The Role of Exercise Test in Stratifying the Risk of Asymptomatic Patients with Moderate/Severe Aortic Stenosis

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Objectives: The role of exercise test in risk stratifying of asymptomatic patients with moderate and severe aortic stenosis (AS) in recent literature is still controversial. The aim of this study was to evaluate the role of exercise test in stratifying the risk of patients with moderate to severe aortic stenosis.

Methods: At the Internal Medicine Clinic, Department of Cardiology in Tuzla, in the period from January 2008 until January 2010 was followed 33 patients with clinical and echocardiographic parameters of moderate to severe asymptomatic aortic stenosis (mean effective orifice area EOA 0,9±0,34 cm²). In statistical analysis we used descriptive statistics, t-test, chi-square test and Kaplan-Meier life table for predictive values, sensitivity and specificity. A significance level of 0.05 was used.

Results: Two patients were excluded due to exclusion criteria, so 31 patient was followed up during 12 months period. Eighteen patients (58%) with EOA £ 0,8cm² had limiting symptoms during the test. During follow-up period, 11 patients developed serious spontaneous symptoms, and out of them 8 patients underwent surgical valve replacement, one patient died (sudden cardiac death), and 2 patients had serious complications (ischemic cerebral stroke). Twenty patients remained asymptomatic. The highest positive predictive accuracy had EOA£ 0,8cm² with limiting symptoms and it was 85%. The highest negative predictive accuracy had ST depression. Conclusion: only limiting symptoms along with EOA£ 0,8cm² had positive predictive accuracy. Key words: asymptomatic aortic stenosis, exercise test, prognosis

1. INTRODUCTION

In most European countries, moderate AS is present in 5% of the population aged > 75 years old, and severe in 3% of cases. More than half of the patients with calcified AS over 75 years of age are asymptomatic (1). This fact represents a major medical problem because there are no specific guidelines for the management of asymptomatic patients with valvular heart disease, and this topic is still subject to debate. The data relating to the management of asymptomatic patients with valvular disease are quite limited. In the absence of specific guidelines for the management of asymptomatic patients with valvular heart disease, the recommendations can be drawn only from the general guidelines (2,3,4). Still, no clinical, hemodynamic, or echocardiographic parameters have been adopted as a first class recommendation for aortic valve replacement in patients with severe aortic stenosis before the onset of symptoms. Published data indicate that the risk of sudden cardiac death in these patients is less than 1% per year, which is less than the risk of surgical treatment, and that the appearance of symptoms should be awaited in these patients before surgical treatment (5,6,7). Three retrospective and six prospective studies have demonstrated that the incidence of sudden cardiac death is low. Sudden cardiac death was registered in only 4 out of 503 patients with asymptomatic AS who were followed 2-4 years which amounts to only 0.3% per year (8,9,10,11,12,13,14,15,16). More echocardiographic studies indicate the importance of monitoring patients and evaluating the progression of the disease (16,17,18,19). Stress test is recommended in all the guidelines in monitoring patients with asymptomatic aortic stenosis (17,18,20,21). All studies in-
dicate that the development of spontaneous symptoms is the best criterion for valve replacement, especially for patients aged < 70.

Objectives

- To determine the rate of positive stress test in patients with moderate to severe asymptomatic aortic stenosis.
- To determine the parameters of positive stress test in patients with moderate to severe asymptomatic aortic stenosis.
- To determine complications and the need for surgical aortic valve replacement in the group of patients with moderate to severe asymptomatic aortic stenosis.

2. METHODS

Patients

At the Internal Medicine Clinic, Department of Cardiology in Tuzla, in the period from January 2008 until January 2010 was followed 33 patients with clinical and echocardiographic parameters of moderate to severe asymptomatic aortic stenosis. Excluded were patients with left ventricular systolic dysfunction, severe aortic regurgitation, and other significant valvular disease or known pulmonary disease. Aortic stenosis was graded according to the degree of the reduction of aortic valve area (EOA) as mild (area > 0.8 cm²), moderate (area 0.8 to 1.3 cm²) or severe (area ≤ 0.8 cm²). All patients were divided according to medical history data in two groups: physically active and physically inactive—those who prefer sedentary lifestyle. At 6-12 months evaluation of disease progression was performed, based on clinical symptoms, signs, echocardiographic parameters and cardiac stress test. Complications were registered in all patients (heart failure, arrhythmias, cerebrovascular accident, acute coronary syndrome), as well as mortality and the need for surgical replacement of aortic valve. All patients gave written, informed consent to participate.

Echocardiography: estimation of severity of aortic stenosis

Echocardiographic examination was performed on GE Vivid 3 echocardiograph. Assessment of the degree of severity of AS was performed on the basis of Doppler measurements: maximum flow velocity (Vmax), maximum and mean gradient pressure (PG max, mean PG). Pulse-wave and continuous-wave Doppler was analyzed after recording. Average was taken from three obtained results. EOA was calculated in cm according to the continuity equation. AS is graded according to the degree of aortic orifice constriction (EOA) as mild (area > 0.8 cm²), moderate (area 0.8 to 1.3 cm²) or severe (area ≤ 0.8 cm²). The criteria for severe aortic stenosis with preserved LV systolic function were: Vmax ≥ 4.5 m/s, mean pressure gradient >50 mmHg, aortic valve area <0.8 cm², and VTI VOT/VTI or the speed ratio ≤ 0.25. According to the maximum gradient value, we graded AS as: mild 16-50 mmHg, 36-50 mmHg moderate, moderately severe 51-71 mmHg, severe >75 mmHg. All patients underwent classical measurements of heart wall thickness, heart cavity dimensions, assessment of regional and global contractility and ejection fraction (EF). We have tried to eliminate all subjective (inappropriate echo beam angle during measurement) and objective difficulties (bad window, machine). The average rate of hemodynamic progression of AS was evaluated by the increase in flow rate through the aortic valve of >0.3 m/s per year, increase in mean pressure gradient of >7 mmHg per year and reduction of the aortic valve area of 0.1 cm² per year (22).

Cardiac Exercise Test

Cardiac Exercise Test was performed on treadmill according to the Bruce protocol on GE appliance. During tests, screened for the appearance of symptoms (dyspnea, angina pectoris, syncope or presyncope), as well as the increase in systolic pressure during exercise (increase in systolic blood pressure less than 20 mmHg or drop in blood pressure was estimated as abnormal). The percentage of the theoretical tax rates for age and sex (<80% assessed the pathological) was monitored. The appearance of horizontal or descendent ST segment depression of >2 mm, which was not associated with other causes, but only with AS was also considered pathological. The occurrence of complex ventricular beats (VT of >4 linked VES were considered pathologic) was monitored. Were performed serial testing at 6-12 months, and patients were instructed to report symptoms during the follow-up. If the echocardiographic parameters showed greater than 4 m/s at the start of examination, carried out...
the re-evaluation every six months: the appearance of symptoms, changes in effort tolerability on stress test and echocardiographic parameters. If maximal flow rate was greater than 0.3m/s per year since the last review, a surgical valve replacement was recommended. If no changes occurred in the echo-parameters or stress test, or the patients remained asymptomatic, retests were performed at 6-12 months.

**Statistical analysis**

Data were analysed with Arcus Quick Stat Profesional and MedCalc. The *t*-test and the Mann–Whitney *U* test were used to compare patients who developed symptoms with those who remained asymptomatic. Qualitative variables were compared using the *χ* test. Results were shown as mean±standard deviation or median (lower quartile, upper quartile) for skewed data. Individual echocardiographic and exercise variables were tested for the ability to predict symptom onset within 12 months by univariate analysis. Variables that predicted symptom onset on univariate analysis were then entered into a multivariate logistic regression model. Qualitative variables were entered directly. Symptom-free survival after exercise testing was also demonstrated using the Kaplan–Meier life table. A significance level of 0.05 was used (*p* <0.005).

### 3. RESULTS

A total of 33 patients, 27 (81.9%) males and 6 (18.1%) females, were recruited from the Department of Cardiology. Out of total number of patients, 2 patients were excluded due to exclusion criteria, so 31 patient underwent follow up during twelve months. As mentioned above, aortic stenosis was graded according to continuity EOA at rest by commonly used although arbitrary criteria as mild (area ≥1.3 cm²), moderate (area 0.8–1.2 cm²), or severe (area ≤0.8 cm²). Mean age of patients was 68.35±3.66. Figures 1 nad 2 are showing echocardiographic pictures-spectral analysis of one patient from the study. Mean EOA in our study was 0.9±0.34cm2. Baseline demographic characteristics of population considering risk factors for aortic stenosis are given in Table 1.

All patients completed a satisfactory treadmill exercise test. One patient experienced self-limiting asymptomatic atrial fibrillation at peak exercise, but there were no other significant adverse events during exercise testing.

Eighteen (58%) patients stopped their exercise because of breathlessness, chest tightness and/or dizziness (limiting symptoms). The remaining 13 patients stopped because of fatigue. No test was terminated for any other reason. There was no significant difference in age between patients with limiting symptoms and those stopping because of fatigue. Seven (22%) patients demonstrated an abnormal blood pressure response to exercise, defined as a systolic blood pressure at peak exercise either the same as or below the baseline level. ST segment depression of ≥2 mm in one or more leads was found in 9 (29%) patients. In one case, the electrocardiographic changes were uninterpretable because of resting right bundle branch block.

At the end of the follow-up period, about one third of total number (11 patients) developed serious spontaneous symptoms. Eight of them underwent surgical treatment (valve replacement), one patient died (sudden cardiac death) at five months period, and 2 patients had serious complications (ischemic cerebral stroke).

Patients who developed symptoms had more severe aortic stenosis on echocardiography (greater peak velocity and smaller EOA) and a higher proportion of positive exercise tests than those that remained symptom-free (Table 2). As mentioned above, statistically significant difference between group of patients who developed symptoms and those who remained symptom free was found (*p*<0.0001), EOA (*p*<0.05). However, statistical significance regarding abnormal blood pressure was

### Table 1. Baseline demographic characteristics of population / risk factors. HLP-Hyperlipoproteinaemia

<table>
<thead>
<tr>
<th>Age (male+female)</th>
<th>Diabetes mellitus</th>
<th>HLP</th>
<th>Smokers</th>
<th>Physically active</th>
<th>Physically inactive (sedentary lifestyle)</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>55-60 years</td>
<td>1(1+0)</td>
<td>1(1+0)</td>
<td>1(1+0)</td>
<td>1(1+0)</td>
<td>1(1+0)</td>
<td></td>
</tr>
<tr>
<td>60-65</td>
<td>1(1+0)</td>
<td>1(1+0)</td>
<td>2(1+1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-70</td>
<td>11(8+3)</td>
<td>3(3+0)</td>
<td>9(7+2)</td>
<td>6 (5+1)</td>
<td>8(5+3)</td>
<td></td>
</tr>
<tr>
<td>&gt;70</td>
<td>3(2+1)</td>
<td>1(1+0)</td>
<td>9 (8+1)</td>
<td>4 (4+0)</td>
<td>7(6+1)</td>
<td></td>
</tr>
<tr>
<td>Number of patients / total number</td>
<td>10/31</td>
<td>14/31</td>
<td>6/31</td>
<td>21/31</td>
<td>10/31</td>
<td>16/31</td>
</tr>
</tbody>
</table>

### Table 2. Comparison between patients developing spontaneous symptoms who underwent valve replacement or had serious complications (endpoint) and those remaining asymptomatic at 12 months (no endpoint). Values are mean±SD, or median (lower quartile, upper quartile), or n (%) of patients.

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Endpoint (n=11)</th>
<th>No endpoint (n=20)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69.72 ±22.87</td>
<td>67.6 ±43.89</td>
<td>0.063</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>9/2</td>
<td>16/4</td>
<td>0.65*</td>
</tr>
<tr>
<td>Echocardiographic data</td>
<td>0.7 ± 0.077</td>
<td>1.02 ± 0.109</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak velocity (m/s)</td>
<td>4.10 ±0.7</td>
<td>3.64 ±0.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Exercise test data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limiting symptoms</td>
<td>9 (81.8%)</td>
<td>9 (45%)</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Abnormal blood pressure response</td>
<td>4 (36.4%)</td>
<td>3 (15%)</td>
<td>Non-significant</td>
</tr>
<tr>
<td>ST depression U2 mm</td>
<td>5 (45.5%)</td>
<td>4 (20%)</td>
<td>&lt;0.05*</td>
</tr>
</tbody>
</table>

### Table 3. Predictive ability for onset of spontaneous symptoms within 12 months. PPA, positive predictive accuracy; NPA, negative predictive accuracy.

<table>
<thead>
<tr>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPA (%)</th>
<th>NPA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limiting symptoms at test (n=18)</td>
<td>81.81</td>
<td>84.6</td>
<td>50</td>
</tr>
<tr>
<td>EOAM0.8 +limiting symptoms (n=10)</td>
<td>63.63</td>
<td>85</td>
<td>70</td>
</tr>
<tr>
<td>ST depression U2 mm (n=9)</td>
<td>45</td>
<td>80</td>
<td>55</td>
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</tbody>
</table>
not found although there was a strong numerical trend toward it. No patient with an EOA≥1.3 cm² at baseline developed symptoms within 12 months. Overall, symptom-free survival at 12 months was 50% for patients with limiting symptoms on exercise testing and 84.6% for those without symptoms.

Furthermore, positive and negative predictive values as well as sensitivity and specificity of exercise stress test in stratification of patients with asymptomatic aortic stenosis (Table 3) were analyzed. We haven't analyzed these parameters for abnormal blood pressure because we haven't found statistically significant difference between patients who became symptomatic and underwent surgical treatment and those who remained asymptomatic. The EOA had the highest positive predictive accuracy at echocardiography ≤0.8, along with occurrence of symptoms during testing. Specificity of this parameter is also high: 85%. The highest negative predictive value in our study had ST depression during the test ≥2mm. All of this is shown in Table 3.

4. DISCUSSION

Out of 31 investigated patients, 11 had high cardiovascular risk. Eight of them underwent surgical treatment, one died refusing the operation (sudden cardiac death), and 2 patients experienced severe complications (stroke). All of them became symptomatic during the 12-month follow-up period, and were recommended surgery, or had complications. Das et al. (16) and other investigators report of similar results. The other 20 patients remained asymptomatic during 12 months, although some of them had positive exercise-test results, which allowed us to follow sensitivity and specificity of exercise test parameters. Eleven patients had significantly smaller EOA, higher transvalvular flow velocity, they developed more symptoms at testing, as well as ST-segment depressions. No significant difference was found regarding blood pressure, which is in concordance with the data from the literature (17,18,20,23). The biggest positive predictive value had EOA=0.8cm² along with the symptom occurrence, while ST-segment depression had the highest negative predictive accuracy, which is also in concordance with the data from the literature (17,18,20,23). In our group of physically active patients under the age of 70, symptoms during the test indicate the need for aortic valve replacement, which elevates the positive predictive accuracy of the test, also in concordance with reports from other authors (19). There are different reports on the value of cardiac stress testing in patients with asymptomatic AS. The mentioned pathological criteria during cardiac stress testing are considered an indication for aortic valve replacement, according to class IIa in the guidelines. This recommendation is based on weak data (23). This is because the dyspnea and angina during physical exertion appear anyway, as a consequence of valvular disease and myocardial demand/supply imbalance (21). Fatigue and syncope, as well as inadequate blood pressure increase can be provoked by inadequate ventricular-barroreceptor response with subsequent peripheral vasodilation and hypotension, but also because of heart's inability to increase cardiac output across the stenotic aortic valve (22). Therefore, cardiac stress test can be useful in physically active patients of less than 70 years of age. Normal test results indicate small probability for the occurrence of symptoms within the next 12 months. Clear symptoms provoked during physical exertion in a physically active person younger than 70 indicate significant probability of symptom occurrence within the next year, and aortic valve replacement is recommended. Inadequate rise in blood pressure of less than 20mmHg per stage, adjusted according to sex and age, or ST-segment depression ≥2mm during effort have low positive predictive accuracy, and cannot be decision-making factors for surgical treatment (16,17,23).

5. CONCLUSION

Echocardiography is still the gold standard in diagnosing and estimating the severity of AS. In asymptomatic patients, during the assessment of haemodynamic severity of the disease, additional stress testing and/or dobutamine stress testing can be of help, as well as estimating plasma levels of brain nephrilysin, brain natriuretic peptide, heart catheterization, magnetic resonance imaging, and heart CT-scan. There are no reliable guidelines for the management of asymptomatic patients with AS. The earliest indication for aortic valve replacement is the occurrence of symptoms. All the data warn that early surgical treatment is not indicated, unless the benefit is proved. Today there are attempts of percutaneous treatment of aortic stenosis, as well as transapical operations in patients in whom the standard aortic valve replacement is contraindicated.

Limitations of the study: The number of patients in our study was relatively low. Low sample size might be reason that we haven't found statistical relation between abnormal blood pressure during the test and prognosis of patients.

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