Determinants of Stroke Volume Response to Exercise in Patients With Mitral Stenosis: A Doppler Echocardiographic Study

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Objectives. The aim of this study was to assess exercise-induced changes in stroke volume and their main determinants in mitral stenosis.

Background. The mechanisms of the stroke volume response to exercise in mitral stenosis are not clearly established.

Methods. Twenty-seven patients with mitral stenosis, aged 47±13 years, and 10 healthy control subjects, aged 46±11 years, were examined by Doppler echocardiography to obtain stroke volume, mitral velocity-time integral and calculated mitral valve area (by continuity equation) at rest and during submaximal supine bicycle exercise. Measured mitral valve area at rest and total mitral score were also obtained.

Results. During exercise, stroke volume increased significantly (p<0.001) in the control subjects (+25±6%) but remained unchanged in the patients. In 10 patients (Group I), stroke volume increased by ≥14% (+23±10%, p<0.001); in the other 17 (Group II), it decreased or increased by <14% (−5±14%, p=NS). Mitral velocity-time integral did not change in the three groups, whereas calculated mitral valve area increased significantly (p<0.001) and similarly in Group I and the control group but remained unchanged in Group II. The exercise change in calculated mitral valve area correlated significantly with both measured mitral valve area at rest (r=0.45, p<0.05) and total mitral score (r=0.53, p<0.005). However, at constant mitral score, exercise change in calculated mitral valve area no longer correlated significantly with measured mitral valve area at rest.

Conclusions. In mitral stenosis, the change in stroke volume during exercise depends on the change in mitral valve area, which itself depends on the degree of mitral valve damage.

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clude all patients whose aortic orifice anatomy was not completely normal. Echocardiographic left ventricular dimensions and function were normal in each patient. Ten healthy control subjects (one man and nine women) 29 to 66 years old (mean age 46 ± 11) were also studied. Age, male/female ratio and body surface area were not significantly different in the two groups. All patients were in sinus rhythm with a heart rate <85 beats/min and normal blood pressure at rest. Written, informed consent to the study was obtained from each patient.

Exercise protocol. Patients and control subjects underwent exercise testing in the supine position on a mechanically braked Monark bicycle ergometer mounted on the front of a bed. The initial work load of 30 W was progressively increased by 10 W/min until a heart rate of 60% of the maximal predicted heart rate was reached. This submaximal exercise level was maintained as a plateau for 3 to 5 min to allow exercise Doppler examination. Blood pressure was recorded at 1-min intervals at rest and during exercise by an oscillometric Dinamap system. The electrocardiogram was recorded at 1-min intervals at rest and during exercise by an oscillographic Dinamap system. The electrocardiogram was also continuously monitored.

Echocardiographic and Doppler examination. A commercially available Doppler echocardiographic system (Advanced Technology Laboratory, Ultramark 9) was used. Two-dimensional imaging was obtained with a 3-MHz mechanical transducer. Aortic velocity and mitral flow velocity were recorded by continuous wave Doppler echocardiography with a 2.25-MHz nonimaging transducer (11). Hard copies of the Doppler velocity tracings were obtained at a paper speed of 30 mm/s. Wall filters were set at 400 Hz. Standard views of the parasternal short and long axis, and apical four- and five-chamber views were recorded on videotape for analysis of mitral valve structure. This procedure permitted assessment of leaflet thickening, subvalvular thickening and calcifications in each case.

Echocardiographic and Doppler measurements. Aortic diameter was measured by using a parasternal long-axis view from inner echo to inner echo just below the aortic orifice (11). The other variables measured were the aortic velocity-time integral, the mitral velocity time integral, the mean mitral gradient and diastolic filling time. Stroke volume was calculated as \( \pi d^4 \times (\text{Aortic diameter})^2 \times \text{Aortic velocity-time integral} \), according to previously published recommendations concerning the choice of subaortic diameter measurement and the continuous wave Doppler method (11,12). Mitral valve area at rest and during exercise was calculated by applying the continuity equation as the ratio of the stroke volume to the mitral velocity-time integral (13). The mitral valve area was also measured at rest by planimetry on a two-dimensional short-axis view and by the pressure half-time method (14). The value measured for the mitral valve area at rest was the average of the values obtained by these two methods. To avoid comparing interdependent variables, this value was used to assess the relation between the changes in stroke volume or mitral valve area during exercise and initial valve area at rest. The changes in mitral valve area during exercise were evaluated from the calculated mitral valve area. All the Doppler and echocardiographic recordings were performed by the same observer, and all the measurements were performed by a different observer in a blinded manner. Each measurement represented the average of five different cardiac cycles. A total mitral score was established for each patient, as previously described (13). It ranged from 0 (entirely normal valve) to 16 (immobile valve, considerable thickening of the leaflet and subvalvular apparatus and severe calcifications).

Stroke volume measurement by thermodilution. In 12 of the 27 patients, a balloon-tipped Swan-Ganz catheter was introduced into the pulmonary artery through the brachial vein. Cardiac output was measured by thermodilution as the average of three measurements with <10% variability. Stroke volume was derived as cardiac output divided by heart rate. This invasive measurement was performed simultaneously with the Doppler determination of stroke volume both at rest and during submaximal exercise.

Day to day intraobserver reproducibility. In a subgroup of eight patients, the same Doppler echocardiographic examination was repeated for each patient, both at rest and during submaximal exercise, on two occasions separated by a 24-h interval. Intraobserver variability was calculated as the absolute difference between the paired measurements for each Doppler echocardiographic variable.

Data analysis. All data were expressed as mean value ± SD. Paired \( t \) tests were used to compare each variable between rest and exercise in the same group. Comparisons of changes (in both relative and absolute values) in each variable between the patient groups were performed by a one-factor analysis of variance (ANOVA). If a significant value was found, the Fisher \( F \) test for multiple comparisons was used to identify differences between the patient groups. Univariate linear regression was used to fit different variables. Partial correlations were used to compare three variables, one of which was maintained constant (16). Statistical significance was defined as \( p < 0.05 \).

Results

Validation of the Doppler method for exercise stroke volume measurement. In the 12 patients whose stroke volume was simultaneously obtained by Doppler and thermodilution methods, a close correlation was found between the two methods at rest (\( r = 0.84, \ p < 0.001 \), SEE = 3 ml) and during submaximal exercise (\( r = 0.82, \ p < 0.001 \), SEE = 10 ml; Fig. 1). The percent changes in stroke volume between rest and exercise given by the two methods were also significantly correlated (\( r = 0.90, \ p < 0.001 \), SEE = 7%).

Day to day intraobserver reproducibility. In the subgroup of eight patients, good agreement was found between the exercise and rest Doppler values recorded by the same observer in two sets of measurements separated by a 24-h interval (Table I). In particular, stroke volume variability was 6 ± 2 ml at rest and 7 ± 4 ml (or 7 ± 4%) during exercise.
Accordingly, we considered that the increase of $\geq 14\%$ in exercise stroke volume was significant. Thus, two groups of patients with mitral stenosis were defined: Group I comprised patients with a normal stroke volume response to exercise (or a $\geq 14\%$ increase) and Group II comprised patients with an abnormal stroke volume response to exercise (or a $< 14\%$ increase).

**Characteristics of the mitral valve area at rest.** The measured mitral valve area at rest, obtained by combining the results obtained with two-dimensional echocardiographic planimetry and Doppler pressure half-time measurement, ranged from 0.55 to 2.20 cm$^2$ (mean $1.20 \pm 0.43$). The calculated mitral valve area at rest, obtained by the continuity equation, ranged from 0.50 to 2.25 cm$^2$ (mean $1.19 \pm 0.44$) and was significantly correlated with the measured mitral valve area at rest ($r = 0.88$, $p < 0.001$). Total mitral valve score ranged from 5 to 14 (mean $8.8 \pm 2.6$).

**Hemodynamic response to exercise.** During exercise, stroke volume increased significantly in the healthy control subjects ($p < 0.001$) by $25 \pm 6\%$ (or $+14 \pm 6$ ml), whereas it did not change in patients with mitral stenosis. Nevertheless, among the patients with mitral stenosis, mean stroke volume increased by $\geq 14\%$ in 10 patients (Group I) and decreased, remained unchanged or increased by $< 14\%$ in 17 (Group II) (Fig. 2). Mean stroke volume increased significantly in Group I ($+23 \pm 10\%$ or $+14 \pm 6$ ml, $p < 0.001$) and decreased slightly but not significantly in Group II ($-5 \pm 14\%$ or $-4 \pm 10$ ml). The magnitude of the change in stroke volume (expressed in both relative and absolute values) was significantly different in the three groups ($p < 0.001$) and significantly higher in the control subjects and Group I patients than in Group II patients (both $p < 0.05$) with no difference between the responses of control subjects and Group I patients. Heart rate and systolic blood pressure were not significantly different at rest and increased significantly and to the same extent during exercise in the three groups. During exercise, aortic orifice diameter did not change in any group, whereas the aortic velocity-time integral rose significantly and similarly ($p < 0.001$ for both variables) in the control subjects and Group I patients ($+26 \pm 8\%$ and $+19 \pm 8\%$, respectively) but did not change in Group II patients (Fig. 3).

**Determinants of the exercise-induced changes in stroke volume.** At the aortic orifice, the aortic velocity-time integral during exercise did not change in any of the three groups, whereas the calculated mitral valve area increased significantly ($p < 0.001$ for both) in control subjects ($+32 \pm 13\%$ or $+1.56 \pm 0.78$ cm$^2$) and Group I patients ($+25 \pm 16\%$ or $+0.37 \pm 0.22$ cm$^2$), but did not change in Group II patients ($+2 \pm 15\%$ or $+0.00 \pm 0.15$ cm$^2$) (Fig. 4). The magnitude of the change in mitral valve area (expressed in both relative and absolute values) was significantly different in the three groups ($p < 0.001$), significantly higher in the control subjects and Group I patients than in Group II patients ($p < 0.05$) and slightly but significantly higher in the control

<table>
<thead>
<tr>
<th>Mean Mitral Gradient (mm Hg)</th>
<th>Mitral Velocity-Time Integral (cm)</th>
<th>Aortic Diameter (mm)</th>
<th>Aortic Velocity-Time Integral (cm)</th>
<th>Stroke Volume (ml)</th>
</tr>
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<tbody>
<tr>
<td>Rest</td>
<td>0.9 ± 0.6</td>
<td>2.00 ± 0.75</td>
<td>0.6 ± 0.3</td>
<td>8.86 ± 0.48</td>
</tr>
<tr>
<td>Exercise</td>
<td>1.3 ± 0.6</td>
<td>2.31 ± 0.88</td>
<td>0.8 ± 0.3</td>
<td>1.32 ± 0.67</td>
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Exercise Stroke Volume in Mitral Stenosis

Two hemodynamic responses were observed in patients with mitral stenosis during submaximal bicycle exercise. One was a normal physiologic response characterized by a significant increase in stroke volume (Group I), and the other was an abnormal response consisting of either a decrease or no significant change in stroke volume (Group II). The normal increase in stroke volume was due, as in the control subjects, to an increase in mitral valve area with no change in mitral velocity-time integral. By contrast, the absence of exercise increase in exercise stroke volume was accompanied by an absence of change in the mitral valve area or mitral velocity-time integral. Therefore, the change in exercise stroke volume was determined by the change in mitral valve area. During exercise, this change chiefly depended on the degree of mitral valve damage.

Determinants of the exercise-induced changes in stroke volume. In mitral stenosis, the exercise-induced changes in stroke volume are not uniform. Thus, Gorlin et al. (2), using cardiac catheterization and supine exercise, found that in seven of nine patients with critical mitral stenosis, stroke volume failed to increase, decreasing in four and remaining unchanged in three. Among 55 patients examined by the same method, Geschwind et al. (17) observed either an increase in stroke volume during exercise (29 patients) or no change (26 patients), whereas the calculated mitral valve area at rest was not significantly different in the two groups. The present results are therefore in agreement with the notion of a spectrum of stroke volume responses and the absence of a close correlation between the change in exercise stroke volume and mitral valve area at rest.

To study the mechanisms governing the response of stroke volume to exercise, we examined the behavior during exercise of the two main determinants of stroke volume—the mitral velocity-time integral and mitral valve area—in healthy subjects and patients with mitral stenosis. In normal subjects, Rassi et al. (8) concluded that during isotonic exercise in the supine position, stroke volume increased because of a significant increase in mitral valve area, without any change in the mitral velocity-time integral at the mitral orifice and because of a significant increase in the aortic velocity-time integral, without any change in aortic area at the aortic orifice. Experimental studies showed that the increase in exercise stroke volume was determined by the increase in mitral valve area until both variables formed a plateau at maximal values (18). Stewart et al. (19) found similar results, and in addition demonstrated that the aortic

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FIGURE 3. Determinants of exercise stroke volume change at the aortic orifice assessed by Doppler echocardiography in patients with mitral stenosis and healthy control subjects. Black bars = stroke volume; hatched bars = velocity-time integral of the aortic velocity curve; grey bars = aortic diameter.

FIGURE 4. Determinants of exercise stroke volume change at the mitral orifice assessed by Doppler echocardiography in patients with mitral stenosis and healthy control subjects. Black bars = stroke volume; hatched bars = velocity-time integral of the mitral velocity curve; grey bars = mitral valve area.

The change in exercise stroke volume was significantly but weakly correlated with the mitral valve area at rest (r = 0.46, p < 0.05) and more strongly with the total mitral score (r = 0.53, p < 0.005). The measured mitral valve area at rest and total mitral score were significantly correlated (r = 0.56, p < 0.005). However, at a constant mitral score, the exercise-induced changes in the calculated mitral valve area and the measured mitral valve area at rest were no longer significantly correlated. In addition, the exercise change in stroke volume during exercise correlated significantly with the measured mitral valve area at rest (r = 0.59, p < 0.01).
that occur when commonly measured mitral valve variables, is not an independent predictor of mitral valve area change and consequently not of volume change. Finally, the capacity of the mitral orifice to increase in size, although surprising, must be compared with the changes in the size of the aortic orifice that occur when cardiac output and hemodynamic conditions vary (9). The specific behavior of the mitral velocity-time integral during exercise in mitral stenosis has not been studied, although Tamai et al. (22) described a significant decrease in this variable; however, their observation was made in patients with severe mitral stenosis who achieved a high level of exercise.

Limitations of the present study. For practical reasons, we used exercise testing in the supine position, at a submaximal level defined by a heart rate reaching 60% of the maximal predicted heart rate. The discontinuation of exercise by most subjects before the maximal exercise capacity was reached was a necessary condition for obtaining good quality Doppler echocardiographic recordings from all patients. In addition, for both normal subjects and those with heart failure it has been established that during exercise, whether in the upright or supine position, stroke volume initially increases and then forms a plateau at 40% of the maximal oxygen uptake (23,24). Above this level, cardiac output increases gradually with the heart rate. Thus, a specific analysis of stroke volume during exercise does not necessitate a maximal exercise level. Furthermore, the exercise response is not the same in the supine and upright positions (25), because stroke volume, which is lower at rest, increases more in the upright than in the supine position, although the peak exercise value is similar in the two positions. Another important limitation of the present study was that exercise mitral valve area was calculated using the continuity equation and was not measured directly. Direct measurement by two-dimensional echocardiography (26) or Doppler study (14) is currently used at rest but cannot be applied during exercise. Thus, during exercise, two-dimensional echocardiographic planimetry of the mitral orifice is not easy, and pressure half-time calculation leads to overestimation of the mitral valve area (14,21). In contrast, the calculation of mitral valve area from the continuity equation has been validated in animals and humans both at rest and during high cardiac output (27) and during exercise (21). Technical difficulties occur with all techniques used to measure cardiac output (5). The ultrasound method is particularly affected by thoracic movements produced by exercise and respiration, leading to measurements of blood velocity at different positions in the aorta. To limit these difficulties we used the supine position and the continuous wave Doppler technique, which allows recording of the higher velocities. Concerning the thermodilution method, the nonstability of the catheter in the pulmonary artery and the worsening of tricuspid regurgitation during exercise indicate why this currently used technique cannot be considered as the reference method.

Conclusions. The present investigation shows that in patients with mitral stenosis 1) stroke volume can be accurately measured by Doppler echocardiography both at rest and during submaximal bicycle exercise, and 2) the exercise-induced change in stroke volume is directly dependent on the change in mitral valve area, which itself depends chiefly on the severity of damage to the mitral valve.

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