The Use of Stress Echocardiography in the Assessment of Mitral Valvular Disease

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Stress echocardiography plays an important role in evaluating asymptomatic patients with significant mitral stenosis and symptomatic patients with only mild disease at rest, as it correlates the exercise-induced symptoms with changes in transmitral gradients, pulmonary pressures, and mitral valve area. In patients with mitral regurgitation (MR), exercise or dobutamine protocols assess for the change in the degree of regurgitation and the pulmonary artery pressure (PAP) in response to high flow states, and detect underlying left ventricular (LV) dysfunction prior to valvular surgery. Exercise echocardiography also helps in the prognostic assessment of patients with mitral valve prolapse as new MR, or latent LV dysfunction may be provoked to identify a group of high risk individuals with normal resting echocardiographic parameters. Finally, it evaluates the proper functioning of prosthetic mitral valves and helps on the monitoring of transmitral gradients and PAPs after mitral valve surgery. (ECHOCARDIOGRAPHY, Volume 21, July 2004)

mitral stenosis, *mitral regurgitation*, *mitral valve prolapse*, *stress echocardiography*, *exercise test*, *heart valve prosthesis*

Timely recognition and treatment of the underlying mitral stenotic or regurgitant lesion can prevent development of irreversible pulmonary hypertension or ventricular dysfunction, among other complications. Until recently, invasive assessment was the only reliable method to determine changes in hemodynamic variables during exercise. However, advances in exercise Doppler echocardiography have allowed this technique to be the screening procedure of choice in mitral disease because of its ability to estimate pressures and visualize valvular anatomy. This review will focus on the use of stress echocardiography in the study of mitral valvular disease.

Technical Setting

Stress echocardiography for mitral valve disease is performed via both exercise and pharmacologic protocols. Exercise echocardiography is usually preferred because patients are studied and the symptoms reproduced in a physiological setting.[1–4] While most research studies test the subjects in a supine bike to allow for ease of image acquisition, upright bicycle or treadmill protocols are more frequently utilized in the practical setting.[4–7] Treadmill exercises can be performed using the standard protocols such as Bruce or modified Bruce, whereas graded increases in resistance using a braked bike are implemented in the bicycle exercise tests. Gradual increase in the bike workload of 20–25 W every 2–3 minutes is often applied until the patient achieves either the target heart rate or develops symptoms of fatigue or shortness of breath.[8–13] Sometimes, pharmacologic stress is necessary and can be administered through the infusion of dobutamine with dose increments every 3 minutes up to doses as high as 50 mcg/kg per minute.[11–13] It is of note that dobutamine echocardiography has not been described in patients with prosthetic mitral valves.

Supine bike protocols allow for serial measurements during various stages of exercise, but elderly population may not exercise well in this position, and its use can be limited by a higher cost of the equipment.[4] On the other hand, treadmill exercise is the most commonly practiced protocol in the United States, and patients usually achieve higher workloads in this exercise.[4–7] The only offset is that data acquisition is restricted to images at baseline

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TABLE I

Sonographer's Protocols for Stress Image Acquisition

Valve Lesions	Parasternal Views	Apical Views
Mitral stenosis	• Long axis 1. Valvular mobility 2. LVOT area • RV inflow 1. TR jet velocity • Short axis 1. TR jet velocity 2. Mitral valve planimetry	1. Mitral inflow jet velocity 2. VTIs (mitral, aortic) 3. $P^{1}/_{2}t$ 4. TR jet velocity
Mitral regurgitation	• Long axis 1. LV dimensions 2. LVOT area 3. MR jet area • RV inflow 1. TR jet velocity • Short axis 1. LV dimensions 2. LV Contractility	1. MR jet area 2. TR jet velocity 3. Pulmonary vein Doppler 4. Vena contracta width 5. PISA 6. VTIs (mitral, aortic) 7. LV volumes
Mitral valve prolapse	• Long axis 1. LV dimensions 2. MR jet area 3. Degree of MVP • Short axis 1. LV dimensions 2. LV contractility	1. MR jet area 2. TR jet velocity 3. LV volumes
Prosthetic mitral valve	• Long axis 1. MR jet area 2. LVOT area • RV inflow 1. TR jet velocity	1. TR jet velocity 2. Inflow jet velocity 3. VTIs (mitral, aortic) 4. $P^{1}/_{2}t$ 5. MR jet area
IV contrast (agitated saline, protein microspheres, lipid microspheres)	• Enhance endocardial border definition for LV dimensions and contractility • Enhance TR jet velocity	• Enhance endocardial border definition for LV volumes • Enhance jet detection and definition 1. Inflow jet 2. VTIs (mitral, aortic)

and postmaximal exercise, and rapid position changes after exercise are required. In order to improve image acquisition, the presence of an experienced sonographer and the appropriate spatial arrangements are clues to maximize hemodynamic variable collection (Table I).[4] We also recommend that the treadmill be placed within easy access and no farther than a step distance from the echocardiographic examination bed.

The collection of echocardiographic data should be performed within 2 minutes of the maximal exercise.[4–8] The pressure tracings should be averaged from 3 to 5 beats in subjects with normal sinus rhythm, and from 7 to 10 beats when atrial fibrillation is present.[2,12] Pulmonary artery pressure (PAP) can be measured reliably both at rest and during exertion using the sum of the right ventriculo-atrial gradient and right atrial pressure.[14,15] The right ventriculo-atrial gradient can be estimated applying the modified Bernoulli equation to the tricuspid regurgitant (TR) velocity.[14] Echocardiographic contrast either in the form of agitated saline, sonicated albumin, or lipid microspheres can be used to enhance TR Doppler signals in patients without clear velocity profiles.[15]

Mitral Stenosis

Mitral stenosis is an obstruction to left ventricular (LV) inflow at the mitral valve level caused by anatomical abnormalities in the valvular apparatus.[16–18] The clinical picture of dyspnea and fatigue usually manifests when the resting mitral valve area is <1.5 cm^2.[18] Surgical and percutaneous valvular commisurotomies or valvular replacement surgery are available to relieve the obstruction in patients with significant mitral stenosis.[16–18] The indications for intervention are the presence of a mitral valve area <1.5 cm^2 and one of the following conditions: symptoms equivalent to NYHA functional class ≥ 2 (≥ 3 for surgery), evidence of a left atrial thrombus (percutaneous procedures contraindicated), or resting PAP $>$ 50 mmHg.[18]

Despite the above recommendations, the management decision is still difficult because of a broad spectrum of the inherent pliability of the diseased mitral valve, as well as the flow-dependence properties of both the mitral valve area and the PAP estimations (by catheter or echocardiography).[5,19] The estimated valve area can vary from rest to exercise, and explains the presence of a variety of patients with similar resting mitral valve areas, but different symptoms on exertion.[10,11] Therefore, stress echocardiography can help in the assessment of this population by correlating the change in mitral valve parameters with stress-induced hemodynamic variations (Table II).[4,5] The determination of transmitral gradients and mitral valve area using exercise echocardiography is feasible and has a good correlation with catheter manometric measurements.[1,8,9] Most authors prefer symptom-limited exercise to assess the changes in the transmitral gradient and PAP, but dobutamine stress is a good alternative if the patient cannot exercise.[2,5,8,19]

The mitral valve area can be estimated by stress echocardiography using planimetry, the pressure-half-time ($P^1/_2t$), the continuity equation, or the flow-convergence methods.[19–26] Planimetry of the mitral valve during stress testing can be accomplished using dobutamine infusion and is a very reliable method when there is good visualization of the valvular structures.[19] The $P^1/_2t$ method is simple, but its accuracy in the valve area determination is controversial in changing hemodynamic conditions.[8,20–24] The continuity equation (velocity time integral of outflow jet at aortic annulus $\times$ aortic area $\div$ velocity time integral of mitral inflow jet) method is more accurate during high flow states than the $P^1/_2t$, and is the preferred method to determine the effective mitral valve area during exercise.[9,23,25] Flow convergence is a new method to estimate the mitral valve area through the ratio of the maximal flow rate in diastole and the maximal diastolic transmitral velocity.[26] The maximal diastolic flow rate in this case is calculated using the flow-convergence method as: $2 \times \pi \times$ (radius of the flow-convergence region)^2 $\times$ aliasing velocity $\times$ (inflow angle of the mitral leaflets $\div$ 180). Although this method has shown good correlation ($r = 0.85$–0.92) with catheter calculations both

TABLE II

Indications for Stress Echocardiography in Mitral Disease

Valve Lesions	Clinical Indication
Mitral stenosis	1. Asymptomatic patients with severe mitral stenosis by resting calculations
	2. Symptomatic patients with only mild stenosis at rest
	3. Follow up of patients after mitral commisurotomy
Mitral regurgitation	1. Symptomatic patients with mild disease at rest
	2. Preoperative assessment of underlying LV dysfunction
	3. Increase specificity in detection of CAD
	4. To assess the efficacy of medical therapy in heart failure
Mitral valve prolapse	1. To assess for exercise-induced MR in symptomatic patients without MR at rest
	2. To detect latent LV dysfunction in symptomatic patients with normal resting LV function and dimension
Prosthetic mitral valve	1. Follow-up of transmitral gradients and PAP
	2. Detection of valvular stenosis

at rest and during exercise, its reproducibility needs to be further confirmed.

Accordingly, we can identify two groups of patients whose symptoms do not correlate well with the resting mitral valve area or gradients.[2,27–29] The first group comprises individuals who lead a sedentary life style and do not complain of symptoms, but have significant mitral stenosis by resting calculations (mitral area < 1.5 cm^2). The second group is formed by those subjects whose severe symptomatology appears to be out of proportion to their resting mitral valve area (>1.5 cm^2). An increase in the mitral valve area calculation without significant changes in the transmitral gradient and PAP during exercise will point toward less severe disease in subjects from the first group. Whereas an exercise-induced augmentation of peak PAP to >60 mmHg, in the mean transmitral gradient to >15 mmHg, and a decrease in the mitral valve area estimation are highly suggestive of mitral stenosis as being the culprit of the symptoms for patients pertaining to the second group. Indeed, findings from exercise echocardiography have been valuable in helping or changing management decisions in these settings.[27,29]

The role of stress echocardiography in mitral stenosis extends beyond preprocedural evaluation. Short- and long-term hemodynamic follow-ups of patients who undergo transvenous or surgical mitral commisurotomy are especially important since restenosis of the mitral valve may occur.[30,31] Tamai et al. and Leavitt et al. have demonstrated that exercise echocardiography is safe and efficacious in reexamining and following the change in the mitral area, PAP, and transmitral gradients postoperatively.[12,29]

In summary, exercise echocardiography plays an important role in evaluating the asymptomatic patient with significant mitral stenosis and symptomatic patients with only mild disease by resting calculations.[5,12,29] It also serves as an important tool for the hemodynamic follow-up of patients after mitral valve commisurotomy.[12,29]

Mitral Regurgitation

Acute, severe mitral regurgitation (MR) is poorly tolerated and urgent surgical intervention is often required.[18] On the other hand, chronic severe MR progresses in a slow and relatively asymptomatic fashion, as LV hypertrophy and dilatation, and left atrial enlargement accommodate the large regurgitant volume.[18] Although the compensatory mechanisms are effective, the prolonged volume overload may eventually result in LV dysfunction. Therefore, the timing of surgical intervention prior to the onset of LV dysfunction is paramount in order to prevent further deterioration of systolic function and improve longevity.[32] The ACC/AHA guidelines call for surgical intervention in severe MR when symptoms arise or when asymptomatic subjects (NYHA functional class $\leq$2) meet any of the following criteria: LV ejection fraction ≤ 0.60, LV end-systolic dimension $\geq$45 mm, atrial fibrillation, or systolic PAP > 50 mmHg at rest or >60 mmHg with exercise.[18]

The evaluation of MR in exercise echocardiography can be performed quantitatively ("regurgitant volume") through the difference between the mitral and the aortic stroke volumes or by using the flow-convergence method.[33] It can also be estimated semiquantitatively using the ratio between the MR area and the area of left atrium, the absolute extent of the MR mosaic area in the left atrium, or the width of the vena contracta.[33,34] Semiquantitative methods are simpler to obtain during exercise, but the results obtained by the quantitative methods are more reproducible.[33]

Exercise echocardiography plays several roles in the assessment of MR. First, in symptomatic patients with a clinical picture suspicious for severe MR, but not evident at the resting echo examination; exercise echocardiography demonstrating worsening of MR helps to correlate the pathology with the patient's symptoms.[27] Similarly, in asymptomatic patients with severe MR and unremarkable PAPs, an exercise-induced increase in PAP (>60 mmHg is significant per ACC/AHA guidelines), usually associated with dyspnea, may contribute with another piece of information in the treatment decisions.[18,27]

Second, in the study of patients with poor exercise tolerance and rheumatic valve disease with only mild degree of MR, exercise echocardiography has been helpful in elucidating the origin of the symptoms by provoking severe MR in some patients and significant mitral stenosis in others with associated pulmonary hypertension.[35] However, these findings may not be generalizable to patients without rheumatic heart disease.

Third, LV contractile function can be impaired even in the presence of a normal ejection fraction in patients with chronic MR because of altered loading conditions.[13,36,37] In these patients, LV dysfunction may occur after mitral valve replacement surgery. Exercise echocardiography can be used prior to the mitral valve surgery to identify those patients who are at risk of developing postoperative LV dysfunction.[6,38] The best echocardiographic predictors of postoperative LV dysfunction are an exercise end-systolic volume index >25 ml/m^2, an exercise ejection fraction $\leq 68\%$ (LV volumes extracted from apical four-chamber view using modified Simpson's rule), or a failure to increase ejection fraction $\geq 4\%$ during exercise.[6]

Fourth, the semiquantitative assessment and finding of a new or worsening MR (change of at least one grade) during routine exercise echocardiography can increase the test's specificity for the prediction of coronary disease.[34] Routine exercise echocardiography using regional wall motion abnormality parameters alone has a sensitivity of 89%–99% and a specificity of 54%–76% in detecting catheter proven coronary artery disease, but the addition of the MR parameter increases the specificity to 83%–97%.[34] Moreover, new or worsening MR during exercise may also indicate severe worsening of ejection fraction related to the presence of multivessel coronary disease.[3,7,39]

Fifth, MR is frequently present in patients with heart failure, is dynamic and a marker of adverse outcome.[33,40] Exercise echocardiography in the form of supine bike or isometric handgrip can be used to assess the severity of MR in heart failure patients after the institution of a new therapy or to evaluate the prognosis of the disease.[33,41] The advantage of Doppler echocardiography in this setting is its ability to quantify the changes of the regurgitant and forward stroke volumes so that small but gradual differences in hemodynamic conditions may be detected and followed.[33,42]

In brief, exercise echocardiography may uncover the worsening of MR and evaluate the PAP in response to exercise, help to correlate the severity of MR with symptoms, and detect underlying LV dysfunction prior to valvular surgery.[6,27,34,35,42]

Mitral Valve Prolapse

Mitral valve prolapse (MVP) is defined as the systolic billowing of one or both mitral leaflets into the left atrium with or without MR.[18] It is associated with a benign prognosis in most patients, except for a high risk subgroup, who seem to have an increased risk of endocarditis, sudden death, tachyarrhythmias, congestive heart failure, and cerebrovascular events.[43–47] Although the presence of MR has identified patients with increased incidence of complications, MR may be intermittent and thus undetected in some patients.[48,49] Exercise echocardiography has a role in symptomatic patients with MVP without regurgitation at rest because a subset of these patients may have exercise-induced MR.[48] In fact, Stoddard and associates examined 94 symptomatic patients with MVP and no regurgitation with symptom limited exercise echocardiography.[48] About 32% of the study cohort were found to have exercise-induced MR, and the same population was more likely to develop syncope, congestive heart failure, and progressive MR requiring valve replacement surgery.

The utility of stress (exercise or dobutamine) echocardiography in MVP also includes the identification of symptomatic individuals with latent LV dysfunction.[50,51] These subjects can have either mild or no MR, but are still at increased risk of cardiac events.[51] In this respect, Yokota and colleagues detected 43% of symptomatic MVP patients with minimal or no regurgitation to have impaired myocardial contractility using exercise echocardiography.[51] The authors noted that those patients who experienced a $<5\%$ increase in the fractional shortening during exercise had a higher incidence of cardiac symptoms, developed progressive LV dilatation, and life-threatening arrhythmias during the follow-up period.

Exercise echocardiography helps in the prognostic assessment of patients with MVP because it may induce new MR or LV dysfunction in those symptomatic patients with otherwise unremarkable resting echocardiographic parameters.[50,51]

Prosthetic Mitral Valves

The prosthetic valves have sewing rings and mechanical components (i.e., valve struts, rocker arm, cage, etc.) that occupy the space within the mitral annulus, thus, have an inherently smaller area than a native healthy valve.[4] As a result, even a normally functioning prosthetic valve has a transvalvular gradient that varies among the different types of valves.[52,53] It is difficult to assess the function of the artificial valve using resting gradients alone, since values of normal and abnormal prostheses may overlap, and resting hemodynamics weakly predict the exercise transmitral gradients.[29,54]

Exercise echocardiography is useful in distinguishing a normal-functioning mitral valve prosthesis from a diseased one through pressure gradient changes during high flow states.[29] In patients with normal prosthetic valve and LV function, it is expected a mild-to-moderate increase in the transmitral gradients during exercise, with similar or slightly increased effective orifice areas (EOA) by the $P\frac{1}{2}t$ method.[29,52,53] Conversely, individuals with stenotic mitral prostheses have severe increases (>100%) in the transmitral gradient with or without associated decrease in the calculated EOA when examined by exercise echocardiography.[53,54] In this setting, Shigenobu and Sano examined 100 patients with St. Jude's Medical mitral valves using exercise echocardiography and found that the mean transmitral gradient increased from 4 ± 2 (at rest) to 7 ± 2 mmHg (during exercise) in subjects with normal functioning mitral prostheses, and from 7 ± 1 to 14 ± 3 mmHg in patients with dysfunctional valves.[52] Similar findings were shared by Reisner and collaborators who demonstrated abnormally high exercise-induced transvalvular gradients (mean gradient of 10 (at rest) and 18 mmHg (at peak exercise)) in the patient with suspected partially occluded mitral prosthetic valve.[53] These exercise hemodynamic results helped to identify candidates that may require further work-up of their prosthetic mitral valve.

Conclusion

The role of stress echocardiography in assessing mitral valvular disease is evolving. In mitral stenosis a patient whose symptom complex is discordant to resting hemodynamic data, stress echocardiography has been successful in clarifying the extent of valvular involvement. Yet, the role of stress echocardiography in MR, MVP, and examination of the mitral valve prosthesis is less defined and its use is not generalized. However, with a better understanding of its utility, there is an expected increase in the use of exercise echocardiography to help management decisions in patients with mitral valve disease.

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