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Excessive Vasoconstriction in Rheumatic Mitral Stenosis With Modestly Reduced Ejection Fraction

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Objectives. **The primary hypothesis examined was that underfilling due to inflow obstruction accounts for modestly depressed ejection performance in mitral stenosis. Having found little evidence to support this hypothesis, we sought to determine other factors that might differentiate patients with different levels of ejection performance.**

Methods. **Ventricular load and performance were compared in two groups of patients before and immediately after successful balloon valvuloplasty that was not complicated by mitral regurgitation: those in whom prevalvuloplasty ejection fraction was ≥0.55 (group I, n = 10) and those in whom it was <0.55 (group II, n = 11).**

Results. **Before valvuloplasty, mitral valve area was less in group II (0.65 cm^2) than in group I (0.84 cm^2, p = 0.02), but end-diastolic pressure (12 vs. 12 mm Hg in group I), end-diastolic wall stress (46 vs. 44 kdynes/cm^2 in group I) and end-diastolic volume (152 vs. 150 ml in group I) were not less in group II, nor were these variables significantly reduced compared with those of a normal control group. In group II, end-systolic volume was larger (77 vs. 55 ml in group I, p = 0.001) and cardiac output was less (3.1 vs. 3.6 liters/min in group I, p = 0.03), possibly owing to higher systemic vascular resistance (2,438 vs. 1,921 dynes·s·cm^{-5} in group I, p = 0.05) and end-systolic wall stress (273 vs. 226 kdynes/cm^2 in group I, p = 0.06), although mean arterial pressure in the two groups was similar (91 vs. 84 mm Hg in group I, p = 0.22). Group II patients also had higher values for pulmonary vascular resistance (712 vs. 269 dynes·s·cm^{-5} in group I, p = 0.03) and mean pulmonary artery pressure (47 vs. 29 mm Hg in group I, p = 0.02) despite similar values for mean left atrial pressure (20 vs. 18 mm Hg in group I, p = 0.35). After valvuloplasty, mitral valve area increased by 2.5- and 3-fold, respectively, in group I (to 2.1 cm^2) and group II (to 2.0 cm^2). Modest increases in left ventricular end-diastolic pressure, end-diastolic stress and end-diastolic volume (+9%) after valvuloplasty were statistically significant only for group II. End-systolic wall stress did not decline in either group II (281 kdynes/cm^2) or group I (230 kdynes/cm^2), and ejection fraction failed to increase significantly (0.49 to 0.51 for group II and 0.62 to 0.61 for group I) after valvuloplasty. Contractile performance estimated with a preload-corrected ejection fraction–afterload relation was within or near normal limits in all 19 patients in whom it was assessed.**

Conclusions. **Excessive vasoconstriction may account for the higher afterload, lower ejection performance and lower cardiac output observed in a subset of patients with mitral stenosis because contractile dysfunction could not be detected and left ventricular filling—which was not subnormal despite severe inflow obstruction—improved only modestly after valvuloplasty.**

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The hemodynamic results of balloon mitral valvuloplasty have been well documented (1–7), but there are few data regarding the effects of mitral valvuloplasty on left ventricular systolic or diastolic performance. Such data might be relevant to the question of whether subnormal filling or abnormal myocardium accounts for modestly depressed ventricular performance in rheumatic mitral stenosis, a question that has been debated for years. A variety of methods have been used to examine preoperative left ventricular performance in mitral stenosis (8–17), the most recent of which have indicated mild, if any, contractile dysfunction (13,15). However, present methods of assessing contractile function are load dependent or have other limitations (18).

Accordingly, we tested the hypothesis that subnormal filling accounts for depressed ejection performance in mitral stenosis by comparing ventricular load and performance immediately before and after relief of inflow obstruction by mitral valvuloplasty not complicated by mitral regurgitation. Having found little evidence to support this hypothesis, we sought to determine other factors that might differentiate patients with different levels of ejection performance.

Methods

Patients. The study group consisted of 21 patients with rheumatic mitral stenosis and normal sinus rhythm referred for percutaneous balloon mitral valvuloplasty between

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October 1988 and January 1991. These 21 patients were selected from >90 patients who underwent balloon valvuloplasty during this time on the basis of 1) availability of a high quality left ventricular cineangiogram with simultaneously measured high fidelity left ventricular pressures in which there were at least two consecutive sinus beats; 2) an increase in valve area >0.5 cm^2 after valvuloplasty; 3) no significant atrial shunts (≥1.5:1) and 4) ≤1+ mitral regurgitation before valvuloplasty and <2+ mitral regurgitation after valvuloplasty. Mitral regurgitation in our laboratory is graded as 1+ if the left atrial silhouette is never fully visualized with regurgitant contrast medium and 2+ for faint visualization. Intermediate grades are sometimes used (for example, 1.5+ when there is faint opacification of the entire atrium during systole which cleared during diastole). All patients gave informed consent for the procedure. Patients were arbitrarily assigned to group I (ejection fraction ≥0.55) or group II (ejection fraction <0.55). The mean age of the patients was 29 ± 7 years (range 17 to 38) in group I and 26 ± 9 (range 14 to 40) in group II (p = NS). The mean body surface area was 1.63 ± 0.17 m^2 in group I and 1.50 ± 0.15 m^2 in group II (p = NS). The 16 female patients were equally divided between the two groups.

Cardiac catheterization. Patients were premedicated with parenteral meperidine or pethidine and a phenothiazine. Each patient was also premedicated with oral atenolol, 100 mg, to minimize reflex changes in heart rate and contractility (19). All were on long-term treatment with furosemide, usually 40 or 80 mg twice daily. The technique of cardiac catheterization was as previously described (20). Micromanometer catheters were used to record left ventricular and left atrial pressures. Thermodilution cardiac output determinations were performed simultaneously with pressure measurements during quiet breathing or held midinspiration. After baseline measurements, biplane (Siemens) cine left ventriculography using 40 ml of sodium meglumine ioxaglate (320 mg of iodine) was performed at 50 or 60 frames/s, while left ventricular (micromanometer) and right atrial pressure and cine frame marks were recorded simultaneously on paper. We used the low ionic contrast agent to minimize possible effects on ventricular performance, which was remeasured after valvuloplasty—approximately 1 h after the first injection.

Valvuloplasty. Balloon valvuloplasty was accomplished as described (20) in each patient using two balloons (Mansfield) ranging from 18 to 25 mm Hg each, except in one patient in whom a single 25-mm balloon was used. After valvuloplasty, micromanometer pressure and cardiac output measurements were again made, followed by repeat cine left ventriculography. A grid was filmed biplane to correct for magnification, and neither the patient nor imaging equipment was moved between the two left ventricular cineangiograms.

Data analysis. Left ventricular and left atrial pressures were digitized at 100 Hz with use of a hand-held cursor of a digitizer interfaced to a microcomputer. Three beats were separately analyzed and results averaged. The mean mitral valve gradient (MVG) was used to determine mitral valve area (MVA) by the Gorlin equation (21): MVA = diastolic flow/(38 × $\sqrt{\text{MVG}}$). The presence of an atrial shunt of 1.5:1 or greater was considered the minimum detectable by oximetry (22) (using the superior and inferior venae cavae saturations for the mixed venous) and was a criterion for exclusion. End-diastolic and end-systolic volumes (area-length method) were obtained from the maximum and minimum of the frame by frame volume-time plot, which was "smoothed" with a 9th- or 10th-order polynomial equation. To corroborate the angiographic assessment of mitral regurgitation, we computed regurgitant fraction from the stroke volume that was measured by thermodilution and that subsequently measured by angiography. This estimated regurgitant fraction was higher than expected before valvuloplasty (0.32 ± 0.21), possibly owing to changes in heart rate between measurements or inaccuracies in either or both methods of measuring stroke volume, but did not increase after valvuloplasty (0.26 ± 0.16).

Contractility was estimated by a previously described angiographic method that makes a correction for preload and afterload (23). Briefly, circumferential stress was computed from frame by frame volumes, pressures and the end-diastolic angiographic wall thickness. Wall thickness values measured at the midanterior wall (6.7 ± 2.4 mm) and at the posterior wall (5.9 ± 1.1 mm) were similar. Anterior wall thickness was chosen to be consistent with previous methods (23), except in one patient with severe right ventricular hypertrophy in whom apparent anterior wall thickness exceeded posterior wall thickness by >2 mm. Thickness values for systolic frames were computed with the method of Hugenholtz (24) by assuming a constant mass. The end-systolic volume and the diastolic volume at a common filling stress of 50 kdynes/cm^2 were used to compute preload-corrected ejection fraction. When vertical shifts in the entire diastolic stress-volume curve occurred after valvuloplasty, the lower of the two curves was used to compute the preload-corrected diastolic volume. A shift of >3 mm Hg occurred in nine patients and was >5 mm Hg in three of these. The normal relation between preload-corrected ejection fraction and afterload was obtained in 24 normal subjects who underwent cardiac catheterization for evaluation of an atypical chest pain syndrome; 23 of these constituted a control group in a previous study (23). Nine of these 24 normal subjects were being treated with beta-adrenergic blocking agents. All were studied by the same angiographer, who used the same catheterization technique and same method of data analysis but in a different laboratory (23) that had similar angiographic equipment (Siemens) as the present laboratory. Load was altered with intravenous ergonovine or sublingual nitroglycerin as described (23).

To assess the possibility that an improvement in regional function might not be reflected by assessment of global performance, we measured chordal shortening perpendicular to two points along the major axis: at the bisection of the long axis, that is, the equatorial minor axis, and also at a

point one third the distance from the aortic plane to the apex, that is, at the base of the ventricle (10).

Left ventricular end-diastolic operative compliance normalized for end-diastolic volume (dV/VdP) was measured by using a two-constant exponential equation fit to the frame by frame angiographic diastolic pressure-volume data (25). To assess the possibility that alterations in right ventricular pressure might have produced vertical shifts in the left ventricular diastolic pressure-volume curve, we measured diastolic pressure at the average mid-diastolic volume common to both curves (before and after valvuloplasty), and no significant difference was found between the mean values (mean 6 ± 5 vs. 5 ± 5 mm Hg), nor was there any relation between the decline in the pulmonary artery pressure and the presence or magnitude of such a shift (Fig. 1). Also, mean right atrial pressure—and therefore, presumably, pericardial pressure—was not elevated and did not change significantly with valvuloplasty (Table 1).

Statistics. The influence of valvuloplasty on the hemodynamic variables was evaluated with the paired *t* test. Comparisons between patients with mitral stenosis and control subjects were made with analysis of variance. When two comparisons were performed (pre- vs. postvalvuloplasty values and prevalvuloplasty value vs. control value), a Bonferroni correction was used and $p < 0.025$ was required for statistical significance. The Tukey test was used for post hoc comparisons for the two groups with mitral stenosis versus the control group. Analysis of covariance was used to assess the effects of valvuloplasty on chordal shortening at the base versus that at the equatorial minor axis. Data are reported as mean value ± SD. A commercially available statistics program was used (26).

Results

Preload. Before valvuloplasty, mitral valve area was slightly less in group II (ejection fraction <0.55) than in group I (ejection fraction ≥0.55) (Table 1), but the lower ejection fraction for group II patients could not be explained by lower values for end-diastolic pressure, end-diastolic stress or end-diastolic volume than were present in group I. Nor were these variables significantly reduced compared with those of the control group (Table 2). End-diastolic chamber compliance measured as dV/VdP was modestly (p = NS) depressed compared with that of the control group and did not change significantly after valvuloplasty (Table 2). After valvuloplasty, mitral valve area increased 2.5-fold in group I and 3-fold in group II, but end-diastolic pressure (Table 1), end-diastolic volume and end-diastolic stress (Table 2) increased modestly only in group II.

Afterload. Before valvuloplasty, end-systolic volume was larger and cardiac output was lower in group II than in group I, possibly owing to higher values of both left ventricular end-systolic stress (Table 2) and systemic vascular resistance (Table 1). Pulmonary vascular resistance and mean pulmonary artery pressure were also greater in group II versus group I despite similar values for mean left atrial pressure (Table 1) before valvuloplasty. End-systolic stress did not decline in either group after valvuloplasty. Although 14% (group I) and 12% (group II) decreases in systemic resistance were computed after valvuloplasty, these values probably underestimated true resistance due to undetected shunt flow, which would spuriously increase the thermodilution values for cardiac output.

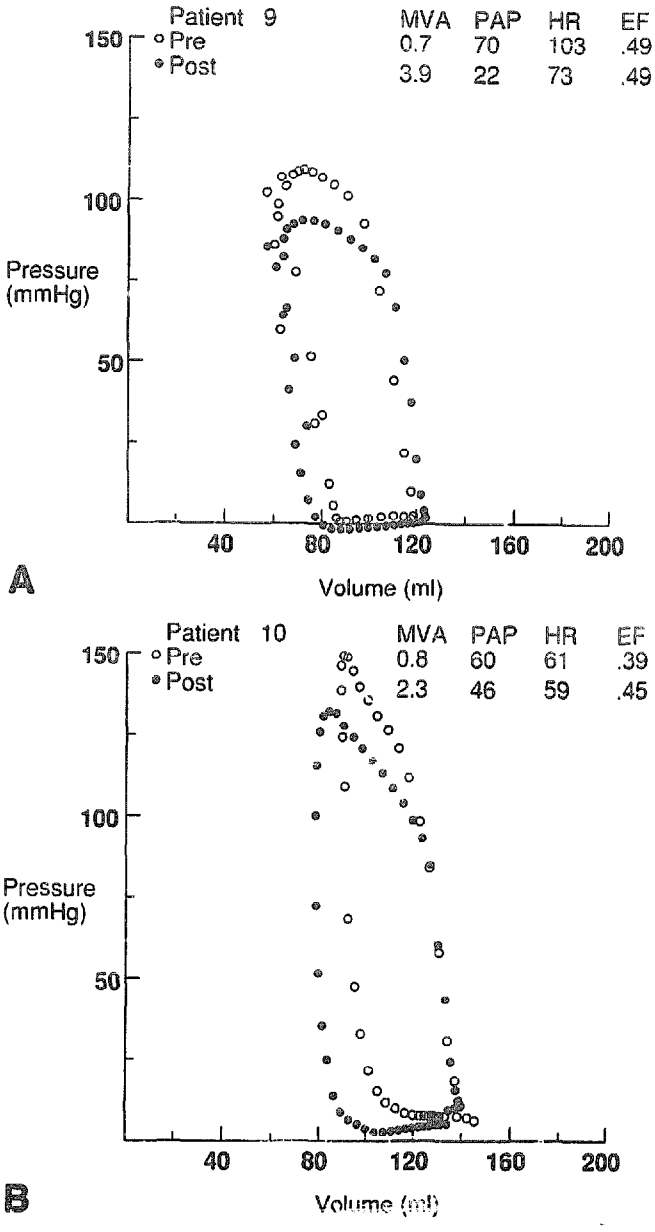


Figure 1. Micromanometer pressure (ordinate) plotted frame by frame against smoothed angiographic left ventricular volume before (Pre) and after (Post) balloon mitral valvuloplasty in Patients 9 (A) and 10 (B) with mitral stenosis. Each circle represents one frame. Despite an increase in mitral valve area (MVA) of three- to fourfold and a decrease in heart rate (HR) in both patients, end-diastolic volume did not substantially increase and ejection fraction (EF) remained <0.55. There were only minor vertical shifts in the diastolic portion of the pressure-volume curve despite dramatic reductions in mean pulmonary artery pressure (PAP).

Table 1. Hemodynamic Results of Balloon Mitral Valvuloplasty

	Pressures (mm Hg)						HR	MVA	Cardiac Output	Vascular Resistance (dynes·s·cm^{-5})	
	LVEDP	MAP	RAP	LAP	MVG	PAP	(beats/min)	(cm^2)	(liters/min)	Systemic	Pulmonary
Group I (n = 10)											
Pre	12 ± 7	84 ± 10	4 ± 3	18 ± 7	11 ± 4	29 ± 14	62 ± 10	0.84 ± 0.23	3.6 ± 0.5	1,921 ± 433	269 ± 279
Post	14 ± 6	85 ± 10	4 ± 3	10 ± 7	4 ± 1	25 ± 12	64 ± 6	2.09 ± 0.73	4.4 ± 0.7	1,659 ± 348	289 ± 163
Group II (n = 11)											
Pre	12 ± 7	91 ± 15	7 ± 4	20 ± 5	13 ± 5	47 ± 17	66 ± 20	0.65 ± 0.11	3.1 ± 0.5	2,438 ± 625	712 ± 455
Post	17 ± 6	90 ± 11	5 ± 3	12 ± 5	3 ± 1	31 ± 10	61 ± 9	1.97 ± 0.85	3.5 ± 0.6	2,153 ± 544	486 ± 201
p values											
Group I (pre vs. post)	NS	NS	NS	0.008	<0.001	0.01	NS	<0.001	0.001	0.04	NS
Group II (pre vs. post)	0.025	NS	NS	0.002	<0.001	0.01	NS	<0.001	0.02	0.001	0.04
Group I vs. II (pre)	NS	NS	NS	NS	NS	0.02	NS	0.02	0.03	0.05	0.06

Comparisons of values before and after valvuloplasty for each group were made with a paired *t* test and the comparison for baseline variables between group I and group II patients was made by one-way analysis of variance. Values are expressed as mean value ± SD. HR = heart rate; LAP = left atrial pressure; LVEDP = left ventricular end-diastolic pressure; MAP = mean arterial pressure; MVA = mitral valve area; MVG = mitral valve gradient; PAP = pulmonary artery pressure; Post = after valvuloplasty; Pre = before valvuloplasty; RAP = right atrial pressure.

Performance. End-systolic volume did not decline and ejection fraction did not increase in either group I or group II after valvuloplasty (Table 2). Pressure-volume loops for two group II patients with an ejection fraction of 0.39 and 0.49, respectively, are shown in Figure 1. Both of these patients had marked elevation in mean pulmonary artery pressure, which decreased with successful valvuloplasty; however, only minor changes in filling and ejection performance are demonstrated. Ejection fraction was <0.50 in three other group II patients and remained <0.50 immediately after valvuloplasty (0.47 to 0.49, 0.44 to 0.45 and 0.45 to 0.44, respectively).

Contractile function. Preload-corrected ejection fraction–afterload relations were assessed in 19 patients, none of whom had values that were outside the 95% prediction bands for normal control subjects (Fig. 2). A similar inverse relation was observed between ejection fraction and systemic vascular resistance (Fig. 3). Thus, it is primarily excessive afterload—and not contractile dysfunction—that accounts for the moderately low ejection fraction, and this abnormality is not immediately reversed by valvuloplasty.

An analysis of regional wall motion showed no improvement in chordal shortening fraction at the base of the ventricle (0.28 ± 0.08 to 0.29 ± 0.10, p = NS) compared with that at the equatorial minor axis (0.28 ± 0.07 to 0.28 ± 0.07, p = NS).

Discussion

Preload and performance. Balloon valvuloplasty did not significantly improve left ventricular performance despite effective relief of inflow obstruction. A long-standing hypothesis is that the ventricle is underfilled (or "unloaded") in mitral stenosis and that this condition is responsible for

Table 2. Angiographic, Wall Stress and Compliance Data

	LVEDV (ml)	LVESV (ml)	EF	ESS (kdynes/cm^2)	EDS (kdynes/cm^2)	dV/Vdp (mm Hg^{-1})
Group I						
Pre	150 ± 37	55 ± 11	0.62 ± 0.08	226 ± 48	44 ± 26	0.018 ± 0.014
Post	151 ± 32	58 ± 9	0.61 ± 0.08	230 ± 56	58 ± 35	0.024 ± 0.024
Group II						
Pre	152 ± 26	77 ± 13	0.49 ± 0.05	273 ± 54	46 ± 32	0.037 ± 0.037
Post	165 ± 26	80 ± 15	0.51 ± 0.07	281 ± 48	69 ± 40	0.021 ± 0.013
Control subjects (n = 24)	164 ± 32	58 ± 13	0.64 ± 0.06	186 ± 51	51 ± 18	0.040 ± 0.024
p value						
Group I (pre vs. post)	NS	NS	NS	NS	NS	NS
Group II (pre vs. post)	0.02	NS	NS	NS	0.01	NS
Group I vs. II (pre)	NS	<0.001	<0.001	0.06	NS	NS
Group I (pre) vs. control subjects	NS	NS	NS	0.06	NS	NS
Group II (pre) vs. control subjects	NS	<0.001	<0.001	<0.001	NS	NS

Values are expressed as mean value ± SD. Statistical analyses as in Table 1. dV/Vdp = operative end-diastolic left ventricular compliance; EDS and ESS = end-diastolic and end-systolic wall stress, respectively; EF = ejection fraction; LVEDV and LVESV = left ventricular end-diastolic and end-systolic volume, respectively; other abbreviations as in Table 1.

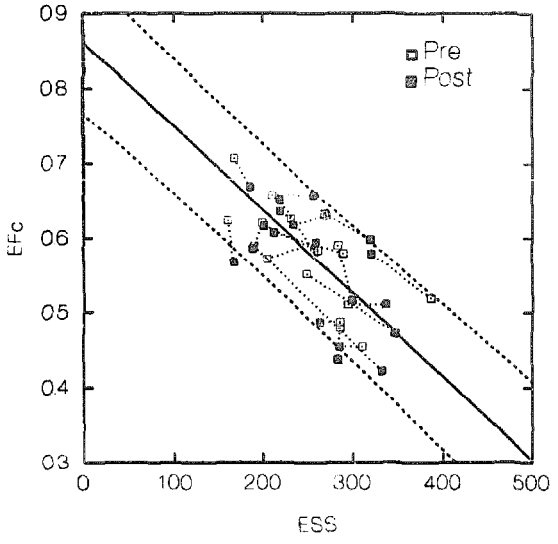
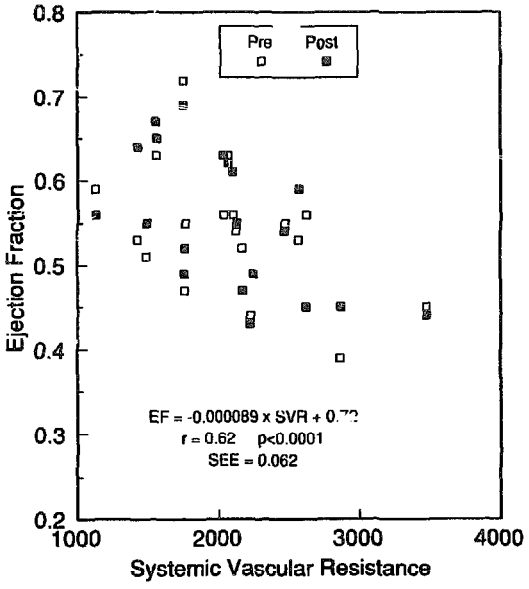


Figure 2. Relation of preload-corrected ejection fraction (EFc) to end-systolic wall stress (ESS) before (Pre) and after (Post) balloon mitral valvuloplasty. The regression line and 95% confidence intervals for a control group (n = 24) of patients in whom afterload was increased with ergonovine are shown for comparison.

impaired ventricular performance. Although some studies (13,17) have found left ventricular end-diastolic volumes to be smaller than normal, others (12,14–16) have found normal or increased chamber volumes. We observed that measures of preload including end-diastolic volume, end-diastolic pressure and end-diastolic wall stress were similar among the three groups: that of mitral stenosis with ejection fraction <0.55, of mitral stenosis with ejection fraction ≥0.55 and that of control subjects. Preload did increase modestly in group II immediately after valvuloplasty, although not enough to normalize the ejection fraction. This result is corroborated by the findings of McKay and coworkers (7), who showed that end-diastolic volumes did not increase at all (−1%) immediately and by little (+6%) at 3 months after valvuloplasty. Thus the "underfilling" hypothesis does not account for modestly reduced performance in most cases.

Figure 3. Relation of ejection fraction (EF) to systemic vascular resistance (SVR [dynes·s·cm^{-5}]) in mitral stenosis before (Pre) and after (Post) balloon mitral valvuloplasty.



Afterload. Valvuloplasty did not reduce afterload measured as end-systolic wall stress. Increased afterload has previously been implicated (13,15,16) as a cause of impaired performance in mitral stenosis, a finding that is corroborated by our results. This finding is puzzling in view of the hypothesis that these ventricles are unloaded, at least in diastole. The only plausible explanation that we can provide at present is that increased sympathetic tone (or some humoral factor such as endothelin) results in vasoconstriction and high peripheral resistance (12). We did find evidence for excessive vasoconstriction—in both the pulmonary and the systemic circuits—associated with increased wall stress, increased end-systolic volume and reduced cardiac output in the patients (group II) with lower ejection fraction. Why the increase in afterload produced by this vasoconstriction does not evoke a compensatory hypertrophy is unclear. Perhaps diastolic stretch is a more potent stimulus to hypertrophy than is the load generated during systole.

It is also unknown whether there might be some degree of irreversibility in the observed changes in vascular resistance, and our data cannot address the probability of gradual improvement in ejection fraction due to a continued decrease in systemic resistance and afterload.

Contractile function. Although contractile junction is difficult to assess, ejection performance–afterload relations seem to provide the most meaningful results (27). Using such a method, we could not detect contractile dysfunction in any of our patients. Thus, increased afterload—and not a myocardial factor—was largely responsible for a low ejection fraction. This result is at least qualitatively similar to the results of Kaku et al. (15) and Mohan et al. (16), who also used performance-afterload relations to assess contractility. It is unlikely that we "missed" contractile dysfunction by studying patients with an unusually good left ventricle because ejection fraction in group II patients was similar to (15), if not less than (16), that of these or other (12–14) previously studied groups of patients with mitral stenosis.

It has been postulated that the so-called myocardial factor might be due to a regional abnormality at the junction of the subvalvular apparatus and the posterior wall of the ventricle. Holzer and coworkers (10) specifically looked for this cause and found that the abnormality in velocity of shortening in patients with mitral stenosis was most commonly generalized, which was also true of our patients. Shortening fraction at the equator and base were similar (p = NS by paired *t* test), and these two regions were affected similarly by valvuloplasty (p = NS by analysis of covariance).

Limitations. 1. A beta$_1$-adrenergic blocking drug was used in all of the patients but in fewer than half of the normal control subjects. However, the more prevalent use of beta-

blockers in patients with mitral stenosis than in control subjects would tend to cause an underestimation of contractility in the former and would not obscure the presence of a myocardial factor. Conversely, present indexes of contractility are not completely independent of load, and the present methods might not detect some degree of contractile dysfunction.

2. Although we did not quantify the degree of alteration in resistances caused by the acute administration of a $beta_1$-blocking drug in this study, we have found in another recent (unpublished) study of mitral stenosis that intravenous atenolol increased systemic resistance by 13% in a subgroup (n = 14) with mild to moderate pulmonary hypertension and by only 6% in a subgroup (n = 17) with severe pulmonary hypertension. It is thus unlikely that the higher systemic resistance and afterload in group II was due to greater sensitivity to beta-blockade. The use of a morphine-like analgesic and a phenathiazine (with some alpha-adrenergic blocking properties) may have also had some effect on vascular resistance values, which we cannot quantify.

3. Although patients with a shunt detectable (22) by oximetry were excluded, a lesser degree of shunting, as is frequently reported after valvuloplasty (28), may have influenced the postvalvuloplasty measurements but not the baseline measurements.

Conclusions. Despite some improvement (+9%) in filling, left ventricular performance remained modestly depressed immediately after successful balloon valvuloplasty in a subset of patients with mitral stenosis. Compared with patients with mitral stenosis and normal ejection performance, these patients had a smaller valve area and higher pulmonary and systemic vascular resistances. This excessive vasoconstriction may account for the higher afterload, lower ejection performance and lower cardiac output observed in these patients because contractile dysfunction could not be detected.

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