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

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Background—This study assessed the chronotropic response to exercise and heart rate (HR) recovery after exercise in a carefully phenotyped group of patients with heart failure with preserved left ventricular ejection fraction (HfP EF) and a control group of similar age and gender distribution.

Methods and Results—We studied 41 patients with HfP EF, 41 healthy controls, and 16 hypertensive controls. None were taking HR-limiting medications. All study participants had clinical examination, 12-lead ECG, 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 and the peak exercise HR as a percentage of predicted maximal HR. Patients with HfP EF were generally women (70%), overweight, aged 69±8 years. Controls were of similar gender (63%) and age (67±6 years). Patients with HfP EF had significantly reduced peak VO2 compared with controls (20±4 mL·kg⁻¹·min⁻¹ versus 31±6 mL·kg⁻¹·min⁻¹, P<0.001) and greater minute ventilation-carbon dioxide production relationship (Ve/VCO2 slope) (33±6 versus 29±4, P<0.001). Chronotropic incompetence was significantly more common in patients with HfP EF compared with matched healthy controls as measured by the percentage of the HR reserve used during maximal exercise (63% versus 2%, <0.001) and percentage of predicted maximal HR (34% versus 2%, <0.001). In addition, abnormal HR recovery 1-minute after exercise (defined as the reduction in the HR from peak exercise 1-minute after exercise) was also significantly more common in patients with HfP EF compared with controls (23% versus 2%, P=0.01). Hypertensive controls showed similar chronotropic response to peak exercise and HR recovery after exercise as healthy controls.

Conclusions—Patients with HfP EF have impaired chronotropic incompetence during maximal exercise and abnormal HR recovery after exercise. (Circ Heart Fail. 2010;3:29-34.)

Key Words: heart rate recovery ■ chronotropic response ■ heart failure with preserved ejection fraction ■ metabolic exercise testing

A pproximately 50% of patients with the clinical features of heart failure are found to have normal left ventricular ejection fraction (LVEF) and normal valvular function. The term heart failure with preserved LVEF (HfP EF) 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.⁵ The prevalence of HfP EF seems to be increasing, and in contrast to systolic heart failure the mortality rate of this disorder is not declining.⁴

Clinical Perspective on p 34

The pathophysiology of HfP EF 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 LVEF), each seem to contribute to exercise limitation. However, one recent study in HfP EF reported an association between an impaired heart rate (HR) response to exercise and an exercise limitation.¹ However, there are a number of important caveats. First, the patients were mainly African Americans with hypertension, and the relevance to HfP EF in a white population is unknown. Second, the patient numbers were relatively small. Third, many of the patients (and the hypertensive controls without breathlessness) were taking β-blockers. Although these were discontinued 24 hours before the study, the potential of either ongoing β-blockade (chronotropic incompetence⁶) or of rebound effects⁶ 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 β-blockers using maximal symptom limited erect treadmill metabolic exercise testing.

Methods

Study Participants

Patients With HfPEF
We studied 41 patients with HfPEF prospectively and consecutively recruited from heart failure clinics. All study participants had clinical examination, 12-lead ECG, pulmonary function test, echocardiogram, and metabolic exercise test. All patients met the criteria of Yturralde and Gaasch7 for the diagnosis of diastolic heart failure. They had (1) signs and/or symptoms of heart failure; (2) objective evidence of exercise limitation on cardiopulmonary exercise testing (peak \( \text{VO}_2 \) < 80% of predicted) with a pattern of gas exchange, indicating a cardiac cause for limitation exercise capacity; (3) normal LVEF and chamber size; and (4) 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 Patients with HfPEF on β-blockers or nondihydropyridines calcium blockers (eg, verapamil and diltiazem) were also excluded to accurately assess chronotropic response and HR recovery. The investigations were performed at the University of Birmingham with the 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 majority of these hypertensive controls were studied before the commencement of any antihypertensive therapy. None was taking HR-lowering medication. All control subjects had a normal clinical cardiovascular examination, 12-lead ECG, 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 group5 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/V\( \text{CO}_2 \) slope), maximal oxygen consumption, carbon dioxide production, and respiratory exchange ratio was used to verify objective effort adequacy. Peak oxygen consumption (peak \( \text{VO}_2 \)) was defined as the average values of \( \text{VO}_2 \) 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 respiratory exchange ratio ≥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, 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 HR and the resting HR [%HHR]). A failure to use 80% 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 greater than 2 SDs below the mean value in healthy controls.

Statistics
Continuous variables are expressed as mean ± SD. Varians of data sets were determined using Levene test. Comparisons were performed with 1-way ANOVA on all 3 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 \( \chi^2 \) test. Pearson correlation coefficient (\( r \)) was used to describe the relationship between variables. A 2-tailed \( P \) value of <0.05 was considered statistically significant. SPSS (version 15.0) was used to perform the statistical analyses.
Table 2. Metabolic Exercise Test and Echocardiographic Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Healthy Controls, n=44</th>
<th>Hypertensive Controls, n=16</th>
<th>Patients With HfPEF, n=41</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic exercise test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak VO₂, mL·kg⁻¹·min⁻¹</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 peak VO₂</td>
<td>93±21</td>
<td>84±13</td>
<td>60±10†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>V̇E/V̇CO₂</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, mm Hg</td>
<td></td>
<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, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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/s</td>
<td>0.62±0.14</td>
<td>0.68±0.16</td>
<td>0.66±0.14</td>
<td>0.30</td>
</tr>
<tr>
<td>Mitral A-wave velocity, m/s</td>
<td>0.71±0.15</td>
<td>0.80±0.17</td>
<td>0.85±0.19†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ratio of E-wave: A-wave velocity</td>
<td>0.95±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, ms</td>
<td>237±62</td>
<td>250±44</td>
<td>265±64</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Values are presented as means±SD. The minute ventilation—carbon dioxide production relationship (V̇E/V̇CO₂ slope).

*P<0.05 vs healthy controls.
†P<0.05 vs hypertensive controls.

Results

Characteristics of Patients

Patients with HfPEF were generally women (70%), overweight, aged 69±8-years old with a history of hypertension. Healthy controls were of similar gender (63% women) and age (67±6 years; Table 1). Patients with HfPEF had significantly reduced peak VO₂ compared with healthy controls (20±4 mL·kg⁻¹·min⁻¹ versus 31±6 mL·kg⁻¹·min⁻¹, P<0.001). The minute ventilation-carbon dioxide production relationship (V̇E/V̇CO₂ slope) was also higher in patients with HfPEF than healthy controls (33±6 versus 29±4, P<0.001; Table 2).

Chronotropic Response to Maximal Exercise Testing

Patients with HfPEF versus matched healthy controls had similar resting HR and predicted maximal HR, 78±14 versus 79±13 (P=0.99) and 160±6 versus 161±4 (P=0.53), respectively. Patients with HfPEF had lower peak HR response and lower change in HR (the difference between peak HR and resting HR) during peak exercise compared with matched healthy controls, 139±22 versus 171±18 (P<0.001) and 60±22 versus 93±21 (P<0.001), respectively (Figure 1). Chronotropic incompetence was significantly more common in patients with HfPEF compared with matched healthy controls as measured by the percentage of the HR reserve used during peak exercise and percentage of predicted maximal HR. In addition, abnormal HR recovery 1-minute after exercise was also significantly more common in patients with HfPEF compared with matched healthy controls (Table 3 and Figure 2).

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Differences in HR response during exercise and after exercise in patients with HfPEF, hypertensive controls, and healthy controls (Only significant differences are shown). *P<0.05, †P<0.001.

Table 3. Chronotropic Incompetence in Patients With HfPEF Compared With Matched Controls

<table>
<thead>
<tr>
<th></th>
<th>Healthy Controls, n=44</th>
<th>Hypertensive Controls, n=16</th>
<th>Patients With HfPEF, n=41</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronotropic incompetence using %Max-PPHR method</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>14 (34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronotropic incompetence using %HRHR method</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</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>9 (23)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Values are presented as n (%). %Max-PPHR indicates percentage of predicted maximal heart rate used during maximal exercise; %HRHR, percentage of the heart rate reserve used during maximal exercise; HfPEF, heart failure with preserved left ventricular ejection fraction.
compared with hypertensive controls. There were no significant differences between hypertensive controls and healthy controls with respect to chronotropic response during peak exercise and HR recovery after exercise.

**Discussion**

The principal findings of this study are (1) patients with HFP EF had similar resting and predicted maximal HR compared with matched healthy controls, but during peak dynamic exercise, patients with HFP EF displayed significant chronotropic incompetence. (2) Abnormal HR recovery 1-minute after exercise was more common in patients with HFP EF compared with matched healthy controls. (3) Hypertensive controls showed similar chronotropic response to peak exercise and HR recovery after exercise as healthy controls.

Chronic heart failure (CHF) is characterized by impaired exercise tolerance often because of 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 VO\(_2\)) and an increase in the ventilatory response to exercise (the relation of ventilation [VE] to carbon dioxide production [V\(_{\text{CO}_2}\)] or VE/V\(_{\text{CO}_2}\) slope). \(^{17}\) In this study, we found that patients with HFP EF have reduced peak VO\(_2\) and higher VE/V\(_{\text{CO}_2}\) slope compared with older controls, which are supported by previous reports. \(^{18}\) Indeed, VE/V\(_{\text{CO}_2}\) 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. \(^{20}\) After exercise sympathetic withdrawal contributes to early HR recovery and at a later stage parasympathetic reactivation plays a larger role in HR recovery. \(^{21}\)

In CHF associated with LV systolic dysfunction, there is impaired autonomic function \(^{22}\) as a result of an impaired vagal tone \(^{23}\) and an overactivity of sympathetic function, which results in reduced responsiveness to \(\beta\) adrenergic stimulation because of both reduced adrenoreceptor number and reduced downstream signaling. \(^{24}\) 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 HR recovery after exercise is also common in patients with systolic heart failure \(^{29}\) and seems to be primarily due to low vagal tone. \(^{23}\) Impaired HR recovery after exercise also seems to be not only a powerful predictor of mortality in patients with systolic heart failure but also predicts cardiovascular mortality in apparently healthy subjects. \(^{14}\)

In this study, we found patients with HFP EF had lower peak HR response during maximal exercise than controls, which is important because peak HR response is associated with coronary disease and cardiovascular mortality. Furthermore, we found that 34% of patients with HFP EF have chronotropic incompetence during maximal exercise when defined by percentage of predicted maximal HR and 63% when defined by the percentage of the HR reserve used during peak exercise. 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 et al.1 showed in patients with hypertension (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, because 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 role32 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.25,34 A review on this topic has been discussed by our group elsewhere.72

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 HR recovery after exercise.

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Disclosures
Professor M. Frenneaux received Honoria from Metronic, St Jude and Biotronik; is a Consultant/Advisory Board for Metronic, St Jude, Menarini and Biotronik; and is a Speaker on panel for Menarini.

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**CLINICAL PERSPECTIVE**

In this study, we have demonstrated that patients with heart failure with preserved left ventricular ejection fraction exhibit chronotropic incompetence during peak exercise and abnormal heart rate recovery after exercise. The latter indicates that these patients have impaired cardiac vagal tone. Chronotropic incompetence may be an overlooked cause of exercise intolerance in this group of patients. Furthermore, an abnormal heart rate recovery is an important prognostic marker. The potential clinical impact of our findings is that it raises the questions of whether the uses of rate-limiting therapy such as β-blockers, nondihydropyridines calcium blockers are appropriate in this group of patients. In addition, it raises the possibility of applying heart rate responsive pacing in this group of patients to improve exercise tolerance and quality of life.
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