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## How Do I Do It

## Stress echo for evaluation of valvular heart disease

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## A B S T R A C T

Resting echocardiography is the most important tool for diagnosing valvular heart disease. However, treatment planning in valvular heart diseases may require additional information in some patients, particularly asymptomatic patients with severe valve disease or symptomatic patients with moderate disease. Stress echocardiography provides invaluable information in these situations and aids decision making. Stress echocardiography is performed using either physical stress or dobutamine stress and various valve parameters are monitored during the stress. Further, the ventricular performance, which is an important determinant of outcome in valve disease is also closely monitored during stress which helps immensely in planning the intervention. Lastly, possibility of associated coronary artery disease can also be evaluated, especially in the elderly. This article discusses the role of stress evaluation in assessment of valve disease in the commonly encountered clinical situations.

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## 1. Introduction

In India, valvular heart diseases are common cardiovascular diseases next to hypertension and coronary artery disease. Aortic valve disease in middle age and mitral valvular disease in comparatively younger age are the common valvular lesions. Percutaneous balloon mitral valvuloplasty (BMV) is being done across the country. Aortic and mitral valve replacement are the common surgeries done by our cardiac surgeons and mitral valve repair is performed in very few cases currently. Most of the patients who undergo these procedures are symptomatic. Many patients by limiting their physical activity may feel they are asymptomatic. When the symptoms progress slowly some patients may not notice the

changes clearly and may feel asymptomatic. The guidelines of American College of Cardiology/American Heart Association and the European Society of Cardiology<sup>1,2</sup> therefore have emphasized the role of exercise testing to provide objective evidence of exercise capacity and symptoms in such apparently asymptomatic patients.

Two dimensional color Doppler echocardiogram is the accepted modality of investigation for the assessment of severity of valvular lesions. Stress echocardiography was proposed in 1980 for assessment of severity of valvular lesions<sup>3,4</sup> but gained recognition only recently by specialized and general guidelines.<sup>1,2,5,6</sup> Most of the guidelines do not have vast clinical evidence. Thus there is a need for clinical research in this area.

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## 2. How do I do stress echo for valvular heart disease?

Stress can be produced either physically as in Treadmill Exercise Test or pharmacologically as in dobutamine stress. Routinely used Treadmill Exercise Test is not suitable for imaging at different stages of exercise and post exercise the effects of exercise would have come down. Semi supine bicycle exercise is preferable but the equipment is not widely available as treadmill in India. Physiologic stress induced by exercise is better for assessment of valvular lesions in general than the pharmacologic stress. In India the supine bicycle exercise is not easily possible at most centers, hence stress test is usually performed using treadmill or dobutamine.

## 3. Exercise stress echo

Supine bicycle exercise is more useful in performing stress echocardiogram as echo can be done continuously during the exercise and immediately following the exercise. However, the supine exercise equipment is not commonly used in Indian setups. The bicycle exercise test is performed in the semi supine position. After an initial workload of 25 W maintained for 2 min, the workload is increased every 2 min by 25 W. Blood pressure and a 12-lead electrocardiogram is recorded every 2 min and development of symptoms is monitored.

A symptom limited treadmill test can be used alternatively with pre-exercise and post-exercise echocardiography, and it is practiced in our routine tests. The general principle remains the same for all valvular heart disease. The standard parasternal long & short axis view, apical 4, 2 & 3-chamber views are recorded. The dimensions are taken in standard format. Then the parameters of interest are particularly monitored before and after exercise. The exercise stress test is particularly useful for evaluation of asymptomatic AS, MS, MR and prosthetic valves. The protocol involves careful measurement of pre & post-exercise mean gradient across the aortic valve for aortic stenosis, pre & post-exercise mean gradient across the mitral valve and PASP by TR jet for mitral stenosis, development of symptoms and functional capacity for aortic and mitral regurgitation.

## 4. Dobutamine stress echo

The aim of dobutamine stress in assessment of valvular lesions is to increase the cardiac output without precipitating significant myocardial ischemia. Hence, a low dose protocol (up to 20  $\mu$ /kg/min) is used. The longer dobutamine stages (5–8 min instead of the 3–5 min for the detection of IHD) are generally used to ensure steady state condition. The gradual increments in dobutamine doses are also helpful in preventing rapid increase in the heart rate. The dobutamine stress test is particularly useful for severe AS with LV dysfunction and ischemic MR. Side effects may occur in up to 20% of patients, most frequent being tachy and brady arrhythmias. The test should be performed only in centers with experience in

pharmacological stress testing and with an experienced cardiologist in attendance.

## 5. Aortic stenosis

Severe symptomatic aortic stenosis is an indication for aortic valve replacement and exercise testing is contraindicated. The main aim of exercise testing in AS, is to unmask symptoms in patients, who claim to be asymptomatic.

Many studies have shown that exercise testing in asymptomatic AS is safe and helps to identify a subset of patients who actually need AVR.<sup>7,8</sup> The role of exercise echocardiography in asymptomatic AS is not studied extensively. In a recent study of asymptomatic severe AS (Aortic valve area <1.0 cm<sup>2</sup>) Lancellotti et al<sup>9</sup> showed that an increase in aortic valve mean pressure gradient of 18 mmHg or more during exercise was an independent predictor of symptom onset during the 15 month follow up period. Stress echocardiogram also helps in assessing LV function in asymptomatic patients with severe AS. Patients showing abnormal LV response (decline in ejection fraction during exercise) have inferior prognosis as compared to those showing normal LV response to exercise (Increase in LVEF during exercise).<sup>10</sup> Thus, increase in mean aortic valve pressure gradient and decline in EF during exercise appear to identify patients who may need early surgical therapy.

### 5.1. How do I do it?

The standard symptom limited Treadmill test is performed with Bruce protocol. The main arena of focus is development of symptoms, BP monitoring during exercise and pre & post-exercise mean gradient across the aortic valve. If patient develops symptoms or there is less than 20 mmHg increase in blood pressure and most importantly the mean gradient increases more than 18 mmHg, the stress test is considered as indicative of significant aortic stenosis.

## 6. Aortic valve stenosis with LV dysfunction

In AS with LV dysfunction the resting transaortic gradient may be low. It is extremely important to identify patients with fixed aortic obstruction from pseudo-severe aortic stenosis. Role for stress echocardiography is well defined in this situation. Patients with a primary cardiomyopathic process and a thickened but non-stenotic aortic valve producing an outflow murmur is termed pseudo-severe AS. Here the aortic valve orifice appears small because of myocardial factor. Patients with pseudo-severe AS obviously do not benefit from AVR and there is a high risk of perioperative mortality.<sup>11</sup> Resting echocardiogram is unable to differentiate these two conditions. On dobutamine stress echo, patients with pseudo-severe AS show increase in aortic valve area with little change in transvalvular gradient. Patients with true Aortic Stenosis the gradient increases and not the aortic valve area. The investigators of the TOPAS (Truly or Pseudo-severe Aortic Stenosis) multicenter study<sup>12</sup> have proposed the projected AVA at a standardized normal flow rate as a new echocardiographic

parameter. A projected AVA  $<1.0 \text{ cm}^2$  is considered as an indicator of true-severe aortic stenosis (Fig. 1 adapted from Ref. 11).

Contractile reserve is defined by Nishimura et al<sup>13</sup> and Monin et al<sup>14</sup> as an increase in stroke volume (SV) more than 20% or more. Patients with severe aortic stenosis and LV dysfunction who have contractile reserve have better outcome with AVR than with medical therapy.<sup>13</sup> Patients with lack of LV functional reserve have poor prognosis with either medical or surgical management.<sup>14</sup> The results of dobutamine stress echocardiography thus aid in decision making in patients with low-flow aortic stenosis (AS) when dobutamine elicits contractile reserve. When contractile reserve is elicited, patients with true severe AS manifest an increase in transvalvular pressure gradient with a low calculated aortic

valve area (AVA). Management decisions are more difficult when contractile reserve is absent.<sup>15</sup>

Dobutamine stress echocardiography also helps in assessing associated ischemic heart disease. Although interpretation of stress echo for ischemic changes needs considerable experience with the technique in this situation. Revascularization has the potential to improve LV function and thus clinical outcome. However coronary angiogram remains the diagnostic standard.

6.1. How do I do it?

Low dose dobutamine echocardiogram is indicated when LVEF is  $<40\%$ , estimated AVA is  $<1.0 \text{ cm}^2$  and the mean gradient across the aortic valve is  $<40 \text{ mmHg}$  (usually

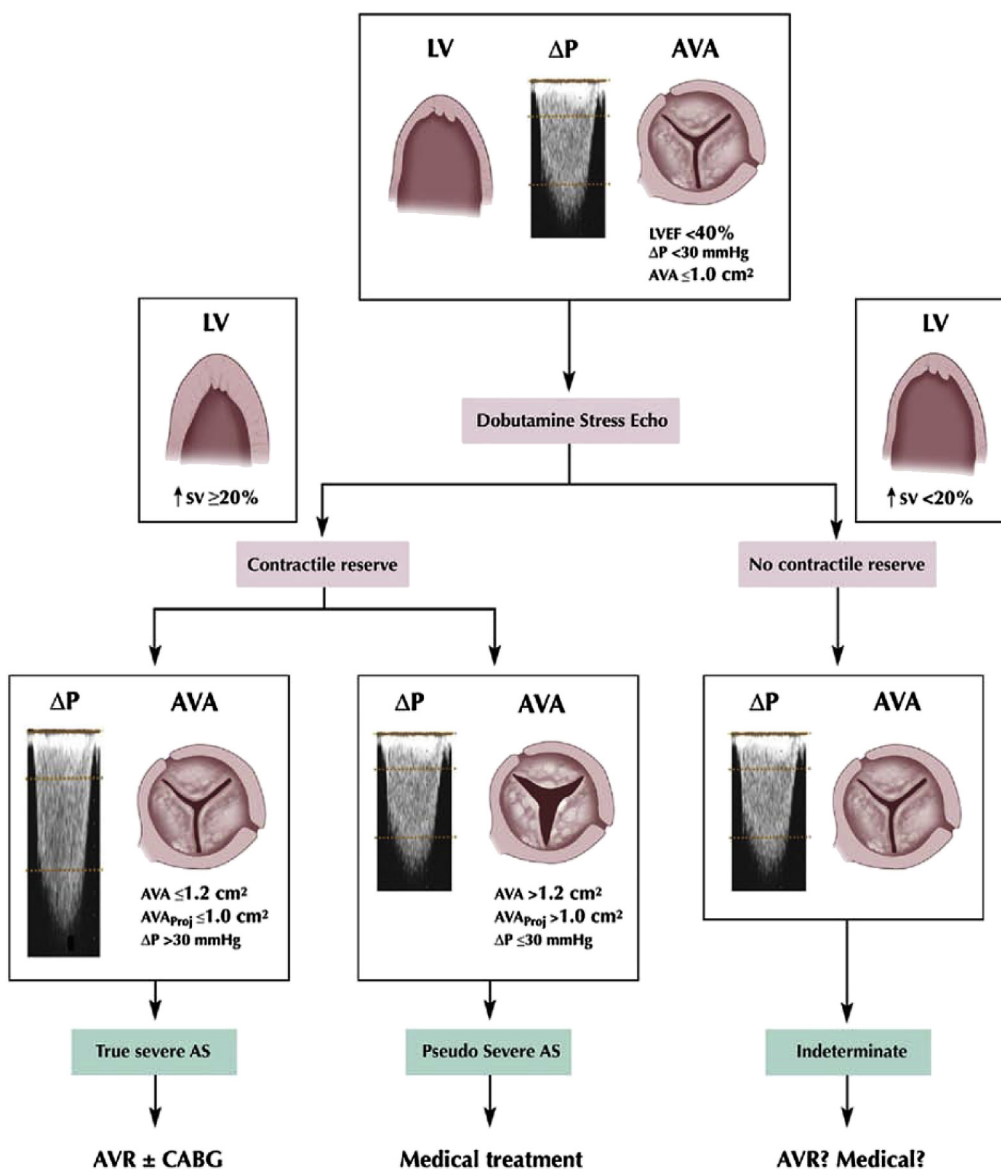


Fig. 1 – Evaluation algorithm for severe aortic stenosis with LV dysfunction. (Adapted from Picano E, Pibarot P, Lancellotti P, Monin J, Bonow RO. The emerging role of exercise testing and stress echocardiography in valvular heart disease. *J Am Coll Cardiol.* 2009; 54(24):2251–2260).

30–40 mmHg). The dobutamine infusion is started at a lower dose than usual 2.5 or 5  $\mu\text{g}/\text{kg}/\text{min}$  and the dose is increased every 3–5 min to a maximum dose of 10–20  $\mu\text{g}/\text{kg}/\text{min}$ . The infusion should be stopped when the heart rate begins to rise more than 10–20 bpm over baseline or exceeds 100 bpm or if it appears that the maximum inotropic effect has been reached. In addition, dobutamine infusion should also be stopped immediately if blood pressure falls or significant arrhythmias occur or if the patient starts complaining of symptoms.

At every stage, aortic valve and LVOT VTI, trans-aortic mean- and peak-gradients, stroke volume (calculated by subtracting LV end-systolic volume from LV end-diastolic volume) and LVEF are recorded. The VTIs and the pressure gradients may be recorded from either the apical five-chamber view or from the window that yields the highest velocity signals but the same window should be used throughout the test to allow comparison across different stages. The LVOT diameter is measured at baseline and the same diameter is used to calculate the continuity-equation valve area at each stage.

If the stroke volume or LVEF increases by more than 20% with dobutamine infusion, it indicates adequate contractile reserve. In this situation, if the mean gradient increases to  $>40$  mmHg but the AVA remains  $<1.0$   $\text{cm}^2$ , it indicates true-severe AS. In contrast, if the AVA increases to  $>1.0$   $\text{cm}^2$ , even if with some increase in trans-aortic gradients, it usually implies pseudo-severe AS. However, if there is no significant contractile reserve (i.e. stroke volume and LVEF do not appreciably increase with dobutamine), the

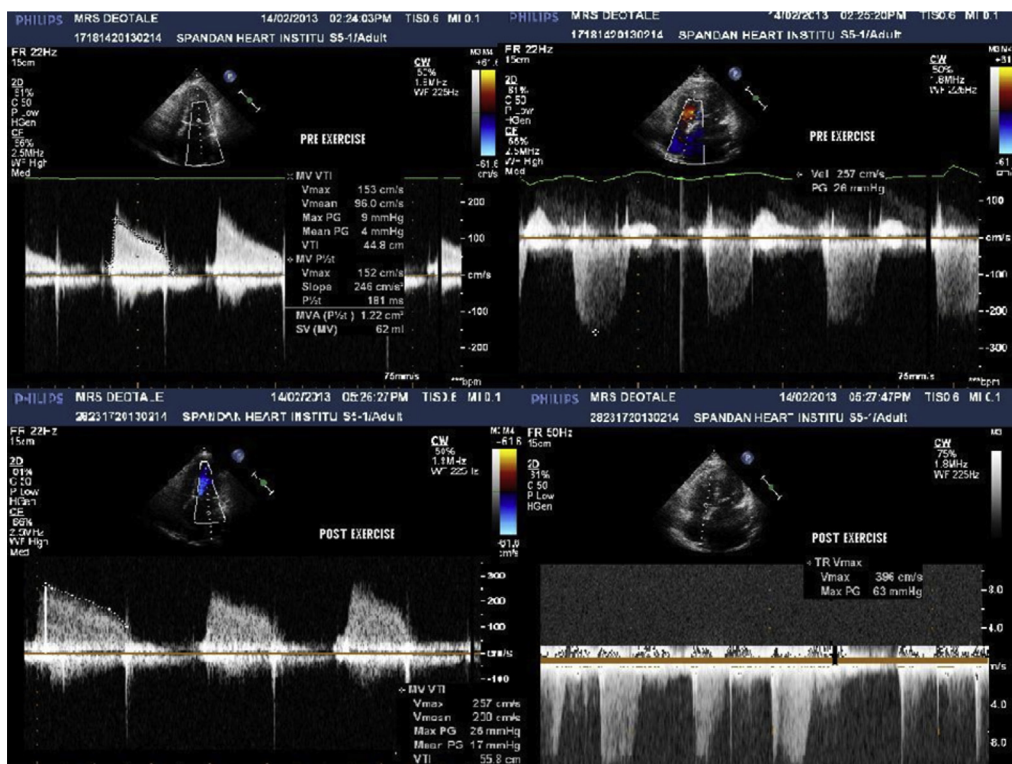
distinction between true-severe and pseudo-severe AS cannot be made.

## 7. Aortic regurgitation

Guidelines recommend AVR in severe AR based on symptoms and echocardiographic evaluation at rest. Symptomatic patients with severe aortic regurgitation benefit from aortic valve replacement.<sup>16</sup> Asymptomatic patients with severe AR and borderline LV cavity dimensions may develop LV dysfunction while awaiting AVR. Exercise testing in such patients helps eliciting symptoms and identifies candidate who have latent LV dysfunction. Stress echocardiograms can be performed both using physical stress or dobutamine in patients with symptomatic severe AR. Physical stress additionally helps in defining exercise capacity in these patients. Although additional value of stress imaging in AR is not clear, it is considered reasonable in the ACC/AHA guidelines for assessment of functional capacity and symptomatic response in patients with equivocal symptoms or before participation in athletic activities.<sup>1</sup>

## 8. Mitral stenosis

Symptomatic severe mitral stenosis needs either percutaneous balloon valvotomy or surgical treatment. However management of symptomatic moderate mitral stenosis needs



**Fig. 2 – Pre and post-exercise mitral stenosis.** Asymptomatic patient of moderate mitral stenosis and resting peak and mean gradient of 9 and 4 mmHg with PASP of 36 mmHg, following exercise on the modified Bruce protocol, post-exercise the peak and mean gradient increased to 26 and 17 mmHg and PASP TO 63 mmHg, thus indicating severe mitral stenosis.



further evaluation to define the treatment modality. Stress echocardiography can provide useful information in this subset of patients. Further, some of the patients with severe mitral stenosis could be asymptomatic or relatively asymptomatic. Stress echocardiography in such patients also adds valuable information in decision making. Evaluation of functional capacity and development of symptoms during exercise test offer objective evidence. In addition multiple echocardiographic parameters have been used to aid management decisions.

Stress protocol recommended for assessment of mitral stenosis is generally exercise stress, which can be done using supine bicycle or treadmill. Dobutamine stress is not a preferred mode of stress evaluation in mitral stenosis. Exercise testing provides information on functional capacity and exercise-induced symptoms.

In asymptomatic severe MS (mean gradient  $>10$  mmHg and  $MVA < 1.0$  cm<sup>2</sup>) or symptomatic moderate MS (mean gradient 5–10 mmHg and  $MVA 1.0$ – $1.5$  cm<sup>2</sup>) the measurement of pulmonary artery pressure (measured from the tricuspid regurgitant velocity) during exercise or dobutamine stress echocardiogram help to identify the individuals who will be benefitted by balloon mitral valvuloplasty (BMV) or mitral valve replacement (MVR). Trans-mitral gradient is more sensitive to heart rate. Moreover for a given MVA, patients with reduced atrio-ventricular compliance show a more pronounced increase in pulmonary arterial pressure during exercise or dobutamine than those with normal compliance.<sup>17</sup> Resting values of trans-mitral gradient and pulmonary

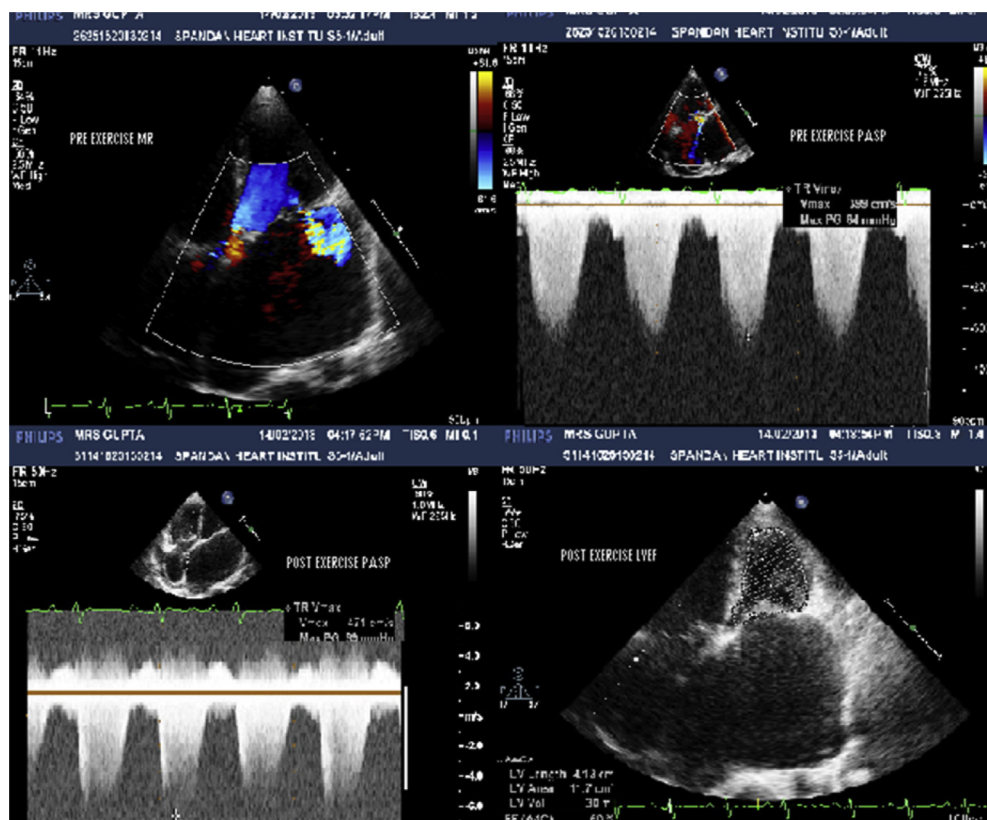
artery pressure do not necessarily reflect the actual severity of disease and stress echocardiography helps in determining the severity of MS in such situations (Fig. 2).

### 8.1. How do I do it?

The exercise stress test is performed using Bruce protocol and apical 4-chamber view is used for recording pre & post-exercise mean gradient across the mitral valve and calculation of PASP by TR jet. The threshold values proposed by the ACC/AHA guidelines for consideration for intervention are a mean trans-mitral pressure gradient  $>15$  mmHg during exercise or a peak pulmonary artery systolic pressure  $>60$  mmHg during exercise.<sup>1</sup> For dobutamine stress echo the post-exercise mean gradient more than 18 mmHg is cut off criteria. Suitable intervention for mitral stenosis is recommended for patients showing exercise induced increase in trans-mitral gradient and pulmonary artery pressure above the suggested cut off values.

## 9. Mitral regurgitation

The current guidelines suggest that the patients of asymptomatic MR with normal LV function should be managed medically and have serial follow up every 6–12 months for the development of LV dysfunction, atrial fibrillation and pulmonary hypertension.<sup>1</sup> These patients can be evaluated by the



**Fig. 3** – Pre and post-exercise mitral regurgitation. A patient with moderate MR and moderate PH, following exercise on Bruce protocol for 4.5 min, patient developed severe breathlessness and PASP increased to 82 mmHg.

exercise stress test to unmask symptoms or latent LV dysfunction.

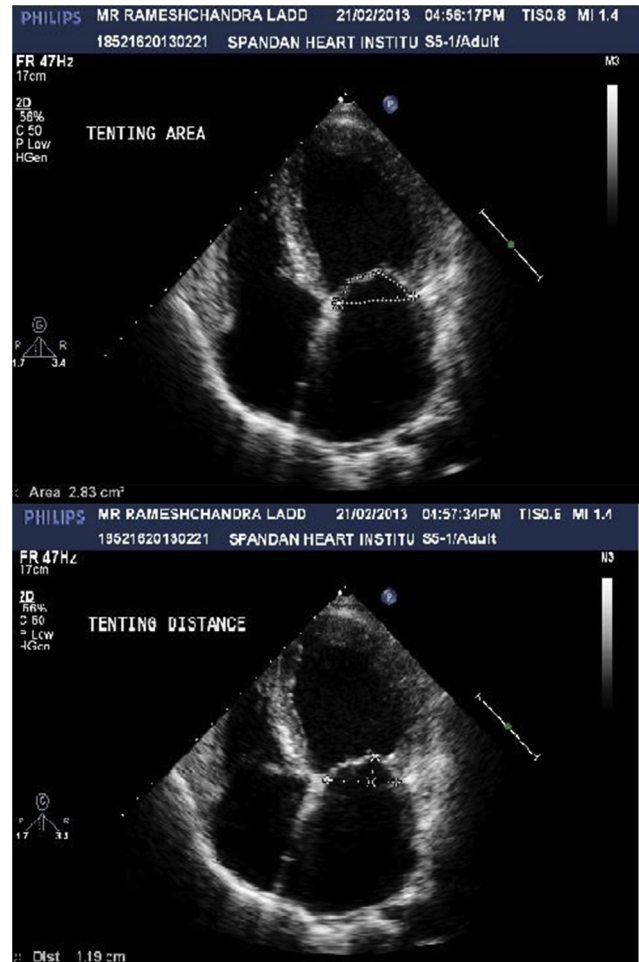
The guidelines for valvular heart disease have advocated the use of exercise induced pulmonary artery pressure more than 60 mmHg as the criteria for identifying patients who are likely to benefit by early surgical intervention.<sup>1</sup> Latent LV dysfunction is unmasked during exercise leads to increase in pulmonary artery pressure, which is measured following exercise.<sup>18,19</sup> The echocardiographic parameters used to assess latent LV dysfunction are contractile reserve, LV end-systolic volume index and post exercise ejection fraction. Contractile Reserve (CR) is defined as >4% increase in ejection fraction following exercise. Presence of contractile reserve indicates better prognosis. Event free survival of surgically treated patients is better when contractile reserve is present. Even in medically managed patients follow up EF is preserved in those with intact CR but progressively deteriorated in patients without CR, in whom functional capacity also deteriorates.<sup>20</sup> The other predictors of post-operative LV dysfunction (LVEF < 50%), like end-systolic volume index more than 25 ml/m<sup>2</sup> and post-exercise ejection fraction <68% have been suggested by Leung et al.<sup>21</sup>

### 9.1. How do I do it?

The exercise stress test is performed either using supine bicycle or using treadmill.<sup>19</sup> MR severity is measured with both Doppler volumetric method (i.e., by the difference between mitral and aortic stroke volumes) and the proximal isovelocity surface area (PISA) method. The LV end-diastolic and end-systolic volumes and left atrial (LA) maximal volume are measured by biplane Simpson's rule. The LV outflow tract stroke volume is calculated by multiplying the LV outflow tract area by the LV outflow tract velocity time integral measured by pulsed-wave Doppler. Mitral annular diameter is measured in apical 4- and 2-chamber views, and mitral annular area is calculated with ellipsoidal formulas. LV inflow velocity time integral is measured in apical 4-chamber view with pulsed-wave Doppler. The LV outflow tract diameter is assumed as constant during exercise, whereas mitral annular dimension is measured both at rest and during exercise. Systolic PAP is derived from the regurgitant jet of tricuspid regurgitation (TR) with systolic pressure gradient calculated by the modified Bernoulli equation (Fig. 3). The exercise induced pulmonary artery pressure more than 60 mmHg is used as the criteria for identifying patients who are likely to benefit by early surgical intervention.<sup>1</sup>

### 9.2. Ischemic mitral regurgitation

Ischemic MR occurs because of upward and outward tethering of posterior mitral leaflet creating the point of non-coaptation, generating eccentric jet MR. Exercise has variable effect on Effective Regurgitant Orifice (ERO). The degree of exercise induced increase or decrease in MR appears to be related to local LV remodeling and mitral valvular deformation and not to changes in global LV function. Similarly changes in ERO were unrelated to the severity of ischemic MR at rest and to the severity of LV dysfunction.



**Fig. 4 – Calculation of tenting area and tenting distance calculation in patient of ischemic MR.**

Dobutamine stress echo has a role in assessing the hibernating viable myocardium and estimating the contractile reserve in patients with ischemic MR. The presence of viable myocardium and contractile reserve helps to predict the response to revascularization therapy.<sup>22</sup> However, the mitral valve deformation is better assessed by exercise stress echo. The mitral valve deformation indices like coaptation distance and tenting area can be used to assess the ischemic MR (Fig. 4). Mitral valve deformation can be quantified by measuring the systolic tenting area (the area enclosed between the annular plane and the mitral leaflets in the para-sternal long-axis view), displacement of mitral coaptation toward the left ventricular apex (the distance between leaflet coaptation and the mitral annulus plane in the apical 4-chamber view) and the inter-papillary muscle distance. Mitral regurgitation should be quantified at rest and during exercise. The PISA (proximal isovelocity surface area) method is reproducible and reliable if the flow-convergence region is appropriate. The Doppler method is an alternative in patients with a suboptimal flow-convergence definition. Regurgitant volumes calculated by the Doppler method are usually slightly larger than those obtained with the PISA method. The results of the two methods are therefore to be averaged.

**Table 1 – Stress echo in valvular disease at a glance.**

Valvular lesion	Stress protocol	Parameters to be monitored	Criteria indicating significant lesion	ACC/AHA 2006 valvular disease guidelines
Asymptomatic AS	Treadmill or supine bicycle paddle Ex or dobutamine	Symptoms, blood pressure response, mean aortic valve gradient	Development of symptoms, <20 mmHg increase in BP, increase in mean gradient >18 mmHg	ACC/AHA class IIB with level of evidence B
Severe AS with LV dysfunction	Low dose dobutamine (upto 20 µg/kg/min)	Stroke volume, aortic valve area, transvalvular mean gradient	SV >20% AVA < 1.2 cm <sup>2</sup> Mean gradient >30 mmHg.	ACC/AHA class IIa level of evidence B
Asymtomatic severe AR	Exercise	Symptoms, functional capacity	Development of symptoms, decreased functional capacity	ACC/AHA class IIA with level of evidence B
Asymtomatic severe MS or symptomatic mild to moderate MS	Treadmill or supine paddle Ex or dobutamine	Transmitral gradient, pulmonary artery systolic pressure	Trans-mitral gradient >15 mm Hg during Ex, >18 mmHg during dobutamine, PASP >60 mmHg	ACC/AHA class I, level of evidence C
Rheumatic MR/ degenerative MR Ischemic MR	Treadmill or supine bicycle paddle Ex Dobutamine	LVEDV, LVESV, EF, PASP, symptoms, Ex tolerance Systolic tenting area, coaptation distance, severity of MR	Development of symptoms, decreased Ex capacity, PASP >60 mmHg Increase in reg vol, reg fraction, PASP >60 mmHg mHg	ACC/AHA Class IIA, level of evidence C
Prosthetic valve	Exercise	Transvalvular gradient	>20 mmHg for aortic prosthesis, >12 mmHg for mitral prosthesis.	

Stress echocardiogram has been shown to unmask hemodynamically significant MR in patients with LV systolic dysfunction and only mild to moderate MR at rest and helps in identifying patients at higher risk for heart failure and death.<sup>23</sup>

## 10. Prosthetic heart valves

Echocardiography helps in assessment of prosthetic valve. Prosthetic valves are inherently stenotic. 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). In the aortic position PPM is considered moderate when the indexed effective orifice area is <0.85 cm<sup>2</sup>/m<sup>2</sup> and severe when it is <0.65 cm<sup>2</sup>/m<sup>2</sup>. In the mitral position the cut off values are 1.2 and 0.9 cm<sup>2</sup>/m<sup>2</sup> respectively.<sup>24</sup> PPM is a frequent cause of increased trans-prosthetic gradient. This should be differentiated from the one produced by leaflet calcification, pannus overgrowth or thrombus formation. Similar gradients are produced by both the groups at rest. A stenotic prosthetic valve or PPM is associated with impaired exercise capacity, marked increase in gradient with exercise (>20 mmHg for aortic prosthesis and >12 mmHg for mitral prosthesis) often with pulmonary arterial hypertension.<sup>25</sup> Stress echocardiogram also helps in LV function assessment. Studies have shown that preoperative dobutamine stress echocardiography proved to be very useful for prediction of the postoperative LV function, even in valvular heart disease.<sup>26</sup>

## 11. Conclusion

Stress echocardiogram has a role in evaluation of valvular heart disease (Table 1). Asymptomatic but severe lesions and in symptomatic mild to moderate lesions stress echocardiogram helps in analyzing the cases. It has the advantage of wide availability, low cost and versatility to assess the severity of lesions. However more evidence-based studies are needed.

## Conflicts of interest

All authors have none to declare.

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