Surgery For Valvular Heart Disease

Prognostic Importance of Quantitative Exercise Doppler Echocardiography in Asymptomatic Valvular Aortic Stenosis

Patrizio Lancellotti, MD, PhD; Florence Lebois, MD; Marc Simon, MD; Christophe Tombeux, MD; Christophe Chauvel, MD; Luc A. Pierard, MD, PhD, FESC

Background—In patients with asymptomatic valvular aortic stenosis, exercise testing may help to stratify the clinical risk. However, data are limited, and the role of quantitative exercise Doppler echocardiography has never been investigated.

Methods and Results—Sixty-nine consecutive patients with severe asymptomatic aortic stenosis (aortic valve area <1 cm²) who prospectively underwent quantitative Doppler echocardiographic measurements at rest and during semisupine exercise test were followed up for 15 ±7 months. Of these, 26 had an abnormal response to exercise [occurrence of ≥1 of the following findings: angina, dyspnea, ≥2 mm ST segment depression, or fall or small (<20 mm Hg) rise in systolic blood pressure during the test] and 18 presented cardiac events during follow-up (symptoms in 2 patients, acute pulmonary edema in 2, aortic valve replacement in 12, and cardiac death in 2). In univariate analysis, patients who had cardiac events exhibited a higher increase in both peak (29 ±16 versus 22 ±14 mm Hg; P=0.019) and mean (23 ±8 versus 12 ±7 mm Hg; P=0.000003) transvalvular pressure gradients, whereas the left ventricular ejection fraction reached at peak stress was lower. These patients experienced more frequently symptoms during exercise (14 of 18 versus 12 of 51; P=0.0008). By multivariate Cox regression analysis, independent predictors of cardiac events were as follows: an increase in mean transaortic pressure gradient by ≥18 mm Hg during exercise (P=0.0015), an abnormal exercise test (P=0.0026), and an aortic valve area <0.75 cm² (P=0.0031). Exercise Doppler echocardiographic findings provided incremental prognostic value over resting echocardiographic and exercise electrocardiographic parameters.

Conclusions—Quantitative Doppler exercise echocardiography could be useful to identify a high-risk subset of patients with asymptomatic valvular aortic stenosis and help for clinical decision making.

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Key Words: aortic valve ■ echocardiography ■ exercise ■ prognosis

Surgery is warranted in patients with symptomatic valvular aortic stenosis. In contrast, the management of asymptomatic patients with severe aortic stenosis remains a source of debate. The wide variation in their individual outcome has recently raised the question of early elective surgery. The high rate of events in some reports could be related to either the unrecognized mildly symptomatic patients, especially in elderly subjects with a decrease in activity or the presence of subclinical hemodynamically significant valvular obstruction. In this respect, resting echocardiography is of limited value.

In contrast, exercise testing is an interesting tool, and recent studies have shown that patients with an abnormal test—exercise-induced symptoms or significant electrocardiographic changes—are at increased risk of cardiac events. Although such testing appears to be safe and of prognostic importance, data are still scarce. Quantitation of Doppler echocardiography during exercise has been shown to be feasible and reliable, but its prognostic implications have never been investigated in patients with aortic stenosis. This study was, thus, undertaken to assess the role of exercise testing in the risk stratification of patients with asymptomatic severe valvular aortic stenosis and to determine whether exercise Doppler echocardiography could be of additional prognostic value.

Methods

Population
We prospectively included 69 consecutive patients (mean age 66±12 years, range 41 to 80 years) with asymptomatic severe valvular aortic stenosis (aortic valve area ≤1 cm²) and normal left ventricular function who were able to perform a semisupine exercise echocardiographic test. The referring cardiologist performed history taking. An asymptomatic patient was defined as a patient who did not report any of the classic triad of symptoms: dyspnea, angina, or syncope. No patient had the following exclusion criteria: technically inadequate echocardiogram, more than trivial aortic regurgitation, intraventricular conduction abnormality, atrial fibrillation or flutter, and
Exercise Echocardiography

A symptom-limited graded bicycle exercise test was performed in a semisupine position on a tilting exercise table allowing continuous 2D and Doppler echocardiographic examination. After an initial workload of 25 W maintained for 2 minutes, the workload was increased every 2 minutes by 25 W. Blood pressure and a 12-lead ECG were recorded every 2 minutes. The exercise test was considered to be abnormal in the presence of \( \geq 1 \) of the following abnormalities: angina, dyspnea, \( \geq 2 \) mm ST segment depression 80 ms after the J point, fall or small (\(<20 \text{ mm Hg}\)) rise in systolic blood pressure as compared with baseline, and significant arrhythmias.\(^2\)

Echocardiographic Measurements

Echocardiographic examinations were performed using a VIVID 7 imaging device (General Electric). All of the echocardiographic and Doppler data were obtained at rest and at peak exercise and were stored on optical disk for off-line analysis. For each measurement, at least 3 cardiac cycles were averaged. Continuous wave Doppler was used to assess the aortic transvalvular maximal velocities; peak and mean gradients were calculated using the simplified Bernoulli equation.\(^12\) Aortic valve area was calculated from the continuity equation.\(^13\) Left ventricular end-diastolic and end-systolic volumes and ejection fraction were measured by the biapical Simpson disk method. The occurrence of regional wall motion abnormalities during exercise indicated myocardial ischemia.

Statistical Analysis

Continuous variables are expressed as mean \( \pm \) SD. Student \( t \) test was used to assess differences between mean values, and categorical variables were compared with \( \chi^2 \) test and Fisher’s exact test when appropriate. The combined end-point included the following: the development of symptoms during follow-up (angina, dyspnea, and syncope), hospital admission for heart failure, cardiac death, and the need for aortic valve replacement. To detect independent predictors of events, a multivariate Cox regression procedure was used to compare the patients who remained asymptomatic during follow-up to those who experienced an event (STATISTICA version 5). Cox regression was also used to assess whether Doppler exercise echocardiographic parameters added prognostic information over clinical, resting Doppler echocardiographic and exercise electrocardiographic parameters. The Kaplan-Meier method was used for cumulative event-free survival analysis with the log-rank test for assessing statistical differences between curves. \( P<0.05 \) was considered significant. Receiver-operator characteristic curve analysis was performed to determine the cut-off values that best distinguished the issue.

Results

Baseline and Exercise Characteristics

At rest, aortic valve area ranged from 0.5 to 1.0 cm\(^2\) (mean\(\pm\)SD, 0.81\(\pm\)0.15 cm\(^2\)), peak transaortic pressure gradient ranged from 40 to 107 mm Hg (mean 65\(\pm\)16 mm Hg), and mean transaortic pressure gradient ranged from 26 to 75 mm Hg (mean 40\(\pm\)12 mm Hg). Aortic valve area was <0.75 cm\(^2\) in 26 patients. Left ventricular volumes and ejection fraction were normal. Heart rate and systolic blood pressure increased significantly from rest to peak exercise (75\(\pm\)13 versus 125\(\pm\)21 bpm and 141\(\pm\)17 versus 171\(\pm\)27 mm Hg, respectively; both \( P<0.0001 \)). Aortic valve area and peak and mean transaortic pressure gradients increased during exercise \(( P<0.05 \)) and were 0.89\(\pm\)0.22 cm\(^2\), 88\(\pm\)20 mm Hg, and 54\(\pm\)14 mm Hg, respectively. Changes in left ventricular volumes and ejection fraction were not significant. The exercise test was abnormal in 26 patients. Angina developed in 4 patients, dyspnea in 2, \( \geq 2 \) mm ST depression in 13, fall or \(<20 \text{ mm Hg}\) rise in systolic arterial pressure in 6, and nonsustained ventricular tachycardia in 1. Only 1 patient developed wall motion abnormalities in the anterior wall at peak exercise. All of the patients recovered normally, and no patient experienced any complication as a result of the test.

Predictors of Outcome

Patients were followed for 15\(\pm\)7 (4 to 36) months. During this period, 2 patients developed symptoms (both angina and dyspnea), 2 were hospitalized for acute heart failure, 12 underwent aortic valve replacement combined with coronary artery bypass grafting in 4, and 3 died (2 from sudden death and 1 in the perioperative period of surgery). Among the 12 patients operated, coronary angiography revealed multivessel disease in 4 and nonsignificant coronary stenosis (<50%) in 4. The clinical and echocardiographic characteristics of the patients who remained asymptomatic or experienced an event are listed in Tables 1 and 2. No clinical and resting echocardiographic parameters allowed the distinction between the 2 groups with the exception of stenosis severity as defined by calculated aortic valve area. The aortic valve area was more severely reduced in subjects who developed events and was more frequently <0.75 cm\(^2\). The exercise test was more frequently abnormal in patients who presented an event. During exercise, the increases in peak and mean transaortic pressure gradients were greater in patients who had events, the increase in aortic valve area was lower, whereas changes in heart rate and in left ventricular ejection fraction were smaller. In multivariate analysis, larger exercise-induced increases in mean transaortic pressure gradient, an abnormal exercise test, and a more severe aortic valve stenosis emerged as independent predictors of events. A \( \geq 18 \text{ mm Hg} \) increase in mean transvalvular pressure gradient was selected by receiver-operator characteristic curve analysis as the best cut-off value for distinguishing the patient’s issue. Aortic valve area <0.75 cm\(^2\) and an increase in mean transaortic pressure gradient by \( \geq 18 \text{ mm Hg} \) were selected when they were entered in the statistical model as categorical variables (Table 3, Figures 1 and 2). Doppler exercise echocardiographic findings provided incremental prognostic value over clinical, resting echocardiographic and exercise electrocardiographic parameters (Figure 3).

Discussion

Currently, prophylactic aortic valve replacement is not recommended in asymptomatic patients with severe aortic stenosis.\(^1\) This study shows, however, a high rate of events in a series of consecutive patients with asymptomatic severe aortic stenosis. Only 57% of patients had an uneventful clinical course during follow-up. This indicates that the lesion severity is not fully appreciated on the basis of resting evaluation. Our results confirm and extend previous reports,
indicating that exercise testing might be of value in identifying a subgroup of asymptomatic patients who are hemodynamically compromised by aortic stenosis. Moreover, this study shows for the first time that quantitative exercise Doppler echocardiography provides incremental prognostic information over clinical, resting echocardiographic, and stress electrocardiographic parameters. The main predictors of outcome were as follows: a $\geq 18$ mm Hg increase in mean transaortic pressure gradient during exercise, an abnormal exercise test, and an aortic valve area $\leq 0.75$ cm$^2$ at baseline.

### Prognostic Value of Clinical and Baseline Echocardiographic Characteristics

The present study emphasizes again the relationship between traditional risk factors for atherosclerosis and valvular aortic stenosis. Age has been recognized as a critical determinant of outcome. However, the impact of age was weakened in this study that mainly included a population of elderly patients. The severity of aortic stenosis was the single predictor among all of the baseline echocardiographic parameters. At the time of inclusion, about one third of our patients had severe aortic stenosis defined as an aortic valve area $< 0.75$ cm$^2$. During follow-up, $61\%$ of them experienced an event. In the present study, peak and mean transaortic pressure gradients were not independent determinants of cardiac events. This contrasted with previous reports, which included patients with moderate-to-severe aortic stenosis and normal or depressed left ventricular function.

### Abnormal Exercise Testing and Outcome

Severe aortic stenosis has traditionally been regarded as a relative contraindication to exercise testing. This study showed that exercise could be safely performed in asymptomatic patients with an aortic valve area $< 1$ cm$^2$. More than one third of our patients (36%) exhibited an abnormal exercise test. Of note, 14 of the 18 patients who displayed an event during follow-up had an abnormal test. All 6 of the patients who developed hypotension or had an inadequate rise in systolic arterial pressure during exercise experienced a clinical end point. Exercise testing provides incremental prognostic value over resting echocardiographic parameters. These results support the hypothesis that valvular aortic stenosis should be considered as a dynamic lesion. The onset of symptoms in the individual patient depends on the severity of the aortic stenosis, as well as on left ventricular function and the status of peripheral circulation. When peripheral demands exceed the cardiac output, symptoms can occur. A clinical event was observed in 7 of the 13 patients who had ST segment depression at peak exercise. This suggests that the dynamic ST segment changes do not necessarily reflect the presence of left ventricular hypertrophy but might indicate myocardial ischemia, resulting from reduced coronary flow reserve with or without coronary artery disease.

### Prognostic Importance of Exercise Doppler Echocardiography

The present study is the first to demonstrate that quantitative Doppler echocardiography is of prognostic importance and

### TABLE 1. Clinical and Resting Echocardiographic Variables According to Outcome

<table>
<thead>
<tr>
<th>Variables</th>
<th>No Event (n=51)</th>
<th>Event (n=18)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>65±14</td>
<td>69±7</td>
<td>NS</td>
</tr>
<tr>
<td>Men (n %)</td>
<td>37 (73%)</td>
<td>11 (61%)</td>
<td>NS</td>
</tr>
<tr>
<td>Smokers</td>
<td>17 (33%)</td>
<td>7 (39%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (20%)</td>
<td>3 (17%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (41%)</td>
<td>9 (50%)</td>
<td>NS</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>27 (53%)</td>
<td>7 (39%)</td>
<td>NS</td>
</tr>
<tr>
<td>Rest hemodynamic and echo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>76±12</td>
<td>73±18</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>141±18</td>
<td>139±15</td>
<td>NS</td>
</tr>
<tr>
<td>Left atrial area (cm$^2$)</td>
<td>17±6</td>
<td>16±6</td>
<td>NS</td>
</tr>
<tr>
<td>LV end-diastolic volume (mL)</td>
<td>89±24</td>
<td>89±27</td>
<td>NS</td>
</tr>
<tr>
<td>LV end-systolic volume (mL)</td>
<td>30±14</td>
<td>31±12</td>
<td>NS</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>67±8</td>
<td>66±9</td>
<td>NS</td>
</tr>
<tr>
<td>Transtricuspid pressure gradient (mm Hg)</td>
<td>26±9</td>
<td>27±10</td>
<td>NS</td>
</tr>
<tr>
<td>LV aortic valve area (cm$^2$)</td>
<td>0.84±0.13</td>
<td>0.73±0.14</td>
<td>0.0028</td>
</tr>
<tr>
<td>LV aortic valve area $&lt; 0.75$ cm</td>
<td>15 (29%)</td>
<td>11 (61%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Aortic jet velocity $&gt; 4$ m/s</td>
<td>22 (43%)</td>
<td>8 (44%)</td>
<td>NS</td>
</tr>
<tr>
<td>Peak transaortic pressure gradient (mm Hg)</td>
<td>65±14</td>
<td>65±16</td>
<td>NS</td>
</tr>
<tr>
<td>Mean transaortic pressure gradient (mm Hg)</td>
<td>41±12</td>
<td>38±9</td>
<td>NS</td>
</tr>
</tbody>
</table>

LV indicates left ventricular; echo, echocardiogram; NS, not significant.
Aortic valve area

Table 3. Multivariate Predictors of Events

<table>
<thead>
<tr>
<th>Categorical Variables</th>
<th>No Event (n=51)</th>
<th>Event (n=18)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean aortic pressure gradient diff ≥18 mm Hg</td>
<td>10</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>Abnormal exercise test</td>
<td>9.1</td>
<td>0.0026</td>
<td></td>
</tr>
<tr>
<td>Aortic valve area &lt;0.75 cm</td>
<td>8.7</td>
<td>0.0031</td>
<td></td>
</tr>
</tbody>
</table>

Diff indicates difference between exercise and rest.

LV indicates left ventricular; NS, not significant; echo, echocardiogram.

Clinical Implications and Conclusions

Although the operative techniques and the prosthetic valves have considerably been improved in the past 4 decades, the decision to operate on asymptomatic patients with severe aortic valve stenosis (<1 cm²) and who are able to exercise. All of the patients examined had a moderately or severely calcified aortic valve. The specific effect of valvular calcification was, thus, not assessable. The decision to perform surgery was made by individual cardiologists in charge of the patients. No patient underwent aortic valve replacement within the first 4 months after the exercise Doppler echocardiographic examination. Serial echocardiographic assessment over time was not performed. As a result, the additional value of the rate of progression of aortic-jet velocity could not be evaluated.

Limitations

Our results pertain only to patients who have asymptomatic severe aortic valve stenosis (<1 cm²) and who are able to exercise. All of the patients examined had a moderately or severely calcified aortic valve. The specific effect of valvular calcification was, thus, not assessable. The decision to perform surgery was made by individual cardiologists in charge of the patients. No patient underwent aortic valve replacement within the first 4 months after the exercise Doppler echocardiographic examination. Serial echocardiographic assessment over time was not performed. As a result, the additional value of the rate of progression of aortic-jet velocity could not be evaluated.

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Aortic stenosis remains difficult.23 Considering the high rate of events in our and previous reports, 3,5,7 early elective surgery could, however, be indicated in a high-risk subset of patients. Our results suggest a role for quantitative exercise Doppler echocardiography by a better appreciation of the lesion and the patient adaptation. Dynamic testing helps to identify the patients who need closer clinical and echocardiographic follow-up. Given the inherent subjectivity in history-taking, and considering the increased risk of death while a patient awaits surgery and the higher operative risk of urgent surgery, elective aortic valve replacement seems to be indicated at least in patients combining the following 3 independent risk predictors: an aortic valve area <0.75 cm², an abnormal exercise test, and a ≥18 mm Hg increase in mean transaortic pressure gradient. The validity of our observations needs to be confirmed in a larger series of patients.

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