Impaired Chronotropic and Vasodilator Reserves Limit Exercise Capacity in Patients With Heart Failure and a Preserved Ejection Fraction

Barry A. Borlaug, MD; Vojtech Melenovsky, MD, PhD; Stuart D. Russell, MD; Kristy Kessler, RN, BSN; Karel Pacak, MD, PhD; Lewis C. Becker, MD; David A. Kass, MD

Background—Nearly half of patients with heart failure have a preserved ejection fraction (HFpEF). Symptoms of exercise intolerance and dyspnea are most often attributed to diastolic dysfunction; however, impaired systolic and/or arterial vasodilator reserve under stress could also play an important role.

Methods and Results—Patients with HFpEF (n=17) and control subjects without heart failure (n=19) generally matched for age, gender, hypertension, diabetes mellitus, obesity, and the presence of left ventricular hypertrophy underwent maximal-effort upright cycle ergometry with radionuclide ventriculography to determine rest and exercise cardiovascular function. Resting cardiovascular function was similar between the 2 groups. Both had limited exercise capacity, but this was more profoundly reduced in HFpEF patients (exercise duration $180 \pm 71$ versus $455 \pm 184$ seconds; peak oxygen consumption $9.0 \pm 3.4$ versus $14.4 \pm 3.4$ mL·kg$^{-1}$·min$^{-1}$; both $P<0.001$). At matched low-level workload, HFpEF subjects displayed $\approx 40\%$ less of an increase in heart rate and cardiac output and less systemic vasodilation (all $P<0.05$) despite a similar rise in end-diastolic volume, stroke volume, and contractility. Heart rate recovery after exercise was also significantly delayed in HFpEF patients. Exercise capacity correlated with the change in cardiac output, heart rate, and vascular resistance but not end-diastolic volume or stroke volume. Lung blood volume and plasma norepinephrine levels rose similarly with exercise in both groups.

Conclusions—HFpEF patients have reduced chronotropic, vasodilator, and cardiac output reserve during exercise compared with matched subjects with hypertensive cardiac hypertrophy. These limitations cannot be ascribed to diastolic abnormalities per se and may provide novel therapeutic targets for interventions to improve exercise capacity in this disorder. (Circulation. 2006;114:2138-2147.)

Key Words: diastole ■ exercise ■ heart failure ■ heart rate ■ hemodynamics ■ nervous system, autonomic

Clinical Perspective p 2147

An important limitation of many prior studies of HFpEF is that cardiovascular analysis was performed under resting conditions, and other mechanisms that could limit exercise performance, such as heart rate, systolic reserve, and arterial vasodilator reserve, remain ill defined. Furthermore, HFpEF patients have rarely been compared with control subjects without heart failure who share common demographic and clinical features of the disorder, including hypertension, cardiac hypertrophy, female predominance, diabetes mellitus, and increased body mass. This is critical, because these features in and of themselves are associated with diastolic abnormalities and could independently diminish exercise capacity. Examination of the
determinants of cardiovascular performance during exercise in HFrEF, compared with such matched controls, may reveal novel pathophysiological mechanisms more specific to the HFrEF phenotype.

Accordingly, the present study assessed mechanisms responsible for exercise limitation in subjects with HFrEF, using a control group that shared many common characteristics and comorbidities but that had never been diagnosed with or treated for heart failure. We show that exercise intolerance in HFrEF correlates with impaired systolic and systemic vasodilator reserve, whereas diastolic filling reserve is similar between the 2 groups. The results highlight potentially novel therapeutic targets for the HFrEF syndrome.

Methods

Study Population

Subjects with HFrEF (n = 17) were identified after hospitalization for pulmonary edema due to heart failure, with a documented ejection fraction ≥50% within 1 to 3 days of admission. The exercise protocol was performed ≥1 month after discharge, with all subjects studied in a stable, compensated state. Exclusion criteria included significant valvular disease; infiltrative, restrictive, or hypertrophic cardiomyopathy; cor pulmonale; pulmonary disease; unstable coronary disease; atrial fibrillation; pregnancy; primary renal or hepatic disease; and inability to exercise on an upright bicycle or to suspend cardiovascular medicines for at least 24 hours.

Control subjects (n = 19) were screened for ventricular hypertrophy principally on the basis of outpatient echocardiograms, and in 4 cases, from ECGs. The former were typically requested to assess cardiac morphology and function as part of an assessment for systemic hypertension. Because most HFrEF cases were older, obese, hypertensive, diabetic black women, we sought to enroll control subjects with as many of these characteristics as possible. No control subject had ever been diagnosed, hospitalized, or treated for congestive heart failure, and this was further confirmed by comprehensive medical history and physical examination performed by 2 independent cardiologists. Subjects were recruited over a 2-year period from September 2003 to June 2005. All were asked to withhold their routine cardiovascular medicines for at least 6 hours before study. Informed consent was obtained from all participants, and the protocol was approved by the Johns Hopkins Medicine Institution Review Board.

Study Design

Baseline ventricular function, diastolic filling characteristics, and left ventricular (LV) mass were assessed by transthoracic echocardiography. Baseline ventricular (LV) mass was assessed by transthoracic echocardiography. LV end-diastolic volume, end-systolic volume, stroke volume, cardiac output, and ejection fraction were derived as reported previously.19,21 Time-activity curves were fit to a 4-term Fourier series and analytically differentiated to yield flow.22 Heart rate was determined from a continuous 12-lead ECG. Ventricular afterload was measured by systemic vascular resistance and effective arterial elastance.23 Cardiac contractility was measured by peak power index (product of peak ejection rate and systolic blood pressure divided by end-diastolic volume), end-systolic elastance (estimated by end-systolic pressure divided by end-systolic volume), and stroke work/end-diastolic volume ratio.20 During exercise, diastolic filling was assessed by radionuclide-derived peak ventricular filling rate and change in end-diastolic volume with exercise.21 Heart rate rise and recovery after exercise24 were determined from continuous ECG recordings and 12-lead tracings obtained after the initial 60 seconds of both exercise and recovery. Arterial baroreflex sensitivity was measured during the overshoot phase of a controlled Valsalva maneuver.25

Cardiac Function Analysis

Gated 99mTc blood pool images were obtained in the left anterior oblique position. LV end-diastolic volume, end-systolic volume, stroke volume, cardiac output, and ejection fraction were derived as reported previously.19,21 Time-activity curves were fit to a 4-term Fourier series and analytically differentiated to yield flow.22 Heart rate was determined from a continuous 12-lead ECG. Ventricular afterload was measured by systemic vascular resistance and effective arterial elastance.23 Cardiac contractility was measured by peak power index (product of peak ejection rate and systolic blood pressure divided by end-diastolic volume), end-systolic elastance (estimated by end-systolic pressure divided by end-systolic volume), and stroke work/end-diastolic volume ratio.20 During exercise, diastolic filling was assessed by radionuclide-derived peak ventricular filling rate and change in end-diastolic volume with exercise.21 Heart rate rise and recovery after exercise24 were determined from continuous ECG recordings and 12-lead tracings obtained after the initial 60 seconds of both exercise and recovery. Arterial baroreflex sensitivity was measured during the overshoot phase of a controlled Valsalva maneuver.25

Metabolic Performance

Minute ventilation with breath-by-breath oxygen consumption and carbon dioxide production was measured and averaged over 10-second increments (MedGraphics, St. Paul, Minn) to quantify functional capacity. Peak oxygen consumption was defined as the mean of the highest 2 of 3 values (10-second averages) during the final minute of exercise and mean of all breath-by-breath values during this same period; both were compared with age-predicted values. The ventilatory (anaerobic) threshold was derived by the ventilatory equivalents method,26 and the peak respiratory exchange ratio was used to verify objective effort adequacy. Subjective effort was quantified by the Borg scale (graded from 6 to 20).

Plasma Catecholamine Levels

Plasma norepinephrine and epinephrine levels were measured at baseline and immediately after peak exercise by high-performance liquid chromatography.27

Pulmonary Blood Volume Ratio

Changes in total lung blood volume (index of pulmonary congestion) were estimated by the radionuclide count method.26 A region of interest was identified in the left lung lateral to the left ventricle, excluding the descending aorta, and count density was measured and normalized to ventricular counts at each stage of exercise. Change in lung blood volume was obtained from the ratio of rest to exercise counts.

Statistical Analysis

The study sample size was based on previously reported exercise duration in elderly hypertensive control subjects23 and in subjects with ventricular hypertrophy and heart failure symptoms.20 On the basis of these data, we estimated 14 patients in each group was a sufficient number to detect a 40% difference in total exercise duration with α = 0.05 and at 80% power. A few additional subjects were recruited to each group to enrich the power of the comparison and to ensure that adequate data were available for final analysis. All results are reported as mean with SD. Within-group comparisons were performed by paired 2-tailed Student’s t test. Groups were compared by repeated-measures ANOVA. Individual time-point differences were compared by unpaired 2-tailed Student’s t test or χ² test (for categorical variables). Linear regression (Pearson coefficient) was performed to test associations between cardiac reserve function and exercise performance. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline Characteristics

Baseline clinical characteristics of the 2 study groups are provided in Table 1. Subjects predominantly were older black
women, all with hypertension, and there was a high prevalence of diabetes mellitus, LVH, and obesity. Control subjects had a lower mean body mass index, although the overall prevalence of obesity was similar between groups. Use of \( \beta \)-blockers (effective metoprolol dose), calcium channel blockers, and other antihypertensive drug therapies was similar with the exception of loop diuretics, which were used chronically by all HFpEF subjects. The number of diabetic medications and the mean hemoglobin A1c levels were not significantly different between groups. HFpEF subjects had a mean New York Heart Association class of 2.7 ± 0.4 and self-assessed quality-of-life score of 52 ± 38.

Table 2 presents baseline cardiovascular function obtained at the time of the exercise protocol (based on radionuclide and pressure data). Heart rate and resting contractile function were similar between the 2 groups. HFpEF subjects had on average

---

**TABLE 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HFpEF (n=17)</th>
<th>Controls (n=19)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65±9</td>
<td>65±9</td>
<td>0.91</td>
</tr>
<tr>
<td>Gender, % female</td>
<td>94</td>
<td>83</td>
<td>0.35</td>
</tr>
<tr>
<td>Race, % black</td>
<td>71</td>
<td>78</td>
<td>0.84</td>
</tr>
<tr>
<td>Obese, %</td>
<td>76</td>
<td>58</td>
<td>0.24</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>36.8±7.5</td>
<td>31.3±5.8</td>
<td>0.02</td>
</tr>
<tr>
<td>New York Heart Association class</td>
<td>2.7±0.4</td>
<td>1.2±0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minnesota Living With Heart Failure questionnaire score</td>
<td>52±38</td>
<td>10±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Comorbidities, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>100</td>
<td>100</td>
<td>1.0</td>
</tr>
<tr>
<td>LVH</td>
<td>100</td>
<td>89</td>
<td>0.18</td>
</tr>
<tr>
<td>No. of diabetic medications</td>
<td>1.4±0.8</td>
<td>1.0±0.5</td>
<td>0.16</td>
</tr>
<tr>
<td>Hemoglobin ( A_1c ), %</td>
<td>7.5±2.1</td>
<td>7.5±1.9</td>
<td>0.99</td>
</tr>
<tr>
<td>Serum hemoglobin, g/dL</td>
<td>11.9±1.4</td>
<td>12.5±1.8</td>
<td>0.39</td>
</tr>
<tr>
<td>Glomerular filtration rate, mL/min</td>
<td>96±23</td>
<td>81±24</td>
<td>0.15</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \beta )-Blockers, %</td>
<td>65</td>
<td>58</td>
<td>0.7</td>
</tr>
<tr>
<td>Mean ( \beta )-blocker dose—metoprolol, mg/d</td>
<td>114±60</td>
<td>118±56</td>
<td>0.9</td>
</tr>
<tr>
<td>Calcium channel blockers, %</td>
<td>18</td>
<td>22</td>
<td>0.8</td>
</tr>
<tr>
<td>ACE inhibitor/angiotensin receptor blocker, %</td>
<td>76</td>
<td>50</td>
<td>0.07</td>
</tr>
<tr>
<td>Loop diuretic, %</td>
<td>100</td>
<td>33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other antihypertensive, %</td>
<td>59</td>
<td>68</td>
<td>0.55</td>
</tr>
</tbody>
</table>

**TABLE 2. Baseline Cardiovascular Function**

<table>
<thead>
<tr>
<th>Ventricular indexes</th>
<th>HFpEF (n=17)</th>
<th>Controls (n=19)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic volume index, mL/m²</td>
<td>61±12</td>
<td>70±11</td>
<td>0.02</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>73±7</td>
<td>70±8</td>
<td>0.25</td>
</tr>
<tr>
<td>Peak power index, mm Hg/s</td>
<td>542±120</td>
<td>551±97</td>
<td>0.81</td>
</tr>
<tr>
<td>End-systolic elastance, mm Hg/mL</td>
<td>4.5±1.9</td>
<td>3.8±1.2</td>
<td>0.18</td>
</tr>
<tr>
<td>Stroke work/end-diastolic volume, mm Hg/s</td>
<td>74±13</td>
<td>79±12</td>
<td>0.22</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>70±13</td>
<td>68±10</td>
<td>0.53</td>
</tr>
<tr>
<td>LV peak filling rate, s⁻¹</td>
<td>2.9±0.7</td>
<td>2.5±0.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Vascular indexes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic vascular resistance index, dyne s⁻¹ m² 10⁻² cm⁻⁵</td>
<td>2.7±0.70</td>
<td>2.8±0.64</td>
<td>0.72</td>
</tr>
<tr>
<td>Effective arterial elastance, mm Hg/mL</td>
<td>1.52±0.38</td>
<td>1.50±0.26</td>
<td>0.80</td>
</tr>
<tr>
<td>Integrated indexes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>151±29</td>
<td>155±19</td>
<td>0.59</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>101±16</td>
<td>112±14</td>
<td>0.03</td>
</tr>
<tr>
<td>Cardiac index, L/min·m⁻²</td>
<td>3.15±0.98</td>
<td>3.31±0.53</td>
<td>0.53</td>
</tr>
</tbody>
</table>
13% smaller end-diastolic volumes but a higher peak filling rate. Total ventricular afterload and systolic pressure were similar, but HFpEF subjects had somewhat lower arterial diastolic blood pressure. Echocardiographic Doppler data are provided in Table 3. For further reference, these data are contrasted to results from age-, gender-, and race-matched nonhypertensive, nonhypertrophic subjects reported in detail elsewhere. The overall prevalence of LVH was similar in both groups. LV mass indexed to body surface area or height was not significantly different, whereas mass indexed to height was higher in HFpEF subjects. HFpEF cases had a higher mean E-wave velocity and E/A ratio and a borderline increased E/E’ ratio, all consistent with elevated LV filling pressures. Other indexes of diastolic function were similarly abnormal in both the case and control groups.

Metabolic Exercise Performance

Table 4 provides metabolic performance data. No subject had evidence of inducible ischemia during exercise on the basis of 12-lead ECG or wall-motion abnormalities. All reached a peak respiratory exchange ratio >1, which indicates at least near-maximal objective effort. Subjects stopped exercising because of dyspnea or fatigue, and this was similar between groups (P=0.33). HFpEF subjects had profoundly limited exercise capacity, with a total exercise time of 180±71 versus 455±184 seconds in controls (P<0.001). Peak oxygen consumption was 70% of age-predicted values in controls but was markedly further reduced in HFpEF subjects. Similar results were obtained with breath-by-breath analysis averaged over the final minute (8.0±2.0 versus 13.2±3.6 mL O₂·min⁻¹·kg⁻¹, P<0.0001). Oxygen consumption at the ventilatory threshold and time to achieve the threshold were significantly lower in HFpEF. Importantly, the ratio of oxygen consumed at ventilatory threshold to that at peak exercise was similar and was higher than would be expected if deconditioning were the primary cause for poor exercise capacity. Peak measures of objective (respiratory exchange ratio) and subjective (Borg scale) exertion were similar.

**TABLE 3. Echocardiographic and Doppler Analysis of Baseline Diastolic Function and Hypertrophy**

<table>
<thead>
<tr>
<th>Variable</th>
<th>HFpEF (n=17)</th>
<th>Controls (n=19)</th>
<th>P</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass/body-surface area, g/m²</td>
<td>133±39*</td>
<td>117±37*</td>
<td>0.24</td>
<td>77±13</td>
</tr>
<tr>
<td>LV mass/height, g/m</td>
<td>169±48*</td>
<td>141±48*</td>
<td>0.1</td>
<td>86±18</td>
</tr>
<tr>
<td>LV mass/height², g/m²</td>
<td>75±24*</td>
<td>60±16*</td>
<td>0.03</td>
<td>36±7</td>
</tr>
<tr>
<td>E-wave velocity, cm/s</td>
<td>91±24†</td>
<td>76±14</td>
<td>0.04</td>
<td>80±16</td>
</tr>
<tr>
<td>A-wave velocity, cm/s</td>
<td>85±21</td>
<td>91±21†</td>
<td>0.37</td>
<td>78±20</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.16±0.49</td>
<td>0.86±0.21†</td>
<td>0.03</td>
<td>1.1±0.3</td>
</tr>
<tr>
<td>Tissue Doppler E’ velocity, cm/s</td>
<td>6.0±2.9*</td>
<td>6.4±1.4*</td>
<td>0.62</td>
<td>9.8±2.3</td>
</tr>
<tr>
<td>E/E’ ratio</td>
<td>16.8±6.5*</td>
<td>12.6±4.98</td>
<td>0.07</td>
<td>8.4±2.2</td>
</tr>
<tr>
<td>Mitral E-wave deceleration time, ms</td>
<td>240±64</td>
<td>258±56†</td>
<td>0.40</td>
<td>219±42</td>
</tr>
<tr>
<td>Isovolumic relaxation time, ms</td>
<td>94±23*</td>
<td>99±12*</td>
<td>0.42</td>
<td>78±11</td>
</tr>
</tbody>
</table>

HFpEF and hypertensive/LVH control values (Controls) were further compared with data from an age-, gender-, and ethnicity-matched nonhypertensive, non-LVH population reported in detail elsewhere. Relevant values are provided under the Reference column. *P<0.001 and †P<0.05 for comparison of HFpEF or Controls with the reference population.

**TABLE 4. Metabolic Performance**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HFpEF (n=17)</th>
<th>Controls (n=19)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise duration, s</td>
<td>180±71</td>
<td>455±184</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak respiratory exchange ratio</td>
<td>1.15±0.11</td>
<td>1.21±0.11</td>
<td>0.18</td>
</tr>
<tr>
<td>Peak work rate, W</td>
<td>37±13</td>
<td>74±28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak heart rate, bpm</td>
<td>87±20</td>
<td>115±22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Borg subjective effort score (6–20)</td>
<td>16±4</td>
<td>16±3</td>
<td>0.97</td>
</tr>
<tr>
<td>Peak oxygen consumption, mL·kg⁻¹·min⁻¹</td>
<td>9.0±3.4</td>
<td>14.4±3.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oxygen consumption at ventilatory threshold, mL·kg⁻¹·min⁻¹</td>
<td>7.1±1.9</td>
<td>11.3±3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to ventilatory threshold, s</td>
<td>66±24</td>
<td>191±124</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ratio of oxygen consumed at ventilatory threshold to peak O₂ consumption, %</td>
<td>81±18</td>
<td>78±11</td>
<td>0.69</td>
</tr>
<tr>
<td>Ratio of observed to predicted peak oxygen consumption, %</td>
<td>50±14</td>
<td>70±13</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
dishes or dressing). This was the only stage completed by many HFpEF subjects and therefore the only one at which matched-workload comparisons were possible in all subjects. HFpEF subjects had a blunted increase in heart rate (14.1 ± 10.3 versus 24.9 ± 12.6 bpm, P = 0.015; 20.5% versus 36.3% increase, P = 0.007) and impaired arterial vasodilation (−262.8 ± 225 versus −420.8 ± 207 dynes·s·cm⁻²·m² fall in resistance, P = 0.04; −19.0% versus −28.16% decline, P = 0.04). As a result, the rise in cardiac index was much less in HFpEF (1.25 ± 0.66 versus 2.02 ± 0.78, P = 0.002; 39.3% versus 61.8% increase, P = 0.007). In contrast, increases in net chamber filling (change in end-diastolic volume), stroke volume, and contractility were similar.

At peak exercise (Figure 1B), heart rate and vasodilator responses remained markedly blunted in HFpEF versus controls, which resulted in a 60% lower increase in cardiac output (all P < 0.001). HFpEF subjects had less of an increase in contractile performance (P ≤ 0.001 for all indexes), whereas net LV filling (end-diastolic volume) and stroke volume increase were similar. Because mean body mass index was somewhat greater in HFpEF cases and could have influenced results indexed to body-surface area, we repeated the analysis using nonindexed data and also after eliminating the 4 subjects in the HFpEF group with the highest body mass index (thereby matching the mean in control subjects). In both instances, these findings remained unchanged.

Exercise capacity, whether indexed by exercise time or peak oxygen consumption, correlated directly with cardiac output (Figure 2A, P < 0.0002), consistent with prior studies. However, the primary determinants were heart rate and afterload responses during exercise (Figure 2B), whereas change in net LV filling (end-diastolic volume) and stroke volume were not correlated with exercise capacity (Figure 2C). Nearly identical results were obtained for each regression with a model that included a categorical patient group parameter (data not shown). To further determine whether individual body mass index, LV mass index (normalized to height².7), β-blockade, or diabetes mellitus explained the differences in exercise capacity, we performed multiple regression analysis testing the dependence of exercise duration on cardiac output, systemic resistance, or heart rate and including these other factors (and patient group) in the model. In each instance, the hemodynamic parameter and patient group correlated with exercise capacity (P < 0.05), whereas the other variables did not provide additional significance (P > 0.25).

**Heart Rate and Autonomic Function**

The impaired heart rate response in HFpEF patients was further examined to test for differences in rate acceleration and postexercise deceleration. Impairment of the latter has
been shown to independently confer increased risk of cardiac
death. As displayed in Figure 3, the rate of heart rate
increase during exercise and rate of decline after exercise
were substantially slower in HFpEF patients than in control
subjects. All control subjects had a normal heart rate recovery
(>12 bpm fall in first minute after exercise), compared with
only 47% of HFpEF cases (P<0.001). Because the latter is
thought to reflect autonomic (parasympathetic) imbalance,
we examined the heart rate response to an increase in blood
pressure during phase 4 of the Valsalva maneuver (arterial
baroreflex sensitivity). In response to an
30 mm Hg rise in
blood pressure, heart rate decline was significantly impaired
in HFpEF subjects (3.7±2.8 versus 6.5±3.6 ms/mm Hg;
P<0.05), which further supports a role for autonomic
dysfunction.

Plasma Catecholamine Levels
Resting norepinephrine (435±225 versus 449±210 pg/mL,
P=0.86) and epinephrine (110±92 versus 116±116 pg/mL,
P=0.89) levels were similar in HFpEF and control subjects.
Norepinephrine rose in both groups at peak exercise
(204±178 and 293±240 pg/mL, respectively; P<0.001),
with no significant difference in the net increase (P=0.26).
Plasma epinephrine levels were unaltered by exercise.

Pulmonary Blood Volume
Radionuclide-assessed total lung blood volume increased
similarly at low-level exercise (11±18% versus 7±11%,
P=0.37) and peak exercise (10±17% versus 9±10%,
P=0.76) in cases and control subjects, respectively. This
suggests that pulmonary congestion was not differentially
greater during exercise in HFpEF than in control subjects.

Discussion
This study provides the first comparison of cardiovascular
responses during exercise in patients with heart failure and a
normal ejection fraction versus nonfailure control subjects
who share many comorbidities, notably hypertension, ventricular hypertrophy, diabetes, and obesity. HFpEF sub-
jects had limited heart rate and arterial vasodilator responses
with exercise, which impaired cardiac output reserve. LV filling, reflected by the change in end-diastolic volume, and pulmonary lung blood volume were similar in both groups. These results challenge the notion that diastolic dysfunction alone primarily explains exercise-related symptoms in this disorder by limiting cardiac filling and thus cardiac reserve. The findings also raise questions about the appropriateness of some currently recommended therapies and suggest novel alternative therapeutic targets.

HFpEF and Exercise Intolerance
Heart failure may be broadly defined as a disorder in which the heart is unable to provide sufficient cardiac output to meet metabolic demands. The increase in cardiac output during exercise is the primary determinant of exercise capacity in normal humans and patients with heart failure.\(^3\text{1,32}\) In systolic failure, hearts overfill to compensate for reduced pump function, which leads to chamber dilation and remodeling. However, in many older patients with hypertension and ventricular hypertrophy who develop heart failure, dilation does not occur, and ejection fraction remains in a normal range, whereas cardiac output reserve is still limited. What explains exercise limitation in this group? A generally accepted theory is that the ventricle is stiffer and slower to relax during diastole, requiring higher pressures to fill adequately.\(^12,13\) Increased diastolic pressures would in turn raise lung blood volumes and trigger dyspnea. This concept stems largely from data acquired at rest, which reveal normal systolic function but abnormal diastolic properties in HFpEF patients.\(^8,10\) Although some of these features remain controversial,\(^9,33\) the question of what occurs during exercise, when symptoms typically occur, remains unsettled.

Among the very few exercise studies is one from Kitzman and colleagues,\(^11\) who examined 7 patients with HFpEF (3 of whom had hypertrophic or restrictive cardiomyopathy) contrasted to 10 age-matched, normotensive, healthy control subjects. Exercise tolerance and cardiac output reserve were markedly depressed in HFpEF subjects. Control subjects increased chamber filling during exercise, whereas HFpEF subjects did not, despite a greater rise in diastolic pressure. This supported the notion that exercise intolerance in HFpEF resulted from failure of the Frank-Starling mechanism due to diastolic dysfunction.

The results of the present study differ somewhat from this earlier study, potentially for several reasons. First, patients with hypertrophic and restrictive cardiomyopathy were excluded, because these diseases are known to markedly impair preload reserve, yet are not the commonly observed causes of HFpEF in the community. Second, control subjects in the present study had relevant comorbidities and also displayed reduced preload reserve, in contrast to the healthy aged heart, which relies more on the Frank-Starling mechanism than heart rate or contractile reserve.\(^21,34\) Although cardiac output rose similarly at 50-W exercise for the present control subjects and a prior study of healthy aged subjects,\(^21\) stroke and end-diastolic volumes increased 2- and 4-fold more, respectively, and heart rate proportionately less in healthy subjects than in the hypertensive/LVH controls in the present study. Thus, limited filling in hypertensive/LVH control subjects appears to be offset by greater reliance on heart rate and arterial vasodilation. Deficits in both responses in HFpEF patients could reflect loss of a key compensatory reserve, which on top of other abnormalities such as diastolic dysfunction\(^10,13\) or ventricular-arterial stiffening,\(^9\) profoundly limits exercise capacity.
Role for Nondiastolic Factors in HFpEF

The present study revealed 3 nondiastolic limitations of cardiovascular reserve in HFpEF patients. First, they had a slower heart rate rise, lower peak heart rate, and impaired recovery. Heart rate changes with exertion are thought to be related to withdrawal and reactivation of vagal tone,24 which suggests HFpEF patients may have abnormal autonomic function. This was further supported by the blunt arterial baroreflex response. The heart rate recovery finding is intriguing, because this appears to be a strong independent predictor of cardiac mortality,24 even after adjustment for heart rate increase with exercise, and because this was abnormal in >50% of the HFpEF subjects. The similar increase in plasma norepinephrine for both groups suggests a peripheral rather than central mechanism, similar to that observed in systolic heart failure.35 The lack of rise in epinephrine may reflect the low level of exercise achieved in both groups, because this requires longer periods of exertion to increase, even in normal subjects.36

A second nondiastolic mechanism was depressed systemic vasodilation, a known contributor to reduced cardiac ejection, muscle perfusion, and exercise capacity in systolic heart failure15,16 due in part to depressed nitric oxide generation.37 We found similar abnormalities in HFpEF patients, which supports treatments to enhance vasodilator reserve.38 Lastly, we observed marked disparities in contractile reserve at peak workload, although there were no differences with low-level exercise. It is possible that HFpEF subjects reached a ceiling of contractile reserve that further limited their exercise capacity, as has been reported previously.14 Alternatively, differences in peak-level contractility may have been secondary to the different workloads achieved.

The present results raise questions about the use of β-blockers in HFpEF. These agents are generally recommended12,13 on the premise that slowing the heart rate will enhance diastolic filling time and exercise performance, as observed in patients with hypertrophic cardiomyopathy.39 However, β-blockers delay relaxation40 and increase net vascular load on the heart.41 Exercise capacity in patients with hypertrophic cardiomyopathy depends primarily on stroke volume response, with little role for heart rate augmentation.42 This is the opposite of what was observed in the present study, which raises questions about the generalizability of results derived from patients with hypertrophic cardiomyopathy to those with HFpEF. If chronotropic and vasodilator reserve are central limitations in HFpEF, β-blockade may not be an optimal treatment.

Exercise Intolerance Versus Pulmonary Edema

All subjects in the HFpEF group had been hospitalized with pulmonary edema, yet in the present study, pulmonary edema was not reproduced. Both groups had a similar ∼10% increase in lung blood volume compared with the ∼10% decrease in volume during exercise in normal subjects.28 However, prior studies have repeatedly shown that LV filling pressures and changes in pressures during exercise do not correlate with exercise performance or symptoms of exertional intolerance.32,43–45 Such symptoms are more related to inadequate cardiac output,32 which we showed to be related primarily to an inadequate heart rate and vasodilator response in HFpEF. Although the present study does not directly identify why HFpEF can decompensate with fulminant pulmonary edema, it seems reasonable that the chronotropic and vascular limitations observed may diminish reserve capacity to hemodynamic insults, such as volume loading, hypertensive crisis, or ischemia. Impaired heart rate and vasodilator reserve may be a “last straw” that separates hypertensive LVH patients from those manifesting clinical heart failure. Future studies are needed to explore this question.

Study Limitations

There are several limitations to this study. LV pressure was not measured directly, and disparities in LV diastolic pressures cannot be ruled out. Marked disparities would be expected to yield differences in pulmonary blood volume,28 and this was not observed. Importantly, even if present, diastolic pressure differences would unlikely explain the disparities in heart rate and vascular dilation. Although groups were matched for the presence of obesity, mean body mass index was higher in HFpEF subjects, and LVH/height2,7 was slightly greater. Both could affect exertional capacity and hemodynamic response but were not significant when examined by multivariate analysis.

HFpEF subjects were all chronically treated with loop diuretics, which can induce reflex neurohormonal activation and potentially affect vascular function. Resting end-diastolic volume index was somewhat lower in HFpEF; however, both groups had similar basal plasma catecholamine levels and peripheral arterial resistance, and estimated central filling pressures were higher in HFpEF. Use of loop diuretics serves as a marker that HFpEF patients indeed had clinical symptoms of fluid overload, because such medications are less often used to treat hypertension.

We did not find evidence of inducible ischemia by wall-motion or 12-lead ECG but cannot exclude subtle ischemia as might be detectable by a dedicated perfusion study. Again, any small, occult differences would be unlikely to explain the primary study findings. Radionuclide studies depend on a regular heart rate; thus, patients with atrial fibrillation were excluded, and the present findings may not be applicable to this subgroup. The control group in the present study displayed somewhat reduced exercise performance compared with age-predicted values, likely associated with their comorbidities. However, this would tend to reduce any observed differences versus the HFpEF group, emphasizing the robustness of the findings.

HFpEF study subjects were predominantly black and were somewhat younger and more obese than the broader HFpEF population.5,6 Nonetheless, they shared many features described in large epidemiological studies in which they are less represented,5,6 and this is an important and large cohort with a relatively high prevalence of HFpEF.5 Lastly, although exercise capacity strongly correlated with cardiac output reserve, other mechanisms such as pulmonary disease and deconditioning could play a role. The exercise test itself may have been too strenuous for the HFpEF subjects to fully assess capacity, although this was a very low-level test. The former was excluded on the basis of entry criteria, and the
latter was less likely to be a major factor given the high ratio of oxygen consumed at the ventilatory threshold relative to peak.

**Conclusions**

Heart failure with a preserved ejection fraction affects a large, expanding proportion of the heart failure population. Binary classification into “systolic” or “diastolic” failure on the basis of ejection fraction is somewhat misleading, because it implies a primary mechanism on which therapy should focus. Although diastolic dysfunction occurs in HFpEF, the present data suggest that other factors such as heart rate and vasodilator reserve also play a role in exertional symptoms. These abnormalities may deserve equal attention in efforts to develop more effective treatments for this disorder.

**Acknowledgments**

The authors thank Jon Clulow and Terry Frank for their assistance with the nuclear velocigraphy, Patricia Fitzgerald, Tricia Marhin, and Laurie Shively for their technical assistance with the exercise studies, and Ella Chamera for her assistance with the echocardiography Doppler studies.

**Sources of Funding**

This study was supported in part by the National Institutes of Health—National Institute of Aging RO1-AG18324, Peter Belfer Laboratory, Abraham and Virginia Weiss Professorship (Dr Kass), and the National Heart, Lung, and Blood Institute T32-HL07227 (Dr Borlaug).

**Disclosures**

None.

**References**


**CLINICAL PERSPECTIVE**

Approximately half of all patients with heart failure have a preserved ejection fraction, exceeding 50% (HFpEF). Their symptoms of dyspnea, fatigue, and effort intolerance are traditionally attributed mainly to diastolic dysfunction; however, few studies have comprehensively examined hemodynamic mechanisms for exertional intolerance, and none have compared data from HFpEF subjects with data from individuals without heart failure who share common clinical features of this disease (eg, hypertension, ventricular hypertrophy, diabetes mellitus, older age, and female predominance). We performed such analysis using combined radionuclide angiography, noninvasive pressures, and metabolic assessment. Patients with HFpEF had profoundly depressed exercise capacity (average duration 4 minutes, peak oxygen consumption <10 mL · kg⁻¹ · min⁻¹). Matched controls exercised approximately twice as long, consuming =50% more oxygen. Baseline hemodynamics were similar, but with low-level exercise, HFpEF patients had depressed cardiac output reserve due to lower heart rate and impaired vasodilation. There were no differences in exercise-induced cardiac preload rise, estimated lung congestion, or plasma catecholamines. Contractility rose similarly with low-level exercise but was blunted at peak exercise in HFpEF patients. Peak exercise performance correlated with changes in cardiac output, heart rate, and peripheral resistance but not preload or stroke volume. Both the rate of chronotropic rise and the decline with exercise/recovery were blunted in HFpEF patients, which suggests autonomic dysfunction. These data reveal the importance of heart rate and vasodilation, both nondiastolic factors, to exertional intolerance in patients with HFpEF. They raise questions concerning the common use of drugs to slow heart rate in HFpEF (eg, calcium and β-adrenergic receptor antagonists) and suggest the potential for novel therapies that specifically target these cardiovascular reserve abnormalities in this disorder.

Go to [http://cme.ahajournals.org](http://cme.ahajournals.org) to take the CME quiz for this article.
Impaired Chronotropic and Vasodilator Reserves Limit Exercise Capacity in Patients With Heart Failure and a Preserved Ejection Fraction
Barry A. Borlaug, Vojtech Melenovsky, Stuart D. Russell, Kristy Kessler, Karel Pacak, Lewis C. Becker and David A. Kass

Circulation. 2006;114:2138-2147; originally published online November 6, 2006;
doi: 10.1161/CIRCULATIONAHA.106.632745
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/114/20/2138

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at: http://circ.ahajournals.org//subscriptions/