

Heart Failure With Preserved Ejection Fraction Is Characterized by Dynamic Impairment of Active Relaxation and Contraction of the Left Ventricle on Exercise and Associated With Myocardial Energy Deficiency

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Objectives	We sought to evaluate the role of exercise-related changes in left ventricular (LV) relaxation and of LV contractile function and vasculoventricular coupling (VVC) in the pathophysiology of heart failure with preserved ejection fraction (HFpEF) and to assess myocardial energetic status in these patients.
Background	To date, no studies have investigated exercise-related changes in LV relaxation and VVC as well as in vivo myocardial energetic status in patients with HFpEF.
Methods	We studied 37 patients with HFpEF and 20 control subjects. The VVC and time to peak LV filling (nTTPF, a measure of LV active relaxation) were assessed while patients were at rest and during exercise by the use of radionuclide ventriculography. Cardiac energetic status (creatine phosphate/adenosine triphosphate ratio) was assessed by the use of ³¹ P magnetic resonance spectroscopy at 3-T.
Results	When patients were at rest, nTTPF and VVC were similar in patients with HFpEF and control subjects. The cardiac creatine phosphate/adenosine triphosphate ratio was reduced in patients with HFpEF versus control subjects (1.57 ± 0.52 vs. 2.14 ± 0.63 ; $p = 0.003$), indicating reduced energy reserves. Peak maximal oxygen uptake and the increase in heart rate during maximal exercise were lower in patients with HFpEF versus control subjects (19 ± 4 ml/kg/min vs. 36 ± 8 ml/kg/min, $p < 0.001$, and 52 ± 16 beats/min vs. 81 ± 14 beats/min, $p < 0.001$). The relative changes in stroke volume and cardiac output during submaximal exercise were lower in patients with HFpEF versus control subjects (ratio exercise/rest: 0.99 ± 0.34 vs. 1.25 ± 0.47 , $p = 0.04$, and 1.36 ± 0.45 vs. 2.13 ± 0.72 , $p < 0.001$). The nTTPF decreased during exercise in control subjects but increased in patients with HFpEF (-0.03 ± 12 s vs. $+0.07 \pm 0.11$ s; $p = 0.005$). The VVC decreased on exercise in control subjects but was unchanged in patients with HFpEF (-0.01 ± 0.15 vs. -0.25 ± 0.19 ; $p < 0.001$).
Conclusions	Patients with HFpEF have reduced cardiac energetic reserve that may underlie marked dynamic slowing of LV active relaxation and abnormal VVC during exercise. (J Am Coll Cardiol 2009;54:402-9) © 2009 by the American College of Cardiology Foundation

There is increasing consensus that approximately 50% of patients with the clinical features of chronic heart failure experience heart failure with preserved ejection fraction

(HFpEF) (1). Epidemiological observations of different populations confirm that the prevalence of HFpEF is increasing as it tracks the demographic transition, especially in obese hypertensive women (2). HFpEF causes as many hospitalizations

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See page 419

and incurs as severe a rate of morbidity as heart failure with reduced left ventricular ejection fraction (LVEF). Finally, HFpEF portends a significant and unimproving rate of mortality (3). Nonetheless, despite its unarguable clinical significance, the pathophysiology of HFpEF remains controversial,

with some investigators (4) proposing that diastolic abnormalities and others (5) proposing that systolic abnormalities play a dominant role. However, although most studies have focused on the parameters of patients at rest, symptoms predominantly occur during exercise (4,6). One study (7) reported a dynamic impairment of left ventricular (LV) active relaxation during isometric (handgrip) exercise, but the relevance of this observation to dynamic leg exercise that usually provokes breathlessness during everyday life is unclear.

The present study was designed to test the hypothesis that exercise limitation in HFpEF is due to a dynamic impairment of LV active relaxation and LV contractile performance during exercise, both of which may be due to an underlying impaired myocardial energetic reserve. We used radionuclide ventriculography to measure LV active relaxation, LV contractile function, and vasculoventricular coupling (VVC) at rest and during exercise. Furthermore, ³¹P cardiac magnetic resonance spectroscopy (MRS) at 3-T was used to measure in vivo myocardial energetics.

Methods

Patients. We studied 37 patients with HFpEF who were prospectively recruited from heart failure clinics. We also studied 20 healthy control subjects with no cardiac history or diabetes mellitus. Study participants had clinical examination, 12-lead electrocardiogram, pulmonary function test, echocardiogram, metabolic exercise test, and radionuclide ventriculography studies, and a subgroup underwent ³¹P cardiac MRS studies to assess cardiac energetic status. All control subjects had a normal cardiovascular examination, 12-lead electrocardiogram, and echocardiogram.

Patients with HFpEF were defined in accordance with American College of Cardiology/American Heart Association recommendations (8) as follows: 1) symptoms and signs of heart failure; 2) ejection fraction (EF) $\geq 50\%$; and 3) no valvular abnormalities. In addition, we stipulated that patients should have: 4) a maximal oxygen uptake (VO_{2max}) $< 80\%$ of age- and sex-predicted values with a pattern of gas exchange on metabolic exercise testing indicating a cardiac cause for limitation; and 5) the absence of objective evidence of lung disease on formal lung function testing and/or absence of arterial desaturation during exercise and with a ventilatory reserve ≥ 15 l at peak exercise.

We chose to use such a definition as advocated by Coats *et al.* (9) to have robust evidence that patients had exercise limitation that was cardiac rather than noncardiac in origin and so as not to prejudge the underlying pathophysiology by stipulating the presence of resting diastolic abnormalities because diastolic abnormalities frequently are present in healthy elderly subjects (10) and do not necessarily predict clinical heart failure (11) or exertional dyspnea (12). Patients with rhythm other than sinus were excluded. The investigations were performed at The University of Birmingham with approval of the Research Ethics Committee. Informed consent was obtained from all patients and control subjects.

Echocardiography. Echocardiography was performed with participants in the left lateral decubitus position with a Vivid 7 echocardiographic machine (GE, Milwaukee, Wisconsin) by the use of a 2.5-MHz transducer. Cardiac quantifications were determined in accordance with the European Association of Echocardiography (13). Left ventricular end-systolic elastance, a relatively load-independent measure of LV contractility, was determined by use of the noninvasive single-beat technique (14). Arterial elastance, a measure of the stiffness of the entire arterial tree, was calculated as the ratio of LV end-systolic pressure/stroke volume. Studies were stored digitally and analyzed offline.

MRS. In vivo myocardial energetics were measured by ³¹P cardiac MRS at 3-T as previously validated and described in detail by our group (15). We performed MRS by using a Phillips Achieva 3 scanner (Da Best, the Netherlands) and a linearly polarized transmitter and receiver ³¹P coil with a diameter of 14 cm. The repetition time was 10,000 ms with 136 averages and 512 samples. Acquisition was electrocardiogram gated, and the trigger delay was set to acquire in diastole. Total scan time was 23 min. Java magnetic resonance user interface version 3.0 (jMRUI, developed by A. van den Boogaart, Katholieke Universiteit Leuven, Leuven, Belgium) was used for analysis (16). Creatine phosphate (PCr) and gamma-adenosine triphosphate (ATP) were used to determine the PCr/ATP ratio, which is a measure of cardiac energetic state (17).

Patients with ischemic heart disease and diabetes ($n = 7$) were excluded from the MRS studies because these conditions are known to have impaired cardiac energetics (17,18). Patients with contraindications were also excluded from the MRS study ($n = 5$). The spectra of 1 patient were excluded from the analysis because of their poor quality. Three control subjects had contraindications to the MRS study. Data were analyzed separately by an investigator who was unaware of participants' clinical status.

Radionuclide ventriculography. The LVEF and diastolic filling were assessed by the use of radionuclide ventriculography with the patient at rest and during graded semierect exercise on a cycle ergometer as previously described in detail by our group (19,20). Three minutes of data were acquired at rest and during exercise after a 30-s period for stabilization of heart rate at the commencement of each stage. Exercise was performed at 50% workloads of heart

Abbreviations and Acronyms

ATP = adenosine triphosphate
HFpEF = heart failure with preserved ejection fraction
HR = heart rate
LV = left ventricular
LVEF = left ventricular ejection fraction
MRS = magnetic resonance spectroscopy
nTTPF = time to peak left ventricular filling
PCr = creatine phosphate
PKA = protein kinase A
SVI = stroke volume index
TDI = tissue Doppler imaging
Tnl = troponin I
VO_{2max} = maximal oxygen uptake
VVC = vasculoventricular coupling

rate reserve. Data were analyzed by the use of LinkMedical MAPS software (Sun Microsystems, Hampshire, United Kingdom).

Peak left ventricular filling rate in terms of end-diastolic count per second and time to peak filling normalized for R-R interval (nTTPF) in milliseconds after end-systole were calculated from the first derivative of the diastolic activity-time curve. Venous blood samples were obtained for weighing and for counting of blood gamma activity during each scan to correct for physical and physiological decay as well as for determination of relative volume changes (21). The validity of these radionuclide measures of diastolic filling at high heart rates has been established previously (22).

All gated blood pool scan-derived volumes were normalized to body surface area, yielding their respective indexes: end-diastolic volume index, end-systolic volume index, stroke volume index (SVI), and cardiac index. The following indexes were calculated: 1) arterial elastance index = end-systolic pressure (ESP) SVI; 2) LV end-systolic elastance index = ESP/end-systolic volume index; and 3) VVC ratio = arterial elastance index/LV end-systolic elastance index = $(1/EF) - 1$ (23).

Metabolic exercise test. All participants underwent a symptom-limited erect treadmill exercise with simultaneous respiratory gas analysis. The incremental ramp protocol was such that the speed and inclination increased in a stepwise manner every minute. Exercise was terminated at the subject's request because of fatigue or breathlessness. VO_{2max} was obtained during peak exercise.

Statistics. Continuous variables are expressed as mean \pm SD. An unpaired Student *t* test (2-tailed) was used to assess differences between mean values. Categorical variables were compared with the Pearson chi-square test. All reported *p* values were calculated on the basis of 2-sided tests, and a *p* value <0.05 was considered to indicate statistical significance. Variances of datasets were determined by the use of the Levene test. SPSS (version 15.0, SPSS Inc., Chicago, Illinois) was used to perform the statistical operations.

Results

Characteristics of the patients. Patients with HFpEF were generally female, overweight, and 67 ± 9 years of age with a history of hypertension; however, the blood pressure of these patients was well treated (systolic blood pressure 138 ± 19 mm Hg vs. 131 ± 23 mm Hg; $p = 0.23$, in patients with HFpEF vs. control subjects) (Table 1). The tissue Doppler mitral E-wave velocity-E' tissue velocity at the basal anterolateral (a measure of LV end-diastolic pressure) (24) was significantly greater in patients with HFpEF than in control subjects. There was also a trend (nonsignificant) to greater end-systolic elastance in patients with HFpEF than in the control group. Patients with HFpEF also had significantly reduced VO_{2max} and reduced peak heart rate (HR) on metabolic exercise testing. During semierect cycle exercise, the relative

stroke volume ($SV_{iEXERCISE}/SV_{iREST}$) was lower in patients with HFpEF compared with control subjects (0.99 ± 0.34 vs. 1.25 ± 0.47 ; $p = 0.04$), and relative cardiac output ($CO_{iEXERCISE}/CO_{iREST}$) was also lower (1.36 ± 0.45 vs. 2.13 ± 0.72 ; $p < 0.001$) (Table 2).

Left ventricular active relaxation. The nTTPF is determined by the rate of LV active relaxation (25) and by transmitral pressure gradient at the time of mitral valve opening. The nTTPF was similar at rest in patients with HFpEF and in control subjects. During exercise, it shortened in control subjects but lengthened in patients with HFpEF (Table 2). Furthermore, peak filling rates during exercise were significantly reduced in patients with HFpEF compared with control subjects (Table 2).

Left ventricular contractile function and VVC. The VVC was similar at rest in patients with HFpEF and in control subjects. During exercise, LV arterial elastance, a measure of the stiffness of the entire arterial tree, increased in both patients with HFpEF and control subjects but tended to increase more in patients with HFpEF. The LV end-systolic elastance, a measure of LV contractile function, markedly increased during exercise in control subjects but increased substantially less in patients with HFpEF. Accordingly, the VVC ratio was essentially unchanged during exercise in patients with HFpEF but decreased substantially on exercise in healthy control subjects. Furthermore, although resting LVEF and peak emptying rate were similar in patients with HFpEF and in control subjects, during exercise both were lower in patients with HFpEF (Table 2).

In vivo myocardial energetic state. At rest, the cardiac PCr/ATP ratio in patients with HFpEF was significantly reduced compared with healthy control subjects at 1.57 ± 0.52 and 2.14 ± 0.63 , respectively, $p = 0.003$ (Fig. 1).

Discussion

The principal findings of this study are as follows: 1) patients with HFpEF manifest a significant reduction in PCr/ATP ratio at rest, indicating impairment of myocardial energy "reserves." 2) As a corollary, during exercise, the energetically demanding active relaxation stage of diastole lengthened in patients with HFpEF (vs. a shortening in control subjects), and there was also a failure of the normal increase in contractile function on exercise in patients with HFpEF. These combined dynamic abnormalities of both diastolic and contractile function together resulted in a lower stroke volume during exercise. 3) Consistent with previous studies, HFpEF patients with HFpEF demonstrated chronotropic incompetence on exercise (26). These findings underline the importance of a dynamic (rather than resting) assessment of cardiac function to comprehensively characterize patients with HFpEF.

The pathophysiology of HFpEF has been the subject of considerable controversy. These patients typically are hypertensive and exhibit impaired LV active relaxation and/or

Table 1 Baseline Characteristics of the Subjects

Variable	Patients With HFpEF (n = 37)	Control Subjects (n = 20)	p Value
Age, yrs	67 ± 9	63 ± 7	0.51
Female sex	28 (76)	10 (50)	0.05
Body mass index, kg/m ²	30 ± 4	26 ± 5	<0.01
Left ventricular hypertrophy	19 (51)	5 (25)	0.05
Diabetes mellitus	4 (11)	0	—
Hypertension	27 (73)	0	—
Ischemic heart disease	4 (11)	0	—
New York Heart Association functional class			
II	29	0	—
III	8	0	—
Drug therapy			
Diuretic	10 (27)	0	—
ACE inhibitor	20 (54)	0	—
ARB	6 (16)	0	—
Beta-blocker	8 (22)	0	—
Calcium blocker	10 (27)	0	—
Alpha blocker	4 (11)	0	—
Spironolactone	2 (5)	0	—
Nitrate	3 (8)	0	—
Metabolic exercise testing			
VO ₂ max (ml/kg/min)	19 ± 4	36 ± 8	<0.001
Respiratory exchange ratio	1.06 ± 0.07	1.13 ± 0.10	0.003
Breathing reserve, l/min	36 ± 15	43 ± 18	0.16
HR, beats/min			
Rest	74 ± 14	83 ± 17	0.03
Peak exercise	127 ± 20	166 ± 11	<0.001
ΔHR	52 ± 16	81 ± 14	<0.001
SBP, mm Hg			
Rest	138 ± 19	131 ± 23	0.23
Peak exercise	182 ± 26	190 ± 30	0.30
DBP, mm Hg			
Rest	181 ± 11	181 ± 12	0.98
Peak exercise	81 ± 13	84 ± 10	0.36
Echocardiography			
Left ventricular ejection fraction, %	64 ± 14	63 ± 6	0.77
Mitral E-wave velocity, m/s	0.72 ± 0.19	0.61 ± 0.12	0.02
Mitral A-wave velocity, m/s	0.80 ± 0.20	0.59 ± 0.17	<0.001
Ratio of E-wave/A-wave velocity	0.96 ± 0.35	1.03 ± 0.32	0.47
Mitral E-wave deceleration, ms	274 ± 70	269 ± 73	0.82
E/E' (lateral)	12 ± 4	8 ± 2	<0.001
E _{es}	3.07 ± 1.07	2.60 ± 0.53	0.09
E _a	2.22 ± 0.63	2.28 ± 0.48	0.69

Values are n (%), n, or mean ± SD. When patients on beta-blockers were excluded from analysis, the levels of significance was similar apart from resting heart rate (HR) (p = 0.14). The body mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; DBP = diastolic blood pressure; E_a = arterial elastance; E/E' = mitral E-wave velocity-E' tissue velocity (PW-TDI) at basal anterior-lateral wall ratio; E_{es} = left ventricular end-systolic elastance; HFpEF = heart failure with preserved ejection fraction; LA = left atrium; MABP = mean arterial blood pressure; NYHA = New York Heart Association; SBP = systolic blood pressure; VO₂max = maximal oxygen uptake.

increased passive LV diastolic stiffness at rest (4). This finding has led some authors (27) to conclude that exercise limitation is primarily a result of impaired LV diastolic filling and to the use of the term diastolic heart failure. However, diastolic dysfunction is also a common finding at rest in healthy elderly subjects (10). Furthermore, subtle abnormalities of systolic function, in particular long-axis systolic function, are also almost universally observed in

patients with HFpEF despite normal LVEF (5). This finding has led others (28) to propose that HFpEF is predominantly a disorder of contractile function. To compare both of these possibilities, we specifically chose to define the syndrome on the basis of a limitation of exercise capacity with a cardiac basis for this limitation rather than by using resting parameter of diastolic function so as to not prejudice the role of diastolic versus systolic mechanisms.

Table 2

Radionuclide Ventriculography at Rest and on Exercise: Diastolic Filling Characteristics, Systolic Function, Relaxation, Stiffness, and VVC

Variable	Patients With HFpEF (n = 37)	Control Subjects (n = 20)	p Value
Exercise HR, beats/min	97 ± 14	114 ± 11	<0.001
Exercise SBP, mm Hg	204 ± 26	198 ± 27	0.45
Exercise DBP, mm Hg	95 ± 15	97 ± 7	0.56
Exercise MABP, mm Hg	132 ± 15	131 ± 9	0.85
Ejection fraction, %			
Rest	65 ± 9	64 ± 9	0.61
Exercise	66 ± 9	72 ± 8	0.05
Peak emptying rates, EDC/s			
Rest	382 ± 106	400 ± 90	0.56
Exercise	477 ± 123	563 ± 144	0.04
Peak filling rates, EDC/s			
Rest	342 ± 120	321 ± 111	0.54
Exercise	504 ± 127	602 ± 163	0.02
Time to peak filling, RR			
Rest	0.18 ± 0.08	0.18 ± 0.09	0.84
Exercise	0.25 ± 0.09	0.16 ± 0.08	0.001
Δ nTTPF	+0.07 ± 0.11	-0.03 ± 0.12	<0.005
VVC ratio, E _a /E _{LV}			
Rest	0.57 ± 0.20	0.62 ± 0.22	0.36
Exercise	0.55 ± 0.19	0.41 ± 0.15	0.01
Δ VVC	-0.01 ± 0.15	-0.25 ± 0.19	<0.001
Relative exercise Δ stroke volume index	0.99 ± 0.34	1.25 ± 0.47	0.04
Relative exercise Δ cardiac output index	1.36 ± 0.45	2.13 ± 0.72	<0.001
Relative exercise Δ E _{LV}	1.35 ± 0.50	1.85 ± 0.63	0.01
Relative exercise Δ E _a	1.52 ± 0.48	1.28 ± 0.44	0.17

Values are mean ± SD. When patients on beta-blockers were excluded from analysis, the levels of significance were similar apart from peak filling rates during exercise (p = 0.08).

EDC = end-diastolic count; relative ΔE_a = E_aEXERCISE/E_aREST; relative ΔE_{LV} = E_{LV}EXERCISE/E_{LV}REST; relative Δ cardiac output index = CO_{EXERCISE}/CO_{REST}; relative Δ stroke volume index = SV_{EXERCISE}/SV_{REST}; ΔnTTPF = time to peak left ventricular filling; RR = values normalized for R-R interval; VVC = vasculoventricular coupling; ΔVVC ratio = (E_a/E_{LV})EXERCISE - (E_a/E_{LV})REST; other abbreviations as in Table 1.

Little attention has been paid to changes in systolic and diastolic function during dynamic exercise, which is when most patients experience their symptoms. In one study, 10 patients with HFpEF were assessed with invasive pressure-volume loops and compared with age-matched control subjects (7). The former had increased arterial elastance (a measure of the stiffness of the entire arterial tree) and increased LV end-systolic elastance (a measure of the stiffness of the ventricle during systole and a relatively load independent measure of the contractile state of the left ventricle) (29). Although diastolic abnormalities were not universally present in patients at rest, marked differences appeared during handgrip exercise. The rate of LV active relaxation increased in healthy subjects but it slowed in patients with HFpEF (7). In another study from the same group, exercise-related symptoms in Afro-Caribbean hypertensive patients appeared to be strongly associated with chronotropic incompetence and an inadequate vasodilator reserve on exercise (26).

The present study examined the pathophysiological mechanisms in HFpEF and found marked dynamic (exercise-induced) abnormalities in both contractile and diastolic function of the LV and a lower peak exercise HR in patients with HFpEF. It is possible for an impaired HR response during exercise to cause a reduction in exercise capacity as measured by VO₂max, which is largely determined by cardiac output on exercise and the latter is simply the product of HR and stroke volume. However, in the setting of a profound slowing of active relaxation and increased LV passive diastolic stiffness, a greater diastolic filling period might be expected to be beneficial.

In this study, despite a longer diastolic filling time, the relative change in stroke volume was lower in patients during submaximal exercise. Impaired HR response may be a consequence of the heart failure because an impaired chronotropic response (associated with slow HR recovery after exercise) is typically present in systolic heart failure and is in part a manifestation of impaired vagal tone (30), or it may be an adaptation to improve diastolic filling. The latter seems at least plausible because increasing heart rate by atrial pacing has been shown to reduce supine resting stroke volume and cardiac output in patients with HFpEF (31). It will be important to undertake further studies to assess whether HR plays a causal role in exercise limitation in HFpEF because, if so, it may be amenable to rate responsive pacing.

The patients in this study had a history of hypertension but were well treated with antihypertensive medications (in most cases including vasodilators); therefore, resting blood pressure and arterial elastance were not significantly greater than in the control group. Consistent with previous studies (7), in patients at rest, LV end-systolic elastance (a measure of contractility or systolic stiffness) tended to be greater in patients with HFpEF, although this finding did not reach significance. The increase in arterial elastance during exercise tended to be greater in patients with HFpEF versus control subjects (presumably reflecting a greater increase in large artery stiffness). However, although LV end-systolic elastance almost doubled during exercise in control subjects, the increase was only 35% in patients with HFpEF; hence, VVC reduced by 33% during exercise in control subjects but was unchanged in patients with HFpEFs. These findings indicate a blunting of the physiological increase in the contractile state of the left ventricle on exercise.

The physiological increase in the rate of LV active relaxation during exercise is a consequence of sympathetic activation, via cAMP-dependent protein kinase A (PKA)-mediated phosphorylation of key proteins, including troponin I, sarco/endoplasmic reticulum Ca²⁺-ATPase, and titin (32-34). In experimental models, large acute increases in afterload resulted in an acute impairment of LV active relaxation (35), with the threshold for this phenomenon being lower in the diseased heart, leading to the concept of "relative load" as a determinant of afterload-related impairment of LV active relaxation (36).

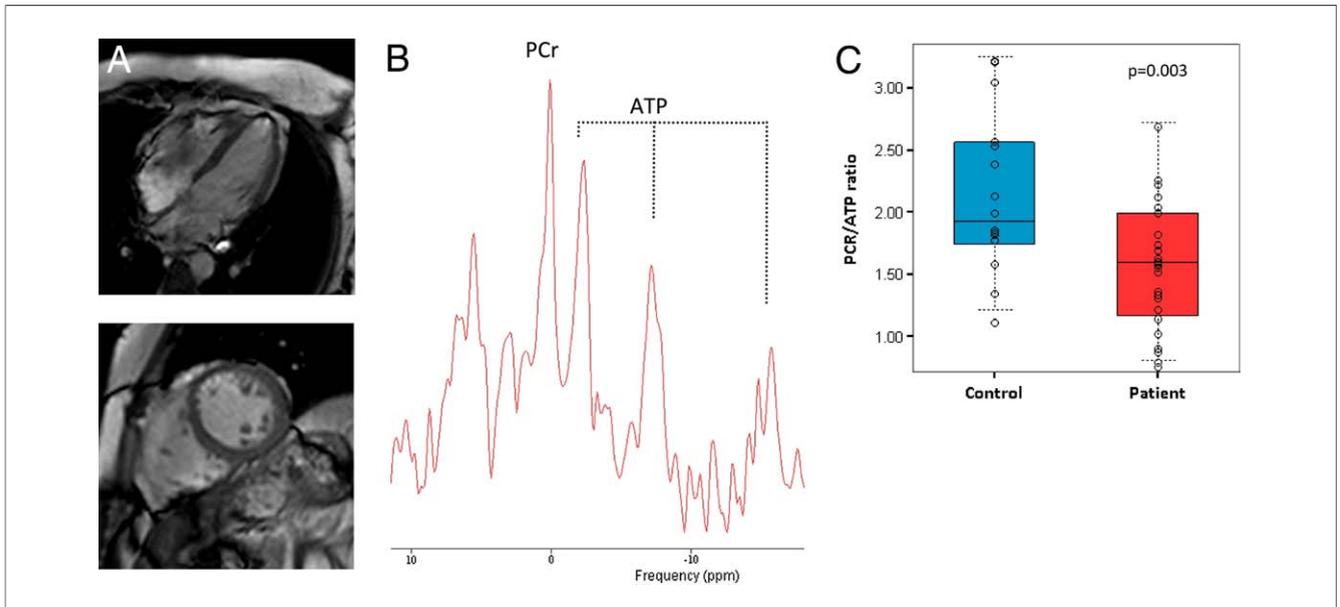


Figure 1 Impaired Myocardial Energetics in Patients With HFpEF

(A) Cardiac magnetic resonance (MR) images of a patient with heart failure with preserved ejection fraction (HFpEF) and (B) the corresponding localized ^{31}P MR spectra from the left ventricle. The corresponding peaks of creatine phosphate (PCr) and the gamma-, alpha-, and beta-phosphate (resonances of the adenosine triphosphate [ATP]) are labeled. (C) Circles represent individual PCr/gamma-ATP ratio in patients with HFpEF and in control subjects. The subjects PCr/gamma-ATP ratio was significantly reduced in patients with HFpEF compared with healthy control subjects ($p = 0.003$).

In the study of patients with HFpEF described previously (7), handgrip exercise was associated with a substantially greater increase in LV end-systolic pressure than in control subjects, potentially explaining the observed slowing of LV active relaxation. A key coupler of this load-dependent LV relaxation is troponin I-protein kinase A (TnI-PKA) phosphorylation (37). It is known that the energy-dependent process of phosphorylation of TnI by PKA decreases myofibrillar calcium sensitivity (38) and increases the rate at which calcium dissociates from troponin C (39), which can lead to an increased rate of LV relaxation. Indeed, in a study involving transgenic mice in which PKA phosphorylation sites on TnI were constitutively active, acute aortic constriction led to a lengthening of Tau (an invasive measure of active relaxation) in the wild-type mice but not in the transgenic mice (37).

Integrating these observations, we speculate that dynamic energy impairment may account for the slowing of LV active relaxation on exercise as well as the failure of LV contractile function to increase. To increase the generalizability of this hypothesis, we avoided positively biasing our study by excluding patients with established causes of cardiac energy deficiency (ischemic heart disease and diabetes) (17,18). Nevertheless, the PCr/ATP ratio was still substantially reduced in patients with HFpEF versus control subjects at rest. The lower PCr/ATP ratio in patients indicates a reduction of high-energy phosphates reserve at rest (40,41).

Although the time required for acquisition of cardiac MRS signals precluded the measurement of high energy

phosphate status during exercise, it is likely that any basal energetic impairment will be exacerbated dynamically. This exacerbation of dynamic energetic impairment would explain the prolongation of the energy demanding active relaxation as manifested by nTTPF. Moreover, the lower HRs and lesser increases in LV end-systolic elastance may represent strategies to limit dynamic cardiac energy demands. The cause for this resting energy deficit may relate to insulin resistance (42), to impaired mitochondrial function as a result of aging (43), and to neuroendocrine activation and aberrant substrate metabolism (44). In addition, increased myocardial fibrosis, as previously reported serologically in patients with diastolic heart failure (45), may also lead to a reduced PCr/ATP ratio in patients with HFpEF. This finding is relevant because in patients with hypertrophic cardiomyopathy, a reduced PCr/ATP ratio has been shown to correlate with the presence of a fibrotic area in the myocardium of the LV (46).

From a clinical perspective, this study has shown that patients with HFpEF have reduced myocardial energetic status, which provides the rationale to assess the therapeutic value of “metabolic agents” (e.g., perhexiline and trimetazidine) that increase cardiac energetic status by altering cardiac substrate use (47). Indeed, the use of trimetazidine and perhexiline have both been shown to be beneficial in patients with systolic heart failure (48,49). Importantly, we have shown that patients with HFpEF have a dynamic pathophysiological process whereby resting parameters may be comparable with control subjects; however, during exercise, patients with HFpEF have impaired LV active relaxation

and exhibit no increase in LV end-systolic elastance. This finding suggests that, in detecting patients with HFpEF, we cannot solely rely on resting parameters and that we perhaps need to consider some form of exercise testing, such as metabolic exercise testing as advocated by Coats et al. (9) or exercise radionuclide ventriculography scans, to detect abnormal LV relaxation during exercise.

Study limitations. Our radionuclide exercise protocol involved asking subjects to maintain an HR that was 50% of HR reserve above their resting HR. Because this HR reserve was calibrated to peak HR rate, the absolute workload in patients was lower. To have compared patients at the same workload would be inappropriate because this comparison would represent a greater relative workload in patients. Moreover, most changes in stroke volume occur in the first part of exercise, with subsequent increases in cardiac output being principally the result of increases in HR (50).

A small proportion of patients were on beta-blockers, which may have affected their cardiovascular response to exercise; however, when these patients were excluded from the analysis, the findings and the level of significance remained unchanged. In addition, some patients were on calcium blockers; however, these drugs were all peripherally acting (dihydropyridine for hypertension) and therefore are not expected to affect the myocardium directly.

Ideally, we would have liked to measure cardiac energetics during exercise; however, the performance of cardiac MRS studies during exercise is currently quite challenging and more so if we tried to replicate the same dynamic leg exercise in the confinement of a MR scanner. A number of problems, such as acquisition at greater heart rates, shorter acquisition times, voxel specificity, pulse design, and shorter repetition times, are currently being addressed by our group and other groups around the world.

The use of MRS and radionuclide studies also requires a regular rhythm; thus, patients with atrial fibrillation were excluded from the study. In contrast, the strength of radionuclide studies is their increasing temporal resolution at greater HRs. This obviates the confounding E:A fusion that is frequently experienced with exercise echocardiography. Radionuclide studies are thus not subject to systematically biasing mechanistic HFpEF toward a subgroup of patients without E:A fusion on exercise.

Conclusions

Patients with HFpEF have reduced cardiac energetic reserves which, when exacerbated dynamically, may contribute to the abnormal LV active relaxation during exercise and a lack of increase in LV end-systolic elastance. In addition, chronotropic response is markedly impaired during exercise in patients.

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Key Words: heart failure ■ diastole ■ radionuclide ventriculography ■ spectroscopy ■ exercise.