Management of asymptomatic aortic stenosis: how helpful is exercise testing?

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This editorial refers to 'Exercise testing to stratify risk in aortic stenosis'13 by P. Das et al., on page 1309

In contrast to symptomatic aortic stenosis (AS), asymptomatic AS has been shown to have a relatively good outcome even if it is haemodynamically severe.1,2 From the current data, it appears unlikely that the potential benefit can outweigh the risk of surgery and the long-term risk of prosthesis related complications in all patients. Surgery is, therefore, not generally recommended in AS before symptom onset.3 The management of asymptomatic AS has, nevertheless, remained controversial for several reasons: sudden death in truly asymptomatic patients has been reported to be extremely rare with an incidence of <1% per year.1,2 However, patients frequently do not present immediately when symptoms develop and mortality has been reported to be quite significant already within the following month after symptom onset.1 In addition, mortality rates up to 7% have been reported for symptomatic patients who must wait for surgery for several months.4 Finally, operative mortality is significantly higher in symptomatic, when compared with asymptomatic, patients.5 Thus, the ideal approach would be to refer patients for surgery just before symptom onset. Besides the finding of a reduced systolic left ventricular function (which is extremely rare in asymptomatic AS), current American3 and European4 practice guidelines list an abnormal response to exercise as an acceptable indication for surgery in asymptomatic patients (class IIa). However, there are few data to support these recommendations and particular uncertainty remains how to define criteria for an abnormal exercise response that justifies surgical referral.

Exercise testing for risk stratification

Of the few studies that evaluated exercise testing in asymptomatic AS, the work by Amato et al.7 provided so far the most helpful information with regard to clinical management. They performed exercise testing in 66 asymptomatic patients with an aortic valve area < 1.0 cm² and followed them for 15 ± 12 months. Criteria for a positive test were occurrence of symptoms, new ST segment depression, systolic blood pressure increase < 20 mmHg, or complex ventricular arrhythmias. At 24 months, event-free survival with events defined as development of symptoms in daily life or death was 85% in 22 patients with negative test, but only 19% (including four sudden deaths!) in patients with a positive test. Although these results look impressive they leave many open questions. The majority of patients with a positive test fulfilled the criterion of symptom development. In particular, three of the patients who died had symptoms during the test. Although the study allowed the conclusion that patients with a negative exercise test appear to have a good outcome and may not require surgery, whereas those limited by typical symptoms should undergo valve replacement, the positive predictive value of an abnormal blood pressure response and/or ST segment depression without occurrence of symptoms remained unclear.

Alborino et al.8 reported a small series of 30 patients, of whom only 10 had severe AS. Although they found a higher rate of need for valve replacement in patients with an abnormal exercise test defined by similar criteria, the positive predictive value was low. Otto et al.9 found on average a smaller increase in blood pressure on exercise in those patients who reached the end point of death or aortic valve replacement compared with those without event. However, there was substantial overlap and the authors could not report a predictive accuracy for any certain exercise response. In addition, their study was limited by the fact that some patients underwent surgery without having developed symptoms during follow-up.

Das et al.10 provide important new information clarifying some of the open questions. In 125 patients with asymptomatic AS (effective valve area 0.9 ± 0.2 cm²), they sought to assess the accuracy of exercise testing in predicting symptom onset within 12 months. Similar to previous reports, approximately one-third of the patients were found to develop symptoms on exercise. Abnormal blood pressure response, more strictly defined as no increase in systolic blood pressure at peak exercise compared with baseline, was found in 23% and ST segment depression of > 2 mm in 26% of patients. There were no deaths during follow-up but 29% of their patients developed spontaneous symptoms. Absence of limiting symptoms had a high
negative predictive accuracy of 87%. An abnormal blood pressure response or ST segment depression, however, gave no statistically significant benefit above limiting symptoms with respect to predictive accuracy. In the absence of limiting symptoms, only two patients with abnormal blood pressure response, two with ST depression and one with both developed symptoms during follow-up. Negative predictive values were 78 and 77% and positive predictive values 48 and 45%, respectively. These findings suggest that abnormal blood pressure response and ST depression are rather non-specific findings and not helpful for identifying asymptomatic patients who may benefit from elective valve replacement. These criteria should probably not be listed in future practice guidelines. Even limiting symptoms on exercise testing had a positive predictive accuracy of only 57% in the present study when including all patients and all symptoms. When considering only physically active patients <70 years, positive predictive accuracy rose to 79%. Apparently, it also matters which symptoms occur on exercise testing: in the entire study group, 83% of patients with dizziness developed spontaneous symptoms compared with only 50% of patients with chest tightness and 54% of patients with breathlessness. The most likely explanation for these findings is, that breathlessness on exercise may be difficult to interpret in patients with only low physical activity and particularly in older patients (>70 years). In this group it will be difficult to decide whether breathlessness on exercise is indeed a symptom of AS. Thus, symptoms on exercise appear to justify valve replacement in asymptomatic patients primarily when they are <70 years and physically active.

Therefore, one can assume that exercise testing may not be sufficient for risk stratification in a significant portion of patients and the question arises whether alternatives are available.

Alternatives to exercise testing

So far, neither pressure gradient and valve area at rest nor their changes with exercise could be shown to allow prospective risk stratification. This was also confirmed by the present study with respect to rest measurements. Positive predictive value was low and by multivariate analysis including symptoms, blood pressure response, ST changes, transvalvular velocity, and valve area, only limiting symptoms on exercise testing turned out to be an independent predictor of symptom onset within 12 months.

We could previously demonstrate that the presence of moderate or severe valve calcification together with an observed rapid haemodynamic progression (increase >0.3 m/s in peak transaortic velocity within 1 year) identifies high-risk patients in whom elective surgery may be reasonable (80% event rate within 2 years). This criterion has been included as a class IIa indication in the European guidelines. More recently, we could report that plasma levels of neurohormones may predict the symptom-free survival in AS. Patients with brain natriuretic peptide (BNP) levels <130 pg/mL or N-terminal BNP levels <80 pmol/L were unlikely to develop symptoms within 9 months (symptom-free survival close to 90%), whereas those with higher levels frequently required surgery within this time period (symptom-free survival <50%).

Management of asymptomatic AS: current status

Currently available data appear to allow the following conclusions:

- Risk stratification is critical for the management of asymptomatic AS, particularly for those who have reached a valve area <1.0 cm². Those patients should be identified who are close to symptom development and would, therefore, likely benefit from elective surgery.
- A normal exercise test indicates a very low likelihood of symptom development within 12 months. It appears safe to follow these patients in 6–12 months intervals depending on symptom development within 12 months and valve replacement should be recommended.
- Breathlessness on exercise in patients with otherwise low physical activity and in those >70 years has a relatively low positive predictive value. Exercise testing is less helpful in this patient group. The test should, therefore, primarily be recommended for physically active patients <70 years.
- Abnormal blood pressure response and/or ST segment depression without symptoms on exercise have a low positive predictive value and may not justify elective surgery.
- The presence of moderate or severe valve calcification together with an observed rapid haemodynamic progression (increase >0.3 m/s in peak velocity within 1 year) identifies high-risk patients in whom elective surgery should be considered.
- In the rare asymptomatic patient with left ventricular dysfunction in the absence of other aetiologies, elective surgery is recommended.
- Recent data suggest that high neurohormone levels may identify high-risk patients who benefit from elective surgery. As this information is particularly easy to obtain and measurements could easily be repeated at every visit, further efforts should be made to confirm the available data in large patient cohorts.

References


