Journal of the American College of Cardiology Vol. 59, No. 5, 2012

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.10.873

Increased Proximal Arterial Stiffness and Cardiac Response With Moderate Exercise in Patients With Heart Failure and Preserved Ejection Fraction

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Objectives This study sought to demonstrate that arterial stiffness is probably underestimated in patients with heart failure with preserved ejection fraction (HFpEF) at rest and may be revealed with moderate exercise.

Background HFpEF is associated with ventriculoarterial stiffening.

Methods We compared 23 patients with stable chronic HFpEF, left ventricular ejection fraction >45%, and impaired relaxation with 15 controls without cardiac disease. Patients were compared at rest and during a 30-W exercise. The following variables were measured or calculated by Doppler echocardiography and tonometry: left ventricular volumes and end-systolic elastance (Ees), peripheral resistance, arterial elastance (Ea), arterial compliance, aortic pulse wave velocity, and carotid Peterson modulus (Ep).

Results Patients with HFpEF were comparable to controls in age, sex ratio, blood pressure, and heart rate. Ventriculoarterial coupling, assessed by Ees/Ea and Ees/Ep ratios, was moderately impaired at rest in patients compared with controls (both $p < 0.01$). HFpEF was associated during exercise with a major increase in Ep ($+155 \pm 193\%$ vs. $-5 \pm 28\%$), pulse wave velocity ($+20 \pm 30\%$ vs. $-7 \pm 24\%$), and Ea ($+12 \pm 15\%$ vs. $-5 \pm 10\%$), and a lower decrease in peripheral resistance ($-17 \pm 12\%$ vs. $-26 \pm 12\%$) ($p < 0.05$ for all). In addition, HFpEF patients showed a lower increase in stroke volume ($+10 \pm 16\%$ vs. $+21 \pm 12\%$) despite a greater increase in Ees ($+20 \pm 18\%$ vs. $+3 \pm 12\%$) ($p < 0.05$ for all). Also during exercise, adaptation of proximal ventriculoarterial coupling was impaired in HFpEF patients (Ees/Ep: $-26 \pm 47\%$ vs. $+20 \pm 47\%$ for controls) ($p < 0.01$), with no difference in Ees/Ea.

Conclusions In HFpEF patients, moderate exercise leads to a steep increase in proximal afterload that is underestimated at rest and is associated with unfavorable ventriculoarterial coupling and exercise intolerance. (J Am Coll Cardiol 2012;59:455–61) © 2012 by the American College of Cardiology Foundation

Heart failure (HF) is a major cause of morbidity and mortality. It is predominantly a disease of elderly people (1). Nearly half of affected patients have an apparently preserved systolic function (2). Rehospitalization rates and prognosis are similar to those for patients with systolic failure (2). In contrast to the improvement in survival observed for patients with HF and reduced left ventricular ejection fraction (LVEF), mortality for patients with HF and preserved LVEF (HFpEF) has remained constant, which emphasizes the lack of therapy with proven benefit for these patients (3).

Diastolic dysfunction is thought to play a dominant role in HFpEF and exercise intolerance (4,5). However, the pathophysiology of the exercise intolerance in this syndrome is incompletely understood and likely multifactorial (6–8). Recently, some authors drew attention to the fact that in older people with HFpEF, impaired exercise tolerance correlates strongly with aortic stiffening (9). Another factor that may contribute to HF pathophysiology is abnormal ventricular-arterial interaction due to stiffening of both systems (6,10), thus contributing to blood pressure lability and higher energy cost to increase cardiac output (6).

In this study, we hypothesized that the arterial stiffness in patients with HFpEF at rest is probably underestimated and could be revealed with moderate exercise.

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Manuscript received April 14, 2008; revised manuscript received October 13, 2011, accepted October 17, 2011.

JACC Vol. 59, No. 5, 2012
January 31, 2012:455–61

Abbreviations and Acronyms

E/E′ = peak velocity of the early diastolic mitral inflow divided by E′

E′ = mitral annular early diastolic velocity

Ea = arterial elastance

EDP = end-diastolic pressure

EDV = end-diastolic volume

Ees = end-systolic elastance

$Ees_{LVM\text{-}V0}$ = Ees after normalization for the left ventricular mass and V0

Ep = Peterson's modulus

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

LV = left ventricular

LVEF = left ventricular ejection fraction

6-MWT = 6-min walking test

PP = pulse pressure

PVR = peripheral vascular resistance

PWV = pulse wave velocity

SV = stroke volume

$V20_i$ = volume at end-diastolic pressure of 20 mm Hg indexed to body surface area

YEM = Young's elastic modulus

Methods

Patients. Twenty-three consecutive patients referred to our laboratory with chronic HFpEF, LVEF >45%, sinus rhythm, and stable hemodynamic conditions were included. The diagnosis of HFpEF was based on criteria defined by the European Society of Cardiology (3). Patients with severe valvular disease or severe wall-motion abnormalities were excluded. In the same period, 15 consecutive patients referred to our laboratory for chest pain with normal electrocardiography stress-test results were included. Medications were not withdrawn for this study. Investigators were not blinded to subject assignment. All patients gave their informed consent. The study was approved by the local hospital institutional review board.

Central pressure measurement. Carotid pulse wave was recorded at rest and during exercise by aplanation tonometry (SphygmoCor Px PWA System, AtCor Medical, West Ryde, Australia) on the right carotid artery, and calibration involved the use of brachial mean blood pressure and diastolic blood pressure (11). Augmentation pressure was defined as carotid systolic blood pressure minus the pressure at the first peak shoulder of the carotid pulse wave.

Determination of vascular geometry. Images were taken by using a commercially available sonographer (Vivid 7, GE Vingmed, Horten, Norway) with a 14-MHz transducer.

Right common carotid measurements involved transversal and longitudinal scanning for measuring the maximum lumen diameter, end-diastolic diameter, and intima-media thickness. At least 10 cycles were averaged. Cross-sectional area of the carotid artery was calculated as follows: $[(\text{maximum lumen diameter}/2)^2 \times \pi] - (\text{maximum lumen diameter}/2 - \text{intima-media thickness})^2 \times \pi]$.

Determination of vascular function. Effective arterial elastance (Ea) was estimated as end-systolic pressure/stroke volume (SV) (12). End-systolic pressure was estimated as carotid systolic pressure × 0.9 (12,13). Arterial compliance was estimated by the ratio of SV to pulse pressure (PP) (14) and peripheral vascular resistance (PVR) by mean arterial pressure/cardiac output × 79.9.

Peterson's modulus (Ep) (in $kPa \cdot 10^2$) was defined as: (carotid PP × carotid end-diastolic diameter)/ΔD. Young's elastic modulus (YEM) (in $kPa \cdot 10^3$) was (carotid PP × carotid end-diastolic diameter^2)/(ΔD × 2 × intima-media thickness), with ΔD indicating the mean carotid distention.

Aortic pulse wave velocity (PWV) was assessed by use of pulsed Doppler and defined as the transit time (in seconds) between the aortic arch and the abdominal aorta divided by the distance (in meters) between these 2 points.

Determination of LV geometry and function. Images were taken using a 3.5-MHz transducer (GE Vingmed). The left ventricular (LV) parameters were recorded or calculated according to the American Society of Echocardiography recommendations (15).

The modified single-beat method was used to estimate end-systolic elastance (Ees) from carotid pressure, SV, and pre-ejection and total systolic periods determined on Doppler analysis of the aortic flow, Simpson LVEF, and an estimated normalized ventricular elastance at arterial end-diastole, as previously validated (13).

Peak velocities of the mitral inflow were derived from pulsed Doppler recordings with the sample volume placed at the tip of the mitral leaflets. Peak E-wave and

Table 1 Baseline Characteristics

	HFpEF (n = 23)	Control (n = 15)	p Value
Age, yrs	66 ± 10	67 ± 7	NS
Female	52 (12)	33 (5)	NS
Height, cm	165 ± 9	168 ± 10	NS
Body surface area, m^2	1.82 ± 0.18	1.82 ± 0.22	NS
Body mass index, kg/m^2	27 ± 4	25 ± 4	NS
Hypertension	78 (18)	47 (7)	0.045
Dyslipidemia	78 (18)	27 (4)	0.001
Diabetes	57 (13)	20 (3)	0.03
Tobacco use	39 (9)	20 (3)	NS
Coronary artery disease	43 (10)	0 (0)	0.002
Creatinine clearance, ml/min*	63 ± 25		
BNP, pg/ml*	204 ± 187		
Functional impairment			
NYHA functional class I/II/III/IV	4/17/2/0	—	—
Exercise duration, min	6 ± 1	8 ± 2	<0.001
Maximum workload, W	76 ± 27	143 ± 54	<0.001
6-MWT, m	369 ± 77	469 ± 69	<0.001
Treatments			
ARB/ACE-I	78	47	0.045
Beta-blockers	65	13	0.001
Diuretics	83	20	<0.001
Spironolactone	9	0	NS
Calcium antagonists	52	0	<0.001
Nitrate	17	0	NS
Aspirin	48	6	0.007
Amiodarone	26	7	NS
Statin	43	7	0.01

Values are mean ± 1 SD, % (n), or %. *N = 21.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BNP = B-type natriuretic peptide; HFpEF = heart failure with preserved ejection fraction; 6-MWT = 6-min walking test; NYHA = New York Heart Association.

Table 2 Sex-Adjusted Blood Pressure, Vascular, and Cardiac Geometry Parameters

Parameter	HFpEF	Control	p Value
Brachial BP, mm Hg			
Systolic BP	132 ± 5	128 ± 6	NS
Diastolic BP	69 ± 3	70 ± 4	NS
Pulse pressure	63 ± 3	58 ± 4	NS
Mean BP	90 ± 3	89 ± 4	NS
Carotid geometry			
Intima-media thickness, mm	0.77 ± 0.03	0.58 ± 0.03	<0.001
Systolic diameter index, mm/m^2	4.78 ± 0.01	4.49 ± 0.01	0.077
Carotid CSA index, mm^2/m^2	19.2 ± 0.9	13.6 ± 1.1	<0.001
YEM, kPa.10^3	1.17 ± 0.18	0.74 ± 0.22	NS
Cardiac geometry			
IVW thickness, mm	12.4 ± 0.5	9.7 ± 0.6	0.002
LVEDD index, mm/m^2	28 ± 1	28 ± 1	NS
RWT, ratio	0.39 ± 0.15	0.33 ± 0.08	NS
LVM index, g/m^2	129 ± 8	92 ± 10	0.008
Left atrial diameter, mm	39 ± 1	30 ± 2	<0.001
Teichholz LVEF, %	57 ± 2	66 ± 3	0.016
Simpson LVEF, %	59 ± 2	67 ± 2	0.003

Values are mean ± 1 SD. p value adjusted for sex.

BP = blood pressure; CSA = cross-sectional area; HFpEF = heart failure with preserved ejection fraction; IVW = interventricular wall; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVM = left ventricular mass; RWT = relative wall thickness; YEM = Young's elastic modulus.

peak A-wave velocities were measured. The mitral annular (mean of lateral and septal annulus) early diastolic velocity (E′) was determined by color-decoded tissue Doppler imaging. The constant tau was calculated as previously published (16). E/E′ was used as a surrogate of LV end-diastolic pressure (EDP) and E/E′ divided by the end-diastolic volume (E/E′/EDV) as an index of absolute chamber compliance. A single-beat approach was used to characterize the EDP volume relationship (where $EDP = \alpha EDV^{\beta}$; α is a curve-fitting constant and β is a diastolic stiffness constant) (17). To account for covariance in α and β (18), both of which are indicative of the shape and position of the EDP volume relationship, derived α and β in each subject were used to predict the EDV at a common EDV of 20 mm Hg. Comparison of EDP of 20 mm Hg indexed to body surface area ($V20_i$) was then used as a comparison of overall diastolic stiffness between groups (8).

All recordings were taken by 2 operators (J.-M.T., L.T.-K.) at rest and during exercise, and analysis was performed offline using the EchoPAC system (GE Vingmed). All Doppler echocardiographic measurements were taken at least 4 times and averaged. Measurements were indexed to body surface area as appropriate. Carotid parameters and PWV were assessed on the basis of the mean of at least 10 measurements. Intra- and interobserver reproducibility at rest and during exercise was analyzed for cardiac and vascular Doppler echocardiographic measurements and tonometry, with correlations >0.89 except for E′ interobserver reproducibility (r = 0.81) and the percentage of difference <5%.

Exercise test and symptoms assessment. Measurements were performed at rest and during 30-W exercise (Ergoline 900, Schiller Medical, Wissembourg, France) with the patient in a semirecumbent position after heart rate stabilization, before fusion between E and A waves. Data were acquired during exercise and stored after heart rate stabilization.

Twenty HFpEF patients and 14 controls underwent the 6-min walking test (6-MWT) without encouragement, and 23 HFpEF patients and 14 controls performed a maximal

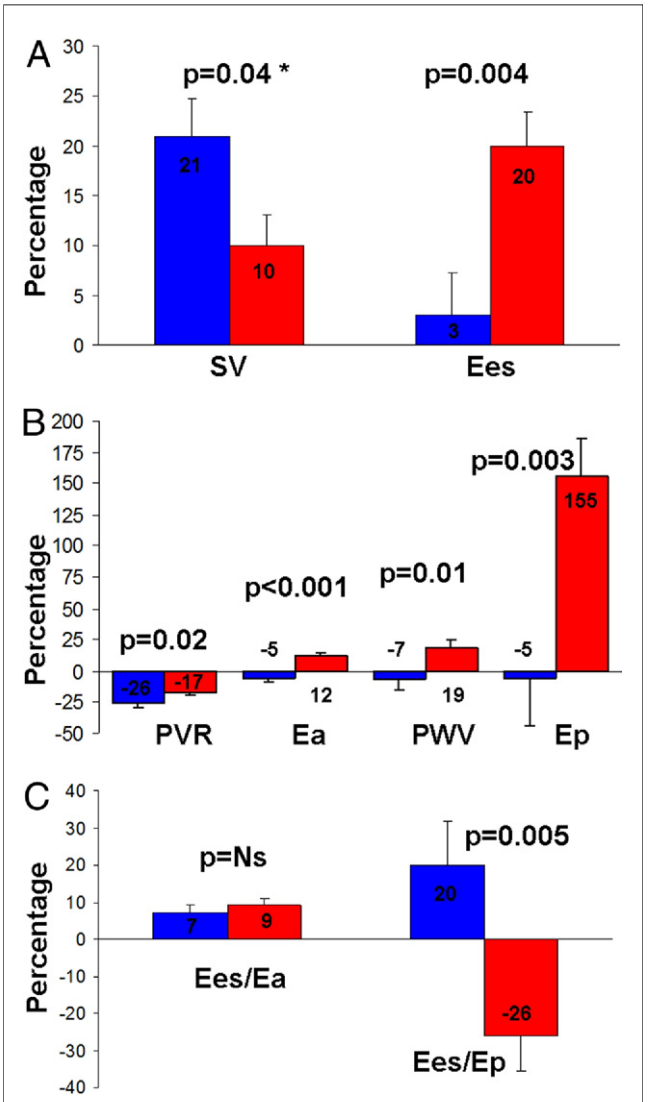

Figure 1 Modification of Cardiac Function, Vascular Function, and Cardiovascular Coupling Parameters During Exercise

Modification of cardiac function **(A)**, vascular function **(B)**, and cardiovascular coupling **(C)** parameters during exercise. Modifications are expressed as a percentage ± 1 SD of decrease or increase compared with the baseline value in each group. HFpEF patients **(red)**, controls **(blue)**. *p = 0.06 after adjustment of stroke volume for sex, without modification for other parameters. Ea = arterial elastance; Ees = end-systolic elastance; Ep = Peterson's modulus; PVR = peripheral vascular resistance; PWV = pulse wave velocity; SV = stroke volume.

JACC Vol. 59, No. 5, 2012
January 31, 2012:455–61

Table 3 Sex-Adjusted Doppler Echocardiography Parameters

	Rest		Exercise		p Value		
Parameter	HFpEF	Control	HFpEF	Control	Group Factor	Exercise Factor	Interaction
Heart rate, beats/min	68 ± 3	67 ± 3	89 ± 3	87 ± 3	NS	<0.001	NS
Stroke volume, ml/m^2	40 ± 2	39 ± 2	43 ± 2	46 ± 2	NS	0.003	NS
E, cm/s	77 ± 4	69 ± 5	103 ± 4	94 ± 5	0.072	<0.001	NS
A, cm/s	70 ± 5	77 ± 6	88 ± 5	97 ± 6	NS	<0.001	NS
E/A, ratio	1.33 ± 0.15	0.91 ± 0.19	1.40 ± 0.15	0.97 ± 0.19	0.017	NS	NS
E′, cm/s	4.0 ± 0.3	6.2 ± 0.4	4.9 ± 0.3	8.0 ± 0.4	<0.001	<0.001	NS
E/E′, ratio*	20 (17–23)	11 (9–12)	22 (18–28)	11 (10–13)	<0.001	NS	NS
Tau, ms	72 ± 2	56 ± 3	66 ± 2	51 ± 3	<0.001	0.024	NS
EDV, ml/m^2	67 ± 2	58 ± 3	66 ± 2	64 ± 3	0.033	NS	NS
E/E′/EDV, ratio	0.17 ± 0.03	0.12 ± 0.03	0.23 ± 0.03	0.11 ± 0.03	0.009	NS	NS

Values are mean ± 1 SD. *Statistical test was applied on log-transformed E/E′ ratio; values are given with geometric mean and 95% lower and upper confidence limits.

A = peak velocity of the late diastolic mitral inflow, derived from pulsed Doppler; E = peak velocity of the early diastolic mitral inflow, derived from pulsed Doppler; E/A = E divided by A; E′ = mitral annular early diastolic velocity; EDV = end-diastolic volume; HFpEF = heart failure with preserved ejection fraction.

exercise test in an upright position on a cycloergometer following the Bruce protocol.

Statistical analysis. Categorical data are presented as percentages, and continuous data as mean ± 1 SD. E/E′ was log-transformed to achieve normal distribution, and values were given by using the geometric mean and 95% lower and upper confidence limits. Ees values were compared after normalization for the LV mass and adjustment for V0 (Ees-$_{LVM-V0}$). The Student *t* test and chi-square test were used as appropriate. Analysis of variance with 2 factors was used to determine the effect of exercise (rest vs. exercise) or the effect of group (HFpEF vs. control). This analysis was adjusted for sex. Spearman rank test was used for calculating partial correlation coefficients adjusted for sex, and another multivariate analysis was performed with sex and height as partial variables. The values in Figure 1 are shown without adjustment, but an asterisk appears next to the unadjusted p value when statistical significance was changed by adjusting for sex. A 2-sided p value of <0.05 was considered significant. Analyses involved the use of NCSS 6.0.21 software (J.L. Hintze, Kaysville, Utah).

Results

Baseline characteristics. Baseline characteristics (Tables 1 and 2) were different between groups with regard to cardiovascular risk factors, which were more frequent in HFpEF patients except for age, sex, and body mass index. Of HFpEF patients, 43% had a history of coronary heart disease.

Patients with HFpEF showed significant functional impairment compared with controls: lower exercise duration ability, lower maximum workload, and shorter 6-MWT

Table 4 Sex-Adjusted Hemodynamic, Cardiac, and Vascular Function Parameters

	Rest		Exercise		p Value		
	HFpEF	Control	HFpEF	Control	Group Factor	Exercise Factor	Interaction
Carotid SBP, mm Hg	126 ± 4	116 ± 5	152 ± 4	132 ± 5	0.005	<0.001	NS
Carotid PP, mm Hg	56 ± 3	47 ± 4	76 ± 3	54 ± 4	<0.001	<0.001	0.046
PP amplification, ratio	1.12 ± 0.02	1.24 ± 0.03	1.18 ± 0.02	1.29 ± 0.03	<0.001	0.013	NS
Augmentation pressure, mm Hg	8 ± 2	9 ± 3	7 ± 2	6 ± 3	NS	NS	NS
V0, ml	−11 ± 5	−17 ± 6	−20 ± 5	−25 ± 6	NS	NS	NS
V20$_i$, ml	70 ± 2	62 ± 3	68 ± 2	69 ± 3	NS	NS	NS
Ees-$_{LVM-V0}$, mm Hg/ml/g · 10^{-2}	0.94 ± 0.13	1.40 ± 0.16	1.20 ± 0.13	1.49 ± 0.16	0.011	NS	NS
PVR, dynes · s · cm^{-5}	1,550 ± 68	1,581 ± 84	1,268 ± 68	1,143 ± 84	NS	<0.001	NS
Ea, mm Hg/ml	1.64 ± 0.10	1.56 ± 0.12	1.82 ± 0.10	1.46 ± 0.12	NS	0.066	NS
Arterial compliance, ml/mm Hg	1.36 ± 0.08	1.52 ± 0.10	1.09 ± 0.08	1.59 ± 0.10	<0.001	NS	0.059
Pulse wave velocity, m/s	12 ± 1	11 ± 1	14 ± 1	10 ± 1	0.047	NS	NS
Ep, kPa · 10^2	1.95 ± 0.41	1.17 ± 0.51	4.27 ± 0.41	1.10 ± 0.51	<0.001	0.017	0.011
Ees/Ea, ratio	1.13 ± 0.02	1.24 ± 0.03	1.17 ± 0.02	1.34 ± 0.03	<0.001	0.011	NS
Ees/Ep, ratio	1.31 ± 0.15	1.71 ± 0.18	0.82 ± 0.15	1.98 ± 0.19	<0.001	NS	0.025

Values are mean ± 1 SD.

Ea = arterial elastance; Ees = end-systolic elastance; Ep = Peterson's modulus; HFpEF = heart failure with preserved ejection fraction; PP = pulse pressure; PVR = peripheral vascular resistance; SBP = systolic blood pressure; V0 = V20$_i$ =volume intercept; volume at end-diastolic pressure of 20 mm Hg indexed to body surface area.

($p < 0.001$ for all). They were more frequently taking antihypertensive agents, aspirin, and statins.

After adjustment for sex, brachial blood pressure was not significantly different between the groups (Table 2). HFpEF patients had a thicker right carotid artery, with increased cross-sectional area, but no difference in YEM. The left ventricle was thicker, with an increased LV mass index, despite no difference in LV end-diastolic diameter index or relative wall thickness. Patients also had an enlarged left atrium and a lower LVEF.

Cardiac adaptation during exercise. After adjustment for sex, the increase of heart rate was similar between groups during exercise (Tables 3 and 4). SV increased significantly during exercise in both groups with a greater increase of EDV in controls compared with HFpEF patients (+8.6 ± 2.7% vs. −0.9 ± 2.2%, respectively; sex-adjusted p value = 0.010). LV relaxation (E′ and tau) was impaired in HFpEF patients, but exercise was associated with improved LV relaxation in both groups (Table 3). HFpEF patients showed increased chamber stiffness (β) without significant modification by exercise. The log-transformed E/E′ ratio was statistically higher in HFpEF patients but was not increased during exercise. However, after adjusting for sex and controlling for covariance in α and β, overall diastolic LV stiffness was not different among groups (same $V20_i$) even if another parameter such as the E/E′/EDV was indicative of an increased diastolic LV stiffness in the HFpEF group (Table 3, Fig. 2A). Moreover, the increase in $V20_i$ during exercise, expressed as a percentage, was significantly higher in controls compared with HFpEF patients (+10.7 ± 3.4% vs. −1.1 ± 2.7%, respectively; sex-adjusted p value = 0.016), but not variations of β, tau, or E/E′/EDV ($p > 0.05$ for all).

Regarding contractile response and after adjustment for sex, the magnitude of increase in Ees from rest to exercise was greater in the HFpEF group than in controls (Fig. 1A). $Ees\text{-}_{LVM\text{-}V0}$ was statistically different between groups ($p = 0.011$), and the magnitude of increase during exercise was greater in HFpEF group (+20 ± 18% vs. +3 ± 12% in controls; $p = 0.004$).

Vascular adaptation during exercise. Exercise was characterized by increased carotid systolic blood pressure, PP and PP amplification in both groups, with higher values of carotid systolic blood pressure and PP, and lower PP amplification in HFpEF group (Table 4, Fig. 2B). A significant interaction was shown in terms of carotid PP, demonstrating a steeper slope of increased PP in the HFpEF group. Modifications of vascular afterload substantially differed between the groups, especially regarding the proximal arterial compartment. Exercise was associated with a significant decrease in PVR and a nonsignificant decrease in Ea ($p = 0.066$). However, the magnitude of the PVR decrease during exercise seems to be different among groups with a blunted phenomenon in HFpEF patients (−26 ± 3% vs. −17 ± 3% in the HFpEF group; $p < 0.05$). When vascular load was assessed only from its proximal compartment (PWV, arterial compliance, and Ep), vascular load seemed to be impaired in HFpEF patients, especially regarding Ep (−5 ± 39% vs. 155 ± 32% for HFpEF patients; $p < 0.01$; and interaction, $p = 0.011$), arterial compliance (6 ± 4% vs. −19 ± 4% for HFpEF patients; $p < 0.001$; interaction, $p = 0.059$) or PWV (Fig. 1B). HFpEF patients showed a steeper slope of the carotid pressure-to-diameter ratio during exercise (Fig. 2B).

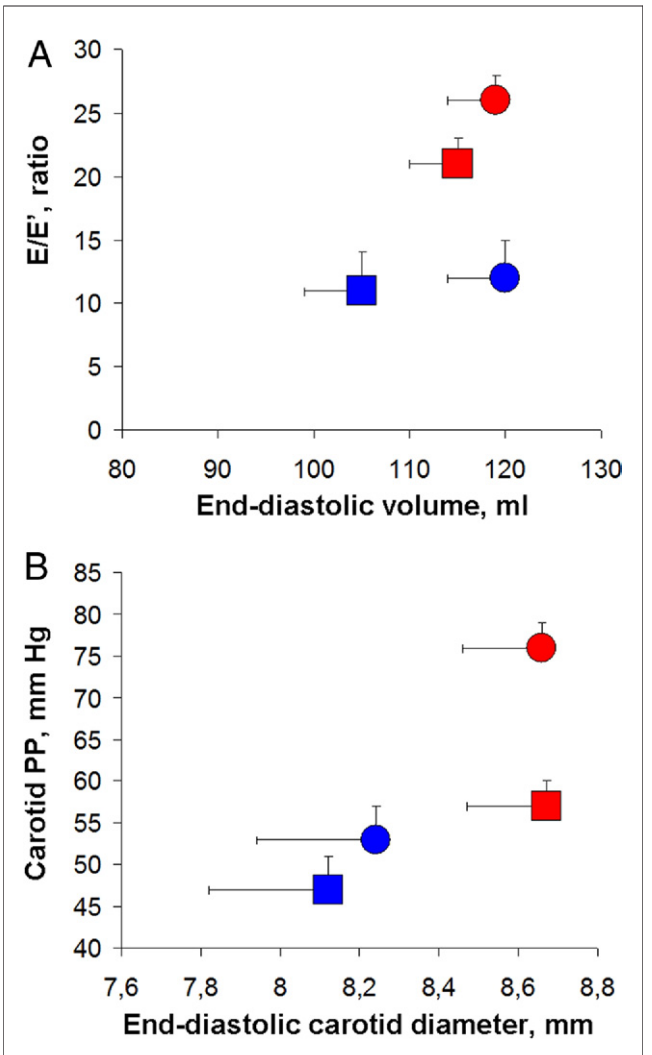

Figure 2 Relationship Between Left Ventricular and Carotid Geometry and E/E′ Ratio or Carotid PP

Values are expressed as a mean ± 1 SD for heart failure with preserved ejection fraction patients **(red)** and controls **(blue)** at rest **(squares)** and during exercise **(circles)**. E/E′ ratio = early filling velocity to tissue Doppler early diastolic mitral annular velocity; PP = pulse pressure.

Ventriculoarterial coupling during exercise. Ventriculoarterial coupling was impaired in the HFpEF group when globally assessed by the Ees/Ea or Ees/Ep ratios (Table 4). Moreover, the magnitude and direction of change of Ees/Ep were extremely unfavorable in the HFpEF group during exercise (+20 ± 47% vs. −26 ± 47% for HFpEF patients; $p = 0.005$; interaction, $p = 0.025$) (Fig. 1C).

JACC Vol. 59, No. 5, 2012
January 31, 2012:455–61

Table 5 Sex-Adjusted Matrix Correlation Between Maximum Workload During Exercise or 6-Min Walking Test and Hemodynamic Parameters

	Maximal Workload				6-MWT			
	Rest		Exercise-Rest		Rest		Exercise-Rest	
Parameter	r	p Value	r	p Value	R	p Value	r	p Value
Heart rate	−0.207	NS	0.198	NS	−0.096	NS	0.123	NS
Stroke volume	−0.209	NS	0.308	0.09	−0.015	NS	0.068	NS
Pulse pressure	−0.232	NS	−0.179	NS	−0.095	NS	−0.401	0.03
E′	0.546	0.003	0.243	NS	0.597	<0.001	−0.119	NS
E/E′	−0.511	0.005	0.066	NS	−0.621	<0.001	0.235	NS
β	−0.534	0.003	−0.091	NS	−0.651	<0.001	0.272	NS
Ees	0.407	0.03	−0.455	0.01	0.214	NS	−0.196	NS
Ea	0.098	NS	−0.435	0.01	−0.012	NS	−0.322	0.08
PVR	0.337	0.08	−0.556	0.001	0.034	NS	−0.237	NS
Ep	−0.167	NS	−0.298	0.10	−0.101	NS	−0.356	0.04

Rest: baseline values for correlation analysis. Exercise-rest: the difference between exercise and rest for correlation analysis.
Abbreviations as in Tables 3 and 4.

Relationship between cardiovascular function and exercise capacity. Sex-adjusted baseline values of impaired LV relaxation, high E/E′ or β and low E′ were correlated with a lower maximal workload and shorter 6-MWT duration (Table 5). Low Ees was correlated only with lower maximal workload. No significant correlation was found with other parameters at rest. There was no modification after adjustment for sex and height.

After controlling for sex, modifications of vascular parameters during exercise, but not modifications of LV diastolic parameters (E′, E/E′, and β), were correlated with maximum workload (Ea, PVR) or 6-MWT (Ep). An increased Ees was also related to greater maximal workload ($r = -0.455$, $p < 0.01$). Ep was no longer related to 6-MWT after adjustment for sex and height, but other correlations were not modified.

Discussion

This noninvasive study examines for the first time ventriculoarterial coupling and its adaptation during exercise in patients with HFpHF. In these patients, a moderate level of exercise revealed a major increase in proximal arterial stiffness, which was absent at rest, compared with age- and sex-matched controls.

In this study, at rest, when considering vascular load, groups are comparable in proximal and peripheral load. However, moderate exercise is associated with a major increase in proximal arterial stiffness in HFpEF patients, corresponding to a dramatic increase in proximal arterial load. This result contrasts with a less impaired peripheral vascular system. This proximal arterial stiffening is probably associated with a steeper slope in the arterial pressure-volume relationship during moderate exercise. Moreover, impairment of arterial load during exercise is related to lower exercise performance in our study. This relationship between aortic stiffening and impaired exercise tolerance was previously demonstrated by Hundley et al. (9) in older individuals with HFpEF. These modifications are revealed despite the frequent use of angiotensin-converting enzyme/angiotensin receptor blocker agents in HFpEF patients, suggesting a more important role of these drugs in peripheral than proximal arteries. These results could suggest a different composition of the arterial wall in HFpEF patients and controls, but no significant difference was found between the groups in our study in terms of YEM. However, if YEM is theoretically more representative of the intrinsic properties of the arterial wall, its interpretation depends on accepting strict homogeneity of the studied material, an assumption that cannot be made with human arteries. Therefore, a different composition of arterial wall between the groups can probably not be excluded in this study.

Several factors are implicated in arterial stiffening and include structural changes with, for example, diabetes, renin-angiotensin-aldosterone system activation, metalloprotease imbalance, and advanced glycation end-product accumulation (19). These factors affect LV afterload, ventriculoarterial coupling, and LV relaxation, as well as kidney function as a fluid-retention regulator (7,20).

In this study, HFpEF patients had a rigid ventricular chamber, with an impaired pre-load reserve. These baseline characteristics are related to exercise intolerance, as previously described (5,20). Theoretically, SV increases during low-level exercise via the Frank-Starling mechanism, by the increased EDV with increased venous return, without significant change in the EDP, as in controls when LV chamber compliance is normal (4). In HFpEF patients, the diastolic pressure-volume relationship, described by an exponential equation, implies that in a rigid ventricular chamber, little increase in EDV occurs, with a major increase in EDP. In this study, several noninvasive parameters demonstrate the failure of the ventricle to dilate (less increase in EDV and $V20_i$ in HFpEF) and to relax (increase in β, tau, E/E′/EDV), which, when coupled with a failure to reduce afterload, permits the delineation of the complex mecha-

nisms underlying the failure to increase SV, despite the use of contractile reserve. In this setting, exercise limitation in HFpEF appears to be the consequence of a preload reserve failure and of an afterload mismatch, resulting in the use of the left ventricular work more to generate pressure than eject volume. Moreover, adaptation of the LV diastolic function is probably blunted by this overcoming of afterload, as previously described (21).

Study limitations. There are some limitations to this analysis. The small sample size could have led to a low-powered analysis, and small differences in terms of hypertension or diabetes between groups could have been statistically significant in a more powered analysis, especially for multivariate analysis. Confounding effects of medications may not be excluded because they were not withdrawn in this study, even if these medications are usually used in HFpEF patients.

Conclusions

This study provides another contributing variable to the phenotype of HFpEF patients by revealing a major increase in proximal afterload and arterial stiffening with moderate exercise. This contributes to abnormal ventriculoarterial coupling and exercise intolerance.

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REFERENCES

1. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol 1993;22 Suppl A:6A–3A.
2. Bursi F, Weston SA, Redfield MM, et al. Systolic and diastolic heart failure in the community. JAMA 2006;296:2209–16.
3. Swedberg K, Cleland J, Dargie H, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): the Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Eur Heart J 2005;26:1115–40.
4. 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.
5. 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.
6. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. Circulation 2003;107:714–20.
7. Maurer MS, Burkhoff D, Fried LP, Gottdiener J, King DL, Kitzman DW. Ventricular structure and function in hypertensive participants with heart failure and a normal ejection fraction: the Cardiovascular Health Study. J Am Coll Cardiol 2007;49:972–81.
8. Lam CS, Roger VL, Rodeheffer RJ, et al. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. Circulation 2007;115:1982–90.
9. 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.
10. Shapiro BP, Lam CS, Patel JB, et al. Acute and chronic ventricular-arterial coupling in systole and diastole. Insights from an elderly hypertensive model. Hypertension 2007;50:503–11.
11. Tartiere JM, Logeart D, Safar ME, Cohen-Solal A. Interaction between pulse wave velocity, augmentation index, pulse pressure and left ventricular function in chronic heart failure. J Hum Hypertens 2006;20:213–9.
12. Kelly RP, Ting CT, Yang TM, et al. Effective arterial elastance as index of arterial vascular load in humans. Circulation 1992;86:513–21.
13. Chen CH, Fetics B, Nevo E, et al. Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. J Am Coll Cardiol 2001;38:2028–34.
14. Chemla D, Hebert JL, Coirault C, et al. Total arterial compliance estimated by SV-to-aortic pulse pressure ratio in humans. Am J Physiol 1998;274:H500–5.
15. 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.
16. Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler-catheterization study. Circulation 2000;102:1788–94.
17. Klotz S, Dickstein ML, Burkhoff D. A computational method of prediction of the end-diastolic pressure-volume relationship by single beat. Nat Protoc 2007;2:2152–8.
18. Burkhoff D, Mirsky I, Suga H. Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. Am J Physiol Heart Circ Physiol 2005;289:H501–12.
19. Yano M, Kohno M, Kobayashi S, et al. Influence of timing and magnitude of arterial wave reflection on left ventricular relaxation. Am J Physiol Heart Circ Physiol 2001;280:H1846–52.
20. Kass DA. Ventricular arterial stiffening: integrating the pathophysiology. Hypertension 2005;46:185–93.
21. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure--abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med 2004;350:1953–9.

Key Words: arterial stiffness ■ contractility ■ diastole ■ exercise ■ heart failure.