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Stress Testing in Patients with Asymptomatic Severe Aortic Stenosis

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1. Introduction

The natural history of valvular aortic stenosis (AS) is characterized by a protracted symptom free period during which morbidity and mortality are very low. During this period the average decrease in the aortic valve area is about 0.1 cm² per year (1-4), although it is impossible to predict the rate of progression in an individual patient. For this reason, regular clinical follow-up is standard of care in all patients with asymptomatic mild to moderate AS (1). The onset of symptoms such as: angina, syncope, or heart failure significantly changes prognosis, with an average survival of 60% at 1 year and has increased risk of sudden cardiac death (5-7).

2. Identifying high risk asymptomatic patients with severe AS

Aortic valve replacement (AVR) is the current standard treatment for patients with severe AS who have symptoms or left ventricular (LV) systolic dysfunction (1, 2). However, the best treatment strategy in asymptomatic patients with severe AS and preserved LV systolic function is debated (8). Conservative approach with a watchful waiting is generally favored although the utility of early elective AVR has been debated in subset of high risk patients. Several predictors have been proposed which predict poor outcomes in patients with asymptomatic severe AS. These include stress testing, severity of AS, rapid hemodynamic progression of AS, elevated left atrial pressure as assessed by E/E′ using tissue Doppler imaging or atrial natriuretic peptide (NPA). Of these stress testing is the most validated way of identifying asymptomatic patients who may benefit from AVR (9-10).

3. Importance of stress testing

Improved life expectancy has resulted in there being more elderly patients with AS, in whom the true symptoms may be underestimated (11). Given the slow progression of disease, patients may reduce their level of physical activity to avoid or minimize symptoms and be unaware of subtle changes in effort tolerance or attribute it to deconditioning or a physical impact due to aging. The accurate determination of symptoms is crucial; as symptoms increase the risk of sudden death worsens as well as protend an overall worst prognosis (12-13).

Valvular heart disease has a varying dynamic components which depend on loading conditions, ventricular contractility, ventricular contractile reserve, volume-dependent compliance of heart chambers, and ventricular arterial coupling. The current primary role of stress testing in asymptomatic severe aortic stenosis is to provide an objective assessment of functional capacity which is of the utmost importance in patients who often adapt and reduce their physical activity, thus masking the symptoms. In addition, exercise testing can identify changes in valvular as well as ventricular function and the changes in the valve gradient with the changes in forward flow and to differentiate true vs. pseudo aortic stenosis in the setting of low cardiac output.

4. Indications of stress testing

Valve replacement is indicated in the presence of symptoms and severe aortic stenosis. In such patients, stress testing is contraindicated. In contrast, exercise testing is recommended in asymptomatic patients with severe aortic stenosis. Exercise testing is strongly advocated in the European guidelines and is a grade IIb recommendation in the American College of Cardiology/American Heart Association (ACC/AHA) 2006 guidelines (1, 2). There is no prospective clinical trial on the use of stress testing in asymptomatic patients with severe AS as an indicator for aortic valve replacement. However, several retrospective small clinical studies have evaluated the predictive value of stress testing in asymptomatic severe AS (14-26), as shown in figure 1 which has been adapted from the American Journal of Cardiology (9). In this meta-analysis there were no sudden deaths in the patients with normal stress test results after 1 year of follow-up, while 5% with abnormal stress test results had sudden cardiac death. Overall, 52 of 253 patients (21%) with normal stress test results had adverse cardiac events, compared with 156 of 238 (66%) with abnormal stress test results. Stress testing can be used for risk stratification and for deciding on the timing of AVR in asymptomatic patients with severe AS.
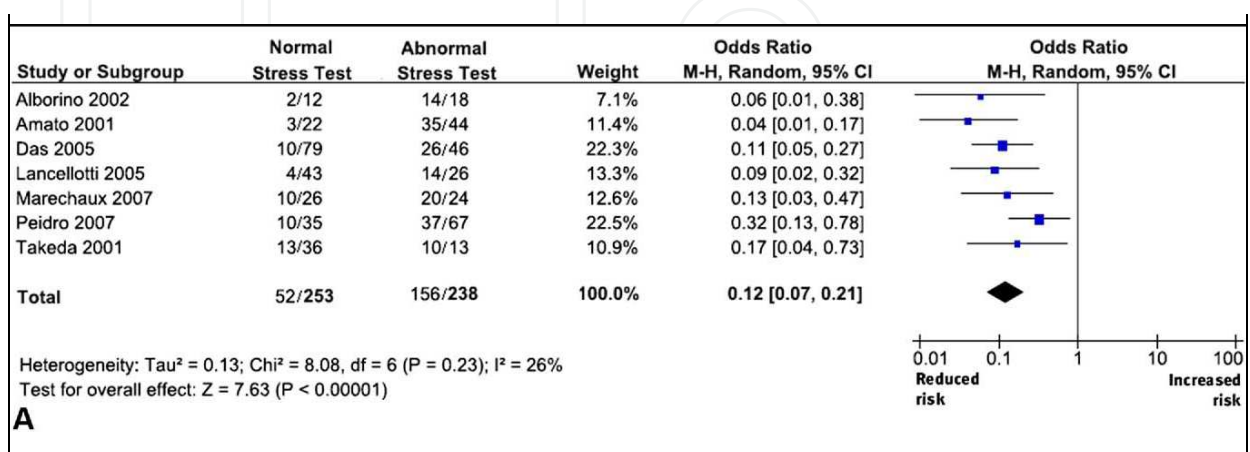
Study or Subgroup	Normal Stress Test	Abnormal Stress Test	Weight	Odds Ratio M-H, Random, 95% CI
Alborino 2002	2/12	14/18	7.1%	0.06 [0.01, 0.38]
Amato 2001	3/22	35/44	11.4%	0.04 [0.01, 0.17]
Das 2005	10/79	26/46	22.3%	0.11 [0.05, 0.27]
Lancellotti 2005	4/43	14/26	13.3%	0.09 [0.02, 0.32]
Marechaux 2007	10/26	20/24	12.6%	0.13 [0.03, 0.47]
Peidro 2007	10/35	37/67	22.5%	0.32 [0.13, 0.78]
Takeda 2001	13/36	10/13	10.9%	0.17 [0.04, 0.73]
Total	52/253	156/238	100.0%	0.12 [0.07, 0.21]

Heterogeneity: Tau² = 0.13; Chi² = 8.08, df = 6 (P = 0.23); I² = 26%
Test for overall effect: Z = 7.63 (P < 0.00001)

A

Fig. 1. Utility of stress testing in predicting cardiac events in patients with Severe AS

5. Prevalence of stress testing

The results of the Euro Heart Survey on Valvular Heart Disease revealed that stress testing is underused in Europe. Only about 5.7% of asymptomatic patients with severe AS undergo exercise testing (27). The reason for the low usage of stress testing include: concern about safety, lack of awareness of its utility and lack of randomized, prospective trials. Stress testing is considered low risk when performed in asymptomatic patients under medically supervised conditions (9).

6. Types of stress test

A symptom-limited exercise test is more physiologic than a dobutamine test and may be performed safely. Treadmill or upright bicycle ergometry are the most frequent tests and the choice is based on individual experience or equipment available in a given laboratory. Symptom-limited graded bicycle exercise in a semi-supine position may be preferable since it allows continuous two dimensional and Doppler echocardiographic examinations. Dobutamine stress echocardiography may be used to assess aortic valve compliance by plotting effective orifice area against flow at each stage of the dobutamine test. However, in asymptomatic patients with severe aortic stenosis it is less likely to be helpful in identifying patients with occult symptoms. In asymptomatic patients with severe AS exercise testing should be repeated every 6 months for severe aortic stenosis and every year for moderate aortic stenosis (14). Testing should be performed in laboratory equipped with a resuscitation cart in the presence of a physician so that potential complications can be treated effectively.

7. Parameters to be evaluated on stress testing

Total exercise time, maximum workload, peak heart rate and blood pressure and the reason for stopping the test are recorded. The criteria of an abnormal exercise test provided in the European recommendations are listed in table 1. It is essential to record the development of symptoms carefully, such as objective dyspnea, angina, dizziness or near-syncope. When Doppler echocardiography is obtained during exercise, aortic velocity–time integral can be regularly recorded from the same window to assess changes in mean pressure gradient.

The assessment of exercise capacity often identifies symptoms that patient has not reported and has important prognostic significance as outlined in multiple clinical studies but simple stress testing fails to identify patients at higher risk for rapid disease progression (9). A representative example of ST changes during stress testing in a patient with AS is shown in figure 2.

8. Pathophysiology during exercise

Multiple studies have shown that the LV response to exercise is abnormal in apparently asymptomatic AS (24-29). Patients with apparently asymptomatic AS with symptoms detected during exercise testing have lower peak myocardial oxygen consumption and lower peak stroke index than those patients who remained asymptomatic (24). Studies have shown that normal increases in stroke volume on exercise in patients with mild and

Symptoms during exercise: dyspnea, angina, syncope or near syncope
Fall in blood pressure or <20 mm Hg rise in systolic blood pressure during exercise
<80% of normal level of exercise tolerance
>2 mm ST segment depression during exercise (horizontal or down sloping, in comparison to baseline, not attributable to other causes)
Ventricular arrhythmias

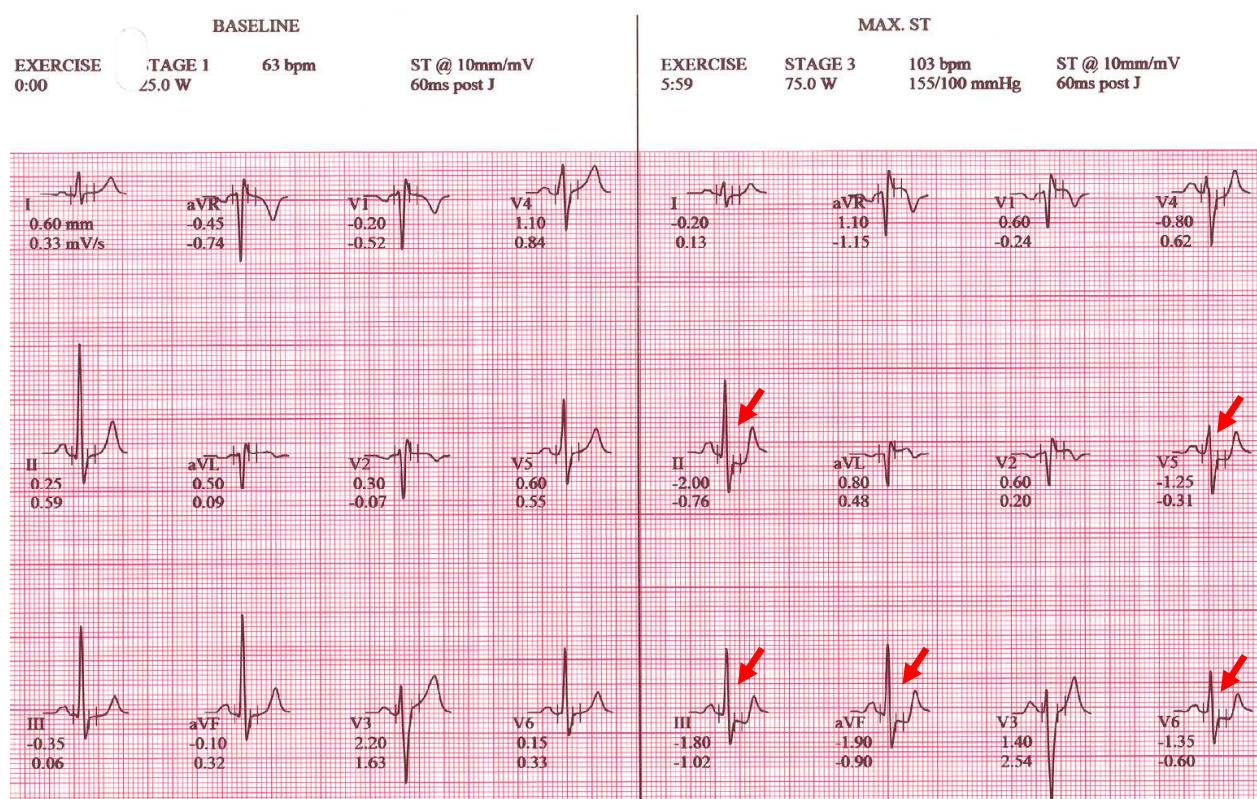Table 1. Criteria of an abnormal exercise test in patients with asymptomatic aortic stenosis

Fig. 2. A representative example of ST changes in infero-lateral leads during stress testing in a patient with AS

moderate AS but stroke volume was significantly decreased in symptomatic patients with severe AS both at rest and on exercise. Otto et al observed a decrease in stroke volume on exercise in asymptomatic patients with AS using Doppler echocardiography (15). Severe calcification has been reported to sometimes represent or be associated with a faster progression of the AS and a higher risk for the rapid progression to symptoms and events (8). Lancellotti et al demonstrated that an abnormal exercise response in patients with asymptomatic AS was mediated by impaired contractile reserve and a relatively large increase in gradient (21). Mare´chaux et al. showed the utility of risk stratification based on

the increase in the mean pressure gradient of >18mmHg as the most predictive of outcomes (24). Peak exercise LV ejection fraction is another parameter for risk stratification in patients with asymptomatic AS, if LVEF does not increase by ≥5% it indicates impaired contractile reserve, and it is suggestive of limited LV functional reserve (23). Aortic physiology due to altered compliance may play a role in the pathophysiology and progression of the disease, and this may become evident on stress testing. Some authors have noted a blunted fall in systemic vascular resistance associated with exercise induced symptoms (24-26). In short, AS, coronary disease and reduced aortic compliance exist as a continuum, and stress testing can play the critical role of revealing symptoms and subsequent referral for intervention.

9. Clinical utility of stress testing

The current ESC guidelines recommend AVR in patients who develop cardiac symptoms (class I) or who develop asymptomatic hypotension (class IIa) or asymptomatic ventricular arrhythmias (class IIb) during the exercise test (2). In contrast, the ACC/AHA guidelines recommend AVR if symptoms or hypotension appear during the exercise test (class IIb) (1).The divergent recommendations can be explained by the lack of definitive evidence from prospective clinical trials and subsequent different interpretation by the two groups. While, exercise stress testing is recommended in the management of asymptomatic patients with severe AS, exercise stress echocardiography is not routinely recommended in the current guidelines.

No randomized trial has been conducted in patients with asymptomatic severe aortic stenosis (30). The risk of sudden death is low and is usually considered to be lower than the risk of operation. However, the mortality is rather high early after the onset of symptoms or if the patient is on a surgical waiting list. In some patients, symptoms are not identified, especially in elderly subjects who are rather inactive (31). On the other hand, dyspnea and chest pain may be non-specific. Exercise testing can identify a limited exercise capacity and unmask symptoms in about one-third of the apparently asymptomatic patients (32-33). The development of symptoms during exercise seems to be more predictive than the other criteria, but this needs to be confirmed. A significant increase in mean transaortic pressure gradient predicts a higher risk of cardiac events and has been shown to provide incremental prognostic information over clinical, resting Doppler echocardiographic and exercise testing (21,24). Further studies using novel echocardiographic techniques may provide additional understanding of the hemodyamics in patients with severe asymptomatic AS and refine the utility of stress testing in risk stratification of AS patients for AVR either surgical or by newer percutaneous techniques (34).

In summary, stress testing appears to be of value in unmasking the symptoms in otherwise asymptomatic patients who may have denial or who unconsciously limit their activity secondarily to progressive AS. In addition, in elderly patients, symptoms may not be identified because of inactivity, thus in these groups of asymptomatic patients stress testing readily provides an objective assessment of functional status.

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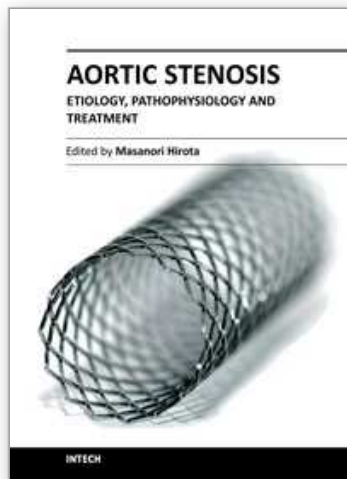
Aortic Stenosis - Etiology, Pathophysiology and Treatment

Edited by Dr. Masanori Hirota

Currently, aortic stenosis (AS) is the most prevalent valvular disease in developed countries. Pathological and molecular mechanisms of AS have been investigated in many aspects. And new therapeutic devices such as transcatheter aortic valve implantation have been developed as a less invasive treatment for high-risk patients. Due to advanced prevalent age of AS, further discovery and technology are required to treat elderly patients for longer life expectancy. This book is an effort to present an up-to-date account of existing knowledge, involving recent development in this field. Various opinion leaders described details of established knowledge or newly recognized advances associated with diagnosis, treatment and mechanism. Thus, this book will enable close intercommunication to another field and collaboration technology for new devices. We hope that it will be an important source, not only for clinicians, but also for general practitioners, contributing to development of better therapeutic adjuncts in the future.

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