Role of stress echocardiography in the functional assessment of prosthetic mitral valve
Dr.P.S.Chakkaravarthi.
Asst. Professor, Department of Cardiology, Govt. Thiruvarur Medical College, Thiruvarur, Tamil Nadu, India- 610 004

Abstract
Objective: To assess the resting echo profile of patients with prosthetic mitral valve and monitor the function of the prosthetic valves by doing stress echocardiography by treadmill exercise and dobutamine infusion.
Methods: An open-labeled prospective randomized comparative study was conducted in 30 patients at Madras Medical College and Hospital, Chennai- 600 003, Tamil Nadu. Patients, who have been done mitral valve replacement, were selected randomly to undergo the stress echocardiography. 14 male and 16 female patients were included and evaluated on the basis of Echocardiographic examination, Exercise studies, Dobutamine stress echocardiography & Estimation of LV outflow.
Results: Upon comparison, the patient's heart rate were increased from rest to exercise by a mean of 24 ±12.5 beats per minute. The paired t-test showed a significant correlation with an increase in the dobutamine group (P <0.001). With respect to peak gradients, it was increased between the two stress protocols was statistically significant (P <0.001). The mean gradient obtained at rest and with exercise and dobutamine stress also showed a similar pattern of increase as seen in the peak gradient. Moreover, the net difference in the Pulmonary artery pressure achieved with both stress protocols was 5.56±4.6mmHg more in the exercise protocol which was statistically significant (P <0.001).
Conclusion: The study reveals Dobutamine produces a greater augmentation in the effective mitral orifice area when compared to exercise. Similarly, the exercise protocol produces a much higher increase in the pressure gradients when compared with dobutamine.

Key words: Valvular heart diseases, Stress Echo, Exercise, Dobutamine.

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*Corresponding Author
Name: Dr.P.S.Chakkaravarthi
Email: sibichakru@gmail.com
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prosthetic valve hemodynamics by using Doppler echocardiography.

Patients and Methods
Study Design
This is an open-labelled prospective randomized comparative study.
Sample Size
A total number of 30 patients from the Out Patient Department of Cardiology and Cardiothoracic Department of Madras Medical College and Rajiv Gandhi General Hospital, Chennai-600 003, Tamil Nadu, India.
Study Period
The study was conducted over period of 12 months from Aug 2012 to July 2013.
Study Site
The study was carried out in Madras Medical College and Rajiv Gandhi General Hospital, Chennai-600 003, Tamil Nadu, India.
Study Protocol
For this study, about 30 patients who came to Rajiv Gandhi General Hospital, Cardiothoracic and Cardiology Department, who have been done mitral valve replacement were selected randomly to undergo the stress echocardiography. 14 male patients and 16 female patients were included in our study. Mitral valve was replaced about 18 to 36 months prior to stress testing. Out 30 patients from our study, 13 patients had St.Jude mitral valve, 12 patients had TTK Chitra valve (tilting disk), 4 patients had ATS bileaflet valve and a single patient had Starr Edward valve.

Inclusion Criteria
1. Patients were included in our study as per International Normalized Ratio normal conditions.

Exclusion Criteria
1. Patients with double valve replacement
2. Patients with atrial fibrillation
3. Patients with left ventricular dysfunction
4. Patients with coexisting other valvular disease
5. Patients who are unable or unwilling to undergo treadmill exercise

Ethical Consideration
All the investigational procedures and protocols used in this study were reviewed & approved by the Institutional Ethical Committee (IEC Reference No: CD/2/2013) and were in accordance with the CONSORT guidelines. Informed consent was obtained from all the study participants after a detailed explanation of the study purpose and methods.

Study Evaluation
(a). Echocardiographic Examination
Echocardiographic examination was done with a 2.5 MHz transducer using the Esaote myLab equipment available in our Echo lab. Echocardiographic examination and measurements were recorded according to the American Society of Echocardiography recommendations. Each patient underwent baseline transthoracic echocardiography at rest and the function of the prosthesis was confirmed to be normal before proceeding further. Randomization found out which stress would be undertaken first in order to eliminate any bias.

(b). Exercise studies
Exercise studies were performed by asking the patient to walk in the Esaote Treadmill and the exertion was undertaken according to Bruce or modified Bruce protocol depending on the previous functional capacity of the patient on daily activities. The patient was advised to walk to achieve 85% THR but the test was stopped according to the symptom limited exercise. The electrocardiography was monitored throughout the procedure and the heart rate and Blood Pressure were noted after each stage of exercise. After the peak stress, patients were asked to assume a left lateral position on the table and the echocardiographic images were taken soon after. Mitral inflow and tricuspid regurgitant signals were acquired with the use of optimal views and various transducer positions which gave the views best at rest and the images were acquired immediately.

(c). Dobutamine stress echocardiography
Then the patients were subjected to dobutamine stress echocardiography using a modified dobutamine protocol after two hours Dobutamine was started at the dose of 5 mcg/kg/min. The dose was increased at the rate of 5 mcg/kg/min for every 4 minute stages. The heart rate was noted and the echocardiographic images were acquired continuously. The dose was increased to a maximum of 40 mcg/kg/min. The test was stopped if the patient is found to have any arrhythmia on the monitor or any symptom of angina or any hemodynamic instability and Blood Pressure was noted after each phase of increase in dobutamine. Images were obtained at peak stress and the variables were calculated.

(d). Estimation of LV(Left Ventricular) outflow
The left ventricular outflow tract diameter was estimated from the parasternal long axis view immediately proximal to the aortic annulus with image frozen in midsystole and measurement taken from inner edge to inner edge. Sub aortic pulse wave Doppler recordings were made in the apical five chamber with the pulse- wave Doppler cursor held in the LVOT immediately proximal to aortic valve. Also from the four chamber view, pulse wave Doppler and continuous wave Doppler recordings of the mitral jet velocity were acquired. Peak and mean gradients were obtained from the planimetry of the envelope. On an average 5 readings were recorded and the measurements were done at rest and during peak stress.

The following calculations were done.

**Stroke volume in ml=CSA LVOTXVTI19** where CSA LVOT is left ventricular outflow cross sectional area in cm² calculated from the diameter assuming the LVOT having a circular cross sectional area and the VT19 represents subaortic velocity time integral in cm.

**Cardiac output in ml/sec=HRXSV**
Where HR is heart rate

Mitral Effective Orifice Area in sq.cm can be calculated using the continuity equation.

\[
\text{EOA=CSALVOTXVTILVOT/VTIMV}
\]
Where VTi MV represents time velocity integral of the mitral diastolic jet9.
(e). Measurement of Pulmonary artery pressure:
Pulmonary artery pressure was measured by obtaining the tricuspid regurgitation signal on the colour Doppler. Continuous wave Doppler is then applied over the signal and the obtained envelope is planimetered to find out the right ventricular systolic pressure by simplified Bernoullie’s equation. To this the right atrial pressure (which was obtained by IVC size and its respiratory variation) is added. The sum is taken as Pulmonary artery systolic pressure in the absence of right ventricular outflow obstruction.

Diastolic flow in mitral valve in ml/sec=SV/DT
Where DT is the diastolic filling time in milliseconds. It is measured between the opening of the mitral valve and its closing of the mitral valve artifacts. Mitral flow volume per second was considered equivalent in the absence of mitral or aortic regurgitation to the stroke volume9,10.

Ethical considerations
The study was approved prior to its commencement by the Local Medical Ethical Committee and all the participants included in the study had given their written informed consent.

Statistical analysis
The parameters were calculated at each stage of stress for every patient and were presented as mean ± SD. Analyses of change in the variables at rest and comparisons between the stress modes were done using a two way analyses of variance for the measures which are repeated. Using the Bonferroni approach, post-hoc adjustments were done for the p-value to take into account the number of tests performed. Applying the Wilcoxon test, nonparametric data were examined. Transmitral pressure gradients were plotted against cardiac flow in every individual patient.

Statistical analysis of the association of multiple variables was done using Pearson’s correlation coefficient and graphs were devised with the corresponding linear regression equation in the patients who had a square of the correlation coefficient more than 0.50. The individual variables were compared using Student ‘s t-test for paired data. All these statistical analysis were performed using Graph Pad Prism Instat Version 3 (USA).

Observation and Results:
In our study all the 30 patients who were all gone for mitral valve replacement results were analysed by using the following parameters,

1. Heart rate at rest compared during exercise and dobutamine stress
2. Peak gradients at rest compared during exercise and dobutamine stress
3. Mean gradients at rest compared during exercise and dobutamine stress
4. EOA (Effective Orifice Area) at rest compared during exercise and dobutamine stress
5. Pulmonary Artery Pressure (PAP) at rest compared during exercise and dobutamine stress
6. Diastolic flow rate at rest compared during exercise and dobutamine stress
7. Mean pressure gradient during dobutamine stress and cardiac flow
8. Mean pressure gradient during exercise stress and cardiac flow
9. Sex wise distribution of patient population
10. Types valves based analysis

Rest and maximum hemodynamics
From our study it was observed that 46.7% were male and 53.3% were female out of 30 numbers of total study population. Table 1 demonstrates about the details of different types valves placed in our study population.

Table 1: Different types of valves placed in our study population.

| S.No | Types of Valves            | Number | Percentage (%) |
|------|---------------------------|--------|----------------|
| 1.   | SJM (St.Jude Mitral Valve) | 13     | 43.3%          |
| 2.   | SE (Starr Edward Valve)   | 1      | 3.3%           |
| 3.   | ATS (ATS Bileaflet Valve) | 4      | 13.3%          |
| 4.   | TTKS (TTK Chitra Valve)   | 12     | 40.0%          |

The resting heart rate, mean blood pressure, end-diastolic diameter of left ventricle and peak and mean pressure gradients were comparable prior to commencement of dobutamine stress and exercise.

At peak stress, exercise caused the mean blood pressure to increase by about 19.3 mmHg. On the other hand, dobutamine did not cause a significant change in mean blood pressure. In fact, it decreased the mean BP to fall by 2.1 mmHg. On analyzing these values statistically, this increase in mean BP with dynamic exercise was found to be significant with a P value of<0.0001.

The ratio between the pressure and flow was plotted in about twenty three patients during both stresses. The slope was significantly higher at peak exercise when compared with dobutamine stress (0.046±0.007 mmHg/ml/sec Vs 0.0280.004 mmHg/ml/sec respectively).This comparison was also statistically significant with a P value of 0.006.(FIG A and B).

On comparing the heart rate response, the heart rate increased from rest to exercise by a mean of 24 ±12.5 beats per minute. The heart response to dobutamine was also similar but more than that of exercise i.e 38±10. Head to head comparison between exercise and dobutamine protocol showed a mean difference of 14 bpm ±6.2 higher in the dobutamine group. The paired t test showed a significant correlation with an increase in the dobutamine group with a P value of <0.001 (95% confidence interval of -16.878 to –12.189)(Table 1, Fig 6)
Table 2: Explains the comparison of heart rate at rest and exercise and dobutamine stress

| S.No | Variable                  | Mean ± SD   |
|------|---------------------------|-------------|
| 1.   | Heart rate at rest        | 81.2 ± 7.9  |
| 2.   | Heart rate at exercise    | 109.5 ± 15.6*** |
| 3.   | Heart rate at dobutamine  | 126.1 ± 12.5***,*,* |

Data represented as Mean±SD, which represents heart rate at rest, exercise and dobutamine in beats per min(bpm). *** denotes p<0.001 compared with heart rate at rest Vs exercise and dobutamine stress. * * * denotes p<0.001 compared with heart rate at exercise Vs dobutamine stress.

Table 4: Explains the comparison of mean gradients at rest and exercise and dobutamine stress

| S.No | Variable                  | Mean ± SD   |
|------|---------------------------|-------------|
| 1.   | Mean gradient mmHg at rest| 5.2 ± 2.1   |
| 2.   | Mean gradient mmHg at exercise | 7.9 ± 2.3*** |
| 3.   | Mean gradient mmHg at dobutamine | 7.0 ± 2.4***,*,* * |

Data represented as Mean±SD, which represents mean gradients at rest, exercise and dobutamine in mmHg. *** denotes p<0.001 compared with mean gradients at rest Vs exercise and dobutamine stress. * * * denotes p<0.001 compared with mean gradients at exercise Vs dobutamine stress.

Table 5: Explains the comparison of Effective Orifice Area (EOA) at rest and exercise and dobutamine stress

| S.No | Variable                  | Mean ± SD   |
|------|---------------------------|-------------|
| 1.   | EOA at rest in sq.cm      | 2.1 ± 0.56  |
| 2.   | EOA at exercise in sq.cm  | 2.4 ± 0.65*** |
| 3.   | EOA at dobutamine in sq.cm | 2.1 ± 0.55***,* * * |

Data represented as Mean±SD, which represents effective orifice area (EOA) at rest, exercise and dobutamine in sq.cm. *** denotes p<0.001 compared with EOA at rest Vs exercise and dobutamine stress. * * * denotes p<0.001 compared with EOA at exercise Vs dobutamine stress.

Table 6: Explains the comparison of Pulmonary Artery Pressure (PAP) at rest and exercise and dobutamine stress

| S.No | Variable                  | Mean ± SD   |
|------|---------------------------|-------------|
| 1.   | PAP at rest in mmHg       | 23.7 ± 6.4  |
| 2.   | PAP at exercise in mmHg   | 39.2 ± 8.5*** |
| 3.   | PAP at dobutamine in mmHg | 33.7 ± 5.5***,* * * |

Data represented as Mean±SD, which represents Pulmonary Artery Pressure (PAP) at rest, exercise and dobutamine in mmHg. *** denotes p<0.001 compared with PAP at rest Vs exercise and dobutamine stress. * * * denotes p<0.001 compared with PAP at exercise Vs dobutamine stress.

Table 7: Explains the comparison of Diastolic Flow Rates at rest and exercise and dobutamine stress

| S.No | Variable                  | Mean ± SD   |
|------|---------------------------|-------------|
| 1.   | Diastolic flow rate at rest (ml/sec) | 143.1 ±15.3 |
| 2.   | Diastolic flow rate at exercise (ml/sec) | 206.2 ± 51.0** |
| 3.   | Diastolic flow rate at dobutamine (ml/sec) | 231.3 ± 58.0***,* * * |

Data represented as Mean±SD, which represents Diastolic flow at rest, exercise and dobutamine in ml/sec. *** denotes p<0.001 compared with diastolic flow at rest Vs exercise and dobutamine stress. * * * denotes p<0.001 compared with diastolic flow rate at exercise Vs dobutamine stress.

Fig 1. Showing the response of the heart rate to exercise and dobutamine stress
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Discussion

Prosthetic Mitral valves are implanted for patients with severe mitral stenosis who are not suitable for PTMC and in patients with severe mitral regurgitation. These patients were on followup and were found to have symptoms of breathlessness on exertion which they think that the valve is malfunctioning. It had been shown that under high flow conditions, the mitral prostheses even though normally functioning can produce pressure gradients that might categorize the patients as having moderate to severe mitral stenosis and hence raise doubts that the prosthesis was malfunctioning.

Effect on pressure gradients

In the study by Tatineni et al in 1989, about 42 patients who were in need of mitral valve replacement were studied by rest and stress echocardiography both preoperatively and postoperatively after implanting St. Jude Medical and Medtronic Hall mechanical prosthetic heart valves. In these patients, no significant differences between St. Jude Medical and Medtronic Hall prostheses was noted with respect to calculated mitral valve areas (3.4 cm² vs. 3.4 cm²) [11]. The rest pressure gradient across both types of prosthetic valves were similar in both rest (2.5 in St. Jude mitral prosthesis vs. 3.0...
mm Hg Medtronic Hall mitral prosthesis) and exercise (5.1 vs. 7.0 mm Hg) mean gradients [11]. Dressler FA et al in 1992, with the use of Doppler echocardiography, 600 patients have been studied before and after stress echocardiography. They have used four different models of prosthetic valves. All the four models showed no significant differences with the pressure gradients showing 18-26 mmHg in the resting state and 35-63 mmHg with exercise in the aortic position. The heart rate achieved or duration of exercise did not influence the gradient achieved with exercise [12]. Shimon A Reisner et al in 1989, 17 patients with mitral prostheses 11 with Björk-Shiley (BS) and six with Starr-Edwards (SE) valves were subjected to submaximal supine exercise. The patients with with Björk-Shiley (BS) valves showed an increment in peak and mean gradients from increased from 10 and 5 mm Hg, respectively, at rest to 16 and 10 at peak exercise and the patients with Starr-Edwards (SE) valves showed an increment in gradient from 8 and 5 mm Hg, respectively, at rest to 22 and 13 mm Hg at peak exercise [13]. Exercise pressure gradient and the increase in peak gradient with exercise were significantly higher in the SE group (p < 0.05) [7]. Our study has a single patient who has been put on Starr-Edward valve which was kept a decade ago. His mean pressure gradient at rest was 11 mmHg and on stress it was found to increase to 14.1 with exercise and with 13.1 dobutamine stress echo. This study has thus proved the durability of the ball and cage valve [14].

In their study of Kadir I et al., the mean transvalvular gradient increased by about 1652.1 mmHg with dobutamine stress and by an equal amount after symptom limited treadmill exercise in aortic prostheses. This increase in the pressure gradient was statistically significant with a P value of less than 0.001 [15]. In the study by Picano et al., in 2009, a marked increase in the mean transprosthetic gradient (more than 20 mmHg for aortic valve and more than 12 mmHg for mitral valve) was associated with a markedly impaired exercise capacity and raise a suspicion for prosthetic dysfunction. But this fact may be compounded by the factor of patient prosthesis mismatch [16]. In our study, one patient had a mean pressure gradient of 12.8 mmHg and the patient had reduced functional capacity. He has been kept on serial echocardiographic follow-up.

The rest and stress pressure gradients recorded in our study compared well with all those reported previously. Rest studies using the tilting disc prosthetic valves of 27 to 31 mm size reported peak and and mean gradients 10.2 to 6.2 mmHg comparable to the previous studies. Similarly, the pressure gradients across the bileaflet valves were comparable to the previous studies (6.1 mmHg to 18.1 mmHg peak gradient and 3.4 to 7.4 mmHg mean gradient). On putting the patient on treadmill, the peak gradient and the mean gradient raised by 6.5 mmHg and 2.78 mmHg respectively which was found to be statistically significant. The stress induced by dobutamine produced similar rate of increase albeit to a lesser extent with as statistical significance. (4.544 mmHg peak gradient and 1.852 mmHg mean gradient).

**Effects of dobutamine and exercise on diastolic filling**

Both methods produced comparable stroke volumes at maximum stress even though the heart rates were more and diastolic filling times were longer with the protocol using dobutamine. This finding was an unexpected one as the diastolic filling fraction of the cardiac cycle (i.e. the ratio of diastolic filling time to cardiac cycle time) tend to reduce at rapid heart rates. This appears completely feasible as the pressure differences are dependent on the flow across the prosthesis and the cross sectional area that is available for flow [17]. In our study, the diastolic filling time appeared to reduce from 450 milli seconds to 231 milliseconds with dobutamine and about 206 millisecond in the exercise group. On the contrary, the diastolic flow rate was more in the exercise arm than dobutamine arm (273 ml/sec vs 241 ml/sec). The relatively more increment in the stroke volume with dynamic exercise might have contributed for this augmentation.

**Effects of stress protocol on effective orifice area (EOA)**

The effective orifice area is defined during the period of diastole i.e from the period of initial valve leaflet separation at the beginning of diastole to the terminal leaflet closure at the end of diastole. The standard continuity equation uses the velocity time integral across the left ventricular outflow tract and prosthetic valve and thus provides an averaged EOA. In the study by Leavitt et al, the mitral valve area was compared in 12 patients with prosthetic mitral valve and in 12 patients with moderate mitral stenosis after treadmill exercise. The mitral valve area increased from 2.5 to 2.9 sq.cm after exercise in the prosthetic group and from 1.4 to 1.6 sq.cm, in the mitral stenosis group [18]. In another study by N.A.Hobson et al, the effective orifice area was calculated at rest and after supine bicycle ergometry and after dobutamine stress echocardiography. The ERO increased from 1.67 sq.cm to 2.17 sq.cm after dobutamine stress and to 1.87 sq.cm after exercise [17]. In the study by Picano et al, they studied the relationship between the effective orifice area and the increase in mean pressure gradient in mitral prosthesis. They suggested that a large increase in the mean gradient in the presence of small effective orifice area would be indicative of prosthesis or patient-prosthesis mismatch [19]. In their study of comparison of exercise and dobutamine echocardiography aortic valve hemodynamics in 2002, Kadir I et al had found out that there were no significant change in the effective orifice area of the prosthetic valve with either protocol [15, 20, 21]. But the study was conducted in patients with small size aortic prosthetic valves and the aortic valve orifice area is relatively less affected by diastolic flow rate when compared with mitral prostheses. In our study, the effective orifice area of the valve at rest was 2.4 sq.cm which increased to 2.8 sq.cm during exercise protocol and 3.1 sq.cm during dobutamine stress protocol. The increase was relatively higher in the dobutamine arm. On comparing the increase in the ERO in both arms, the results were found to be statistically significant. These results were comparable to previous studies. It is possible that the apparent increase in effective orifice area is a reflection of a increased rate of change of valve leaflet opening and closing as the cardiac flow increases. It is thus hypothesized that dobutamine results in a maximum ERO being achieved more rapidly and for a greater length of time proportionally when related to the diastolic filling time [17]. The observed increase in effective orifice area may be affected by various confounding factors and thus may be erroneous. In the presence of undetected mitral regurgitation, errors may have occurred. In
the transthoracic echocardiography, detection of mitral regurgitation is limited. But this difficulty may be nullified by assessing the ratio of velocity time integral over the mitral valve and over the left ventricular outflow tract. This Doppler velocity index has been a predictor of mitral regurgitation with a sensitivity of 89% and specificity of 91% when the index exceeds 2.5. In our study, the Doppler velocity index did not exceed 2.5 [17]. Data variability during exercise might also had contributed to the observed differences, but data variability for exercise and dobutamine stress were not found to be statistically significant. The calculation of effective orifice area may also be confounded by the fact that the 3three minute stepwise protocol used during stress studies was not enough time to allow the stabilization of chronotropic and hemodynamic conditions. Thus, the study revealed that Dobutamine produces a greater augmentation in the effective mitral orifice area when compared to exercise. Normally functioning prosthetic valves in the mitral position can produce significant increases in valvular pressure gradients under conditions of high flow, and thus an estimation of diastolic cardiac flow must be measured before concluding that the valve dysfunction has occurred. Moreover, Exercise protocol produces much higher increase in the pressure gradients when compared with dobutamine. An abnormal increase in the pressure gradient without an increase in EOA signifies significant valve dysfunction and these patients should be monitored periodically for further deterioration and further action. Thus this study helps in finding dysfunction of prosthetic valves in the earlier stages itself.

Conclusion
The study reveals Dobutamine produces a greater augmentation in the effective mitral orifice area when compared to exercise. Similarly, the exercise protocol produces a much higher increase in the pressure gradients when compared with dobutamine.

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Conflict of interest
The authors have no disclosures, conflicts, or competing interests.

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