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EDITORIAL COMMENT

Stress Echocardiography in Mitral Stenosis: When Is it Useful?*

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Of all valve lesions, mitral stenosis has the most options for intervention and in many ways is the valve lesion where it is easiest to make a decision that intervention is necessary. This was the first acquired valve lesion where patient symptoms and ultimate prognosis could be improved surgically even before cardiopulmonary bypass was available. The indications for the timing of valve repair or replacement are well presented in the American College of Cardiology/American Heart Association guidelines for the management of patients with valvular heart disease (1). Intervention is recommended in symptomatic patients (New York Heart Association [NYHA] class II, III, and IV) with mitral stenosis and a mitral valve area of ≤1.5 cm (2). Intervention

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is also indicated in patients with a similar valve area and pulmonary hypertension (pulmonary artery systolic pressure of 50 mm Hg at rest, 60 mm Hg with exercise). In a symptomatic patient, the presence of left atrial thrombus and/or 3 to 4+ mitral regurgitation is a contraindication to balloon valvotomy. The presence of a thrombus that does not lyse with several months of anticoagulation in an otherwise-favorable valve is an indication for open mitral valve repair. The presence of heavy calcification, marked subvalvular obstruction, and/or 3 to 4+ mitral regurgitation is an indication for valve replacement. Because the mortality and late morbidity are higher in valve replacement than in valve repair, the patient should be symptomatic despite medical management, at least NYHA class III, before valve replacement is recommended.

For a long time it has been recognized that patients can have severe mitral stenosis and yet be asymptomatic, although this state does not usually last long. Conversely, a patient can have mitral stenosis that objectively ought to be mild, with valve areas ≥1.5 cm^2, and be quite symptomatic. It is these patients where there is a need to evaluate beyond a history, physical examination, and a resting echo Doppler. Symptoms of dyspnea at rest or on exertion, orthopnea, and paroxysmal nocturnal dyspnea can be related to either medically treatable hemodynamic changes with mitral stenosis or to concomitant diseases, such as chronic obstructive pulmonary disease or coronary artery disease. To better evaluate such patients, measurement of the hemodynamics during exercise, in the past by catheterization and more recently by Doppler echocardiography, has been used.

To understand how exercise can help to sort out these problems, the hemodynamics in mitral stenosis that result in the symptoms of dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea must be reviewed. In mitral stenosis these symptoms depend on the elevation of the left atrial, pulmonary venous, and pulmonary capillary pressure to a level where neural receptors that stimulate the sensation of dyspnea are activated and also to levels where the pulmonary capillary pressure overcomes the colloid osmotic pressure in the blood, resulting in a net flow of fluid out of the capillaries into the pulmonary interstitium. In addition to left atrial pressure increase, atrial fibrillation with rapid ventricular response is frequently the first precipitator of symptoms.

A second hemodynamic reason for these signs and symptoms is the development of pulmonary hypertension and secondary afterload on the right ventricle. In most patients, the rise in pulmonary artery pressure is passive, an elevation secondary to the elevated pressure in the left atrium, without a change in pulmonary vascular resistance. In 10% to 15% of patients with severe mitral stenosis, there is a marked rise in pulmonary arteriolar resistance and pulmonary artery pressure beyond that expected from the elevated left atrial pressure. This increase in pulmonary artery pressure places an afterload burden on the right ventricle, resulting in right ventricular hypertrophy, dilation, and eventually failure. With right ventricular dilation, increasing tricuspid regurgitation can occur, and with a failing right ventricle, the cardiac output (CO) decreases. The patient now has less shortness of breath and orthopnea and complains of decreased exercise tolerance. Finally, the development of atrial fibrillation markedly increases the risk of thrombus formation in the left atrium and subsequent systemic embolization.

To address the effect of exercise on the hemodynamic determinants of symptoms, the elevated pulmonary capillary pressure reflected by the left atrial pressure and the decreased CO, rearrangement of the elements of the Gorlin equation for determining valve area is useful.

$$MVA \propto \frac{CO}{38 \times DFP \times \sqrt{LA_D - LV_D}}$$

where MVA = mitral valve area, CO = cardiac output, DFP = diastolic filling period, LA_D = left atrial pressure in diastole, LV_D = left ventricular pressure in diastole, and 38

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is a constant accounting for the smaller orifice stream than orifice area (coefficient of orifice contract) and other factors, such as conversion of units.

With rearrangement, the following is observed:

$$LA_D - LV_D \propto \left(\frac{CO}{38 \times DFP \times MVA}\right)^2$$

With exercise, the CO and heart rate increase, and the DFP decreases. With a fixed mitral valve orifice, there is an exponential increase in left atrial and pulmonary capillary pressure. Clearly, the left atrial pressure is determined by more than the degree of mitral valve stenosis. Even with mild mitral stenosis, the left atrial pressure could still markedly rise if the heart rate and/or CO increases markedly. Here, decreasing the rise in CO (e.g., correcting anemia) or preventing an inordinate increase in heart rate with exercise by beta-blockers might make the patient asymptomatic.

Exercise is the ideal way to evaluate the symptomatic patient with only mild-to-moderate mitral stenosis because this is the activity that usually precipitates the symptoms. However, dobutamine, which simulates the effects of exercise by increasing CO and heart rate, is more amenable to use with echocardiography, because the marked increase in respiratory activity and chest motion, which makes imaging difficult, is absent.

In this issue of the *Journal*, Reis et al. (2) used dobutamine stress Doppler echocardiography (DSE) in evaluating patients with mitral stenosis, which has been reported in the past, to a new level in their prospective follow-up of 53 mitral stenosis patients with a wide range of mitral valve areas, from under 1 cm^2 to over 1.5 cm^2. Resting hemodynamics were measured and the mitral valve area measured by planimetry. Dobutamine stress Doppler echocardiography was then performed with hemodynamics again measured at peak infusion. The patients were followed for a mean of 60 ± 11 months. The clinical end points recorded were: 1) hospitalization for progressive dyspnea, pulmonary edema, or complications related to mitral stenosis; 2) surgical or balloon intervention, a decision made by the patient's physician using conventional indications; 3) atrial or ventricular arrhythmias associated with hemodynamic instability requiring urgent cardioversion or hospitalization; and 4) death (there were no deaths).

A total of 29 (55%) patients had a clinical end point during follow-up, 16 with progressive dyspnea, 6 with atrial arrhythmias, and 7 with pulmonary edema. They found that DSE was able to best detect those patients who would have a clinical event on follow-up if they used a cutpoint of 18 mm Hg mean diastolic gradient with dobutamine stress, which was determined by the point where the sensitivity and specificity curves crossed. At this level, there was a sensitivity of 90%, a specificity of 87%, and an overall accuracy of 90%.

There are problems with using these excellent results in applying this strategy to all patients with mitral stenosis. The study eliminated all patients with NYHA class IV symptoms as well as patients with known episodes of tachyarrhythmias associated with hemodynamic instability, patients with other valve disease, those with more than 2+ mitral regurgitation, and anyone with life-threatening medical conditions. Although they admitted patients with NYHA class III symptoms, all those patients with a mitral valve area <1 cm^2 were considered for mitral valve surgery after the initial evaluation. They also found that in patients with a mitral valve area of >1.5 cm^2, 85% of whom had had a previous commissurotomy, that DSE does not appreciably add to the clinical evaluation and resting echocardiogram. This left only 22 patients with a mitral valve area of 1 to 1.5 cm^2. Of those, only patients who were NYHA class I or II were the ones in whom DSE was able to predict future clinical events if the dobutamine stress mean diastolic gradient was 18 mm Hg or more.

Is there value in performing DSE in patients with mitral stenosis? Certainly those with a mitral valve area <1 cm^2 who are class III or IV should have a mitral intervention, balloon or repair if possible, and replacement if necessary. Those who are asymptomatic with a satisfactory lifestyle should be followed, with the exception of those with moderate or severe pulmonary hypertension and those who can have a repair by balloon valvuloplasty or surgery.

The clinical end points chosen in this study are valid end points in themselves, but it is questionable whether a DSE is indicated in a relatively asymptomatic patient with mild-to-moderate mitral stenosis simply to identify a group who may sometime in the future develop symptoms to the point where intervention is deemed appropriate. In this group, it would be just as well to wait for increasing symptoms to intervene. Only those who developed pulmonary edema, 7 patients (24%) of the 29 who reached end points, would have been better served by being identified before this occurred because patients with sudden pulmonary edema out of the hospital have a life-threatening complication. If this could be prevented by previous intervention, certainly these seven patients, 13% of the entire group, would have benefited by previous risk stratification by DSE.

Dobutamine stress Doppler echocardiography is most useful where we used catheterization with exercise in the past: in those patients with symptoms not explainable by the calculated valve area, where a rise in mean mitral valve gradient to 18 mm Hg or above is consistent with a patient whose symptoms are due to obstruction to flow and who would benefit from mitral valve intervention. Therefore, it appears that the role for DSE is not so much in predicting the asymptomatic or minimally symptomatic patient who may have difficulty in the future but in selecting those

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patients with symptoms out of proportion to the severity of their calculated mitral valve area who will most probably benefit from an intervention that may be either medical or invasive.

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