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REVIEW

Exercise echocardiography in severe asymptomatic aortic stenosis

L'échocardiographie à l'effort dans la sténose aortique sévère asymptomatique

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Summary The management of asymptomatic patients with severe aortic stenosis is challenging. Unfortunately, evaluation of symptoms such as dyspnoea remains subjective. The use of exercise echocardiography may help to predict major events in patients with asymptomatic severe aortic stenosis. This article explains how to perform the test and discusses which echocardiographic measurements should be obtained, focusing on the diagnostic and prognostic value of these measurements. An increase in mean transaortic pressure gradient ≥ 18 mmHg predicts a worse prognosis in patients with severe aortic stenosis. The absence of left ventricular contractile reserve also has an important prognostic impact. Evaluation of filling pressures and looking for a worsening or a new mitral regurgitation are also part of the exam. Further studies are required to determine whether surgery should be recommended in the presence of an abnormal exercise echocardiogram in severe asymptomatic aortic stenosis.

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MOTS CLÉS

Rétrécissement
aortique ;
Échocardiographie ;
Effort ;

Résumé La prise en charge des patients présentant un rétrécissement aortique (RA) sévère asymptomatique reste difficile. L'évaluation des symptômes tels que la dyspnée est souvent subjective. L'utilisation de l'échocardiographie à l'effort permet de mieux stratifier le risque de survenue d'événements majeurs. Cet article détaille les différentes mesures utiles lors de l'échocardiographie à l'effort ainsi que la valeur diagnostique ou pronostique de ces mesures. Une augmentation du gradient transaortique moyen de supérieure ou égale à 18 mmHg prédit

Abbreviations: AS, aortic stenosis; BNP, brain natriuretic peptide; E/E' , ratio of early diastolic mitral inflow velocity to early annular diastolic velocity; LV, left ventricular; LVEF, left ventricular ejection fraction; MR, mitral regurgitation.

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Fonction
ventriculaire ;
Pronostic

un moins bon pronostic chez les patients avec RA sévère. L'absence de réserve contractile du ventricule gauche à l'effort est également un facteur pronostique important. Enfin, l'évaluation des pressions de remplissage et la recherche d'insuffisance mitrale à l'effort font partie intégrante de l'échocardiographie à l'effort dans cette population. D'autres études sont requises pour valider l'indication de procéder à un remplacement valvulaire aortique précoce suite à une échocardiographie d'effort anormale chez le sujet avec RA sévère asymptomatique.

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Introduction

Valvular aortic stenosis (AS) is the most prevalent valvular heart disease in Europe [1]. The European Society of Cardiology guidelines recommend prompt aortic valve replacement when patients with severe AS are symptomatic or develop left ventricular (LV) dysfunction (ejection fraction < 50%) [2]. However, the management of asymptomatic patients with severe AS remains challenging. Although symptoms of angina and syncope are relatively easy to identify, dyspnoea, fatigue or dizziness are more difficult to elicit in sedentary and elderly patients, and remain substantially subjective. In addition, the operative risk of asymptomatic patients with severe AS is probably equivalent to or even higher than the risk of sudden death. Indeed, the risk of sudden death in these patients is around 1% per year and is a rare phenomenon in patients without preceding symptoms [3]. To help to guide clinician decisions, exercise stress testing is advocated strongly by the European Society of Cardiology guidelines, and is a Class IIb recommendation by the American College of Cardiology/American Heart Association [2,4]. Nevertheless, exercise stress testing does not discriminate accurately between the signs and symptoms of masked symptomatic severe AS and severe coronary artery disease. In this situation, stress echocardiography may help to make a diagnosis of ischaemic heart disease in patients with severe asymptomatic AS. One of the most important roles of stress echocardiography in patients with AS is to discriminate the haemodynamic effects on the valve itself and on the left ventricle, and to assess the mechanisms behind a positive exercise stress test in asymptomatic severe AS [5]. This article describes how to perform exercise echocardiography in asymptomatic severe AS, which echocardiographic measurements should be obtained and how to interpret exercise-induced changes.

How to perform stress echocardiography in asymptomatic severe aortic stenosis

Before performing this test, it is mandatory to ensure that the patient is truly asymptomatic. Some patients may reduce their level of daily activities as an adaptation to the disease. Table 1 summarizes the contraindications to perform an exercise stress test in patients with severe AS. An exercise echocardiogram should be performed under the strict supervision of an experienced physician, with close monitoring of heart rate and blood pressure. A symptom-limited exercise with a stepwise protocol is used. Dobutamine echocardiography has been analysed in the

assessment of valve compliance but it is less physiological and the clinical value of valve compliance requires further study [6,7]. A post-exercise echocardiogram, after treadmill or upright bicycle ergometry, can be obtained but a supine or a semi-supine bicycle exercise test is probably preferable. First, there is a reduced risk of haemodynamic collapse in this position and second, it allows continuous two-dimensional and Doppler echocardiographic examination. The sensitivity and specificity of having an abnormal test may be influenced by the position. The treadmill test may induce dizziness and angina more frequently, and may provide higher rate-pressure product at peak exercise; it has demonstrated a higher sensitivity than cycling for the diagnosis of ischaemic heart disease [8]. However, exercise in the supine position may enhance ST-segment depression, increasing the sensitivity of the test [9]. It should also be emphasized that abnormal stress testing was described initially in the context of coronary heart disease and fewer data are available for valvular heart disease. In particular, the evolution of systolic blood pressure differs according to the patient's position. A decrease in blood pressure – a classical criterion of positivity – is indeed observed less frequently in the supine position. Special attention should be given to patients with confounding factors like chronic obstructive pulmonary disease or obesity. In the first case, breathlessness may be the result of pulmonary disease or the valve disease, or both. In this setting, a cardiopulmonary exercise test with gas exchange may be useful to distinguish whether the symptoms are related to cardiac, pulmonary or peripheral limitations.

A stepwise protocol of 25 watts every 2 min is used. Electrocardiography is monitored continuously and blood pressure is measured every 2 min. Evaluation of symptoms such as angina, syncope or dizziness is mandatory during exercise. At the end, maximum workload, total exercise time, peak heart rate and blood pressure, and the reason for

Table 1 Contraindications to perform an exercise stress test in patients with severe aortic stenosis.

Contraindications

Symptoms (angina, heart failure symptoms, syncope)
Low left ventricular ejection fraction (< 50%)
High blood pressure (systolic > 200 mmHg or diastolic > 110 mmHg)
Uncontrolled or symptomatic arrhythmias
Systemic illness
Physically or mentally incapable of performing an exercise stress test adequately

Table 2 Criteria of an abnormal exercise test in patients with asymptomatic aortic stenosis.

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

stopping the examination are recorded. The exercise test is considered abnormal in the presence of at least one of the following criteria: symptoms; fall in systolic blood pressure or a rise < 20 mmHg during the exercise; < 80% of normal level of exercise tolerance; > 2 mm ST-segment depression compared with resting electrocardiography; and occurrence of ventricular arrhythmias (Table 2).

Which echocardiographic measurements?

Performing exercise stress echocardiography in valve disease requires in-depth training with a learning curve. In the case of AS, obtaining the maximal gradients is sometimes limited by the supine position of the patient. The right parasternal position is not suitable on a left tilting table. The duration of exercise should be long enough to record different variables. This part of the article will focus on the echocardiographic measurements that are important to obtain in patients with asymptomatic severe AS. A complete echocardiographic examination should be performed before the exercise stress test in all patients. Moreover, at

the time of echo, the measurement of systolic blood pressure is mandatory, as it could affect the assessment of AS severity. New measurements, such as energy loss index and global LV afterload (valvulo-arterial impedance) are of growing interest and may allow the identification of patients with paradoxical low-flow AS and preserved LV function [10]. Echocardiographic measurements may be separated into valvular components, LV components and other components, such as mitral regurgitation (MR) and pulmonary pressures (Table 3). Of course, exploring for concomitant coronary artery disease is part of the examination. The occurrence of new wall motion abnormalities during stress echocardiography in patients with AS should be interpreted with caution because it not only reflects the presence of exhausted coronary flow reserve but could also be a sign of significant coronary artery disease. In this situation, a coronary angiography should be scheduled in cases of low ischaemic threshold and extensive exercise-induced ischaemia.

Valvular components

Lancellotti et al. have demonstrated that an increase in mean transaortic pressure gradient of ≥ 18 mmHg with exercise predicts a poor outcome in asymptomatic patients with an aortic valve area < 1.0 cm² [11]. Recently, in a larger population, the same group demonstrated that an abnormal response to exercise was determined by a larger increase in mean transaortic pressure gradient and a limited contractile reserve (a small change in ejection fraction) [12]. In this study, a smaller, exercise-induced change in aortic valve area was associated with an increase in mean transaortic gradient. Patients with severe AS who have this kind of response with exercise have fixed severe AS, with a greater leaflet thickness and less valvular compliance (Fig. 1). It should be acknowledged that a limited rise in transaortic gradient during exercise could involve not only the cardiac haemodynamic response to

Table 3 Abnormal stress echocardiographic measurements in asymptomatic aortic stenosis.

Component	Findings
Valvular components	
Aortic valve area	Increased: compliant valve Stable: fixed and non-compliant valve
Mean gradient	Increased: fixed and non-compliant valve or presence of contractile reserve (should be correlated to ejection fraction) Decreased: no contractile reserve
Left ventricular components	
Systolic function	
Ejection fraction	Increased: presence of contractile reserve Stable or decreased: absence of contractile reserve
Strain imaging by TDI or speckle tracking	Decreased: absence of contractile reserve
Diastolic function	
E/E'	Increased: elevated filling pressure
Other components	
Mitral regurgitation	Worsening or occurrence: elevated global afterload
Transtricuspid gradient	Increased > 50 mmHg: elevated pulmonary pressure

E/E' : ratio of early diastolic mitral inflow velocity to early annular diastolic velocity; TDI: tissue Doppler imaging.

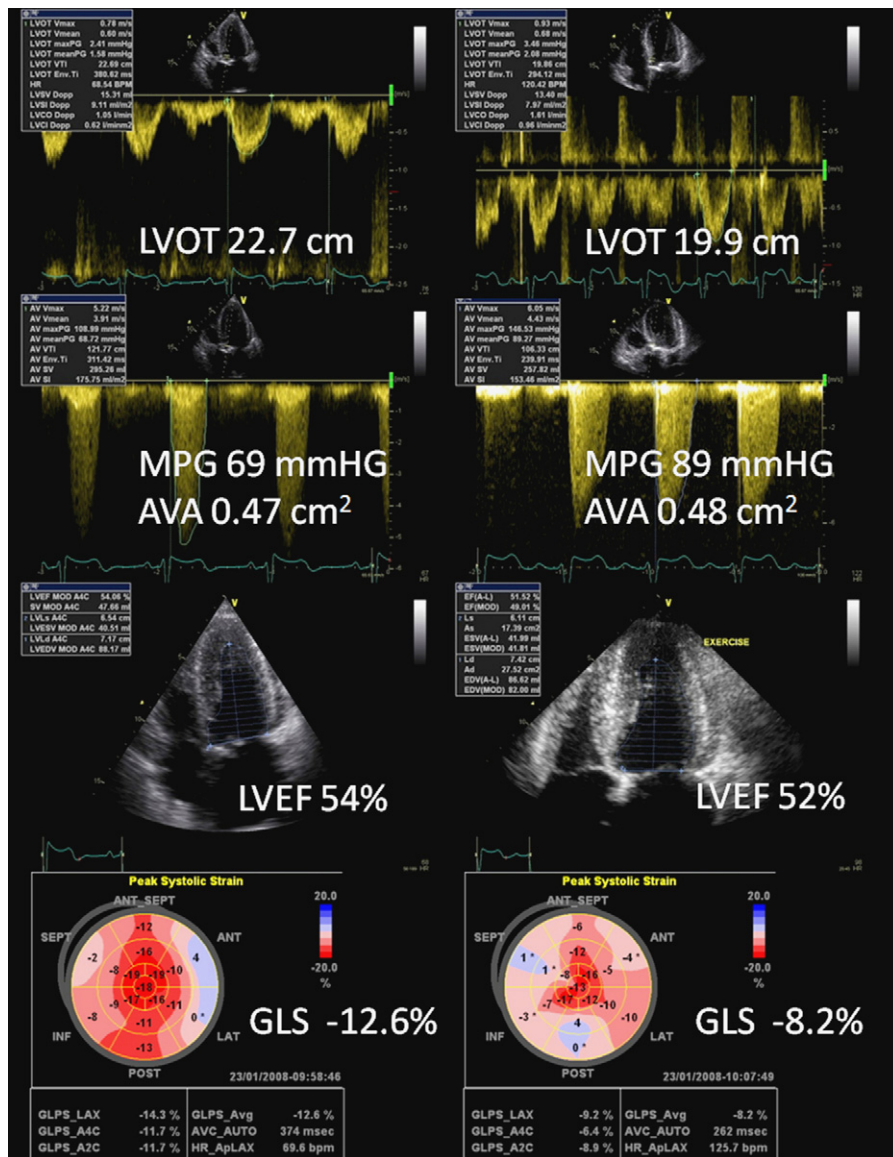


Figure 1. Two-dimensional echocardiography, Doppler findings and global longitudinal strain by two-dimensional strain method in a patient with asymptomatic severe aortic stenosis, absence of contractile reserve and increase in transaortic pressure gradient with exercise. This patient has a fixed severe aortic stenosis, with no modification of aortic valve area at exercise. Left: rest recordings with LVEF > 50%, high transaortic pressure gradients and altered longitudinal function. Right: exercise recordings demonstrating absence of increase in LVEF, increase in mean transaortic pressure gradients (20 mmHg) and decreased GLS. AVA: aortic valve area; GLS: global longitudinal strain; LVOT: left ventricular outflow tract time velocity integral; MPG: mean transaortic pressure gradient.

exercise but also several peripheral components, such as vascular dysfunction related to cardiovascular comorbid conditions and skeletal muscle deconditioning. Changes in transaortic pressure gradient at exercise in severe AS should be interpreted according to the global condition of the patient.

Myocardial components

Systolic function

Left ventricular ejection fraction (LVEF) increases with exercise in normal subjects. In patients with severe AS, LVEF may increase, decrease or remain unchanged. Marechaux et al. demonstrated that patients with $\Delta\text{LVEF} \geq 0\%$ at exercise

have a significantly lower event-free survival than patients with no increase in ejection fraction [13]. Lancellotti et al. also demonstrated that patients with a small change in ejection fraction have a poor prognosis [12]. In the study by Marechaux et al., patients with an increase in transaortic gradients also had an increase in LVEF. Compared with the results of Lancellotti et al., this discrepancy may be explained by a different population of patients with severe AS. Patients with an increase in both LVEF and transaortic gradient at exercise probably have a better contractile reserve and/or a more compliant valve (Fig. 2).

Recently, a biphasic response to exercise in patients with asymptomatic severe AS has been described by our

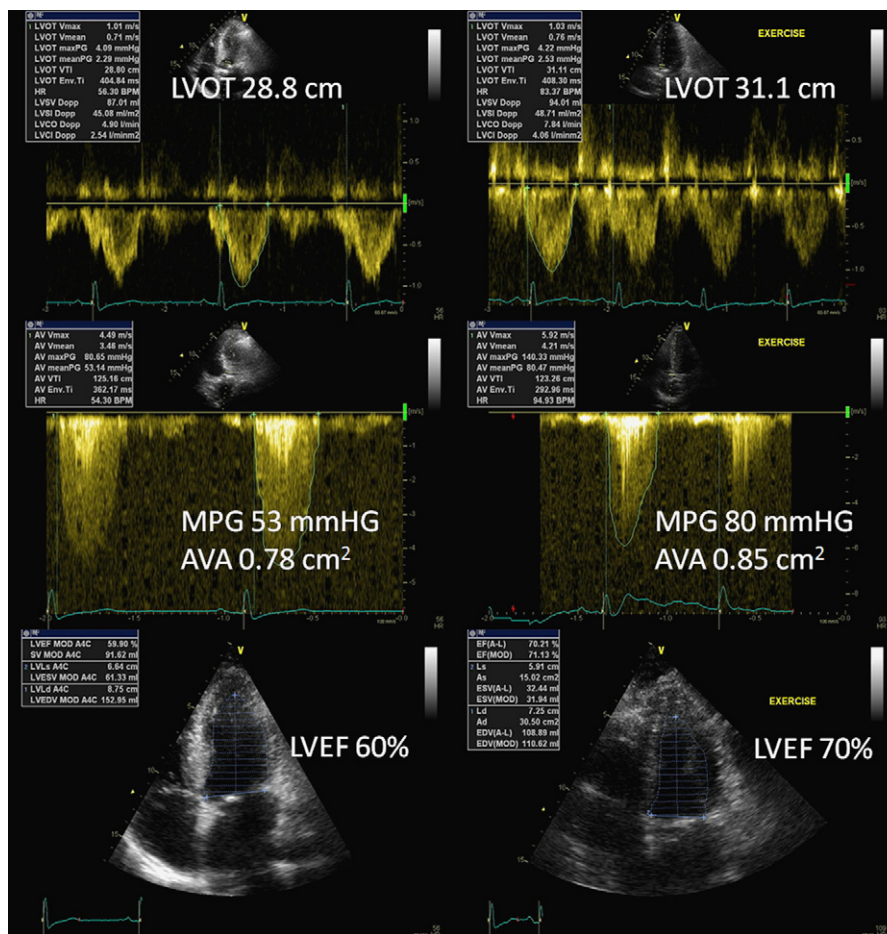


Figure 2. Two-dimensional echocardiography and Doppler findings in a patient with asymptomatic severe AS showing the presence of contractile reserve (MPG and LVEF increased at exercise) and a still compliant aortic valve. Left panel: rest recordings. Right panel: exercise recordings. AVA: aortic valve area; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract time velocity integral; MPG: mean transaortic pressure gradient.

group [14]. As seen in Fig. 3, in these patients, the heart adapts appropriately to increased afterload initially. Indeed, there is an increase in longitudinal deformation and a significant rise in transaortic pressure gradient. The haemodynamic changes observed during exercise could modulate the changes in transaortic pressure gradients and in LV function. Normally, at low level, the increase in heart rate is usually accompanied by a positive inotropic effect and an increase in the force–contraction relationship. At higher exercise level, the increase in heart rate is accompanied by an increase in cardiac output only by augmenting the heart rate, as the stroke volume has reached its peak value. In the presence of LV hypertrophy, the increase in heart rate could, however, be associated with a rather negative inotropic effect due to the presence of exhausted coronary flow reserve. In this situation, the transaortic pressure will decrease, reflecting the mismatch between LV load and contractility (reduction of long-axis function). A biphasic response could be observed if the transaortic pressure is monitored continuously during the test. The rapid rise in pressure gradient could be missed or absent in patients with severe reduction in coronary flow reserve. Interestingly, this biphasic response can occur in the absence of significant coronary heart disease.

Few studies have evaluated contractile reserve at exercise in patients with AS. Van Pelt et al. have shown that the increase in peak systolic velocity of the lateral mitral annulus measured after exercise by tissue Doppler imaging was lower in patients with moderate AS [15]; this small change was correlated with lower exercise capacity and a higher plasma concentration of brain natriuretic peptide (BNP). The evaluation of strain and strain rate by tissue Doppler imaging or by speckle tracking probably has the potential to provide more information on contractile reserve during exercise in patients with severe AS, to predict subclinical LV dysfunction. Lafitte et al. demonstrated recently that global longitudinal strain at rest in asymptomatic patients with severe AS was significantly lower than in a control group [16]. This was especially true for basal longitudinal segments even in the presence of similar LVEF. In this study, patients with global longitudinal strain $< -18\%$ and basal longitudinal strain $< -13\%$ experienced inadequate response to treadmill exercise more frequently. Furthermore, patients with basal longitudinal strain $< -13\%$ presented more cardiac events at follow-up. Interestingly, circumferential and radial strains were similar in patients with AS compared to control subjects in this study. Whether these observations are real similarities

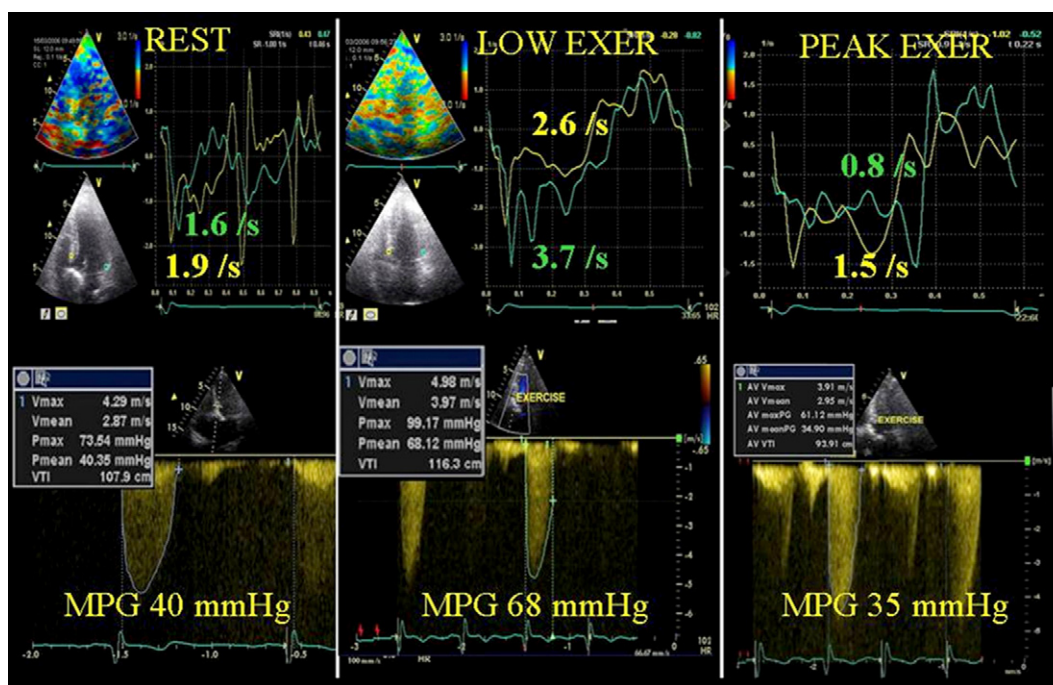


Figure 3. Exercise Doppler echocardiographic evaluation of a patient with severe asymptomatic aortic valve stenosis and a biphasic response to exercise. Left panel: rest recordings demonstrating a mean transaortic pressure gradient of 40 mmHg and the basal state of the long-axis function, with a peak negative strain rate obtained off-line by tissue Doppler reconstruction at the level of the septal and lateral walls. The aortic valve area of this patient was 0.78 cm² at rest. Centre panel: low-level exercise recordings demonstrating the increase in longitudinal function and a significant rise of 28 mmHg in transaortic pressure gradient. Right panel: peak-level exercise recordings showing a decrease in transaortic pressure gradient related to significant impairment of left ventricular function (decrease of peak negative strain rate compared with the basal state). No inducible ischaemia was observed during the test and the coronary angiogram revealed no concomitant artery stenosis. MPG: mean transaortic pressure gradient.

or are related to technical issues requires further studies.

Diastolic function

Elevation of filling pressure and diastolic dysfunction could explain exertional dyspnoea in patients with severe AS [17]. The ratio of early diastolic mitral inflow velocity to early diastolic annular velocity (E/E'), recorded by pulsed-wave Doppler and tissue Doppler echocardiography, provides an accurate estimate of LV filling pressure at rest [18]. Furthermore, $E/E' > 13$ at exercise has been shown previously to correlate with high filling pressures, assessed by invasive measurements and with exercise capacity [19]. More recently, in a group of 2867 patients, Grewal et al. identified that exercise capacity was highly associated with abnormal LV diastolic function expressed by an $E/E' > 15$ at rest or at exercise [20]. However, all patients with valvular disease were excluded from these studies. Indeed, few studies have evaluated the variation of E/E' at exercise in AS (Fig. 4). However, an $E/E' > 13$ at rest identifies patients with LV end-diastolic pressure > 15 mmHg with a sensitivity of 93% and specificity of 88% [21]. A recent study by Dalsgaard et al. demonstrated that in patients with severe AS, the ratio of peak E during exercise to E' at rest better estimates pulmonary capillary wedge pressure [22]. In this study, patients with high pulmonary capillary wedge pressure showed a similar increase in E and E' at exercise, resulting in an unchanged E/E' ratio, probably because E' is not

preload independent at high filling pressure [23]. Additional evaluation is needed to confirm these contrasting results.

Other components

It is well known that mitral regurgitation (MR) may occur concomitantly with AS. However, the prevalence of this phenomenon may vary between 13 and 90% among different series of patients [24]. Some of these patients have, however, functional MR related directly to the increased overload of the elevated transaortic pressure gradient. In a study of 128 patients with asymptomatic AS, new or worsening MR occurred in 34% of patients [12]. Patients with symptoms during exercise developed or increased MR more frequently than patients who remained asymptomatic. Furthermore, in our experience, some patients may have an elevation of transtricuspid gradient that often follows the development of MR and may explain exertional dyspnoea. Elevation of pulmonary pressure may also be related to increasing filling pressures of the hypertrophied left ventricle at exercise [25].

Prognostic value of stress echocardiography in asymptomatic aortic stenosis

The safety of exercise testing is established in asymptomatic severe AS [2]. However, in the Euro Heart Survey on valvular

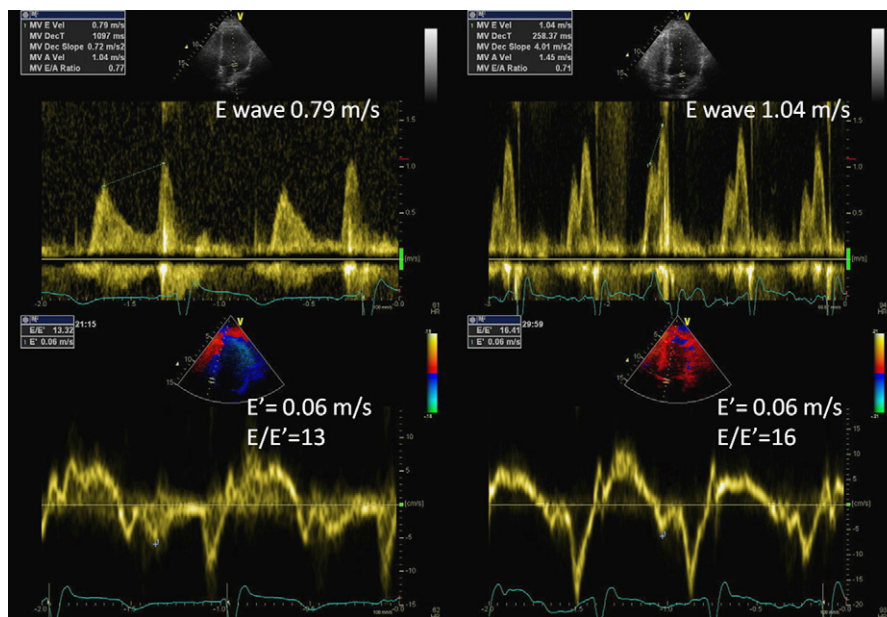


Figure 4. The ratio of early diastolic mitral inflow velocity to early diastolic annular velocity (E/E') recorded by pulsed-wave Doppler and tissue Doppler echocardiography in a patient with asymptomatic severe AS. Left panel: findings at rest. Right panel: recordings at exercise demonstrating the increase in E wave velocity but no modification of the E' velocity.

heart disease, only 7.9% of the entire cohort was submitted to a stress test, which was exercise electrocardiography in 70% of patients [1]. In severe AS, an exercise test was performed in 5.9%, while it is recommended by the American College of Cardiology/American Heart Association guidelines [4]. No randomized trial has been conducted in patients with asymptomatic severe AS, which probably explains, in part, the difficulty for physicians in managing this condition. Performing a stress test may identify up to one-third of apparently asymptomatic patients [26]. In contrast, a normal test reveals an excellent prognosis at one year [27]. A recent meta-analysis of stress testing in AS demonstrated no sudden deaths in patients with a normal stress test, whereas 5% with an abnormal test had sudden cardiac death. Moreover, 66% of patients with an abnormal stress test had cardiac events at follow-up [28]. A paper by Weisenberg et al. questioned the added value of exercise echocardiography in severe asymptomatic AS [29]; however, patients were studied with treadmill exercise stress echocardiography and, in our experience, this technique may have some limitations in terms of adequately studying the valvular and myocardial components of AS at exercise. Lastly, the prognostic value of stress echocardiography has not been validated against models that include BNP. The goal of risk stratification in patients with asymptomatic AS is to provide to the physician enough arguments to refer their patient for early elective aortic valve surgery. Instead of classical measurements (degree of calcifications, rate of progression, presence of coronary artery disease), BNP has been shown recently to be of interest in terms of predicting clinical outcome. A recent paper from the groups of Monin and Lancellotti has proposed a risk score that includes sex, peak aortic velocity and the natural logarithm of BNP to stratify the risk of patients with asymptomatic severe AS [30]. In this study, two risk groups (one low risk and one high risk) were clearly identifiable. The low-risk patients could

be followed up medically until symptoms occur whereas the high-risk group should be referred to surgery. However, the question remains open in the intermediate group, where the exercise test could obviously be of additive value.

Conclusion

Exercise stress testing is a good method for identifying patients with apparently asymptomatic severe AS. As described in this paper, the incremental value of exercise echocardiography is of prognostic importance, as it identifies patients at risk of cardiac events [31]. Exercise echocardiographic measurements define more precisely how the aortic valve and the ventricle respond to exercise. Exercise stress testing may also explain why some patients remain asymptomatic at exercise while others have a limited exertional capacity, despite having the same echocardiographic measurements at rest. In this regard, cardiologists should not hesitate to perform this examination or to refer these patients to experienced physicians familiar with this technique. Whether surgery should be recommended in the presence of abnormal exercise echocardiogram in severe asymptomatic AS requires further study.

Conflict of interest

None.

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