Analysis of Left Ventricular Function in Response to Afterload Changes in Patients with Mitral Stenosis

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SUMMARY

In order to assess left ventricular function in patients with rheumatic mitral stenosis, left ventricular function curves (plotting stroke work index vs left ventricular end-diastolic pressure) were constructed using angiotensin to augment, and nitroprusside to reduce, afterload. Hemodynamic responses to these alterations in afterload were measured. Resting ejection fractions and qualitative assessment of left ventricular angiographic contraction abnormalities were also determined.

Changes in left ventricular end-diastolic pressure following afterload interventions could be linearly related to changes in mean aortic pressure, but mitral valve gradients were unaffected. Afterload reduction with nitroprusside did not augment cardiac output. Afterload elevation with angiotensin significantly depressed both cardiac output and calculated mitral valve areas. Patients with normal resting ejection fractions evidenced normal ventricular function curves and those with depressed ejection fractions showed flat or declining function curves. Contraction abnormalities, generally in the posterobasal area, correlated well with abnormal left ventricular function curves.

Much evidence exists which suggests that left ventricular function is abnormal in many patients with rheumatic mitral stenosis. Immobilization of the left ventricular posterobasal area due to a rigid "mitral complex" and impaired contractility of the anterolateral left ventricular wall of uncertain etiology have been observed radiographically and suggested as causes of left ventricular dysfunction. Ventricular function curves constructed using angiotensin, isometric handgrip, or atrial pacing have been interpreted as indicative of abnormal left ventricular function in significant numbers of mitral stenosis patients as compared to normals.

Previous reports suggest that not all patients with mitral stenosis have detectable radiographic or function abnormalities. This study was undertaken to correlate the results of left ventricular function curves with radiographic contraction abnormalities and overall ejection fraction in the same patients. These function curves were constructed by afterload elevation with angiotensin and reduction by nitroprusside. The over-all hemodynamic response of patients with mitral stenosis to these afterload changes was also examined.

Methods

Fourteen patients with isolated mitral stenosis were included in the study. Informed consent was obtained from all participants. Patients with other valvular disease were excluded by physical examination, echocardiography, and by the results of catheterization. Any patient exhibiting more than trivial mitral regurgitation at the time of left ventricular angiography was excluded.

Resting cardiac catheterization was performed after premedication with 100 mg secobarbital intramuscularly. Wedge or NIH catheters with Statham P23Db transducers were employed for right-sided pressures, and 6.7 polyethylene end-hole catheters with Micron MP-15 transducers for left-sided pressures. Cardiac outputs were determined either by the direct Fick method or by duplicate indocyanine green dye dilution techniques. Pressures, mitral valve gradients, and stroke work indices were computer-determined and checked manually. Mitral valve area was calculated according to a modified Gorlin formula, using the mean pulmonary artery wedge-left ventricular pressure difference as the mitral valve gradient and an empirical constant of 44.5. The use of 44.5 reflects our reservations concerning the precision of constants derived from operative measurements of orifice size and preference for standardization with aortic valve measurements.

Resting left ventricular angiography was performed using a 6.7F angiographic catheter passed retrogradely across the aortic valve, and with the patient in the 30° right anterior oblique position. End-diastolic and end-systolic left ventricular volumes and ejection fraction were determined by

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light-pen computer processing of video disc-recorded left ventricular images, as previously detailed. A fixed external coordinate system was employed. For patients in sinus rhythm, these systolic-diastolic cycles, excluding those postextrasystolic, were analyzed and averaged. For patients in atrial fibrillation, five such cycles were analyzed and the results averaged.

After resting hemodynamics and left ventricular angiography were performed, aortic pressure was monitored until values returned to baseline levels. Nitroprusside was then administered via a peripheral vein, beginning at 20 μg/min and increasing by 10-20 μg/min each 3-5 minutes until mean aortic pressure had decreased by 10 to 25%. This infusion rate was then continued and stability checked for 10 minutes. Final dosages of nitroprusside employed were 30-80 μg/min. Following stabilization of aortic pressures, repeat pressure measurements and cardiac output were determined. Nitroprusside was discontinued and pressures were allowed to return to resting values. Angiotensin was then infused, beginning at a rate of 0.4 μg/min and increased until 20 to 80% augmentation in mean aortic pressure was obtained. Hemodynamics were then allowed to stabilize for 10 minutes, at which time pressures and cardiac output were determined. Dosages of angiotensin required to produce the desired effects ranged from 0.4 to 2.0 μg/min.

Data were obtained in 14 patients. One patient (2) did not receive nitroprusside. Three patients (6, 8, 9) were not given angiotensin; two (6, 8) because significant hypertension was present at rest, and one (8) because discomfort at the sites of catheter introduction did not permit continuance of the procedure. Technical factors precluded analysis of one patient’s (9) angiographic study. No patient suffered any significant ill effects.

Data analysis was performed by computation of mean and standard error of the mean. Analysis of paired data and statistical significance was evaluated by means of the paired Student’s t-test.

Results

The relevant patient and hemodynamic data are presented in table 1. The patients’ ages ranged from 36 to 67 years (mean 51 years). All previously had had rheumatic fever without recent acute episodes. All patients in atrial fibrillation were receiving digitals, as were three of the patients in sinus rhythm. Disease severity as indexed by New York Heart Association criteria ranged from moderate to severe. Three patients had previous mitral commissurotomies, and five had concurrent cardiopulmonary diseases described in table 1. No patient had angina pectoris, and only one (10) had electrocardiographic evidence of an infarction. Coronary arteriography revealed an occluded right coronary artery, thought to be embolic. Routine coronary arteriography was not performed. Three patients (6, 8, 9) had a history of mild hypertension. None had left ventricular hypertrophy by electrocardiographic or echocardiographic criteria. Calculated resting mitral valve areas varied from 0.5 to 2.1 cm² (mean 1.0 cm²).

Pressures

Mean aortic pressure fell an average of 17% following nitroprusside, and rose 23% following angiotensin (table 2). Left ventricular end-diastolic pressure (LVEDP) changes closely paralleled the changes in afterload, as shown in figure 1. The magnitude of induced changes in LVEDP was also quite similar with either increase (angiotensin) or decrease (nitroprusside) of afterload within the limits studied here. Pulse rate was usually, but not invariably, increased by nitroprusside. Over-all, nitroprusside caused about a 13% increase in rate. Such small changes in heart rate have been found previously to have no effect on hemodynamics in mitral stenosis. Angiotensin caused no consistent or significant alteration of rate.

Figure 2 illustrates the linear relationship between induced changes in LVEDP and mean pulmonary artery wedge pressure, and suggests that changes in LVEDP are generally reflected by similar changes in mean pulmonary artery wedge pressure. Mean pulmonary artery pressure changes follow the directional perturbations in mean pulmonary artery wedge pressure, though to a greater magnitude in terms of absolute pressures (tables 1 and 2).

Cardiac Flows

The nitroprusside-induced fall in afterload produced no consistent change in cardiac index, but augmentation of afterload with angiotensin effected a consistent and significant fall in cardiac index (tables 1 and 2). Mitral valve gradient was unchanged with both nitroprusside and angiotensin (fig. 3), reflecting the parallel increases in both LVEDP and pulmonary pressures.
artery wedge pressures. The calculated mitral valve areas were unchanged following nitroprusside (table 2, fig. 3), but fell significantly with angiotensin, primarily as a result of the decline in cardiac index (table 2).

**Ventricular Function**

Calculated stroke work index, ejection fraction, and volumetric data are presented in table 1. Left ventricular end-diastolic volumes varied from 70 to 222 cm³, with a mean of 142 ± 10.8 cm³, which is slightly greater than a series of 26 normal patients (no heart disease, or mild angina without evidence of left ventricular dysfunction) whose mean left ventricular end-diastolic volume was 128 ± 7 cm³ (unpublished observations).

Ventricular function curves, plotting stroke work index as a function of LVEDP, were constructed. Nitroprusside declines in LVEDP were consistently associated with reductions in stroke work index. However, in patients receiving angiotensin, stroke work index increased in five, remained unchanged in three, and declined in three. Flat or declining curves were observed in all patients who had depressed ejection fractions. The range and mean ejection fractions in 26 normal patients for this laboratory are 0.51 to 0.80 and 0.65, respectively (unpublished observations). If patients were therefore divided into two groups on the basis of normal ejection fraction (≥ 0.50) and abnormal ejection fraction (< 0.50), striking correlation with normal and abnormal ven-
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<th>Cardiac index (L/min/m²)</th>
<th>Stroke work index (g-m/m²²)</th>
<th>MV gradient (mm Hg)</th>
<th>MV area (cm²)</th>
<th>Control EDV (cm³)</th>
<th>Control EF</th>
<th>Posterobasal defority (0 - 4+)</th>
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**Table 2**
Summary of Hemodynamic Data

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<th>Nitroprusside</th>
<th>Angiotensin</th>
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<tr>
<td>Number of patients</td>
<td>14</td>
<td>13</td>
<td>11</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>76.1 ± 4.9</td>
<td>88.0 ± 6.6</td>
<td>76.6 ± 6.3</td>
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<td></td>
<td>+13.6%</td>
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<td>Mean pulmonary artery pressure (mm Hg)</td>
<td>25.9 ± 3.6</td>
<td>21.6 ± 3.0</td>
<td>33.8 ± 5.1</td>
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<td>-25.1%</td>
<td>P &lt; 0.01</td>
<td>+31.8%</td>
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<tr>
<td>Mean pulmonary artery wedge pressure (mm Hg)</td>
<td>17.4 ± 1.5</td>
<td>14.6 ± 1.9</td>
<td>24.5 ± 2.9</td>
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<td>-19.0%</td>
<td>P &lt; 0.01</td>
<td>+49.4%</td>
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<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>10.1 ± 1.0</td>
<td>5.2 ± 0.8</td>
<td>14.6 ± 1.3</td>
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<td></td>
<td>-51.2%</td>
<td>P &lt; 0.01</td>
<td>+70.6%</td>
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<td>Mean aortic pressure (mm Hg)</td>
<td>98.2 ± 6.1</td>
<td>82.7 ± 5.3</td>
<td>112.0 ± 5.7</td>
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<td>-16.7%</td>
<td>P &lt; 0.01</td>
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<td>Cardiac index (L/min/m²)</td>
<td>2.2 ± 0.02</td>
<td>2.1 ± 0.1</td>
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<td></td>
<td>-19.7%</td>
<td>P &lt; 0.01</td>
<td>NS</td>
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<tr>
<td>Mitral valve gradient (mm Hg)</td>
<td>10.1 ± 0.9</td>
<td>10.8 ± 1.3</td>
<td>11.8 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>NS</td>
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</tr>
<tr>
<td>Mitral valve area (cm²)</td>
<td>1.0 ± 0.11</td>
<td>0.9 ± 0.07</td>
<td>0.76 ± 0.10</td>
</tr>
<tr>
<td></td>
<td>-23%</td>
<td>NS</td>
<td>P &lt; 0.01</td>
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</tbody>
</table>

**Figure 3**
Bar graphs of cardiac index, mitral valve gradient, and mitral valve area during the control state and nitroprusside and angiotensin infusions. Figures below each bar graph indicate mean ± SEM and significance of this number compared to the control state using Student's t-test. NS = not significant.

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merely by a differential fall in cardiac index or heart rate between the normal and abnormal ejection fraction groups.

Contraction Abnormalities

Each of the left ventricular angiograms was graded qualitatively by two observers in a "blind" fashion, and estimates were made of the degree of posterobasal deformity and hypokinesis and other areas of hypokinesis (table 1). Of the five patients with impaired ventricular function and reduced ejection fraction, three showed severe posterobasal deformities and hypocontractility, as well as other areas of significant hypokinesis (patients 11, 12, and 14). Enddiastolic and end-systolic frames from one such patient (12) are shown in fig. 5B. One patient (10) with a history of inferior myocardial infarction showed little posterobasal deformity but striking inferior akinesis and an apical aneurysm. One patient (13) evidenced only minimal mild posterobasal abnormalities and generalized hypocontractility.

Of the eight patients with normal function and satisfactory angiographic data, seven showed some posterobasal abnormalities, but in only three were these of a significant degree (table 1; fig. 5 A and C). Thus, in contrast to the group with left ventricular dysfunction, the degree of posterobasal deformities and hypokinesis was less, and the severe generalized contraction disorders were never seen.

Hemodynamic studies

Discussion

Considerable interest has been generated in afterload reducing agents for the treatment of patients with congestive heart failure due to chronic myopathy, acute myocardial infarction, or mitral regurgitation. Conversely, pharmacological agents for augmentation of afterload have been used in order to evaluate myocardial function. The effects of afterload reduction and augmentation have not been systematically studied in patients with mitral stenosis, either from a physiologic or clinical standpoint.

Sodium nitroprusside was chosen as an afterload reducing agent because of its demonstrated safety and stability in reducing blood pressure for periods of 15–45 minutes. Nitroprusside acts primarily on the smooth muscle vasculature and is free of effects on the central or peripheral nervous system. Angiotensin was selected because it is also devoid of direct effects upon the vasomotor centers or cardiac muscle.

Our results show that LVEDP in patients with mitral stenosis respond to augmentation and diminution of afterload in a linear manner. This relationship seems independent of any changes in cardiac output (venous return) or resting ejection fraction. These findings are in general agreement with previous studies. Ross and Braunwald administered angiotensin to eight patients with variable severity of mitral stenosis. Their data show a consistent elevation of LVEDP with rise in mean aortic pressure but no significant or consistent changes in cardiac index. Handgrip-induced pressor responses in six patients with mitral stenosis raised LVEDP but did not change stroke volume; cardiac output was elevated due to a rise in heart rate. Rothbaum et al. reported in abstract form the effects of nitroglycerin in six patients with mitral stenosis. They found reductions of pulmonary artery, left atrial and left ventricular enddiastolic pressures after sublingual nitroglycerin. Cardiac index was not consistently altered.

Alterations in pulmonary artery wedge pressure only passively reflect changes in LVEDP (fig. 2), since mitral valve flow was unchanged (nitroprusside) or slightly decreased (angiotensin). Consequently, the mitral valve gradient was unaffected by either increase or decrease in afterload. The calculated fall of mitral valve area with angiotensin (fig. 3) was generally the result of an unchanged gradient and a decrease in cardiac index. This direct relationship of mitral valve area and cardiac index has been described with exercise and has been attributed to a "dynamic mitral valve orifice area" which may increase in response to flow and pressure augmentation. Our data show that this phenomenon is not limited to exercise.
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changes alone, nor are changes in mitral valve gradient necessary.

The failure of cardiac index to rise with "unloading" of the left ventricle with nitroprusside is in striking contrast to patients with severe heart failure or significant mitral regurgitation. This finding is consistent with the hypothesis that the major cause of a subnormal cardiac output in patients with mitral stenosis is obstruction of inflow into the left ventricle rather than left ventricular dysfunction itself.

It is difficult to explain the decline in cardiac index observed following angiotensin. Although a reflex fall in heart rate might be anticipated, this was not observed (table 2). Previous studies in patients with mitral stenosis with angiotensin and isometric exercise failed to observe a decline in cardiac output. Reported effects of angiotensin on cardiac output in the normal heart are variable; however, in patients with definite left ventricular dysfunction, cardiac index falls consistently with angiotensin. Thus, the decline in cardiac output which we observed in all but one patient following angiotensin may indicate left ventricular dysfunction in some patients or may just reflect increased impedance to left-sided filling in an already compromised situation of mitral stenosis. Our data show that the mitral valve gradient does not change, and therefore suggest that the mitral valve area may vary dynamically with afterload and flow changes.

Left Ventricle Function and Contraction Abnormalities

Our data suggest that patients with mitral stenosis can be divided into two groups on the basis of both ventricular function curves and ejection fraction (fig. 4). These curves are similar to those of Ross and Braunwald, which showed both "normal" and "abnormal" responses among their eight patients with mitral stenosis. Several recent angiographic papers have compared patients with mitral stenosis to normals and have found a high incidence of posterobasal and sometimes anterolateral contraction abnormalities. As a group, these patients also have reduced ejection fraction compared to normals. These contraction abnormalities are attributed to a rigid
"mitral complex" and/or fibrosis near or in the papillary muscles, which correlates with pathologic observations. Despite minor posterobasal abnormalities in many of our patients, most still exhibit normal hemodynamics and normal ejection fractions. Nonetheless, significant left ventricular dysfunction is present in some patients, due to severe rheumatic scarring of the mitral papillary muscle complex, to concomitant artery disease, or to coronary artery embolization, as was seen in patient 12.

Our data thus indicate a spectrum of left ventricular dysfunction in patients with mitral stenosis which is correlated with abnormalities of left ventricular contraction and with abnormalities of left ventricular function curves.

Clinical Implications

Despite the success of afterload reduction in improving hemodynamics in patients with severe left ventricular failure or mitral regurgitation and the early suggestion that this might have therapeutic value in patients with mitral stenosis, it would appear from these data that afterload reduction would have little benefit in most patients with mitral stenosis. Afterload reduction did not increase cardiac output. The degree to which mean pulmonary artery wedge pressure can be reduced is limited by the reduction in LVEDP, and hence, unless there is gross left ventricular failure with elevation of LVEDP, only relatively small reductions in pulmonary artery wedge pressure could be achieved. Pulmonary artery pressure might well be significantly lowered with afterload reduction, especially if the initial pulmonary artery pressure is high (patient 8).

It is also evident from these studies that afterload increases in patients with mitral stenosis have detrimental effects in raising mean pulmonary artery wedge pressure and diminishing cardiac output. Control of concomitant hypertension should have beneficial hemodynamic effects in patients with mitral stenosis.

Acknowledgment

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