Impaired Heart Rate Recovery and Chronotropic Incompetence in Patients with Heart Failure with Preserved Ejection Fraction

Brief title: Autonomics in HfpEF

Word Count: Total: 4264 Abstract: 268

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Abstract

Background:
This study assessed the chronotropic response to exercise and heart rate (HR) recovery following exercise in a carefully phenotyped group of patients with heart failure with preserved left ventricular systolic function (HfpEF) and a control group of similar age and gender distribution.

Methods and Results:
We studied 41 HfpEF patients, 41 healthy controls and 16 hypertensive controls. None were taking HR-limiting medications. All study participants had clinical examination, 12-lead electrocardiogram, pulmonary function test, echocardiogram and metabolic exercise test with HR monitoring throughout exercise. Chronotropic response was measured by the percentage of the HR reserve used during maximal exercise (%HHR) and the peak exercise HR as a percentage of predicted maximal HR (%Max-PHR).

HfpEF Patients were generally females (70%), overweight, aged 69±8 years old. Controls were of similar gender (63%) and age (67±6 years old). Patients with HfpEF had significantly reduced peak VO₂ compared to controls (20±4 ml/Kg/min vs. 31±6 ml/Kg/min, p<0.001) and greater minute ventilation--carbon dioxide production relationship (VE/VCO₂ slope) (33±6 vs. 29±4, p<0.001). Chronotropic incompetence was significantly more common in patients with HfpEF compared to matched-healthy controls as measured by %HHR (63% vs. 2%, <0.001) and %Max-PPHR (34% vs. 2%,
<0.001). In addition, abnormal HR recovery 1-minute post exercise (defined as the reduction in the HR from peak exercise one minute post-exercise) was also significantly more common in patients with HfpEF compared to controls (23% vs. 2%, p=0.01). Hypertensive controls showed similar chronotropic response to peak exercise and HR recovery following exercise as healthy controls.

Conclusions

Patients with HfpEF have impaired chronotropic incompetence during maximal exercise and abnormal heart rate recovery post exercise.

Keywords: Heart rate recovery, chronotropic response, heart failure with preserved ejection fraction and metabolic exercise testing.
Introduction

Approximately 50% of patients with the clinical features of heart failure are found to have normal left ventricular ejection fraction and normal valvular function. The term heart failure with preserved LV ejection fraction (HfpEF) is applied to these patients. (1) They are typically elderly women who frequently have associated hypertension, diabetes, and/or coronary artery disease. (2) They have similar hospital length of stay, admission rates (3, 4) and mortality rate to that of patients with systolic heart failure (3). The prevalence of HfpEF appears to be increasing and in contrast to systolic heart failure the mortality rate of this disorder is not declining. (4)

The pathophysiology of HfpEF has been a matter of considerable controversy. Impaired left ventricular relaxation, increased passive left ventricular stiffness and contractile dysfunction (despite the presence of a normal left ventricular ejection fraction) each appear to contribute to exercise limitation. However one recent study in HfpEF reported an association between an impaired heart rate (HR) response to exercise and exercise limitation. (1) However there are a number of important caveats. Firstly, the patients were mainly African American hypertensives and the relevance to HfpEF in a Caucasian population is unknown. Secondly, the patient numbers were relatively small. Thirdly, many of the patients (and the hypertensive controls without breathlessness) were taking beta blockers. Although these were discontinued 24 hours prior to the study the potential of either ongoing beta blockade (chronotropic incompetence (5)) or of rebound effects (6) to have influenced the findings cannot be excluded. Thus, in this
study we aimed to assess HR response to exercise and during recovery in a larger group of patients with HfpEF who were not taking beta-blockers using maximal symptom limited erect treadmill metabolic exercise testing.

Methods

Study Participants

*HfpEF patients*

We studied 41 HfpEF patients prospectively and consecutively recruited from heart failure clinics. All study participants had clinical examination, 12-lead electrocardiogram, pulmonary function test, echocardiogram and metabolic exercise test. All patients met the criteria of Yturralde and Gaasch for the diagnosis of diastolic heart failure. (7) They had (i) signs and/or symptoms of heart failure, (ii) objective evidence of exercise limitation on cardiopulmonary exercise testing (peak VO2 <80% of predicted) with a pattern of gas exchange indicating a cardiac cause for limitation exercise capacity, (iii) normal LVEF and chamber size, and (iv) LV hypertrophy and/or evidence of diastolic dysfunction on echocardiographic doppler. Patients with severe pulmonary disease, significant valvular heart disease, atrial fibrillation, or evidence of hypertrophic cardiomyopathy were excluded similar to previous studies (1). HfpEF patients on beta-blockers or non-dihydropyridines calcium blockers (e.g. verapamil and diltiazem) were also excluded in order accurately assess chronotropic response and HR recovery. The investigations were performed at The University of Birmingham with approval of the Research Ethics Committee. Informed consent was obtained from all subjects.
Healthy controls

We studied 41 healthy controls with similar age and gender as our HfpEF population. They were volunteers recruited prospectively from the community with no cardiac history, hypertension or diabetes mellitus. In addition 16 newly diagnosed hypertensive controls from the community were studied to explore the possibility of hypertension per se as a cause of cardiac autonomic dysfunction. The vast majority of these hypertensive controls were studied prior to the commencement of any antihypertensive therapy. None was taking heart rate lowering medication. All control subjects had a normal clinical cardiovascular examination, 12-lead electrocardiogram, echocardiogram and metabolic exercise test.

Metabolic Exercise Testing

The metabolic exercise testing was performed on a Schiller CS-200 Ergo-Spiro exercise machine which was calibrated before every study. Subjects underwent spirometry and this was followed by symptom-limited erect treadmill exercise testing using incremental ramp protocol (speed and inclination was increased every minute) as described previously by our group (8) with simultaneous respiratory gas analysis (9, 10). Samplings of expired gases were performed continuously, and data were expressed as 30-second means. The minute ventilation – carbon dioxide production relationship (VE/VCO₂ slope), maximal oxygen consumption, carbon dioxide production, and respiratory exchange ratio (RER) was used to verify objective effort adequacy. Peak oxygen consumption (peak VO₂) was defined as the average values of VO₂ measured during the
last 30 seconds of exercise. Blood pressure and ECG were monitored throughout. Subjects were encouraged to exercise to exhaustion with a minimal requirement of RER > 1.

Chronotropic incompetence is defined as an inadequate HR response to exercise. Two methods were used to assess chronotropic response. The first, was percentage of the HR reserve used during peak exercise (%HHR) which was determined as the change in HR from rest to peak exercise as a percentage of HR reserve (the difference between the predicted maximal heart rate and the resting heart rate). A failure to use 80 percent of the HR reserve was considered to be evidence of chronotropic incompetence, (11) which is an independent predictor of mortality. (12) The second method was to calculate the peak exercise HR as a percentage of predicted maximal HR (%Max-PHR). In this case, chronotropic incompetence was defined as a peak exercise HR less than 80% of the maximum age predicted peak HR. (13) HR recovery post exercise was defined as the reduction in the HR from the HR at peak exercise to the HR at one minute after the cessation of exercise. Abnormal HR recovery was defined as a reduction of ≤12 beats per minute in the first minute of exercise. (14) Predicted maximal HR for an individual was calculated using the more recently determined formula of Tanaka et al (208 - 0.7 x age in years). (15)

Resting Echocardiography
Echocardiography was performed with participants in the left lateral decubitus position with a Vivid 7 echocardiographic machine and a 2.5-MHz transducer. Resting scans were acquired in standard apical 4-chamber and apical 2-chamber views. All echocardiographic measurements were averaged from 3 heart beats. LV ejection fraction was calculated from LV volumes (LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV)) by the modified biplane Simpson rule in accordance with the guidelines. (16) From the LV-inflow pattern (measured at the tips of the mitral valve), peak early (E) and late (A) filling velocities, E/A ratio, and E-velocity deceleration time (DcT) were measured.

**Statistics**

Continuous variables are expressed as mean ± SD. Variances of data sets were determined using Levene’s test. Comparisons were performed with one-way ANOVA on all three groups. All presented continuous data in the results section were normally distributed and meets the assumptions of ANOVA. Post-hoc test were performed on ANOVA to examine individual mean differences (Tukey test). Categorical variables were compared using the Chi-Square test. Pearson correlation coefficient (r) was used to describe the relationship between variables. A two-tailed p value of <0.05 was considered statistically significant. SPSS (v15.0) was used to perform the statistical analyses.

**Results**
Characteristics of Patients

HfpEF Patients were generally females (70%), overweight, aged 69±8 years old with a history of hypertension. Healthy controls were of similar gender (63% females) and age (67±6 years old). (Table 1) Patients with HfpEF had significantly reduced peak VO₂ compared to healthy controls (20±4 ml/Kg/min vs. 31±6 ml/Kg/min, p<0.001). The minute ventilation--carbon dioxide production relationship (VE/VCO₂ slope) was also higher in patients with HfpEF than healthy controls (33±6 vs. 29 ± 4, p<0.001). (Table 2)

Chronotropic response to maximal exercise testing

HfpEF patients vs. matched healthy controls had similar resting heart rate and predicted maximal HR, 78±14 vs. 79±13 (p=0.99) and 160±6 vs. 161±4 (p=0.53), respectively. HfpEF patients had lower peak HR response and lower change in HR (the difference between peak HR and resting HR) during peak exercise compared to matched healthy controls, 139±22 vs. 171±18, p<0.001 and 60±22 vs. 93±21, p<0.001, respectively. (Figure 1). Chronotropic incompetence was significantly more common in patients with HfpEF compared to matched healthy controls as measured by %HHR and %Max-PPHR. In addition, abnormal HR recovery 1-minute post exercise was also significantly more common in patients with HfpEF compared to matched healthy controls. (See table 3 and figure 2). Peak oxygen consumption (peak VO₂) correlated directly with peak exercise heart rate (r=0.57, p<0.001). (Figure 3) Chronotropic incompetence and impaired heart recovery remained highly significant in patients with HfpEF when compared with hypertensive controls. There were no significant differences between hypertensive controls.
controls and healthy controls with respect to chronotropic response during peak exercise and heart rate recovery following exercise.

Discussion

The principal findings of this study are: a) HfPEF patients had similar resting and predicted maximal HR compared to matched-healthy controls, but during peak dynamic exercise, HfPEF patients displayed significant chronotropic incompetence. b) Abnormal HR recovery 1-minute post exercise was more common in HfPEF patients compared to matched healthy controls. c) Hypertensive controls showed similar chronotropic response to peak exercise and heart rate recovery following exercise as healthy controls.

Chronic heart failure is characterised by impaired exercise tolerance often due to breathlessness and fatigue. Metabolic exercise testing is an objective tool to measure exercise limitation in patients with CHF as indicated by reduced maximal oxygen consumption (peak VO₂) and an increase in the ventilatory response to exercise (the relation of ventilation (VE) to carbon dioxide production (VCO₂) or VE/VCO₂ slope). (17) In this study we found that patients with HfPEF have reduced peak VO₂ and higher VE/VCO₂ slope compared to older controls, which are supported by previous reports. (18) Indeed, VE/VCO₂ slope has been shown to have prognostic value in patients with diastolic heart failure with respect to both mortality and hospitalization. (19)
In healthy subjects, the initial increase in HR during exercise results from a withdrawal of the physiological vagal tone present at rest and sympathetic tone is responsible for further increases in HR as exercise continues. (20) Post exercise sympathetic withdrawal contributes to early HR recovery and at a later stage parasympathetic reactivation plays a larger role in HR recovery. (21)

In chronic heart failure (CHF) associated with LV systolic dysfunction there is impaired autonomic function (22) as a result of an impaired vagal tone (23) as well as an over-activity of sympathetic function which results in reduced responsiveness to beta adrenergic stimulation due to both reduced adrenoreceptor number and reduced downstream signalling (24). The clinical sequelae of these autonomic changes include an impaired HR response to exercise (chronotropic incompetence) which may contribute to exercise limitation. (25, 26) Indeed studies have shown that as the severity of systolic heart failure worsens the more common chronotropic incompetence during exercise becomes in patients with CHF. (27) Nevertheless, even in asymptomatic patients with reduced LVEF and LV dilatation poor HR response has been reported. (28) An impaired heart rate recovery following exercise is also common in patients with systolic heart failure (29) and appears to be primarily due to low vagal tone (23). Impaired HR recovery following exercise also appears to be a powerful predictor of mortality not only in patients with systolic heart failure but also predicts cardiovascular mortality in apparently healthy subjects. (14)
In this study, we found HfpeF patients had lower maximal HR response during maximal exercise than controls, which is important because maximal HR response is associated with coronary disease and cardiovascular mortality. Furthermore, we found that 34% of patients with HfpeF have chronotropic incompetence during maximal exercise when defined by, %Max-PPHR and 63% when defined by %HHR. These proportions are quite similar to findings in patients with CHF due to systolic dysfunction. (30) HR recovery was also found to be impaired in a significant proportion of patients with HfpeF, which suggest the presence of parasympathetic imbalance.

Borlaug BA et al. (1) showed in hypertensives (mainly African Americans) that chronotropic incompetence was a powerful predictor of the presence of symptoms of heart failure. However, this relationship between chronotropic incompetence and HfpeF may or may not be causal. Chronotropic incompetence in HfpeF may be an adaptation to improve diastolic filling, since increasing HR 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, this may be amenable to rate responsive pacing.

The precise mechanism of impaired autonomic dysfunction in HfpeF is unclear, some have proposed a peripheral factor responsible rather than central. (1) Studies in CHF have revealed a blunted baroreflex control could play an important role (32) secondary
to reduced arterial compliance (33), impaired central reflex integration, and a decrease in end-organ responsiveness (32). Increased sensitivity of muscle ergoreceptors and peripheral chemoreceptors has also been linked to autonomic impairment in CHF. (34, 35) A review on this topic has been discussed by our group elsewhere. (22)

**Study limitations**

Ideally we would have liked to have recruited a control group of obese normotensive subjects for comparison with our HfpEF population; however this in practice might be difficult given that these obese normotensive subjects would also have to have no cardiac history, hypertension or diabetes mellitus. We have performed multiple statistical tests to examine individual mean differences; however our findings are highly significant and are consistent with previous reports.

**Conclusions**

Patients with HfpEF have chronotropic incompetence during maximal exercise and abnormal heart rate recovery post exercise.

**Funding sources**

We would like to thank the British Heart Foundation for funding this study.

**Disclosures**
Prof Michael Frenneaux:

Prof Michael Frenneaux: Honoraria from Metronic, St Jude and Biotronik; Consultant/Advisory Board for Metronic, St Jude, Menarini and Biotronik; Speaker on panel for Menarini.
Reference List


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*Circulation* 1989;**80**:314-323.


Legends

Figure 1: Differences in heart rate response during exercise and post exercise in patients with HfpEF, hypertensive controls and healthy controls. (Only significant differences are shown)
*p<0.05
†p<0.001

Figure 2: Abnormal chronotropic response in patients with HfpEF compared to hypertensive controls and healthy controls during exercise. Panel A: chronotropic incompetence in HfpEF patients as measured by peak exercise HR as a percentage of predicted maximal HR (%Max-PPHR). Panel B: chronotropic incompetence in HfpEF patients as measured by % of heart rate reserved used at peak exercise (%HHR)

Figure 3: Peak oxygen consumption correlating directly with peak exercise heart rate. Black dots – HfpEF patients, triangles – hypertensive controls and squares healthy controls.
Table 1: Baseline characteristics

<table>
<thead>
<tr>
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<th>Healthy Controls</th>
<th>Hypertensive Controls</th>
<th>HfpEF Patients</th>
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<td>n=41</td>
<td>n=16</td>
<td>n=41</td>
<td></td>
</tr>
<tr>
<td>Females no. (%)</td>
<td>26 (63)</td>
<td>7 (43)</td>
<td>29 (70)</td>
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<td>Age (years)</td>
<td>67±6</td>
<td>68±6</td>
<td>69±8</td>
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<tr>
<td>BMI</td>
<td>26±4</td>
<td>27±3</td>
<td>31±4*†</td>
<td>&lt;0.001</td>
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<td>Obesity no. (%)</td>
<td>21 (51)</td>
<td>13 (81)</td>
<td>35 (85)</td>
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<td>Hypertension no. (%)</td>
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<tr>
<td>Diabetes no. (%)</td>
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<td>3 (7)</td>
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<tr>
<td>NHYA functional class no. (%)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>II</td>
<td></td>
<td></td>
<td>34 (83)</td>
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<tr>
<td>III</td>
<td></td>
<td></td>
<td>7 (17)</td>
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<tr>
<td>Medications</td>
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<td>Diuretic</td>
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<td>2 (13)</td>
<td>9 (22)</td>
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<td>ACE inhibitor</td>
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<td>1 (6)</td>
<td>18 (44)</td>
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<tr>
<td>ARB</td>
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<td>7 (17)</td>
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<td>Calcium blocker</td>
<td>0</td>
<td>1 (6)</td>
<td>14 (34)</td>
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<td>Spironolactone</td>
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<tr>
<td>Nitrate</td>
<td>0</td>
<td>0</td>
<td>3 (7)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Plus-minus values are means ± SD. NYHA denotes New York Heart Association, ACE angiotensin-converting enzyme, ARB angiotensin II receptor blockers. BMI body mass index. Obesity defined as BMI>25.
*P<0.05 vs. Hypertensive controls
†P<0.05 vs. Healthy controls
Table 2: Metabolic exercise test and Echocardiographic parameters

<table>
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<tr>
<th></th>
<th>Healthy Controls n=44</th>
<th>Hypertensive Controls n=16</th>
<th>HfPEF Patient n=41</th>
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<tr>
<td><strong>Metabolic exercise test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO₂ max (ml/Kg/min)</td>
<td>31 ± 6</td>
<td>29 ± 5</td>
<td>20 ± 4†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory Exchange Ratio (RER)</td>
<td>1.11 ± 0.10</td>
<td>1.12 ± 0.09</td>
<td>1.07 ± 0.09</td>
<td>0.04</td>
</tr>
<tr>
<td>% Predicted VO₂ max</td>
<td>93 ± 21</td>
<td>84 ± 13</td>
<td>60 ± 10†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VE/VCO₂</td>
<td>29 ± 4</td>
<td>30 ± 3</td>
<td>33 ± 6†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Breathing Reserve (L/min)</td>
<td>38 ± 14</td>
<td>34 ± 17</td>
<td>35 ± 14</td>
<td>0.58</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>79 ± 13</td>
<td>87 ± 13</td>
<td>78 ± 14</td>
<td>0.07</td>
</tr>
<tr>
<td>Peak</td>
<td>171 ± 18</td>
<td>163 ± 11</td>
<td>139 ± 22†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>135 ± 20</td>
<td>153 ± 16†</td>
<td>139 ± 21</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Peak</td>
<td>190 ± 20</td>
<td>193 ± 21</td>
<td>183 ± 26</td>
<td>0.29</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
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<td></td>
<td></td>
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<tr>
<td>Rest</td>
<td>82 ± 9</td>
<td>87 ± 9</td>
<td>82 ± 11</td>
<td>0.16</td>
</tr>
<tr>
<td>Peak</td>
<td>88 ± 10</td>
<td>93 ± 9</td>
<td>82 ± 11†</td>
<td>&lt;0.01</td>
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<tr>
<td><strong>Echocardiography</strong></td>
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<td></td>
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<tr>
<td>Left ventricular ejection fraction - %</td>
<td>64 ± 5</td>
<td>63 ± 7</td>
<td>64 ± 10</td>
<td>0.88</td>
</tr>
<tr>
<td>Mitral E-wave velocity - m/sec</td>
<td>0.62 ± 0.14</td>
<td>0.68 ± 0.16</td>
<td>0.66 ± 0.14</td>
<td>0.30</td>
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<tr>
<td>Mitral A-wave velocity - m/sec</td>
<td>0.71 ± 0.15</td>
<td>0.80 ± 0.17</td>
<td>0.85 ± 0.19†</td>
<td>&lt;0.001</td>
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<tr>
<td>Ratio of E-wave: A-wave velocity</td>
<td>0.93 ± 0.25</td>
<td>0.88 ± 0.23</td>
<td>0.80 ± 0.18†</td>
<td>0.03</td>
</tr>
<tr>
<td>Mitral E-wave deceleration - msec</td>
<td>237 ± 62</td>
<td>250 ± 44</td>
<td>265 ± 64</td>
<td>0.13</td>
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</table>

Plus-minus values are means ± SD. The minute ventilation – carbon dioxide production relationship (VE/VCO₂ slope)

*P<0.05 vs. Hypertensive controls
†P<0.05 vs. Healthy controls
<table>
<thead>
<tr>
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<th>HfpEF Patients (N=41)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronotropic incompetence using %Max-PPHR method, No. (%)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>14 (34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronotropic incompetence using %HHR method, No. (%)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>26 (63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal heart rate recovery, No. (%)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>9 (23)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Figure 1
Figure 2
Figure 3

$r = 0.57$
$p < 0.001$
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Circ Heart Fail. published online November 16, 2009;
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

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