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

Eugenio Picano, MD, PhD, Philippe Pibarot, MD, PhD, Patrizio Lancellotti, MD, PhD; Jean Luc Monin, MD, PhD, Robert O. Bonow, MD

Pisa, Italy; Quebec City, Quebec, Canada; Liege, Belgium; Creteil, France; and Chicago, Illinois

Exercise testing has an established role in the evaluation of patients with valvular heart disease and can aid clinical decision making. Because symptoms may develop slowly and indolently in chronic valve diseases and are often not recognized by patients and their physicians, the symptomatic, blood pressure, and electrocardiographic responses to exercise can help identify patients who would benefit from early valve repair or replacement. In addition, stress echocardiography has emerged as an important component of stress testing in patients with valvular heart disease, with relevant established and potential applications. Stress echocardiography has the advantages of its wide availability, low cost, and versatility for the assessment of disease severity. 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 to subsequent clinical decisions. Nevertheless, there is a lack of convincing evidence that the results of stress echocardiography lead to clinical decisions that result in better outcomes, and therefore large-scale prospective randomized studies focusing on patient outcomes are needed in the future. (J Am Coll Cardiol 2009;54:2251–60)

© 2009 by the American College of Cardiology Foundation
tial and rapid changes in heart rate and loading conditions. On the other hand, supine exercise is not as physiologic as is treadmill exercise, and the equipment is not nearly as widely available as is the treadmill.

AS

Asymptomatic patients with severe AS. The onset of symptoms in patients with severe AS represents a clear indication for aortic valve replacement (AVR) (1,2). Exercise testing clearly has no role, and is contraindicated in patients with definite cardiac symptoms or symptoms that are highly suspicious. On the other hand, it is apparent that some patients, especially elderly patients, may ignore or not report mild dyspnea and fatigue, which are difficult to differentiate from the effects of aging or deconditioning. Patients also may reduce their level of physical activity to avoid or minimize symptoms. The principal role of exercise testing is to unmask symptoms or abnormal blood pressure responses in patients with AS who claim to be asymptomatic.

Numerous studies have shown that exercise testing, with appropriate physician supervision and close monitoring of the electrocardiogram and blood pressure, is safe in patients without apparent symptoms (10–15) and that the results can identify a subset of patients with a high likelihood of death or symptom onset over the next 1 to 2 years (13–15). Both the ACC/AHA and the ESC guidelines (1,2) support the role of exercise testing in asymptomatic AS patients, with recommendations that AVR be considered in those with exercise-induced symptoms or abnormal blood pressure responses. The strength of this recommendation differs between the 2 guidelines, with a Class IIb recommendation from the ACC/AHA compared with Class I (symptoms) and Class IIa (abnormal blood pressure) recommendations from the ESC. The divergent strengths of these recommendations arise from the lack of definitive evidence from prospective clinical trials and the consensus of 2 different writing groups in interpreting the available data. For example, it is often difficult to ascertain in aging and deconditioned patients with AS whether symptoms on treadmill testing truly represent cardiac symptoms. In addition, physicians may have a lower threshold for referring a patient for AVR after a treadmill test in which the patient had impaired exercise tolerance, presumed symptoms, or an abnormal blood pressure response compared with patients with excellent exercise capacity and a normal blood pressure response. This could result in a post-test referral bias in studies of exercise testing in AS, in which patients with abnormal exercise results are preferentially referred to AVR.

The role of exercise echocardiography in asymptomatic patients with AS is less clear because this has not been studied extensively (16,17). A recent study (17) investigating 69 asymptomatic patients with severe AS (aortic valve area [AVA] <1.0 cm²) has shown that an increase in the mean aortic valve pressure gradient of 18 mm Hg or more during exercise was an independent predictor of symptom onset during the 15-month mean follow-up period, as were an AVA <0.75 cm² and abnormal exercise results (symptoms, ST-segment depression, or <20 mm Hg increase in blood pressure). This increase in mean pressure gradient during exercise reflects the presence of fixed valve stenosis with limited valve compliance (18). Stress echocardiography also provides assessment of the LV functional response to exercise (19,20), with evidence suggesting that patients with limited LV functional reserve (those with a lower increase in ejection fraction) are at increased risk for untoward events (20). Whether an increase in the mean aortic valve pressure gradient and/or a limited increase in ejection fraction should be considered criteria for early elective surgery requires additional investigation.

Aortic valve stenosis with low-flow, low-gradient, and LV dysfunction. In contrast to patients with severe AS and preserved LV function, there seems to be a well-defined role of stress echocardiography in patients with LV dysfunction (21–27) (Fig. 1). Patients with anatomically severe AS and LV systolic dysfunction (ejection fraction <40%) often present with a relatively low-pressure gradient, such as a mean gradient of 30 to 40 mm Hg or less. These patients represent a diagnostic challenge because it is often difficult to differentiate them from other patients with a primary cardiomyopathic process and a thickened but nonstenotic aortic valve producing an outflow murmur. This latter condition is often termed pseudosevere AS. In true severe AS, the small and relatively fixed AVA contributes to an increase in afterload, a decrease in ejection fraction, and a reduction stroke volume. In pseudosevere 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 caused by 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 (≤1.0 cm²) (Fig. 1). Hence, the resting echocardiogram does not distinguish between these 2 situations. Yet, this distinction is essential because patients with true severe AS and poor LV function will generally benefit significantly from AVR, whereas the patients with pseudosevere AS will not and may also have a higher risk of perioperative mortality.

The main objective of dobutamine stress echocardiography in the context of low-flow AS is to increase the transvalvular flow rate while not inducing myocardial ischemia. Side effects are not infrequent with full-dose dobut-
Amine in unselected patients with normal or moderately reduced LV ejection fraction (9,28) and can occur in up to 20% of patients with low-flow, low-gradient AS (29). Arrhythmias are the most frequent serious adverse reactions. Tachyarrhythmias (including ventricular fibrillation) can arise from ischemia or ischemia-independent direct arrhythmogenic effects of adrenergic stimulation, and bradyarrhythmias (including cardiac asystole) can result from a vasodepressor reflex triggered by LV mechanoreceptor stimulation. Both mechanisms are magnified by LV hypertrophy (28,29). Hence, a low-dose protocol (i.e., up to 20 μg/kg/min) should be used in these patients. Moreover, it is preferable to use longer dobutamine stages (5 to 8 min instead of the 3 to 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 gradual increments in dobutamine dose are also helpful in preventing rapid increases in heart rate that may predispose to myocardial ischemia, because ischemic myocardial dysfunction may override the inotropic effect, thereby limiting the increase in transvalvular flow.

The results of dobutamine stress echocardiography aid in decision making in patients with low-flow aortic stenosis (AS) when dobutamine elicits contractile reserve. Management decisions are more difficult when contractile reserve is absent. Contractile reserve is defined as an increase in stroke volume (SV) ≥20% using the criteria of Nishimura et al. (24) and Monin et al. (25). When contractile reserve is elicited, patients with true severe AS manifest an increase in transvalvular pressure gradient (ΔP) with a low calculated aortic valve area (AVA). One can also determine the projected AVA at a standardized normal flow rate (AVAprojected). An AVAprojected ≤1.0 cm² is considered an indicator of true severe stenosis (30). Figure illustration by Rob Flewell. AVR = aortic valve replacement; CABG = coronary artery bypass graft surgery.
Aortic Regurgitation (AR)

The development of symptoms has important prognostic implications in patients with AR. Natural history studies indicate that symptomatic patients have an excessive mortality rate compared with asymptomatic patients (36), and the severity of pre-operative symptoms is a strong determinant of survival after AVR (37). As with patients with AS, exercise testing may elicit symptomatic responses in patients with AR who are apparently asymptomatic based on the medical history, thus identifying candidates for surgery. In addition, pre-operative exercise capacity in patients with AR and LV systolic dysfunction, together with duration of pre-operative LV dysfunction, is helpful in predicting survival and recovery of function after AVR (38).

The additional value of stress imaging in patients with AR 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 resistance (1). The validity of stress echocardiography in predicting outcome of patients with asymptomatic AR is limited by the small number of available studies (39,40) compared with the more extensive and consistent experience with exercise radionuclide angiography (41–44). With the sparse data supporting the incremental prognostic value of stress echocardiography, this specific application is not recommended for routine clinical use (1).

Mitral Stenosis (MS)

A resting transthoracic echocardiogram is usually sufficient to guide management in asymptomatic patients with mild to moderate MS and in symptomatic patients with severe MS who are candidates for either percutaneous balloon valvuloplasty or surgical mitral valve repair or replacement. Management considerations are less clear in asymptomatic patients with severe MS and in symptomatic patients with only mild to moderate MS at rest, and in these 2 groups of patients exercise testing can provide critical information on functional capacity and exercise-induced symptoms. Stress echocardiography provides added value when more detailed assessment of valve function and its hemodynamic consequences is needed, particularly in the asymptomatic patient and the patient in whom symptoms and Doppler findings at rest are discordant.

In asymptomatic patients with severe MS (mean gradient >10 mm Hg and mitral valve area [MVA] <1.0 cm²), or symptomatic patients with moderate MS (mean gradient of 5 to 10 mm Hg and MVA of 1.0 to 1.5 cm²), the measurement of pulmonary artery pressures (measured from the tricuspid regurgitant velocity) during exercise or dobutamine stress echocardiography can help distinguish those who could benefit from valvuloplasty or valve replacement from those who should be maintained on medical therapy...
(1,45,46). As is the case with the aortic valve, the transmitral valve pressure gradient is related to the MVA. However, it should be emphasized that the transmitral gradient is much more sensitive to heart rate than is the transaortic gradient and that the degree of this heart rate sensitivity may vary extensively from one patient to another. Moreover, for a given MVA, patients with reduced atrioventricular compliance show a more pronounced increase in pulmonary arterial pressure during exercise or dobutamine than those with normal compliance (45,47). Hence, in some patients determined to have only moderate MS at rest, the physiologic effects of heart rate sensitivity and atrioventricular compliance can produce exercise-induced pulmonary hypertension and exertional dyspnea. Because the resting values of transmitral gradient and pulmonary arterial pressure do not necessarily reflect the actual severity of the disease, stress echocardiography may provide the necessary clues in determining the severity of MS, assessing its hemodynamic impact, and explaining exercise-induced symptoms.

The current ACC/AHA guidelines have given a Class I recommendation (Level of Evidence: C) for stress echocardiography in patients with MS and discordance between symptoms and stenosis severity (1). The threshold values proposed by the ACC/AHA guidelines (1) for consideration for intervention are a mean transmitral pressure gradient $>15$ mm Hg during exercise or a peak pulmonary artery systolic pressure $>60$ mm Hg during exercise (Fig. 2). In patients with pulmonary artery pressures or valve gradients above these values, percutaneous balloon valvotomy or surgical intervention is recommended, even for patients with apparently moderate MS at rest (1,7,9). There are important caveats in applying these recommendations in clinical practice because they are all based on a level C weight of evidence, and the proposed cutoff values remain arbitrary and consensus driven and not supported by evidence of improved outcomes. Therefore, this represents another area in which further clinical research is needed.

Mitral Regurgitation (MR)

Degenerative MR. The severity of degenerative MR can be reliably assessed by resting color-flow Doppler echocardiography with the use of semiquantitative or quantitative methods (1,2,48). Such information is useful to predict the development of LV dysfunction and of symptoms (49). Presently, there is an important ongoing controversy regarding whether asymptomatic patients with severe MR should undergo early elective mitral valve repair (49–52). In selected patients with MR, exercise testing may aid in this critical management decision.

Exercise capacity itself is a predictor of the development of symptoms or LV dysfunction in asymptomatic patients with MR (53). In asymptomatic patients with severe MR, exercise stress echocardiography may help identify patients with unrecognized symptoms or subclinical latent LV dysfunction.

In symptomatic patients in whom the severity of MR is estimated to be only mild at rest, exercise echocardiography may be useful in elucidating the cause of symptoms by determining whether the severity of MR increases or pulmonary arterial hypertension develops during exercise (54). It is noteworthy that the data supporting this concept were derived in patients with rheumatic MR, and the data supporting this application for degenerative MR are limited. Moreover, data supporting this application in asymptomatic patients are limited. However, worsening of MR severity, a marked increase in pulmonary arterial pressure, impaired exercise capacity, and the occurrence of symptoms during exercise echocardiography can be useful findings for identifying a subset of apparently asymptomatic patients at higher risk who may benefit from early surgery. A pulmonary artery systolic pressure $>60$ mm Hg during exercise has been suggested as a threshold value above which asymptomatic patients with severe MR might be referred for surgical valve repair (1,8). This application of stress echocardiography is rated as a Class IIa recommendation with Level of Evidence: C (1). Recommendations for early surgery in asymptomatic patients should only be made in those patients who
are candidates for mitral valve repair and in experienced centers in which there is expertise both in noninvasive evaluation and in surgical correction, with a high likelihood (>90%) of successful mitral repair without residual MR (1). Valve replacement has particularly serious negative consequences for asymptomatic patients. Large prospective studies are needed to establish the usefulness of stress echocardiography for risk stratification and clinical decision making in degenerative MR.

The spectrum of LV responses to exercise stress in patients with MR is not dissimilar to that described for patients with AR (55), but the prognostic impact of this functional heterogeneity remains unsettled, and the importance of LV functional reserve in MR as assessed by changes in LV ejection fraction remains to be defined. A recent report, using 2-dimensional speckle tracking of myocardial deformation, has shown that reduced LV longitudinal functional reserve with exercise predicts midterm impairment in LV function in medically-treated patients with MR as well as post-operative LV dysfunction in patients who have undergone surgery for MR (56). This novel application of stress echocardiography is the subject of ongoing investigation.

**Ischemic MR.** MR is a common feature of ischemic LV systolic dysfunction (57–59). Patients with ischemic MR have more severe LV dysfunction compared with patients without associated MR, and the available data indicate that MR also confers a greater mortality risk and a greater risk of developing overt heart failure (57–60). MR arises in chronic CAD from global and regional LV remodeling (apical and posterior displacement of papillary muscles) leading to papillary muscle displacement, tenting of the mitral valve leaflets, and loss of systolic annular contraction (61–63). Hence, ischemic MR is primarily a disease of the LV myocardium, and therapies that produce beneficial reverse LV remodeling, such as myocardial revascularization (64), beta-blocker therapy (65), and cardiac resynchronization (66–68), have the potential to reduce or eliminate MR. In the case of revascularization, this can usually only be achieved with concomitant mitral valve repair with restrictive annuloplasty or mitral valve replacement (1,2,69,70).

A principal role of stress echocardiography in ischemic MR is to determine the extent of dysfunctional but viable hibernating myocardium. Identification of viable myocardium with pharmacologic stress echocardiography predicts the likelihood of recovery of function and beneficial reverse remodeling with revascularization (64,71–73), beta-blockade (74), and cardiac resynchronization therapy (75). Changes in MR severity can also be observed during dobutamine stress testing for myocardial viability, but the direct effect of dobutamine on loading conditions is a major confounding variable. Moreover, the role of surgical intervention targeted to eliminate MR remains uncertain because there is a high rate of recurrent MR related to ongoing LV remodeling (76), and long-term survival of patients with ischemic MR.

![Figure 3](image-url) **Exercise Echocardiography in Ischemic Mitral Regurgitation**

Apical 4-chamber views of color-flow Doppler and proximal flow-convergence region (left panels) are shown in a patient with ischemic mitral regurgitation (MR) along with the systolic tricuspid regurgitation velocity (right panel). With exercise, there is a major increase in both the severity of mitral regurgitation and the estimated pulmonary artery systolic pressure. ERO = effective regurgitant orifice measured by the proximal isovelocity surface area; R Vol = regurgitant volume; TTPG = systolic transtricuspid pressure gradient.
is poor whether treated medically or surgically (77,78), in large part related to the severity of LV dysfunction.

The role of Doppler echocardiography in assessing dynamic changes in MR severity with exercise, to identify higher-risk patients for surgery, is the subject of current investigation. The magnitude of ischemic MR varies dynamically in accordance with changes in loading conditions, LV regional wall motion, and annular size and the balance of tethering versus closing forces applied on the mitral valve leaflets (79). Hence, the severity of MR assessed by Doppler echocardiography at rest does not necessarily reflect the severity of MR that develops during exercise. Exercise stress echocardiography has been shown to unmask hemodynamically significant MR in patients with ischemic LV systolic dysfunction and only mild to moderate MR at rest (Fig. 3), and in doing so to identify patients at higher risk for heart failure and death (80–82). The magnitude of increase in effective regurgitant orifice during exercise often cannot be predicted from the resting effective regurgitant orifice.

Pierard and Lancellotti (82,83) have proposed that exercise Doppler echocardiography can provide useful information in the following patients with ischemic MR: 1) those with exertional dyspnea out of proportion to the severity of MR or the degree of LV dysfunction at rest; 2) those in whom acute pulmonary edema occurs without an obvious cause; and 3) those with moderate MR before surgical revascularization. A large prospective multicenter registry of surgery in patients with ischemic MR is underway, designed to assess the role of exercise echocardiography in identifying determinants of adverse outcomes, progressive LV remodeling, and efficacy of treatment (84).

**Prosthetic Heart Valves**

Echocardiography is the method of choice for evaluating prosthetic valve function (1,2). Because most prosthetic valves are inherently stenotic, the effective orifice area of a prosthetic valve is occasionally too small in relation to body size, a phenomenon known as valve prosthesis–patient mismatch (PPM) (85,86). In the aortic position, PPM is considered moderate when the indexed effective orifice area is ≤0.85 cm²/m² and severe when it is ≤0.65 cm²/m² (87). In the mitral position, the cutoff values are 1.2 and 0.9 cm²/m², 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 (88–93). PPM is a frequent cause of increased transprosthetic gradient (86,94). It is important to differentiate this condition from acquired prosthetic stenosis, which may result from leaflet calcification, pannus overgrowth, or thrombus formation.

Because normally and abnormally functioning prostheses can produce similar estimated gradients at rest by transthoracic echocardiography, 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 patient’s symptomatic status and the prosthetic valve hemodynamics measured at rest (87,95,96). In contrast to a normally functioning and well-matched prosthesis (including a bileaflet mechanical valve with a localized high gradient at rest), a stenotic prosthetic valve or PPM is generally associated with impaired exercise capacity and a marked increase in gradient with exercise, often with pulmonary arterial hypertension (97,98). A disproportionate increase in transvalvular gradient (>20 mm Hg for aortic prostheses or >12 mm Hg for mitral prostheses) generally indicates severe prosthesis dysfunction or PPM (Fig. 4). High resting and stress gradients occur more often with smaller (≤21 for aortic

### Figure 4 Exercise Echocardiography and Prosthetic Heart Valves

The mean transprosthetic pressure gradients at rest and during sustained physical exercise are shown as a function of the indexed effective orifice area (EOA) for aortic (A) and mitral (B) prostheses. Compared with Patients #2 and #4, who have large prosthetic EDAs, Patients #1 and #3, with small EDAs, show a major increase in gradient with exercise, thus suggesting the presence of severe prosthetic stenosis or valve prosthesis–patient mismatch in these latter patients. Figure illustration by Rob Flewell.
and ≤25 for mitral) rather than larger-sized prostheses, and mismatched rather than nonmismatched prostheses.

Conclusions

Exercise testing has an established role in the evaluation of patients with valvular heart disease and 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. Stress echocardiography has the advantages of its wide availability, low cost, and versatility for the assessment of disease severity (1,2,8,9). Hence, together with exercise capacity and symptomatic responses to exercise, it provides the clinician with diagnostic and prognostic information that can contribute to subsequent clinical decisions.

Guidelines, restricted to the rigors of evidence-based data, may underemphasize the utility of exercise testing in valve disease. Nevertheless, it is also true that most of the guidelines and society recommendations are based on Level of Evidence: C, that is, the consensus of the writing committees in the absence of a firm evidence base (99). Convincing evidence is lacking that the results of stress echocardiography lead to clinical decisions that result in better outcomes. Prospective large-scale, and when possible, randomized (medical vs. interventional treatment) outcome studies are needed at this point to support more evidence-based rather than consensus-based treatment strategies in patients with valvular heart disease.

Reprint requests and correspondence: Dr. Robert O. Bonow, Division of Cardiology, Northwestern University Feinberg School of Medicine, 676 North St. Clair, Suite 600, Chicago, Illinois 60611. E-mail: r-bonow@northwestern.edu.

REFERENCES


Key Words: exercise testing • valve • echocardiography • stress echocardiography.