Left Ventricular Function and Exercise Capacity

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Many factors, including age, female sex, body mass index, and comorbid medical conditions, are known to be associated with a decrement in exercise capacity, as reflected by a decrease in maximal workload achieved or maximal oxygen consumption. Aerobic exercise capacity decreases progressively with age and is associated with reductions in functional capacity, increases in disability, and decreases in independence and quality of life. Determining the most important parameters affecting exercise performance, especially in relation to age, is complex, given the numerous confounding factors. The most consistently reported mechanism contributing to this decrease in exercise capacity with aging is a reduction in maximal heart rate; this appears to be a nonmodifiable and inevitable consequence of aging. Similarly, the difference in exercise capacity between men and women has largely been attributed to nonmodifiable differences in cardiac output and skeletal muscle mass. Identifying potentially reversible mechanisms underlying the decline in maximal exercise capacity with aging and between men and women could have important implications.

Elucidating the mechanisms of cardiac-related exercise limitation has been technically difficult to date. Previous studies have suggested that measurements of left ventricular systolic function do not predict maximal exercise time in individuals with normal or impaired left ventricular systolic function. However, differences in exercise capacity related to small changes in ejection fraction within the normal range would require evaluation in a large population. Doppler echocardiography can now characterize left ventricular systolic function with routine measurements of left ventricular systolic and diastolic function by 2-dimensional and Doppler techniques. Analyses were conducted to determine the strongest correlates of exercise capacity and the age and sex interactions of these variables with exercise capacity.

Context Limited information exists regarding the role of left ventricular function in predicting exercise capacity and impact on age- and sex-related differences.

Objectives To determine the impact of measures of cardiac function assessed by echocardiography on exercise capacity and to determine if these associations are modified by sex or advancing age.

Design Cross-sectional study of patients undergoing exercise echocardiography with routine measurements of left ventricular systolic and diastolic function by 2-dimensional and Doppler techniques. Analyses were conducted to determine the strongest correlates of exercise capacity and the age and sex interactions of these variables with exercise capacity.

Setting Large tertiary referral center in Rochester, Minnesota, in 2006.

Participants Patients undergoing exercise echocardiography using the Bruce protocol (N=2867). Patients with echocardiographic evidence of exercise-induced ischemia, ejection fractions lower than 50%, or significant valvular heart disease were excluded.

Main Outcome Measure Exercise capacity in metabolic equivalents (METs).

Results Diastolic dysfunction was strongly and inversely associated with exercise capacity. Compared with normal function, after multivariate adjustment, those with moderate/severe resting diastolic dysfunction (−1.30 METs; 95% confidence interval [CI], −1.52 to −0.99; P<.001) and mild resting diastolic dysfunction (−0.70 METs; 95% CI, −0.88 to −0.46; P<.001) had substantially lower exercise capacity. Variation of left ventricular systolic function within the normal range was not associated with exercise capacity. Left ventricular filling pressures measured by resting E/e’ of 15 or greater (−0.41 METs; 95% CI, −0.70 to −0.11; P=.007) or postexercise E/e’ of 15 or greater (−0.41 METs; 95% CI, −0.71 to −0.11; P=.007) were similarly associated with a reduction in exercise capacity, each in separate multivariate analyses. Individuals with impaired relaxation (mild dysfunction) or resting E/e’ of 15 or greater had a progressive increase in the magnitude of reduction in exercise capacity with advancing age (P<.001 and P=.02, respectively). Other independent correlates of exercise capacity were age (unstandardized β coefficient, −0.85 METs; 95% CI, −0.92 to −0.77, per 10-year increment; P<.001), female sex (−1.98 METs; 95% CI, −2.15 to −1.84; P<.001), and body mass index greater than 30 (−1.24 METs; 95% CI, −1.41 to −1.10; P<.001).

Conclusion In this large cross-sectional study of those referred for exercise echocardiography and not limited by ischemia, abnormalities of left ventricular diastolic function were independently associated with exercise capacity.

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tricular diastolic function through a combination of measurements, which show evidence of slowed ventricular relaxation, increased left ventricular stiffness, or abnormal left ventricular filling. Doppler echocardiography can also provide an estimate of left ventricular filling pressures, one component of diastolic function that reflects pulmonary capillary wedge pressure. In prior small series, these parameters have been shown to correlate with exercise capacity.15-16 Whether abnormalities of diastolic function explain age- or sex-related changes in exercise capacity is unknown. The aims of this study were to determine the relationship between left ventricular diastolic function parameters as determined by echocardiography and exercise capacity and to determine if there is a difference in the magnitude of association of diastolic function parameters with exercise capacity with advancing age or sex.

**METHODS**

**Patient Population**

This study was approved by the Mayo Clinic institutional review board, and verbal consent was obtained at the time of the stress echocardiogram. During 2006, 4705 patients had a clinically indicated exercise echocardiogram at the Mayo Clinic, Rochester, Minnesota. For this analysis, we excluded patients who underwent exercise testing with a protocol other than the Bruce protocol (n=365); refused to participate in research (n=230); were in atrial fibrillation/flutter at the time of exercise (n=118); had moderate or severe valvular heart disease (n=76); had poor image quality, which prohibited a final impression (n=7); had ejection fractions of less than 50% (n=88); or had echocardiographic evidence of exercise-induced myocardial ischemia (n=790). The latter group of patients was excluded because symptoms or signs of ischemia would be expected to contribute to premature termination of exercise. Assessment of diastolic function was not possible in 164 patients because of missing values that were the result of fusion of pulsed-wave Doppler measurements of the early and late mitral inflow velocities or poor apical windows; baseline characteristics of these patients were similar to those studied.

The remaining 2867 patients constituted the study population. Of these, 1402 (49%) were referred for exercise echocardiography for shortness of breath or chest pain, 632 (21%) because of the presence of multiple risk factors for cardiovascular disease, 278 (10%) because of abnormal resting electrocardiogram findings, 250 (9%) for evaluation of suspected coronary artery disease, 232 (8%) for preoperative assessment, and 73 (2%) for increased coronary calcium scores on computed tomography.

Clinical variables and body mass index (calculated as weight in kilograms divided by height in meters squared) were recorded at the time of the exercise echocardiogram. Medication use and a history of diabetes mellitus, hypertension, hyperlipidemia, smoking, and coronary artery disease were abstracted from the medical record and entered into a prospectively maintained database by specially trained nurses. Coronary artery disease was defined as previous coronary revascularization or history of myocardial infarction.

**Exercise Echocardiography**

Echocardiography was performed before starting exercise and immediately after symptom-limited treadmill exercise according to the Bruce protocol. The Diastolic Function Initiative of 2006, undertaken at the Mayo Clinic, was a routinely performed assessment of left ventricular diastolic function done in addition to assessment of regional wall motion according to the usual exercise echocardiography protocol. The baseline resting assessment included pulsed-wave Doppler measurements of the early (E) and late (A) mitral inflow velocities, deceleration time of early left ventricular filling, the peak early diastolic velocity of the medial mitral annulus (e’) with tissue Doppler in the 4-chamber view, and 2-dimensional measurement of the left atrial size.

The ratio E/e’, a measurement of left ventricular filling pressures, was feasible in all patients at rest. Shortly after exercise, mitral inflow and annulus Doppler data were obtained again. These were measured in early recovery (within 2-7 minutes of cessation of exercise) after regional wall motion assessment and at the earliest time that the E and A velocities were sufficiently separated to permit measurement. Measurement of postexercise E/e’ was feasible in 2366 patients (82%). Increased left ventricular filling pressure at rest and with exercise was defined as an E/e’ of 15 or greater.15,16 Resting diastolic function was graded as normal, mild dysfunction (impaired relaxation), moderate dysfunction ( pseudonormal), or severe dysfunction (restrictive). The classification of diastolic function was modified from the algorithm outlined by Khoury et al. Instead of pulmonary vein flow measurements, left atrial volume was measured as part of our assessment because it has been shown to be a marker of diastolic dysfunction.18,19 Relaxation and restrictive abnormalities were classified based on the mitral inflow patterns, an E/A less than 0.75 and E/A greater than 1.5, respectively.

To diagnose a restrictive abnormality, left atrial volume index had to be increased 28 mL/m² or more, and E/e’ had to be increased 10 or more, respectively; otherwise, patients were classified as normal. This is especially important in young people because a normal E/A is often greater than 1.5 due to increased early filling with no other echocardiographic evidence of diastolic dysfunction.18 To distinguish pseudonormal from normal diastolic function (0.75 ≤ E/A ≤ 1.5), both left atrial volume index and E/e’ had to be increased as described. Left atrial volume was measured according to the area-length method and indexed to body surface area.20 Left ventricular ejection fraction was assessed by a combination of the modified Quinones method21 and visual assessment.
Wall motion was scored according to a 16-segment model, in which 1 was considered normal or hyperdynamic, 2 was hypokinetic, 3 was akinetic, 4 was dyskinetic, and 5 was aneurysmal. The exercise echocardiogram was considered normal if there were no wall motion abnormalities at rest or with exercise. “Fixed” wall motion abnormalities were those present at rest and unchanged by exercise. Global hypokinesis present at rest and improved with exercise was considered to represent cardiomyopathy. Baseline and peak exercise blood pressure, heart rate, and pulse pressure (systolic–diastolic blood pressure) were determined. Heart rate increase with exercise was defined as the difference between peak exercise heart rate and baseline heart rate.

### Statistics

The primary end point was maximal exercise tolerance defined by the achieved metabolic equivalents (METS). Data are expressed as mean and standard deviation or number and percentage. Multiple comparisons of continuous variables were made with analysis of variance. Tukey honestly significant difference approach was used to adjust for multiple comparisons. Categorical data were compared by the χ² test. Collinearity diagnostics were performed to look for multicollinearity between the independent variables in the linear models. Collinearity between systolic blood pressure and pulse pressure was present, and the latter was included in the final multivariate models. Similarly, diastolic function grade and resting E/e’ demonstrated collinearity, and 2 separate multivariate models were constructed to evaluate each of these separately in the 2867 patients with baseline diastolic function assessment.

Stepwise multivariate linear regression models were used to estimate the relative contributions of the baseline clinical and echocardiographic variables to exercise performance. Because of the small numbers of patients with moderate and severe diastolic dysfunction, these groups were combined for analysis. In a subgroup of 2366 patients in whom postexercise E/e’ measurements were also feasible, a separate multivariate linear regression model was used to evaluate the relative contributions of the peak exercise clinical and echocardiographic variables to exercise performance.

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### Table 1. Clinical Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal (n = 1784)</th>
<th>Mild Dysfunction (n = 785)</th>
<th>Moderate/Severe Dysfunction (n = 298)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>53 (11)</td>
<td>67 (9)</td>
<td>66 (11)</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>964 (54)</td>
<td>433 (55)</td>
<td>172 (53)</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>123 (18)</td>
<td>130 (19)</td>
<td>131 (19)</td>
</tr>
<tr>
<td>Pulse pressure, mean (SD), mm Hg</td>
<td>48 (15)</td>
<td>54 (16)</td>
<td>56 (16)</td>
</tr>
<tr>
<td>Heart rate, mean (SD), beats/min</td>
<td>74 (13)</td>
<td>76 (14)</td>
<td>78 (13)</td>
</tr>
<tr>
<td>Body mass index, mean (SD)</td>
<td>27 (5)</td>
<td>28 (4)</td>
<td>29 (6)</td>
</tr>
<tr>
<td>History of CAD, No. (%)</td>
<td>162 (9)</td>
<td>138 (19)</td>
<td>60 (20)</td>
</tr>
<tr>
<td>History of diabetes mellitus, No. (%)</td>
<td>107 (6)</td>
<td>126 (16)</td>
<td>57 (18)</td>
</tr>
<tr>
<td>History of hypertension, No. (%)</td>
<td>676 (38)</td>
<td>406 (63)</td>
<td>232 (71)</td>
</tr>
<tr>
<td>Previous/current smoker, No. (%)</td>
<td>750 (42)</td>
<td>368 (47)</td>
<td>157 (48)</td>
</tr>
<tr>
<td>Body mass index, mean (SD)</td>
<td>27 (5)</td>
<td>28 (4)</td>
<td>29 (6)</td>
</tr>
<tr>
<td>Heart rate, mean (SD), beats/min</td>
<td>74 (13)</td>
<td>76 (14)</td>
<td>78 (13)</td>
</tr>
<tr>
<td>Pulse pressure, mean (SD), mm Hg</td>
<td>48 (15)</td>
<td>54 (16)</td>
<td>56 (16)</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>123 (18)</td>
<td>130 (19)</td>
<td>131 (19)</td>
</tr>
<tr>
<td>Exercise capacity, METs</td>
<td>10.7 (2.6)</td>
<td>8.5 (2.3)</td>
<td>8.0 (2.1)</td>
</tr>
<tr>
<td>Duration exercise, min</td>
<td>9.7 (2.6)</td>
<td>7.6 (2.3)</td>
<td>7.0 (2.1)</td>
</tr>
</tbody>
</table>

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### Table 2. Echocardiography Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal (n = 1784)</th>
<th>Mild Dysfunction (n = 785)</th>
<th>Moderate/Severe Dysfunction (n = 298)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV ejection fraction, mean (SD), %</td>
<td>61 (4)</td>
<td>60 (6)</td>
<td>60 (8)</td>
</tr>
<tr>
<td>LV diastolic dimension, mean (SD), mm</td>
<td>47 (4)</td>
<td>47 (5)</td>
<td>49 (6)</td>
</tr>
<tr>
<td>Wall motion score index, mean (SD)</td>
<td>1.0 (0.1)</td>
<td>1.1 (0.2)</td>
<td>1.1 (0.3)</td>
</tr>
<tr>
<td>Deceleration time, mean (SD), ms</td>
<td>198 (34)</td>
<td>239 (51)</td>
<td>201 (39)</td>
</tr>
<tr>
<td>Left atrial volume index, mean (SD), mL/m²</td>
<td>25 (7)</td>
<td>28 (9)</td>
<td>37 (10)</td>
</tr>
<tr>
<td>Resting E/e’, mean (SD)</td>
<td>8 (5)</td>
<td>10 (4)</td>
<td>14 (5)</td>
</tr>
<tr>
<td>Postexercise E/e’, mean (SD)</td>
<td>8 (5)</td>
<td>10 (4)</td>
<td>14 (5)</td>
</tr>
</tbody>
</table>
distribution of continuous variables was tested to ensure that normality assumptions were fulfilled. Interaction terms of diastolic function parameters with age and sex were also evaluated to determine whether the magnitude of reduction in exercise capacity among those with abnormal diastolic parameters varied with increasing age or between sexes. To detect a clinically meaningful difference in exercise capacity of 0.5 METS with 90% power, a sample size of n = 256 was required in each diastolic function group (normal, mild dysfunction, and moderate/severe dysfunction). This was with an SD of 3.5 METs, assuming a 2-sided analysis and α = .05. An a priori level of significance was assigned at less than .05. All computations were performed using JMP statistical software for Windows (version 6.0; SAS Institute Inc, Cary, North Carolina).

RESULTS

Study Population

The baseline clinical and echocardiographic characteristics are outlined in Table 1 and Table 2. Normal diastolic function was present in 1784 patients (62%), mild diastolic dysfunction in 785 (27%), and moderate/severe diastolic dysfunction in 298 (10%). The exercise echocardiogram was normal in 2655 patients (93%), showed a fixed abnormality in 202 (7%), and was considered to indicate dilated cardiomyopathy in 10 (0.3%). Target heart rate (≥85% age-predicted maximal heart rate) was achieved in 2146 patients (75%). The primary reason for stopping exercise was fatigue in 1759 patients (61%), dyspnea in 801 (28%), leg discomfort in 281 (10%), arrhythmias in 18 (1%), and atypical chest discomfort in 8 (0.3%).

Clinical and Echocardiographic Correlates of Exercise Capacity

Resting univariate and multivariate correlates of exercise capacity as measured by METs are shown in Table 3 and Table 4. Compared with normal diastolic function, the presence of mild and moderate/severe diastolic dysfunction were associated with a mean (SD) reduction in exercise capacity of 2.17 (0.10) METs and 2.74 (0.15) METs, respectively, before adjusting for other clinical and echocardiographic factors (Table 3). Considering all variables in Table 3 in the multivariate analysis, the strongest independent correlates of reduced exercise tolerance were increasing age, female sex, body mass index greater than 30, moderate/severe diastolic dysfunction vs normal, and mild diastatic dysfunction vs normal as shown by the standardized β coefficients in Table 4.

The presence of mild or moderate/severe diastolic dysfunction as compared with normal was associated with a mean (SD) reduction of exercise capacity of 0.70 (0.10) METs (95% confidence interval [CI], −0.88 to −0.46) and 1.30 (0.13) METs (95% CI, −1.52 to −0.99), respectively. Every 10-beat increase in resting heart rate was associated with a mean (SD) reduction of 0.24 (0.03) METs (95% CI, −0.30 to −0.18) in exercise capacity. In multivariate analysis, increasing age was associated with a reduction of 0.85 (0.04) METs (95% CI, −0.92 to −0.77) per 10 years of age. Overall, women exercised 1.98 (0.07) METs less than their male counterparts (95% CI, −2.15 to −1.84). Patients with a body mass index greater than 30 exercised 1.24 (0.08) METs less than those with a body mass index of 30 or lower (95% CI, −1.41 to −1.10).

The other correlates in the final multivariate model, although significant,
were associated with smaller reductions in exercise capacity: previous/current smoker vs nonsmoker (−0.43 [0.07] METs; 95% CI, −0.59 to −0.29), β-blocker vs no β-blocker (−0.39 [0.09] METs; 95% CI, −0.61 to −0.21), hypertension vs no hypertension (−0.27 [0.88] METs; 95% CI, −0.48 to −0.13), and diabetes vs no diabetes (−0.36 [0.12] METs; 95% CI, −0.67 to −0.16). The $R^2$ of this model was 0.51, with exclusion of diastolic function grade, $R^2$ decreased to 0.40.

This multivariate model did not include resting E/e′ because of its colinearity with diastolic function grade, and a separate multivariate model substituting diastolic function grade with resting E/e′ was constructed (Table 4). Resting E/e′ of 15 or greater was associated with a mean (SD) reduction in exercise capacity of 1.81 (0.19) METs compared with E/e′ of less than 15 in univariate analysis (Table 3). After adjustment for clinical and echocardiographic variables, resting E/e′ of 15 or greater was associated with a reduction in exercise capacity of 0.41 (0.15) METs compared with E/e′ of less than 15 (95% CI, −0.70 to −0.11) (Table 4).

In univariate analysis, postexercise E/e′ of 15 or greater was associated with a −1.86 (0.20) MET change in exercise capacity (P < .001), every 10-beat increase in the change in heart rate from rest to exercise with a 0.77 (0.02) MET increase in exercise capacity (P < .001), and every 10-beat increment in peak exercise heart rate with a 0.59 (0.02) MET increase in exercise capacity (P < .001). After adjusting for clinical and echocardiographic parameters in multivariate analysis, the strongest peak exercise correlates of exercise capacity were heart rate increase (0.43-MET increase in exercise capacity per 10-beat increment) and postexercise E/e′ of 15 or greater (0.41-MET reduction [0.15] in exercise capacity; 95% CI, −0.71 to −0.11) (Table 5).

Heart rate at rest was increased and the increase at peak exercise was blunted with diastolic dysfunction (Table 1). The correlation between resting heart rate and diastolic function was poor ($r = 0.08, P < .001$) as was the relationship with resting E/e′ ($r = 0.13, P < .001$) and postexercise E/e′ ($r = 0.09, P < .001$). There was only a modest correlation between heart rate increase and worsening diastolic function ($r = 0.31, P < .001$), resting E/e′ ($r = 0.24, P < .001$), and postexercise E/e′ ($r = 0.23, P < .001$).

Among the 2366 patients with postexercise E/e′, 742 had mild or moderate/severe resting diastolic dysfunction and resting E/e′ less than 15. Of these, 57 (8%) developed an E/e′ of 15 or greater after exercise. This is in contrast to the 1472 individuals with normal diastolic function and resting E/e′ less than 15 of whom 38 (2.6%) developed postexercise E/e′ of 15 or greater.

### Table 4. Multivariate Analysis of Association of Resting Clinical and Echocardiographic Variables With Exercise Capacity in Metabolic Equivalents

<table>
<thead>
<tr>
<th>Resting Variables</th>
<th>$\beta$ Unstandardized SE</th>
<th>$\beta$ Unstandardized 95% CI</th>
<th>$\beta$ Standardized $^{2}|_{3}$</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1 With Diastolic Function Grade $^{a}$</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild dysfunction vs normal</td>
<td>−0.70 (0.10)</td>
<td>−0.88 to −0.46</td>
<td>−0.12</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Moderate/severe dysfunction vs normal</td>
<td>−1.30 (0.13)</td>
<td>−1.52 to −1.09</td>
<td>−0.16</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age, per 10 y</td>
<td>−0.85 (0.04)</td>
<td>−0.92 to −0.77</td>
<td>−0.40</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>−1.19 (0.07)</td>
<td>−1.25 to −1.14</td>
<td>−0.26</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Body mass index $&gt;30$</td>
<td>−1.21 (0.08)</td>
<td>−1.31 to −1.11</td>
<td>−0.21</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heart rate, per 10 beats/min</td>
<td>−0.24 (0.03)</td>
<td>−0.30 to −0.18</td>
<td>−0.11</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Previous/current smoker</td>
<td>−0.43 (0.07)</td>
<td>−0.50 to −0.29</td>
<td>−0.08</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>−0.31 (0.09)</td>
<td>−0.38 to −0.24</td>
<td>−0.07</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pulse pressure, per 10 mm Hg</td>
<td>−0.10 (0.02)</td>
<td>−0.15 to −0.05</td>
<td>−0.06</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>−0.27 (0.09)</td>
<td>−0.34 to −0.20</td>
<td>−0.06</td>
<td>.01</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>−0.36 (0.12)</td>
<td>−0.47 to −0.25</td>
<td>−0.06</td>
<td>.03</td>
</tr>
<tr>
<td><strong>Model 2 With Resting E/e′</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E/e′$\geq$15</td>
<td>−0.41 (0.15)</td>
<td>−0.70 to −0.11</td>
<td>−0.04</td>
<td>.007</td>
</tr>
<tr>
<td>Age, per 10 y</td>
<td>−1.00 (0.03)</td>
<td>−1.05 to −0.95</td>
<td>−0.46</td>
<td>&lt;.001</td>
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<tr>
<td>Female sex</td>
<td>−2.00 (0.08)</td>
<td>−2.19 to −1.81</td>
<td>−0.37</td>
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<tr>
<td>Body mass index $&gt;30$</td>
<td>−1.34 (0.08)</td>
<td>−1.50 to −1.18</td>
<td>−0.22</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heart rate, per 10 beats/min</td>
<td>−0.28 (0.03)</td>
<td>−0.33 to −0.23</td>
<td>−0.13</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>−0.53 (0.10)</td>
<td>−0.71 to −0.35</td>
<td>−0.08</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Previous/current smoker</td>
<td>−0.44 (0.08)</td>
<td>−0.50 to −0.29</td>
<td>−0.08</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pulse pressure, per 10 mm Hg</td>
<td>−0.09 (0.03)</td>
<td>−0.15 to −0.04</td>
<td>−0.05</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>−0.28 (0.10)</td>
<td>−0.44 to −0.08</td>
<td>−0.04</td>
<td>.007</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>−0.41 (0.13)</td>
<td>−0.64 to −0.12</td>
<td>−0.04</td>
<td>.002</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; E/e′, ratio of the Doppler measurements of early mitral inflow velocity and peak early diastolic velocity of the medial mitral annulus.

The linearity with diastolic function grade,

The $R^2$ value was 0.45; intercept, 19.0.

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the magnitude of reduction in exercise capacity with advancing age (Figure 1). In contrast, individuals with moderate/severe diastolic dysfunction had a reduced exercise capacity compared with those with normal function, but the magnitude of this reduction was similar across the age spectrum ($P = .46$). This was also true for those with resting $E/e^{\prime}$ of 15 or greater ($P = .46$). Compared with those with a postexercise $E/e^{\prime}$ of less than 15, however, individuals with a postexercise $E/e^{\prime}$ of 15 or greater had a progressive increase in the magnitude of reduction in exercise capacity with advancing age (Figure 1). Although an increase in resting heart rate had a negative correlation with exercise capacity, the strength of this correlation diminished with age. Specifically, every 10-beat increase in resting heart rate predicted a 0.54-MET decrease in exercise capacity among patients younger than 50 years and a 0.24-MET decrease in patients 50 years or older ($P < .001$). Exercise capacity was reduced in women as compared with men, and the magnitude of this reduction in each diastolic dysfunction grade was similar between the sexes (Figure 2). This was also true for resting and postexercise $E/e^{\prime}$ ($P = .14$ and $P = .20$, respectively).

**COMMENT**

In a large, consecutive population free of valvular heart disease or exercise-induced ischemia referred for exercise echocardiography, we found resting diastolic function to be the strongest echocardiographic correlate of exercise tolerance. This was superseded only by the clinical factors of advancing age, female sex, and increasing body mass index. This relationship remained significant after taking into account resting heart rate, blood pressure, medication use, comorbid medical conditions, and other echocardiographic parameters.

Unlike previous studies that have shown modest correlations of $E/A$ ratio and deceleration time with exercise capacity, we found that diastolic function grade was strongly associated with a decrement in exercise capacity. Similarly, resting left ventricular filling pressure ($E/e^{\prime}$) was also found to correlate with exercise capacity, although this association was less robust. $E/e^{\prime}$ could be used as a surrogate if assessment of diastolic function grade is not feasible. In a previous smaller study, exercise $E/e^{\prime}$ of 15 or greater was shown to strongly correlate with invasively determined left ventricular end-diastolic pressure at peak exercise; we found that increased filling pressures with exercise were also associated with a decrement in exercise capacity. We found that exercise capacity is not importantly influenced by variations of ejection fraction within the broad range of normal values; for example, an ejection fraction of 70% would not portend a better exercise capacity than an ejection fraction of 55%.

We also documented that a history of previous or current smoking is associated with exercise limitation. An increase in resting heart rate was also a marker of poor exercise capacity; resting heart rate was higher in those with worse diastolic function. However, this may be a marker of overall deconditioning and had a minimal relationship with the extent of diastolic dysfunction or filling pressures. Similarly, a large chronotropic response was associated with improved exercise capacity but was only modestly associated with diastolic function grade and filling pressures. Clearly, the mechanisms underlying relationships of heart rate with exercise capacity are complex and cannot be entirely explained by diastolic dysfunction parameters.

One mechanism by which diastolic parameters may affect exercise capacity relates to their role in generating a maximal cardiac output. During exercise, the maintenance of adequate left ventricular filling to ensure a normal cardiac output includes the ability to achieve diastolic filling rates greater than the ejection rates during systole. In the setting of exercise-induced tachycardia, abnormalities in diastolic relaxation and filling of the left ventricle can result in filling rates that might be too low to achieve adequate cardiac output during exercise even if ventricular systolic properties are normal.
Exercise capacity within each diastolic function grade is similar between the sexes. Boxes indicate interquartile range; horizontal lines, median; error bars, range. METs indicates metabolic equivalents.

In the mild diastolic dysfunction group vs the normal function group, exercise capacity was reduced, but the steeper slope in the mild group indicates that the magnitude of this reduction increased with age. Derived from age x diastolic function interaction analysis, a P<.001 for the diastolic function comparison shows that the slopes of the 2 lines are statistically different. Exercise capacity was also reduced in the group with a post-exercise E/e’ ratio of 15 or greater vs that with E/e’ less than 15. The magnitude of this reduction also increased with age, as shown by the steeper slope in the group with E/e’ of 15 or greater. A P=.02, derived from analysis of age x diastolic function interaction, shows that the slopes of the 2 lines are statistically different. All curves were fit to the data by group using linear regression analysis. Dashed lines indicate the upper and lower 95% confidence limits for the mean values. E/e’ indicates the ratio of the Doppler measurements of the early (E) mitral inflow velocity and the peak early diastolic velocity of the medial mitral annulus (e’). METs indicates metabolic equivalents.

It has been suggested that stimulation of J receptors in the lungs by congestion or increases in transmitted left atrial pressures to the pulmonary vascular system would tend to result in more tachypneic breathing, thus altering the normal breathing patterns and resulting in exercise intolerance.24,25 A normal diastolic function response to exercise is characterized by normal and similar resting and exercise E/e’ measurements.26 In our study, just over half of the patients that developed increased filling pressures with exercise had a resting E/e’ of less than 15, suggesting that they adapted poorly to the cardiac physiology of exercise contributing to exercise intolerance. In part, this may be related to resting diastolic abnormalities, because 77% of patients with postexercise E/e’ of 15 or greater had evidence of resting diastolic dysfunction. Additionally, only 8% of patients with resting diastolic dysfunction and E/e’ of less than 15 developed increased filling pressures after exercise. This suggests that the mechanism by which diastolic dysfunction contributes to exercise intolerance is not limited to the development of increased filling pressures.

As shown in our study and others, older age is strongly associated with decreased exercise capacity. Mechanisms proposed to explain this association include reduced peak heart rates or a decrease in arteriovenous oxygen content difference affecting maximal cardiac output generation.27,28 Aging is also associated with a reduction in skeletal muscle mass and decreases in muscle capillarization and mitochondrial enzyme activity, all of which can also contribute to reduced exercise capacity. While aging is known to be associated with an increasing prevalence of impaired cardiac relaxation, our study shows that even after adjusting for age, diastolic function was strongly associated with exercise capacity. Moreover, our findings reveal that an important interaction between age and diastolic dysfunction exists, such that absolute reduction in exercise capacity among those with impaired relaxation vs those with normal diastolic function progressively increases with advancing age. This remains the case for those with elevated exercise filling pressures.

Although women have a lower exercise capacity compared with men, our findings confirm that there is a greater age-associated decline in exercise capacity in men.3,29 Further, our data suggest that the absolute reduction in exercise capacity in women vs men is similar across the spectrum of diastolic dysfunction, so diastolic parameters do not account for the sex differences in exercise tolerance.

In identifying diastolic function parameters as strong correlates of exercise capacity, we have identified potentially modifiable and preventable
factors in the development of exercise intolerance. It is well known that exercise training improves diastolic function in healthy individuals, demonstrating an increase in peak diastolic filling rates. However, although patients with diastolic dysfunction show an improvement in exercise tolerance with training, the effects of training on diastolic function are less clear. Similarly, pharmacologic treatment of patients with diastolic dysfunction enhances exercise capacity, but improvement in diastolic function is limited and occurs in few patients. Treatment with angiotensin receptor blockers has appeared to be most promising because they block angiotensin II action that is thought to be responsible for slowed left ventricular relaxation during exercise. Although data with respect to modifying diastolic function are unclear and merit further study, current approaches should include aggressive treatment of risk factors such as hypertension and coronary artery disease to prevent development of diastolic abnormalities and related exercise limitations.

Although this is a very large study characterizing the association of age and sex with exercise capacity, results are limited to patients in whom a complete echocardiographic assessment as outlined was possible. This should not affect overall results, because the demographic characteristics of patients who did not have baseline diastolic function assessment were similar to those who did. The mechanism by which diastolic dysfunction affects exercise capacity may relate to cardiac output. This was not measured in these patients and was not our focus but merits further study.

Because patients recruited into our study were middle-aged and referred for a clinically indicated stress echocardiogram, there is the potential for a referral bias related to a higher prevalence of comorbidities. However, compared with a contemporary community-based cohort of Olmsted County, the prevalence of systolic and diastolic dys-

function was only slightly higher. Our results should be validated in other populations.

The presence of anemia and obstructive lung disease was not ascertained, although we did account for a smoking history. Lastly, we used calculated METs rather than oxygen consumption as a measure of exercise tolerance. Although the latter is preferable, calculation of achieved METs is a widely accepted clinical tool for determining functional capacity that is relevant to the daily activities of patients. Absolute exercise capacity measured in METs has been shown to be the most powerful predictor of long-term mortality.

CONCLUSION

In this large population referred for exercise echocardiography and not limited by ischemia, we demonstrated that diastolic dysfunction was strongly related to decreased exercise capacity. Increased resting and postexercise left ventricular filling pressures are also associated with a reduction in exercise capacity. Other correlates of exercise intolerance include age, sex, and body mass index. Although these data require confirmation in prospective studies, they point to a potential modifiable factor that might be a target for interventions that could maintain exercise capacity with aging. Unlike many other factors that are an inevitable consequence of aging, diastolic dysfunction may be a preventable factor in the development of exercise intolerance.

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