Reduced Left Ventricular Compliance in Human Mitral Stenosis
Role of Reversible Internal Constraint

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Background. The mechanisms of depressed left ventricular (LV) pump performance in human mitral stenosis (MS) remain poorly understood, because reduced filling alone affects many hemodynamic measurements. Therefore, pressure–volume relations were examined in nine subjects with MS and compared with eight age-matched normal controls.

Methods and Results. Data were obtained by conductance catheter/micromanometer technique with transient inferior vena cava occlusion used to alter load and generate pressure–volume relations. In a subset of patients (n=5), data were obtained both acutely and at 3 months (n=4) after balloon valvuloplasty. MS patients had reduced cardiac output (3.3±0.9 versus 5.6±1.7 l/min) and end-diastolic volume (68.0±6.9 versus 115±31 ml) versus controls (p<0.001), with a mean transvalvular gradient of 14±6 mm Hg and estimated valve area of 0.6±0.2 cm². Systolic function as assessed by the end-systolic pressure–volume relation was virtually the same in MS and control subjects. In contrast, end-diastolic pressure–volume relations in MS were consistently shifted leftward and had an increased slope (lower compliance) at matched pressure ranges (6.5±3.0 versus 2.2±0.53 ml/mm Hg at a mean diastolic pressure of 8 mm Hg, p<0.001). This change was not a result of reduced LV filling or probably of increased right heart loading. Valvuloplasty acutely returned chamber compliance to near normal, a change that was sustained at 3-month follow-up. Systolic function was little altered at this time.

Conclusions. These data indicate an impairment of diastolic function in human MS that can be acutely reversed by balloon valvuloplasty. Lowered LV compliance probably results from a functional restriction caused by ventricular attachment to a thickened and immobile valve apparatus. (Circulation 1992;85:1447-1456)

KEY WORDS • valves • ventricular function • valvuloplasty • diastole • systole • pressure–volume relation

Since 1955, when Harvey et al1 reported that some patients failed to increase their cardiac output after seemingly successful mitral commissurotomy, investigators have hypothesized the existence of primary ventricular dysfunction with rheumatic mitral stenosis (MS). Both systolic and diastolic abnormalities have been suggested to result from chronically reduced chamber loading ("disuse hypofunction"),2 endocardial fibrosis from rheumatic inflammation and/or vasculitis,3 elevated right heart loading and thus abnormal right–left heart interactions,4 and valvar "tethering".5 Several investigations have attempted to characterize this dysfunction; however, the results have been contradic-

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nisms for abnormal chamber function with MS. Our results do not support the presence of primary systolic chamber dysfunction. However, they demonstrate significant abnormalities in diastolic compliance that can be rapidly reversed by valvuloplasty.

Methods

The study populations consisted of nine patients (age, 48±13 years) with pure rheumatic MS (MS group) and eight age-matched (40±12 years) control subjects. All but two of the control patients were of Taiwanese nationality. MS patients were in New York Heart Association functional class 2 or 3 with an estimated valve area (by invasive hemodynamic measurements) of ≤1.0 cm². Patients had neither significant mitral nor aortic regurgitation at baseline nor other known cardiac disease (i.e., coronary artery disease, previous infarction, cardiac surgery, etc.). All subjects were in normal sinus rhythm at time of study. Mean body weight and estimated surface area were slightly smaller in the MS subjects than in controls (52.3±6.3 versus 67.3±11.4 kg and 1.5±0.12 versus 1.7±0.2 m², both p<0.05).

Control subjects were referred for cardiac catheterization for atypical chest pain syndrome. They had normal ECG, echocardiogram, coronary arteriogram, and contrast ventriculogram. Informed consent was obtained in all patients, and the protocol was approved by the Veterans General Hospital Taipei, Taiwan Clinical Research Committee, with a similar protocol approved by the Johns Hopkins Joint Committee on Clinical Investigation.

Catheterization Procedure

All chronic medications were withheld at least 10 days before study. Premedications were benzo diazepam (10 mg p.o.) and diphenhydramine (50 mg p.o.). Patients underwent both right and left heart catheterization, with vascular access obtained in a femoral artery and vein by the Seldinger technique.

The details of the PV catheterization technique have been described elsewhere. Briefly, an 8F multielectrode conductance catheter (Webster, Baldwin Park, Calif.) was advanced via the femoral artery, passed retrogradely across the aortic valve, and positioned over a flexible J guide wire to the left ventricular (LV) apex. A Tuhey-Borst adapter was attached to the catheter hub, and a 3F (or 2F) micromanometer-tipped catheter (Millar, Houston, Tex.) was advanced through the adapter to near the distal end of the catheter. The manometer did not emerge from the distal lumen but rather was positioned just short of the pigtail tip.

The volume catheter was connected to a stimulator/microprocessor (Sigma V, CardioDynamics, Rijnsburg, The Netherlands) (n=15) or VCU (Cardiac Pacemakers Inc., St. Paul, Minn.) (n=2), which provided a low-amp, high-frequency excitation current at apex and base electrodes and measured voltages at intervening electrode pairs along the catheter. These voltages were inversely related to blood volume within multiple segments (≤5) defined by the electrode pairs. Segment volumes were summed in real time to provide a continuous analog volume signal. At time of catheter placement, each individual segment—pressure loop was examined to determine which segments were within the ventricular chamber. Segments at or above the aortic valve produced an isovolumic or clockwise-oriented segment—pressure loop and were eliminated from the total volume sum.

A 7F balloon occlusion catheter (SP-9168, Cordis, Miami, Fla.) was introduced through a femoral venous sheath (9F) and advanced to the right atrial–inferior vena caval (IVC) junction. Inflation of the balloon with 15–25 ml of CO₂ permitted transient alteration in preload volume and generation of PV relations. Last, in MS patients, right heart pressures were obtained by a dual micromanometer/flow sensor catheter (Millar, Houston, Tex.) placed across the pulmonary artery so that both right ventricular and pulmonary arterial pressures were obtained simultaneously.

All micromanometers were soaked in a warm water bath for at least 30 minutes before study and were calibrated to mercury manometers. Data signals were displayed and digitized at 200 Hz using a custom-designed 286 processor-based data acquisition system.

Protocol

PV data, right heart pressures, and cardiac outputs were obtained at baseline. Then venous return was transiently reduced by inflation of the balloon at the right atrial–IVC junction. After approximately 10 seconds, the balloon was deflated and hemodynamic status restored to baseline. This procedure was repeated several times. Catheters were removed, and the volume catheter was replaced with a standard ventriculography pigtail catheter. Single-plane right anterior oblique (RAO) left ventriculography (11–12 ml/sec nonionic contrast) was performed and used for volume signal calibration (see below).

Mitral Valvuloplasty Protocol

All nine patients with MS underwent double balloon valvuloplasty, generally 2 days after the baseline study described above. Right and left heart catheterization was performed by femoral approach for baseline hemodynamic measurements. The left atrium was entered via routine transseptal technique, and patients were then given heparin (100 units/kg i.v.). A double-lumen sheath (Mansfield, Boston, Mass.) was advanced to the left atrium, allowing passage of two exchange guide wires. A balloon dilatation catheter was placed over each guide wire and positioned across the mitral valve. The balloons were inflated with a 50% mixture of saline and contrast for no more than 30 seconds with maximal inflation pressures of 3–5 atm. Immediately after valvuloplasty, hemodynamic pressures and flow measurements were repeated. After the left heart catheter was removed, it was replaced with a volume/micromanometer catheter, and an IVC balloon occlusion catheter was advanced to the right atrium. PV relations were obtained as previously described. These catheters were removed and replaced by a pigtail ventriculography catheter. A ventriculogram (RAO projection) was then obtained to assess for mitral insufficiency and wall motion abnormalities and for use in volume catheter calibration.

Of the nine patients, four did not provide acute response PV data: one because of technical difficulties in catheter placement, a second because of valvuloplasty complication (left heart puncture), and a third
from unsuccessful valvuloplasty (no change in valve area). This patient subsequently underwent valve replacement surgery. A fourth patient developed atrial fibrillation acutely after valvuloplasty. This patient resumed normal sinus rhythm at 3-month follow-up, enabling study at that time. Of the remaining patients, one developed mild to moderate (2+) mitral regurgitation after PBMV, the others had no significant mitral regurgitation, and no patients had an atrial septal defect (<3% oxygen step-up). Three-month follow-up data were obtained in four patients. This group included the patient with atrial fibrillation after initial valvuloplasty but excluded two of the patients studied acutely, one because of late development of moderate to severe mitral regurgitation and one because the patient refused follow-up. The catheterization procedure for the 3-month follow-up study was as described for the initial baseline study.

**Volume Signal Calibration**

The volume catheter signal has been shown to be linearly proportional to volume, but the slope and offset are neither unity nor zero, respectively. The offset stems from conductance of the LV muscle wall and surrounding structures, whereas the slope is thought to be primarily due to nonuniform current density resulting from stimulation from point sources. We and others have previously determined the offset by an indicator technique (injection of hypertonic saline) and slope by comparison of catheter to thermomediation cardiac outputs. A simpler and more direct approach, however, is simply to calibrate the catheter signal to near simultaneous steady-state ventriculographic volumes. Therefore, in the present study, steady-state end-systolic and end-diastolic catheter volumes were set equal to the respective single-plane (RAO) contrast ventriculogram volumes, the latter calibrated with a 5x5-cm grid, filmed at midaxillary level at the center of the imaging area.

**Data Analysis**

Steady-state chamber pressures, volumes, and other indices were determined from 5 or 6 sequential cardiac cycles, synchronized by the R wave of the ECG, and then signal averaged. End-diastolic pressure was defined at the lower right corner of the pressure-volume loop. This was automatically determined by finding the point of maximal \((V-V_s)/(P-P_s)\) ratio, where \(V_s\) is (minimal volume = 5 ml) and \(P_s\) is (minimal pressure = 30 mm Hg) and using the pressure at this point. End-systolic pressure was determined at the point of maximal \(P/(V-V_s)\) ratio, using \(V_s\) obtained from the end-systolic PV relation (ESPVR) (see below).

End-diastolic and end-systolic volumes were determined by averaging five volume points centered at mean LV pressure during isovolumetric contraction and relaxation phases, respectively. In the patient with 2+ mitral regurgitation after PBMV, maximal volume at end-diastolic pressure was used. Stroke volume was the average width of the PV loop, and stroke work was the digitally integrated area within the loop.

The derivative of pressure \((dP/dt)\) was determined using a five-point weighted running slope. The time constant of isovolumetric relaxation was determined from linear regression of the natural logarithm of pressure versus time, using pressures between the point of \(dP/dt_{min}\) to when \(P(t)\) fell below end-diastolic pressure.

**End-Systolic and End-Diastolic PV Relations**

In addition to steady-state parameters, PV relations were derived from multiple cardiac cycles (average, 12±4 beats) determined at varying preload by transient IVC occlusion. The end-systolic PV point for each beat was determined at maximal \(P/(V-V_s)\) using an iterative method described previously and the set of points fit by linear regression with slope \(E_{es}\) (end-systolic elastance) and volume intercept \(V_s\).

End-diastolic points from the latter third of cardiac filling were selected from each beat during IVC occlusion and used to derive the end-diastolic PV relation (EDPVR) as previously described. To minimize effects of respiration, data were limited to expiration and to two points per beat (separated by 0.1 stroke volume). EDPVRs were fit by linear regression applied over the full as well as upper and lower half volume ranges. Linear rather than monoexponential fits were used for two reasons. First, the diastolic data were adequately described by a linear model over each respective load range (mean, \(r=0.85\)), and this facilitated compliance estimation and analysis by linear multivariate regression (see below). Second, monoexponential parameters have limitations because of considerable covariance. This translates to having many combinations of values that “fit” a given set of data nearly identically.

Last, the stroke work–end-diastolic volume relation was determined by linear regression. The slope \(M_{es}\) provided a measure of chamber function. This index has been shown to display less variability between subjects than \(E_{es}\) and it is little influenced by cardiac size \(M_{es}\) has units of mm Hg, and thus is volume-size independent.

**Statistical Analysis**

Steady-state hemodynamic parameters for control versus MS groups were compared by nonpaired \(t\) tests. Data from before and immediately after valvuloplasty \((n=5)\) and before versus 3-months follow-up \((n=4)\) were compared by paired \(t\) tests.

To compare ESPVRs, stroke work–end-diastolic volume and diastolic PV relations, individual patient data (all points) were combined into a single regression model in the form

\[ y = b_0 + b_1 \cdot x + b_2 \cdot \text{GROUP} + b_3 \cdot x \cdot \text{GROUP} + \Sigma p_i \cdot \text{MS} + \Sigma q_i \cdot Ci \]

where \(b_0\) is the mean offset, \(b_1\) the mean slope, \(b_2\) and \(b_3\) the mean difference between MS and control group offset and slope, respectively, and \(p_i\) and \(q_i\) dummy coefficients for each MS and control patient, respectively. This approach is analogous to an analysis of covariance and is more robust than fitting each regression separately and comparing the derived slopes and offsets by \(t\) tests.

Data analysis was performed with customized software on an AT-compatible 286-MHz personal computer. Statistical analyses were performed with commercial software (SYSTAT, Version 5.0, IL).
Results

Hemodynamics

Mean steady-state hemodynamic parameters for MS and control groups are provided in Table 1. MS subjects had an average estimated valve area of 0.56±0.2 cm² (mean±SD), a mean transvalvular pressure gradient of 13.9±6 mm Hg, and elevated mean pulmonary artery pressure and resistance (30.3±10.9 mm Hg and 325.8±253.8 dyne·sec·cm⁻⁵, respectively). Cardiac output, end-diastolic volumes, end-diastolic and end-systolic pressures, and stroke work were all significantly reduced in the MS patients. Peripheral vascular resistance was increased compared with controls. Heart rate, dP/dt max, ejection fraction, and the time constant of relaxation were not significantly different between the two subject groups.

Pressure–Volume Relations

Figure 1 displays an example of PV loops and ESPVR and EDPVVR for a typical control and MS patient. Two important features are to be noted. The ESPVR is essentially the same between the two patients both in slope and in placement along the volume axis. In contrast, the EDPVR is shifted to smaller volumes; yet rather than displaying a shallow slope as would be anticipated if diastolic chamber properties were unchanged, the EDPVR was steeper.

Similar results were obtained for the group data and are provided in Table 2. ESPVRs had a similar slope and volume axis placement (end-systolic volume at pressure of 100 mm Hg) in both patient groups. Calculation of the latter required some extrapolation (9 mm Hg) in 23% of the subjects. Multiple regression analysis combining all measured ESPVR data (see "Methods") yielded a mean slope of 1.8±0.05 mm Hg/ml, with no change in slope between subject groups. This analysis did reveal a small but statistically significant leftward shift of the ESPVR in the MS patients (average shift of −8±2.4 ml). Group data (mean linear

![Figure 1. Tracings of pressure-volume loops and end-systolic (ESPVR) and end-diastolic (EDPVR) pressure-volume relations from a normal control subject (upper panel) and mitral stenosis (MS) subject (lower panel). The ESPVRs (upper left dashed line) were very similar between patients; the EDPVR, however, (lower dashed line) was shifted leftward in the MS patient with a relatively greater slope (reduced compliance).](http://circ.ahajournals.org/lookup/doi/10.1161/01.CIR.85.4.1450)
Table 2. End-Systolic and End-Diastolic Pressure–Volume Relations

<table>
<thead>
<tr>
<th></th>
<th>ESPURs</th>
<th></th>
<th></th>
<th></th>
<th>EDPURs</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>E_{es}</td>
<td>V_{100}</td>
<td>r</td>
<td>No. loops</td>
<td>Cmp_{0}</td>
<td>Cmp_{1}</td>
<td>n</td>
</tr>
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<td></td>
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<tr>
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<td>1.51</td>
<td>13.9</td>
<td>0.992</td>
<td>9</td>
<td>4.55</td>
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<td>18</td>
</tr>
<tr>
<td>2</td>
<td>1.89</td>
<td>18.5</td>
<td>0.958</td>
<td>9</td>
<td>4.28</td>
<td>10.24</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
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<td>10</td>
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</tr>
<tr>
<td>4</td>
<td>1.77</td>
<td>54.8</td>
<td>0.966</td>
<td>17</td>
<td>3.00</td>
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<td>44.6</td>
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<td>10</td>
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<td>6.36</td>
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<tr>
<td>7</td>
<td>1.87</td>
<td>44.5</td>
<td>0.998</td>
<td>9</td>
<td>4.90</td>
<td>6.55</td>
<td>35</td>
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<tr>
<td>8</td>
<td>1.26</td>
<td>29.1</td>
<td>0.995</td>
<td>6</td>
<td>5.65</td>
<td>10.01</td>
<td>21</td>
</tr>
<tr>
<td>Mean</td>
<td>1.77</td>
<td>32.8</td>
<td>0.986</td>
<td>10.2</td>
<td>5.17</td>
<td>12.93</td>
<td>21.6</td>
</tr>
<tr>
<td>SD</td>
<td>0.33</td>
<td>14.1</td>
<td>0.015</td>
<td>3.2</td>
<td>2.67</td>
<td>7.39</td>
<td>6.0</td>
</tr>
</tbody>
</table>

Mitral stenosis patients

|                |        |           |            |                |        |            |            |
|----------------|--------|------------|------------|----------------|--------|------------|            |
| 1              | 1.57   | 49.9      | 0.980      | 13             | 1.32   | 2.92       | 24         |
| 2              | 1.27   | 37.7      | 0.974      | 24             | 2.45   | 2.07       | 21         |
| 3              | 1.87   | 27.9      | 0.979      | 19             | 2.63   | 8.07       | 33         |
| 4              | 1.95   | 14.3      | 0.986      | 16             | 1.36   | 2.41       | 24         |
| 5              | 1.39   | 34.2      | 0.950      | 10             | 2.59   | 9.15       | 27         |
| 6              | 2.08   | 14.6      | 0.980      | 14             | 1.64   | 4.36       | 26         |
| 7              | 3.16   | 16.4      | 0.990      | 7              | 2.98   | 10.83      | 24         |
| 8              | 2.71   | 26.2      | 0.998      | 6              | 2.30   | 4.59       | 15         |
| 9              | 1.74   | 18.7      | 0.943      | 16             | 2.86   | 6.66       | 18         |
| Mean           | 1.97   | 26.7      | 0.976      | 13.9           | 2.24   | 5.7        | 23.5       |
| SD             | 0.61   | 12.2      | 0.018      | 5.7            | 0.64   | 3.2        | 5.2        |

Systolic data are for the end-systolic pressure–volume relation slope (E_{es}) and volume at 100 mm Hg (V_{100}). The number of pressure–volume loops used in the end-systolic pressure–volume relation (ESPUR) and linear correction coefficient (r) are also provided. Diastolic data are compliance calculated in upper half (Cmp_{0}) and lower half (Cmp_{1}) of the volume load range. The number of points in each end-diastolic pressure–volume relation (EDPUR)(r) is also noted.

ESPURs, end-systolic pressure–volume relations; EDPUR, end-diastolic pressure–volume relations.

ESPVR fits) are graphically displayed in Figure 2 (upper panel).

In contrast to the systolic data, MS EDPVRs fell to the left of controls and had a steeper slope (Figure 2, lower panel). Linear compliance analysis was performed in two ranges (upper and lower halves of the measured diastolic volume range, Table 2). The mean diastolic pressures for these ranges were quite similar (8.1±8.6 versus 8.0±2.8 mm Hg for high range, 4.9±5.1 versus 5.2±5.2 mm Hg for low range, p=NS). Compliance values in both ranges, however, were significantly lower in the MS subjects than in controls (see Table 2). Similar results were obtained by the combined multiple regression analysis using a single linear regression to the entire range of diastolic PV data (average r values were 0.86±0.11 for linear fits). Mean compliance was 6.0±0.19 ml/mm Hg for controls versus 2.6±0.26 for MS (p<0.001). Group data averaged over equispaced pressure ranges are also displayed in Figure 2 (lower panel). Thus, diastolic PV data in MS patients did not simply reflect reduced filling volumes caused by restricted inflow but also indicated primary reduction in chamber compliance.

Integration of Systolic and Diastolic Changes

The net effect of an essentially unchanged systolic PV boundary relation and a leftward-shifted and steeper diastolic boundary could be indexed by the relation between stroke work and end-diastolic volume. Although this relation has been previously reported for assessment of systolic chamber performance, it can also be altered by changes in diastolic compliance. Stroke work links PV data between the diastolic and systolic boundaries (similar to developed pressure for isovolumic contractions); thus, abnormalities in either relation can affect the stroke work–end-diastolic volume relation. Stroke work–end-diastolic volume relations were obtained using the same PV loops during transient IVC occlusion used to construct the ESPVRs and EDPVRs. The slopes for these relations (Figure 3) were significantly lower in the MS group versus controls (61.7±21.2 versus 82.7±11.3) (p<0.05). This was confirmed by multiple regression analysis, which revealed both a significantly lower slope and a slight leftward shift of the relation (−13 ml) in MS versus control subjects. Thus, for a given increase in filling volume of the heart, the MS ventricle displayed a smaller increment in external work compared with controls.

Mechanisms of Altered Compliance: Valvuloplasty Results

There are a number of mechanisms whereby chamber compliance could be reduced by mitral stenosis, including 1) delayed relaxation, 2) abnormal right–left heart
interaction, 3) myocardial endocardial fibrosis,4,11 4) chronic chamber atrophy and remodeling (i.e., small hearts),11 and 5) a mechanical constraint resulting from the rigid mitral valve apparatus.4,5,11,12 The time constant of pressure relaxation was 40±10 msec in controls versus 33±3 msec in MS patients (p=NS), so this factor probably did not contribute to the disparity. The EDPVRs used to derive compliance were obtained during IVC occlusion, which rapidly and markedly lowers right heart loading by nearly 50% (to within control range). This does not entirely rule out a role for right ventricle–LV interaction, but it minimizes the likelihood that it is a major mechanism.

To examine the latter three mechanisms, data obtained before and after PBMV were compared. All nine MS subjects underwent valvuloplasty, and PV relations were obtained acutely (30 minutes after the procedure) in five and at 3-month follow-up in four of these patients.

Hemodynamic and PV relation mean responses before and after valvuloplasty are provided in Tables 3 and 4. Heart rate, ejection fraction, and peak pulmonary artery pressure did not significantly change acutely. Estimated valve area and cardiac output, however, increased to 1.7±0.6 cm² and 5.5±1.0 l/min, respectively (both p<0.05 versus before PBMV). End-diastolic volume also rose by 29.2±25.7 ml (+45%, p<0.05), whereas end-diastolic pressures increased only slightly (3.9±4.6 mm Hg, p=0.07). Generally similar findings were obtained in the four subjects at 3-month follow-up after valvuloplasty. End-diastolic volume continued to increase by an additional 22.8% from baseline (p<0.05). Pulmonary artery pressures also fell (mean, −18.7 mm Hg).

In addition to enhanced chamber volumes, compliance also increased both acutely and 3 months after PBMV. Figure 4 shows EDPVR data from one patient before and acutely following PBMV. Regressions for both upper and lower halves of each relation are also shown. There was a marked reduction in the slope of the relation after PBMV (in both load ranges), indicating increased compliance. Group data are provided in Table 4 and Figure 4. In the upper-half range of the EDPVRs, compliance increased from 2.3±0.6 to 5.6±1.3 ml/mm Hg (p<0.001) acutely after valvuloplasty, bringing it close to control values. This occurred with no change in the mean diastolic pressure measured over the same range (8±2.8 versus 8.1±8.6 mm Hg). At 3-month follow-up, diastolic compliance remained at 5.9±2.5 ml/mm Hg (p<0.05 versus before valvuloplasty). The slope of the ESPVR fell acutely after PBMV by 62.2±16.4% (p<0.01), perhaps reflecting transient ischemic effects induced by PBMV. However, Eo returned to normal at 3-month follow-up.

Comparison With Other Valvuloplasty Patient Data

To assess how representative these pre- and post-PBMV results were of the larger MS population, we reviewed data from all patients who underwent PBMV during the ½-year period of the study (n=58, all subjects Taiwanese). Mean age, body weight, height, and estimated surface area for these additional 49 patients were identical to those reported for the study group. Ventriculographic data were obtained in a random sample of these patients (n=21). In nine of the 21 subjects, baseline end-diastolic volume was less than 100 ml (78±12.6 ml), similar to the study group, whereas the remaining subjects had baseline end-diastolic volume >100 ml (128.3±16.3). Interestingly, PBMV resulted in an acute volume increase only in those subjects with small baseline volumes (+19±25% versus 0.5±8.6% in the other subgroup, p<0.05). Patients with larger volumes had three times the incidence of significant coexistent aortic insufficiency, whereas mitral regurgitation...
TABLE 3. Hemodynamic Changes With Percutaneous Balloon Mitral Valvuloplasty

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=5)</th>
<th>Acute PBMV (n=5)</th>
<th>Baseline* (n=4)</th>
<th>3-Month follow-up PBMV (n=4)</th>
</tr>
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<tr>
<td>HR (bpm)</td>
<td>92.2±7.6</td>
<td>86.6±10.3</td>
<td>86.8±13.6</td>
<td>73.8±17.7</td>
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<tr>
<td>CO (l/min)</td>
<td>3.7±1.0</td>
<td>5.5±1.0†</td>
<td>3.3±0.9</td>
<td>5.3±1.4†</td>
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<tr>
<td>EF (%)</td>
<td>58.7±11.8</td>
<td>67.9±13.3</td>
<td>54.9±9.4</td>
<td>64.2±8.4*</td>
</tr>
<tr>
<td>Pao (mm Hg)</td>
<td>116.6±16.5</td>
<td>96.2±10.9*</td>
<td>115.8±16.0</td>
<td>138.6±22.1</td>
</tr>
<tr>
<td>Pag (mm Hg)</td>
<td>8.6±3.7</td>
<td>12.8±5.1</td>
<td>6.1±1.6</td>
<td>12.0±5.3</td>
</tr>
<tr>
<td>Vao (ml)</td>
<td>27.9±6.7</td>
<td>32.0±19.8</td>
<td>30.6±4.4</td>
<td>40.5±11.9</td>
</tr>
<tr>
<td>Vag (ml)</td>
<td>68.3±7.8</td>
<td>97.5±22.2*</td>
<td>68.9±9.5</td>
<td>113.3±22.8*</td>
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<tr>
<td>PAPes (mm Hg)</td>
<td>41.2±13.3</td>
<td>42.8±19.8</td>
<td>54.2±13.9</td>
<td>32.8±2.2*</td>
</tr>
<tr>
<td>PCWPes (mm Hg)</td>
<td>19.5±7.5</td>
<td>13.8±5.3</td>
<td>20.9±7.8</td>
<td>13.5±5.9</td>
</tr>
<tr>
<td>MVA (mm Hg)</td>
<td>15.0±6.0</td>
<td>6.2±3.3*</td>
<td>13.5±6.4</td>
<td>6.8±2.8</td>
</tr>
<tr>
<td>MVG (mm Hg)</td>
<td>0.61±0.24</td>
<td>1.74±0.64*</td>
<td>0.62±0.28</td>
<td>1.76±0.78*</td>
</tr>
<tr>
<td>Ees (mm Hg/ml)</td>
<td>2.0±0.44</td>
<td>1.10±0.45*</td>
<td>1.74±0.34</td>
<td>1.50±0.91</td>
</tr>
<tr>
<td>V100 (ml)</td>
<td>25.5±14.6</td>
<td>44.6±18.5</td>
<td>18.9±6.3</td>
<td>25.5±14.2</td>
</tr>
</tbody>
</table>

Data are provided for acute post-PBMV results (five patients compared before and after) and at 3-month follow-up (four patients compared before and after). Although there were slightly different patients in each comparison, the two baseline means were nearly the same. Mean baseline data was determined for each comparison because these were slightly different in patients in each subgroup. These baseline means, however, were nearly the same.

PBMV, percutaneous balloon mitral valvuloplasty; HR, heart rate; bpm, beats per minute; CO, cardiac output; EF, ejection fraction; Peso, end-systolic pressure; Pesd, end-diastolic pressure; Veso, end-systolic volume; Veds, end-diastolic volume; PAPes, systolic pulmonary arterial pressure; PCWPes, mean pulmonary capillary wedge pressure; MVG, mean transmirtal valve pressure gradient; MVA, mitral valve area; Ees, end-systolic elastance; V100, volume at 100 mm Hg.

*p<0.05 vs. baseline, †p=0.07 vs. baseline.

both at baseline and after PBMV was similar in both groups. Thus, small baseline chamber volumes and acute increases in end-diastolic volume after PBMV were not unique to the principal study group reported above but rather represented the response in as much as 50% of MS subjects undergoing PBMV. These results also suggest that in chambers with normal or increased volumes at baseline, PBMV was unlikely to lead to further acute dilation.

Discussion

The principal findings of the present study are that ESPVRs differ little between control and MS subjects; however, the EDPVRs are both steeper (reduced compliance) and shifted leftward. Furthermore, these diastolic abnormalities can be acutely reversed by mitral valvuloplasty. This procedure provides a unique method to assess and separate acute and chronic functional changes caused by mechanical valve alteration with little direct effect on the myocardium. On the basis of these data, we propose that increased diastolic chamber stiffness with MS does not result from a permanent myocardial abnormality but rather represents a functional restriction, perhaps a result of mechanical constraining effects of a thickened immobile valve apparatus.

Systolic Function in MS

Although it has long been recognized that a subset of patients with rheumatic MS fail to respond to mechanical

TABLE 4. Compliance Changes Before and After PBMV

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pre-PBMV</th>
<th>Acute</th>
<th>3-Month follow-up</th>
<th>Pre-PBMV</th>
<th>Acute</th>
<th>3-Month follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>2.57</td>
<td>7.67</td>
<td>5.27</td>
<td>7.06</td>
<td>11.08</td>
<td>9.64</td>
</tr>
<tr>
<td>4</td>
<td>1.36</td>
<td>4.42</td>
<td>2.61</td>
<td>2.06</td>
<td>5.59</td>
<td>6.23</td>
</tr>
<tr>
<td>5</td>
<td>2.35</td>
<td>6.17</td>
<td>...</td>
<td>7.40</td>
<td>16.85</td>
<td>...</td>
</tr>
<tr>
<td>6</td>
<td>1.90</td>
<td>...</td>
<td>7.14</td>
<td>5.03</td>
<td>...</td>
<td>8.60</td>
</tr>
<tr>
<td>7</td>
<td>2.88</td>
<td>4.65</td>
<td>8.40</td>
<td>10.83</td>
<td>6.5</td>
<td>24.81</td>
</tr>
<tr>
<td>9</td>
<td>2.43</td>
<td>5.17</td>
<td>...</td>
<td>5.92</td>
<td>6.28</td>
<td>...</td>
</tr>
<tr>
<td>Mean</td>
<td>2.25</td>
<td>5.62*</td>
<td>5.86†</td>
<td>6.38</td>
<td>9.25</td>
<td>12.3*</td>
</tr>
<tr>
<td>SD</td>
<td>0.54</td>
<td>1.33</td>
<td>2.51</td>
<td>2.90</td>
<td>4.77</td>
<td>8.40</td>
</tr>
</tbody>
</table>

Data are in ml/mm Hg and obtained in upper and lower load ranges as in Table 2.
PBMV, percutaneous balloon mitral valvuloplasty; Acute, immediately after PBMV.

*p<0.02 vs. control.
†p<0.05 vs. control.
The current investigation demonstrated little to no difference in chamber systolic function between MS and normal control subjects. Our data do not answer whether myocardial properties are similarly unaltered, because to do so would require transforming the PV data to stress–strain information. This was not attempted because the equations involve a variety of modeling assumptions that are not currently testable. However, our data are unique in that systolic function relations were obtained for each patient by nonpharmacological transient load alterations. This represents the most direct evidence to date to suggest that systolic chamber function is not altered in human MS.

**Diastolic Function in MS**

The most intriguing observation made in the present study was the finding of reduced diastolic compliance in MS patients that was reversed shortly after valvuloplasty. Feigenbaum et al.15 previously attempted to assess mean compliance from the ratio of mean mitral valve flow to change in chamber pressure versus time. These calculations revealed no difference between normals and MS patients. Others, however, have suggested that the rigid mitral apparatus can immobilize the posteriobasal region of the ventricle, leading to reduced compliance4,5 and chamber atrophy.11 Pathology studies have also suggested that endomyocardial fibrosis may also play a role in reduced diastolic distensibility.3 Finally, a contribution from right heart loading has been emphasized.4

The current data address many of these hypotheses. Our estimation of compliance was based not on a single steady-state beat analysis but on combined late diastolic PV data from multiple beats at varying preload volumes. We have previously shown this to be valuable for separating out effects of chamber load (from right ventricle or perhaps pericardium interactions) and early relaxation and filling from intrinsic chamber diastolic properties.8 Two observations suggest that right ventricular loading was not a major factor: 1) the EDPVRs were obtained while the right ventricle was substantially unloaded (via IVC occlusion), and 2) the immediate post-PBMV data demonstrated a marked increase in chamber compliance despite almost identical right heart pressures. Although endocardial fibrosis could be present, valvuloplasty should not acutely alter the structure of the myocardium; thus, this mechanism is inconsistent with the immediate post-valvuloplasty data. Another hypothesis, that of chronic cardiac remodeling and/or atrophy resulting from low filling,11 would also appear less prominent because the EDPVRs were restored so quickly after valvuloplasty. Chamber volumes continued to increase another 25% during the 3-month follow-up period, however, so chamber remodeling could still play a secondary role in the diastolic abnormalities with MS.

The most compelling mechanism is mechanical, related to the immobility of the valve apparatus tethered via the chordae and papillary muscles to the ventricular chamber. In a sense, the valve apparatus acts much like pericardial constriction—but inside the heart. In addition to restricted filling as a result of the narrowed orifice area, the tethering of the muscle wall to the immobile valve ring increases the apparent diastolic stiffness much as a constraining membrane on the
outside surface would. Removal of the pericardium results in rapid reversal of net stiffness much as release of the rigid valve apparatus by valvuloplasty does. We suggest that PBMV sufficiently improves valve apparatus mobility to release this constraining effect on the ventricle, thereby revealing far more normal diastolic function than is otherwise apparent.

The role of the mitral chordal apparatus, particularly during mitral valve replacement, has been the focus of several recent studies.23–25 These investigations have focused largely on systolic properties. In studies performed in isolated in situ canine hearts, Hansen et al24,25 reported that the slope of the ESPVR fell by 21–50% when the chordae were severed. Diastolic relations have not been found to change.25 It is quite possible, however, that in normal hearts, the diastolic effects from chordal support or the valve apparatus are already so minor that severing the connections has little effect on diastolic compliance. In MS, in contrast, the thickened immobile valve would result in a much greater baseline effect, so we would anticipate a much larger change in compliance if the chordae were severed. This hypothesis remains to be directly confirmed.

Influence of Chamber Volume

An alternative interpretation of both systolic and diastolic data in MS is based upon the notion that the MS hearts are in fact chronically shrunken. Since the ESPVR varies inversely with chamber size,26 one might expect a higher slope in the MS group. The finding of similar ESPVRs between MS and control could then be argued to represent contractile depression with MS. Likewise, if MS leads to chronically smaller hearts, then the measured reduction in diastolic compliance might be appropriate for the reduced chamber size. This view depends on the ventricle itself having chronically remodeled to become smaller. The acute PBMV data, both in the study group and in the nine additional subjects who also had reduced baseline volumes, however, suggest that this “smallness” can be rapidly reversed. Acute increases in filling volumes in a dog heart, for example, do not result in PV data typical of a human heart. It is for this reason that we favor the alternative interpretation: that dysfunction with MS is a result of a mechanical constraint and that release of this constraint reveals relatively normal underlying myocardial chamber properties. Most likely, the truth is somewhere in between, with cardiac remodeling (smallness) and a mechanical constraint both playing roles.

Stroke Work: End-Diastolic Volume Relations

An interesting finding in the present study was reduction of the slope of the stroke work–end-diastolic volume relation, which occurred despite the similar ESPVR slopes. The former has been proposed as a measure of chamber systolic function,27 and in many previous animal studies, it correlates directly with changes in chamber end-systolic elastance.28 A major caveat, which is often ignored, is that the diastolic properties must be comparable and normal for this index to reflect systolic properties. Like developed pressure, stroke work links diastolic and systolic PV boundaries, and changes in either one can limit net external work. The steepness and leftward shift of the EDPVRs in the MS patients indeed represent a profound difference in diastolic properties compared with normal (extend the group relation in Figure 2 so that it overlaps with the normal volume range to appreciate this). Indeed, at 3-month follow-up after valvuloplasty, with little change in E\(_{\text{es}}\), from control, the slope of the stroke work–end-diastolic volume relation had increased by 24% (\(p=0.046,\) by Friedman). Investigators using the stroke work–end-diastolic volume relation must bear in mind diastolic property changes when interpreting this index.

Limitations

The major limitation of this study is the lack of precise three-dimensional geometric data for each beat during preload change, so that stress-strain analysis could not be used. As a result, we can address chamber but not estimated myocardial function indices. Nevertheless, the data are important, because it is chamber function that determines observed hemodynamic variables such as cardiac output, ejection fraction, etc.

A second potential limitation relates to the volume calibrations. We used a single-plane ventriculographic technique, and there are no existing data that confirms its accuracy specifically in patients with MS. It is possible that cardiac rotation with MS caused by elevated right heart pressures could alter the regression parameters used in volume estimation. It is unlikely, however,
that chamber geometry or orientation changed dramatically acutely after valvuloplasty, so this would probably not contribute to the changes observed.

The volumes we obtained in the MS patients at baseline were somewhat small, although similar to several other published studies.\(^4\,^16\) This may in part relate to racial factors, the severity of disease, and age of the patients. There was also a 10% difference in mean mass and estimated surface area between MS and control subjects. Although not large enough to explain the volume or other disparities between the groups, it suggests an effect of MS itself on body size. Finally, our analysis of the additional 21 MS subjects indicates that the reduced chamber volumes are not atypical for this study population.

**Conclusions**

We have demonstrated in patients with severe pure rheumatic MS that systolic chamber function is nearly identical to age-matched controls, whereas the diastolic compliance is reduced and the PV relations shifted to lower volumes. Furthermore, the nearly immediate recovery of diastolic compliance after balloon mitral valvuloplasty suggests that the latter change is probably not because of intrinsic myocardial fibrosis nor primarily the result of chronic chamber remodeling and/or atrophy. Instead, the compliance reduction appears to be a consequence of a functional restriction from tethering to a rigid valve apparatus. These data support the notion that mobilization of a stenosed mitral valve, whether surgically or by valvuloplasty, can improve overall cardiac performance by mechanisms other than pure increase in orifice size.

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