

The Emerging Role of Exercise Testing and Stress Echocardiography in Valvular Heart Disease

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Major advances in diagnosis and risk stratification, combined with enormous progress in surgical valve replacement and repair, have led to improved outcomes of patients with valvular heart disease over the past 30 years. The most important indication for surgical intervention in patients with hemodynamically significant aortic or mitral valve disease is the development of symptoms, as emphasized in recent guidelines [1–3]. As symptoms may develop slowly and indolently in these chronic conditions, many patients are unaware of subtle changes in effort tolerance, even when questioned directly by their physicians. Hence, recent guidelines of both the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) [2, 3] have placed renewed emphasis on the role of exercise testing to provide objective evidence of exercise capacity and symptom status. In addition, while Doppler echocardiography is the method of choice for assessing severity of valvular disease, there is a growing utilization of stress two-dimensional and Doppler echocardiography to assess dynamic changes in hemodynamics in concert with the clinical findings of exercise testing.

Stress echocardiography has become an established method for evaluating patients with coronary artery disease [4–6]. The role of stress echocardiography has been recently expanded to the assessment of the hemodynamic consequences of valvular lesions during stress [7–9]. In a number of clinical conditions, particularly in patients with low-flow, low-gradient aortic valve stenosis (AS), the use of stress echocardiography in the decision-making process has significantly modified the clinical outcome. Evidence accumulated over the last 5 years has led to the incorporation of stress echocardiography in the guidelines of the ACC/AHA [2], the ESC [3], the American Society of Echocardiography [10], and the European Association of Echocardiography [11]. On the basis of the recent recommendations of these scientific organizations, the use of stress echocardiography in valve disease has been ranked as shown in Table 36.1. Applications are either proven (3 stars in the table), probable (2 stars), or possible but not yet established (1 star). Indications of “proven useful” have been incorporated in either one or more of the general cardiology guidelines [2, 3], and those of “probable usefulness” are supported in the stress echocardiography special recommendations [10, 11]. However, indications “of possible value” are not yet supported by the guidelines since they are based only on initial encouraging, but

Table 36.1 Stress echocardiography applications in valvular heart disease

	Aortic gradients (CW)	EF (2D) and SV (2D, PW)	Mitral gradient (CW) PASP (CW)	MR (color), ERO (color; CW), PASP (CW)	Prosthesis gradient (CW) and EOA (2D, PW, CW)	Symptoms
<i>Aortic stenosis</i>						
Low flow, low gradient	√ ^a	√ ^a				√ ^b
High flow, high gradient	√ ^c					
<i>Aortic regurgitation</i>						
Asymptomatic, LV dysfunction		√ ^c				√ ^b
<i>Mitral stenosis</i>						
Symptomatic, mild–moderate			√ ^a			√ ^b
Asymptomatic, severe			√ ^a			
<i>Organic MR</i>						
Symptomatic, mild–moderate				√ ^b		√ ^b
Asymptomatic, severe				√ ^a		
<i>Ischemic MR</i>						
Symptomatic, mild–moderate						√ ^b
Pulmonary edema (unknown origin)						√ ^a
Moderate, before CABG						√ ^b
<i>Valve Prosthesis</i>						
Symptomatic, equivocal rest findings					√ ^b	
Asymptomatic, high gradient					√ ^b	√ ^b

Color color Doppler, *CW* continuous-wave Doppler, *EF* ejection fraction, *MR* mitral regurgitation, *EOA* effective orifice area, *ERO* effective regurgitant orifice area, *PASP* pulmonary artery systolic pressure (from tricuspid regurgitant jet velocity), *PW* pulsed-wave Doppler, *SV* stroke volume, *CABG* coronary artery bypass graft

^a AHA/ACC and/or ESC guidelines

^b ASE and/or EAE recommendations

^c Promising reports

limited, experience reported in the literature. The applications of “proven value” should be implemented in daily clinical practice, the applications of “probable value” can be implemented in selected cases, and the applications of “possible value” remain limited to the research domain.

36.1 Aortic Stenosis

Aortic Valve Stenosis with Low Flow, Low Gradient, and Left Ventricular Dysfunction

Patients with severe AS and left ventricular (LV) systolic dysfunction (ejection fraction < 40%) often present with a relatively low pressure gradient, i.e., mean gradient less than 40 mmHg (Fig. 36.1). This entity represents a diagnostic challenge because it is difficult to distinguish between patients having true anatomically severe AS from those having pseudo-severe AS. In true severe AS, the primary culprit is the valve disease, and

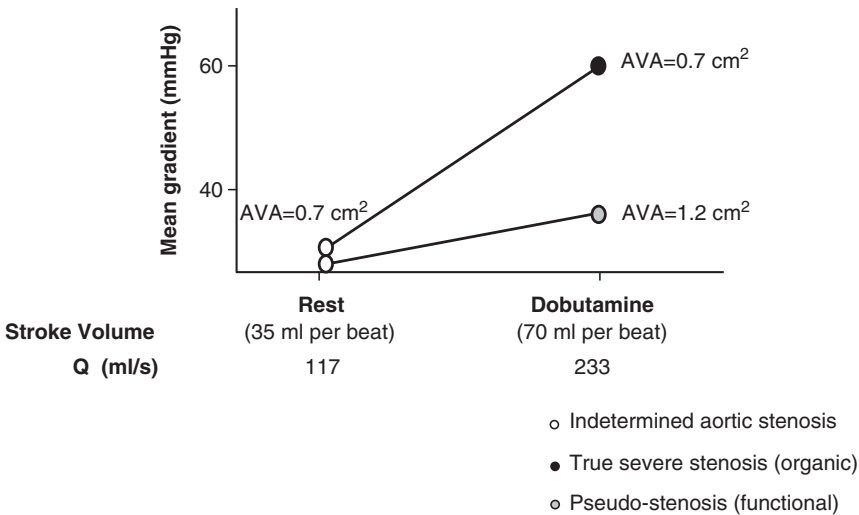


Fig. 36.1 Hemodynamic principles supporting use of dobutamine stress echocardiography in low-flow, low-gradient aortic stenosis. At rest, the mean gradient is low regardless of aortic valve area (AVA) because the transvalvular flow rate is low (white dot). The stroke volume (SV) on the x-axis is low at rest (35 ml; white dot) and may normalize following dobutamine (70 ml). For a given left ventricular ejection time of 0.3, the mean transvalvular flow rate (Q) will increase from 117 to 233 ml s⁻¹. With augmentation of flow with dobutamine, there is a marked increase in gradient (14–57 mmHg in this example) in the case of a true severe stenosis (AVA = 0.7 cm²), whereas there is only a modest increase in gradient (7–19 mmHg) in the case of moderate stenosis (AVA = 1.2 cm²)

the LV dysfunction is a secondary or concomitant phenomenon. The small and relatively fixed aortic valve area (AVA) contributes to raising afterload, decreasing ejection fraction, and reducing stroke volume. In pseudo-severe AS, the predominant factor is myocardial disease, and the severity of AS is overestimated on the basis of AVA because there is incomplete opening of the valve due to reduction in the opening force generated by the weakened ventricle. In both situations, the low-flow state and low-pressure gradient contribute to a calculated AVA that meets criteria for severe AS at rest ($\leq 1.0 \text{ cm}^2$) (Fig. 36.1). Hence, the resting echocardiogram does not distinguish between these two situations. Yet, this distinction is essential since patients with true-severe AS and poor LV function will generally benefit significantly from aortic valve replacement (AVR), whereas the patients with pseudo-severe AS will not.

In patients with low-flow, low-gradient AS and LV dysfunction, it may be useful to determine the transvalvular pressure gradient and to calculate AVA during a baseline resting state and again during low-dose dobutamine stress, to determine whether the stenosis is severe or only moderate [12–20] (Figs. 36.1, 36.2). Side effects are not infrequent with full-dose dobutamine in unselected patients with normal or moderately reduced LV ejection fraction [11, 21], and can occur in one out of five patients with low-flow, low-gradient AS [22]. The main objective of dobutamine stress echocardiography in the context of low-flow AS is to increase transvalvular flow rate while not inducing myocardial ischemia. Hence, a low-dose protocol (i.e., up to $20 \mu\text{g kg}^{-1} \text{ min}^{-1}$) should be used for these patients. Moreover, it is preferable to use longer dobutamine stages (5–8 min instead of the 3–5 min generally used for the detection of ischemic heart disease) to ensure that the patient is in a steady-state condition during Doppler echocardiography data acquisition and before proceeding to the next stage. The increase in heart rate should also be taken into consideration given that it may predispose the patient to myocardial ischemia and at one point may override the inotropic effect, thereby limiting the increase in transvalvular flow.

The dobutamine stress approach is based on the notion that patients who have pseudo-severe AS will exhibit an increase in the AVA and little change in transvalvular gradient in response to the increase in transvalvular flow rate [13] (Figs. 36.2, 36.3). In contrast, patients with true severe AS will have no or minimal increase in AVA and a marked increase in gradient when flow is increased because the valve is rigid (Figs. 36.2, 36.4). Several criteria have been proposed in the literature to differentiate pseudo- from true severe AS including a peak stress mean gradient less than 30 or less than 40 mmHg depending on the study, a peak stress AVA greater than 1.0 or greater than 1.2 cm^2 , and an absolute increase in effective orifice area (EOA) greater than 0.3 cm^2 during dobutamine stress [14–20]. Although the dichotomization of patients into two categories (true or pseudosevere AS) is convenient, it is an oversimplification, and the classification of the individual patient may not always be as easy as it may appear. The changes in gradient and AVA during dobutamine stress depend largely on the magnitude of the flow augmentation achieved, which may vary considerably from one patient to another. The AVA and gradient are therefore measured at flow conditions that differ dramatically from one patient to another, and the utilization of these indices which are not normalized with respect to the flow increase may lead to misclassification of stenosis severity in some patients. To overcome this limitation,

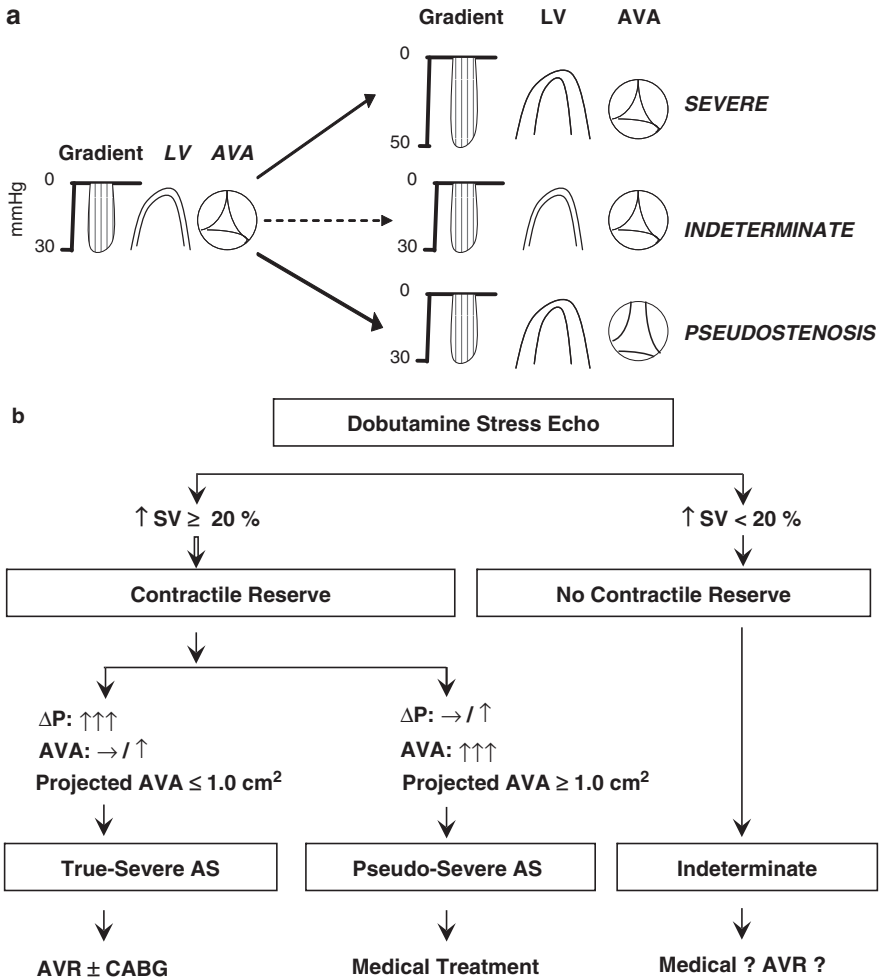


Fig. 36.2 **a** Hemodynamic principles supporting dobutamine stress echocardiography in low-gradient aortic stenosis (AS) with left ventricular dysfunction. The resting transaortic gradient (<40 mmHg), left ventricular (LV) function (<40%), and calculated aortic valve area (AVA, <1 cm²) are depicted on the left. On the right, the three possible responses to dobutamine are shown: in severe AS, the increase in stroke volume (>20%) leads to an increase in gradient with no or only a minimal increase in AVA, but in pseudostenosis, there is only a mild increase in gradient associated with an increase in AVA. The stenosis severity remains “indeterminate” when there is no inotropic response of the left ventricle and thus no significant increase in stroke volume and transvalvular flow rate. **b** Algorithm for the interpretation of the results of dobutamine stress echocardiography in patients with low-flow aortic stenosis. AVA aortic valve area, ΔP transvalvular pressure gradient, SV stroke volume, AVR aortic valve replacement, CABG coronary artery bypass graft surgery, sideward arrow no change, upward arrow mild increase, multiple upward arrows marked increase

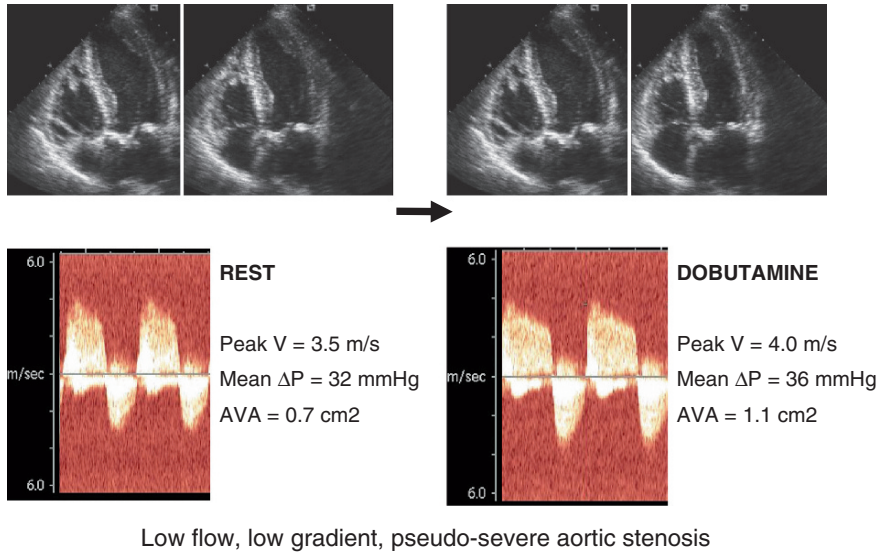


Fig. 36.3 Pseudosevere aortic stenosis unmasked by dobutamine stress echocardiography in a patient with reduced left ventricular function and low gradient at rest. *Upper panels*: end-diastolic and end-systolic frames at rest (*left*) and after dobutamine (*right*), showing an increase in regional thickening. *Lower panels*: slight increase in pressure gradient (ΔP) and significant increase in aortic valve area (AVA)

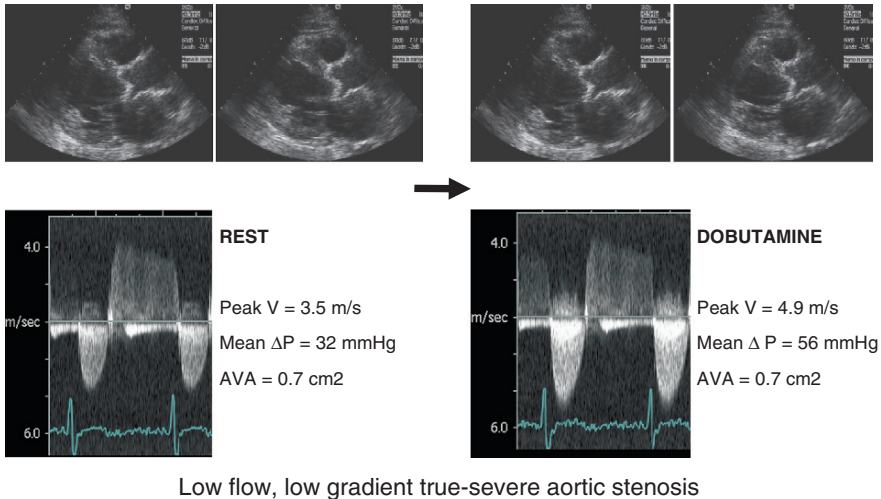
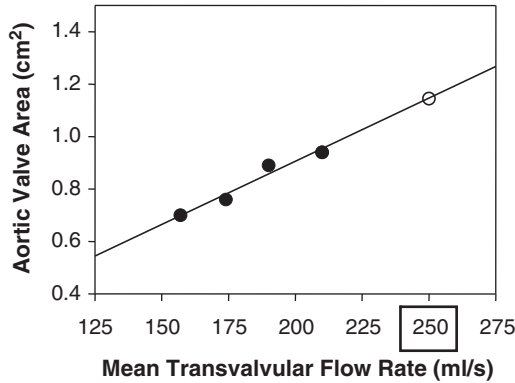


Fig. 36.4 True severe aortic stenosis unmasked by dobutamine stress echocardiography in a patient with reduced left ventricular function and low gradient at rest. *Upper panels*: end-diastolic and end-systolic frames at rest (*left*) and after dobutamine (*right*), showing an increase in regional thickening. *Lower panels*: marked increase in pressure gradient (ΔP) and no increase in aortic valve area (AVA)



Projected AVA = Baseline AVA + VC × (250 – Baseline flow rate)

Projected AVA = 0.7 + 0.0048 × (250 – 157) = 1.15 cm²

Fig. 36.5 Concept of the projected aortic valve area (AVA). Values of AVA obtained at different stages of dobutamine infusion are plotted as a function of flow rate (stroke volume divided by ejection time). The slope of the regression line is the valve compliance (VC). The VC can also be obtained using a simplified method by dividing the absolute increase in AVA measured during dobutamine stress by the absolute increase in flow rate. The projected AVA (open circle) at a normal flow rate (250 ml s⁻¹) is calculated using the regression equation. In this example, the peak AVA (*) obtained during dobutamine is 0.94 cm², and the absolute increase in AVA is 0.24 cm², which would suggest true severe stenosis. However, calculation of the projected AVA using the baseline values of AVA (0.7 cm²) and flow rate (157 ml s⁻¹) and the valve compliance (0.48 cm² 100 ml⁻¹ s⁻¹) yields a value of 1.15 cm², which is consistent with moderate stenosis

the investigators of the Truly or Pseudo-Severe Aortic Stenosis (TOPAS) multicenter study [23] have proposed a new echocardiographic parameter: the projected AVA at a standardized normal flow rate (Fig. 36.5). A projected AVA of less than 1.0 cm² is considered as an indicator of true severe stenosis [23]. Patients who fail to manifest an increase in stroke volume with dobutamine of 20% or greater have a lack of contractile reserve and have been shown to have a poor prognosis with either medical or surgical management [20]. Moreover, in this subset of patients, it is difficult to determine the true severity of the stenosis. Patients identified as having true severe AS and contractile reserve on dobutamine stress have a much better outcome with AVR than with medical therapy [18, 20]. A number of patients without contractile reserve may also benefit from AVR [20], but decisions in these high-risk patients must be individualized, in the absence of clear guidelines. To this effect, plasma brain natriuretic peptide (<550 pg ml⁻¹) may be useful to identify the patients with lack of contractile reserve who may benefit from AVR [24]. Also, the assessment of aortic valve calcification by multislice computed tomography may be helpful to corroborate the stenosis severity in these patients [25].

In patients with low-flow, low-gradient AS, the indication for dobutamine stress echocardiography is rated as class IIa, with level of evidence B [2], with the caveat that dobutamine stress testing in patients with AS should be performed only in centers with experience in pharmacological stress testing and with a cardiologist in attendance.

Asymptomatic Severe Aortic Stenosis with High Gradient

Management of asymptomatic patients with severe AS, defined as peak velocity greater than 4 m s^{-1} and/or mean pressure gradient greater than 40 mmHg and/or AVA less than 1 cm^2 [2, 3], remains a source of debate. The wide interindividual variation in the rate of progression and in the outcome of the disease has recently prompted some authors to recommend early elective surgery in asymptomatic patients with severe AS. The rationale for using this approach is that if one applies a strategy of waiting for symptoms before recommending surgery, the patient may be operated too late in the course of the disease at a stage in which myocardial damage is, at least in part, irreversible.

In this regard, it is also important to emphasize that some patients, and especially elderly patients, may ignore or not report their symptoms, while others may reduce their level of physical activity to avoid or minimize symptoms. The principal role of exercise testing is to unmask symptoms in a significant proportion of patients with AS who claim to be asymptomatic, as these symptoms can predict outcome [26–29]. Reduced exercise tolerance, with development of dyspnea or ST-segment depression, is associated with a worse outcome [27–29]. In this respect, exercise testing is an important tool, and several studies have shown its prognostic value. Moreover, an increase in the mean aortic pressure gradient of more than 20 mmHg during exercise in asymptomatic patients is another predictor of symptom onset in the short term, suggesting that this may also be used as a criterion to recommend early elective surgery (Fig. 36.6) [30]. However, more confirmatory data are

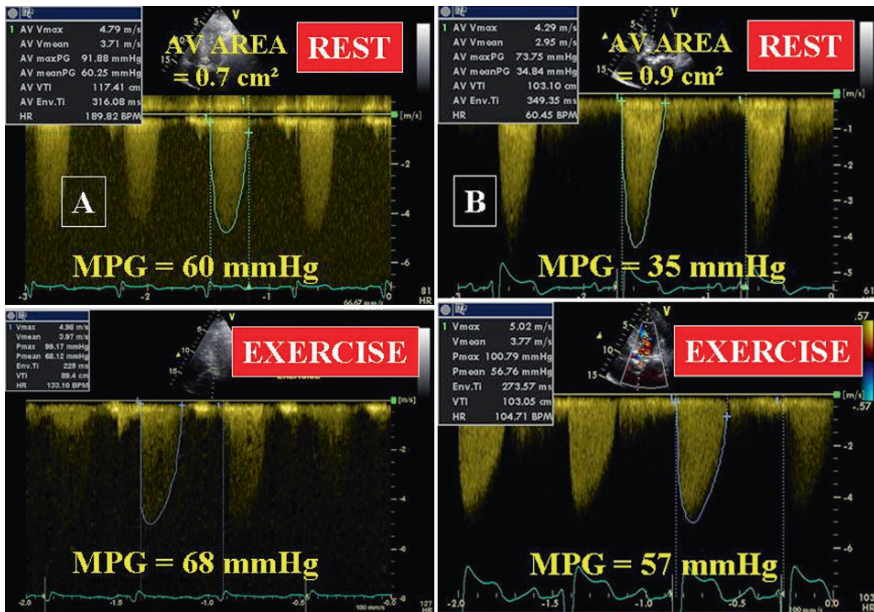


Fig. 36.6 Examples of exercise-induced changes in mean transaortic pressure gradient (MPG) in two asymptomatic patients with severe aortic stenosis. **A** Small increase in MPG with exercise. **B** Significant exercise-induced increase in MPG

needed to support the inclusion of this parameter in the routine management of asymptomatic patients with severe AS.

36.2 Aortic Regurgitation

As is the case with AS and chronic mitral regurgitation (MR), development of irreversible LV dysfunction is a major concern in asymptomatic patients with severe aortic regurgitation (AR). In those with normal resting LV systolic function, an increase in LV ejection fraction during either exercise or pharmacologic stress prior to surgery indicates the presence of contractile reserve, and this may predict improvement in LV function after AVR [31]. The assessment of contractile reserve can be extended for the evaluation of patients with AR who have developed LV dysfunction. In these latter patients, exercise tolerance is an important predictor of reversal of LV dysfunction and survival after AVR [32, 33].

The development of symptoms during exercise testing is useful in predicting outcome in patients with severe AR who are apparently asymptomatic at rest. The additional value of stress imaging is unclear. The observed magnitude of change in ejection fraction or stroke volume from rest to exercise is related not only to myocardial contractile function but also to severity of volume-overload and exercise-induced changes in preload and peripheral resistances [2]. The validity of stress echocardiography in predicting outcome of patients with asymptomatic AR is limited mainly by the small number of available studies [34, 35], but is supported by a number of studies using exercise radionuclide angiography [36–39]. Some data supporting the prognostic value of this functional stratification exist in the literature, but they are too few to recommend this specific application for routine clinical use.

To this effect, the ACC/AHA guidelines do not recommend exercise or dobutamine stress echocardiography for routine assessment of LV function in patients with AR [2]. More data are needed to corroborate this application, since the incremental value of stress imaging to LV dimensions and ejection fraction at rest remains unclear [10].

36.3 Mitral Stenosis

A baseline resting transthoracic echocardiography examination is usually sufficient to guide management in asymptomatic patients with mild-to-moderate mitral stenosis (MS) and in symptomatic patients with moderate-to-severe MS who are candidates for either percutaneous balloon valvuloplasty or surgical mitral valve repair or replacement. In some patients, more detailed assessment of valve function and its hemodynamic consequences is needed, particularly when symptoms and Doppler findings are discordant. In asymptomatic patients with severe MS (mean gradient >10 mmHg and mitral valve area <1.0 cm²), or symptomatic patients with moderate MS (mean gradient of 5–10 mmHg and mitral valve area of 1.0–1.5 cm²), the measurement of pulmonary artery pressures during exercise or dobutamine stress echocardiography may help distinguish those who could benefit from

valvuloplasty or valve replacement from those who should be maintained on medical therapy [2, 40–42]. As is the case with the aortic valve, the transmitral valve pressure gradient is related to the valve orifice area. However, it should be emphasized that the transmitral gradient is much more sensitive to the chronotropic conditions than that of the transaortic gradient and that these conditions may vary extensively from one patient to another. Moreover, for a given valve orifice area, patients with reduced atrioventricular compliance exhibit a more pronounced increase in pulmonary arterial pressure during exercise or dobutamine stress than those with normal compliance [41, 43]. Hence, the resting values of transmitral gradient or pulmonary arterial pressure do not necessarily reflect the actual severity of the disease. Stress echocardiography may therefore be highly useful for confirming the severity of MS and assessing its consequences on the hemodynamic and symptomatic status of the patient under exercise conditions. This test is clearly indicated when there is discordance between the severity of MS as assessed by resting echocardiography and the patient's symptomatic status.

The usually adopted cut-off values, proposed by the ACC/AHA and the ESC guidelines [2, 3], are a peak pulmonary artery systolic pressure greater than 60 mmHg (measured from the tricuspid regurgitant velocity) during exercise (Fig. 36.7) or a mean transmitral pressure gradient greater than 15 mmHg (Fig. 36.8) [2]. Above these threshold values, valvuloplasty or valve replacement is recommended, even for patients with apparently

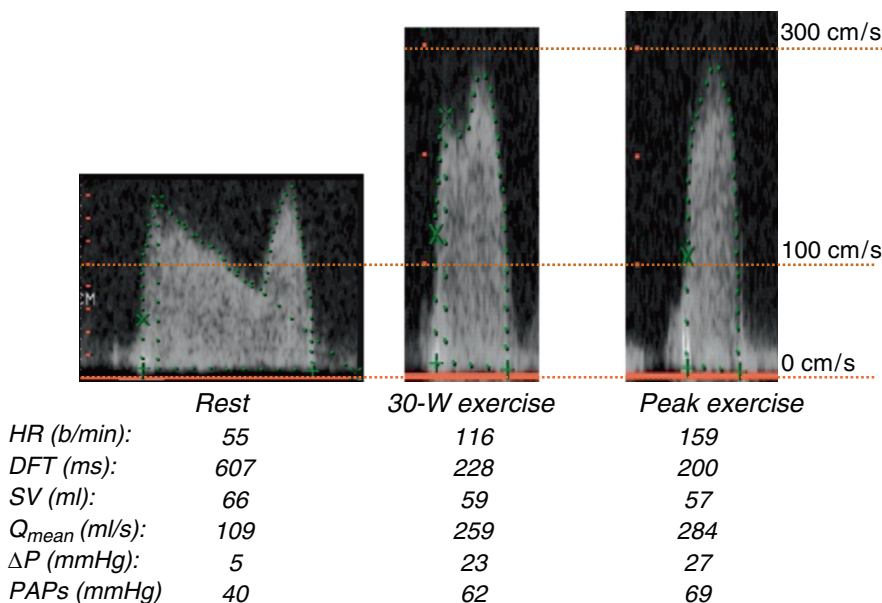


Fig. 36.7 Exercise stress echocardiography in a symptomatic patient with mitral stenosis (mitral valve area: 1.2 cm^2) and relatively low resting mean transmitral pressure gradient (ΔP). With exercise, there is a marked increase in the transvalvular gradient and systolic pulmonary arterial pressure (PAPs). In this patient the exercise-induced increase in mean transvalvular flow rate (Q_{mean}) was caused by the dramatic shortening in diastolic filling time (DFT). HR heart rate, SV stroke volume

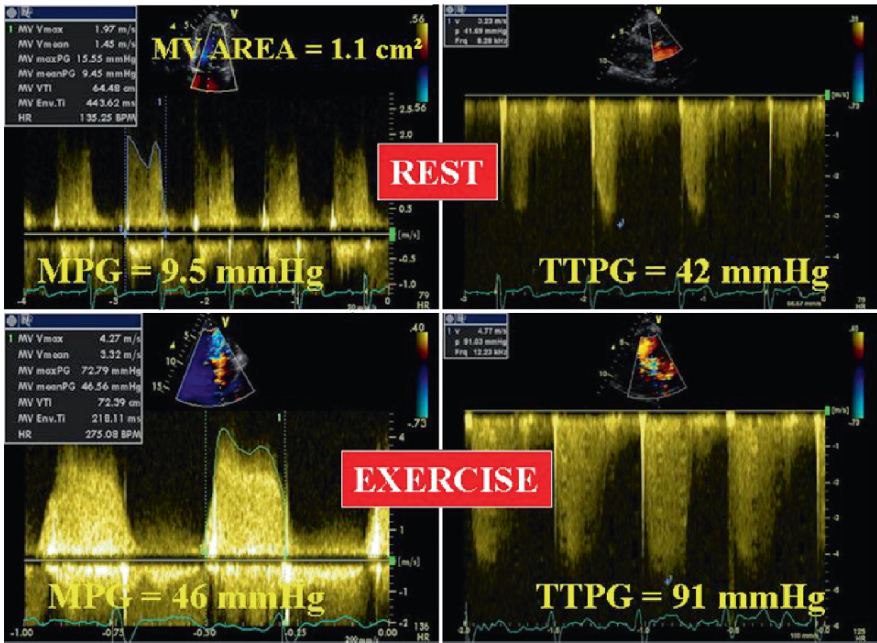


Fig. 36.8 Example of an asymptomatic patient with severe mitral valve stenosis but with moderately elevated mean transmitral pressure gradient (MPG) at rest. During exercise, the MPG increases markedly as does the systolic transcutaneous pressure gradient (TTPG) indicative of pulmonary hypertension

moderate MS at rest [2, 10, 11]. The use of this stress echocardiography application in MS is rated as class I with level of evidence C for patients with discordant symptoms and stenosis severity [2]. As with other valve conditions, a major role of stress testing in patients with MS is to evaluate exercise capacity and exercise-induced symptoms.

36.4 Mitral Regurgitation

Organic Mitral Regurgitation

The severity of organic MR can be reliably assessed by resting color-flow Doppler echocardiography with the use of semiquantitative or quantitative methods [2, 3, 44]. Such information is useful to predict the development of LV dysfunction and of symptoms [45]. There is presently an important ongoing controversy on whether asymptomatic patients with severe MR should undergo early elective mitral valve repair [45–47]. In selected patients in whom there is a discrepancy between symptoms and severity of MR, and especially in asymptomatic patients with severe MR, exercise stress echocardiography may help to identify patients with subclinical latent LV dysfunction and poor

clinical outcome. Worsening of MR severity, a marked increase in pulmonary arterial pressure, the absence of contractile reserve, impaired exercise capacity, and the occurrence of symptoms during stress exercise echocardiography can be useful findings to identify the subset of high-risk patients who may benefit from early surgery. Exercise capacity itself predicts the development of symptoms or LV dysfunction in asymptomatic patients with MR [48]. Recommendations for early surgery in asymptomatic patients should only be made in those who are candidates for mitral valve repair and in experienced centers in which there is a high likelihood (>90%) of successful mitral repair without residual MR [2].

Exercise echocardiography has also been used to unmask the development of severe MR with exercise in patients with rheumatic mitral valve disease and only mild or moderate MR at rest [49]. The spectrum of LV responses to stress is not dissimilar from that described for AR, but the prognostic impact of this functional heterogeneity remains unsettled. Although still relatively unexplored, the assessment of contractile reserve in patients with MR may provide important information for risk stratification and clinical decision making, especially in asymptomatic patients with severe MR. A threshold value of pulmonary artery systolic pressure greater than 60 mmHg during exercise may also identify patients with severe MR who might be referred for surgery [2, 10]. The application of stress echocardiography in asymptomatic patients with severe MR is rated as a class IIa recommendation with level of evidence C [2].

Ischemic Mitral Regurgitation

Exercise stress echocardiography is valuable in identifying hemodynamically significant MR in patients with LV systolic dysfunction, especially when ischemic heart disease is the underlying etiology. Ischemic MR is primarily a disease of the LV myocardium and develops with a structurally normal mitral valve. The magnitude of ischemic MR varies dynamically in accordance with changes in loading conditions, annular size, and the balance of tethering versus closing forces applied on the mitral valve leaflets. Hence, the severity of MR assessed by resting echocardiography does not necessarily reflect the severity under exercise conditions. In patients with ischemic MR, quantitative assessment of exercise-induced changes in the degree of MR may be useful to unmask patients at high risk of poor outcome. An increase in the effective regurgitant orifice area to 13 mm² or greater or an increase in the systolic pulmonary arterial pressure to 60 mmHg or greater (Fig. 36.9) at peak exercise stress is predictive of increased morbidity and mortality [50]. Furthermore, the magnitude of increase in effective regurgitant orifice during exercise cannot be predicted from the resting regurgitant orifice. Hence, exercise Doppler echocardiography provides important incremental information over resting echocardiography in patients with ischemic MR.

Pierard and Lancellotti [51–53] have proposed that exercise stress echocardiography in patients with ischemic MR can provide useful information in the following situations: (1) patients with exertional dyspnea out of proportion to the severity of resting LV dysfunction or MR; (2) patients in whom acute pulmonary edema occurs without an obvious cause; and (3) patients with moderate MR before surgical revascularization. Their data also suggest that exercise echocardiography may be helpful in identifying patients at high risk of mortality and heart failure.

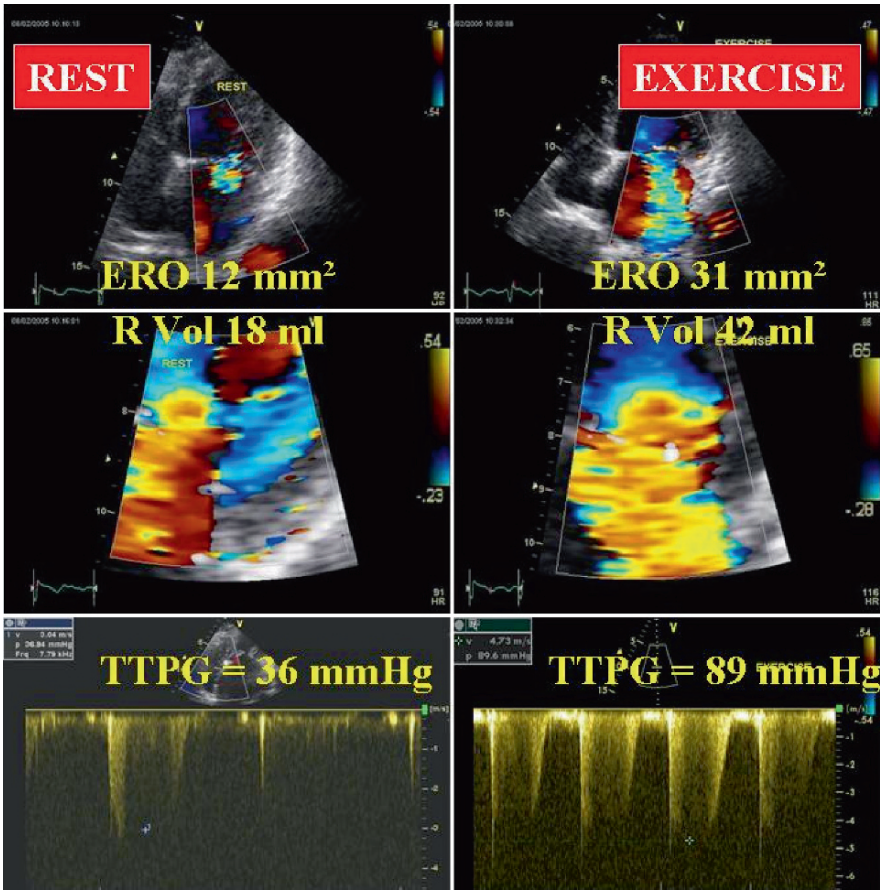


Fig. 36.9 Apical 4-chamber view showing color-flow Doppler and proximal flow-convergence region at rest and during exercise in a patient with a large exercise-induced increase in mitral regurgitation and estimated pulmonary artery systolic pressure. *ERO*, effective regurgitant orifice; *RVol*, regurgitant volume; *TTPG*, systolic transtricuspid pressure gradient

36.5 Prosthetic Heart Valves

Echocardiography is the method of choice for evaluating prosthetic valve function. This evaluation follows the same principles used for the evaluation of native valves with some important caveats [54, 55]. First, imaging of the valve occluder and assessment of transprosthetic flow are limited by reverberations and shadowing caused by the valve components. Second, the fluid dynamics of mechanical prosthetic valves may differ substantially from that of a native valve. The flow is eccentric in monoleaflet valves and is composed of three separate jets in bileaflet valves, with the flow velocity potentially higher in the central orifice jet than in the two lateral orifice jets.

Because most prosthetic valves are inherently stenotic, the EOA of a prosthetic valve is often too small in relation to body size, a phenomenon known as prosthesis–patient mismatch (PPM). In the aortic position, PPM is considered moderate when the indexed EOA is less than or equal to $0.85 \text{ cm}^2 \text{ m}^{-2}$ and severe when it is less than or equal to $0.65 \text{ cm}^2 \text{ m}^{-2}$ [55]. In the mitral position, the cut-off values are 1.2 and $0.9 \text{ cm}^2 \text{ m}^{-2}$, respectively. PPM has been linked to impaired exercise capacity, suboptimal symptomatic improvement, incomplete regression of LV hypertrophy and pulmonary hypertension, and increased cardiac events and mortality following valve replacement [56–60]. PPM is, by far, the most frequent cause of increased transprosthetic gradient. It is important to differentiate this condition from acquired prosthetic stenosis, which may result from leaflet calcification of bioprostheses and pannus overgrowth or thrombus formation on mechanical prostheses.

The presence of increased mean transprosthetic gradient (15–20 mmHg for aortic prostheses and 5–7 mmHg for mitral prostheses) and/or symptoms should prompt further evaluation. In particular, it is important to determine whether the elevated gradient, and eventually the associated symptoms, are due to PPM, an intrinsic stenosis of the prosthesis, or a localized high gradient, a phenomenon that occurs only in bileaflet mechanical valves. Occasionally, an abnormally high jet velocity corresponding to a localized gradient may indeed be recorded by continuous wave Doppler through the smaller central slit-like orifice of bileaflet mechanical prostheses. This phenomenon yields measurement of an abnormally high gradient and low EOA, thus mimicking the findings of intrinsic prosthesis dysfunction.

As normally and abnormally functioning prostheses can produce similar estimated gradients at rest by transthoracic echocardiography, it may be difficult to distinguish between high gradients caused by artifactual phenomena from those caused by prosthetic valve stenosis or PPM. In these situations, stress echocardiography may be valuable in confirming or excluding the presence of hemodynamically significant prosthetic valve stenosis or PPM, especially when there is discordance between the prosthetic valve hemodynamics measured by echocardiography at rest and the patient's symptomatic status [55, 61–65]. In contrast to a normally functioning and well-matched prosthesis (including a bileaflet mechanical valve with a localized high gradient at rest), a stenotic valve prosthesis or PPM is generally associated with a marked increase in gradient with exercise, often associated with pulmonary arterial hypertension, the development of symptoms, and impaired exercise capacity on exercise echocardiography [66–73]. A disproportionate increase in transvalvular gradient ($>20 \text{ mmHg}$ for aortic prostheses or $>12 \text{ mmHg}$ for mitral prostheses) generally indicates severe prosthesis dysfunction or PPM (Fig. 36.10). High resting and stress gradients occur more often with biological rather than mechanical prostheses, stented rather than stentless bioprostheses, smaller (≤ 21 for aortic, and ≤ 25 for mitral) rather than larger prostheses, and mismatched rather than nonmismatched prostheses. In fact, the behavior of the transprosthetic pressure gradient under exercise conditions is essentially determined by the indexed EOA (Fig. 36.10), which in turn may be influenced by the patient's body size, prosthesis model and size, mismatch between body size and prosthesis size, and pathologic obstruction of the prosthesis caused by leaflet calcification, pannus, or thrombus.

As is the case in native aortic valves that have developed low-flow, low-gradient AS, dobutamine stress echocardiography may be useful in differentiating true prosthesis stenosis from pseudostenosis or PPM in patients with prosthetic valves and low cardiac output. In the case of pseudostenosis with low output, the resting transprosthetic flow rate and

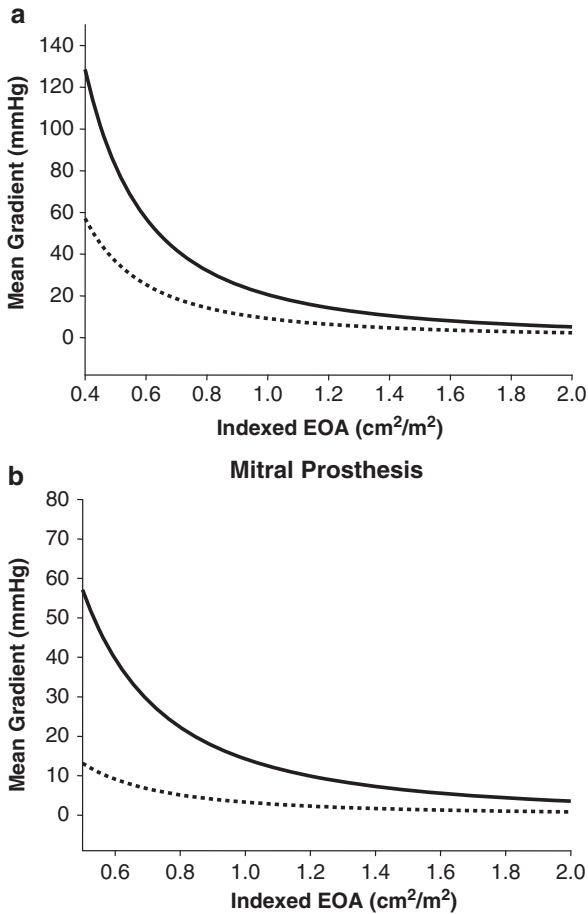


Fig. 36.10 Mean transprosthetic pressure gradient at rest (dotted lines) and during sustained physical exercise (continuous lines) as a function of the indexed effective orifice area (EOA) for aortic (a) and mitral (b) prostheses. Compared to patients no. 2 and 4 who have large prosthetic EOAs, patients 1 and 3 with small EOAs exhibit a major increase in gradient with exercise, thus suggesting the presence of severe prosthetic stenosis or prosthesis–patient mismatch in these latter patients

thus the force applied on the leaflets are too low to completely open the prosthetic valve. During infusion of dobutamine, however, these patients manifest a substantial increase in the prosthesis EOA with the increasing flow rate, with no or minimal elevation in the prosthetic gradient. In contrast, true severe prosthetic stenosis or PPM is associated with no significant increase in EOA and a marked increase in gradient with dobutamine, often with additional diagnostic changes (such as LV dysfunction or marked elevation in pulmonary arterial pressure) and symptoms.

It should be emphasized that exercise or dobutamine stress echocardiography does not distinguish between acquired prosthesis stenosis and PPM, as in both cases the EOA remains

small and the gradient increases markedly with stress. In this situation, one should compare the EOA values obtained during stress echocardiography with the normal reference values of EOA for the model and size of the specific prosthesis that has been implanted in the patient [55]. If the measured EOA is substantially lower than the normal reference EOA, one should suspect prosthesis dysfunction. If, on the other hand, the measured EOA is within the normal reference range, and the indexed EOA is low, one should consider the presence of PPM.

In patients undergoing surgical correction of ischemic MR, a restrictive annuloplasty combined with coronary artery bypass grafting is the most common approach. However, this procedure is associated with a relatively high rate of recurrence of MR, and restrictive annuloplasty may result in functional MS in some patients [74]. In patients with postoperative symptoms or evidence of either residual MR or functional MS, exercise testing may be useful to assess symptoms and exercise capacity, and the assessment of exercise hemodynamics with stress echocardiography can provide additional important information regarding the significance of MS and/or of dynamic MR.

There are relatively few studies investigating the added value of stress echocardiography for the management of patients with prosthetic valves or mitral annuloplasty rings, and the available studies are generally based on small numbers of patients. Although stress echocardiography has been shown to be useful in the evaluation of prosthetic valve dysfunction and PPM, its value in risk stratification and prediction of clinical outcomes is not well established. Thus, further studies are needed in this challenging field.

36.6

Coronary Artery Disease and Coronary Flow Reserve

Diagnosis of Coronary Artery Disease in Patients with Valvular Heart Disease

Although stress echocardiography is a widely accepted, accurate, and safe noninvasive technique to diagnose the presence and severity of coronary artery disease in patients without valvular heart disease, relatively few data are available on its accuracy and safety in patients with hemodynamically significant valve disease. In general, one can expect that the sensitivity of stress echocardiography will be similar in patients with and without valvular heart disease but the specificity will be lower [75, 76]. Coronary flow reserve can be severely reduced in patients with AS or AR even when the epicardial coronary arteries are normal [77–79]. For this same reason, the specificity of perfusion imaging is also suboptimal in patients with LV hypertrophy secondary to valvular heart disease [75]. For practical purposes, conventional coronary angiography remains the established investigation for ruling out significant coronary artery disease in the preoperative evaluation of patients awaiting valve surgery, although cardiac computed tomography may also have a role in patients without coronary calcification.

Coronary Flow Reserve in Valvular Heart Disease

In patients with severe AS and normal coronary arteries, the reduced coronary flow reserve is more closely related to the severity of the stenosis than to the degree of LV hypertrophy [80].

The impairment of coronary flow reserve classically observed in AS may be caused by several factors including extravascular compression of the coronary microvasculature due to elevated LV diastolic pressures, a shortening of diastolic perfusion time, and an increase in myocardial metabolic demand resulting from the LV pressure overload.

Following AVR, normalization of coronary flow reserve is directly related to the augmentation in valve EOA [79]. Stentless bioprostheses are associated with greater improvement in coronary flow reserve compared to that of stented bioprostheses or mechanical valves [80], presumably because stentless bioprostheses generally provide a larger EOA for a given annulus size. In the future, the assessment of coronary flow reserve is likely to play an increasingly important role in the assessment of patients with valvular heart disease, especially aortic valve disease, before and after AVR. Positron emission tomography has an established role in quantifying coronary flow reserve, and cardiac magnetic resonance imaging is evolving as another noninvasive method for this assessment [81], with the potential to quantify the transmural gradient of flow reserve across the myocardial wall [82]. Both techniques have been applied to study changes in coronary flow reserve in patients with AS after AVR [79, 80]. Transthoracic echocardiography also has the potential to study coronary flow reserve of the middistal left anterior descending coronary artery [83], and this technique has been applied to patients with AS [84] (Fig. 36.11).

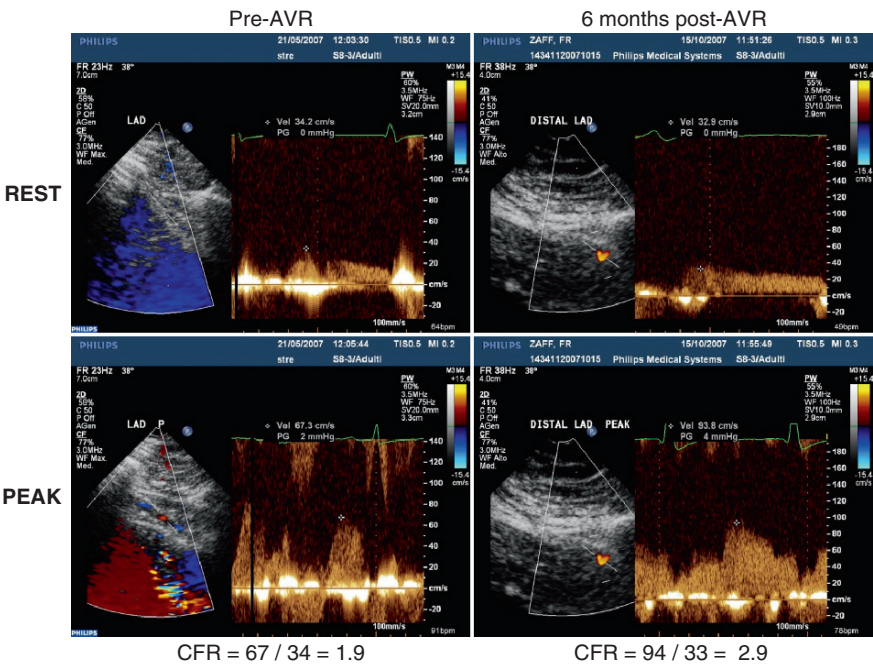


Fig. 36.11 Coronary flow reserve (CFR) assessed at rest and during adenosine administration by transthoracic stress echocardiography in a patient with severe aortic stenosis and angiographically normal coronary arteries before (left panel) and 6 months after (right panel) aortic valve replacement (AVR). In the postoperative assessment, left ventricular hypertrophy is not yet regressed but CFR has substantially improved. (Courtesy of Dr. Fausto Rigo, Venice, Italy)

Echocardiography has the obvious advantage of wide availability and relatively low cost, and with further experience, this technique could be added to the standard, routine applications of echocardiography in evaluating valve disease [85, 86].

36.7

Conclusions

Exercise testing has an established role in the evaluation of patients with valvular heart disease that can aid significantly in clinical decision making. Stress echocardiography has emerged as an important component of stress testing, in which the noninvasive assessment of dynamic changes in valve function, ventricular function, and hemodynamics can be coupled with assessment of exercise capacity and symptomatic responses. Surprisingly, this role is much more clearly established in American [2] than European [3] general cardiology guidelines, despite the larger and earlier acceptance of stress echocardiography in the European practice for the diagnosis of coronary artery disease [1, 5, 6]. Stress echocardiography has the advantages of wide availability, low cost, and versatility for the assessment of disease severity [2, 3, 10, 11]. In addition to its established applications in valvular heart disease, transthoracic Doppler echocardiography also has the potential to assess coronary flow reserve. The versatile applications of stress echocardiography can be tailored to the individual patient with aortic or mitral valve disease, both before and after valve replacement or repair. Hence, exercise-induced changes in valve hemodynamics, ventricular function, and pulmonary artery pressure, together with exercise capacity and symptomatic responses to exercise, provide the clinician with diagnostic and prognostic information that can contribute importantly to subsequent clinical decisions.

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