Left and Right Ventricular Function during Symptom-Limited Exercise in Patients with Isolated Mitral Stenosis

Donald L. Johnston, M.D.,† and William J. Kostuk, M.D.

Ventricular function during exercise in patients with mitral stenosis has not been widely studied. Accordingly, 20 patients with isolated mitral stenosis were assessed during supine, symptom-limited equilibrium radionuclide ventriculographic studies. All patients had a normal left ventricular (LV) ejection fraction at rest (≥50 percent), and all were in sinus rhythm. Left ventricular ejection fraction rose (p<0.001) from 64±9 percent at rest to 74±11 percent during exercise. This normal response was due solely to a decrease (p<0.01) in exercise LV end-systolic volume. A significant (p<0.01) decrease in end-diastolic volume during exercise limited the increase in ejection fraction during exercise. The decrease in end-diastolic volume during exercise caused stroke volume to remain unchanged; cardiac output rose according to heart rate alone. Right ventricular (RV) ejection fraction did not rise with exercise due to an increase in end-systolic volume. With exercise, LV end-diastolic volume was smaller (p<0.05) with severe mitral stenosis compared to mild mitral stenosis. With exercise, RV ejection fraction was decreased (p<0.05) with severe compared to mild mitral stenosis. In conclusion, LV function during exercise is normal in patients with normal resting LV ejection fraction. A decrease in LV diastolic filling with exercise prevents a rise in stroke volume, and cardiac output increases by heart rate alone. With exercise, RV ejection fraction does not rise, due to an increase in RV end-systolic volume.

There have been relatively few studies of cardiac function during exercise in patients with mitral stenosis. With exercise, left ventricular end-diastolic pressure has been shown to increase in some studies, suggesting the presence of systolic muscular dysfunction; however, end-diastolic pressure also depends on diastolic compliance, limiting the use of this parameter for the measurement of systolic function. Abnormalities of wall motion have also indicated systolic dysfunction. A limitation of several of these studies was the employment of submaximal rather than symptom-limited exercise during hemodynamic measurements. Cohen et al showed either no change or a slight decrease with exercise in right ventricular ejection fraction prior to corrective mitral valve surgery; with exercise the ejection fraction consistently rose after surgery. These findings suggest that impaired loading conditions, not diminished contractility, determine the right ventricular response to exercise.

The purpose of the present study was to examine noninvasively both left and right ventricular ejection fraction and volume changes during symptom-limited exercise in a large number of patients with mitral stenosis who were in sinus rhythm. Supine radionuclide ventriculographic studies were used to assess ventricular function at rest and during exercise.

MATERIALS AND METHODS

Patient Population

Twenty patients in sinus rhythm (two men and 18 women) with a mean age of 49±11 years (range, 26 to 75 years) were studied. The diagnosis of mitral stenosis was confirmed, and the severity of the disease was determined by two-dimensional echocardiograms in all patients. No patient had evidence of coronary arterial disease by history or physical examination or during supine exercise testing (judged by the absence of pain in the chest and ST-segment depression of ≥1 mm), and there was no clinical or echocardiographic evidence of other significant valvular heart disease. All patients had a resting left ventricular ejection fraction of 50 percent or more. Patients were required to exercise for at least three minutes at a workload of 25 W during supine exercise.

Echocardiograms

A phased-array ultrasonicographic system (Varian 3400) was used to obtain two-dimensional echocardiograms. With an attached video imager (Matrix), five to six static images of the smallest visualized mitral valve orifice were obtained on a roentgenogram. Each image was projected onto a screen and measured by planimeter, and an average valve area was obtained. In 19 previously studied patients, eight of whom were in atrial fibrillation (mean age, 49±10 years; 6 male and 13 female patients), echocardiograms (E) were compared to cardiac catheterization (C) for calculation of mitral valve area. A significant linear correlation was obtained between the two methods (C = 0.96 E + 0.19 sq cm; SEE = 0.1 sq cm; r = 0.88; p<0.0001). Mitral valve areas of 1.4 sq cm or more, 1.1 to 1.4 sq cm, and 1.1 sq cm or less were considered to represent mild, moderate, and severe mitral stenosis, respectively.

Radionuclide Ventriculograms

Supine, electrocardiographically multigated, equilibrium radionuclide ventriculograms were obtained at rest and during symptom-limited exercise. After i.v. labelling of red blood cells with 20 mCi
of technetium 99m pertechnetate, cardiac scintigraphic studies were performed in the left anterior oblique position that best isolated the left ventricle. All images were collected for two minutes using a conventional Anger-type scintillation camera equipped with a high-sensitivity parallel-hole collimator interfaced to a dedicated medical computer system (Ohio Nuclear 460). Patients commenced supine exercise with an initial workload of 25 W, and this was increased successively by 25 W every three minutes until termination of exercise due to symptoms, usually fatigue of the legs and dyspnea. A 12-lead electrocardiogram was obtained at the end of each stage of exercise and at two minutes after exercise. Blood pressure was recorded at the same intervals.

Analysis of data was done using a mobile medical computer (Ohio Nuclear 550). Left ventricular ejection fraction and volumes were calculated using previously described methods. For the left ventricle, analysis of variance showed that a change of 5 percent (absolute value) or more in ejection fraction was significant. Calculation of right ventricular ejection fraction was based on a previously described technique. After subtraction of background activity along the left ventricular free wall in a manner similar to that described for the left ventricle, right ventricular end-systolic and end-diastolic regions of interest were identified. The superior right ventricular edge was considered to border on a parallel line drawn from the mitral valve plane in both diastole and systole. Each region of interest was manually outlined three times and an average value obtained. For the right ventricle, analysis of variance showed that a change of 11 percent (absolute value) or more in ejection fraction was significant. Since calculation of right ventricular volumes has not been validated in our laboratory, we did not examine absolute right ventricular volumes.

The percentage of change in radioactive counts from rest to exercise at the end of systole and the end of diastole was used to determine changes in left and right ventricular volumes.

Statistical Analysis

Student's t-test for paired samples was used to determine significant changes in heart rate, blood pressure, ejection fraction, and volumes from rest to exercise. Probability of 5 percent or less was considered significant. All results are mean values ± SD unless otherwise indicated. The relationship between right and left ventricular volume changes was determined by regression analysis (program fit line in RS/1; Bolt, Beranek, and Newman, Cambridge, Mass).

RESULTS

Nine patients (one man and eight women) with a mean age of 47 ± 10 years (range, 26 to 68 years) had mild mitral stenosis. All patients with mild mitral stenosis were New York Heart Association (NYHA) functional class 1 or 2. Seven patients (one man and six women) with a mean age of 49 ± 11 years (range, 38 to 70 years) had moderate mitral stenosis. Two patients with moderate mitral stenosis were NYHA class 3. Four patients (all women) with a mean age of 52 ± 10 years (range, 47 to 75 years) had severe mitral stenosis. All patients with severe mitral stenosis were NYHA class 3.

Heart Rate and Blood Pressure

Heart rate increased significantly (p < 0.001) at peak exercise (Table 1). This was accompanied by a significant (p < 0.001) increase in systolic blood pressure and the rate-pressure product.

Table 1—Supine Hemodynamics, Left and Right Ventricular Ejection Fraction and Change from Rest to Exercise in Ventricular Counts*

<table>
<thead>
<tr>
<th>Data</th>
<th>Rest</th>
<th>Exercise</th>
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</thead>
<tbody>
<tr>
<td>Hemodynamics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats per min</td>
<td>75 ± 16</td>
<td>122 ± 27†</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>122 ± 18</td>
<td>159 ± 32†</td>
</tr>
<tr>
<td>Rate-pressure product (10⁷)</td>
<td>91 ± 17</td>
<td>193 ± 32†</td>
</tr>
<tr>
<td>Left ventricular function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction, percent</td>
<td>64 ± 9</td>
<td>74 ± 11†</td>
</tr>
<tr>
<td>End-diastolic volume index, ml/sq m</td>
<td>98 ± 24</td>
<td>82 ± 24‡</td>
</tr>
<tr>
<td>End-systolic volume index, ml/sq m</td>
<td>37 ± 15</td>
<td>22 ± 11‡</td>
</tr>
<tr>
<td>Stroke volume index, ml/sq m</td>
<td>62 ± 14</td>
<td>59 ± 22</td>
</tr>
<tr>
<td>Cardiac index, L/min/sq m</td>
<td>4.7 ± 0.9</td>
<td>7.3 ± 2.1†</td>
</tr>
<tr>
<td>Right ventricular function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction, percent</td>
<td>48 ± 9</td>
<td>49 ± 13</td>
</tr>
</tbody>
</table>

*Values are means ± SD.
†p < 0.001 for exercise vs rest.
‡p < 0.01 for exercise vs rest.
§LV, left ventricular; and RV, right ventricular.

Left Ventricular Function

Ejection fraction rose significantly (p < 0.001) with exercise (Table 1 and Fig 2). Fifteen patients had a significant (≥5 percent, absolute value) rise in ejection fraction with exercise, and one patient had a significant

![Figure 1. Individual and mean values for left ventricular (LV) ejection fraction at rest and during exercise. Star indicates p < 0.001 for exercise vs rest.](http://journal.publications.chestnet.org/pdaccess.ashx?url=/data/journals/chest/21505/ on 04/19/2017)
fall in ejection fraction with exercise. Both end-diastolic and end-systolic volume index decreased (p<0.01) during exercise (Table 1 and Fig 2). As a result of the decrease in end-diastolic volume index, stroke volume index with exercise did not change significantly. Cardiac index increased (p<0.001) with exercise due to an increase in heart rate.

**Right Ventricular Function**

Mean ejection fraction did not change significantly from rest to exercise (Table 1 and Fig 3). Five patients had a significant increase (>11 percent, absolute value) rise in ejection fraction with exercise, and three patients had a significant fall in ejection fraction during exercise. Both end-diastolic and end-systolic volume increased from rest to exercise (Fig 4).

**Ventricular Function vs Severity of Mitral Stenosis**

Neither resting nor exercise-associated left ventricular ejection fraction was affected by the severity of mitral stenosis (Table 2). The increase in ejection fraction from rest to exercise was significant (mild mitral stenosis, p<0.01; moderate and severe mitral stenosis, p<0.05). Resting left ventricular cardiac volumes did not change with increasing severity of mitral stenosis. Left ventricular end-diastolic volume with exercise was smaller (p<0.05) with severe than with mild mitral stenosis. With exercise, left ventricular end-systolic volume did not change with increasing severity of mitral stenosis. Resting right ventricular ejection fraction did not decrease significantly with severe mitral stenosis, whereas with exercise, right ventricular ejection fraction fell significantly (p<0.05). The changes in right ventricular ejection fraction from rest to exercise were not significant. Right ventricular
end-diastolic volume during exercise did not change with increasing severity of mitral stenosis. The gradual increase in right ventricular end-diastolic volume with exercise was not significant.

**Right Ventricular Dilatation and Left Ventricular Function**

To determine if right ventricular dilatation affected left ventricular filling, we examined changes in left and right ventricular volumes during exercise. There was no significant correlation (r = 0.2; p < 0.4) between left and right ventricular end-diastolic volume changes. Similarly, there was no significant correlation (r = 0.42; p = <0.07) between left and right ventricular end-diastolic volume changes. These findings suggest that in this study, left ventricular function was not significantly altered by right ventricular dilatation.

**DISCUSSION**

An increase in left ventricular ejection fraction with exercise is generally considered to be evidence of normal left ventricular function during exercise. Thus, the present study, by demonstrating a significant increase in ejection fraction from rest to exercise, would suggest that left ventricular function with exercise is normal in the presence of mitral stenosis. Although five patients failed to have a significant (≥5 percent) increase in ejection fraction, this may not be different from subjects found to have no cardiac disease. Change in ejection fraction is determined by change in cardiac volumes. Thus, patients with mitral stenosis were able to increase their left ventricular ejection fraction during exercise by decreasing left ventricular end-systolic volume proportionately more than end-diastolic volume. Inadequate left ventricular filling prevented stroke volume from rising during exercise. Consequently, cardiac index rose due to an increase in heart rate.

The degree of severity of mitral stenosis did not cause a decrease in resting left ventricular ejection fraction or size. This finding suggests that diastolic filling was sufficient to preserve left ventricular function regardless of the severity of mitral stenosis. With exercise, a further reduction in diastolic filling time caused a significant decrease in end-diastolic volume but was not enough to prevent a significant rise in left

**Table 2—Severity of Mitral Stenosis and Left and Right Ventricular Ejection Fraction and Volumes**

<table>
<thead>
<tr>
<th>Data</th>
<th>Mild Mitral Stenosis</th>
<th>Moderate Mitral Stenosis</th>
<th>Severe Mitral Stenosis</th>
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<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise</td>
<td>Rest</td>
</tr>
<tr>
<td>Left ventricular function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction, percent</td>
<td>63±6</td>
<td>74±10</td>
<td>61±9</td>
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<tr>
<td>End-diastolic volume index, ml/sq m</td>
<td>101±25</td>
<td>88±32</td>
<td>95±16</td>
</tr>
<tr>
<td>End-systolic volume index, ml/sq m</td>
<td>38±13</td>
<td>24±12</td>
<td>37±10</td>
</tr>
<tr>
<td>Right ventricular function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction, percent</td>
<td>55±4</td>
<td>64±9</td>
<td>50±14</td>
</tr>
<tr>
<td>Change in counts (rest to exercise)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>End-diastolic volume, percent</td>
<td>...</td>
<td>5±15</td>
<td>...</td>
</tr>
<tr>
<td>End-systolic volume, percent</td>
<td>...</td>
<td>1±13</td>
<td>...</td>
</tr>
</tbody>
</table>

*Values are means ± SD.
†p<0.05 severe vs mild mitral stenosis.
ventricular ejection fraction. Mean end-diastolic volume was slightly larger than that found in a population of normal subjects studied in our laboratory. It is possible that some patients had left ventricular dilatation due to undetected mitral or aortic regurgitation.

Impaired left ventricular filling at rest has been reported in patients with mitral stenosis, causing resting left ventricular ejection fraction to be reduced. Gash et al. found that of five patients with a left ventricular ejection fraction of less than 50 percent, four had normal intrinsic muscular function. Reduced systolic performance appeared to be the result of an increased afterload without adequate Frank-Starling compensation. Other, earlier studies have suggested a more prominent role for impaired muscular function as a cause of the reduction in resting left ventricular ejection fraction. Some studies have suggested that right ventricular dysfunction may depress left ventricular function. We did not detect any deterioration in left ventricular function as a result of right ventricular dilatation in this study.

The present study showed that right ventricular end-systolic volume, instead of decreasing normally, rose with exercise, while end-diastolic volume increased slightly. Together, these changes in volume resulted in an attenuated response of right ventricular ejection fraction to exercise. Most likely, a portion of the increase in end-systolic volume was due to a change in loading conditions associated with exercise. In keeping with this hypothesis, Brent et al., using pharmacologic interventions, showed that right ventricular systolic function was highly sensitive to changes in pulmonary arterial pressure. Wroblewski et al. found that in the presence of moderate pulmonary hypertension, removal of pulmonary arterial pressure from the calculation of right ventricular performance showed that contractility was not impaired. Cohen et al. recently studied right ventricular function in eight patients during symptom-limited exercise and found that loading conditions determined the right ventricular response to exercise; however, it still remains possible that irreversible right ventricular myocardial damage from the hemodynamic stress of a chronically elevated pulmonary arterial pressure may contribute to abnormal systolic function in certain individuals.

Newman et al. used first-pass radionuclide ventriculographic studies to measure left ventricular ejection fraction and volumes in nine patients prior to undergoing mitral commissurotomy. Like the present study, presurgical ejection fraction during exercise rose significantly without an increase in end-diastolic volume. End-systolic volume decreased, but the response was not adequate to significantly increase stroke volume, and cardiac index increased due to an increase in heart rate. After surgery, end-diastolic volume and stroke volume increased significantly, suggesting that left ventricular inflow obstruction contributed to the impaired preoperative response to exercise.

In summary, left ventricular function during exercise was found to be normal in patients with mitral stenosis and normal resting left ventricular ejection fraction. A decrease in left ventricular end-diastolic volume with exercise prevented a rise in stroke volume. Thus, cardiac output increased by heart rate alone. With exercise, right ventricular ejection fraction did not rise, due to an increase in right ventricular end-systolic volume.

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REFERENCES
14. Rozanski A, Diamond CA, Berman D, Forrester JS, Morris D,
International Symposium on Noninvasive Cardiac Imaging

The Page and William Black Postgraduate School of Medicine, Mount Sinai School of Medicine, New York, and the Heart Institute, Chaim Sheba Medical Center and Sackler School of Medicine, Tel Aviv, will present this program in Tel Aviv, Israel, April 1-3. For information, contact Richard Meltzer, M.D., Cardiology Division, Mount Sinai Medical Center, One Gustave Levy Place, New York 10029.

Electrocardiography of Pacemaker Rhythms

The North American Society of Pacing and Electrophysiology will present this course at the Parker House Hotel, Boston, April 3-5. For information, contact NASPE, 13 Eaton Court, Wellesley Hills, MA 02181.