Expert Reviews

Stress testing in valvular heart disease: clinical benefit of echocardiographic imaging

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Symptom development represents one of the most important indications for surgical intervention in patients with significant valvular heart disease. Exercise testing has an established role in the assessment of exercise capacity and symptomatic status in patients with severe valvular heart disease who claim to be asymptomatic. In these patients, clinical decision can be influenced by the results of exercise testing. In addition to the assessment of symptomatic response to exercise, stress echocardiography can provide valuable information on exercise-induced changes in valve hemodynamics, ventricular function and pulmonary artery pressure. Abnormal left ventricular response to exercise, increase in pulmonary pressure or change in the hemodynamic severity of the valvular disease adds to the prognostic value of elicited symptoms. In this article we discuss the validated indications, proven prognostic values and potential influence on clinical decisions of stress echocardiography in left valvular heart diseases.

Keywords: exercise stress testing • prognosis • stress echocardiography • valvular heart disease

Asymptomatic severe aortic stenosis

Indication

Aortic stenosis (AS) is a gradually progressive disease that, when severe and symptomatic, leads to the only established therapy of surgical valve replacement [1,2]. Exercise testing is contraindicated in symptomatic AS patients [1,2]. However, symptomatic status can be difficult to establish in elderly patients, who may ignore their symptoms or may reduce their level of physical activity to avoid or minimize symptoms. Thus, exercise testing could be useful to unmask symptoms in patients with severe AS who claim to be asymptomatic or who have equivocal symptoms. A recent meta-analysis confirmed that symptom-limited stress testing is safe and has an important prognostic value [3]. Exercise testing is strongly advocated in the European Society of Cardiology (ESC) guidelines [1] and is a class IIb recommendation in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines [2]. It has been suggested recently that asymptomatic patients with severe AS who are surgically treated may have better outcomes than those who are treated medically [4]. Thus, the identification of asymptomatic patients who may benefit from early elective aortic valve replacement is of clinical interest. Stress echocardiography may provide important additional information regarding left ventricular (LV) function, valvular hemodynamic or ventricular arterial coupling, refining the risk stratification of asymptomatic AS patients [5], even if the current guidelines do not recommend it in the management of these patients [1,2]. Exercise testing is more physiologic than dobutamine testing and a supine or semi-supine bicycle exercise could be preferable because of a reduced risk of hemodynamic collapse in this position [5].

Prognostic value

Changes in clinical, electrocardiographic and echocardiographic parameters during the stress test proved to influence the prognosis and subsequent clinical decision making in asymptomatic AS patients (Table 1). Approximately one third of the patients who claim to be asymptomatic develop symptoms on exercise. The occurrence of exercise-limiting symptoms (dizziness, dyspnea at low workload, angina or syncope) predicts the rapid development of symptoms in daily life, cardiac death (including sudden death) and need for aortic valve replacement [6–9], particularly in patients under 70 years of age and physically active [8]. Dizziness during a treadmill test has

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Table 1. Impact on outcomes and clinical decision making of stress echocardiographic data in patients with asymptomatic severe aortic stenosis.

Stress data	Parameters	Impact on outcome	Impact on clinical decision (AVR)	
			ESC guidelines	ACC/AHA guidelines
Clinical	– Symptoms (dizziness, dyspnea at low workload, angina, syncope)	Onset of symptoms in daily life, cardiac death, AVR [6–9]	Class I	Class IIb
	– Abnormal blood pressure response (absence of increase or fall in blood pressure)		Class IIa	Class IIb
Electrocardiographic	– Ventricular arrhythmias	Onset of symptoms in daily life, cardiac death, AVR [6,7,9]	Class IIb	–
	– ST depression (≥2mm)		–	–
Echocardiographic	– Increase in mean transvalvular gradient: >18 mmHg [9]; >20 mmHg [10]	Spontaneous symptoms, cardiac death, AVR [9,10]	–	–
	– Decrease [11]/smaller increase [12] in LV ejection fraction	Spontaneous symptoms, cardiac death [11], abnormal exercise test [12]	–	–

ACC: American College of Cardiology; AHA: American Heart Association; AVR: Aortic valve replacement; ESC: European Society of Cardiology; LV: Left ventricular.

a higher positive predictive value for development of symptoms during the next year [8]. The occurrence of rapidly reversible dyspnea at high workloads (close to the age–gender predicted maximum workloads) is considered to be normal [10]. Abnormal blood pressure response (<20 mmHg increase in systolic blood pressure or fall in blood pressure), ST-depression (>2 mm, horizontal or down-sloping) or complex ventricular arrhythmia during exercise may predict adverse outcomes in asymptomatic AS patients [6,7,9] but does not seem to improve the accuracy of the test [8].

Exercise-induced changes in LV function or AS indices have been related to an increased risk of cardiac death, development of spontaneous symptoms and need for aortic valve replacement. An increase in mean pressure gradient of 18 mmHg or more during exercise was associated with outcome, independently of resting evaluation of AS severity and clinical or electrocardiographic exercise-induced changes [9]. Moreover, it has recently been shown that a large increase in mean gradient during exercise (≥20 mmHg) is associated with a marked increase in event risk even in the subset of patients with a normal exercise test [11]. Patients with a decrease or a smaller increase in LV ejection fraction during exercise were more likely to develop a clinical abnormal exercise response and cardiac events [12,13]. A significant increase in pressure gradient reflects the greater leaflet stiffness with limited valve compliance, thus a more severe disease. This suggests that exercise may reveal the true hemodynamic severity of the lesion. A decrease in LV ejection fraction during exercise reflects the subclinical dysfunction of the LV and provides *per se* a negative prognostic value, even in the absence of transvalvular gradient increase. Thus, stress echocardiography may be helpful to further improve risk stratification in this population (Figure 1). Exercise-induced changes in arterial compliance may also influence the LV function and symptomatic status in this setting. Recently, it has been shown that abnormal vascular response to exercise is an important contributor to the diminished stroke output and possibly to the development of effort-related symptoms in AS patients [14].

Impact on clinical decision making

Current ACC/AHA and ESC guidelines recommend surgery in asymptomatic severe AS patients who develop symptoms during exercise [1,2]. Abnormal blood pressure response and complex ventricular arrhythmias have a lower level of indication (Table 1). The lack of evidence from prospective clinical trials and the different interpretations of the available data by the experts, led to different classes of recommendation in the two guidelines [15]. Whether exercise-induced changes in echocardiographic indices should be considered criteria for early aortic valve replacement requires further investigation. However, a close clinical and echocardiographic follow-up at rest and during exercise is warranted in these patients.

Low-flow low-gradient AS

Indication

'Low-flow, low-gradient AS' is defined as an aortic effective orifice area under 1.0 cm^2, LV ejection fraction under 40%, and mean pressure transvalvular gradient less than 30 mmHg,

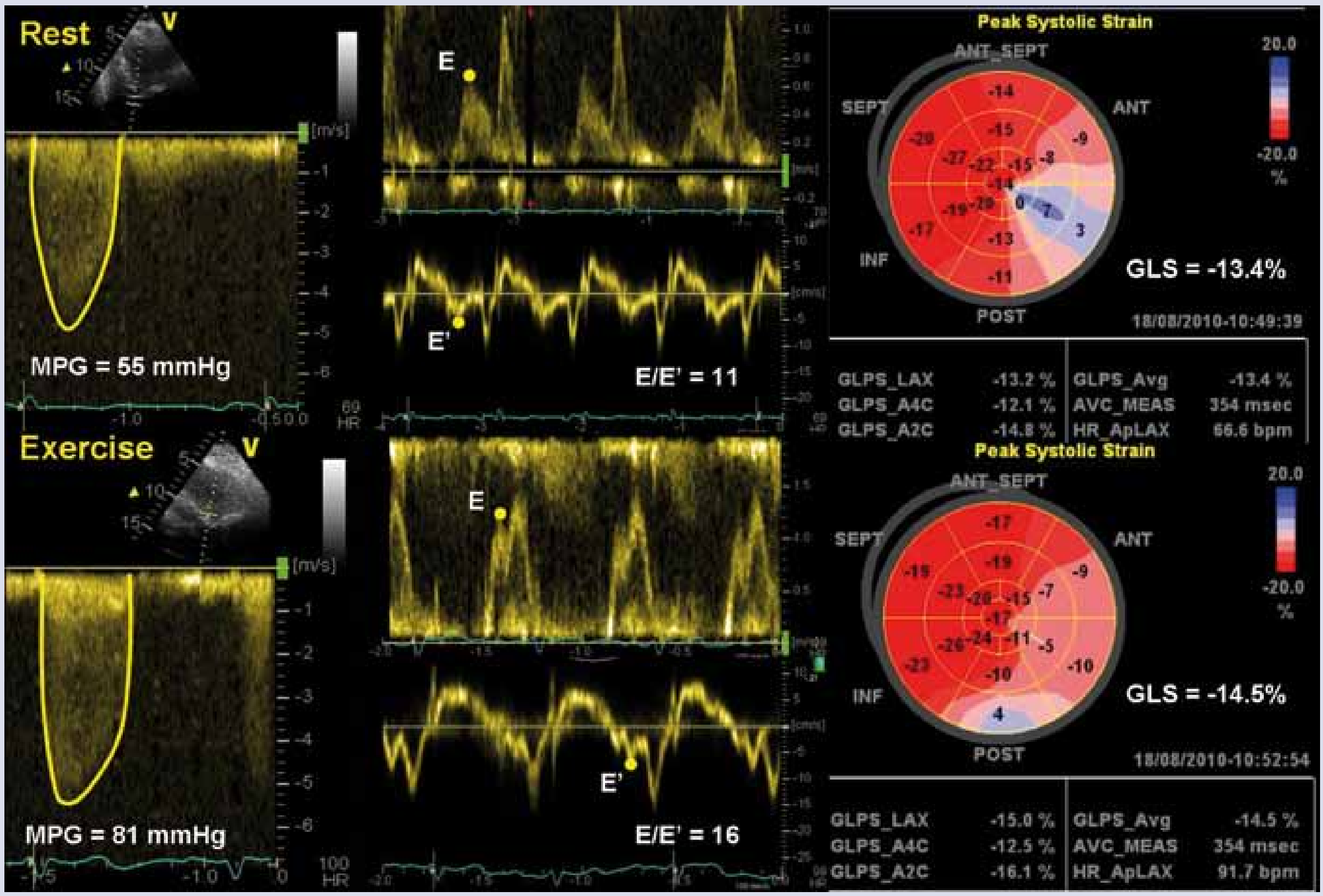

Figure 1. Echocardiographic findings in a patient with asymptomatic severe aortic stenosis (aortic valve area: 0.83 cm^2) and preserved left ventricular ejection fraction (65%). Upper panels: Rest recordings showing an increased mean transaortic pressure gradient (MPG: 55 mmHg), LV diastolic (E': 5.6 cm/s; E/E': 11) and LV longitudinal systolic dysfunction (GLS: -13.4%) despite preserved LVEF. Lower panels: Exercise-induced increase in mean transaortic pressure gradient (MPG: 81 mmHg), increase in LV filling pressures (E/E': 16) without LV longitudinal contractile reserve (GLS: -14.5%), suggesting high risk for cardiac events. GLS: Global longitudinal strain; LV: Left ventricular; LVEF: Left ventricular ejection fraction; MPG: Mean transaortic pressure gradient.

according to the ACC/AHA guidelines [2] or less than 40 mmHg according to the ESC guidelines [1]. This state can correspond to two different situations. It can be a true anatomically severe AS with depressed EF caused by excessive afterload (afterload mismatch) or a relative (pseudo-severe) AS in which the primary myocardial contractile dysfunction is responsible for the decreased ejection fraction and low stroke volume with reduced valve opening forces and apparent stenosis. In such patients, the first step must be to recognize that the AS is truly severe. Dobutamine stress aids the grading of AS and, more importantly, the assessment of the presence and extent of left ventricular contractile reserve (class IIa recommendation in the ACC/AHA practice guidelines) [2].

A low-dose protocol (up to 20 µg/kg/min) with gradual increments in dobutamine dose (2.5 µg/kg/min) at 5–8 min is recommended to prevent rapid increases in heart rate that may predispose to myocardial ischemia [5]. Criteria for terminating the infusion are the attainment of maximal dose, an increase in heart rate over 10–20 beats/min, or an obvious inotropic response [5]. However, the risk of side effects (arrhythmias, hemodynamic abnormalities, ischemia) remains high [16], imposing a need for careful monitoring and the presence of personnel trained in cardiac resuscitation during testing.

Prognostic value

The major aim of the dobutamine test is to identify the presence of contractile reserve, which has important prognostic implications. Patients with true severe AS and contractile reserve (defined as >20% increase in forward stroke volume) have a much better survival with aortic valve replacement than with medical therapy [17,18]. Criteria used to establish the diagnosis of true severe AS based on dobutamine response are: significant increases in mean gradient with small changes in valve area (increase <0.2 cm^2) and/or an aortic valve area (AVA) of 1.2 cm^2 or less at peak dobutamine dose (Figure 2) [1]. In the absence of contractile reserve, however, it is difficult to differentiate a true severe stenosis from a pseudo-severe stenosis. Recently, a new echocardiographic parameter has been proposed to better

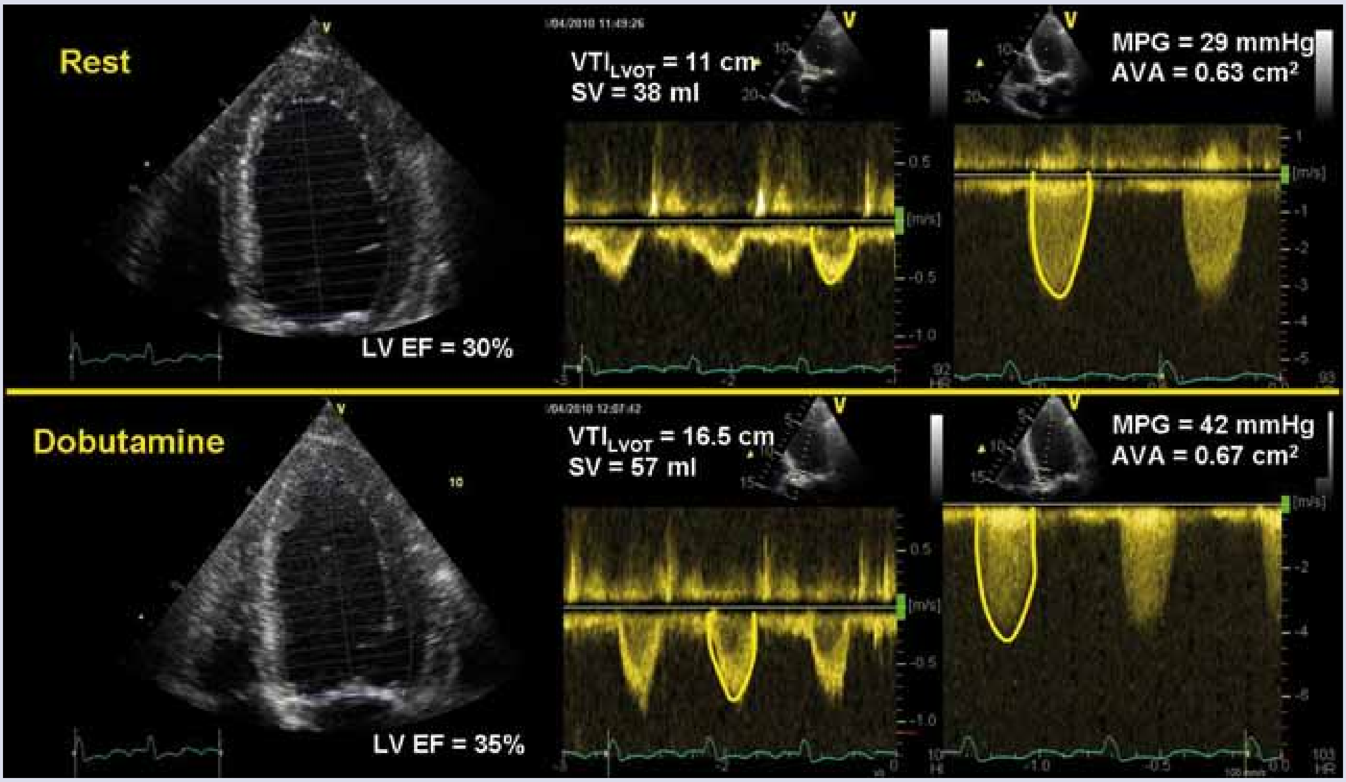

Figure 2. Two dimensional echocardiography and Doppler findings in a patient with aortic stenosis and severe left ventricular dysfunction. Upper panels: Rest recordings showing a severe decrease in calculated aortic valve area (AVA: 0.63 cm^2) with low mean transaortic pressure gradient (MPG: 29 mmHg) in presence of severe LV dysfunction (LVEF: 30%) and low stroke volume (SV: 38 ml). Lower panels: Dobutamine infusion (10 mg/kg/min) induce a 50% increase in stroke volume (SV: 57 ml), revealing the presence of LV contractile reserve, and increase in mean transaortic pressure gradient (MPG: 42 mmHg) without significant change of calculated aortic valve area (AVA: 0.67 cm^2), demonstrating the presence of true severe aortic stenosis.
AVA: Aortic valve area; LV: Left ventricular; LVEF: Left ventricular ejection fraction; MPG: Mean transaortic pressure gradient; SV: Stroke volume; VTI_{LVOT}: Left ventricular outflow tract velocity time integral.

distinguish between these two conditions: the projected effective orifice area at normal transvalvular flow rate (projAVA ≤1 cm^2 is a marker of a true severe AS) [19,20]. Moreover, projAVA 1.2 cm^2 or less was an independent predictor of mortality in medically treated low-flow, low-gradient AS patients [21].

Patients without contractile reserve have higher mortality with either surgical or medical therapy [22]. Absence of contractile reserve, baseline mean pressure gradient of 20 mmHg or less and associated coronary artery disease are predictors of high operative mortality [23,24]. However, the lack of contractile reserve on dobutamine test does not predict the absence of LV ejection fraction recovery in patients who survive to the aortic valve replacement [18]. Moreover, 5-year survival was higher in operated patients compared with those medically treated, despite a high operative mortality [24]. In this regard, it has been suggested that even patients without contractile reserve could benefit from aortic valve replacement [24].

Impact on clinical decision making

In patients with low-flow, low-gradient severe AS with evidence of contractile reserve, surgery is advised (ESC class IIa) since it carries an acceptable risk and leads to improved functional status and survival. Aortic valve replacement may be considered in patients with low-flow, low-gradient AS without contractile reserve but decisions should be made on an individual basis (ESC class IIb) [1]. The absence of contractile reserve should not be taken *per se* as a contraindication of surgery. Surgery should not be performed on patients in whom echocardiography has shown pseudo-severe AS. However, it has been recently suggested that in patients with severe LV dysfunction, an associated moderate AS is not a completely innocent condition and that replacement of a nonsevere stenotic aortic valve could be beneficial in this condition [25].

Aortic regurgitation

Indication

When severe, aortic regurgitation (AR) gradually leads to LV dysfunction, heart failure and increased risk of sudden death. Symptomatic patients, even those with transient or mild symptoms, have an excessive mortality rate [26] and firm indication for aortic valve replacement [1,2]. Moreover, the severity of preoperative symptoms is a strong determinant of survival after aortic valve replacement [27]. Thus, exercise stress testing is reasonable for the assessment of functional capacity and symptomatic status in patients with severe AR and equivocal symptoms (ACC/AHA class IIa) [2]. Stress testing may also be useful when there is a discrepancy between clinical and echocardiographic data [1].

Irreversible impairment of myocardial contractility can be present in the absence of significant symptoms [28] and can adversely affect prognosis even after aortic valve replacement [29]. The duration of preoperative LV dysfunction predicts survival and recovery of LV function after aortic valve replacement [30]. Thus, early detection of subclinical LV dysfunction could be of clinical relevance. As most of the available data in this setting were provided by exercise radionuclide angiography studies, this type of investigation may be considered for the assessment of LV function in asymptomatic or symptomatic patients with chronic AR (ACC/AHA class IIb) [2].

Prognostic value

Data on the prognostic value of stress echocardiography in patients with AR are sparse. The absence of contractile reserve on exercise, defined as a failure to increase LV ejection fraction during test, is a useful and reliable predictor of progressive LV dysfunction on medical treatment [31]. The presence of contractile reserve is a predictor of improvement of LV function after aortic valve replacement [31].

Impact on clinical decision making

Patients with severe AR who develop symptoms during stress test should be referred to surgery. Measurement of contractile reserve may be useful to monitor the early development of myocardial dysfunction in asymptomatic patients with AR, especially when borderline values of LV ejection fraction (50–55%) or end-systolic diameter (closed to 50 mm or 25 mm/m^2) are present, and may help to optimize the timing of surgery [32]. Asymptomatic patients with severe AR, without contractile reserve, might be considered for surgery, even if not stipulated in the current guidelines [5].

Mitral stenosis

Indication

In mitral stenosis (MS) patients, symptoms develop insidiously over years and their severity strongly relates to survival [33]. Symptoms are only roughly correlated to measurements of valve area at rest [34]. Stress echocardiography represents a clinically established tool for assessing the functional significance of MS, particularly when discrepancies exist between the clinical and resting echocardiographic data. In asymptomatic patients with severe MS and in symptomatic patients with mild to moderate MS, stress echocardiography can provide important information regarding functional capacity, exercise-induced symptoms, valve function or its hemodynamic consequences (ACC/AHA, class I recommendation) [2].

The level of pulmonary pressure is an indicator of the overall hemodynamic consequence of MS and has an important impact on survival [35].The ability to assess the response of pulmonary artery pressure to exercise is one of the most important aspects of stress echocardiography in MS. Increase in pulmonary artery pressure during exercise can be dramatically different in patients

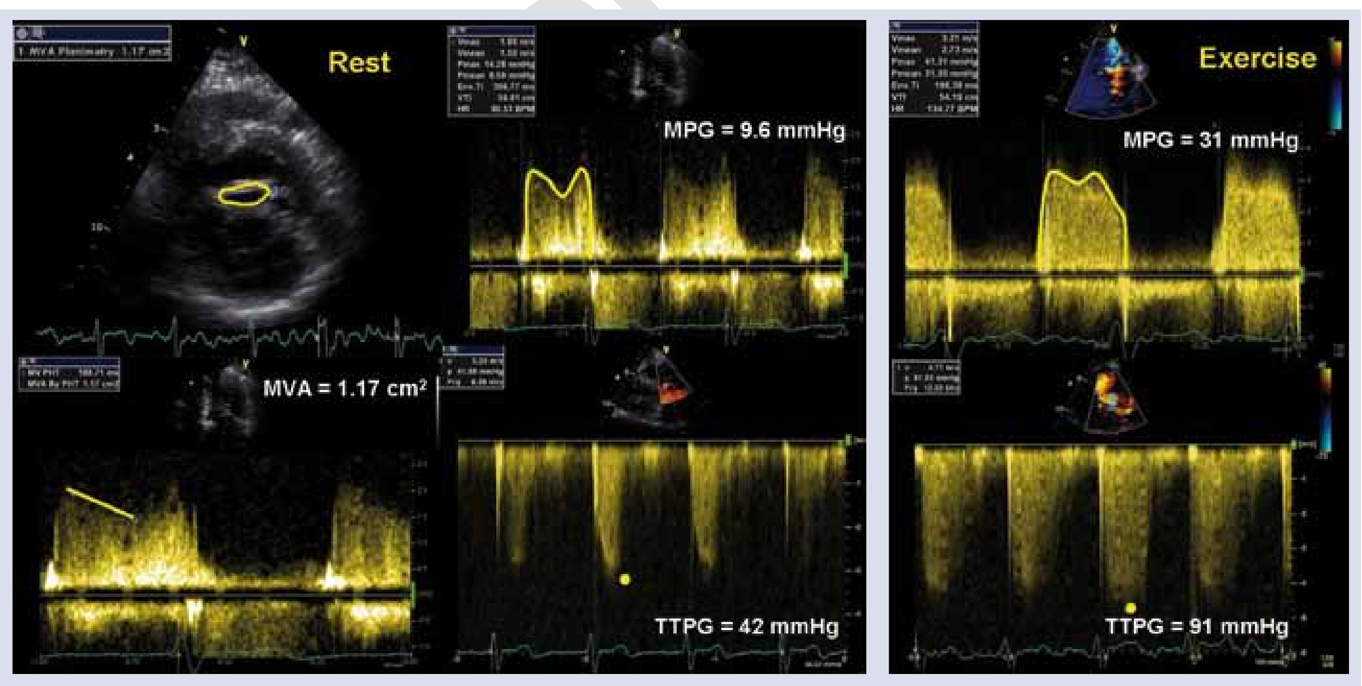

Figure 3. Echocardiographic assessment of an asymptomatic patient with rheumatic mitral stenosis. Left panels: Rest recordings suggest significant mitral stenosis (MVA: 1.17 cm^2 by planimetry and pressure half time method) with mean transmitral pressure gradient of 9.6 mmHg and transtricuspid pressure gradient of 42 mmHg. Right panels: Exercise recordings show a significant increase in mean transmitral pressure gradient (MPG: 31 mmHg) and in transtricuspid pressure gradient (TTPG: 91 mmHg), indicating the need for surgery or percutaneous valvotomy.
MPG: Mean transmitral pressure gradient; MVA: Mitral valve area; TTPG: Transtricuspid pressure gradient.

with comparable resting values of mitral valve area and pulmonary artery pressure [36]. Reduced atrioventricular compliance can particulary contribute to a severe increase in pulmonary artery pressure during stress, explaining the symptoms in the presence of a nonsevere MS [37].

Exercise echocardiography is preferable but, with some limits, dobutamine stress test may also be performed.

Prognostic value

There is no evidence on the prognostic role of data derived from exercise echocardiographic testing in MS. The recommended cut-off values are consensus driven (ACC/AHA guidelines): mean transmitral pressure gradient over 15 mmHg or pulmonary artery systolic pressure over 60 mmHg during exercise are markers of hemodynamically significant MS (Figure 3). A mean transmitral pressure gradient of more than 18 mmHg during the dobutamine test predicts clinical deterioration and the need for surgery [38].

Impact on clinical decision making

Asymptomatic patients with significant MS (mitral valve area <1.5 cm^2) who show poor exercise tolerance or rise in pulmonary artery systolic pressure greater than 60 mmHg during stress testing have indication for percutaneous valvotomy if the MV morphology is suitable (Table 2). Symptomatic patients with mild to moderate MS (mitral valve area >1.5 cm^2) with a mean transmitral pressure gradient over 15 mmHg or pulmonary artery systolic pressure over 60 mmHg during stress testing, may be considered for percutaneous valvotomy (ACC/AHA class IIb) (Table 2).

Organic mitral regurgitation

Indication

In patients with severe mitral regurgitation (MR), severe symptoms predict poor outcome after valve repair or replacement [39]. LV ejection fraction is also an important predictor of postoperative LV dysfunction [40] and subsequent cardiac morbidity and mortality in this setting [41]. Thus, once the patients with severe MR become symptomatic or develop LV dysfunction (decrease in LV ejection fraction or increase in LV end-systolic diameter) mitral valve surgery, especially repair, is mandatory [1,2]. However, the absence of symptoms or a preserved LV ejection fraction do not necessarily reflect a normal LV function. Indeed, in this setting, LV ejection fraction is the sum of forward LV ejection fraction and the regurgitant fraction. LV dysfunction may develop insidiously and may become evident only after successful surgical correction of the MR, resulting in significant postoperative morbidity and mortality. Stress echocardiography may be helpful in severe asymptomatic MR and borderline values of LV ejection fraction (60–65%) or LV end-systolic diameter (closed to 40 mm or 22 mm/m^2) in identifying unrecognized symptoms and unmasking latent LV dysfunction (Figure 4) [42]. Exercise echocardiography is reasonable in asymptomatic patients with severe MR to assess exercise tolerance and the effects of exercise on pulmonary artery pressure and MR severity (ACC/AHA class IIa) [2]. It may be also useful when there is a discrepancy between the symptoms and the severity of the lesion (e.g., symptomatic patients with mild MR) in elucidating the cause of symptoms [42,43].

Prognostic value

Exercise capacity is a predictor of the development of symptoms or LV dysfunction in asymptomatic patients with MR [44]. Degenerative MR might be dynamic and markedly increases during exercise in one-third of patients [45]. Important changes in MR severity (increase ≥15 ml in regurgitant volume, or increase 10 mm^2 or more in effective regurgitant orifice area) are associated with exercise-induced changes in systolic pulmonary artery pressure and reduced symptom-free survival [45]. Recently it has been shown that exercise pulmonary hypertension is more accurate than resting pulmonary artery pressure in predicting the occurrence of symptoms during follow-up [46]. Development of severe dynamic MR during exercise associated with increase in pulmonary artery pressure has been also reported in symptomatic patients with mild rheumatic mitral valve disease, helping in elucidating the cause of symptoms [47].

Table 2. Impact on outcomes and clinical decision making of stress echocardiographic data in patients with mitral stenosis.

Indication	Stress data	Parameters	Impact on outcome	Impact on clinical decision (percutaneous valvotomy)	
				ESC guidelines	*ACC/AHA guidelines*
Asymptomatic MS (MVA < 1.5 cm^2)	Clinical	– Symptoms or	–	Class IIa	Class I
	Echocardiographic	– Pulmonary artery systolic pressure >60 mmHg (exercise testing)	–	–	Class I
Symptomatic MS (MVA > 1.5 cm^2)	Echocardiographic	– Pulmonary artery systolic pressure >60 mmHg or	–	–	Class IIb
		– Mean pressure transmitral gradient >15 mmHg (exercise testing)	–	–	Class IIb
		– Mean pressure transmitral gradient >18 mmHg (dobutamine stress)	Clinical deterioration, need for surgery [38]	–	–

ACC: American College of Cardiology; AHA: American Heart Association; ESC: European Society of Cardiology; MS: Mitral stenosis; MVA: Mitral valve area.

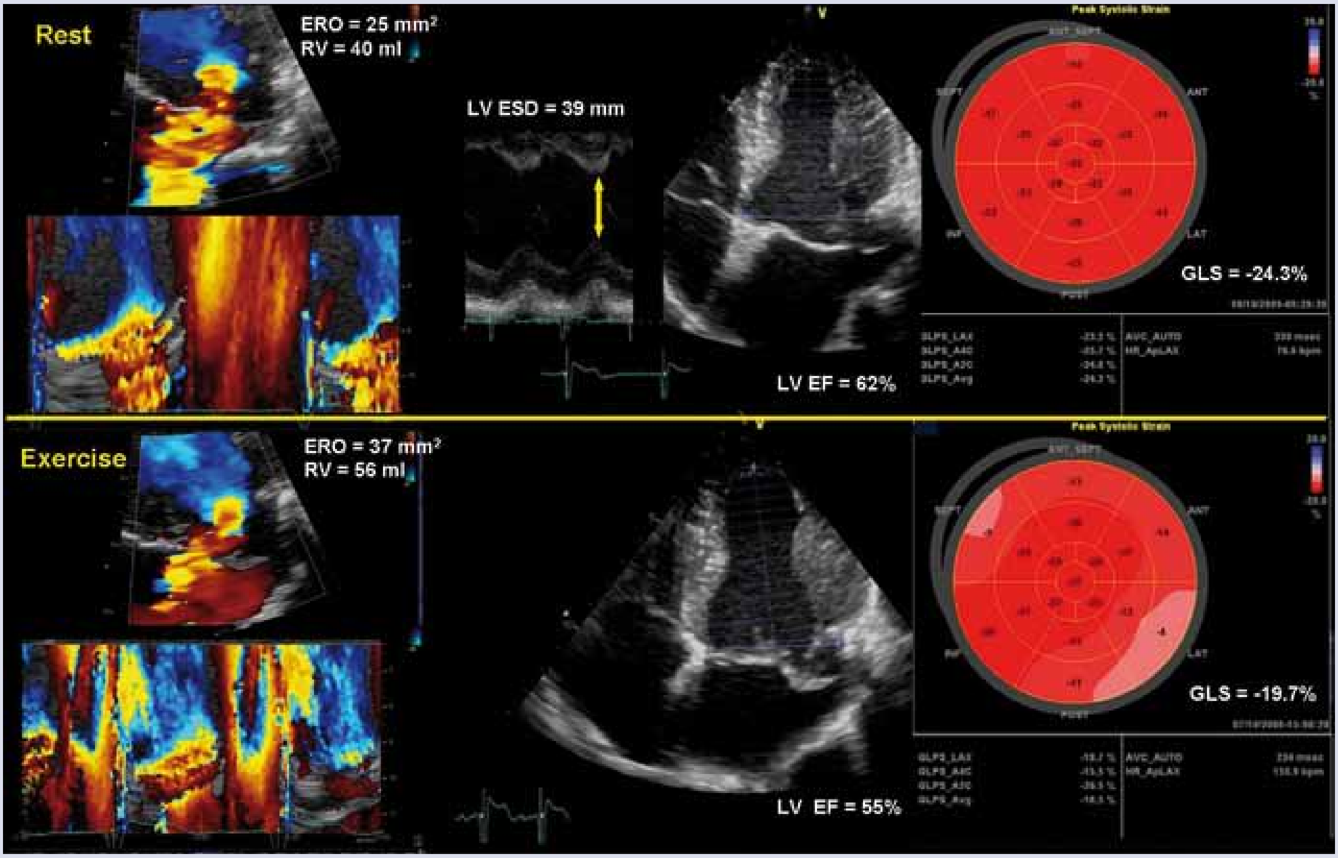

Figure 4. Echocardiographic assessment of an asymptomatic patient with degenerative mitral regurgitation, at rest and during exercise. Upper panels: Resting moderate mitral regurgitation (ERO: 25 mm^2; RV: 40 ml) with an end-systolic peak of PISA radius using color M-mode. Increased left ventricular (LV) end-systolic diameter (LV ESD: 39 mm) with preserved global and longitudinal LV systolic function (LV EF: 62%; GLS: -24.3%). Lower panels: Exercise-induced marked increase in mitral regurgitation severity (ERO: 37 mm^2; RV: 56 ml), with proximal flow convergence zone larger and the PISA radius higher in mid and late systole using color M-mode. Decrease in LVEF (55%) and GLS (-19.7%) reflecting the absence of contractile reserve and predicting poor outcomes.
ERO: Effective regurgitant orifice area; GLS: Global longitudinal strain; LV EF: Left ventricular ejection fraction; LV ESD: Left ventricular end-systolic diameter; PISA: Proximal izovelocity surface area; RV: Regurgitant volume.

Contractile reserve, assessed by stress echocardiography, can identify subclinical LV dysfunction and predict postoperative LV function after mitral valve surgery. An inability to increase the LV ejection fraction or reduce the end-systolic volume with stress reflects the presence of an impaired contractile reserve. An exercise end-systolic volume index over 25 cm^3/m^2 was the best predictor of postoperative LV dysfunction in minimally symptomatic patients with severe MR [48]. In asymptomatic patients with chronic severe MR and normal LV function, an increase of less than 4% in ejection fraction with exercise predicts the development of postoperative LV dysfunction and cardiac morbidity in surgically treated patients and progressive deterioration of LV function in medically treated patients [49]. Preliminary results suggest that 2D strain obtained during exercise could be useful to better identify contractile reserve in these patients. An increase of less than 1.9% in global longitudinal strain during exercise predicts postoperative LV dysfunction as well as impairment in LV function in medically treated patients with a better sensitivity and specificity than an inadequate increase in LV ejection fraction [50].

Impact on clinical decision making

The finding of a pulmonary artery pressure over 60 mmHg during exercise is a reasonable indication for mitral valve surgery in asymptomatic patients with chronic severe MR and preserved LV function (Table 3) [2]. Asymptomatic patients with preserved LV function, high likelihood of durable repair and low risk for surgery may be considered for mitral valve repair in experienced centers (ESC class IIb) [1]. Stress echocardiography could be an important tool for risk stratification, identifying those patients who may benefit from early surgery (with impaired exercise capacity, symptoms, worsening of MR severity or lack of contractile reserve during exercise) [42,43].

Ischemic MR

Indication

Ischemic mitral regurgitation (IMR) is caused by changes in left ventricular geometry and function related to chronic coronary artery disease. IMR can be acute (complicating an acute myocardial infarction or due to a transient ischemic phenomenon)

Table 3. Impact on outcomes and clinical decision making of stress echocardiographic data in patients with organic mitral regurgitation.

Indication	Stress data	Parameters	Impact on outcome	Impact on clinical decision	
				ESC guidelines	*ACC/AHA guidelines*
Asymptomatic MR	Clinical	– Exercise capacity	Development of symptoms [44]	–	–
		– Symptoms	–	–	–
	Echocardiographic	– Pulmonary artery systolic pressure >60 mmHg	Occurrence of symptoms [45,46]	–	Class IIa
		– Increase in ERO ≥10 mm²	Reduced symptom-free survival [45]	–	–
		– Increase in RV ≥15 ml	Reduced symptom-free survival [45]	–	–
		– End-systolic volume index at peak exercise >25 ml/m²	Postoperative LV dysfunction [48]	–	–
		– Increase in LV EF <4% [49]	Postoperative LV dysfunction [49,50] and cardiac morbidity [49]; progressive deterioration of LV function [49,50]	–	–
		– Increase in global longitudinal strain <1.9% [50]		–	–
Symptomatic nonsevere rheumatic mitral disease	Echocardiographic	– Pulmonary artery systolic pressure >60 mmHg	–	–	Class IIb
		– Severe regurgitation during exercise	–	–	–

ACC: American College of Cardiology; AHA: American Heart Association; EF: Ejection fraction; ERO: Effective regurgitant orifice area; ESC: European Society of Cardiology; LV: Left ventricular; MR: Mitral regurgitation; RV: Regurgitant volume.

or chronic functional MR (secondary to increased mitral leaflet tethering caused by annular dilatation and displaced papillary muscle, and decreased closing force of the mitral valve caused by LV dysfunction) [51].

Ischemic mitral regurgitation, even when mild, is associated with an increased risk of heart failure and death independent of LV ejection fraction [52]. Moreover, IMR is a dynamic lesion and its severity may largely vary with hemodynamic conditions. The dynamic changes in IMR can be quantitatively measured (proximal izovelocity surface area method) during semisupine exercise (Figure 3) [53]. Exercise-induced changes in MR severity (increase in effective regurgitant orifice area) is not related to the degree of MR at rest [53] but is related to changes in mitral deformation (increase in tenting area, coaptation distance or mitral annulus diameter) [54,55] and to changes in LV dyssynchrony [56,57]. Thus, stress echocardiography could play an important role in this setting, providing information regarding exercise-induced changes in MR, mitral valve deformation and LV geometry and function (Box 1).

The established role of stress echocardiography in IMR is to determine the presence of viable myocardium as this will further influence the clinical decision making (revascularization, cardiac resynchronization therapy) and the prognosis [1]. Moreover, the 2010 European Association of Echocardiography recommendations for the assessment of valvular regurgitation emphasize the potential important role of the assessment of exercise-induced changes in ischemic MR in patients with exertional dyspnea out of proportion to the severity of resting LV dysfunction or MR, in those in whom acute pulmonary edema occurs without an obvious cause, and in those with moderate MR before surgical revascularization [42]. Exercise-induced changes in dyssynchrony and severity of MR associated with preserved contractile reserve may help to better identify potential responders to cardiac resynchronization therapy [58]. Exercise echocardiography could be also useful in the assessment of surgery or cardiac resynchronization therapy results in patients with IMR. It has been demonstrated that cardiac resynchronization therapy attenuates functional MR during dynamic exercise in patients with LV dilatation and asynchrony [59–61].

Prognostic value

An increase in mitral regurgitant volume during dynamic exercise correlates well with elevation of systolic pulmonary artery pressure [53]. Exercise-induced increase in the effective regurgitant orifice area and in the systolic pulmonary artery pressure was independently associated with the occurrence of acute pulmonary edema [62]. Dynamic changes in IMR provide additional prognostic information over resting evaluation and unmask patients at high risk of poor outcome [63]. Large exercise-induced increase in MR, defined as an increase in effective regurgitant orifice area over 13 mm², is associated with increased mortality and morbidity [64]. Dynamic IMR is also a determinant of rapid QRS widening, which may lead to permanent electromechanical dyssynchrony and further deterioration of LV function [65].

The presence of viable myocardium predicts LV reverse remodeling and a better outcome after revascularization [66], β-blocker therapy [67] and cardiac resynchronization therapy [68]. LV reverse remodeling and reduced mitral apparatus deformation after cardiac resynchronization therapy are associated with a reduction in both resting and exercise-induced MR and an improvement in cardiopulmonary performance [69]. Moreover, IMR decreases significantly in patients with viability in the region of the pacing lead without regard to MR severity in patients with cardiac resynchronization therapy [70].

Impact on clinical decision making

There is a trend favoring valve repair, using undersized rigid ring annuloplasty, to correct IMR, even if it carries a higher risk of mortality [51] and of recurrence of MR [71,72]. The presence of significant myocardial viability is a predictor of good outcome after mitral valve repair combined with bypass surgery. Severe MR should be corrected at the time of bypass surgery (ESC class I in patients with LV ejection fraction >30%, class IIa in patients with LV ejection fraction <30%) [1]. Moderate IMR is reasonable to be repaired at the time of bypass surgery (ESC class IIa). The additional benefit of valve repair in mild IMR at rest is debated. If a significant increase in effective regurgitant orifice area (>13 mm^2) develops with exercise, a combined treatment, bypass and mitral valve surgery might be proposed [5,15]. A large prospective, multicenter, nonrandomized registry was designed to assess the role of exercise echocardiography in identifying determinants of LV remodeling, residual IMR and adverse outcome of mitral repair in patients with IMR [73].

Even more controversial is the management of chronic functional MR in patients without solution of revascularization. Optimal medical treatment, including ACE inhibitor and β-blocker, or cardiac resynchronization therapy in appropriate candidates, are the recommended therapeutic options in this setting [1,2]. Stress echocardiography could be useful in the assessment of exercise-induced changes in dyssynchrony and in guiding the choice of pacing lead site, given that the patients with viability in the region of the pacing lead are more frequently ‘responders’. However, limited available data suggest that mitral valve surgery may be considered in selected patients with severe functional MR and severely depressed LV function who remain symptomatic despite optimal therapy, even if bypass surgery is not indicated (ESC class IIb) [1]. The potential role of stress echocardiography in this setting is not yet established.

Box 1. Parameters that should be measured and followed during stress echocardiography in patients with ischemic mitral regurgitation.

Stress echocardiographic parameters

- LV parameters:
  - LV end-diastolic volume
  - LV end-systolic volume
  - LV ejection fraction
  - Regional wall thickening
  - Color TDI for dyssynchrony assessment
- Mitral valve deformation parameters:
  - Mitral annulus diameter
  - Tenting area
  - Coaptation distance
- Mitral regurgitation parameters:
  - Effective regurgitant orifice area (PISA or volumetric Doppler method)

LV: Left ventricular; PISA: Proximal izovelocity surface area; TDI: Tissue doppler imaging.

Expert commentary & five-year view

Most valvular heart diseases have a dynamic component reflected in changes in the severity of valvular lesion and its hemodynamic consequences with changes in loading conditions or LV contractility. Thus, stress echocardiography seems to be ideally suited for the assessment of valvular heart disease because of its ability to provide valuable hemodynamic information. However, not all guidelines for the management of valvular heart disease recognize a specific role for this

Key issues

- Exercise echocardiography is the technique of choice in the assessment of valvular heart disease, providing more physiological information on the dynamic changes in valve function, ventricular function or pulmonary artery pressure associated with information on exercise capacity and symptomatic status.
- Dobutamine echocardiography is recommended in patients with low-flow low-gradient aortic stenosis, its main role being the assessment of contractile reserve. The absence of contractile reserve carries a high operative mortality risk but should not be taken *per se* as a contraindication of surgery.
- In asymptomatic severe aortic stenosis, exercise testing and exercise echocardiography may impact the clinical decision making. Increase in mean transaortic pressure gradient and lack of contractile reserve with exercise are associated with a poor outcome.
- The severity of increases in mean transmitral pressure gradient and pulmonary artery pressure during exercise can help in clinical decision making in patients with mitral stenosis.
- The absence of contractile reserve predicts postoperative left ventricular dysfunction and deterioration of left ventricular function in medically treated patients with organic mitral regurgitation. Stress echocardiography could be an important tool for risk stratification identifying those patients who may benefit from early surgery.
- A large increase in effective regurgitant orifice area during exercise is associated with high risk of morbidity and mortality in patients with ischemic mitral regurgitation. A combined treatment, bypass and mitral valve surgery might be proposed in these patients.
- Prospective, randomized studies are needed to demonstrate that changes in clinical decision as a result of stress echocardiography lead to better outcomes.

technique: the ESC document recommends only exercise testing and does not specify any role for exercise echocardiography, whereas the ACC/AHA document defines particular subsets of patients in which exercise echocardiographic parameters are useful in clinical decision-making. In the American Society of Echocardiography (ASE) appropriateness criteria for stress echocardiography document, the stress testing in severe aortic or mitral stenosis is considered to be inappropriate [74]. The majority of the recommendations are level of evidence C, based on experts' opinion, underscoring the need for more clinical investigations in this area. A formal agreement between recommendations and an update according to the new evidence of the usefulness of echocardiographic stress testing in valvular heart disease are required. Significant improvements in surgical techniques with decrease in perioperative mortality and improvement of long-term outcomes led to the tendency to lower the threshold for surgery in patients with valvular heart disease. Exercise echocardiography could have an important role in risk stratification and further clinical decision making in these patients. Prospective, randomized studies are needed to demonstrate that changes in clinical decision as a result of stress echocardiography lead to better outcomes.

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