ventricular-vascular reserve function that contribute in a coordinated

fashion in patients with HFpEF. We speculate and the epidemiology studies suggest that HFpEF is not due to 1 systemic disease, but rather, in the majority of cases, represents a culmination of a number of different disease processes associated with aging, hypertension, and diabetes mellitus. Understanding the pleiotropic nature of reserve limitation of HFpEF may allow for more focused and tailored therapies for individual patients, and it is hoped that future research will identify the specific mechanistic processes that produce global reserve dysfunction in HFpEF.

Study limitations. This is a cross-sectional study and cannot assess causality. Pressure and flow were not directly measured, but rather estimated from noninvasive surrogates. While these derived parameters have been validated in prior studies against invasive hemodynamic measurements (10–13), there is inherently greater variability compared with the gold standard measures. Because of image foreshortening during exercise, EDVI was determined from SV and EF rather than from 2-dimensional imaging alone. This assumes that mitral regurgitation, which was not measured directly, was not significant.

Conclusions

Heart failure is often conceptualized as being caused by isolated, discrete disease mechanisms, such as diastolic or systolic dysfunction. However, HFpEF is a disease of the elderly, and with aging, patients acquire multiple comorbidities and processes that integrate in complex ways to produce symptoms and exercise intolerance. The current results, taken in concert with other recent studies, suggest that in most cases, HFpEF is not simply the result of a single impairment in 1 component of cardiovascular function, but rather a culmination of global limitations of cardiovascular reserve function—chronotropy, inotropy, lusitropy and vasodilation—all resulting in impaired ventricular arterial coupling, depressed cardiac output response, and subjective and objective exercise intolerance. Recognition that reserve dysfunction in HFpEF is a global process affecting many cardiovascular responses to stress will aid in the design and testing of future therapeutic strategies for HFpEF.

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