The relationship of afterload to ejection performance in chronic mitral regurgitation

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ABSTRACT  Simultaneous left ventricular micromanometry and biplane cineangiography were performed in nine control subjects (group 1), 14 patients with chronic mitral regurgitation and an ejection fraction of 57% or greater (group 2), and 13 patients with mitral regurgitation and an ejection fraction of less than 57% (group 3). End-diastolic volume index was increased in both groups with mitral regurgitation (p < .001) compared with the control group. Left ventricular end-diastolic wall thickness did not differ among the three groups, but the left ventricular muscle mass index was greater in both groups with mitral regurgitation than in controls (p < .001). End-diastolic pressure was elevated in both groups 2 and 3 compared with group 1 (p < .05), but peak systolic, mean systolic, and incisural pressure were not different among the three groups. End-diastolic stress was larger in groups 2 and 3 than in group 1 (p < .05). Muscle fiber stretch was greater in group 2 than in the control group (p < .05) but was not different between the controls and group 3. End-systolic stress, determined as the circumferential stress at aortic valve closure, at the maximal pressure/volume ratio, or using a non simultaneous method, was larger in group 3 than in groups 1 and 2. Mean systolic stress was evaluated from aortic opening to aortic valve closure in all patients; mean stress from end-diastolic to aortic valve closure and from end-diastole to minimum volume was assessed in mitral regurgitation alone. For all three intervals, mean stress determinations were larger in group 3 than the mean stress from aortic valve opening to closure in the controls (p < .05), whereas only the mean stress determined from aortic valve opening to closure was greater in group 2 than in the control group (p < .01). For each of the intervals, the calculated mean stress was larger in group 3 than in group 2 (p < .05). Evaluation of the end-systolic stress-- and mean ejection stress--ejection fraction relationships revealed an overlap of control with group 2 data, group 3 values were downwardly displaced. The absence of an upward shift of group 2 values in the setting of an augmented preload suggests that these patients maintained only a normal level of ventricular performance with the use of preload reserve and were operating at a somewhat reduced contractile state. The downward displacement of group 3 data points in the presence of only moderately higher levels of afterload than in groups 1 and 2 implies impaired myocardial contractility. Recognition of chronic mitral regurgitation as a stress overload state may provide insight into the mechanism of myocardial injury that occurs in both volume and pressure overload.


IN CHRONIC mitral regurgitation, the preserved left ventricular ejection performance and paucity of clinical symptoms during the course of the disease are attributed to favorably altered loading conditions.1–4 Studies of acute and chronic volume overload have demonstrated normal myocardial contractility and energetics,5–8 but other investigation has indicated diminished left ventricular function in the chronic state.9, 10 Evaluation of the myocardium has been performed by determining ejection phase indexes relating afterload with shortening. Since these measures are affected by changes in preload and afterload,11–13 assessment of inotropic state must account for alterations in load in the setting of mitral regurgitation.

Valvular regurgitation increases preload, reflected by greater left ventricular end-diastolic pressure, volume, circumferential length, and stress.1, 2, 7, 9 To accommodate the larger filling volume in acute volume overload, existing sarcomeres are stretched, thereby
increasing ventricular volume and circumferential length. In chronic regurgitation, further augmentation of these dimensions is due to sarcomeres added in series and in parallel, and possibly to fiber slippage; not to extension of individual sarcomeres beyond their optimal contractile length.\(^{14}\)

The effect of the low pressure left atrium upon ejection and systolic afterload is manifested in several ways. Early regurgitation allows the ventricle to empty against a relatively low afterload. The consequently reduced dimensions and thickened wall act to decrease stress throughout ejection. Emptying into the low impedance left atrium occurs during the entire time that the aortic valve is open and it continues after aortic valve closure. Ventricular pressure is falling in this latter period. The net effect is to extend ejection time, enhance overall ventricular emptying, and diminish mean systolic afterload.\(^{1}\)

In this study we investigated the effect of chronic volume overload on preload and afterload in patients with chronic mitral regurgitation. Accounting for the effects of increased volume on loading conditions, we assessed systolic function using the afterload-shortening relationship and reexamined contractility in mitral regurgitation.

**Methods**

**Patients.** All patients with isolated mitral regurgitation undergoing diagnostic cardiac catheterization at our institution from January 1977 to July 1986 were reviewed. Patients with any of the following characteristics were excluded: mitral stenosis (mean gradient \(>5\) mm Hg), aortic stenosis (mean gradient \(>5\) mm Hg), greater than trace aortic regurgitation, evidence of significant (50% or greater stenosis) coronary artery disease. Twenty-seven patients with chronic mitral regurgitation were evaluated (age 58 \(\pm\) 10 years), including 23 men and four women. All but one patient were clinically asymptomatic at the time of catheterization. Nineteen patients were in sinus rhythm; atrial fibrillation was present in eight. Nine patients (age 36 \(\pm\) 11 years) evaluated for symptoms of chest pain but who were found to be without significant coronary artery or cardiovascular disease served as control subjects.

Medications in use before catheterization included digoxin, furosemide, thiazides, nitrates, prazosin, and captopril.

**Catheterization.** Informed consent was obtained from all patients. Premedication consisted of 10 mg of chloral hydrate orally 1 hr before catheterization; cardiovascular medications were withheld 12 to 24 hr before the procedure. All patients underwent both right and left heart catheterization. Biplane contrast left ventriculography was performed in the right anterior or oblique (RAO, 30 degree) and left anterior oblique (LAO, 60 degree) projections with the patient supine; 35 mm film was used at a rate of 50 frames/sec.

Left ventricular pressure was measured simultaneously with cineangiography with a Millar No. 7F micromanometer-angiographic catheter introduced into the left ventricle through a No. 11.5F Brockenbrough catheter. Aortic pressure was assessed by means of a fluid-filled pigtail catheter introduced from the femoral artery. Aortic pressure was recorded simultaneously with cineangiography in 20 patients and six controls. All pressures were recorded at a paper speed of 250 mm/sec (Electronics for Medicine, VR-16) with the electrocardiogram, left ventricular pressure, dP/dt, aortic pressure, and cineangiographic time markers inscribed simultaneously.\(^{15,16}\) Cardiac index (liters/min/m²) was determined by the Fick method; regurgitant fraction was quantified by the angiographic-Fick method. Regurgitant volume was determined as the product of the angiographic stroke volume and the regurgitant fraction. Systemic vascular resistance (SVR) was calculated as:

\[
SVR = 80 \times \frac{AoP - RA}{CO}
\]

where AoP = mean aortic pressure (mm Hg), RA = mean right atrial pressure (mm Hg), and CO = cardiac output (liters/min).

**Data analysis.** Data were selected from beats during simultaneous left ventricular micromanometry and cineangiography. Extrasystolic and postextrasystolic beats were excluded and, in general, the first beat providing adequate opacification was analyzed. In the eight patients with atrial fibrillation, 2 or 3 beats were evaluated and the results averaged.

Left ventricular volumes were calculated by the area-length method\(^{17}\) from biplane frame-by-frame analysis in 21 patients and eight control subjects and from RAO monoplane analysis in six patients and one control subject. The left ventricular long axis was the measured longest axis from either the RAO or LAO views. The short axis was calculated as a geometric mean of the derived short axes in the RAO and LAO views:

\[
\text{short axis (SA)} = \sqrt{SA_{\text{RAO}} \times SA_{\text{LAO}}}
\]

The dimension and volume data were smoothed with a five-point formula:

\[
x(f) = \frac{x(f-2) + 2 \times x(f-1) + 3 \times x(f) + 2 \times x(f+1) + x(f+2)}{9}
\]

where \(x(f)\) is the relevant frame and \(x(f-)\) and \(x(f+)\) represent preceding and subsequent frames, respectively.

End-diastole was defined as the cineangiographic frame occurring immediately before the upstroke of the simultaneously inscribed dP/dt. Aortic valve opening was defined as the first frame after end-diastole in which the intraventricular pressure exceeded aortic pressure. Aortic valve closure was defined as the last frame in systole in which intraventricular pressure was greater than incisural pressure. Aortic pressure was available from simultaneously inscribed aortic pressures in 20 patients with mitral regurgitation and in six control subjects. In those 10 patients without simultaneous measurement, the aortic pressure used was from a beat immediately preceding angiography and matched to the angiographic beat by the maximum systolic pressure and RR interval. The ejection period was defined as aortic valve opening to aortic valve closure for control subjects and end-diastole to minimum volume for patients with mitral regurgitation.

The mean velocity of fiber shortening (Vcf, circumferences/second) was calculated for the systolic segment from aortic valve opening to aortic valve closure in all patients and for the entire ejection period in patients with mitral regurgitation.

Circumferential stress was calculated for each frame within the cardiac cycle from a simplified version of Mirsky’s thick wall model.\(^{18}\)
midwall stress \((\text{dyne} \cdot 10^3/\text{cm}^2) = (P-b/h) \cdot (1-(h/2b)-(b^2/2a^2)) \cdot 1.332\)

where \(P\) = intraventricular pressure (mm Hg), \(h\) = left ventricular wall thickness (cm), \(a\) = midwall semimajor axis \([(L+h)/2, \text{cm}]\), and \(b\) = midwall semiminor axis \([(D+h)/2, \text{cm}]\).

Peak systolic stress was defined as the single greatest circumferential stress in each beat. A precise definition of end-systole in mitral regurgitation remains elusive. We therefore assessed end-systolic stress as the circumferential stress at the following points in the cardiac cycle: aortic valve closure (SS-AVC), the maximal pressure/volume ratio (SS-P/V), and, for comparison with previous work, \(19\)–\(21\) with the incisural pressure and the nonsimultaneous ventricular dimensions at minimum ventricular volume (SS-IMV).

Mean systolic stress was determined in control subjects as the arithmetic mean of the stress calculation in each frame from aortic valve opening to aortic valve closure (MSS 1). In patients with mitral regurgitation, mean systolic stress was determined at three different intervals: from aortic valve opening to aortic valve closure (MSS 1) as in the control group; from end-diastole to aortic valve closure (MSS 2); and from end-diastole to minimum ventricular volume (MSS 3), in order to include the entire ejection period. Results obtained from the evaluation of MSS 1 in control subjects were compared with MSS 1, MSS 2, and MSS 3 in patients with mitral regurgitation.

In an effort to evaluate relative sarcomere length in control subjects and patients with chronic mitral regurgitation, the muscle fiber stretch and end-diastolic compliance were calculated for each patient at end-diastole:

\[
\text{muscle fiber stretch} = 100 \cdot \text{EDS-end-diastolic compliance}
\]

\[
\text{end-diastolic compliance} (1/\text{mm Hg}) = \left( \frac{\Delta V/\Delta P}{V_0} \right)_{\text{ed}} 
\]

where EDS = end-diastolic stress \((\text{dyne} \cdot 10^3/\text{cm}^2)\), \(\Delta V/\Delta P_{\text{ed}}\) = the incremental volume/pressure change during the final 20 msec of diastole \((\text{ml/mm Hg})\), and \(V_0\) = end-diastolic volume \((\text{ml})\).

To assess the effect of early and late ejection on the ability of mean ejection stress (MSS 3) to appropriately represent afterload in patients with mitral regurgitation, the myocardial work index \((\text{dyne} \cdot 10^3 \text{ cm}^2/\text{m}^2)\) was evaluated in two ways: as the product of the stroke volume index and mean ejection stress \((\text{SV-MSS 3})\) and as the sum of the work performed during the three segments: end-diastole to aortic valve opening, aortic valve opening to aortic valve closure, and aortic valve closure to minimum volume. Close agreement of these two values in our patients would support our use of mean stress to represent afterload during the entire period of ventricular emptying.

End-diastolic wall thickness was determined after the method of Rackley et al. \(22\) These results were compared with the posterior wall thickness by M mode echocardiography performed in all but two control subjects during cardiac catheterization. \(24\) The instantaneous wall thickness was calculated by the method of Hugenholz et al. \(25\) for each frame throughout the cardiac cycle.

Results for controls (group 1), patients with mitral regurgitation and an ejection fraction of less than 57% (group 2), and patients with mitral regurgitation and an ejection fraction of less than 57% (group 3) were statistically compared with a one-way analysis of variance, with Scheffe’s test for intergroup comparisons. When relevant data were not present in the control group, groups 2 and 3 were compared by a Student t test for independent groups. A two-way analysis of variance was used to compare the results of mean stress obtained with the three intervals of systole in patients with mitral regurgitation. Correlation and regression were determined with a linear least-squares method. All differences with a statistical probability of less than .05 by a two-tailed approach were considered significant.

Results

Clinical data. All but one patient with mitral regurgitation were taking digoxin and a diuretic before catheterization. Mitral valve prolapse was the cause of mitral regurgitation in 15 patients and ruptured chordae were responsible in none; the remainder of cases were due to rheumatic heart disease and endocarditis. Patients were significantly older than control subjects \((p < .01)\), but there was no difference in age between the two groups with mitral regurgitation. The body surface area was 1.74 ± 0.15 m\(^2\) in group 1, 1.98 ± 0.19 m\(^2\) in group 2, and 1.72 ± 0.21 m\(^2\) in group 3 (NS).

Hemodynamic data. The heart rate did not differ between controls and patients with mitral regurgitation (table 1). There was an increase in end-diastolic stress in both groups with mitral regurgitation compared with controls \((p < .05)\), but peak systolic pressure, mean systolic pressure, and incisural pressure were not different in the three groups. Left atrial v-wave pressure was similar in the two groups with mitral regurgitation. The cardiac index was greater in the control group than in both groups with mitral regurgitation \((p < .01)\). Systemic vascular resistance was greater in

| TABLE 1 |
| Hemodynamic and angiographic data |
| Group 1 | Group 2 | Group 3 |
| n | 9 | 14 | 13 |
| HR | 77 ± 15 | 75 ± 11 | 77 ± 13 |
| EDP | 10.4 ± 3.2 | 18.0 ± 5.5* | 18.3 ± 9.2* |
| PSP | 128 ± 14 | 116 ± 15 | 115 ± 18 |
| MSP | 118 ± 13 | 108 ± 14 | 106 ± 16 |
| IP | 103 ± 8 | 94 ± 12 | 93 ± 15 |
| VV | — | 32 ± 17* | 34 ± 13 |
| CI | 4.3 ± 0.7 | 2.7 ± 0.6* | 2.2 ± 0.6* |
| EDVI | 83 ± 19 | 191 ± 44* | 211 ± 53* |
| EF | 0.65 ± 0.03 | 0.65 ± 0.05 | 0.44 ± 0.08* |
| RF | — | 0.62 ± 0.11 | 0.65 ± 0.12 |
| ET | 260 ± 30 | 340 ± 40* | 310 ± 40* |
| H | 0.81 ± 0.09 | 0.82 ± 0.07 | 0.82 ± 0.06 |
| LMMI | 86 ± 16 | 133 ± 27* | 148 ± 25* |

HR = heart rate (bpm); EDP = end-diastolic pressure (mm Hg); PSP = peak systolic pressure (mm Hg); MSP = mean systolic pressure (mm Hg); IP = incisural pressure (mm Hg); VV = left atrial v-wave pressure (mm Hg); CI = cardiac index (l/min/m\(^2\)); EDVI = end-diastolic volume index (ml/m\(^2\)); EF = ejection fraction; RF = regurgitant fraction; ET = ejection time (msec); H = end-diastolic wall thickness (cm); LMMI = left ventricular mass index (g/m\(^2\)).

*p < .05 vs controls; *p < .01 vs controls; **p < .001 vs controls.
group 3 (1830 ± 530 dyne-sec-cm⁻²) than in group 2 (1230 ± 290 dyne-sec-cm⁻²; p < .01) or group 1 (980 ± 150 dyne-sec-cm⁻²; p < .001), but the latter two groups did not differ statistically.

**Angiographic data.** Both groups with mitral regurgitation had a larger left ventricular end-diastolic volume index than did controls (p < .001). The left ventricular end-systolic volume index was larger in group 3 (118 ± 36 ml/m²) than in group 2 (68 ± 21 ml/m²; p < .01) and group 1 (29 ± 8 ml/m²; p < .001) and greater in group 2 than in group 1 (p < .05). Mitral regurgitant fraction was similar in group 2 and group 3. Ejection time was significantly prolonged in both groups with mitral regurgitation compared with controls (p < .05). End-diastolic wall thickness did not vary among the three groups, but the left ventricular muscle mass index was significantly greater in groups 2 and 3 than in group 1 (p < .001). Angiographically and echocardiographically determined end-diastolic wall thicknesses were highly correlated (r = .97) and did not differ significantly. Our results for wall thickness and left ventricular muscle mass were consistent with data from previous studies of chronic mitral regurgitation.20, 26, 27

Comparing groups 2 and 3, the percentage of regurgitant volume occurring before aortic valve opening was not different (28 ± 7% vs 29 ± 11%; NS). The proportion of stroke volume ejected before aortic valve opening (17 ± 6% vs 18 ± 6%) and after aortic valve closure (5 ± 3% vs 5 ± 5%) did not differ. The maximal pressure/volume ratio occurred at 10 ± 20 msec before aortic valve closure in group 2 and 30 ± 30 msec in group 3 (NS) and 40 ± 30 msec before minimum volume in group 2 and 60 ± 30 msec in group 3 (NS).

The mean Vcf from aortic valve opening to aortic valve closure was greater in group 1 (1.24 ± 0.17 circ/sec) and group 2 (1.22 ± 0.13 circ/sec) than in group 3 (0.73 ± 0.18 circ/sec; p < .001). Considering the entire ejection period in each group, mean Vcf was greater in group 1 (1.24 ± 0.17 circ/sec; p < .001) than in group 2 (1.03 ± 0.11 circ/sec) and group 3 (0.62 ± 0.11 circ/sec) and greater in group 2 than in group 3 (p < .001), but ejection time was significantly longer in the groups with mitral regurgitation than in controls.

**Stress data.** Stress levels were uniformly higher in group 3 than in group 1, but the relative load levels between groups 1 and 2 varied (table 2). End-diastolic and peak systolic stress were greater in both groups with mitral regurgitation (p < .05). End-systolic stress, determined as the circumferential stress at aortic valve closure, the maximal pressure/volume ratio, or by the nonsimultaneous method, was greater in group 3 than in either group 2 or group 1 (p < .001). Group 2 showed no increase in any of the end-systolic stress determinations compared with group 1.

Mean stress from aortic valve opening to aortic valve closure (MSS 1) was greater in group 3 than in groups 1 and 2 (p < .001) (figure 1) and was larger in group 2 than in group 1 (p < .01). When mean stress was calculated in patients with mitral regurgitation from end-diastole to aortic valve closure (MSS 2) or for the entire ejection period from end-diastole to minimum volume (MSS 3), it was greater in group 3 than in both groups 1 and 2 (MSS 1) (p < .05). Mean stress was significantly larger in both groups 2 and 3 when calculated for MSS 1 than for MSS 2 and MSS 3, and larger for MSS 2 than MSS 3 (p < .01). The muscle fiber stretch was determined to better assess end-diastolic length in our three groups of patients. The fiber stretch was significantly greater in group 2 (112 ± 67; p < .05) than it was in group 1 (58 ± 40) but did not statistically differ from that in group 3 (63 ± 44). End-diastolic compliance did not differ among the three groups (group 1, 0.017 ± 0.010; group 2, 0.016 ± 0.0096; group 3, 0.010 ± 0.0045, NS).

To evaluate the ability of mean stress to adequately represent afterload during ejection in patients with mitral regurgitation, the myocardial work index, calcul-

### TABLE 2

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<tr>
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<th>Group 1 (controls)</th>
<th>Group 2</th>
<th>Group 3</th>
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<tr>
<td>EDS</td>
<td>36 ± 11</td>
<td>77 ± 25</td>
<td>73 ± 25</td>
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<tr>
<td>PSS</td>
<td>348 ± 44</td>
<td>391 ± 41</td>
<td>401 ± 33</td>
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<tr>
<td>SS-AVC</td>
<td>162 ± 19</td>
<td>194 ± 27</td>
<td>265 ± 37</td>
</tr>
<tr>
<td>SS-P/V</td>
<td>197 ± 25</td>
<td>202 ± 37</td>
<td>296 ± 43</td>
</tr>
<tr>
<td>SS-IMV</td>
<td>162 ± 19</td>
<td>177 ± 27</td>
<td>236 ± 45</td>
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<tr>
<td>MSS 1</td>
<td>267 ± 30</td>
<td>314 ± 37</td>
<td>351 ± 30</td>
</tr>
<tr>
<td>MSS 2</td>
<td>—</td>
<td>288 ± 38</td>
<td>316 ± 26</td>
</tr>
<tr>
<td>MSS 3</td>
<td>—</td>
<td>272 ± 35</td>
<td>305 ± 27</td>
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EDS = end-diastolic stress; PSS = peak systolic stress; SS-AVC = systolic stress at aortic valve closure; SS-P/V = systolic stress at maximal pressure/volume ratio; SS-IMV = systolic stress using incisural pressure and minimum ventricular volume; MSS 1 = mean stress from aortic valve opening to aortic valve closure; MSS 2 = mean stress from end-diastolic to aortic valve closure (mitral regurgitation only); MSS 3 = mean stress from end-diastole to minimum volume (mitral regurgitation only).

*p < .05 vs controls; ^p < .01 vs controls; °p < .001 vs controls; †p < .05 group 2 vs group 3; ‡p < .01 group 2 vs group 3; ‡p < .001 group 2 vs group 3.
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FIGURE 1. Mean systolic stress for controls (C), group 2 (2), and group 3 (3) for three different intervals of systole: from aortic valve opening to aortic valve closure (MSS 1), from end-diastole to aortic valve closure (MSS 2, mitral regurgitation only), and from end-diastole to minimum volume (MSS 3, mitral regurgitation only). The bars indicate the mean and 1 SD. The asterisks represent differences determined by a one-way analysis of variance, and the stars indicate statistical comparison with a two-way analysis of variance. Mean stress was elevated in group 3 compared with both group 2 and controls for all three definitions of systole. For both groups 2 and 3, stress levels were greater for MSS 1 than MSS 2 and MSS 3, and greater for MSS 2 than MSS 3.

lated as the product of the total stroke volume index and mean ejection stress (MSS 3) (30,700 ± 8400 dyne·10⁹ cm/m²) was compared with the sum of the work performed during the three segments of ejection: before, during, and after the period that the aortic valve was open (31,200 ± 8900 dyne·10⁹ cm/m²; NS). The close correlation (r = .98) and similarity of the values obtained indicate that, despite ejection during periods of low stress in mitral regurgitation, mean ejection stress may be used to represent afterload.

Discussion

Systolic ejection is a function of myocardial contractility as well as the hemodynamic conditions under which the heart functions. Most important among these factors are preload and afterload. To assess ventricular function by means of ejection phase indexes in mitral regurgitation, it is essential to clarify the loading conditions. Preload, the sarcomere length at the beginning of contraction, has been approximat-ed for the entire ventricle by the end-diastolic pressure, volume, and stress.

The short-term response to volume overload is an increase in left ventricular volume with a lengthening of sarcomeres along their normal length-tension curve. Progressive dilation of the ventricle leading to augmented volume in the chronic state is a result of the increased number of sarcomeres added in series and in parallel as the myocardium hypertrophies. Sarcomere length remains relatively constant during this period and the fiber is not extended beyond its optimal contractile length. In both control and chronic volume overloaded ventricles, extension and recruitment of sarcomeres constitute the functional reserve of Starling’s curve; this reserve is used to an increasing extent as diastolic pressure and stress are elevated.

In agreement with previous work, the results of this study indicate that the end-diastolic pressure and stress are augmented in chronic mitral regurgitation. These indexes might not adequately provide a measure of sarcomere length, since diastolic compliance may be abnormal in disease states; the muscle fiber stretch has been proposed as a method to compare relative sarcomere length. Because of the elevated end-diastolic stress and normal end-diastolic myocardial compliance, there was a greater muscle fiber stretch in patients with chronic mitral regurgitation and an intact ejection fraction than in the controls. These findings support the view that preload is increased in this group with mitral regurgitation. In contrast, despite their higher pressure and stress, the end-diastolic muscle fiber stretch in those with chronic mitral regurgitation and a depressed ejection performance did not differ from that in controls.

Afterload, the force opposing ventricular ejection, has been represented by the peak systolic stress. The prevailing view is that afterload is reduced in mitral regurgitation. We found no reduction in afterload in patients with mitral regurgitation. Rather, peak systolic stress was increased in both groups of patients with mitral regurgitation, whereas end-systolic stress and mean systolic stress were elevated in those patients with a diminished ejection performance.

Chronic mitral regurgitation has presented a paradox: patients typically remain asymptomatic for long periods, while hemodynamic studies have described depressed myocardial contractility. To resolve this incongruity, investigators have described left ventricular dependence on an increased preload and decreased afterload, which clinically conceal the diminished contractility and maintain ejection performance.
Systolic afterload. Urschel et al.,2 in an animal preparation of acute mitral regurgitation, found that peak systolic pressure and tension were not changed compared with the control state, but the shape of the pressure-time and tension-time curves were substantially altered. The result was a decrease in mean left ventricular systolic pressure and integrated systolic wall tension in mitral regurgitation. However, one must be cautious in extrapolating these findings to the chronic state. Grossman et al.,27 using simultaneous manometry and M mode echocardiography to determine ventricular dimensions, found that systolic afterload was not changed in the volume overload state. However, their use of one-dimensional echocardiography, which may not optimally assess the geometric changes that occur in chronic mitral regurgitation, and their investigation of only five patients with isolated mitral regurgitation preclude any definitive conclusions. Eckberg et al.28 found no increase in peak systolic tension in patients compared with controls. The majority of patients in their control group, taken from the study of Karliner et al.37 had either coronary artery or valvular disease, and the data determined may not represent true control values.

In contrast, Zile et al.21 using nonsimultaneous, noninvasive pressure and echocardiographic ventricular dimensional data, found that peak systolic stress was greater in patients with chronic mitral regurgitation compared with controls and that end-systolic stress was elevated in those with decompensated function. Cohn et al.6 demonstrated elevated peak systolic tension in patients with chronic mitral regurgitation. Wisenbaugh et al.20 demonstrated no difference in mean systolic or end-systolic stress between patients with chronic mitral regurgitation and controls. Their patients with mitral regurgitation had normal ejection fractions, and these results are therefore consonant with ours.

Using simultaneous left ventricular micromanometry and biplane cineangiography, we found that peak systolic pressure was similar in patients with mitral regurgitation compared with controls, but peak systolic stress was augmented. The increase in peak stress was a result of the change that occurs in the hemodynamic determinants of circumferential stress in chronic mitral regurgitation: left ventricular pressure and wall thickness were within the normal range but the ventricular minor axis was significantly greater7,20 (table 3).

Because of the difficulty of precisely defining end-systole in mitral regurgitation due to the continued ejection after aortic valve closure and the time varying nature of stress during ejection, we assessed afterload as both end-systolic and mean systolic stress. Examining circumferential stress at aortic valve closure, at the maximal pressure/volume ratio, or by a nonsimultaneous method, we found that end-systolic stress is elevated in patients with mitral regurgitation and a depressed ejection fraction but within the normal range in those with a preserved ejection performance.

There are several segments to the ejection period in mitral regurgitation. From aortic valve opening to aortic valve closure a period of normal ventricular pressure, the mean systolic stress was elevated in both groups of patients with mitral regurgitation. Relatively low stress levels during early and late ejection reduced the calculated mean stress in all patients with mitral regurgitation. For those with an intact ejection performance, mean ejection stress was essentially equivalent to that found in controls, whereas these levels remained elevated in patients with a depressed ejection fraction.

Myocardial stroke work is determined by stroke volume and the afterload against which the volume is ejected. In patients with mitral regurgitation, we determined stroke work both as a function of the total stroke volume index and mean ejection stress and as the sum of the work done before aortic valve opening, during the time that the aortic valve is open and from aortic valve closure to minimum volume. These two methods provided similar results for the total myocardial stroke work, indicating that mean stress is a valid representation of afterload for the entire ejection period.

The ejection of (the regurgitant) volume into the low-pressure left atrium before aortic valve opening acts to reduce afterload: ejection during this period occurs at low myocardial stress. Initial emptying allows an earlier decrease in ventricular dimensions and thickening of the ventricular wall than would occur in the normal hemodynamic state. During the subsequent ejection, afterload is reduced from the levels it might otherwise attain without this early leak. The proportionately small volume ejected after aortic valve clo-

<table>
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<td><strong>Left ventricular pressure, wall thickness, and minor axis at peak systolic stress</strong></td>
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<td></td>
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P = left ventricular pressure (mm Hg); H = left ventricular wall thickness (cm); MA = left ventricular minor axis (cm). *p < .001 vs controls.
The increased pressure and afterload have shifted the afterload-shortening relationship to a lower level, with the ejection fraction falling below normal. The regression equation defined by the control group and the 95% confidence interval are indicated. Group 2 data fall within this confidence interval, but the downward displacement of group 3 data indicates a depressed contractile state.

Afterload-shortening relationship. The afterload-shortening relationship has been used to examine myocardial contractility in the papillary muscle, in the isolated left ventricle, and in clinical investigation.* A similar degree of shortening (or ejection) at given levels of preload and afterload has implied an equivalent inotropic state. Defining afterload as either end-systolic stress at the maximal pressure/volume ratio or as mean ejection stress, the results of this study (figures 2 and 3) reveal a virtual overlap in the afterload-shortening relationship between controls and patients with mitral regurgitation and a normal ejection fraction. The increased preload in the group with mitral regurgitation and a preserved ejection performance, represented by elevated end-diastolic pressure and stress and greater end-diastolic muscle fiber stretch, should have shifted the afterload-shortening relationship upward and rightward. The absence of such a displacement suggests that these ventricles may have been operating with diminished contractility and were using preload reserve to merely maintain a normal level of performance.

In contrast, patients with mitral regurgitation and a reduced ejection fraction were downwardly displaced. The precise response of the normal ventricle to a sustained increase in afterload remains to be elucidated; however, group 3 patients clearly fell below the confidence interval defined by the control group. In the setting of normal muscle fiber stretch and elevated end-diastolic pressure and stress, the depression of ventricular function implies that myocardial contractility is reduced in these patients.

Using the mean Vcf, Eckberg et al. investigated myocardial function in patients with chronic mitral regurgitation. Compared with controls, patients with chronic mitral regurgitation exhibited reduced contractility. In contrast, Cohn et al. reported that mean Vcf was within the normal range for patients with primary mitral regurgitation. Our results are in agreement with those of Eckberg et al., but this derives largely from the pathophysiologic prolongation of the ejection period in mitral regurgitation. Comparison of mean Vcf from aortic valve opening to aortic valve closure revealed no difference between controls and patients with mitral regurgitation and an intact ejection fraction, whereas those patients with a reduced ejection fraction also demonstrated a diminished mean Vcf.

Recognition of mitral regurgitation as a stress overload state due to increased ventricular volume, in contrast to the stress overload in aortic stenosis caused by elevated ventricular pressure, allows for a unified concept of myocardial injury. In the environment of chronically elevated systolic afterload present in each of these valvular lesions, myocardial contractility may ultimately become depressed. Once ejection fraction declines, further dilation may occur and afterload is further increased. The larger afterload against which the impaired myocardium must then contract reduces shortening, while the elevated levels of stress might continue to have an adverse effect. This cause-and-effect spiral could be responsible for the myocardial depression that is observed.

Clinical implications. In the presence of normal left ventricular peak and mean systolic pressure, and despite the presence of the "low impedance" left atrium, afterload was not reduced in patients with mitral regurgitation.
gitation. This is because of the geometric change that occurs in chronic volume overload. The results of this study suggest the importance of lowering left ventricular pressure and volume in patients with chronic mitral regurgitation.

In mitral regurgitation, even the normally functioning ventricle (i.e., with an ejection fraction of 57% or greater) faces a significant sustained increase in afterload during the period that the aortic valve is open. Consideration of elevated stress levels in this setting and their possible deleterious effect, may influence decisions concerning the timing of surgery. Only by weighing the inherent risks of cardiac surgery and postoperative complications against the possibly damaging effects of continued stress overload will a more optimal clinical approach to mitral regurgitation be found.

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References

FIGURE 3. Afterload-shortening relationship for controls (closed squares, n = 9), group 2 (open squares, n = 14), and group 3 (crosses, n = 13). Afterload is represented by mean circumferential stress during the entire ejection period: in controls, from aortic valve opening to aortic valve closure; in mitral regurgitation, from end-diastole to minimum volume. The regression equation defined by the control group and the 95% confidence interval are indicated. Group 2 data fall within this confidence interval but group 3 data are displaced downward, indicating a depressed contractile state.

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disease before and after valve replacement. Circulation 69: 855, 1984
The relationship of afterload to ejection performance in chronic mitral regurgitation.

W J Corin, E S Monrad, T Murakami, H Nonogi, O M Hess and H P Krayenbuehl

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