Hemodynamic Assessment of Mitral Mechanical Prostheses under High Flow Conditions: Comparison between Dynamic Exercise and Dobutamine Stress

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Background and aim of the study: **The study aim was to compare the effects of dobutamine stress and exercise on prosthetic mitral valve hemodynamics.**

Methods: **Twenty-three patients who had recently (3 ± 1 months) undergone mechanical mitral valve implantation were studied. Hemodynamic variables, two-dimensional echocardiographic and Doppler mitral/aortic flows were recorded at rest, and then repeated during exercise and dobutamine stress. The investigations were randomized place to determine which stress would be performed first.**

Results: **Heart rates and pressure drops rose significantly from resting values. At maximum stress, exercise produced maximum and mean pressure drops which were statistically greater than with dobutamine (19.4 ± 6.0 versus 12.8 ± 4.7 mmHg ($p < 0.001$) and 10.2 ± 3.5 versus 6.8 ± 2.8 ($p < 0.01$), respectively). Exercise was associated with statistically shorter diastolic filling times and higher transvalvular diastolic flow rates. Dobutamine produced a greater augmentation in mitral effective orifice area (EOA) ($p < 0.05$). The slopes of pressure drop/cardiac flow were calculated for stress type and shown to be significantly lower during dobutamine administration ($p = 0.03$).**

Conclusion: **Normally functioning mitral prostheses can generate significant increases in valvular pressure drops under high flow conditions. Physiological differences exist between dobutamine stress and exercise when assessing diastolic filling. At a given flow rate, dobutamine produces a greater augmentation in the mitral EOA and a smaller drop in transvalvular pressure.**

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Valvular assessment by Doppler echocardiography is usually performed at rest. The resting situation is not representative of the patient's daily activities when symptoms normally occur. It is therefore conceivable that hemodynamic abnormalities seen under high flow conditions may not be evident at rest, since pressure drops across valves are related to flow (1).

Physical exercise is physiological but requires considerable patient cooperation and often-reliable images are difficult to obtain. Pharmacological stress using dobutamine offers an alternative method of assessment which is non-physiological but alleviates the problem of poor imaging. Dobutamine is a synthetic catecholamine, which stimulates post-synaptic α- and β-receptors of the cardiovascular system. It is considered to cause a balanced effect on the peripheral vascular resistance by stimulating both β2 and α1 adrenergic receptors (2), which may be different from the effect that occurs during exercise.

Comparing results from studies that have utilized exercise and dobutamine stress modalities is difficult because minimal data are available that have directly compared the two for the variable of cardiac flow. Since both stresses are in general use, a direct comparison would be useful.

The study aim was to assess the normal hemodynamic response of mechanical mitral prosthetic valves under high flow conditions and to compare the diastolic cardiovascular physiology of dynamic exercise and pharmacological stress.

Materials and methods

Patient population

The study population comprised 23 patients (12 men, 11 women; mean age 64.3 ± 7.0 years), of whom three underwent valve replacement for severe mitral stenosis, 11 had severe mitral regurgitation, and nine had mixed mitral valve disease. Five patients underwent accompanying coronary artery bypass surgery. The

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interval between surgical intervention and echocardiographic follow up ranged from two to four months. Of the 23 patients studied, 12 received a CarboMedics (bileaflet) valve and 11 an Ultracor (tilting-disc) valve. Four patients received 27 mm valves, nine 29 mm, five 31 mm, and five 33 mm. Eighteen patients were in normal sinus rhythm, while five were in established atrial fibrillation. The mean baseline left ventricular ejection fraction, as measured using two-dimensional echocardiography, was 54 ± 6% (range: 30 to 75%).

Study design

The study was prospective, comparative in design, and was conducted in a single center at the South Yorkshire Cardiothoracic Unit, Sheffield, UK. All patients aged 18 to 75 years and undergoing elective mitral valve replacement with a mechanical prosthesis, either in isolation or in combination with coronary artery surgery, were invited to participate.

Stress protocol

A commercially available echocardiographic unit (Hewlett-Packard 5500) was used in these studies. Each subject underwent baseline resting transthoracic echocardiography to confirm that the device was functioning normally. Randomization determined which stress would be undertaken first in order to eliminate any bias.

Exercise studies were performed using an adjustable horizontal table equipped with a bicycle ergometer. Each subject exercised in 3-min stages, with the ergometer load being increased after each stage by 20 W. The exercise was symptom-limited.

Dobutamine stress echocardiography was performed using a modified dobutamine protocol. This was administered in 4-min stages, with incremental doses of 5 μg/kg/min being given from 5 μg/kg/min up to a maximum dosage of 40 μg/kg/min. Dobutamine infusion was stopped prematurely if the patient achieved a maximum heart rate of 85% age-predicted to reduce the likelihood of complications (e.g. cardiovascular collapse, severe ventricular/atrial arrhythmia, persistent ischemia, or hemodynamic instability). Heart rates and electrocardiograms were continuously recorded from an ECG monitor, whilst blood pressure was recorded at baseline and after each stage of exercise and dobutamine stress.

Doppler echocardiography

The diameter (D, in cm) of the left ventricular outflow tract (LVOT) was estimated from the long-axis parasternal view, immediately beneath the aortic annulus. The image was frozen in mid-systole and measured from inner edge to inner edge. Subaortic pulsed recordings were made in the apical five-chamber view with the pulsed-wave (PW) Doppler cursor placed in the LVOT immediately proximal to the aortic valve. Continuous-wave and PW Doppler recordings were made of the mitral jet velocity from the apical four-chamber view. Peak and mean pressure drops were obtained by planimetry of the waveform. An average of five waveforms was taken in sinus rhythm, and 10 in atrial fibrillation. Measurements were made at rest and during each stage of dobutamine stress and bicycle exercise.

The following calculations were performed:

Stroke volume (SV, in ml) = $CSA_{LVOT} \times VTI_1$, where CSA_{LVOT} is left ventricular outflow cross-sectional area (cm^2) calculated from the diameter, assuming a circular cross-sectional area, and the VTI_1 is the subaortic velocity-time integral (cm).

Cardiac output (CO, in ml/min) = SV × HR, where HR is heart rate (bpm).

Mitral effective orifice area (EOA, in cm^2), using the standard continuity equation = $[CSA_{LVOT} \times VTI_1/VTI_{MV}]$, where VTI_{MV} is the velocity-time integral of the mitral diastolic jet.

Diastolic valve flow (ml/s) = SV/DT, where DT is diastolic filling time in milliseconds (ms), measured between the opening and closing of the mitral valve artifacts. Mitral flow volume per beat was considered equivalent to the stroke volume in the absence of mitral or aortic regurgitation.

Statistical analysis

Parameters were calculated for each subject at each stage of stress, and were presented as mean ± SD. Analyses of variable change from rest and comparisons between the two stresses were performed using a two-way analysis of variance for repeated measures. Post-hoc adjustments were made to the p-value to take account of the number of tests performed, using the Bonferroni approach. Non-parametric data were examined using the Wilcoxon test. Transmitral pressure drops were plotted against cardiac flow in individual patients. Both variables were calculated during each stage of exercise and dobutamine stress. During the exercise protocol there were three data points in four patients, four data points in 12 patients, and five data points in four patients. During dobutamine infusion, there were eight data points in two patients, seven data points in 10, six data points in three, five data points in three, and four data points in two patients

Statistical analysis of the association of variables was performed using Pearson's correlation coefficient, and graphs were constructed with the corresponding linear regression equation in only those that had a square of the correlation coefficient (R^2) >0.50. The individual slopes were compared using Student's *t*-test for paired data. Statistical analysis was performed using the SPSS package for Windows.

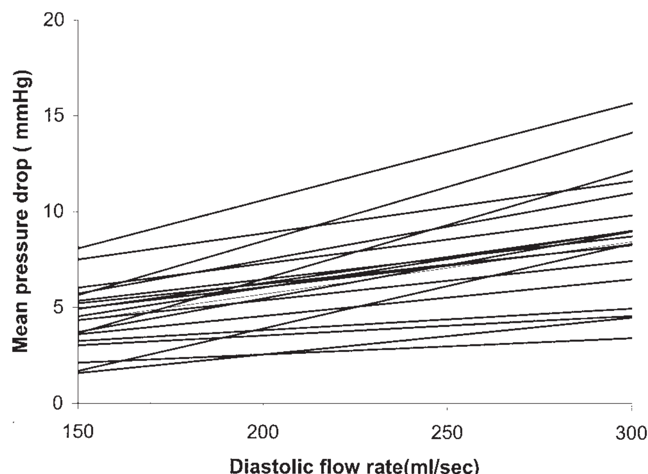

Figure 1: Comparison of mean pressure drop and cardiac flow during dobutamine stress across prosthetic mitral valves.

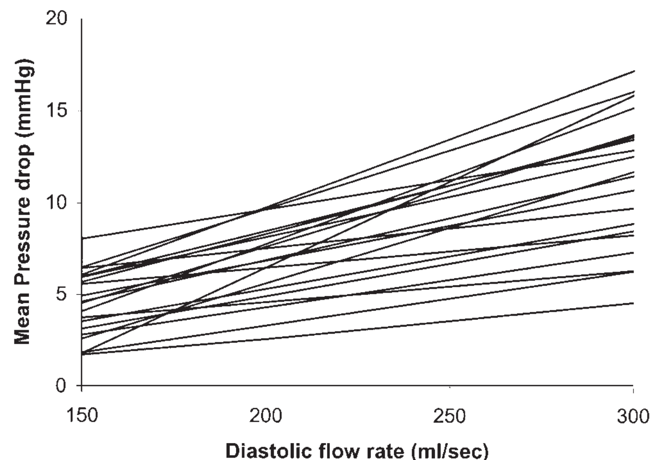

Figure 2: Comparison of mean pressure drop and cardiac flow during dynamic exercise across prosthetic mitral valves.

Ethical considerations

Prior to its commencement, the study was approved by the local Medical Ethics Committee, and all patients provided their written, informed consent.

Results

Rest and maximum hemodynamics

Mean blood pressure (BP), left ventricular end-diastolic diameter (LVIDd) and maximum/mean pressure drops were comparable prior to commencement of exercise and dobutamine stress. At maximum stress, exercise caused the mean BP to increase by 19.4 mmHg ($p < 0.0001$), whilst dobutamine did not cause any significant change (decreased by 2.1 mmHg). Heart rates rose appreciably from their resting values ($p < 0.001$). The exercise heart rate exceeded the dobutamine heart rate in 11 of the 23 patients. The 85% predicted maximum heart rate was achieved in 81.5 ± 4.1% of patients during exercise, and in 85.6 ± 3.6% of patients throughout dobutamine stress ($p = 0.76$). Both stresses produced comparable stroke volumes. The baseline EOA was increased by 0.5 cm^2 ($p < 0.01$) with dobutamine, and by 0.17 cm^2 ($p < 0.05$) with exercise. The augmented EOA was significantly higher during dobutamine stress ($p < 0.002$). Both stresses produced a notable rise in maximum and mean pressure drops from their resting values ($p < 0.0001$). Maximum and mean pressure differences were statistically greater during ergometric exercise (Tables I and II).

Comparison between stresses at the same flow rates

It was possible to plot individual pressure/flow

Table I: Resting values across mitral prosthetic valves.

Parameter	Dobutamine group	Exercise group	p-value
Systolic BP (mmHg)	123.9	125.7	0.45
Diastolic BP (mmHg)	67.7	69.1	0.35
Mean BP (mmHg)	98.2	96.7	0.43
LVIDd (cm)	4.46	4.47	0.9
Heart rate (bpm)	85.8 ± 17.1	86.5 ± 16.9	0.63
Cardiac output (ml/min)	4253 ± 1027	4283 ± 1165	0.78
Effective orifice area (cm^2)	1.67 ± 0.35	1.64 ± 0.38	0.52
Maximum pressure gradient (mmHg)	11.08 ± 4.9	11.56 ± 5.4	0.53
Mean pressure gradient (mmHg)	4.31 ± 1.67	4.30 ± 2.0	0.95
Diastolic flow rate (ml/s)	143.1 ± 15.3	144.3 ± 16.8	0.84

Values are mean ± SD.
BP: Blood pressure; LVIDd: Left ventricular end-diastolic diameter.

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Table II: Maximum stress values across mitral prosthetic valves.

Parameter	Dobutamine group	Exercise group	p-value
Systolic BP (mmHg)	128	139	0.04
Diastolic BP (mmHg)	64	90.8	<0.001
Mean BP (mmHg)	96.1	116.1	<0.001
Heart rate (bpm)	136.1 ± 20.3	132.5 ± 27.9	0.45
Stroke volume (ml)	56.9 ± 13.5	55.1 ± 10.9	0.30
Effective orifice area (cm^2)	2.17 ± 0.5	1.81 ± 0.4	0.002
Maximum pressure gradient (mmHg)	12.8 ± 4.7	19.4 ± 6.0	<0.001
Mean pressure gradient (mmHg)	6.8 ± 2.8	10.2 ± 3.5	<0.01
Diastolic flow rate (ml/s)	241 ± 17.1	273 ± 20.1	<0.001
Diastolic filling time (ms)	231 ± 58.0	206 ± 50.0	<0.001

Values are mean ± SD.
BP: Blood pressure.

slopes during both stresses in 20 patients. The slopes were significantly higher during exercise (0.046 ± 0.007 $mmHg/ml.s^{-1}$ versus 0.028 ± 0.004 $mmHg/ml.s^{-1}$, respectively; p = 0.006) (Figs. 1 and 2).

Discussion

It has been shown that, under high flow conditions, normally functioning mitral prosthetic valves can generate pressure gradients that would categorize these patients as having moderately severe mitral stenosis, and hence raise suspicion that the prosthesis was malfunctioning. The resting and stress pressure drops recorded in the present study compared well with those reported previously. Rest studies using the Allcarbon (tilting-disc) mitral prosthesis (25 to 31 mm) reported peak and mean pressure drops ranging from 8 to 19 mmHg and 3 to 8 mmHg, respectively (3). The CarboMedics prosthetic valves have recorded peak drops of 18 to 8.7 mmHg, though there was considerable overlap between valve sizes (4,5). Supine exercise has been observed to produce a marked increase in pressure drop across the Björk-Shiley (tilting-disc) mitral prostheses, with peak and mean differences increasing from 10 mmHg and 5 mmHg respectively at rest, to 16 and 10.7 mmHg at peak exercise (6-8).

Effects of dobutamine and exercise on diastolic filling

At maximum stress, both methods produced comparable stroke volumes, although heart rates were higher and diastolic filling times longer with dobutamine. This was an unexpected finding, since the diastolic filling fraction of the cardiac cycle (diastolic filling time/cardiac cycle time) is reduced at faster heart rates. Dobutamine also caused a greater augmentation in EOA, with a resultant lower transvalvular pressure drop. This seems completely feasible since pressure differences are dependent on flow rate and cross-sectional area available for flow (9).

Effective orifice area (EOA)

The standard continuity equation utilizes the VTI, which provides an averaged EOA during diastole (i.e. from initial valve leaflet separation at the beginning of diastole to the terminal valve leaflet closure at the end of diastole). It is plausible that as cardiac flow increases, the apparent increase in EOA is a reflection of a higher rate of change of valve leaflet opening and closing. It is therefore hypothesized that, compared to bicycle exercise, dobutamine results in a maximum valve area being achieved more rapidly and proportionally for a greater length of time, when related to the overall diastolic filling time.

The observed increase in EOA may be erroneous and secondary to confounding factors. Errors may have occurred in the presence of undetected mitral regurgitation (MR). The assessment of prosthetic MR is limited using transthoracic echocardiography. The ratio of the VTI of mitral inflow to VTI in the LVOT ($VTI_{MV/LVOT}$) accounts for flow, and has been shown to be a significant predictor of MR, having a sensitivity and specificity of 89% and 91% respectively when the $VTI_{MV/LVOT}$ exceeds 2.5 (12). Reassuringly, the $VTI_{MV/LVOT}$ did not exceed 2.5 in any of the mitral prostheses studied. Data variability during exercise may also have contributed to the observed differences, although variability of data for exercise and dobutamine stress were not statistically different. Finally, it could be suggested that the 3- and 4-min stepwise protocol utilized during stress studies was insufficient time to allow the stabilization of hemodynamic and chronotropic conditions. It could be argued, therefore, that errors would occur when the LVOT and transmi-

tral velocities were acquired sequentially, as the flow rates may not have stabilized.

Study limitations

Dobutamine and exercise produce inotropic changes of left ventricular relaxation, and both are associated with a reduction in the time constant of left ventricular decay (13,14). The differences in diastolic filling may be related to dobutamine producing a more augmented effect on left ventricular relaxation than ergometric exercise. This improved relaxation may arise from the reduced afterload produced by dobutamine and/or the direct effect that dobutamine has on lowering the time constant of left ventricular decay. Ideally, some calculation of wall stress and thus an estimation of changes in afterload may have revealed a mechanism as to why diastolic filling time was different. Interestingly, in a recent study patients had markedly lower left ventricular diastolic and systolic wall stress during dobutamine when compared to exercise (15). The observed differences in EOA between ergometric exercise and dobutamine should also be investigated further. The hypothesis relating to dobutamine producing a quicker rate of valve leaflet opening/closing could have been quantified by performing M-mode echocardiography across the valve leaflets during stress.

In conclusion, normally functioning prosthetic mitral valves can generate significant increases in valvular pressure drops under high flow conditions, and therefore an estimation of cardiac flow should be calculated before concluding that the valve is working suboptimally. There are marked physiological differences between the two stresses when analyzing diastolic filling across prosthetic mitral valves. Even when comparing valvular performance for a given flow rate, differences in transmitral gradients were still evident. Compared to ergometric exercise, dobutamine produces a greater augmentation in the mitral EOA, producing lower transvalvular pressure gradients.

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