Left Ventricular Ejection Performance and Systolic Muscle Function in Patients with Mitral Stenosis

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SUMMARY The status of systolic left ventricular (LV) performance in patients with isolated mitral stenosis (MS) is controversial. Potential alterations in LV architecture as well as loading conditions may have complex effects on LV ejection performance and muscle function. Therefore, we determined hemodynamic and angiographic LV ejection indexes (ejection fraction [EF], velocity of circumferential fiber shortening [Vcf] and stroke work index [SWI]), the level of preload (end-diastolic volume index [EDVI]), afterload (end-systolic wall stress [ESSI]), and an index of LV contractile function thought to be independent of loading conditions (end-systolic wall stress/end-systolic volume index [ESS/ESVI]) in nine normal subjects and 16 patients with isolated MS.

Although the EF in patients with MS (0.59 ± 0.03) was not statistically different from that in normal subjects (0.66 ± 0.04) (mean ± SEM), 31% of MS patients had an EF < 0.50. Vcf was lower in MS patients than in normal subjects (1.01 ± 0.06 vs 1.32 ± 0.10 sec⁻¹, p < 0.01), as were SWI (45.0 ± 2.9 vs 69.1 ± 3.9 g·m⁻²·sec⁻¹, p < 0.001) and EDVI (71.3 ± 5.2 vs 93.0 ± 3.9 ml/m² ·p < 0.005). End-systolic volume index (ESVI) was similar in MS patients and normal subjects (29.5 ± 3.6 vs 33.0 ± 3.6 ml/m²), whereas stroke volume index (SVI) was lower in MS patients (41.8 ± 2.8 vs 61.6 ± 4.4 ml/m² ·p < 0.001). On the basis of ejection performance, MS patients were divided into two groups. Patients with normal ejection performance (MSREP) had EF > 0.50 and Vcf > 1.00 sec⁻¹. Patients with reduced ejection performance (MSREP) had EF < 0.50 or Vcf < 1.00 sec⁻¹. MSREP patients had higher ESS (157 ± 19 dyn · 10⁻³/cm²) than MSREP (107 ± 11 dyn · 10⁻³/cm²) (p < 0.025), yet EDVI was similar in MSREP (70.6 ± 7.8 ml/m²) and MSREP (72.0 ± 7.3 ml/m²), ESS/ESVI in MS patients was not different from that in normal subjects (5.3 ± 0.5 vs 5.2 ± 0.8 dyn · 10⁻³·m²/cm²). Even four of five MS patients with EF < 0.50 and all six MS patients with Vcf < 1.00 sec⁻¹ had a normal ESS/ESVI.

We conclude that MS patients as a group have reduced ejection performance and reduced preload. The reduction in ejection performance is due to increased afterload without adequate Frank-Starling compensation. LV muscle function, however, is normal in most MSREP patients.

THE STATUS of left ventricular (LV) systolic performance in patients with isolated mitral stenosis (MS) is controversial. Although rheumatic disease alters the architecture of the left ventricle,1-5 and the rheumatic inflammatory process is present within the myocardium of patients with long-standing mitral disease,6,7 it is not clear that this results in abnormal LV systolic muscle function in MS. Hemodynamic and angiographic studies3,5,8-18 have failed to yield a uniform concept of LV systolic muscle function in MS. The potentially altered loading conditions under which the left ventricle operates in MS have not been clearly defined. If loading conditions are altered in MS, such alterations might have affected several previous methods of measuring LV systolic muscle function and led to divergent results and conclusions.

We therefore studied LV systolic performance in patients with isolated MS and in normal subjects. We determined hemodynamic and angiographic indexes of preload, afterload and ejection performance and assessed LV systolic muscle function by an index that appears independent of loading conditions.

Methods

Nine normal subjects and 16 patients with isolated MS constitute the study population. The normal subjects were catheterized because of atypical chest pain syndromes. MS patients were catheterized because of symptoms related to their valvular disease.

Right- and left-heart catheterizations, cardiac output determinations, biplane left ventriculography and coronary angiography were normal in all normal subjects.

All MS patients underwent right- and left-heart catheterization by the brachial or femoral technique. Pressures were measured under basal conditions by fluid-filled catheter systems utilizing Statham P23DB strain gauges; tracings were recorded on Electronics for Medicine DR-8 or VR-12 multichannel recorders. Cardiac output was determined by the dye-dilution or Fick technique, and in 11 of the 16 patients by both. Mitral valve orifice area was calculated by the Gorlin method,19 using simultaneous pulmonary wedge and LV diastolic pressures. Biplane (30° right anterior oblique and 60° left anterior oblique) left ventriculograms were performed in 14 patients and single-plane (30° right anterior oblique) left ventriculograms in two patients. Coronary angiography was performed in 14 of 16 MS patients; the findings were normal in all 14. The two patients in whom coronary angiograms were not done were females, ages 31 and 32 years, without a history of chest pain, and in whom coronary artery disease was not suspected clinically.

LV volumes were determined at end-diastole and
end-systole by previously described methods. Six MS patients were in atrial fibrillation at the time of study; in these patients, LV volume was analyzed from three separate beats, excluding premature ventricular complexes. Data for these beats were averaged. All ventriculographic analysis was confined to the first four opacified beats. Segmental systolic wall motion was assessed qualitatively and any regional contraction abnormalities were classified as mild, moderate or severe.

The following indexes of LV systolic performance were determined:

Ejection fraction (EF) was calculated as

\[
\text{EF} = \frac{\text{EDV} - \text{ESV}}{\text{EDV}}
\]

where EDV and ESV = left ventricular end-diastolic and end-systolic volumes, respectively.

Velocity of circumferential fiber shortening (Vcf) was calculated as

\[
\frac{D_d - D_s}{D_d \times \text{LVET}}
\]

where \(D_d\) and \(D_s\) = left ventricular minor-axis dimensions at end-diastole and end-systole, respectively, and LVET = left ventricular ejection time. LVET was measured as the time from the initial rise of the central aortic pressure to the dicrotic notch from tracings recorded just before left ventriculography. Five successive pressure pulses were analyzed and averaged. In three MS patients in whom the LVET could not be accurately measured, Vcf was not calculated.

Stroke work index (SWI) was calculated as

\[
(\text{AoP} - \text{LVEDP}) \times \text{SVI} \times 0.0136
\]

where \(\text{AoP}\) and LVEDP = mean aortic and LV end-diastolic pressures, respectively; \(\text{SVI} = \text{stroke volume index; and 0.0136 = factor to convert mm Hg to g-m/m}^2\).

The ratio of end-systolic stress to end-systolic volume index (ESS/ESVI) was calculated as

\[
\frac{P \times b \left[1 - \frac{h_{es}^2}{2b} - \frac{b^2}{2a^2}\right]}{\text{ESVI}},
\]

where \(P = \text{aortic diastolic pressure, } h_{es} = \text{end-systolic LV wall thickness determined by the method of Hugenholtz et al.}^{21} a = \text{end-systolic hemi-major axis} \frac{L + h_{es}}{2}, \text{and } b = \text{midwall hemi-minor axis at end-systole} \frac{D_s + h_{es}}{2}.\) The above quantity was converted to dyn × cm² by multiplying by 1332 dyn/cm²/mm Hg.

Systemic vascular resistance was calculated as

\[
\frac{\text{AoP} - \text{RA}}{\text{CO}}
\]

where \(\text{AoP}\) and \(\text{RA}\) = mean aortic and right atrial pressures, respectively, and \(\text{CO} = \text{cardiac output.}\) The above quantity was multiplied by 80 to convert mm Hg/l/min to dyn-sec-cm⁻⁵.

Statistical comparisons were made by \(t\) test for unpaired groups.

**Results**

Table 1 shows clinical hemodynamic variables in normal subjects and MS patients. Resting heart rate was significantly higher in MS patients, whereas cardiac index was not statistically different. The mean aortic pressure was slightly lower and the mean pulmonary artery and mean pulmonary capillary pressures were significantly higher in MS patients. Left ventricular end-diastolic pressures were similar in the two groups. The mean mitral valve orifice area for MS patients was 1.1 cm².

The three derived indexes of LV ejection performance were EF, Vcf and SWI (fig. 1). EF for MS patients tended to be lower than that of normal subjects. Five of 16 MS patients had an EF less than 0.50, a value substantially below that of the normal subjects and below the usual lower limit of normal. Six MS patients had Vcf below 1.00 sec⁻¹, which is below normal.³ Three MS patients had both reduced EF and reduced Vcf, whereas eight had reduction in either EF or Vcf. SWI was significantly lower in MS patients than in normal subjects. Thus, MS patients tended to have reduced ejection performance.

EDVI and SVI both were significantly lower in MS patients than in normal subjects (fig. 2), but ESI was similar. Thus, MS patients tended to begin LV systole with a small ventricular volume, contracted to a normal volume at end-systole, and thereby ejected a smaller-than-normal stroke volume.

The MS patients were then divided into two groups. Eight patients had normal ejection performance (MSNP) and eight had reduced ejection performance (MSNP) (EF less than 0.50 or Vcf below 1.00 sec⁻¹). Of the three patients in whom Vcf was not determined, two had an EF less than 0.50 and were included in the MSNP group and one had normal EF and was included in the MSNP group.

Posterobasal systolic wall motion abnormalities were seen in three MSNP patients and in three MSNP patients. The posterobasal wall motion abnormality was severe in only one of the MSNP patients and moderate in only one of the MSNP patients. In the other four patients with posterobasal wall motion abnormalities, the disorder was mild. Thus, segmental hypokinesis did not, by itself, explain reduced ejection performance.

Since an increase in afterload (LV systolic wall stress) can decrease ventricular ejection, we examined ESS in MS patients. ESS was significantly higher in the MSNP group than in the MSNP group (fig. 3). Thus, MSNP patients had higher afterload than MSNP patients.

Since inadequate LV wall thickness at end-systole or peripheral arterial constriction in response to a re-
duced stroke volume could have increased the afterload in these patients, we examined end-systolic LV wall thickness and systemic vascular resistance in MS patients. End-systolic wall thickness was significantly less in the MSREP group than in the MSREP group (fig. 4A). Two MSREP patients had markedly elevated vascular resistance, although MSREP and MSREP groups did not differ significantly as a whole (fig. 4B).

To ascertain whether an increase in EDVI acting as a Frank-Starling compensation was offsetting the high afterload in MSREP patients, we examined EDVI in MSREP and MSREP groups (fig. 5). No significant difference in EDVI was found between the two groups. In fact, five of eight MSREP patients and four MSREP patients had EDVIs less than the lowest values in normal subjects.

Thus, three of eight MSREP patients had posterobasal wall motion abnormalities and five had uniform LV contraction. Yet, all three with posterobasal wall motion abnormalities had other LV loading abnormalities to explain reduced ejection performance. One had high ESS related to elevated systemic vascular resistance and reduced end-systolic wall thickness and EDVI; another had high ESS and small EDVI; the third and high ESS alone. Of the five remaining patients, one had both small EDVI and high SVR, one had small EDVI and high ESS, one had high SVR only, one had reduced end-systolic wall thickness only, and one had small EDVI only.

LV systolic muscle performance assessed by the ESS/ESVI ratio among MS patients was compared with that in normal subjects (fig. 6). No difference in ESS/ESVI was found between MS patients and normal subjects. In fact, four of the five MS patients with EF less than 0.50 and all six MS patients with Vcf less than 1.00 sec\(^{-1}\) had a normal ESS/ESVI ratio.

**Discussion**

Rheumatic inflammation of the myocardium is common in adult patients with mitral stenosis. Although this process may be associated with anatomic distortion of the left ventricle and mitral apparatus and abnormal patterns of contraction, it is not clear that these features are related to abnormalities of LV contractile performance.

The incidence, means of detection and causes of abnormalities in systolic performance of the left ventricle in the presence of isolated MS are unsettled issues. Furthermore, the loading conditions or potential alterations in loading conditions that affect LV contraction in MS have not been clearly established. Using a combined hemodynamic and angiographic approach, we have shown that isolated MS is associated with reduced LV systolic ejection performance in many patients. LV systolic muscle function, determined by the ESS/ESVI ratio, appears to be normal in patients with MS, and is therefore not the cause of reduced ejection performance. The reduction in ejection performance can be explained in part by high LV afterload that is not compensated for by an increase in preload, due to apparent limitation of preload by the stenotic mitral orifice. The higher LV afterload is a result of inadequate end-systolic wall thickness as a group, thereby causing high LV wall stress at normal LV systolic pressure.

**TABLE 1. Clinical and Hemodynamic Variables in Normal Subjects and Mitral Stenosis Patients**

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects</th>
<th>Mitral stenosis</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44 ± 5</td>
<td>50 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>67 ± 2</td>
<td>83 ± 5</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>CI (/min/m(^2))</td>
<td>3.1 ± 0.3</td>
<td>2.8 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>AoP (mm Hg)</td>
<td>94 ± 3</td>
<td>87 ± 3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PAP (mm Hg)</td>
<td>13 ± 1</td>
<td>31 ± 4</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>8 ± 1</td>
<td>19 ± 1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>9 ± 1</td>
<td>9 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>MVA (cm(^2))</td>
<td>—</td>
<td>1.1 ± 0.1</td>
<td>—</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

Abbreviations: AoP = mean aortic pressure; CI = cardiac index; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; MVA = mitral valve orifice area; PAP = mean pulmonary artery pressure; PCWP = mean pulmonary capillary wedge pressure.
pressures. The high LV afterload may be related to elevated systemic vascular resistance in a few patients.

Previous studies have addressed the question of myocardial performance in MS. Harvey et al. described myocardial dysfunction to half of MS patients based on the degree of pulmonary hypertension, abnormal exercise blood flow response and, in some, poor surgical outcome. Fleming and Wood noted a much lower incidence (3.2%) using similar hemodynamic methods. Angiographically, Hildner et al. described qualitative LV enlargement and abnormal contractility in half of patients with isolated MS. Bolen et al. found slightly higher EDV in MS patients than in normal subjects, and frequently detected posterobasal wall motion abnormalities in patients with normal and low EF, although the latter tended to have more pronounced segmental abnormalities. Horwitz et al. also found reduced posterobasal shortening and, in addition, abnormalities of anterior wall motion. They reported normal EDV, but ESV was high and EF low. Heller and Carleton found normal EDV among MS patients in sinus rhythm and increased EDV in those with atrial fibrillation. Posterobasal contractile abnormalities were seen in almost all patients with EF less than 0.65. In contrast, Curry et al. found reduced EDV in MS patients, and noted subnormal EF as well as posterobasal, anterior and long-axis shortening abnormalities. Our finding of significantly reduced EDVI supports the concept that MS is associated with underfilling of the LV.

Various methods have been used to further assess the systolic performance of the left ventricle in MS. LVEDP examined at rest and during exercise has not been a reliable indicator of systolic performance. Furthermore, LVEDP may itself be affected by the right ventricular pressure or volume overload associated with MS. Horwitz et al. concluded that LV dysfunction was present in patients who had increased heart rate and LVEDP, yet no increase in stroke volume or SWI in response to handgrip exercise. Bolen et al. found that patients with low EF had flat or blunted LV function curves based on changes in aortic pressure, LVEDP, cardiac output and mitral gradient in response to nitroprusside and angiotensin infusions. Kasalicky et al. found no increase of SVI in MS patients during exercise, despite an appropriate increase in cardiac index and LVEDP. He concluded that the LV muscle was abnormal. Wroblewski et al. noted that curves of SVI vs EDVI were slightly (but not statistically) lower in MS patients than normal sub-

![Figure 2. End-diastolic volume index (EDVI), end-systolic volume index (ESVI), and stroke work volume index (SVI) in normal subjects (N) and patients with mitral stenosis (MS). The mean ± SEM is shown for each group.](image)

![Figure 3. End-systolic stress (ESS) in mitral stenosis patients with normal ejection performance (MS_{Nep}) and those with reduced ejection performance (MS_{Rep}). The mean ± SEM is shown for each group.](image)
In contrast, Ahmed et al.9 found reduced EF, but an index of contractile element velocity corrected for preload was normal in MS.

In these and other studies,8, 18 patients with EFs below 0.50 constituted 12–38% of MS groups. That 31% of our MS patients had similar reduction in EF is consistent with these findings. In addition, we have shown that Vcf and SWI are reduced in MS patients as a group, further supporting the concept that ejection performance is impaired in many patients with isolated MS.

At this point, two issues must be addressed. First, what factor or factors are responsible for the reduced ejection performance in MS? Second, does reduced ejection performance in MS necessarily indicate LV muscle dysfunction?

LV pump or ejection phase indexes (EF, Vcf and SWI) depend not only on contractile state, but also on preload and afterload.27, 28 Our finding of a reduced EDVI probably identifies an abnormally low preload, especially in a setting where increased Frank-Starling compensation is needed. This reduction in EDVI among MS patients is probably related to obstruction to LV filling, although the higher heart rate among MS patients taking diuretic therapy could also have been a factor. However, over-diuresis did not appear to be the cause, since all but one patient had normal blood urea nitrogen levels at the time of study. Increased LV

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**Figure 4.** (A) End-systolic left ventricular wall thickness ($h_{es}$) in mitral stenosis patients with normal ejection performance ($MS_{NEP}$) and those with reduced ejection performance ($MS_{REP}$). The mean ± SEM is shown for each group. (B) Systemic vascular resistance (SVR) in mitral stenosis patients with normal ejection performance ($MS_{NEP}$) and those with reduced ejection performance ($MS_{REP}$). The mean ± SEM is shown for each group.

**Figure 5.** End-diastolic volume index (EDVI) in mitral stenosis patients with normal ejection performance ($MS_{NEP}$) and those with reduced ejection performance ($MS_{REP}$). The mean ± SEM is shown for each group.
afterload is clearly present in some MS patients with reduced ejection indexes. This increased LV afterload (high ESS) is explained primarily by thinner LV wall at end-systole, but also in a few patients, by elevated systemic vascular resistance. The reason for inadequate systolic wall thickness in our MS$_{rep}$ patients has not been defined. Regional or global myocardial fibrosis or atrophy of various degrees related to rheumatic disease might have played a role. It is evident from studies cited previously that segmental wall motion abnormalities are not restricted to patients with low ejection performance. In fact, our study showed an even distribution of posterobasal abnormalities among MS$_{rep}$ and MS$_{rep}$ patients. Therefore, it is not clear that rheumatic myocardial fibrosis or atrophy correlates totally with the degree of segmental LV wall motion abnormality seen on angiography or solely accounts for reduced ejection indexes. Furthermore, to our knowledge, end-systolic wall thickness has not been examined in MS, although Dodge et al.$^{29}$ suggested that myocardial atrophy may have a role in the reduction of LV mass seen in some patients with severe MS. High systemic vascular resistance may contribute to increased afterload in some patients with MS. Two patients with reduced ejection indexes had markedly elevated systemic resistance, although MS patients as a group did not differ from normal subjects. These two patients had a low cardiac index due to critically severe MS and severe pulmonary hypertension. That EDVI is reduced in half or more of MS patients (both those with normal as well as those with reduced ejection performance) and that EDVI is not increased in patients with MS indicate that complete Frank-Starling compensation for high afterload is prevented. Obstruction to LV filling by MS probably deprives the left ventricle of this compensation.

Therefore, altered loading conditions are present in MS, and reduced ejection performance can be largely explained by this fact, despite the presence or absence of posterobasal wall motion abnormalities. Nevertheless, the issue of LV muscle performance in MS remains. Dodge et al.$^{29}$ suggested that low EF in MS patients is not necessarily due to LV myocardial disease. We approached this question by examining the ESS/ESVI ratio. The linear relationship between LV wall stress and LV volume at end-systole has been considered a measure of contractile state that is independent of loading conditions.$^{30-34}$ Although this relationship is completely described by plotting several determinations of stress against volume, ESS/ESVI, under resting conditions has been suggested as an indicator of LV contractile performance in patients with valvular heart disease.$^{35-37}$ When MS patients are examined in this fashion as a group, there is wide overlap with normal values. However, this finding must be interpreted with caution, for the ratio of ESS/ESVI in three MS patients did not overlap with values among normal subjects. One of these three patients had reduced EF and the other two had normal EF and Vcf.

We conclude that the low LV ejection performance indexes found in many patients with MS are frequently due to altered loading conditions. The high afterload is caused by reduced end-systolic LV wall thickness and, occasionally, by high systemic vascular resistance. Because LV filling is impaired by the stenotic mitral valve, this elevation in afterload is not offset by the Frank-Starling mechanism. Low ejection performance indexes underestimate LV systolic muscle function in most of such patients.

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