Contribution of Exercise-Induced Mitral Regurgitation to Exercise Stroke Volume and Exercise Capacity in Patients With Left Ventricular Systolic Dysfunction

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**Background**—Functional mitral regurgitation (MR) is common in patients with heart failure and left ventricular (LV) dysfunction, and its severity may vary over time, depending primarily on the loading conditions. Because dynamic changes in the severity of functional MR may affect forward stroke volume, we hypothesized that exercise-induced changes in MR severity influence the stroke volume response of patients with LV dysfunction to exercise, and hence their exercise capacity.

**Methods and Results**—Heart failure patients (n=25; mean age 53±12 years) with LV dysfunction underwent dynamic bicycle exercise at steady-state levels of 30%, 60%, and 90% of predetermined peak VO₂. During each exercise level, right heart pressures, cardiac output, VO₂, and MR severity were measured simultaneously. During exercise, MR severity, as evaluated by the ratio of MR jet over left atrium area, increased from 15±8% to 33±15%. Peak VO₂, exercise-induced changes in stroke volume, and those in capillary wedge pressure correlated with the changes in MR severity, as evaluated by the ratio of MR jet over left atrium area, increased from 15±8% to 33±15%. Peak VO₂, exercise-induced changes in stroke volume, and those in capillary wedge pressure correlated with the changes in MR severity, as evaluated by the ratio of MR jet over left atrium area, increased from 15±8% to 33±15%. Peak VO₂, exercise-induced changes in stroke volume, and those in capillary wedge pressure correlated with the changes in MR severity, as evaluated by the ratio of MR jet over left atrium area, increased from 15±8% to 33±15%. Peak VO₂, exercise-induced changes in stroke volume, and those in capillary wedge pressure correlated with the changes in MR severity, as evaluated by the ratio of MR jet over left atrium area, increased from 15±8% to 33±15%. Peak VO₂, exercise-induced changes in stroke volume, and those in capillary wedge pressure correlated with the changes in MR severity, as evaluated by the ratio of MR jet over left atrium area, increased from 15±8% to 33±15%. Peak VO₂, exercise-induced changes in stroke volume, and those in capillary wedge pressure correlated with the changes in MR severity, as evaluated by the ratio of MR jet over left atrium area, increased from 15±8% to 33±15%. Peak VO₂, exercise-induced changes in stroke volume, and those in capillary wedge pressure correlated with the changes in MR severity, as evaluated by the ratio of MR jet over left atrium area, increased from 15±8% to 33±15%. Peak VO₂, exercise-induced changes in stroke volume, and those in capillary wedge pressure correlated with the changes in MR severity, as evaluated by the ratio of MR jet over left atrium area, increased from 15±8% to 33±15%

**Conclusions**—Our data indicate that in patients with LV dysfunction, exercise-induced changes in MR severity limit the stroke volume adaptation during exercise and therefore contribute to limitation of exercise capacity. *(Circulation. 2002; 106:1342-1348.)*

**Key Words:** regurgitation ■ heart failure ■ catheterization ■ echocardiography ■ oxygen

Much of the previous research into the determinants of exercise capacity in patients with heart failure has focused on the relative contribution of the heart and the periphery in limiting O₂ transport to and O₂ uptake by the exercising muscles. 1–6 Although the mechanisms of exercise intolerance are multifactorial, they depend at least in part on the maximal pumping capacity of the heart, ie, maximal stroke volume and cardiac output.

It is generally accepted that in the absence of significant mitral regurgitation (MR), the increase in stroke volume during dynamic exercise is largely brought about by a combined increase in preload and contractility. 7,8 In the presence of MR, however, dynamic changes in the severity of regurgitation during exercise may compromise the normal increase in forward stroke volume and hence reduce maximal cardiac output and exercise capacity. Because functional MR is common in patients with heart failure due to left ventricular (LV) dysfunction9–11 and may vary depending on the loading conditions,10–13 we tested the hypothesis that exercise-induced changes in MR severity influence the forward stroke volume response to exercise and consequently exercise capacity.

**Methods**

**Study Population**

The study population consisted of 25 consecutive heart failure patients (mean age 53±12 years, range 31 to 76 years) who met the following inclusion criteria: (1) LV dilatation and dysfunction at echocardiography (M-mode LV end-diastolic dimension >60 mm, LV fractional shortening <25%, and an increased E point-septal separation); (2) peak exercise VO₂ ≤20 mL · min⁻¹ · kg⁻¹; and (3) mild-to-moderate degrees of MR by color Doppler under resting conditions. Patients with atrial fibrillation, excessive tachycardia, primary mitral valve disease, a prosthetic mitral valve, greater than mild aortic insufficiency, or evidence of inducible myocardial ischemia, chronic obstructive pulmonary disease, or other noncardiac conditions that limit exercise capacity were not considered for inclusion in the study. The presumed cause of heart failure was...
ischemic heart disease in 12 patients (48%) and nonischemic dilated cardiomyopathy in the remaining 13 (52%). Ischemic heart disease was considered in the presence of a documented previous myocardial infarction or a >50% luminal diameter narrowing on a proximal major epicardial coronary artery at coronary arteriography. Nonischemic dilated cardiomyopathy was considered only in the presence of angiographically normal coronary arteries. Each subject was informed of the investigative nature of the study, which had been approved by the ethics committee of our institution.

Exercise Testing
All patients performed 3 symptom-limited multistage dynamic bicycle exercise tests, 1 selection and 2 study tests. The first test was performed for patient selection and to acquaint them with the laboratory environment. The 2 study tests were performed 1 week later. These 2 tests were conducted on consecutive days, at the same time of day and under the same dietary conditions, ie, at least 2 hours after a controlled light meal. The first study test was used for determination of peak $V_{O2}$ and selection of the submaximal and maximal workloads to be applied during the second study test. During this test, the initial workload was set at 10 W, and exercise intensity was increased by 10 W every minute.\(^{15}\) In each case, patients were encouraged to perform maximal exercise. The second study test was performed at steady-state levels of 30%, 60%, and 90% of the peak $V_{O2}$ determined during the first test.\(^{16}\) During the second test, arterial and right heart pressures, cardiac output, $V_{O2}$, and MR severity were measured simultaneously at baseline, in both supine and upright positions, and during the last 3 minutes of each exercise level. Throughout the exercise tests, the 3 Frank orthogonal ECG leads were monitored continuously, recorded on paper, and analyzed by computer as described previously.\(^{17}\) In patients with ischemic heart disease, the presence of inducible myocardial ischemia was excluded by use of thallium imaging as described previously.\(^{18}\)

Gas Exchange Analysis
Expired gases were measured at rest and during exercise by use of an automated breath-by-breath gas exchange ergospirometer (MedGraphics CPX/D metabolic cart) to calculate total body $O_2$ consumption ($V_{O2}$) and the respiratory exchange ratio. Exercise capacity was defined either as the peak $V_{O2}$ normalized for body weight during the last minute of exercise or the fraction of the age- and sex-adjusted predicted $V_{O2}$.\(^{19}\)

Right Heart Catheterization
Cardiac output and right heart hemodynamics were measured in every patient by use of a 7F Swan-Ganz thermodilution catheter introduced into the aortic root via the right internal jugular vein and connected to a P23Db pressure gauge transducer (Gould Laboratories). An 18-gauge catheter was also introduced in the left brachial artery for measurement of arterial pressure and withdrawal of arterial blood samples. Cardiac output was measured by the Fick method.

M-mode, 2D, and Doppler echocardiograms were obtained with an HP SONOS 5500 echocardiographic system (Hewlett Packard) equipped with a broadband, wide-angle, phased-array transducer and analyzed as described previously.\(^{4}\) In addition to the usual indices, end-diastolic (largest dimension or onset of QRS complex) and end-systolic (smallest dimension or aortic valve closure) LV volumes and ejection fraction were calculated by use of the Simpson biplane method. LV shape was assessed by computation of end-diastolic and end-systolic sphericity indexes, ie, the ratio of the major to the minor axis at end diastole and end systole.\(^{20}\) The size of the mitral anulus and the distance separating the plane of the mitral anulus plane from the coaptation between the mitral leaflets at end systole was also measured.\(^{21}\) The presence and magnitude of MR were assessed by use of the regurgitant color jet over left atrium area.\(^{22}\) MR volume and fraction were also calculated as the difference between the aortic and mitral stroke volumes, measured by pulsed-wave Doppler at the level of the aortic and mitral anulus.\(^{23}\) For technical reasons, however, this measure could not be obtained in 3 patients.

Day-to-Day Variability in Doppler Echocardiographic Studies
Six patients (mean age 46±10 years) agreed to repeat the baseline and exercise echocardiographic studies 48 hours after the first studies to assess the day-to-day variability in exercise-induced changes in MR. Data were analyzed in a blinded fashion by 2 observers (R.L. and B.L.G.) to evaluate the day-to-day variability in the various measurements and their interobserver and intraobserver variability.

Statistical Methods
Data are expressed as mean values ±1 SD. Each M-mode and Doppler data point represents the average of 3 to 5 consecutive beats. Their interobserver and intraobserver variability has been reported previously.\(^{5,14}\) Comparisons between groups were performed by use of the Student t test for paired or unpaired data, the Fisher exact test, or $\chi^2$ contingency analysis (with Yates’ correction), where appropriate. All tests were 2-sided, and a probability value <0.05 was considered statistically significant. Comparison between the different exercise stages was performed by use of 2-way ANOVA with the Bonferroni correction for post hoc comparisons. Day-to-day variability of color Doppler measurements was assessed by computation of intraclass correlation coefficients with a 1-way ANOVA random factor and by calculation of the limits of agreement between day-to-day measurements by use of Bland-Altman analysis. The relationship between hemodynamic parameters, MR severity, and $V_{O2}$ was tested by linear regression analysis and nonlinear fitting routines. To identify potentially independent determinants of exercise capacity, all variables that correlated with $V_{O2}$ were submitted to a forward stepwise multiple regression analysis. At each step, variables were entered until there was no improvement in the value of the generalized $r^2$ coefficient.

Results
Patient Characteristics
Of the 25 patients included in the study, 12 (48%) had no symptoms or were minimally symptomatic (New York Heart Association class I or II), whereas 13 (52%) had moderate to severe symptoms (New York Heart Association class III or IV). Medical treatment included diuretics in 17 patients (68%), digitalis in 6 (24%), nitrates in 14 (56%), and ACE inhibitors in 24 (96%). Of the 12 patients with ischemic heart disease, 4 (33%) had prior coronary revascularization, and the remaining patients had sustained at least 1 previous myocardial infarction. A history of hypertension was noted in 11 patients (44%), and 5 patients (20%) were diabetic.

According to their peak $V_{O2}$ during the first exercise test, patients were categorized into 2 groups: group 1, which included 10 patients with mild-to-moderate exercise limitation (peak $V_{O2} \geq 50\%$ of the age- and sex-adjusted predicted $V_{O2}$); and group 2, which included 15 patients with severe exercise intolerance (peak $V_{O2} \leq 50\%$). Their baseline characteristics are summarized in Table 1.

Hemodynamic Responses to Exercise
On average, patients exercised for 8±3 minutes (range 4 to 10 minutes). The peak $V_{O2}$ achieved during the first exercise test averaged 14±4 mL · kg\(^{-1}\) · min\(^{-1}\) (range 6 to 20 mL · kg\(^{-1}\) · min\(^{-1}\)), which corresponded to 46±16% of the maximal age- and sex-predicted peak $V_{O2}$ (range 20% to 75%). Dyspnea, rather than leg fatigue, was the most frequent cause of exercise cessation (64%).
TABLE 1. Clinical Characteristics and Baseline LV Function

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Group 1 (n=10)</th>
<th>Group 2 (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53±12</td>
<td>56±11</td>
<td>50±12</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>75±14</td>
<td>85±12</td>
<td>69±11†</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.6±0.6</td>
<td>2.3±0.5</td>
<td>2.7±0.6</td>
</tr>
<tr>
<td>LV systolic function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic dimension, mm</td>
<td>73±7</td>
<td>75±6</td>
<td>71±8</td>
</tr>
<tr>
<td>LV end-systolic dimension, mm</td>
<td>61±7</td>
<td>63±7</td>
<td>58±7</td>
</tr>
<tr>
<td>Fractional shortening, %</td>
<td>17±4</td>
<td>17±4</td>
<td>16±4</td>
</tr>
<tr>
<td>Vcfc, cm/s</td>
<td>0.55±0.12</td>
<td>0.55±0.12</td>
<td>0.55±0.13</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association; Vcfc, rate-adjusted velocity of circumferential fiber shortening.

*p<0.05; †p<0.01 vs group 1.

Hemodynamic changes during the second exercise test are summarized in Table 2. With dynamic exercise, heart rate, systolic blood pressure, the rate-pressure product, cardiac output, stroke volume, mean pulmonary pressure, pulmonary wedge pressure, and right atrial pressure all increased significantly. The rise in cardiac output and stroke volume was larger, however, in group 1 patients. As illustrated in Figure 1, the individual stroke volume responses varied considerably, with most patients experiencing an increase in stroke volume, whereas others (30%) experienced no change or a decrease in stroke volume.

Doppler echocardiographic changes during exercise are summarized in Table 3. LV ejection fraction increased significantly in both groups. LV end-diastolic volume also increased, albeit slightly more in group 2 patients. LV shape did not change significantly in group 1 patients. By contrast, in group 2 patients, the LV became more spherical. As a consequence, the distance between the mitral leaflet coaptation and the plane of the mitral annulus increased with exercise in group 2 patients.

Figure 2 illustrates the changes in MR severity during exercise in a representative patient from each group. Figure 1 summarizes the results in both groups. On average, MR was mild to moderate at baseline (MR jet/left atrium area 15±8%, regurgitant volume 11±21 mL) and increased with exercise (MR jet/left atrium area 33±15%, regurgitant volume 26±35 mL). However, it increased significantly more in group 2 than in group 1 patients. Similar findings were obtained when mitral regurgitant volume and fraction were compared. The exercise-induced changes in MR severity were found to correlate with those in the end-diastolic sphericity index (r=-0.75), the end-systolic sphericity index (r=-0.72), and the coaptation distance (r=0.86; Figure 3).

Relation of Exercise Capacity to Exercise-Induced MR

To investigate the potential role of exercise-induced MR in determining exercise hemodynamics and peak VO₂, all clinical,

TABLE 2. Hemodynamic Changes During Upright Dynamic Exercise

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (VO₂ &gt;50%)</th>
<th>Group 2 (VO₂ &lt;50%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Peak Exercise</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>81±12</td>
<td>124±12</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>138±25</td>
<td>180±36</td>
</tr>
<tr>
<td>Rate-pressure product, bpm×mm Hg (×1000)</td>
<td>8.9±1.0</td>
<td>11.3±1.2</td>
</tr>
<tr>
<td>VO₂, L/min</td>
<td>0.35±0.04</td>
<td>1.35±0.30</td>
</tr>
<tr>
<td>VO₂, mL·kg⁻¹·min⁻¹</td>
<td>4.0±5</td>
<td>16.3</td>
</tr>
<tr>
<td>VO₂, %</td>
<td>16±3</td>
<td>61±9</td>
</tr>
<tr>
<td>Respiratory exchange ratio</td>
<td>0.89±0.10</td>
<td>1.13±0.12</td>
</tr>
<tr>
<td>Right atrial pressure, mm Hg</td>
<td>7±4</td>
<td>10±4</td>
</tr>
<tr>
<td>Pulmonary wedge pressure, mm Hg</td>
<td>14±8</td>
<td>28±13</td>
</tr>
<tr>
<td>Mean pulmonary pressure, mm Hg</td>
<td>25±6</td>
<td>46±14</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>5.0±0.6</td>
<td>10.5±2.4</td>
</tr>
<tr>
<td>Stroke volume, mL/min</td>
<td>62±11</td>
<td>83±17</td>
</tr>
<tr>
<td>Systemic vascular resistance, dyne·s⁻¹·cm⁻⁵</td>
<td>1,511±339</td>
<td>854±243</td>
</tr>
<tr>
<td>(A-V) O₂ difference, mL</td>
<td>7.0±0.7</td>
<td>13.1±2.1</td>
</tr>
<tr>
<td>O₂ extraction, %</td>
<td>38±5</td>
<td>66±8</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>0.5±0.1</td>
<td>2.5±1.0</td>
</tr>
</tbody>
</table>

*p<0.001; †p<0.01; ‡p<0.05 vs. group 1.
hemodynamic (with the exception of those tautologically associated with VO\textsubscript{2}), and Doppler echocardiographic data available were proposed for inclusion into a multiple regression model. At the end of the stepwise selection process, the exercise-induced changes in MR (partial r = 0.55, P<0.001) and those in pulmonary capillary wedge pressure (partial r = 0.62, P<0.001) were found to independently correlate with peak VO\textsubscript{2} (generalized r\textsuperscript{2} = 0.66, P<0.001). A similar analysis was performed for the changes in stroke volume with exercise. With stepwise multiple linear regression analysis, the changes in MR severity (partial r = 0.87, P<0.0001; Figure 4) and those in systolic blood pressure (partial r = 0.28, P<0.17) were found to be independently correlated with the changes in exercise stroke volume (generalized r\textsuperscript{2} = 0.89, P<0.0001). The changes in the severity of functional MR also correlated with the increase in left atrial pressure during exercise (Figure 4).

**Day-to-Day Variability**

None of the measured parameters showed relevant day-to-day variation; the 95% confidence limits of the difference between measurements during exercise and at rest were all below 20% of the mean value.

### Table 3. Doppler Echocardiographic Changes During Upright Dynamic Exercise

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (VO\textsubscript{2} &gt;50%)</th>
<th>Group 2 (VO\textsubscript{2} ≤ 50%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest Peak Exercise</td>
<td>Rest Peak Exercise</td>
</tr>
<tr>
<td>LV end-diastolic volume, mL</td>
<td>210±58 218±52</td>
<td>214±52 233±58</td>
</tr>
<tr>
<td>LV end-systolic volume, mL</td>
<td>143±47 136±41</td>
<td>148±36 144±35</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>33±5 40±7</td>
<td>30±6 38±6</td>
</tr>
<tr>
<td>End-diastolic sphericity index</td>
<td>1.39±0.10 1.46±0.14</td>
<td>1.39±0.13 1.25±0.12*</td>
</tr>
<tr>
<td>End-systolic sphericity index</td>
<td>1.48±0.13 1.54±0.14</td>
<td>1.45±0.14 1.30±0.13*</td>
</tr>
<tr>
<td>MR grade</td>
<td>1.3±0.5 1.7±0.7</td>
<td>1.5±0.5 2.5±0.6†</td>
</tr>
<tr>
<td>MR jet area, cm\textsuperscript{2}</td>
<td>3±2 6±3</td>
<td>4±2 11±5‡</td>
</tr>
<tr>
<td>MR jet area/left atrial area, %</td>
<td>11±7 23±13</td>
<td>17±8 39±13‡</td>
</tr>
<tr>
<td>MR regurgitant volume, mL</td>
<td>3±13 11±37</td>
<td>10±21 40±27†</td>
</tr>
<tr>
<td>MR regurgitant fraction, %</td>
<td>1±22 7±39</td>
<td>15±35 40±22†</td>
</tr>
<tr>
<td>Mitral annulus, cm</td>
<td>3.0±0.2 3.2±0.3</td>
<td>3.2±0.4 3.2±1.0</td>
</tr>
<tr>
<td>Coaptation distance, cm</td>
<td>0.88±0.12 1.01±0.18</td>
<td>0.93±0.08 1.35±0.13*</td>
</tr>
</tbody>
</table>

*P<0.001; †P<0.01; ‡P<0.05 vs group 1.
between 2 measurements were always narrow. In particular, peak exercise measurements of the MR jet area (14±5 and 13±6 cm², \( R = 0.82 \)), left atrium area (30±5 and 29±6 cm², \( R = 0.95 \)), and their ratio (45±11% and 44±12%, \( R = 0.69 \)) were found to be reproducible over time. Interobserver and intraobserver variabilities in the measurements of MR severity varied between 0.2% and 3.4%. Intraclass correlation coefficients were always >0.93.

**Discussion**

Functional MR is common in patients with heart failure, and its severity may vary over time, depending primarily on the loading conditions.\(^{10–13}\) Because dynamic changes in the severity of functional MR may affect forward stroke volume, we hypothesized that exercise-induced changes in its severity could be an important determinant of the stroke volume response of patients with heart failure to exercise, and hence of their exercise capacity. Our results can be summarized as follows. (1) The stroke volume response of heart failure patients with LV dysfunction to dynamic exercise varied substantially from patient to patient; most patients experienced an increase in stroke volume during exercise, whereas others (≈30%) experienced no change or even a decrease in exercise stroke volume. (2) The severity of functional MR, which, by study design, was only mild to moderate at baseline, increased in almost every patient with exercise. However, this increase varied substantially from patient to patient and was considerably greater in patients with severe exercise intolerance. (3) The exercise-induced changes in the severity of functional MR correlated strongly with those in forward stroke volume. They also correlated with peak \( \dot{V}O_2 \) and with the changes in pulmonary wedge pressure induced by exercise. (4) In patients in whom MR severity increased with exercise, the LV became more spherical during stress, and mitral leaflet coaptation became more displaced into the LV cavity than in patients with no or minimal increases in MR.

**Central Hemodynamic Determinants of Exercise Capacity**

Exercise intolerance is a cardinal symptom of patients with heart failure. Although the mechanisms of exercise intolerance are multifactorial, they depend at least in part on the maximal pumping capacity of the heart, ie, maximal stroke volume and cardiac output. Because forward stroke volume depends not only on LV mechanical performance but also on the presence and severity of functional MR, exercise-induced changes in MR severity may influence the maximal stroke volume and cardiac output response to exercise. The results
of the present study support this hypothesis. Our data show that in patients with LV dysfunction, the increase in stroke volume during exercise strongly correlates with 2 parameters: the exercise-induced changes in MR severity and those in systolic blood pressure. The data further suggest that among these parameters, the change in the severity of functional MR is the strongest determinant of peak exercise stroke volume and thus of exercise capacity. This factor appears to be even more potent than factors previously related to exercise limitation, such as resting E/A ratio or resting systemic vascular resistance. Our data are in agreement with those of previous investigators who showed that directional changes in MR severity during isometric exercise or nitroglycerin were associated with opposite changes in forward stroke volume. However, none of these previous studies related the observed changes in MR severity to exercise tolerance.

The mechanisms whereby exercise-induced changes in the severity of functional MR affect exercise capacity are probably several. First, as indicated above, they likely limit the expected increase in forward stroke volume during exercise, and hence maximal cardiac output. Second, they also probably trigger the increase in left atrial and pulmonary artery pressures with exercise, which in turn may result in right ventricular overload, a shift of the interventricular septum to the left, and a further decrease in LV distensibility. Finally, they may also aggravate pulmonary congestion and thereby affect pulmonary gas exchanges. The significant correlation between the exercise-induced changes in MR severity and both exercise stroke volume and exercise capillary wedge pressure on the one hand and the lack of a significant exercise-induced decrease in arterial oxygen content in the present study on the other hand suggests that the first 2 mechanisms probably make the greatest contribution.

Mechanisms of Exercise-Induced MR

Although functional MR is frequently observed in patients with LV dysfunction, the mechanisms that determine its presence and severity are incompletely understood. Several factors, including LV size, extent of emptying, mitral annular diameter, papillary muscle function, and left atrial size, have been implicated. Experimental and clinical studies have also shown that the severity of functional MR often varied over time as a result of dynamic changes in the mitral regurgitant orifice, changes in ventricular-atrial pressure gradients, or both. For instance, the severity of functional MR has been shown to increase during isometric exercise and to decrease during dobutamine and nitroglycerin infusion. The present study confirms and extends these previous observations. It demonstrates that changes in the severity of functional MR can also be seen during dynamic exercise. It further shows that these changes are likely not solely related to dilatation of the mitral annulus, as previously suggested, but also to the apical displacement of the mitral leaflet coaptation, which reduces the contact between the leaflets and compromises its competence. Our data also suggest that the displacement of the mitral leaflet coaptation in the LV cavity is due to the more spherical shape of the LV during exercise, which in turn could be due to the lesser ability of patients with severe exercise limitation to vasodilate periph-

Clinical Implications

The results of the present study may have important clinical implications. They show that worsening of functional MR with exercise contributes to limit the exercise capacity of heart failure patients, even when they exhibit only mild-to-moderate degrees of MR at baseline. They also emphasize the role of exercise echocardiography in the evaluation of these patients, particularly when the symptoms appear to be out of proportion to the severity of the underlying disease. In these patients, demonstration of a significant worsening of functional MR during exercise may help in the selection of those who could benefit most from specific therapeutic interventions, such as vasodilator therapy, or, although this remains speculative, surgical mitral valve repair.

Study Limitations

Some aspects of the interpretation of the results of the present study require further consideration. Although the assessment of the severity of functional MR was made by previously validated methods, these methods have important limitations that should be acknowledged. For instance, the color Doppler appearance of MR jets is influenced by several parameters unrelated to MR severity, such as gain settings, packet size, aliasing velocities, and frame rate. Also, despite good agreement between MR jet/left atrium area and MR severity under resting conditions, it has been suggested that this parameter may be less accurate with exercise. In addition, in eccentric jets, it may vary according to the imaging plane, leading to underestimation of its severity. On the other hand, calculation of aortic and mitral stroke volume critically depends on image quality. In this regard, the reasonable interobserver and intraobserver variabilities, as well as the reproducibility of the major parameters on 2 consecutive days, are reassuring.

Conclusions

The results of the present study indicate that in patients with heart failure due to LV systolic dysfunction, peak VO2 and the exercise-induced changes in forward stroke volume during exercise are strongly influenced by exercise-induced changes in the severity of functional MR. Our data therefore suggest that exercise-induced changes in the severity of functional MR may contribute to limit exercise capacity in heart failure patients.

References


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