DEPRESSED MYOCARDIAL CONTRACTILITY IN MITRAL STENOSIS  
—An Analysis by Force-Length and Stress-Shortening Relationships—

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To determine whether low ejection fraction (EF) in mitral stenosis (MS) is the result of depressed contractility or is mediated by other factors, left ventricular (LV) function was analyzed by force-length and stress-shortening relationships. Thirty patients without heart disease served as normal controls (Group 1). Forty-three patients with MS were divided into 2 subgroups: Group 2 (n = 19) had EF within one standard deviation of the mean of Group 1, and Group 3 (n = 24) had EF below it. Normal EF (Group 2) was associated with low preload (end-diastolic stress) and low afterload (end-systolic stress), and preload and afterload were in the normal range in patients with low EF (Group 3). A significant negative correlation was observed in the whole group of patients with MS between EF and end-systolic stress (Y = -0.14X + 72.8, r = -0.61, p < 0.001), and a positive correlation between end-systolic stress and volume (Y = 1.39X + 65.4, r = 0.45, p < 0.01). These observations suggest that systolic shortening and end-systolic volume of the left ventricle are in part governed by afterload in this disease.

It is concluded that low EF of MS is not mediated by reduced preload or inappropriately elevated afterload, and contractility of the ventricle is mildly depressed in MS.

Approximately one-third of patients with mitral stenosis (MS) have an ejection fraction (EF) below normal. The cause of this low EF is not clear. Several hypotheses have been put forward, such as myocardial fibrosis from chronic rheumatic myocarditis, extension of the scarring process from the mitral valve to the myocardium, or microcirculation disturbance of the coronary artery system. Cardiac output does not increase following the surgical repair of the mitral valve in some cases. Several investigators consider that this failure to improve after surgery is due in part to left ventricular (LV) dysfunction. This ventricular abnormality has been referred to as the "myocardial factor." Currently, it is believed that such a myocardial factor does not exist; the depressed EF is the result of inadequate preload and/or inappropriately elevated afterload, and the poor outcome of surgery is due entirely to poor surgical technique.

Evaluation of either the force-length or stress-shortening relationship is now considered to be a good method of analyzing the LV contractile state. In this study, a detailed analysis of LV function was performed in patients with MS.

Key words:
Contractility 
EF 
Preload 
Afterload 
Stress

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using simultaneously recorded high fidelity pressure and LV cineangiograms.

METHODS

Patients
The study population, shown in Table I, included 73 patients who underwent diagnostic cardiac catheterization between July 1978 and June 1983. They were 43 consecutive patients with pure MS and 30 normal subjects without significant heart disease (Group 1). The patients with MS were divided into 2 subgroups according to their EF; EF within one standard deviation of the mean of Group 1 (Group 2, n = 19, EF = 67 ± 6%) and EF below it (Group 3, n = 24, EF = 48 ± 10%).

Procedure
The precise description of the catheterization technique and data analyses have been reported elsewhere. In brief, cardiac catheterization was performed by the brachial approach in the fasting state under mild sedation. All medication except digitalis was withheld 12 to 18 hours before this procedure. The right heart pressures were recorded with a Swan-Ganz catheter, and cardiac output was measured by the thermodilution method in a triplicate fashion. The left heart pressures were recorded with a Mikrotip angiocatheter (Model PC-471 or 481, Millar Instruments). The zero level was calibrated electronically by a transducer control unit (Model TCB-100, Millar Instruments) before the insertion of the catheter, and zero shift was adjusted at the mid-chest position via the fluid-filled system of the same catheter. LV and pulmonary capillary wedge pressures were recorded simultaneously. Photographic recordings were obtained at a paper speed of 100 mm/s, with an 8 channel optical recording system (Model 4588D, Hewlett-Packard). Five consecutive complexes in patients with normal sinus rhythm and 10 consecutive complexes in those with atrial fibrillation were averaged for the determination of pressures and the data derived from the pressure tracings.

Left ventriculogram were recorded in a 30° right anterior oblique projection with the same catheter. Thirty to 45 ml of contrast material (Angioconray®) was injected over 3 s by a power injector (Contrac 4T, Siemens). Films were exposed at a rate of 60 frames/s with a 35 mm cine camera (Arritechno 35, Arritechno) mounted on a 25 cm image intensifier (Cardoscope U, Siemens). LV pressure was recorded during cineangiography. Also in all cases of MS, aortography was performed with 15–25 ml of Angioconray®, and coronary arteriography was performed using Sones technique. Patients who had concomitant coronary artery disease or other valvular heart diseases were excluded from this study.

The mitral valve area was calculated by an equation of Gorlin. Systemic vascular resistance (SVR) was obtained from the formula: $SVR = \left(\frac{\text{mean AoP} - \text{mean RAP}}{\text{CO}} \times \frac{80}{\text{dynes} \cdot \text{cm}^{-5}}\right)$, where mean AoP is mean aortic pressure measured by the fluid filled system, mean RAP is mean right atrial pressure, and CO is cardiac output. Pulmonary arterial resistance (PAR) was obtained from the formula: $PAR = \left(\frac{\text{mean PAP} - \text{mean PCWP}}{\text{CO}} \times \frac{80}{\text{dynes} \cdot \text{cm}^{-5}}\right)$, where mean PAP is mean pulmonary arterial pressure, and mean PCWP is mean pulmonary capillary wedge pressure. LV volumes, short and long axes, and wall thickness were calculated at end-diastole and end-systole by the area-length method using a semi-computerized system (Cardias GP2000, NAC). EF was calculated by a standard formula.

Mid-wall circumferential stress was calculated from an ellipsoid model of an equation due to Minsky: $\text{stress} = \frac{\text{P} \cdot (1 - \frac{\text{h}}{2 \cdot \text{B}})}{\left(\frac{(L + 2h)}{2} - V\right) \times 1.05}$, where P is the pressure, A and B are the major and minor radii to the mid-wall, respectively, and h is the wall thickness at the mid-anterior portion. For the assessment of preload and afterload, end-diastolic stress and end-systolic stress were calculated from LV end-diastolic and end-systolic pressures, and the end-diastolic and end-systolic frames of the film, respectively. End-systolic pressure was defined as the pressure at the first component of the aortic closing sound of the intracardiac phonocardiogram. LV wall thickness at end-systole could not be measured in two patients in Group 3.

LV mass was calculated by the equation of Rackley et al: $\text{LV mass} = \left\{\frac{1}{2} \cdot \pi \cdot (D + 2h)^2 \cdot \frac{[L + 2h]}{2} - V\right\} \times 1.05$, where D is the short axis, L is the long axis, h is the wall thickness, V is the volume at end-diastole, and 1.05 is the specific gravity of heart muscle.

The non-parametric method of Kruskal and Wallis was employed for the statistical analysis in comparing all groups. Analyses of contractility using force-length (end-systolic stress-volume) and stress-shortening (end-systolic stress-EF) relationships were performed in 41 patients with

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### TABLE I STUDY POPULATION AND HEMODYNAMIC DATA

<table>
<thead>
<tr>
<th>Groups</th>
<th>No.</th>
<th>Sex</th>
<th>Age</th>
<th>MVA (cm²)</th>
<th>CI (l/min·m²)</th>
<th>SP (mmHg)</th>
<th>edp (mmHg)</th>
<th>esp (mmHg)</th>
<th>SVR (dynes·s·cm⁻¹)</th>
<th>PAR (dynes·s·cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Subjects</td>
<td>30</td>
<td>M 21</td>
<td>42</td>
<td></td>
<td>3.3</td>
<td>122</td>
<td>8.8</td>
<td>105</td>
<td>1414</td>
<td>88</td>
</tr>
<tr>
<td>(Group 1)</td>
<td></td>
<td>F 9</td>
<td>± 14</td>
<td>± 0.9</td>
<td>± 14</td>
<td>± 3.1</td>
<td>± 15</td>
<td>± 392</td>
<td>(n = 29)</td>
<td></td>
</tr>
<tr>
<td>Mitral Stenosis</td>
<td>43</td>
<td>M 12</td>
<td>50</td>
<td>1.1</td>
<td>2.5</td>
<td>123</td>
<td>8.7</td>
<td>101</td>
<td>2044</td>
<td>214</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F 31</td>
<td>± 10</td>
<td>± 0.5</td>
<td>± 0.6</td>
<td>± 20</td>
<td>± 3.3</td>
<td>± 13</td>
<td>(n = 41)</td>
<td>(n = 41)</td>
</tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Normal EF</td>
<td>19</td>
<td>M 4</td>
<td>50</td>
<td>1.2</td>
<td>2.7</td>
<td>121</td>
<td>8.2</td>
<td>100</td>
<td>1749</td>
<td>200</td>
</tr>
<tr>
<td>(Group 2)</td>
<td></td>
<td>F 15</td>
<td>± 10</td>
<td>± 0.5</td>
<td>± 0.6</td>
<td>± 16</td>
<td>± 3.8</td>
<td>± 11</td>
<td>(n = 18)</td>
<td>(n = 18)</td>
</tr>
<tr>
<td>Poor EF</td>
<td>24</td>
<td>M 8</td>
<td>49</td>
<td>1.0</td>
<td>2.3</td>
<td>124</td>
<td>9.2</td>
<td>102</td>
<td>2274</td>
<td>226</td>
</tr>
<tr>
<td>(Group 3)</td>
<td></td>
<td>F 16</td>
<td>± 9</td>
<td>± 0.4</td>
<td>± 0.5</td>
<td>± 23</td>
<td>± 2.9</td>
<td>± 16</td>
<td>(n = 23)</td>
<td>(n = 23)</td>
</tr>
</tbody>
</table>

Group 1 versus 2  

- NS  
- NS  
- NS  
- NS  
- p < 0.05  
- p < 0.01  

Group 1 versus 3  

- NS  
- NS  
- NS  
- NS  
- p < 0.01  
- p < 0.01  

Group 2 versus 3  

- NS  
- NS  
- NS  
- NS  
- p < 0.05  
- NS  

Values are mean ± standard deviation. CI = cardiac index; edp = end-diastolic pressure; esp = end-systolic pressure; MVA = mitral valve area; PAR = pulmonary arteriolar resistance; SP = systolic pressure; SVR = systemic vascular resistance.
<table>
<thead>
<tr>
<th>Groups</th>
<th>EDVI (ml/m²)</th>
<th>ESVI (ml/m²)</th>
<th>EF (%)</th>
<th>LVMI (g/m²)</th>
<th>WTed (cm)</th>
<th>WTes (cm)</th>
<th>aed (g/cm²)</th>
<th>aes (g/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Subjects (Group 1)</td>
<td>70 ± 19</td>
<td>25 ± 9</td>
<td>65.1 ± 6.1</td>
<td>79 ± 18</td>
<td>0.9 ± 0.2</td>
<td>1.4 ± 0.3</td>
<td>28 ± 10</td>
<td>131 ± 51</td>
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<td></td>
<td>(n = 30)</td>
<td>(n = 30)</td>
<td>(n = 30)</td>
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<td>(n = 30)</td>
<td>(n = 30)</td>
<td>(n = 30)</td>
<td>(n = 30)</td>
</tr>
<tr>
<td>Mitral Stenosis</td>
<td>85 ± 24</td>
<td>38 ± 18</td>
<td>56.1 ± 12.7</td>
<td>101 ± 43</td>
<td>0.9 ± 0.3</td>
<td>1.3 ± 0.4</td>
<td>21 ± 10</td>
<td>119 ± 57</td>
</tr>
<tr>
<td></td>
<td>(n = 43)</td>
<td>(n = 43)</td>
<td>(n = 43)</td>
<td>(n = 43)</td>
<td>(n = 43)</td>
<td>(n = 43)</td>
<td>(n = 43)</td>
<td>(n = 41)</td>
</tr>
<tr>
<td>Normal EF (Group 2)</td>
<td>81 ± 17</td>
<td>27 ± 7</td>
<td>67.1 ± 6.1</td>
<td>101 ± 43</td>
<td>0.9 ± 0.2</td>
<td>1.6 ± 0.3</td>
<td>19 ± 11</td>
<td>82 ± 28</td>
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<tr>
<td></td>
<td>(n = 19)</td>
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<td>(n = 19)</td>
<td>(n = 19)</td>
<td>(n = 19)</td>
<td>(n = 19)</td>
<td>(n = 19)</td>
</tr>
<tr>
<td>Poor EF (Group 3)</td>
<td>89 ± 28</td>
<td>46 ± 19</td>
<td>47.5 ± 9.6</td>
<td>101 ± 52</td>
<td>0.9 ± 0.3</td>
<td>1.2 ± 0.4</td>
<td>22 ± 9</td>
<td>150 ± 57</td>
</tr>
<tr>
<td></td>
<td>(n = 24)</td>
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<td>(n = 24)</td>
<td>(n = 24)</td>
<td>(n = 24)</td>
<td>(n = 22)</td>
<td>(n = 24)</td>
<td>(n = 22)</td>
</tr>
</tbody>
</table>

Group 1 versus 2
NS NS NS NS NS NS p < 0.05 p < 0.01

Group 1 versus 3
NS p < 0.01 p < 0.01 NS NS p < 0.05 NS NS

Group 2 versus 3
NS p < 0.01 p < 0.01 NS NS p < 0.01 NS p < 0.01

Values are mean ± standard deviation. EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; LVMI = left ventricular mass index; aed = end-diastolic stress; aes = end-systolic stress; WTed = wall thickness at end-diastole; WTes = wall thickness at end-systole.
Myocardial Contractility in Mitral Stenosis

Fig.1. Relation between end-systolic stress and end-systolic volume. A significant correlation was present between these 2 variables (○) (solid line; $Y = 3.68X + 40.2$, $r = 0.64$, $p < 0.001$) and in patients with MS with normal EF (●) and poor EF (△) (dashed line; $Y = 1.39X + 65.4$, $r = 0.45$, $p < 0.01$). This observation suggests that end-systolic volume is dependent on end-systolic stress or vice versa even at rest in normal human ventricle as well as left ventricle in MS. As end-systolic volume in the majority of patients was greater than that of normal subjects with the same level of end-systolic stress, contractility of the LV myocardium seems to be depressed in MS.

MS and 30 normal subjects. Linear regression was performed by the least-squares method. A significance of the regression line and the line of identity were determined by the analysis of variance of the correlation of coefficient. Data are presented as mean ± SD.

RESULTS

Of the 43 patients with MS, 28 had atrial fibrillation and 15 had normal sinus rhythm. Two patients were symptom free, 12 had mild dyspnea on exertion or fatigue and they were considered to be in New York Heart Association²⁹ (NYHA) functional class II. Twenty-nine had severe symptoms of dyspnea or hemoptysis, and were considered to be in NYHA class III or IV. Five had restenosis of the mitral valve. Eight had another serious diseases such as cervical cancer, chronic obstructive lung disease, systemic lupus erythematosus, cerebral embolism or Parkinsonism. Seventeen were followed medically and 26 had surgical treatment, 20 open mitral commissurotomy and 6 artificial valve replacement.

All patients with MS had significantly reduced mitral valve area (1.1 ± 0.5 cm²). Hemodynamic and angiographic characteristics of MS were low cardiac output (2.5 ± 0.6 versus Group 1; 3.3 ± 0.9 l/min/m², $p < 0.01$), elevated systemic vascular resistance (2044 ± 718 versus 1414 ± 392 dyne·s·cm⁻⁵, $p < 0.01$), and slightly increased LV end-systolic volume (38 ± 18 versus 25 ± 9 ml/m², $p < 0.01$). EF was low (56.1 ± 12.7 versus 65.1 ± 6.1%, $p < 0.01$), preload (end-diastolic stress) was reduced (21 ± 10 versus 28 ± 10 g/cm², $p < 0.01$), and afterload (end-systolic stress) stayed in the normal range (119 ± 57 versus 131 ± 51 g/cm², NS)(Tables I and II).

These 43 patients were divided into two subgroups, normal EF (Group 2, n = 19) and low EF (Group 3, n = 24). In Group 2, cardiac output,
LV pressures, volumes and wall thickness were in the normal range, and calculated wall stress at end-diastole and end-systole were significantly lower than normal (end-diastolic stress: 19 ± 11 versus 28 ± 10 g/cm², p < 0.05, end-systolic stress: 82 ± 28 versus 131 ± 51 g/cm², p < 0.01). On the other hand, in Group 3, cardiac output was reduced (2.3 ± 0.5 versus 3.3 ± 0.9 l/min/m², p < 0.01), LV volumes were slightly increased (end-diastolic volume: 89 ± 28 versus 70 ± 19 ml/m², p < 0.05, end-systolic volume: 46 ± 19 versus 25 ± 9 ml/m², p < 0.01), wall thickness at end-systole was thinner (1.2 ± 0.4 versus 1.4 ± 0.3 cm, p < 0.05), and wall stress stayed in the normal range (end-diastolic stress: 22 ± 9 versus 28 ± 10 g/cm², NS, end-systolic stress: 150 ± 57 versus 131 ± 51 g/cm², NS).

There was a significant positive correlation between end-systolic stress and volume in patients with MS (Y = 1.39X + 65.4, r = 0.45, p < 0.01). The majority of patients with MS located in the right side of the normal subjects (Fig. 1). This observation indicates that end-systolic volume or muscle length is greater than normal with the same level of end-systolic force in MS.

The stress-shortening, or afterload-EF relationship is shown in Fig. 2. A majority of patients in Group 2 were in the left side of normal, and Group 3 located below normal. There was a significant inverse correlation between EF and afterload in those patients (Y = −0.14X + 72.8, r = −0.61, p < 0.001). This observation also demonstrates that normal systolic shortening in Group 2 is maintained with low afterload, and normalization of afterload in Group 3 is associated with reduced systolic shortening.

These two figures indicate that contractility of the left ventricle is somewhat depressed in MS as compared to that of the normal left ventricle.

DISCUSSION

MS is characterized by obstruction of the inflow tract to the left ventricle. The mechanical block at the mitral valve causes elevation of the left atrial and pulmonary arterial pressures, and clinical disability in this disease is related to the effects of these abnormally elevated pressures in the pulmonary circulation. However, some patients have markedly reduced cardiac output in spite of relatively mild elevation of pulmonary pressure, or do not show enough symptomatic improvement after proper surgical treatment.

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Therefore, it has been postulated that myocardial dysfunction may be the least understood cause of these low cardiac output states or poor surgical outcome.16–18

The possibility of LV dysfunction in patients with MS was suggested at least half century ago by Kirch30 and continues to be a subject of investigation. In 1953, Grant12 suggested on the basis of anatomical studies that atrophy, fibrosis and shortening of the postero-basal area of the LV wall could impair LV function. Harvey et al19 reported the possibility of myoccardial damage after observing that patients who failed to improve after commisurotomy had preoperative hemodynamic characteristics of fixed cardiac output without pulmonary hypertension by exercise. Fleming and Wood15 considered that myocardial disease might occur in patients with MS as a consequence of coexisting atrial fibrillation. They suggested that chronic atrial fibrillation might impair coronary perfusion and produce myocardial damage. In the 1960s, Feigenbaum et al9 showed distinctly elevated LV end-diastolic pressure with exercise in some patients and suggested that this abnormality might be related to depressed LV compliance. In addition, they reported that 20 of 24 patients with MS who underwent cardiac surgery showed evidence of active carditis in their atrial appendages. They deduced that the same changes might exist in the myocardium of the ventricle. Heller and Carlton13 noted LV cineangiographic evidence of hypokinesis in the postero-basal region of the LV wall, which supported the anatomical findings of Grant et al.12 Curry et al14 also reported abnormal LV wall motion not only in the postero-basal but also in the antero-lateral area. They considered, however, that this ventricular dysfunction was due to right ventricular enlargement and was not related to the rheumatic process.

As EF is below normal in approximately one-third of patients with MS1–5 myocardial contractility has been considered possibly to have been adversely affected by rheumatic processes or hemodynamic abnormalities secondary to the morphological changes of the subvalvular tissue and right ventricle. EF, however, is affected by the degree of loading of the ventricle and varies directly with preload and inversely with afterload.31–33 Therefore, myocardial contractility must be estimated from both preload and afterload.32 Braunwald20 considered that this reduced EF was the result of chronic reduction in preload because of the mechanical block at the mitral valve.

In this study, 56% of the patients had an EF below one standard deviation of the normal value. The end-diastolic stress, an index of preload, was decreased in the MS group. This observation agrees with the opinion of Braunwald20. A more detailed analysis showed, however, that the preload stayed in the normal range in patients with reduced EF, and decreased in patients with normal EF. So the reduction of EF in MS cannot be explained by inadequate preload.

An index of afterload, end-systolic stress, was decreased in patients with normal EF and was in the normal range in patients with reduced EF. Gash et al.5 have also reported that end-systolic stress was higher in patients with reduced EF than that in those with normal EF. They concluded that the reduction in EF was secondary to the elevation of afterload or to afterload mismatch, and the myocardial contractility itself was normal. In their report, however, the normal range of end-systolic stress was not indicated. In our study, afterload was not elevated in the reduced EF group but stayed in the normal range, whereas it was decreased in the normal EF group. From this observation, low EF cannot be explained by disproportionately elevated afterload. Our observation of normal preload, afterload and reduced shortening rate in MS is completely in agreement with the results of Hood et al.1 They measured end-diastolic and peak-systolic stress in MS and found that these indices of preload and afterload stayed in the normal range in this disease with significantly reduced EF compared to normal left ventricle.

Compared to 30 normal subjects, the relation between end-systolic stress and volume index showed a rightward shift in patients with MS. As LV end-systolic volume or muscle length is greater in MS compared to normal ventricle with the same level of end-systolic stress, this observation suggests a depressed inotropic state in this disease (Fig. 1). This force-length relationship is, however, limited in the end-systolic phase, and accumulating evidence suggests that analysis of the stress-shortening relationship is preferable.22–34 From this viewpoint, we examined the afterload-EF relationship. A majority of patients with MS had curves to the left and below those of normal subjects, and there was an inverse correlation in patients with MS (r = −0.61) (Fig. 2). Since normal EF is associated with low afterload, and reduced EF is seen with normal afterload, this observation also indicates that contractility...
of the left ventricle is somewhat depressed in MS. The sensitivity of EF to afterload is considered to be different between MS group and normal subjects, which may be due to the so-called myocardial factor.

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