PATHOPHYSIOLOGY AND NATURAL HISTORY

VALVULAR HEART DISEASE

Does normal pump function belie muscle dysfunction in patients with chronic severe mitral regurgitation?

THOMAS WISENBAUGH, M.D.

ABSTRACT Left ventricular cineangiography and micromanometry were performed simultaneously in 27 patients with chronic severe mitral regurgitation (MR group) and in 23 normal subjects (NL group). Stress (σ) and volume (V) were computed frame by frame. Measurements were repeated after pharmacologic load manipulation in subsets of MR (n = 10) and NL (n = 11) groups. An inverse relationship (r = - .90) between EFc (ejection fraction determined from a common preload) and σes (afterload) was observed for the NL group. For the MR group, 10 of 14 with EFs less than 0.60 and four of 13 with EFs greater than 0.60 had muscle dysfunction, falling below the 95% prediction band of the normal EFc-σes relationship. Maximum myocardial stiffness (maxEs) determined from the end-systolic stress-strain relationship of Mirsky, αes = maxEs-γ-log(Ves/V0), was 1398 ± 716 in the MR (n = 10) vs 1165 ± 394 in the NL group (n = 11, NS). EF was 0.62 ± 0.13 in the MR and 0.65 ± 0.08 in the NL group. Mitral valve surgery was performed on 19 of the patients with MR. All survived and all but one were symptomatically improved; that patient required reoperation in the early postoperative period because of transverse midventricular disruption. Thus, contractile function as assessed by stress-strain and EFc-afterload relationships is frequently normal in individuals with MR when EF is normal. When EF is depressed, contractile function as assessed by EFc-afterload relationships is frequently depressed, but this does not preclude a satisfactory surgical result.


EJECTION FRACTION is often depressed after chronic mitral regurgitation (MR) is corrected with a prosthetic valve. This occurs even when preoperative ejection fraction is normal.1 Since reduced afterload tends to augment ejection performance in acute MR,2,3 it seems logical that correction of chronic MR might cause the ejection fraction to be depressed by afterloading the ventricle, thereby "unmasking" preoperative contractile dysfunction. This hypothesis, which has long been accepted as an explanation for the disappointing surgical results in patients with chronic MR,4-9 has not been confirmed with studies of preoperative contractile function, since no load-independent methods have been available for clinical use.

Accordingly, the purpose of the present study was to assess preoperative contractile state in patients with chronic, severe MR by use of recently developed methods that are relatively independent of load. The possible prognostic significance of these measures of contractile state were then examined in patients undergoing mitral valve surgery.

Methods

Subjects. Patients with mitral regurgitation in whom simultaneous cineangiography and micromanometry were performed in our laboratories between March 1983 and September 1987 were included in the present analysis if: (1) MR was judged to be the predominant mitral lesion, i.e., there was 3+ to 4+ regurgitation of contrast into the left atrium on angiography, and a mitral valve area of 1.3 cm² or greater according to angiographic flow and the Gorlin equation, (2) there was no significant aortic valve disease, i.e., no more than 1+ aortic insufficiency and no more than 5 mm Hg aortic valve gradient, and (3) there was no history of myocardial infarction or segmental wall motion abnormalities on angiography. Twenty-seven patients who had predominant or isolated severe mitral regurgitation by these criteria and who had left ventriculograms adequate for edge detection were included in this study, and comprise the MR group. The mean estimated regurgitant fraction for the MR group was 0.54 ± 0.15 (n = 23; table 1). MR was judged to be chronic in all but one of these patients on the basis of symptoms or physical findings that were present for at least 3 months; the remaining patient had symptoms for only 3 weeks but had increased end-diastolic diameter (6.1 cm) as assessed by echocardiography. All but six patients were in normal sinus rhythm.
TABLE 1
Clinical and angiographic data

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FC NYHA = preoperative New York Heart Association functional class; BSA = body surface area; RF = regurgitant fraction; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; EF = ejection fraction; LVMI = left ventricular mass index. Atrial fibrillation (Afib) precluded computation of an accurate RF in two patients.

aCause of mitral disease was myxomatous (Myx), rheumatic (RHD), myopathic (CCM), or healed endocarditis (SBE).

bPorcine heterograft degeneration after surgery for RHD.

cSignificant difference from normal in MR group.

rhythm: four of these were in atrial fibrillation but had well-opacified beats preceded by a cycle length that differed by no more than 15% from the average cycle length; two others, one of whom was also in atrial fibrillation, had VVI pacemakers, and thus had a regular rhythm at the time of study. Coronary arteriograms were normal in all but three patients who had significant single-vessel disease but no history of myocardial infarction, unstable angina, or wall motion abnormalities on cineangiography.

An NL group was comprised of 23 "normal" subjects who underwent catheterization for evaluation of chest pain syndromes that were not typical of angina, and who were found to have: (1) normal coronary arteries, (2) normal left ventricular function as defined by an angiographic ejection fraction of 0.60 or more or, in four patients who did not undergo a baseline cineangiography until after intervention (see below), a minor-axis shortening fraction of 0.30 or more by echocardiography, (3) left ventricular angiographic wall thickness less than 1.1 cm, and (4) no evidence of valvular heart disease.

Long-term cardiac medications taken by the patients were β-blockers (three in MR group, nine in NL group), digoxin (20 in MR group, one in NL group), diuretics (15 in MR group, three in NL group), long-acting nitrates (seven in MR group, 11 in NL group), calcium-channel antagonists (five in MR group, seven in NL group), either hydralazine or captopril (nine in MR group, one in NL group), and amiodarone (one in MR group). Medications were not discontinued for catheterization, with the exception of nitrates and calcium antagonists that were omitted for ergonovine challenges in four members of the NL group (see below).

Each patient gave informed consent to a protocol approved by the joint University of Kentucky/VA Institutional Review Board.

Procedure. Patients were premedicated with oral diazepam, 5 to 10 mg. Right heart catheterization was performed in all
patients in the MR group. Left heart catheterization was performed retrograde via femoral or brachial artery with the use of an 8F micromanometer catheter with a pigtail configuration. Left ventricular pressure was recorded simultaneously with injection of 39 to 54 ml meglumine diatrizoate into the left ventricle during biplane cineangiography (30 degree right anterior oblique and 60 degree left anterior oblique).

In subsets of the MR group (n = 10) and normal group (n = 11), angiography was performed twice: once with, and once without pharmacologic afterload manipulation. In all patients in the MR group, load was reduced by an infusion of sodium nitroprusside beginning at 0.25 μg/kg/min, and increasing by 0.25 μg/kg/min every 3 min to decrease aortic systolic pressure by 20% to 40% but to no less than 80 mm Hg. In the NL group, load was altered by one of three methods: 0.35 mg ergonovine in three divided intravenous doses in four subjects, 0.8 mg nitroglycerin in two equally divided sublingual doses in three subjects, or intravenous nitroprusside by the method described above in the remaining subjects. A 15 to 20 min interval separated the first and second ventriculograms to allow the hemodynamic effects of the contrast agent to dissipate. During this time neither the patient nor the imaging equipment was moved. Patients were instructed not to perform a Valsalva maneuver during inspiration held for the ventriculographic examination. Immediately after the second contrast cineangiogram, a radiographic grid positioned at midchest was imaged biplane to provide corrections for magnification.

During the early period of study, a baseline cineangiogram was obtained before the infusion of nitroprusside and second cineangiogram was obtained 15 to 20 min later. This allowed for a greater difference in load between the two cineangiograms since the volume-loading effect of contrast further elevated pressures above baseline.

Precise synchronization between pressure and cineangiography was achievable with a cine frame marker, which records a mark for each film exposure (60/sec) simultaneously with the pressure recording, and exposes every hundredth frame with a diode simultaneously with an accentuated mark on the pressure recording.

No patient experienced any symptom other than mild facial flushing during the infusion of nitroprusside, and there were no complications.

**Analysis of catheterization data.** Methods were similar to those used previously in this laboratory. Briefly, left ventricular silhouettes for each frame of the first well-opacified beat of each left ventricular cineangiogram not preceded by an ectopic beat were digitized with a hand-held cursor. Left ventricular wall thickness was measured at the mid third of the anterior wall in the right anterior oblique view for the end-diastolic frame. Correction factors for ventricular measurements were derived from the grids positioned at the center of the ventricle. Left ventricular volume was computed by the area-length method and a regression equation. Since the silhouette borders in the left anterior oblique view were sometimes unclear over the spine and diaphragm, and since segmental dyssynergy was absent, volumes were computed from the single-plane right oblique view. Left ventricular mass was computed with wall thickness measured at end-diastole. Dynamic wall thickness was computed for all frames subsequent to end-diastole assuming a constant mass for each frame according to the method of Hugenholzt et al. Left ventricular pressure for the corresponding cardiac cycle was digitized with use of the midportion of the QRS complex as a reference point for end-diastole.

Mean circumferential wall stress was computed with Mirsky’s equation:

$$\sigma_0 = 1.332 \cdot (PD_m/2h) \cdot [1 - h/D_m - D_m^2/(2L_m)^2]$$

where P is pressure, h is wall thickness, and D_m and L_m are diameter and length, respectively, at the midwall. Lagrangian strain was defined as:

$$\varepsilon_L = (D_m - D_{om})/D_{om}$$

and natural strain was defined as:

$$\varepsilon_N = \gamma \cdot \log(V/V_0)$$

where D_{om} is the theoretical D_m at zero stress. In terms of cavity volume, natural strain can be defined alternatively as:

$$\varepsilon_N = \gamma \cdot \log(V/V_0)$$

where V_0 is the zero stress volume, and γ is the geometric factor relating systolic D_m to V in the equation:

$$D_m = A \cdot V^\gamma$$

where A is a regression constant. Briefly, end-systolic relationships are obtained by fitting the data, which was not smoothed, to the equations:

$$\sigma_{es} = \max \varepsilon_L \cdot (D_m - D_{om})/D_{om}$$

for Lagrangian strain and

$$\sigma_{es} = \max \varepsilon_N \cdot \gamma \cdot \log(V_{es}/V_0)$$

for natural strain, where maxE is the maximum myocardial stiffness and V_{es} is the volume at maximum stiffness. For this analysis, an initial value of D_{om} or V_0 was approximated by the appropriate extrapolation; the maximum slope of the $\sigma$-ε relationship was obtained by a modification of the method of Kono et al. Briefly, this is an iteration that first finds the maximum quotient of $\sigma(t)/\varepsilon(t)$ for each loop (t = time), then performs a three-point linear regression with use of these two values and with the first approximation of D_{om} (or V_0) as the third point. A second intercept is obtained from this regression equation, and the process is repeated until convergence occurs on a maximum value for the slope with a final value for D_{om} (or V_0).

To determine diastolic volume at a common preload for all patients, a three-constant exponential equation was fit to each patient’s diastolic stress-volume data:

$$\sigma_d = a + b \cdot e^{-c \cdot V_d}$$

and solved for V_d at $\sigma_d = 50$ (figure 1). For the patients receiving nitroprusside, the best fit to the available data from both loops was obtained. V_d and ESV (end-ejection volume) were then used to compute ejection fraction from a common preload:

$$EF_e = (V_d - ESV)/V_d$$

Mean normalized systolic ejection rate was computed as:

$$MNSER = EF/ET$$

where EF is ejection fraction and ET is ejection time. Data are reported as mean ± SD. Group comparisons were
FIGURE 1. The diastolic stress-volume relationship for two differently loaded beats (open squares are data points during baseline cineangiogram, solid squares are data points after load augmentation with ergonovine) in a normal subject. These data were used to determine diastolic volume at a common preload of 50 kdynes/cm$^2$. This volume was then used to compute EF$_c$ as described in Methods.

performed with analysis of variance, with .05 as the critical level.

**Results**

Clinical and angiographic data for each individual patient with MR are listed in table 1. Left ventricular end-diastolic volume was increased and ejection fraction was decreased in the MR compared with the NL group, but there was wide variation for both of these variables. Ejection fraction was less than 0.60 in 14 of the 27 patients with MR. There was a modest depression in ejection fraction for those with rheumatic disease (0.56 ± 0.05) compared with those with mitral disease of another cause (0.63 ± 0.10, p = .06).

Afterload estimated as end-systolic stress was not reduced in the group with chronic MR (204 ± 70 kdynes/cm$^2$) vs the NL group (192 ± 54 kdynes/cm$^2$, NS), and in only one of the patients in the MR group did end-systolic stress fall below the lowest value in the NL group (82 kdynes/cm$^2$). Preload estimated as end-diastolic stress was increased in the MR (71 ± 29 kdynes/cm$^2$) vs the NL group (49 ± 19 kdynes/cm$^2$, p < .01).

There was a strong inverse correlation (r = −.90, SEE = 0.046) between ejection fraction corrected for preload (EF$_c$) and end-systolic stress among the 23 normal subjects (figure 2, top). Load manipulation in 11 of these normal subjects resulted in shifts in individual EF$_c$-end-systolic stress relationships that were nearly parallel to those for the entire group (figure 2, bottom), suggesting that significant changes in contractile state did not occur during load manipulation.

Figure 3 shows EF$_c$-end-systolic stress coordinates for the 27 patients in the MR group vs the normal 95% prediction band (top panel); load manipulation was performed in 10 (bottom panel). Of the 13 patients in the MR group in whom baseline ejection fraction was greater than 0.60 (mean ejection fraction 0.68 ± 0.06, NS vs normal group), nine had values that fell within or above the 95% prediction band for the normal EF$_c$-end-systolic stress relationship; thus, normal pump function did not belie muscle dysfunction in these patients. However, contractile state estimated as EF$_c$-end-systolic stress was depressed in four of 13, despite preservation of ejection fraction by augmented preload (end-diastolic stress 82 ± 35 kdynes/cm$^2$).

Of the 14 patients in the MR group in whom baseline ejection fraction was depressed below 0.60 (mean ejection fraction 0.54 ± 0.05, p < .001 vs normal), three had normal EF$_c$-end-systolic stress relationships, suggesting preservation of contractile state and a depression in ejection fraction due to increased afterload (end-diastolic stress 272, 223, and 253 kdynes/cm$^2$). An additional patient who had a depressed ejection fraction (0.45) and fell along the lower limit of the 95% prediction band also had increased afterload (end-systolic stress 343 kdynes/cm$^2$). In the remaining 10 the EF$_c$-end-systolic stress relationship fell below normal due to muscle dysfunction. Thus, pump function as assessed by ejection fraction accurately reflected muscle function (EF$_c$-end-systolic stress) in 19 of 27 patients with MR, but overestimated it in four, and underestimated it in four.

Since diastolic wall stress is affected by factors extrinsic to the left ventricle, such as pericardial restraint and left ventricular–right ventricular interaction, preload may have been overestimated in some of the patients in the MR group due to subacute cardiac dilatation. This possibility is supported by the downward shifts that were apparent in the diastolic stress-volume curves of three of 10 of these patients after infusion of nitroprusside. The velocity-stress relationship has been suggested as a preload-insensitive alternative to the shortening-stress relationship, and analysis with its use (figure 4) revealed fewer contractile abnormalities than did the analysis using the EF$_c$-end-systolic stress relationship (figure 3).

Stress-strain analysis was assessed from two differently loaded beats in subsets from the NL (n = 11) and MR (n = 10) groups for whom the mean ejection fraction was 0.65 ± 0.08 and 0.62 ± 0.13, respectively. The influence of pharmacologic load manipulation on hemodynamic variables, and the resulting
stress-strain data, are presented in table 2. Figure 5 shows the derivation of $D_{om}$ from $\sigma$-diameter loops (left panel); $D_{om}$ was then used to compute the $\sigma$-$e_L$ relationship (middle panel). The $\sigma$-$e_N$ relationship is non-linear when expressed in terms of cavity volume (right panel). Maximum myocardial elastance ($\text{max}E_N$) was preserved in the MR group (table 2), despite significant ventricular dilatation, as illustrated in figure 6. Use of the Lagrangian definition of strain did not alter this result ($\text{max}E_L 1792 \pm 1306 \text{ vs } 1259 \pm 562 \text{kdynes/cm}^2$ in NL, NS). In only one patient did $\text{max}E_N$ fall below the lowest normal value (778 kdynes/cm$^2$); this patient was believed to have primary cardiomyopathy based on a catheterization done 3 years earlier, which showed a depressed ejection fraction at a time when the severity of MR was only mild to moderate.

Relaxation measured as the maximum rate of early diastolic pressure decay ($-dP/dT_{\text{max}}$) was depressed in the MR group ($1339 \pm 455 \text{ vs } 1699 \pm 274 \text{ mm Hg/sec}$ in the NL group, $p < .002$). However, in 10 of

FIGURE 2. Linear regression line ($r = -.90$, SEE = 0.046, $p < .0001$) and 95% prediction band for $E_F$ vs end-systolic stress ($\sigma_{es}$) in 23 normal subjects (top), 11 of whom had a second cineangiogram performed during load manipulation (see Methods). Paired $E_F$-$\sigma_{es}$ coordinates from differently loaded beats are connected by solid lines (bottom).
 FIGURE 3. \(E_F\)-end-systolic stress (\(\sigma_{es}\)) data point in the 27 patients with MR vs the normal 95% prediction band generated for figure 2 (top). Load intervention was performed in 10 of the patients in the MR group, and the paired data points are connected by solid lines in the bottom panel.

the 11 patients in the MR group with abnormal relaxation (i.e., that 2SDs below the normal mean value of \(-dP/dT_{max}\)), there was a concomitant depression in contractile performance as assessed by the \(E_F\)-end-systolic stress relationship, suggesting that relaxation abnormalities often accompany — but do not precede — contractile abnormalities.

Although there has been speculation that the ventricle might continue to empty into the left atrium after the end of mechanical systole in the presence of mitral regurgitation, figures 5 and 6 illustrate the proximity of end-ejection to the frame at which elastance was maximum. End-ejection volume (63 ± 25 ml/m²) was only 7% less than the maximal elastance volume (68 ± 31) in the 10 patients in the MR group in whom max\(E_N\) was measured.

Nineteen patients underwent mitral valve surgery and received a Björk-Shiley prosthesis \((n = 9)\), Omnisiscience prosthesis \((n = 1)\), St. Jude prosthesis \((n = 5)\), tissue valve \((n = 2)\), or mitral valve reconstruction
FIGURE 4. Mean normalized systolic ejection rate (MNSER) was inversely related to end-systolic stress ($\sigma_{es}$) in normal subjects ($n = -0.72, \text{ SEE } = 0.33, p < 0.0001$), as represented by open squares. The correlation was not improved after correcting MNSER for heart rate ($r = -0.64$). MR group patients are represented by solid squares. The solid and broken lines are the regression line and 95% prediction band, respectively, for the NL group.

(n = 2). There were no perioperative deaths and no late deaths after a mean postoperative follow-up interval of 19 ± 11 months.

All but one patient was in New York Heart Association functional class I or II after surgery; the remaining patient required emergency reoperation in the early postoperative period for transverse midventricular disruption (figure 7). Clinical improvement occurred despite $E_{F_c}$--end-systolic stress relationships that were depressed in nine of the 19. Stress-strain data were available on eight operated patients, all of whom improved; $\text{max}E_{A_v}$ was within the normal range in all eight. The end-systolic stress-volume index ratio was $3.7 \pm 1.7$ in the MR group (vs $6.3 \pm 1.3$ in the NL group, $p < 0.001$), and in five of the 19 operated patients, this ratio was 2.7 or less, a level associated...
TABLE 2
Hemodynamic and stress-strain data resulting from load manipulation

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>LVP_{peak} (mm Hg)</th>
<th>LVP_{es} (mm Hg)</th>
<th>V_{les} (ml/m^2)</th>
<th>\sigma_{es} (kdynes/cm^2)</th>
<th>V_{o} (ml)</th>
<th>maxE_{es} (kdynes/cm^2)</th>
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<td>MR group</td>
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<td>18</td>
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<td>125 69</td>
<td>83 72</td>
<td>354 155</td>
<td>111 311</td>
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<tr>
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<td>71 50</td>
<td>229 123</td>
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<tr>
<td>SD</td>
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<td>NL group</td>
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<tr>
<td>Mean</td>
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<td>134 100</td>
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<td>233 139</td>
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<td>21 18</td>
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<td>84 61</td>
<td>8 394</td>
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</table>

Influence of load manipulation on peak left ventricular pressure (LVP_{peak}), pressure at maximal elastance (LVP_{es}), and the corresponding volume index (V_{les}) and stress (\sigma_{es}) at maximal elastance (maxE_{es}). V_{o} is the zero stress volume (not indexed for BSA). 1 = before nitroprusside; 2 = after nitroprusside.

^Significant difference from normal in MR group.

Discussion
Intuitively we would expect that correction of chronic MR, by removing the so-called low-impedance leak into the left atrium, would increase the afterload on the ventricle, and thereby reduce the ejection frac-

FIGURE 6. Stress (\sigma)-volume data in a normal subject (left) and a patient with MR (right). Although the relationship between end-systolic stress and end-systolic volume (solid curve) is depressed compared with normal (due to ventricular dilatation), the V_{o}-normalized maxE_{es} value indicates preservation of contractile force at any degree of stretch in the patient with MR. The simple end-systolic stress-end-systolic volume index (\sigma_{es}V_{les}) ratio is also much lower than normal (at a common afterload, \sigma_{es} \approx 200 kdynes/cm^2) in the MR patient due to ventricular dilatation.
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This concept derives support from studies in dogs that demonstrated that abrupt MR results in decreased ventricular wall stress and augmented ejection performance. Reversal of this condition has the opposite effect on ventricular load and performance. Studies by Wong and Spotnitz demonstrating increased wall stress immediately after discontinuation of cardiopulmonary bypass in patients undergoing mitral valve replacement also supports the concept that correction of MR afterloads the ventricle. It has therefore been assumed that preoperative contractile dysfunction, masked by favorable loading conditions, is the basis for depressed postoperative ejection fraction in patients who have normal ejection fractions before surgery.

That chronic volume overload depresses myocardial contractile state has been inferred from clinical observations but never directly proven. Cooper et al., in fact, found normal muscle function with experimental volume-induced hypertrophy that was of severity comparable to that associated with muscle dysfunction when produced by pressure overload. However, it is possible that muscle function might deteriorate with a more severe overload applied for a longer duration. Depressed performance has long been recognized in patients with volume overload due to MR, but whether this can be attributed to the volume overload per se or an associated condition, such as rheumatic myocarditis or other cardiomyopathy, is uncertain. The present study confirms the presence of contractile dysfunction by load-independent methods in a substantial portion of patients with chronic, severe MR. However, contractile function estimated as maxE_N or EF_c—end-systolic stress was frequently normal when the ejection fraction was preserved, which casts doubt on the concept that reduced afterload masks contractile dysfunction in chronic MR. Indeed, previous studies have also shown that afterload is normal or slightly increased in chronic MR, and a recent experimental study demonstrated that reduced afterload returns to normal a short while after MR is abruptly produced. Thus, some degree of pump dysfunction in patients with MR may actually be due to pressure overload, as has previously been recognized in the presence of aortic stenosis.

If correction of MR were to reduce ejection performance by increasing afterload, an increase in end-systolic volume would be expected. To the contrary, Boucher, Schuler and their colleagues found end-systolic volume and diameter, respectively, to be essentially unchanged after mitral valve replacement. Particularly interesting are the findings after repair of mitral incompetence without the use of prosthetic valves. Lessana and Bonchek and their colleagues found that end-systolic volume decreased after repair of mitral incompetence, and ejection fraction fell only slightly. These data suggest that afterload may actually decline after repair of the incompetent mitral valve. Removal of excessive preload probably accounts for the slight fall in ejection fraction after repair of MR, since the mean end-diastolic volumes returned to normal (40% reduction) in both of these studies.

An alternative to this time-honored hypothesis, that correction of chronic MR decreases ejection fraction by afterloading the ventricle, is the hypothesis that severing the chordae tendineae during mitral valve replacement redistributes stresses within the myocardial wall in such a way as to "untether" the ventricle. This may explain why global and regional ventricular function seem to be better when chordal attachments are preserved. An extreme form of "untethering" may account for the catastrophic phenomenon of transverse midventricular disruption described by Cobb et al. after mitral valve replacement. What factors predispose to this type III rupture, which occurred in one of our patients, is unknown.

The lack of a suitable index of contractility has impeded our understanding of the effects valvular lesions on the myocardium. Both the slope of the pres-
sure-volume relationship (E_{max}) and the simple ratio of stress/volume index at end-systole have recently been used to estimate contractile state,\(^4\)\(^5\) but both are dependent on the size of the ventricle\(^3\)\(^0\) (figure 6). To normalize for the load and/or size-dependence of these indexes, alternatives have recently been proposed. The relationship between ejection fraction and afterload in patients compared with that in normal subjects is one method that has been used by other investigators.\(^3\)\(^1\) Although this method takes afterload into account, preload remains a variable. In the present study, therefore, ejection fraction was computed from diastolic volume at a common preload derived from the passive stress-volume curves for each patient. A method of correcting E_{max} for size dependence, recently proposed by Mirsky,\(^1\)\(^5\) is the analysis of stress and strain to derive systolic myocardial stiffness (maxE\(_{max}\) and maxE\(_{syst}\) in the present study). The stress-strain relationship for the ventricle should be directly related to the relationship between force and normalized length for isolated muscle, and this relationship describes the total systolic force that can be attained at any given degree of stretch.\(^3\)\(^2\)

As previously discussed,\(^1\)\(^0\) the major methodologic limitations imposed by considerations of patient safety in this study are the use of only two differently loaded beats to determine maxE\(_{max}\) and the fact that autonomic blockade was not routinely used. Thus, scatter in the stress-strain data produced by changes in contractile state during load manipulation (figure 3, bottom) might obscure deficits in maxE\(_{max}\) for patients with MR vs normal subjects. The fact that E_{max}-end-systolic stress relationships were depressed in three patients in whom maxE\(_{max}\) was normal raises questions again\(^1\)\(^0\) about the sensitivity of this index as we have measured it.

The usefulness of the E_{max}-end-systolic stress relationship is limited by the extent to which corrections for preload (end-diastolic stress) are affected by factors extrinsic to the left ventricle. Ludbrook et al.\(^3\)\(^3\) demonstrated downward displacement of the diastolic pressure-volume relationship with nitroglycerin, and suggested a reduction of right ventricular filling pressure as the mechanism. Studies of Tyberg et al.\(^3\)\(^4\) demonstrating a close correlation between right atrial pressure and left ventricular pericardial surface pressure also suggested that external constraint on the left ventricle is in part determined by right ventricular filling pressure. However, Herrmann et al.\(^3\)\(^5\) were not able to completely negate nitroprusside-induced displacements in the diastolic pressure-volume curves by correcting for right atrial pressure. Likewise, among the patients with MR in the present study, an obvious shift occurred in a patient with a right atrial pressure of only 4 mm Hg, whereas little or no shift was observed in patients with right atrial pressures of 12 to 17 mm Hg. Thus, estimation of preload (i.e., transmural diastolic stress) is beset by problems that are not immediately solvable. Colan et al.\(^1\)\(^7\) suggested velocity of shortening corrected for heart rate as a less preload-dependent index than extent of shortening. As shown in figure 4, there was a greater standard error of the estimate for the ejection rate-end-systolic stress relationship than for the E_{max}-end-systolic stress relationship, and this scatter was not improved by correcting for heart rate. However, this analysis does support the conclusion also derived from E_{max}-end-systolic stress analysis that contractile impairment is uncommon in patients with mitral regurgitation when ejection fraction is normal.

The failure of depressed contractile state as measured by E_{max}-end-systolic stress to predict a poor surgical outcome may not be applicable to all patients undergoing surgery for MR. The number of patients with MR undergoing surgery was small (n = 19). The surgical mortality was nil. Few patients were in atrial fibrillation. Patients without two consecutive well-opacified nonectopic beats during angiography were excluded. Thus, the predictive value of E_{max}-end-systolic stress and maxE\(_{max}\) needs further study. The finding of Carabello et al.\(^5\) that the end-systolic stress/volume index ratio, when corrected for ventricular size, had no predictive value independent of end-systolic volume index suggests that ventricular size may influence surgical outcome more than contractility per se. The present findings likewise indicate that impaired contractility as measured by E_{max}-end-systolic stress does not preclude symptomatic improvement after surgical correction of chronic, severe MR. The findings also cast doubt on some long-held beliefs about the mechanics of this lesion and its influence on myocardial function and load.

The assistance of Dr. David Booth in collecting the catheterization data on patients 15 and 26 is appreciated.

References
4. Carabello BA, Nolan SP, McGuire LB: Assessment of preoperative
33. Ludbrook PA, Byrne JD, McKnight RC: Influence of right ventricular hemodynamics on left ventricular diastolic pressure-volume relations in man. Circulation 59: 21, 1979
Does normal pump function belie muscle dysfunction in patients with chronic severe mitral regurgitation?
T Wisenbaugh

Circulation. 1988;77:515-525
doi: 10.1161/01.CIR.77.3.515
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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