Argument for a Doppler echocardiography during exercise in assessing asymptomatic patients with severe aortic stenosis

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Aims Exercise stress testing (EST) is recommended by guidelines to risk-stratify patients with asymptomatic valvular aortic stenosis (AS), though the role of quantitative exercise-Doppler echocardiography has rarely been studied. This prospective study sought to correlate standard EST results with the haemodynamic measurements made during exercise by Doppler echocardiography.

Methods and results We performed rest and semi-supine exercise Doppler echocardiography in 44 consecutive patients (mean age = 68 ± 12 years) with aortic valve areas ≤0.6 cm²/m². The effective aortic valve area (EOA), cardiac output (CO), maximal transvalvular velocity, and pulmonary pressure were monitored over the test. No serious adverse event was observed. EST was positive in 26 (Group 1) and negative in 18 (Group 2) patients. Baseline echocardiographic measurements were similar (EOA 0.77 ± 0.15 vs. 0.78 ± 0.14 cm²; CO 5.5 ± 1.6 vs. 5.9 ± 2 L/min) in both groups. Exercise-induced changes in CO (+2.9 ± 2 vs. +4.3 ± 1.8 L/min, P = 0.04) and EOA (−0.04 ± 0.18 vs. +0.15 ± 0.24 cm², P = 0.015) were significantly greater in Group 2. A correlation between changes in EOA and changes in CO during exercise was observed, but significantly higher in Group 2 (P = 0.04).

Conclusion In the presence of severe asymptomatic AS, exercise Doppler echocardiography, assessing the mechanisms behind a positive EST, appears very promising but further studies with prognosis assessment remain necessary.

Key words Aortic valve stenosis; Exercise stress test; Doppler echocardiography

Introduction

Surgical aortic valve replacement (AVR) is recommended for patients presenting with manifestations associated with haemodynamically significant valve stenosis (effective area ≤0.6 cm²/m²). A considerable proportion of patients, however, present with haemodynamic abnormalities consistent with severe aortic stenosis (AS) in the absence of corresponding functional symptomatology. Therefore, measurements of valve area and transvalvular gradient limited to the resting state appears unreliable to predict the risk of adverse clinical events and pose an indication for AVR in a sizable number of patients suffering from severe AS.1–7 Few studies tend to demonstrate the value of standard treadmill or bicycle exercise stress testing (EST) in these patients, in the presence of preserved left ventricular (LV) systolic function.1–9 During testing, performed in a suitable environment,5–7 one-third of patients who claim to be asymptomatic develop exercise-induced symptoms.10 This has allowed the identification of predictors of adverse events, though questions remain with respect to the specificity of the abnormalities that are detected.8 Although a ≥20 mmHg fall in systolic blood pressure is a source of concern, the predictive value of repolarization changes on surface electrocardiogram seems considerably lower.5–7

Haemodynamic measurements made by means of Doppler echocardiography during exercise on a tilt-table might then provide information helpful to the clinical decision and prognosis making. As a matter of fact, the effective aortic valve area (EOA) depends on cardiac output (CO).11–14 And studies have correlated valve compliance with risk of death or valve replacement at 30 months.13

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Therefore, we conducted a single-centre, prospective study in asymptomatic patients suffering from severe AS, and compared information gathered by standard, recommended EST, with haemodynamic data obtained during exercise echocardiography. We hypothesized that, as previously suggested by Otto et al., exercise echocardiography would provide the haemodynamic mechanisms related to the positivity of the EST and so, Doppler echocardiography would improve the understanding and the management of asymptomatic patients, despite a severe aortic valve stenosis.

Methods

The objectives and protocol of the study, approved by the local Ethics Committee, were explained to all patients, who consented to participate. All asymptomatic patients referred to our echocardiography laboratory between 1 January and 1 August 2005 for evaluation of EOA ≤1 cm² (<0.6 cm²/m² body surface area) were considered for inclusion in the study. Patients whose echocardiographic imaging was of poor quality, unable to exercise, or who refused to participate were excluded. Patients presenting with more than moderate disease of another valve, or with an LV ejection fraction (EF) <40%, were also excluded.

Study protocol

Transthoracic echocardiography (TTE) was performed at rest and during exercise, using SONOS 7500 (Hewlett-Packard, Palo Alto, CA, USA) and Vivid 7 (GE healthcare, Horten, Norway) on a table initially tilted at 60°, interfaced with an Ergometrics e900 (Ergoline, Bitz, Germany) electromagnetic ergometer. The table could be tilted to the left to optimize the quality of the recordings. All measurements were made at least in triplicate, and according to the recommendations of the American Society of Echocardiography. EOA was calculated by a continuity equation. The velocity of tricuspid regurgitation, when present, was measured, and the presence and grade of insufficiency of other valves were recorded. Quantification of valvular disease was made according to the recommendations of the American Society of Echocardiography.

After these measurements were made at rest, exercise began with an initial workload of 20 W, increased every 3 min in increments of 20 W. Patient monitoring, as well as the criteria for the interruption of the exercise, was performed according to the guidelines of the European Society of Cardiology (ESC). The carried out performance of each patient was compared with the theoretical one, calculated according to the gender and the age using a Wasserman equation. Dyspnoea was considered only when occurring before 80% of the theoretical performance. Exercise test criteria of positivity were the ESC ones:

- occurrence of symptoms (fatigue, angina pectoris, syncope, or near syncope);
- increase in systolic blood pressure during exercise ≥20 mmHg (or a fall in blood pressure);
- patient does not reach 80% of the normal exercise capacities according to age- and gender-adjusted levels;
- more than 2 mm horizontal or down-sloping ST-segment depression during exercise in comparison with baseline, which are not attributable to other causes than severe AS;
- complex ventricular arrhythmias.

Statistical analyses

Qualitative variables are presented as numbers and percentages of observations, and quantitative variables as means ± standard deviation (SD). Relationships between two qualitative variables were examined by χ² test. Comparisons of means were made with the Kruskall–Wallis non-parametric test. The correlation between changes in EOA and changes in CO between rest and peak exercise were examined using Pearson’s correlation coefficient or, when the variables were normally distributed, using Kolmogorov–Smirnov’s test.

A simple linear model was constructed for each EST, and all hypotheses were verified, including that of residual-based normality, homoscedasticity, and residual non-autocorrelation. Regression lines (y = αx + b) between differences in EOA (y) and CO (x) were estimated in function of the results of EST. Comparisons of the correlation lines were made using the dedicated STATISTICA software (StatSoft Inc.; http://www.statsoft.com/). A P-value of <0.05 was considered significant.

Results

Patient population

During the enrolment period, 49 patients satisfied the study inclusion criteria. Of five patients who were excluded, two had unsatisfactory imaging studies, two were unable to exercise, and one refused to participate. The mean age of the 44 included patients was 68 ± 11.5 years, and 13 (29.5%) were women. No patient was paced; a normal sinus rhythm was present for every patient at the time of the stress test. Systolic arterial pressure at the onset of exercise was 139 ± 19 mmHg. Treatment with a beta-adrenergic blocker was stopped at least 48 h before the test (27.2%) (Figure 1).

Transthoracic echocardiography at rest

On TTE at rest, including images obtained in the right parasternal view, mean EOA was 0.77 ± 0.14 cm² (0.44 ± 0.09 cm²/m²), mean gradient 43.9 ± 20.9 mmHg, peak gradient 75 ± 32 mmHg, and peak trans-aortic velocity 4.32 ± 0.8 m/s. The LVEF was ≥50% for every patient. The mean CO was 5.67 ± 1.8 L/min, and mean stroke volume 77.2 ± 22 mL. Trivial aortic valve regurgitation was present in 23 (52.2%), and moderate insufficiency in 12 (27.2%) patients. Associated trivial mitral valve regurgitation was present in 13 (29.5%), and moderate mitral regurgitation in 2 (4.5%) patients. Tricuspid insufficiency was observed in 32 patients (72.7%), with a measured velocity of 2.59 ± 0.44 m/s.

Exercise stress testing

All patients were exercised to a satisfactory level (mean=5.02 ± 1.4 MET), without the development of adverse events. Exercise stress testing was positive...
according to the ESC criteria in 26 (59%) patients (Group 1) and was negative in 18 (41%) patients (Group 2) (Figure 1).

The test was stopped if the symptoms were requesting to stop the exercise or when the blood pressure dropped during the test. In the absence of these two reasons, the test was performed until the patient reached 85% of his/her maximal theoretical heart rate.

In Group 1, one patient (3.8%) developed a 12-cycle salve of right bundle branch block morphology, asymptomatic VT at a rate of 150 bpm, 12 patients (46.1%) developed prominent deviation of the ST segment on surface electrocardiogram, 10 patients (38.4%) had an abnormal blood pressure response to exercise, and 20 patients (76.9%) developed symptoms during exercise: dyspnoea, fatigue: 14 patients, near syncope: 1 patient (concomitant with a decrease in blood pressure to 80/60 mmHg), chest pain (concomitant to an EKG deep ST depression in three consecutive derivations): 5 patients. The main patient characteristics with respect to the results of EST are shown in Figure 1. The baseline clinical characteristics and echocardiographic measurements were similar in both groups of patients (Table 1).

**Exercise-induced changes in haemodynamic measurements**

The exercise-induced changes in haemodynamic measurements in Groups 1 and 2 are shown in Table 2. The changes in CO and EOA were significantly greater in Group 2 than in Group 1. In contrast, the increase in trans-aortic gradients or velocity of tricuspid leak was similar regardless of the outcome of EST. In addition, a significant, positive relationship was observed between changes in EOA and changes in CO in patients with positive, as well as negative EST (Figure 2). However, the correlation coefficient, \( r \), that tests the linear correlation between these two variables was significantly \( (P = 0.04) \) greater when EST was negative \( (r = 0.67; P = 0.003) \) than when it was positive \( (r = 0.51; P = 0.007) \).

**Discussion**

This study showed the changes in aortic valve EOA according to the change in cardiac output. A significant difference, between the positive and the negative exercise stress test groups, was observed. It suggests that the difference in response to exercise between the groups might be related to a significant difference in valve’s compliance. This haemodynamic assessment during exercise more readily explained why, for a given degree of stenosis, a patient did or did not develop symptoms than a conventional exercise stress test.

**Severe aortic stenosis and exercise testing**

No serious adverse event occurred during exercise in this study, confirming published observations, which have reported the absence of serious undesirable clinical events during exercise testing in asymptomatic patients presenting with severe AS and relatively preserved LV function, as long as the test is performed as recommended. Among 44 patients claiming to be asymptomatic, 26 (59%) had a positive EST, of whom 20 (45.4%) developed exercise-induced symptoms. This is a higher proportion than reported by others (~30%), probably because EOA was not as severely narrowed in these other studies. Our observations confirm the importance of EST as part of the evaluation of these ‘asymptomatic’ patients with a view of detecting those who are spuriously asymptomatic, as currently recommended. As it has previously been reported, we found no correlation between haemodynamic measurements made at rest and outcome of EST. Similarly, although patients with coronary artery disease were few, it did not significantly influence the EST. The correlation, in this study, between presence of coronary artery disease and results of EST, development of angina pectoris or depression of the ST segment in particular, was weak.

**Added contributions of echocardiography during exercise testing**

Lancellotti et al. observed that haemodynamic monitoring by echocardiography during exercise contributed prognostic factors that appeared useful and complementary to EST alone. Exercise echocardiography allowed the evaluation of the degree of valve leaflet stiffness, which, at rest, is uncertain, since the importance and consequences of echocardiographically visible valvular calcifications might be

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Main patient characteristics according to the outcome of exercise stress testing</th>
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<tr>
<td></td>
<td>Exercise stress test</td>
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<tr>
<td>Clinical</td>
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Unless specified otherwise, values are means ± SD.
No statistical difference was found between these two groups \( (P > 0.05) \).

Vmax, maximum velocity.
difficult to appraise. Furthermore, despite the assessment of several haemodynamic indices, including valvular resistance, stroke work loss, energy loss index, or valvulo-arterial impedance, none has advantageously replaced transvalvular aortic output. Therefore, the degree of leaflet stiffness can only be ascertained by calculating compliance, while varying the cardiac output. Accordingly, we observed that patients with the most compliant valves were those with a negative exercise test (Group 2) and, consequently, those whose prognosis was supposed to be more favourable. Conversely, echocardiography allows the attribution of equivocal effort-induced symptoms to the non-adaptation of CO to exercise because of severe and fixed aortic valve obstruction. This was manifest as a significant and positive correlation between an increase in EOA and an increase in CO, a correlation which was considerably weaker in the presence of a positive EST.

Limitations of our study
We really believe that exercise echocardiography was providing a more robust assessment of patients with asymptomatic severe aortic valve stenosis. We observed that the electrocardiographic criteria (ST-modification) can be considered controversial and we never stopped an exercise stress test for an isolated ST-change (these electrocardiographic abnormalities were also associated with symptoms or abnormal tensional pattern).

Unfortunately, our population, selected to be severe, remains rather small. She/he did not allow a gradation between parameters proposed to determine whether a patient is really or not asymptomatic. Furthermore, we were not able to perform a real follow-up as soon as many patients went to surgery, despite a normal exercise stress test, AVR being request before another surgery or medical treatment. We observed some degree of mitral regurgitation increase during the exercise stress test. This increase in degree of mitral regurgitation was sometimes astonishing. This mitral regurgitation should certainly account for symptoms such as dyspnoea and should be carefully quantitated that was not initially plane in the study and do not rigorously performed in most patients.

Conclusions
This study showed that, in asymptomatic patients presenting with severe AS, no clinical or haemodynamic index at rest was correlated with the outcome of EST on tilt-table, interpreted according to the ESC criteria. In contrast, changes in the haemodynamic measurements were observed during this physiologic stress, which varied significantly according to the EST results. Since exercise Doppler echocardiography on a tilt-table has the potential of contributing supplemental comprehensive and prognostic information, it seems legitimate to take into account our result and to look forward for further large multicentric study assessment prognosis.

Conflict of interest: none declared.

References

Table 2 Changes in haemodynamic measurements between rest and peak exercise in patients with positive vs. negative exercise stress tests

<table>
<thead>
<tr>
<th>Exercise stress test</th>
<th>Positive (Group 1) (n = 26)</th>
<th>Negative (Group 2) (n = 18)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic area (cm²)</td>
<td>−0.04 ± 0.18</td>
<td>+0.15 ± 0.24</td>
<td>0.015</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>+2.9 ± 2</td>
<td>+4.3 ± 1.8</td>
<td>0.04</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>+51.8 ± 15</td>
<td>+50.5 ± 8</td>
<td>0.9</td>
</tr>
<tr>
<td>Mean gradient (mmHg)</td>
<td>+12 ± 11</td>
<td>+8 ± 8</td>
<td>0.3</td>
</tr>
<tr>
<td>Peak gradient (mmHg)</td>
<td>+20 ± 17</td>
<td>+11 ± 15</td>
<td>0.09</td>
</tr>
<tr>
<td>Trans-aortic Vmax (m/s)</td>
<td>+2.17 ± 0.9</td>
<td>+1.5 ± 1.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>−6.2 ± 19</td>
<td>+3.6 ± 16</td>
<td>0.08</td>
</tr>
<tr>
<td>Tricuspid leak Vmax (m/s)</td>
<td>+1.36 ± 0.5</td>
<td>+1.1 ± 0.6</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Values are means ± SD.
Vmax, maximum velocity.

Figure 2 Linear regression analysis between flow and effective orifice area according to the positivity (red, lighter dots) or the negativity (black, darker dots) of the exercise stress test.

Figure 2


