# Left Ventricular Mechanical Load and Contractile Function in Patients with Chronic Mitral Regurgitation

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*Background and aim of the study:* **Left ventricular adaptation to chronic volume overload results in dramatic changes in ventricular geometry and hemodynamics. These changes are reflected in alterations in mechanical load and, eventually, contractile function.**

*Methods:* **The study included 17 patients undergoing clinically driven invasive evaluation for mitral regurgitation (MR). Simultaneous catheter-tip manometry and M-mode echocardiography allowed for derivation of meridional and circumferential wall stress at end-diastole, end-systole, peak systole, and the average over the systolic ejection period. Assessment of contractile function was performed by analysis of: the overall group relationship between baseline end-systolic stress (ESS) and end-systolic dimension (ESD); subject-specific analysis of the relationship between ESS and ESD derived from pharmacologic load alteration; and subject- specific analysis of the relationship between left ventricular minor axis shortening and ESS. The acquired data were compared to data from 10 control subjects who were undergoing invasive evaluation and were free from cardiovascular disease.**

*Results:* **Compared to controls, patients with chronic MR (mean regurgitant fraction 57%) were characterized by significantly increased angiographic end-diastolic and end-systolic volumes, lower cardiac indices, and similar left ventricular ejection fractions. Patients with chronic MR were also characterized by increased preload (end-diastolic stress) and afterload (mean systolic stress). ESS was not consistently increased in these patients, despite the increased chamber size. The severity of clinical symptoms was associated with the magnitude of alteration in afterload (mean systolic stress). Using different methodologies, a substantial prevalence of depressed contractile function was identified in those patients with preserved ejection fraction.**

*Conclusion:* **When compared to an age- and gender-matched controls, symptomatic patients with MR have similar left ventricular ejection performance in the setting of increased pre-load and after-load. Symptom severity was associated with increased afterload. The prevalence of contractile dysfunction in this setting was substantial.**

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The evaluation of left ventricular systolic function in patients with chronic mitral regurgitation (MR) is essential for clinical decision-making (1), as well as for the assessment of benefit following mitral valve intervention (2-8). Any evaluation of left ventricular systolic function in the setting of chronic MR must take into account alterations in mechanical load (9-11). Increased preload (3,4,12,13) and afterload (3,6-8,12) have been variably described. Inconsistencies among these classic studies derive from variability in the definition of terms, as well as patient selection criteria. The majority of these detailed invasive hemodynamic studies have been retrospective analyses of data obtained from symptomatic patients who were either destined for, or who had undergone, mitral valve surgery. The relationship between the severity of symptoms and the extent of load alteration in patients with chronic MR remains poorly defined. Furthermore, the assessment of left ventricular (contractile) function, in the setting of marked mechanical load alterations, presents numerous challenges (2-12,14,15).

The left ventricular mechanics of 17 patients with known MR and varying levels of symptom severity were analyzed. The patients had been referred for invasive hemodynamic and angiographic assessment of the

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severity of their MR. The data acquired were compared with data from an age- and gender-matched group of subjects found to be free from cardiovascular disease. While patients with chronic MR were found, in general, to be characterized by both increased preload and afterload compared to controls, there remain important inter-individual variations. This variation also contributes to the known difficulty in assessing left ventricular contractile function in chronic MR (2,4,12,13).

## Clinical material and methods

### Study population

The study population comprised 17 subjects referred for invasive hemodynamic and angiographic evaluation of the severity of mitral valve regurgitation secondary to myxomatous degeneration (Table I). Significant MR was identified on echocardiographic examination in all patients, and had been present at physical examination for at least three months. No patient had any history of change in clinical status within the previous three months. At the time of the present study, patients were generally referred for cardiac catheterization for hemodynamic and angiographic evaluation, and not solely as part of a preoperative strategy. Six patients were in NYHA class I, eight in class II, and three in class III. No patient had any history of frank congestive heart failure (CHF)

*Table I: Demographic and hemodynamic characteristics of the study population.*

| Group/ Patient no. | Age/ gender | HR | SBP | LVEDP | CI | LVEDVI | LVESVI | LVEF | LVRF |
|---|---|---|---|---|---|---|---|---|---|
| *Controls* | | | | | | | | | |
| 1 | 18/M | 72 | 125 | 8 | 2.7 | 63 | 25 | 0.60 | - |
| 2 | 29/F | 80 | 118 | 11 | 3.3 | 55 | 28 | 0.49 | - |
| 3 | 43/M | 75 | 135 | 12 | 3.1 | 68 | 19 | 0.72 | - |
| 4 | 52/M | 68 | 140 | 14 | 3.1 | 72 | 18 | 0.75 | - |
| 5 | 28/M | 70 | 120 | 10 | 2.8 | 70 | 22 | 0.69 | - |
| 6 | 35/F | 72 | 110 | 6 | 2.7 | 65 | 16 | 0.75 | - |
| 7 | 45/F | 65 | 95 | 10 | 3.0 | 68 | 20 | 0.71 | - |
| 8 | 48/M | 83 | 145 | 12 | 2.6 | 77 | 19 | 0.75 | - |
| 9 | 61/M | 80 | 140 | 8 | 2.9 | 63 | 28 | 0.56 | - |
| 10 | 50/F | 75 | 128 | 2 | 2.8 | 54 | 25 | 0.54 | - |
| Mean ± SD | 41 ± 13 | 74 ± 6 | 126 ± 15 | 9 ± 3 | 2.9 ± 0.2 | 65.5 ± 7.2 | 22.0 ± 4.3 | 0.66 ± 0.1 | - |
| *Mitral regurgitation* | | | | | | | | | |
| 11 | 28/F | 83 | 112 | 19 | 2.1 | 105 | 39 | 0.63 | 0.53 |
| 12 | 43/M | 88 | 120 | 18 | 2.3 | 122 | 38 | 0.69 | 0.55 |
| 13 | 45/M | 76 | 116 | 20 | 2.4 | 115 | 44 | 0.62 | 0.48 |
| 14 | 57/M | 70 | 98 | 12 | 2.4 | 104 | 62 | 0.40 | 0.44 |
| 15 | 55/F | 72 | 114 | 16 | 2.6 | 108 | 55 | 0.49 | 0.62 |
| 16 | 38/M | 80 | 133 | 17 | 2.2 | 105 | 56 | 0.47 | 0.36 |
| 17 | 43/F | 76 | 119 | 14 | 2.3 | 110 | 42 | 0.62 | 0.54 |
| 18 | 51/M | 90 | 122 | 10 | 2.6 | 136 | 49 | 0.64 | 0.69 |
| 19 | 62/F | 68 | 115 | 12 | 3.0 | 118 | 62 | 0.47 | 0.56 |
| 20 | 63/M | 72 | 105 | 17 | 2.0 | 121 | 35 | 0.71 | 0.61 |
| 21 | 75/M | 85 | 110 | 22 | 1.9 | 100 | 44 | 0.56 | 0.66 |
| 22 | 42/F | 83 | 108 | 18 | 2.6 | 118 | 52 | 0.56 | 0.68 |
| 23 | 32/F | 88 | 120 | 15 | 2.5 | 145 | 36 | 0.75 | 0.73 |
| 24 | 50/F | 90 | 120 | 16 | 2.3 | 107 | 54 | 0.50 | 0.60 |
| 25 | 55/F | 86 | 132 | 10 | 2.3 | 106 | 49 | 0.54 | 0.52 |
| 26 | 49/M | 100 | 115 | 14 | 2.1 | 112 | 52 | 0.54 | 0.53 |
| 27 | 31/M | 78 | 110 | 11 | 1.9 | 126 | 35 | 0.72 | 0.63 |
| Mean ± SD | 48 ± 12 | 81± 9 | 116 ± 9 | 15 ± 4 | 2.3 ± 0.3 | 115.2 ± 12.1 | 47.3 ± 9.0 | 0.58 ± 0.1 | 0.57 ± 0.1 |
| p-value* | 0.16 | 0.02 | 0.04 | 0.002 | <0.001 | <0.001 | <0.001 | 0.08 | - |

*Control versus MR.

CI: Cardiac index (L/min/$m^2$); HR: Heart rate (bpm); LVEDP: Left ventricular end-diastolic pressure (mmHg); LVEDVI: Left ventricular end-diastolic volume index (ml/$m^2$); LVEF: Left ventricular ejection fraction; LVESVI: Left ventricular end-systolic volume index (ml/$m^2$); LVRF: Left ventricular regurgitant fraction; MR: Mitral regurgitation; SBP: Peak left ventricular systolic pressure (mmHg).

requiring hospitalization, and all patients were in sinus rhythm. In order to ensure clinical stability, patients were required to have been on a stable medical regimen for at least one week prior to the invasive evaluation, at which time none was receiving vasodilator therapy.

## Control population

Ten subjects, who were age- and gender-matched to the study population, were selected from a larger population of patients evaluated at the authors' laboratory and found to have no detectable cardiovascular disease on hemodynamic and angiographic evaluation (Table I). These patients were generally referred for evaluation of chest pain syndromes or the clinical suspicion of myocardial, congenital, or valvular heart disease. None of the control subjects was receiving cardioactive medication at the time of evaluation.

## Study protocol

Following the acquisition of baseline hemodynamic data, but prior to angiography, all subjects underwent combined hemodynamic and M-mode echocardiographic evaluation, as described previously (16-18). In brief, a catheter-tip manometer (Millar Instruments, Inc., Houston, TX, USA) was advanced to the left ventricle and balanced against an atmospheric reference. Simultaneous M-mode ultrasound recordings were obtained, with careful attention being paid to consistent image acquisition, allowing for the quantitative assessment of left ventricular function. After having acquired the baseline hemodynamic and dimensional data, sublingual nitroglycerine or intravenous phenylephrine was administered in order to achieve a minimum change in aortic systolic blood pressure of 10 mmHg. After stabilization of the newly achieved systolic pressure for at least 3 min, the left ventricular pressure and echocardiographic information were reacquired. At this point, the investigative portion of the procedure was terminated and the remainder of the diagnostic catheterization procedure completed.

Coronary angiography was notable for the absence of obstructive disease in all subjects (this was a criterion for study inclusion). No complications were encountered in any subject.

All subjects provided their written consent for the investigative portion of the procedure, in accordance with the University of Pennsylvania Committee on Studies Involving Human Beings.

## Measurements obtained, and data analysis

High-fidelity left ventricular pressure and dimensional data were digitized off-line at 10- ms intervals. Left ventricular meridional wall stress was derived as described previously (18,19), and reported at: end-diastole (peak of R wave of simultaneously acquired ECG); peak systole (maximum value over the ejection period); end-systole (minimum left ventricular dimension); and integrated over the ejection period (mean systolic stress). Results were reported as dyne/cm$^2$ (1 mmHg = 1,332 dyne/cm$^2$). Corresponding circumferential wall stresses were derived, as reported previously (20), by measuring the left ventricular long axis obtained from the single-plane, right anterior oblique left ventriculogram.

Assessment of left ventricular contractile function was obtained from: (i) the mean slope and intercept of the baseline end-systolic stress (ESS)/end-systolic diameter (ESD) relationship for each group; (ii) the slopes and intercepts of the ESS/ESD relationship derived from the pre- and post-nitroglycerine or phenylephrine interventions (Fig. 1) in each subject (18,19,21). Slopes and intercepts for both meridional and circumferential ESS/ESD relationships were calculated with and without adjustment for baseline ventricular size; and (iii) the relationship between left ventricular minor axis fractional shortening (% ΔD) and circumferential ESS (22).

## Statistical analysis

All results were summarized as mean ± SD. All reported stress data represented the mean of a minimum of five consecutive cycles. Unpaired $t$-tests were used for comparisons between the control and MR groups. A single-factor ANOVA was used to compare hemodynamic measures among the NYHA categories. Least-squares linear regression was used to model both inter-group and intra-individual ESS versus ESD relationships. All analyses were performed using

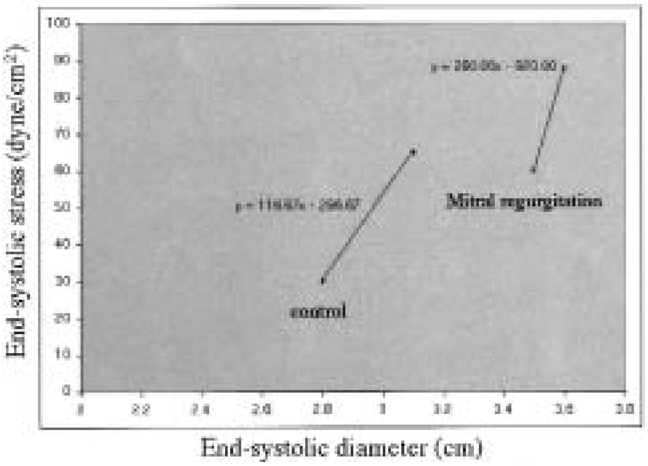

*Figure 1: Relationship between end-systolic stress and end-systolic dimension for a normal control subject and a patient with mitral regurgitation, under basal conditions (higher points) and after pharmacologic load alteration with nitroglycerine (lower points).*

Statview (Version 5.0; SAS Institutes, Inc., Cary, NC, USA). Exact p-values were reported throughout; a p-value <0.05 was considered to be statistically significant.

## Results

### Baseline hemodynamics and left ventricular pump function

Statistically significant differences were identified in all fundamental hemodynamic and ventriculographic measurements between groups (see Table I). Symptomatic patients with MR (mean regurgitant fraction 0.57 ± 0.1) were characterized by higher heart rates, lower left ventricular systolic pressures, higher left ventricular end-diastolic pressures, lower cardiac indexes, larger ventricular volumes, and a numerically - but not statistically significant - lower left ventricular ejection fraction (LVEF). The ratio of the angiographically determined left ventricular major and minor axes at end-diastole was significantly different between groups (control 1.85 ± 0.2; mitral regurgitation 1.61 ± 0.1; p = 0.0003).

### Baseline left ventricular mechanics

Important (statistically significant) differences in mechanical load were identified between groups (see Table II). In agreement with the increased ventriculographic volumes at end- diastole, M-mode end-diastolic dimensions were increased in patients with MR, as was end-diastolic stress (EDS) (both meridional and circumferential), or preload. Despite a lower left ventricular peak systolic pressure in patients with MR, peak systolic stress (meridional and circumferential) was significantly elevated. Mean systolic stress, a measure of afterload, was increased in patients with MR. However, while meridional ESS was marginally increased in MR patients, circumferential ESS was similar to control values. ESS may be viewed as the afterload limiting further shortening or ejection.

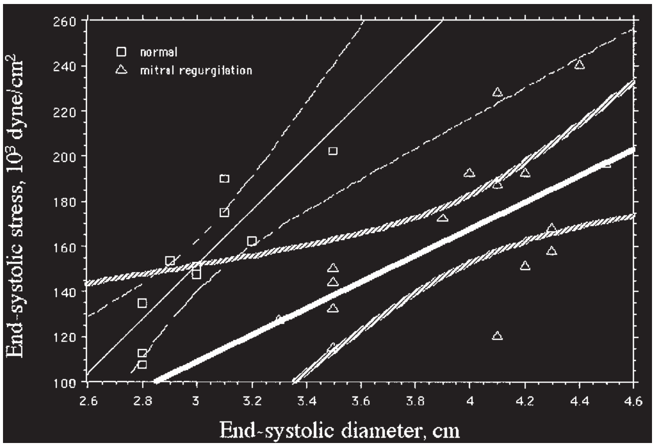

*Figure 2: Scattergram of resting end-systolic circumferential stress versus end-systolic diameter for control subjects and patients with mitral regurgitation. Data shown are the least-squares linear regression lines and their 95% confidence intervals. The overall relationship in controls (thin lines) was highly significant, whereas that in mitral regurgitation patients (heavy lines) showed more scatter and was displaced downwards.*

### Left ventricular contractile performance

The overall group relationship between ESS and ESD at baseline was linear in both groups, although there was a wider scatter in the MR group (Fig. 2). The slope of the baseline ESS/ESD relationship for MR patients was less than that for controls (p <0.01). When the slopes of the unadjusted individual ESS/ESD relationships (derived from the pharmacologic manipulation) were compared, there were no significant differences between groups (Fig. 3A). Following adjustment for baseline ventricular size (multiplying by end-diastolic volume index), again

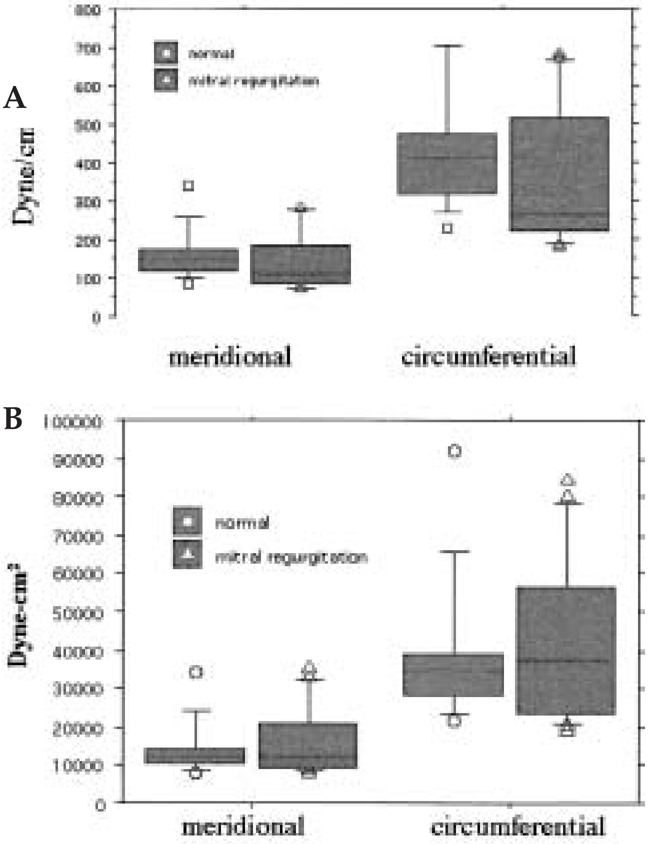

*Figure 3: Distribution (box-and-whisker plots) of slopes of individual end-systolic stress/end-systolic diameter plots derived from pharmacologic load alteration. There were no significant differences between controls and MR patients in unadjusted (A) or adjusted (B) meridional or circumferential stress-diameter relationships. See text for details.*

there were no statistically significant differences in slopes between the two groups (Fig. 3B).

There were significant differences in the mean X-intercept for both meridional (controls 2.63 ± 0.23 cm; MR 3.39 ± 0.42 cm; $p < 0.0001$) and circumferential (controls 2.70 ± 0.25 cm; MR 3.48 ± 0.44 cm; $p < 0.0001$) ESS/ESD relationships. Although there was overlap among the data points defining the inverse relationship between % ΔD and circumferential stress for each group (Fig. 4), 10 of the 17 data points for the MR patients fell below the lower 95% confidence bound of the control relationship, which suggested depressed contractile function.

There were no differences in any of the above measures of contractile performance in the MR patients when the latter were stratified by baseline ESD ≥4.0 cm or <4.0 cm.

### Relationship between NYHA class and left ventricular mechanics

There was a weak association between NYHA class and LVEF ($p = 0.06$). Although there was no association between EDS and NYHA class, significant associations were observed for peak ($p = 0.006$) and mean ($p = 0.01$) systolic stress and NYHA class. There was no significant association between ESS and NYHA class, nor was there an association between the slope of either the meridional or circumferential ESS/ESD relationship and NYHA class.

*Table II: Baseline left ventricular mechanics.*

| Group/ Pt no. | EDD | ESD | $\text{EDS}_m$ | $\text{EDS}_c$ | $\text{PSS}_m$ | $\text{PSS}_c$ | $\text{ESS}_m$ | $\text{ESS}_c$ | $\text{MSS}_m$ | $\text{MSS}_c$ |
|---|---|---|---|---|---|---|---|---|---|---|
| *Controls* | | | | | | | | | | |
| 1 | 5.4 | 3.1 | 25 | 62 | 114 | 285 | 65 | 175 | 85 | 212 |
| 2 | 4.8 | 3.1 | 17 | 42 | 96 | 240 | 70 | 190 | 78 | 195 |
| 3 | 5.5 | 2.8 | 20 | 50 | 135 | 337 | 50 | 135 | 93 | 232 |
| 4 | 5.3 | 2.8 | 28 | 70 | 120 | 300 | 42 | 113 | 70 | 175 |
| 5 | 5.7 | 2.9 | 28 | 72 | 109 | 272 | 57 | 154 | 62 | 155 |
| 6 | 4.8 | 2.8 | 21 | 52 | 97 | 242 | 40 | 108 | 58 | 145 |
| 7 | 5.6 | 3.0 | 33 | 82 | 130 | 325 | 55 | 148 | 95 | 237 |
| 8 | 5.5 | 3.0 | 40 | 100 | 126 | 315 | 56 | 151 | 72 | 180 |
| 9 | 5.6 | 3.5 | 22 | 55 | 144 | 360 | 75 | 202 | 98 | 245 |
| 10 | 5.4 | 3.2 | 15 | 38 | 120 | 300 | 60 | 162 | 62 | 155 |
| Mean ± SD | 5.36 ± 0.32 | 3.02 ± 0.22 | 25 ± 8 | 62 ± 19 | 119 ± 6 | 298 ± 9 | 57 ± 11 | 154 ± 30 | 77 ± 15 | 193 ± 37 |
| *Mitral regurgitation* | | | | | | | | | | |
| 11 | 6.1 | 3.5 | 50 | 110 | 155 | 356 | 60 | 144 | 93 | 204 |
| 12 | 6.1 | 3.5 | 62 | 136 | 184 | 423 | 62 | 150 | 123 | 270 |
| 13 | 6.05 | 4.0 | 55 | 121 | 210 | 483 | 80 | 192 | 126 | 277 |
| 14 | 6.0 | 4.4 | 43 | 95 | 225 | 517 | 100 | 240 | 157 | 345 |
| 15 | 6.05 | 4.3 | 55 | 121 | 155 | 356 | 70 | 168 | 93 | 204 |
| 16 | 5.9 | 4.3 | 52 | 114 | 192 | 441 | 66 | 158 | 128 | 281 |
| 17 | 6.1 | 4.1 | 45 | 99 | 215 | 494 | 78 | 187 | 108 | 237 |
| 18 | 6.3 | 4.3 | 75 | 165 | 154 | 354 | 66 | 158 | 108 | 238 |
| 19 | 6.1 | 4.5 | 52 | 114 | 195 | 448 | 82 | 196 | 117 | 257 |
| 20 | 6.2 | 3.9 | 55 | 121 | 154 | 354 | 72 | 172 | 103 | 226 |
| 21 | 5.8 | 4.1 | 40 | 88 | 186 | 427 | 92 | 228 | 111 | 244 |
| 22 | 6.1 | 3.3 | 57 | 125 | 127 | 430 | 53 | 127 | 89 | 195 |
| 23 | 6.4 | 3.5 | 44 | 97 | 139 | 319 | 55 | 132 | 91 | 200 |
| 24 | 6.1 | 3.5 | 56 | 123 | 144 | 331 | 48 | 115 | 94 | 207 |
| 25 | 6.1 | 4.2 | 51 | 112 | 166 | 381 | 63 | 151 | 103 | 226 |
| 26 | 5.9 | 4.1 | 51 | 114 | 120 | 276 | 50 | 120 | 84 | 184 |
| 27 | 6.2 | 4.2 | 75 | 165 | 128 | 279 | 81 | 192 | 89 | 188 |
| Mean ± SD | 6.09 ± 0.14 | 3.98 ± 0.38 | 54 ± 10 | 119 ± 21 | 167 ± 33 | 392 ± 73 | 69 ± 15 | 166 ± 36 | 107 ± 19 | 234 ± 42 |
| p-value | <0.001 | <0.001 | <0.001 | <0.001 | 0.002 | 0.009 | 0.06 | 0.36 | 0.003 | 0.017 |

EDD: M-mode left ventricular end-diastolic dimension (cm); EDS: End-diastolic stress ($\times 10^3$ dyne/cm$^2$); ESD: M-mode left ventricular end-systolic dimension (cm); ESS: End-systolic stress ($\times 10^3$ dyne/cm$^2$); MSS: Mean systolic stress ($\times 10^3$ dyne/cm$^2$); PSS: Peak systolic stress ($\times 10^3$ dyne/cm$^2$).
Subscripts: c, circumferential; m, meridional.

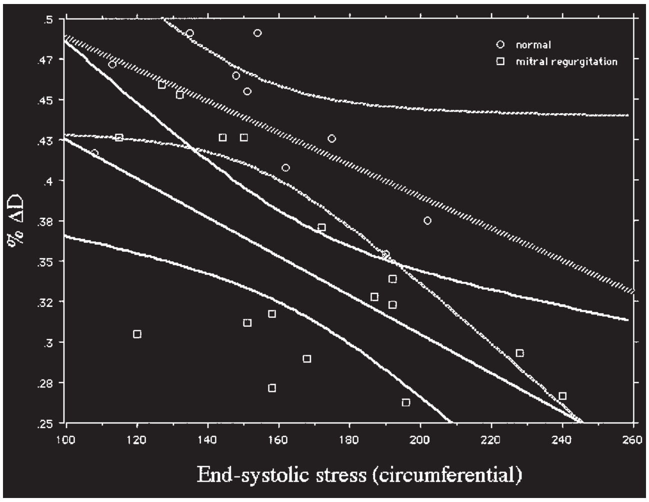

*Figure 4: Inverse relationship between resting minor axis fractional shortening (% ΔD) and circumferential end-systolic (and mean systolic) stress for control subjects (○) and MR patients (□). Data shown are least-squares linear regression lines with 95% confidence intervals (thin lines) for controls (thick checkered line) and MR patients (thick solid line). See text for details.*

## Discussion

Among the present patients with MR, significant increases were found in virtually all measures of left ventricular mechanical load. Despite similarities in afterload at end-systole, the afterload, when averaged over all of systole, was uniformly elevated. The assessment of left ventricular contractile function in a given patient with MR, independent of these changes in mechanical load, requires careful analysis of the relationship between ESS and ESD, or between ESS and minor axis fractional shortening.

### Mechanical load and symptoms

Currently, the decision to refer patients for mitral valve intervention in the setting of chronic MR is based upon symptom status, as well as left ventricular size and systolic function. In the absence of overt CHF, patient symptomatology is highly variable in its expression and subject to overestimation by the examiner, and underestimation by the patient. The quantitative assessment of left ventricular function, however, should be less subject to observer and patient bias.

Previous invasive studies of left ventricular mechanical function in symptomatic patients with MR have provided conflicting data with regards to the degree of alteration in preload (3,4,12,13) and afterload (3,6-8,12). This is especially true for 'afterload', which represents the totality of the mechanical load opposing ventricular emptying. Whilst the load at end-systole is an important parameter, it is the integral of wall stress throughout systole that best represents afterload (23) and is correlated with myocardial oxygen consumption (17,23). The latter correlation may also explain the significant association between symptom severity and afterload observed in the present study.

Invasive studies of left ventricular mechanical function in asymptomatic patients with varying degrees of MR are limited. Non-invasive studies of systolic (including peak, mean and end-systolic) wall stress in asymptomatic individuals with MR are critically needed to further examine the relationship between load alteration and the development of symptoms. Given the relationship between symptom severity and post-operative outcome (24,25), the association between increased afterload and symptom severity noted in the present study may have important clinical implications.

### Mechanical load and contractile function

The study conclusions regarding the variable prevalence of contractile dysfunction in patients with MR are, in general, in agreement with those of previous invasive studies. Specifically, patients with MR and elevated preload and afterload, despite a 'preserved' LVEF, may demonstrate an abnormal contractile function (at least as assessed by present methods). Whether such load alterations truly confound the assessment of inherent contractile function, or are universally present, cannot be answered in the present study. Longitudinal studies conducted in both symptomatic and asymptomatic patients are the only reliable way to answer these challenging questions.

The relationship between ventricular pressure and volume (26-28), or stress and dimension (29), at end-systole provides a clinically useful means of assessing contractile function. While this relationship is exquisitely sensitive to acute manipulation of contractility, its comparison among individuals in the resting state is more problematic (14,27,30). In the present study, the (pooled) group relationship between ESS and ESD in patients with MR exhibited a diminished slope compared to age- and gender-matched controls, suggesting a depressed contractile function (28). The slope of the ESS/ESD relationship, however, is also sensitive to ventricular enlargement (27). Thus, conclusions regarding alterations in contractile state assessed solely with this methodology are likely confounded by alterations in heart volume. When individual ESS/ESD plots, derived from pharmacologic load manipulations, were examined, there was no difference in the unadjusted or adjusted (for ventricular size) slopes of these relationships using either meridional, or the more appropriate circumferential stress, at end-systole. Thus, conclusions based on single determination group mean data must be guarded, given these patient-specific observations from multiple data points.

The significance of the numerically higher x-intercept of this relationship in patients with chronic severe MR remains controversial, but is suggestive of depressed contractile function (22,29). Consistent with the latter observation is the location of many values for left ventricular minor axis fractional shortening in MR patients below the lower 95% confidence bound of the control relationship between fractional shortening and circumferential (mean and end-) systolic stress.

In the present study, while the relationship between ESS and ESD was highly linear in the control group, the variability in the MR group was striking. The dependence of ESD on both the load at end-systole, as well as the underlying contractile state, precludes conclusions from being drawn regarding the latter from ESD alone. This is particularly so in the setting of an increase in ESS, which was variably encountered in the present study. To this point, there were no differences in any measure of contractile function in patients with ESD ≥4.0 cm or <4.0 cm. The choice of 4.0 cm as a stratification variable was based on current recommendations for intervention in patients with 'normal' left ventricular function (1).

Given current trends to intervene earlier during the course of MR, the relationship between symptoms and left ventricular mechanical function, and the accurate assessment of left ventricular contractile function, remain important areas of inquiry. While theoretical limitations remain regarding the estimation of meridional and circumferential stress (31), the assessment of orthogonal stresses in the present study yielded internally consistent findings. The absence of obstructive coronary arterial disease and regional dyssynergy allow for additional assumptions regarding ventricular shape and uniformity of wall thickening and motion. Most importantly, while the most accurate and truly load-independent measure of inherent myocardial contractile function has yet to be reported, the methods used herein have been extensively applied by numerous other groups in different clinical settings. The present approach, using three parallel testing methods to estimate contractile function, is perhaps the most comprehensive of any investigation in patients with chronic MR.

### Study limitations

The main limitation to the present study was the small sample size, which provided only modest confidence in the observations, although this was enhanced by the inclusion of a control group. The use of two physiologically distinct points to define contractile state is subject to measurement error, particularly with the small dimensional changes achieved. However, care was to taken to establish a hemodynamic steady state, thereby mitigating one important source of variability. The inclusion of a third datum point would have posed additional logistical difficulties and uncertainties regarding a true steady state.

The small sample size also tended to limit conclusions regarding the lack of any association between measures of mechanical load and symptoms (beta error). However, the fact that it was possible to identify a physiologically sound association between mean systolic stress and symptoms lent additional credence to these observations. While patients were studied prior to any clinical decision regarding mitral valve intervention, the absence of such selection bias provided greater applicability of these findings to a more general setting of patient evaluation. Finally, although the invasive nature of the current study precludes widespread application in all patients with chronic MR, it did provide a foundation for the non-invasive assessment of contractile function in chronic MR.

*In conclusion*, patients with chronic MR function under a significant mechanical burden. Elevations in both preload and afterload are necessary features to the development of clinical symptoms. However, the presence of mechanical load alterations at rest does not necessarily indicate changes to the contractile state; indeed, the latter must be carefully assessed from the relationship between load and systolic function.

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