Dynamic Assessment of Stenotic Valvular Heart Disease by Stress Echocardiography

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During the past 2 decades, the dynamic nature of valvular heart disease has become a recognized phenomenon. Changes in loading conditions, heart rate, and ventricular contractility that occur with exercise can alter the physiological effects of valvular disease.1,2 Disparity between resting evaluation of valve dysfunction and patient symptoms is not uncommon. Stress echocardiography (SE) has emerged as a modality able to provide new diagnostic information by identifying dynamic changes in the severity of valve stenosis on exertion responsible for symptoms and evaluate the severity of valve disease in altered flow states.3 This review seeks to review critically the existing evidence base, identify new emerging prognostic markers, evaluate their role in clinical practice, and identify future directions for research.

Aortic Stenosis

The clinical scenarios where SE aids diagnosis and prognostic value include the evaluation of asymptomatic severe aortic stenosis (AS), low-flow (LF), low-gradient (LG) AS, and moderate AS with symptoms (Table).

Asymptomatic Aortic Stenosis

The prognosis of patients with symptomatic, severe AS is dismal.4 The prognosis for those who are asymptomatic is more favorable with a <1% per year mortality.5 However, one third of patients who claim to be asymptomatic actually develop symptoms on exertion. Therefore, physiological testing may be used to uncover symptoms in an apparently asymptomatic individual.6,7 The use of exercise SE in asymptomatic severe AS is slowly emerging.8 An increase in mean aortic pressure gradient by ≥18 mmHg during exercise has been reported to be an independent predictor of cardiac events (development of symptoms, death, aortic valve replacement [AVR], or hospital admission).9 This has been validated more recently in a larger cohort of patients showing that a resting mean gradient of 35 mmHg and an increase in mean gradient of >20 mmHg are associated with a 9-fold increase in event rate (AVR because of symptom development or death) during the next 2 years.9 Importantly, the exercise-induced increase in gradient could not be predicted from resting clinical or echocardiographic data. Recently, exercise-induced pulmonary hypertension (estimated pulmonary artery systolic pressure [PASP], >60 mmHg) has shown to be an independent predictor of cardiac events.10 The heterogeneity of the response to exercise may be related to valve compliance, which is a measure of the change in the effective orifice area of a valve in response to alterations in flow.11,12 The increased flow rate during exercise may allow a more compliant valve to open more effectively (thereby reducing the rise in transaortic gradient during exercise) compared with a less compliant valve. Indeed, valve compliance is lower in patients who develop symptoms during exercise than in those who remain asymptomatic.12

Exercise SE can be performed using either a treadmill or semisupine bicycle. Treadmill-based protocols require post-stress images to be obtained immediately after the patient has transferred from the treadmill to the examination couch. Therefore, the data obtained may not truly represent hemodynamics at peak exercise. However, during bicycle exercise, images can be obtained throughout the test and at peak exercise and this is, therefore, the preferred technique.

Implications for Clinical Practice

Both the American Heart Association/American College of Cardiology and European Society of Cardiology guidelines advocate the use of exercise testing to unmask symptoms in patients who may have sedentary lifestyles.13,14 A positive test (development of symptoms, hypotension, or ventricular arrhythmia during exercise) is graded as an indication to consider AVR. The use of exercise SE is more difficult to establish. This is in part because of the end points used in studies being a composite of death and AVR (especially where AVR was decided on by individual clinicians likely influenced by test results). The new European Society of Cardiology 2012 guidelines recommend consideration of AVR in asymptomatic patients with an exercise increase in mean AV gradient of ≥20 mmHg (Class IIb).14 It may be reasonable to use exercise SE to risk stratify patients and help identify patients at high risk of developing symptoms and who thereby warrant AVR or closer follow-up (Figures 1 and 2).
The severity of AS is defined by the degree of reduction in AV area (AVA). An AVA <1 cm² suggests severe stenosis irrespective of the valve gradient. The transvalvular gradient is flow dependent and varies according to the square of the flow rate and inversely to the square of the AVA. In situations where AVA is <1 cm² and the mean gradient is moderate (<40 mm Hg), the discrepancy between the 2 measurements could be because of a reduction in stroke volume in both patients with impaired and normal left ventricular (LV) ejection fraction (EF). Low stroke volume, in the latter, can occur in patients with severe, eccentric LV hypertrophy and small LV volumes, or reduced longitudinal function but preserved radial function. In both of these groups of patients, the reduction in AVA may be because of true severe AS or the so-called pseudo (nonsevere) AS.1 In severe AS, the valve has limited compliance and a fixed valve area; therefore, an increase in transvalvular flow will increase the transvalvular gradient as the square of flow. In lesser degrees of AS (pseudosevere AS), the valve is more compliant and an increase in transvalvular flow will have a much less significant effect on transvalvular gradient. SE can induce altered flow rates and detect change in hemodynamics, thereby differentiating between truly severely and pseudosevere AS.19

Table. Clinical Use of Stress Echocardiography in Stenotic Valvular Heart Disease

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AS indicates aortic stenosis; AVA, aortic valve area; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MS, mitral stenosis; PASP, pulmonary artery systolic pressure; and VTI, velocity time integral.

**Figure 1.** Exercise stress echocardiogram in a 58-year-old man with severe asymptomatic aortic stenosis. A. At rest mean transaortic gradient=58 mm Hg. Patient exercised on the treadmill for 9 minutes. No adverse hemodynamic changes occurred during exercise and no symptoms were reported. B. Immediately after exercise transaortic gradient. The mean gradient increased to 82 mm Hg. A total of 24 mm Hg increase in mean transaortic gradient during exercise places patient in high-risk group and according to European Society of Cardiology guidelines and this patient could be considered for aortic valve replacement. PG indicates pressure gradient; Vmax, maximum velocity; Vmean, mean velocity; and VTI, velocity time integral.
(<40%). This entity encompasses 2 distinct pathologies. In patients with truly severe AS, the excess afterload imposed by the severe AS leads to LV dysfunction and a consequent reduction in the AV gradient because of inadequate driving forces through the valve (afterload mismatch). The second group consists of patients with pseudosevere AS in whom there is reduced opening of the AV and moderate stenosis, but the primary pathology is underlying LV myocardial disease, causing the reduced EF and low AV gradient.

**Test Protocol**

A low-dose dobutamine protocol is followed starting at 5 mcg/kg per minute and increasing in 5 mcg/kg per minute increments every 3 to 5 minutes up to a maximum of 20 mcg/kg per minute. We recommend discontinuation of β-blockers ≥24 hour before the test because they may attenuate the response of the myocardium to inotropic stimulation. The LV outflow tract velocity time integral, AV velocity time integral, and LVEF are measured at each stage. The test examines whether there is LV contractile reserve (increase in stroke volume by 20%) and if present, whether this leads to a change in AV A and transaortic gradient. In patients with contractile reserve, there should be an increase in LV outflow tract velocity time integral and in those with truly severe AS, this should lead to an increase in the mean transaortic gradient (>40 mm Hg), but no change in the AVA (<1 cm²). In patients with pseudosevere AS, the AVA should increase (>1 cm²), but the mean gradient will remain <40 mm Hg (Figure 3). At this point, higher doses of dobutamine may be used to exclude ischemia as the cause of LV dysfunction.

The main limitation of this test is that it is dependent on flow augmentation, which is highly variable between patients. In patients without contractile reserve, it is not possible to differentiate between true and pseudosevere AS. The concept of projected valve area at normal transvalvular flow rate (250 mL/s) was developed to better differentiate between true and pseudosevere AS. To calculate the projected valve area, AVA is plotted against mean transvalvular flow rate (Q) at different stages of the dobutamine SE protocol. Valve compliance is derived from the regression line of this plot. The projected AVA (AVAproj; at a standardized flow rate of 250 mL/s) is then calculated (AVA at rest+valve compliance×[250−flow at rest]). A simplified formula to calculate AVAproj has been validated:

\[
AVA_{proj} = \frac{AVA_{peak} - AVA_{rest} \times (250 - Q_{rest}) + AVA_{rest}Q_{peak} - Q_{rest}}{250 - Q_{rest}}
\]

**Figure 2. Algorithm for investigation and management of asymptomatic aortic stenosis. Aortic valve (AV), aortic valve replacement (AVR), European Society of Cardiology (ESC), American Heart Association (AHA), American College of Cardiology (ACC). *Emerging parameters which require further validation.**

**Figure 3. Low-dose dobutamine stress echocardiogram in a 75-year-old patient with exertional dyspnoea. Left ventricular outflow tract (LVOT) 2.3 cm. A, LVOT velocity time integral (VTI) 20 cm. B, Mean aortic valve (AV) gradient 30 mm Hg but calculated aortic valve area (AVA) of <1 cm² suggested severe AS. After 10 mcg/kg per minute dobutamine infusion. C, There is an increase in LVOT VTI from 20 to 24.5 cm (increase in VTI>20%) suggesting the presence of LV contractile reserve. D, Although there is a mild increase in mean AV gradient to 35 mm Hg, the AVA increases to 1.3 cm² suggesting pseudosevere (moderate) AS.
The use of A_VAproj significantly improves the accuracy of discriminating severe (A_VAproj ≤ 1 cm²) from pseudosevere AS compared with conventional dobutamine SE indices.21,22 Furthermore, an A_VAproj < 1.2 cm² is an independent predictor of prognosis in LF, LG severe AS.23 A suggested algorithm for investigation is displayed in Figure 4. Recent data have validated this concept in patients with LFLG severe AS with preserved EF.24

**Implications for Clinical Practice**

The prognosis of patients with severe AS and poor LVEF is poor. In a study of 136 patients with LFLG AS, patients were stratified according the results of a dobutamine stress echocardiogram (DSE) into those with or without contractile reserve.17 Within the group of patients who underwent AVR, the perioperative mortality in patients with contractile reserve was 5% compared with 31% in patients without contractile reserve (Figure 5). The long-term outcome of patients without contractile reserve is very poor, although AVR (albeit at a higher perioperative risk) is still associated with a better long-term outcome than medical therapy.25 Therefore, contractile reserve can be used to risk stratify this group of patients, although patients should not be denied AVR on this basis alone and it should be used as a part of the overall management decision.

A recent multicenter registry of 305 LF/LGAS patients found the survival of patients with pseudosevere AS was significantly better than patients with truly severe LFLG AS and comparable with that of a group of propensity-matched patients with systolic heart failure and no evidence of valve disease.26 This study supports the medical management of these patients.

Guidelines advocate DSE in patients with LFLG AS to distinguish between patient with truly severe AS and those with pseudosevere (moderate) AS.13,14 Furthermore in patients with truly severe AS, the findings can be used to risk stratify operative risk and long-term mortality.

**Evaluation of Concomitant Coronary Artery Disease**

Nearly 50% of patients with AS have concomitant coronary artery disease.27 In patients with moderate AS, symptoms of chest pain or exertional dyspnoea may be attributable to underlying coronary artery disease rather than AS per se. In our practice, we routinely perform SE using exercise or dobutamine, not only to determine transaortic parameters, but also to identify stress-induced ischemia, which may clarify the causes of symptoms. In symptomatic patients with LV dysfunction where the severity of AS is in question, if low-dose dobutamine indicates moderate AS, high doses of dobutamine may be used to uncover ischemia as the cause of LV dysfunction (Figure 6). Evaluation of coronary artery disease in patients with significant AS using higher doses of dobutamine to assess for myocardial ischemia has been shown to be safe.28

**Mitral Stenosis**

In patients with mitral stenosis (MS), the effective mitral valve orifice area is dynamic and may increase during exercise. The degree of change in valve area is related more to mitral valve morphology (calcification, thickening, and leaflet mobility) than to resting valve area per se.29 Variability in response to exercise may also be because of left atrial
compliance.\textsuperscript{29,30} Left atrial compliance is inversely correlated with exercise PASP and functional class.\textsuperscript{30} Therefore, the mechanism of dyspnoea and an increase in PASP may be because of a combination of diminished atrial and mitral valve compliance in combination with an increase in heart rate and reduction in diastolic filling time.

Figure 6. Dobutamine stress echocardiogram in a 72-year-old patient with low-gradient, low-flow aortic stenosis with impaired left ventricular function. Resting heart rate 83 bpm and blood pressure 135/84 mmHg. At rest, the mean transaortic gradient was 32 mmHg, aortic valve area=0.9 cm\(^2\), left ventricular ejection fraction=29\%, flow rate=192 mL/s. After low-dose dobutamine (heart rate 88 bpm; blood pressure 140/90 mmHg), the flow rate increased to 215 mL/s, the mean gradient increased to 38 mmHg but remained <40 mmHg and the aortic valve area increased to 1 cm\(^2\). The calculated projected aortic valve area (at normal flow rate of 250 mL/s) was 1.2 cm\(^2\) confirming moderate stenosis. As the severity of aortic stenosis was moderate, intermediate (30 mcg/kg per minute) and high doses (40 mcg/kg per minute) of dobutamine were infused to identify myocardial ischemia. Myocardial contrast echocardiography to assess for perfusion defect in addition to wall motion abnormality was performed. A, Left ventricular cavity and myocardium opacified with contrast agent. B, Flash—an ultrasound impulse of high mechanical index (0.65) for 8 frames is applied. C, This causes destruction of microbubbles from within the myocardium (arrow). D, Within 2 beats there is replenishment of microbubbles into the anterior wall (dashed arrow). However, there is a perfusion defect in the mid to apical inferior wall suggesting right coronary artery territory ischemia.

Figure 7. Exercise stress echocardiogram in a patient with moderate symptomatic mitral stenosis. Resting heart rate 65 bpm, blood pressure 110/70 mmHg. A, Mean gradient across mitral valve=8 mmHg. B, Estimated pulmonary artery systolic pressure (PASP)=40 mmHg. Patient exercises on the treadmill before becoming markedly short of breath. Heart rate 110 bpm, blood pressure 130/78 mmHg. C, Mean gradient across mitral valve increases to 20 mmHg. D, PASP increases to 74 mmHg.
Accordingly, a proportion of patients with MS develop significant exertional symptoms, despite having MS which is quantified as moderate at rest (Figure 7). The clinical scenarios where SE provides incremental diagnostic information are for the evaluation of patients with severe MS who are asymptomatic and patients with mild/moderate MS who have significant symptoms (Table).³

The clinical use of SE in determining the cause of symptoms was demonstrated in 46 patients with moderate MS whose symptoms were out of proportion to the severity of MS. The test was stopped because of dyspnea in 35 patients (76%) all of whom developed a mean transmitral gradient of 15 mm Hg or PASP>60 mm Hg.¹¹ Although physiological exercise would seem to be the most appropriate and clinically relevant form of dynamic assessment, the prognostic value of DSE in MS has also been investigated.³² If a patient develops a mean gradient of 18 mm Hg during DSE, this had a 90% sensitivity and 87% specificity for prediction of a clinical event (death, mitral valve intervention, arrhythmia, or dyspnea).

In patients with resting measurements suggesting severe MS who are asymptomatic, SE is helpful in uncovering symptoms and demonstrating a significant increase in mean gradient and pulmonary artery pressure. In truly asymptomatic patients, high mitral valve compliance improves valve opening with increasing flow rate during exercise with minimal rise in gradient and pulmonary artery pressure.

Implications for Clinical Practice
Both European Society of Cardiology and American Heart Association/American College of Cardiology guidelines recommend that either dobutamine or preferably exercise SE is performed in patients who are symptomatic, despite Doppler measurements which do not indicate significant MS. An increase in mean mitral gradient to ≥15 mm Hg or PASP to ≥60 mm Hg is considered a Class IIb indication for consideration of percutaneous mitral valvotomy in the American College of Cardiology/American Heart Association Guidelines (Table). The European Society of Cardiology guidelines do not specify exercise criteria but recommend valve intervention in patients with mitral valve area ≤1.5 cm² and symptoms.¹⁴

Conclusions
Dynamic evaluation of the severity and hemodynamic effects of valvular stenosis can provide additional diagnostic information and provide prognostic information, which may help refine risk stratification of patients to aid management decisions (Table). The lack of translation of many of the current studies into clinical practice guidelines is because of the lack of multicenter, randomized trials testing the use of stress-induced markers to determine therapy. Second, the use of more refined markers of disease severity (projected valve area) needs further evaluation.

Disclosures
None.

References
outcome: a multicenter study using dobutamine stress hemodynamics.


**Key Words:** echocardiography, stress ■ heart valve diseases
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