Disparity between ejection and end-systolic indexes of left ventricular contractility in mitral regurgitation

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ABSTRACT To examine left ventricular function in mitral regurgitation (MR), we compared the ejection phase indexes of left ventricular contractility with maximal systolic elastance (Emax) in an experimental preparation of MR. In eight anesthetized open-chest dogs, pressure-volume loops were derived during afterload manipulation with methoxamine and nitroprusside from simultaneous left ventricular pressure and dimensional (sonomicrometry techniques) data before and after creation of MR. From these data maximal systolic elastance (Emax), the end-systolic pressure-volume relationship (ESPVR), and the end-systolic stress-volume relationship (ESSVR) were determined by linear regression analysis. After creation of MR, end-diastolic volume increased significantly (40 ± 13 to 53 ± 18 ml, p < .001); likewise end-systolic volume increased (28 ± 11 to 33 ± 15 ml, p < .05). Ejection fraction increased after MR (35 ± 6% to 44 ± 8%, p < .005), as did the mean velocity of fiber shortening (0.62 ± 0.20 to 1.02 ± 0.39 sec⁻¹, p < .02). In contrast, Emax declined significantly (4.63 ± 2.5 to 3.54 ± 1.94 mm Hg/ml, p < .05); ESPVR and ESSVR showed similar directional changes. An inverse relationship was found between systolic elastance and end-diastolic volume in both control and MR states. When Emax, ESPVR, and ESSVR were normalized to end-diastolic volume, they were unchanged after MR. These results suggest that either there was a decline in left ventricular contractile state after MR, or that contractility was unchanged (if elastance is normalized for the increase in heart size). In this preparation of MR the observed increase in shortening was not due to increased contractility, but occurred as a consequence of increased preload with no significant change in afterload.


EXPERIMENTAL and clinical studies have demonstrated exaggerated myocardial shortening in the presence of mitral regurgitation (MR) and it has been suggested that this is due to favorable left ventricular loading conditions imposed by the regurgitant leak.¹⁻⁴ The standard ejection or shortening phase indexes of left ventricular contractility are known to be influenced by alterations in preload and afterload⁵⁻⁷ and thus it is likely that the loading conditions present in MR can mask significant myocardial dysfunction that may become manifest after valve replacement.⁸⁻¹⁵ The left ventricular end-systolic pressure-volume relationship has been proposed as an index of contractile state that is independent of acute changes in preload and afterload. This relationship is a linear function with a slope (maximal systolic elastance or Emax) that is sensitive to changes in inotropic state.¹⁶⁻²⁰ Because of its “load independence,” systolic elastance may provide a more accurate assessment of left ventricular function in the presence of MR than standard ejection phase indexes of contractility. We therefore developed an animal preparation in which to compare the ejection phase indexes with Emax in MR. We then tested the hypothesis that the widely observed increase in shortening merely reflects altered loading conditions present in this setting. Since we did not anticipate a change in left ventricular contractile state, we expected that Emax would remain unchanged in the presence of MR.

Methods

Experimental preparation. Ten mongrel dogs weighing 20 to 25 kg were sedated with morphine sulfate (2.0 mg/kg im).
Anesthesia was induced with intravenous sodium pentobarbital (10 mg/kg) and morphine sulfate (60 mg iv). Thereafter, a surgical level of anesthesia was maintained with continuous intravenous infusion of morphine sulfate (20 to 25 mg/hr). Respiration was controlled with a mechanical ventilator with intermittent positive pressure and supplemental O\textsubscript{2} to maintain an arterial PO\textsubscript{2} in excess of 90 mm Hg. A left thoracotomy was performed through the fifth intercostal space and the heart was suspended in a pericardial cradle. To maintain intravascular volume each dog was transfused with 100 to 200 ml of whole blood.

Two pairs of pulse-transit ultrasonic (piezoelectric) transducers\textsuperscript{21} were sewn to the epicardial surface of the left ventricle to measure the external long-axis (D\textsubscript{L}) and short-axis (D\textsubscript{S}) dimensions. Equatorial wall thickness was obtained from a pair of small cylindrical ultrasonic crystals placed across the ventricular wall in the area between the anterior papillary muscle and the septum. The orientation of these crystals is shown in figure 1. The sampling rate of the sonomicrometer is 250 samples/sec. All three-dimensional signals obtained from the sonomicrometer were calibrated and were simultaneously recorded on direct-current input channels of a multichannel physiologic recorder (Electronics for Medicine, model VR 12) with a frequency response bandwidth of 250 Hz. Aortic, left ventricular, and left atrial pressures were measured with high-fidelity micromanometer-tipped catheters (Model PC-350, Millar Instruments) that were balanced and calibrated from 0 to 200 mm Hg just before insertion. Calibrations were verified at the end of each experiment to ensure minimal drift. The aortic catheter was positioned just above the aortic valve via the carotid artery, the left ventricular catheter was introduced into the ventricular cavity from the left ventricular apex, and the left atrial catheter was placed via the atrial appendage. The first derivative of left ventricular pressure (dP/dt) was obtained by electronic differentiation of the left ventricular pressure signal. Simultaneous recordings of the electrocardiogram, aortic and left ventricular pressures, dP/dt, and the three-dimensional signals were all obtained on the multichannel physiologic recorder at a paper speed of 100 mm/sec.

**Study protocol.** After the dogs were instrumented, atropine (0.5 mg iv) and propranolol (0.15 mg/kg iv) were administered to blunt reflex responses to arterial pressure manipulations. Baseline measurements of pressure and dimension were made; examples of control and baseline MR records are shown in figure 2. Afterload was then manipulated to obtain multiple pressure-volume loops (derived from pressure-dimension data). All dogs received methoxamine by continuous intravenous infusion at a rate sufficient to increase systolic pressure by at least 20 mm Hg. In six dogs nitroprusside was also administered to reduce systolic pressure. For each animal, simultaneous pressures and dimensions were recorded at multiple pressure levels.

In eight dogs MR was created in the following manner. A purse-string suture was sewn around the left atrial appendage and a metal hook placed through the appendage was used to sever chordae tendineae. Severe MR was indicated by the development of a systolic thrill over the left atrial wall, marked left atrial distention, and left atrial regurgitant (v) waves of 25 to 50 mm Hg. Animals were then allowed to stabilize for 90 min; inspired oxygen was adjusted to maintain physiologic arterial blood gases. Pressure and dimensional data were then obtained at baseline and during afterload manipulation (just as in the control state). At the end of each experiment the heart was dissected to check the position of the endocardial thickness crystal and to confirm that chordae tendineae or mitral leaflets were torn without significant damage to the ventricular wall.

Two dogs were used in sham experiments to determine that the preparation would not deteriorate over time. In these animals the experimental preparation and baseline measurements were performed exactly as described for the dogs with MR except that MR was not created. Instead, measurements were made during a "baseline" period and again 90 min later; data were obtained during afterload manipulation just as in the MR dogs.

**Calculations.** Analog data were recorded on a multichannel physiologic recorder and were analyzed with an Apple II computer with an x-y digitizing tablet. The internal volume of the left ventricle was calculated according to a prolate ellipsoid model with the formula:

\[ V = \frac{\pi}{6} (b - 2h)^2 (a - 1.1h) \]

where b is the measured external D\textsubscript{S}, a is the external D\textsubscript{L}, and h is the equatorial wall thickness. This method has been validated by Rankin et al.\textsuperscript{22} The ejection fraction was calculated from the end-diastolic volume (EDV) and the end-systolic volume (ESV), defined as the largest and smallest attained volumes. The left ventricular volumes and ejection fractions in our anesthetized open-chest dogs are lower than those reported in studies of conscious closed-chest dogs with the use of similar sonomicrometric techniques.\textsuperscript{22} This is probably the result of alterations in left ventricular size and geometry known to occur in open-chest preparations.\textsuperscript{23}

An index of the left ventricular ejection time was derived from the interval between peak positive dP/dt and the smallest systolic minor-axis dimension (ESD). The normalized mean

**FIGURE 1.** Schematic representation of the orientation of the ultrasonic transducers on the left ventricle. D\textsubscript{L} represents epicardial crystals positioned at the base between the aorta and pulmonary artery and the apex to measure external long-axis dimension. D\textsubscript{S} are crystals placed on the anterior and posterior epicardial surfaces near the interventricular septum to measure external short-axis dimension. Th represents a pair of cylindrical crystals on the anterior endocardial and overlying epicardial surfaces to measure wall thickness.
velocity of circumferential fiber shortening \( V_{CF}, \) sec\(^{-1}\) was calculated as the endocardial fractional shortening (largest internal diastolic short-axis dimension [EDD] minus ESD, divided by EDD) divided by the left ventricular ejection time. A "rate corrected" mean \( V_{CF} \) was also determined with use of the rate-corrected ejection time.

Circumferential midwall stress (in mm Hg) was calculated by Mirsky's formula for a prolate ellipsoid:

\[
\text{Stress} = \frac{Pb}{h} \left[ 1 - \frac{h}{2b} - \frac{b^2}{2a^2} \right]
\]

where \( P = \) pressure; \( h = \) wall thickness; \( a = \) midwall semimajor axis \((D_L - 1.1h)/2\); \( b = \) midwall semiminor axis \((D_S - 2h)/2\). Peak systolic stress was taken as the maximal circumferential stress achieved during systole. "End systolic" wall stress was calculated at the time of the aortic incisura; it was also determined from coordinates at the time of smallest systolic volume. Mean systolic stress was determined by integrating the wall stress throughout the period of ejection and dividing by the time interval; mean developed systolic stress was derived by subtracting end-diastolic stress.

Left ventricular volume was calculated from the dimensional data, and for each animal eight to 20 pressure-volume loops were plotted during the control state and again after creation of MR (figure 3). Simultaneous left ventricular pressure (or stress) and volume coordinates at the time of the incisura were identified. Because of uncertainties regarding a precise definition of end-systole in the presence of MR, we used three different methods of calculating the slope of the "end-systolic" pressure-volume relationship:

1. Em: The slope of the pressure-volume relationship was determined from linear regression analysis of multiple pressure-volume coordinates taken at the time of maximal pressure-volume ratio (maximal elastance).
2. End-systolic pressure-volume relationship (ESPV): The slope of the pressure-volume relationship was determined from linear regression analysis of multiple pressure-volume coordinates taken at the time of the aortic incisura.
3. End-systolic stress-volume relationship (ESSVR): The slope of the stress-volume relationship was determined from linear regression analysis of multiple stress-volume coordinates at the time of the aortic incisura.

Linear regression analysis by the least squares method was used to determine the three elastance variables listed above. An inverse relationship was found between elastance and baseline EDV for each state before load manipulation (see Results), such that a linear relationship existed between elastance and 1/EDV (linear correlation coefficients for Em vs 1/EDV, \( r = .87; \) ESPVR vs 1/EDV, \( r = .92; \) ESSVR vs 1/EDV, \( r = .81 \)). This implies a hyperbolic function relating elastance and EDV. Based on this apparent dependence of elastance on heart size, elastance was normalized for heart size according to this relationship. Thus, normalized elastance was calculated by multiplying the value for manifest elastance by the baseline EDV for each of the two states. This is mathematically equivalent to

![FIGURE 2. Baseline pressure and dimensional data from a typical experiment. Left, Control data; right, data after creation of MR. Simultaneous recordings of left ventricular (LVP) and aortic (Ao) pressures, external D_L and D_S, and wall thickness (Th) are shown. The dP/dt is recorded above the other signals and the electrocardiogram (ECG) below. After creation of MR the systolic pressure is slightly lower, wall thickness is decreased, and D_L and D_S are increased.](http://circ.ahajournals.org/doi/abs/10.1161/01.CIR.0000011575.30986.01)
FIGURE 3. Left ventricular pressure-volume loops from a representative experiment before (left) and after (right) creation of MR. The broken line represents baseline data (before administration of methoxamine). The slope, intercept (V₀), and correlation coefficients (r) are given for the end-systolic pressure-volume relationship (Emax in this example) in each state. After MR, the linear relationship between end-systolic pressure and volume was shifted to the right and the slope (Emax) decreased.

Results

Pressure-volume loops from a single representative experiment are shown in figure 3. Each loop was generated from approximately 60 pressure-volume coordinates. In this example, EDV and stroke volume increased, the range of systolic pressure was lower, and there was an increase in shortening after creation of MR. The end-systolic pressure-volume coordinates were shifted down and to the right and Emax declined from 5.19 to 4.29 mm Hg/ml.

Immediately after creation of MR, peak systolic wall stress declined from 186 ± 82 to 129 ± 67 mm Hg (p < .005); after the 90 min stabilization period wall stress had nearly returned to control levels. All control and MR data (after the equilibration period) are listed in tables 1 and 2. There was a tendency for left ventricular systolic pressure to decline, but not to a statistically significant extent; the average value for dividing the systolic volume of each of the pressure-volume coordinates by the baseline EDV (i.e., each of the ESVs obtained by load manipulation is divided by the same EDV).

Diastolic pressure-volume relationships were analyzed by linear regression analysis of pressure-volume data from individual baseline cardiac cycles from the time of minimal left ventricular pressure to the next R wave. Pressure-volume coordinates for each state were fit to a linear relationship and to a simple exponential function such that \( P = Be^{kt} \), where \( P \) = left ventricular pressure; \( V \) = volume; \( e \) = base of the natural logarithm, and \( B \) and \( k \) are constants. These constants were derived from the relationship \( \ln P = kV + \ln B \). Data could be equally well fit to either the linear \( (r = .93 \pm .005, \text{control}; r = .96 \pm .04, \text{MR}) \) or exponential \( (r = .92 \pm .06, \text{control}; r = .92 \pm .09, \text{MR}) \) relationships. To compare the diastolic pressure-volume curves before and after MR in each animal, these relationships were derived from baseline data in each state, and the lines were compared with the use of statistical tests for parallelism and common intercepts.

Statistical analysis. All results are reported as the mean ± one SD. A two-tailed Student’s t test for paired data was used to compare control and MR data and a p value of less than .05 was considered indicative of a statistically significant difference.

![Table](image.png)

**TABLE 1**

Hemodynamic variables before and after mitral regurgitation

<table>
<thead>
<tr>
<th></th>
<th>Pressure (mm Hg)</th>
<th>Stress (mm Hg)</th>
<th>Volume (ml)</th>
<th>Ejection indexes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PSP</td>
<td>ESP</td>
<td>LVEDP</td>
<td>PSS</td>
</tr>
<tr>
<td>Control</td>
<td>134 ± 15</td>
<td>95 ± 14</td>
<td>7 ± 2</td>
<td>184 ± 76</td>
</tr>
<tr>
<td>MR</td>
<td>117 ± 11</td>
<td>95 ± 14</td>
<td>19 ± 8</td>
<td>184 ± 73</td>
</tr>
<tr>
<td>p value(^{A})</td>
<td>NS</td>
<td>NS</td>
<td>&lt;.005</td>
<td>NS</td>
</tr>
</tbody>
</table>

All values are mean ± SD.

PSP = peak systolic pressure; ESP = end-systolic pressure at the incisura; LVEDP = left ventricular end-diastolic pressure; PSS = peak systolic wall stress; MDSS = mean developed systolic stress; ESWS = end-systolic wall stress at the incisura; EF = ejection fraction.

\(^{A}\)Paired t test of control vs MR; NS = not significant at p > .05.
TABLE 2
Systolic elastance before and after MR

<table>
<thead>
<tr>
<th></th>
<th>ESPVR</th>
<th></th>
<th></th>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Slope</td>
<td>V₀</td>
<td>r value</td>
<td>Slope</td>
<td>V₀</td>
<td>r value</td>
</tr>
<tr>
<td>Control</td>
<td>5.33±2.33</td>
<td>8±9</td>
<td>.959±.030</td>
<td>9.43±2.67</td>
<td>17±9</td>
<td>.984±.008</td>
</tr>
<tr>
<td>MR</td>
<td>4.16±1.93</td>
<td>-3±33</td>
<td>.912±.032</td>
<td>7.18±2.71</td>
<td>15±13</td>
<td>.953±.025</td>
</tr>
<tr>
<td>p value*</td>
<td>&lt;.05</td>
<td>NS</td>
<td>&lt;.005</td>
<td>NS</td>
<td>&lt;.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

All values are the mean ± SD.
Slope = slope of linear regression line for each relationship (in mm Hg/ml); V₀ = volume intercept (in ml) at zero pressure or stress; r = linear correlation coefficient.

*Paired t test of MR vs control.

end-systolic pressure did not change. Left atrial pressure increased significantly and large V waves developed after MR, with a wave/v wave pressures increasing from 9 ± 4/11 ± 5 mm Hg in the control state to 20 ± 6/31 ± 12 mm Hg after MR. Left ventricular end-diastolic pressure increased, and both EDV and ESV increased significantly. Accompanying this volume increase the ventricular chamber became more spherical, as manifested by a decline in the ratio of the major-to-minor internal dimensions from 1.69 ± 0.20 in the control state to 1.61 ± 0.16 after MR (p < .01). On visual inspection, the diastolic pressure-volume relationship was shifted to the right after MR. This difference in the diastolic curves was confirmed by statistical comparison of the lines relating lnP and volume (or pressure and volume) throughout diastole in the control state and after MR. The intercepts (B) were significantly different after MR in all animals, and the slopes (k) were significantly different in six of eight.

There was a tendency for mean systolic stress to decline after MR, but the average value for systolic stress was not significantly different from the control value. Peak systolic stress, mean systolic stress, and end-systolic stress (whether defined at the aortic incisura or at the time of smallest systolic volume) were not significantly different after MR from the control state. Ejection fraction and mean V CF increased significantly (figure 4). Because of the increase in heart rate (113 ± 15 to 150 ± 26 beats/min, p < .01), V CF was normalized for heart rate; the rate-corrected V CF also increased from 0.46 ± 0.16 to 0.65 ± 0.22 sec⁻¹ (p < .05). Peak positive dP/dt was unchanged after MR (control, 1886 ± 241 mm Hg/sec; MR, 1796 ± 353 mm Hg/sec, NS).

The average results for the three end-systolic indexes are shown in table 2 and figure 5. In all animals the maximal pressure-volume ratio, used to derive Emax, occurred within 30 msec before aortic valve closure in both the control and MR states. All of the end-systolic relationships were highly linear in the control state and after creation of MR, but there was a tendency for the linear correlation coefficient to be lower after MR. This trend was least apparent when stress was used in the calculation of elastance. All three methods revealed a significant decline in the slope of the end-systolic pressure (or stress)-volume relationship, and there was no significant change in the volume intercept.

Based in part on the suggestion of Sagawa and others that Emax should be normalized for heart or body size, we plotted the slope of the pressure-volume relationship against the baseline (before pharmacologic afterload manipulation) EDV for the control and MR states to determine the relationship between elastance and heart size. The data shown in figure 6 indicate an inverse relationship between Emax and EDV, which can be described by a hyperbolic function. This inverse relationship, which was present in the control and MR states, forms the basis for normalizing systolic elastance by the baseline EDV; our rationale for such
normalization is given in the discussion below. When Emax was normalized for the baseline EDV, the normalized values were essentially equal in the control and MR states (table 3). This was also true for ESPVR and ESSVR (table 3).

To confirm the stability of our anesthetized open-chest dog preparation we performed two sham experiments. The hemodynamic variables were measured during a control state and again 90 min later (at a time equivalent to that for MR data acquisition). In the first dog the ejection fraction values were 42% vs 42%, ESPVR values were 5.61 vs 6.39 mm Hg/ml, and Emax values were 4.97 vs 4.92 mm Hg/ml. In the second dog the ejection fraction values were 27% vs 29%, ESPVR values were 3.34 vs 3.80 mm Hg/ml, and Emax values were 2.61 vs 3.33 mm Hg/ml.

**Discussion**

The problems encountered in the assessment of myocardial function in the presence of an incompetent mitral valve have been appreciated for many years. Early studies by Braunwald et al.1 in a preparation of acute MR demonstrated a substantial increase in total left ventricular output and stroke volume and it was suggested that this might be due to facilitated ejection into the lower pressure left atrium during systole. Subsequent studies by Urschel et al.2 and others3, 4, 13, 14 revealed an increase in both the extent and velocity of fiber shortening after MR, which was attributed to an increase in preload and reduction in late systolic wall tension. Under these conditions, they found no change in $V_{max}$ (an isovolumetric index of contractility) and they concluded that myocardial contractility is un-

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**FIGURE 6.** The relationship of Emax and EDV. Emax is plotted against the baseline EDV before load manipulation for control (closed circles) and MR (arrow) in each dog. The curve represents a least squares best fit (hyperbolic function) of all 16 coordinates. In seven of eight experiments, the decline in Emax was associated with an increase in EDV.

**FIGURE 5.** Systolic elastance before and after creation of MR. Solid circles represent individual data from each dog in the control state (C) and after MR. Open circles represent mean data, with one SD shown. Data are shown for three different methods of determining systolic elastance (see text for definitions of ESPVR, ESSVR, and Emax). Data shown are the slopes of each relationship in mm Hg/ml. The slopes of all three relationships decreased significantly after MR.

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**TABLE 3**

<table>
<thead>
<tr>
<th>Normalized elastance before and after MR</th>
<th>ESPVR&lt;sub&gt;n&lt;/sub&gt;</th>
<th>ESSVR&lt;sub&gt;n&lt;/sub&gt;</th>
<th>Emax&lt;sub&gt;n&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.92 ± 0.41</td>
<td>3.84 ± 2.20</td>
<td>1.67 ± 0.44</td>
</tr>
<tr>
<td>MR</td>
<td>1.99 ± 0.72</td>
<td>3.90 ± 2.81</td>
<td>1.61 ± 0.53</td>
</tr>
<tr>
<td>p value&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

All values represent the mean ± SD; ESPVR<sub>n</sub>, ESSVR<sub>n</sub>, and Emax<sub>n</sub> represent normalized elastance (slope normalized for baseline EDV); units are mm Hg × 10<sup>2</sup>.

<sup>a</sup>Paired t test of control vs MR.
changed in acute MR; they also suggested that the ejection phase indexes overestimate contractile state in the presence of this lesion. Alterations in preload are known to affect $V_{\text{max}}$, and the use of an isovolumetric index is at best questionable when no true isovolumetric phase exists. For these reasons, $V_{\text{max}}$ has not proven to be a reliable index of left ventricular contractility in this disorder.

To assess left ventricular function in the setting of MR it is necessary to use an index of contractile state that is not affected by altered loading conditions. The end-systolic pressure-volume relationship has been proposed as such an index. In the isolated canine left ventricle Suga et al. found that the maximum slope of the end-systolic pressure-volume relationship was independent of acute changes in preload and afterload, but was sensitive to changes in inotropic state, becoming steeper with increased contractility. While the unique load-independence of this relationship would seem to make it ideal for examining ventricular function in the setting of MR, its use is complicated by continued ejection of blood into the left atrium after aortic valve closure. Thus precluding a simple definition of end-systole. Early studies by Suga et al. indicate that the slope of the instantaneous relationship of pressure and volume increases with time throughout systole, reaching a maximum value near the end of ejection, nearly coincident with the uppermost left corner of the pressure-volume loop. Several approximations of this relationship have been developed, the most commonly used being the end-systolic pressure-volume relationship determined at the aortic incisura and the simple ratio of pressure or wall stress over volume at end-ejection. Since “end systole” is not clearly synonymous with “end ejection” in the setting of MR, we chose to evaluate three different methods of approximating systolic elastance. Using a wide range of loading conditions we determined $E_{\text{max}}$ and two other end-systolic indexes, the pressure-volume and the stress-volume relationships at the time of the aortic incisura. It is of interest that in all animals the maximal pressure-volume ratio (used to define coordinates for $E_{\text{max}}$) occurred before aortic valve closure in both the control state and after MR, suggesting that continued ejection into the left atrium after aortic valve closure with MR has no significant impact on systolic elastance and that aortic valve closure closely approximates other definitions of end-systole.

Our results are consonant with previous studies demonstrating a significant increase in both the extent and velocity of fiber shortening after the creation of MR. In sharp contrast are the results of the systolic elastance analysis: regardless of the method used to determine systolic elastance, a significant decrease in this variable was observed after the development of MR. Systolic elastance is known to be sensitive to changes in left ventricular contractile state, and thus data indicate a decline in contractility with MR. We therefore considered what factors might result in a decrease in contractility and/or a decrease in chamber elastance with no change in contractility in our preparation of MR.

Although the animals became transiently hypoxemic and on occasion mildly acidotic with the creation of MR, these abnormalities were corrected during the equilibration period, and the studies were performed without hypoxemia or acidosis. Temperature was carefully monitored and no dog became hypothermic during the course of an experiment. The stability of our preparation over time was documented in the two sham experiments; no decline in maximum elastance was found during the course of these experiments. Likewise, the effect of changes in heart rate on elastance would not be expected to cause a decrease in contractile state. If it has any effect, increased heart rate should result in an increase in inotropic state, not a decline. Within the range of heart rates observed in our study, others have not found a major effect of heart rate on maximum elastance. Therefore, the observed decrease in systolic elastance cannot be attributed to “external” factors resulting from experimental design.

It is widely accepted that the end-systolic pressure-volume relationship is insensitive to acute changes in loading conditions, but under experimental circumstances this relationship does exhibit some load dependence. For example, at a constant end-systolic volume, the end-systolic pressure declines as the ejection fraction increases; this can result in a decrease in systolic elastance. The mechanisms underlying this phenomenon are not well understood, but it is probably due, at least in part, to shortening deactivation. The magnitude of the dependence of maximum elastance on shortening is said to be quite small relative to its dependence on left ventricular contractility. Therefore, while the effect of increased shortening may contribute to a decline in elastance, it is unlikely that increased shortening alone could explain the considerable decrease in systolic elastance that was observed in our study.

Another possible cause of the decline in systolic elastance is the mechanical effect of ventricular dilatation itself. It is conceivable that short-term mechanical stresses sufficient to cause ventricular dilatation could produce myocardial injury resulting in a depression of
myocardial function. Although one cannot definitively rule out the possibility that some myocardial damage has occurred to depress contractile state, there are no published data to support this notion. Therefore, we considered the effect of a change in heart size as an independent factor that might influence systolic elastance. It is apparent that a larger ventricular chamber will result in a shift of the pressure-volume loop to the right, although myocardial contractile state may be unchanged. In fact, we found an inverse relationship between systolic elastance and baseline EDV (figure 6) similar to that observed by Bogen et al. The observation that elastance is lower in larger hearts prompted us to normalize the elastance variables for the baseline EDV before and after creation of MR. This type of normalization is not appropriate for very acute changes in preload in which the ventricle merely moves up or down a single diastolic pressure-volume curve. However, in our study the MR data were obtained 1 to 2 hr after creating MR, during which time several important changes in the left ventricle had occurred. The large increase in EDV after MR was accompanied by a rightward shift in the diastolic pressure-volume relationship, a more spherical left ventricular geometry, and an increase in systolic stress (returning to control levels) after an initial decline. This constellation of variables suggests that the ventricular chamber has undergone considerably greater changes than simply an acute increase in preload; the pressure-volume relationship may already be reset to a different baseline, comparable to that in subacute or chronic MR. Thus, it seems reasonable to normalize elastance to account for the change in heart size, much as one might if these changes were more chronic. We have considered what other methods of normalization might be used to account for heart size changes, including $V_o$, the extrapolated volume at zero pressure, and left ventricular mass. Neither $V_o$ nor left ventricular mass changed in these short-term experiments, and therefore there is no rationale for such normalization.

When the baseline EDV for each state was used, the normalized values of all three elastance parameters were unchanged, implying that there may be no change in left ventricular contractile state with MR (table 3). This conclusion is supported by our observation that peak positive dP/dt did not change after creation of MR. These results are similar to those reported by Tajimi et al., who reported data from dogs with MR that were studied repeatedly over several weeks. They found a progressive increase in ventricular volume and ejection fraction, but the end-systolic pressure-volume relationship decreased. However, when they normalized their data for the baseline EDV, no significant difference was found between the slopes of the ESPVR before and after MR. They interpreted these results as indicating that there is no change in contractility after MR when the dependence of systolic elastance on baseline EDV is considered.

It seems possible, therefore, that the decline in manifest (non-normalized) systolic elastance could be the result of adaptive mechanical changes such as fiber rearrangement and slippage. Although such adaptive changes are known to occur in chronic dilatation, it is not known whether they play a significant role in short-term experiments such as those conducted in the preparation of MR we used. In this study, an equilibration period of 90 min was allowed after the creation of severe MR, and during this period progressive ventricular dilatation occurred; consequently, systolic wall stress, which was initially decreased, returned to baseline levels. This would suggest adaptation to a new mechanical baseline, as in compensated subacute or chronic MR. Fiber rearrangement, slippage, and other phenomena, such as stress relaxation and creep, can occur over a very short time period, and it is likely that such processes occurred in our experiments, although pathologic confirmation is not available. Thus, the rightward shift in the end-systolic pressure-volume relationship may be a result of ventricular dilatation and remodeling, and not necessarily a change in the contractile state of the myocardium.

We interpret our data as supporting the hypothesis that augmented fiber shortening in MR does not reflect an increase in left ventricular contractility; this is the case whether normalized or non-normalized elastance is used in the analysis. The increased extent and velocity of shortening were due to increased preload; afterload, as assessed by systolic wall stress, had returned to baseline levels and thus a systolic unloading effect did not contribute significantly to the observed increase in shortening.

Clinical implications. These findings have several implications for the clinical use of systolic elastance as a measure of left ventricular function in the presence of MR. Although the pressure-volume coordinates can be reasonably fit by a linear function, we observed slightly greater scatter after creation of MR. If one were to assume linearity and rely on only two or three pressure-volume coordinates to derive systolic elastance, considerable error could be introduced. The need to obtain multiple coordinates to ensure an accurate assessment of elastance is thus apparent. Previous studies have also shown that single point pressure-volume ratios are, in fact, load dependent. Incorpora-
tion of wall stress values in the analysis would seem especially relevant to the assessment of patients with chronic MR in whom myocardial hypertrophy is also present.

The observed disparity between the ejection phase indexes and Emax has clear implications in the clinical setting. These data support the concept that ventricular function is overestimated by ejection indexes when MR is present. Numerous clinical studies demonstrate a significant decrease in ejection fraction in patients undergoing mitral valve replacement for severe MR, suggesting that irreversible myocardial dysfunction may become unmasked when the regurgitant lesion (favoring enhanced shortening) is no longer present. While this is especially common in patients with decompensated ventricles, there is evidence that a postoperative decline in fiber shortening is not always due to an increase in afterload. In any case, ejection indexes are poor predictors of myocardial function; based on our results and the clinical data of others, systolic elastance may provide a better definition of left ventricular function in the setting of MR. However, the dependence of this relationship on heart size requires further elucidation before this relationship is applied to the clinical evaluation of left ventricular function in patients with MR. Likewise, a consideration of EDV may be important in aortic regurgitation, dilated cardiomyopathy, and even in the comparison of data from children and adults.

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