Afterload Mismatch and Preload Reserve in Chronic Aortic Regurgitation

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SUMMARY We examined the interrelationship of afterload, preload and left ventricular (LV) performance at two levels of systolic loading in 20 patients with chronic aortic regurgitation to determine if the concept of afterload mismatch and preload reserve can be applied to this clinical entity. We identified two groups of patients at different stages in the natural history of volume overload. Patients in group 1 had moderate LV enlargement (LV end-diastolic volume < 150 ml/m²), and patients in group 2 had severe LV enlargement (LV end-diastolic volume > 150 ml/m²). Both groups had sufficient eccentric hypertrophy, measured by LV mass, to keep afterload as measured by mean systolic LV wall stress only slightly above normal; LV mean systolic wall stress was similar in each group. Patients in group 2 had a lower LV ejection fraction and velocity of circumferential fiber shortening than those in group 1 at a similar lower level of afterload. At a similar higher level of afterload, which increased end-diastolic volume from 134 ± 4 to 157 ± 6 ml/m² in group 1 and from 191 ± 9 to 218 ± 13 ml/m² in group 2 (average increase 18% vs 14%, NS), patients in group 1 maintained their ejection fraction and forward stroke volume and had a significant increase in total LV stroke volume, whereas patients in group 2 had a decrease in ejection fraction and in forward stroke volume and no significant change in LV stroke volume. The velocity of circumferential fiber shortening decreased in both groups in response to increased afterload. These data indicate that patients with moderate LV dilatation due to aortic regurgitation and sufficient hypertrophy to normalize afterload have a preload reserve that permits normal LV performance during a basal state as well as during acute increases in afterload. Patients with severe LV dilatation, however, despite sufficient hypertrophy to normalize afterload, have afterload mismatch due to a depressed inotropic state, and have exhausted preload reserve such that acute increases in afterload worsen the afterload mismatch and cause further deterioration of LV performance. The velocity of circumferential fiber shortening appears to be a less useful indicator of afterload mismatch than other ejection-phase indexes of contractility. Thus, the concept of afterload mismatch and preload reserve describes the natural history of hemodynamic alterations in chronic aortic regurgitation.

THE TIMING of valve replacement in chronic aortic regurgitation is a topic of intense study. The natural history of aortic regurgitation is characterized by a long, asymptomatic period, followed by the gradual but progressive development of dyspnea and fatigue. The hemodynamic adaptations during volume overload include gradual ventricular dilatation and hypertrophy with maintenance of normal ventricular performance until left ventricular dysfunction develops and progresses. The correlation between clinical and hemodynamic states is generally poor in chronic aortic regurgitation. Aortic valve replacement, especially late in the clinical course, is sometimes associated with less than optimal symptomatic improvement, increased mortality and persistent left ventricular dysfunction. The major therapeutic problem, therefore, is to choose a time for aortic valve replacement during the protracted clinical course before irreversible left ventricular dysfunction has occurred. Left ventricular dimension and geometry analyzed serially in the basal state, during altered loading conditions and during exercise have been suggested as means to guide this critical choice, but such studies generally have not taken into account all of the factors that affect ventricular performance. Integrating the changes in left ventricular functional state that occur during volume overload with other factors influencing left ventricular performance, Ross formulated a hypothesis that provides a framework for understanding how the left ventricle responds to chronic volume overload. We examined the interrelationship of afterload, preload and ventricular performance at two levels of systolic loading in patients with chronic aortic regurgitation to determine if the concept of afterload mismatch and preload reserve applies to the actual response of the left ventricle to chronic volume overload. The potential application of this model to patients with chronic pressure and volume overload recently has been discussed, and the left ventricular hemodynamic alterations observed with chronic pressure overload are consistent with those predicted by the model.

Materials and Methods

We studied 20 patients with isolated chronic aortic regurgitation during diagnostic cardiac catheterization after they gave informed consent. The patients were premedicated with oral diazepam, 10 mg. After complete right- and left-heart hemodynamic study and measurement of cardiac output by the Fick or thermodilution method, each patient underwent quantitative left ventricular angiography during held inspiration. Left ventriculography was performed with the patient in the 30° right anterior oblique projection during pow-
er injection of 52–56 ml of meglumine sodium diatrizoate (Renografin 76) at 12–13 ml/sec. Images were recorded at 60 frames/sec on Vari-X film with a 35-
mm Arritechno camera mounted on a Siemens cesium-iodide image intensifier. After the basal hemodynamic state was reestablished, the patients received an i.v.
infusion of phenylephrine until aortic systolic pressure increased 25–50%.
After aortic pressure had been stable for 15–20 minutes during the phenylephrine infusion, we repeated left ventricular and aortic pressures, cardiac output measurements and left ventricular cine-
angiography. Thirteen patients were studied by coronary angiography; seven patients, ages 15–33 years, did not undergo coronary angiography, as the likelihood of their having coronary artery disease was low. We determined left ventricular volumes using the areal-
length method for the right anterior oblique projection;24 a grid system was used to correct for image magnification. The earliest opacified beat that allowed analysis of the same cardiac cycle (second to fourth cycle) after the start of contrast injection for each of the control and intervention ventriculograms was used. Millar micromanometer-tipped catheters were used for high-fidelity left ventricular pressure measurement in five patients, and fluid-filled catheters connected to Statham P23Db transducers were used in the remaining 15 patients. Pressures were referenced to atmospheric pressure at the midchest level. Simultaneous left ventricular and aortic pressures were recorded immediately before ventriculography in each case. The largest ventricular volume and the left ventricular pressure after the ‘‘a’’ wave were labeled end-diastole, and the smallest ventricular volume and the aortic dicrotic notch pressure were labeled end-systole. The dicrotic notch pressure measured with a high-fidelity catheter in five patients was less than 10 msec before and within 5 mm Hg of that measured with the fluid-filled system. The left ventricular pressure wave form during ejection was then divided into the same number of segments as there were cineangiographic frames for synchronization of pressure and dimension. Ejection fraction (EF) was calculated as

$$\frac{EDV - ESV}{EDV},$$

where EDV = end-diastolic volume (ml/m²) and ESV = end-systolic volume (ml/m²). Velocity of circumferential fiber shortening (Vcf) was calculated as

$$\frac{D_{ES} - D_{ED}}{D_{ED} \times ET},$$

where $D_{ES}$ = minor diameter of the left ventricle at end-diastole, $D_{ED}$ = minor diameter of the left ventricle at end-systole, and ET = systolic ejection time. Regurgitation fraction (RF) was calculated as

$$\frac{SV_{LV} - SV_{F}}{SV_{LV}},$$

where $SV_{LV}$ = left ventricular stroke volume and $SV_{F}$ = forward stroke volume. We calculated left ventricular wall thickness (h) and mass,25 using a regression

equation for the right anterior oblique projection,26 from the end-diastolic frame and calculated wall thickness throughout ejection, assuming constant mass and an ellipsoid model of the left ventricle after the method of Hugenholtz et al.27 Major diameter (L) and area (A) were measured for every second left ventricular image (1/30 second), and minor diameter (D) was calculated as $4A/\pi L$. As a measure of afterload, we used Mirký’s formula28 to determine meridional wall stress ($\sigma_m$):

$$\frac{PD}{4h (1 + h/D)},$$

where P = left ventricular pressure (g/cm²), D = left ventricular minor diameter, and h = wall thickness. Circumferential wall stress ($\sigma_c$) was calculated as

$$\frac{Pb}{h} \left( 1 - \frac{h}{2b} - \frac{b^2}{2a^2} \right),$$

where a and b are the midwall major (L/2 + h/2) and minor (D/2 + h/2) semiaxes, respectively.

Measurement of myocardial midwall stress assumes that the myocardium is a freely deforming body composed of an isotropic and homogeneous elastic material, that the left ventricle is represented by a surface of revolution with uniform wall thickness, and that instantaneous measurements of left ventricular geometry and pressure are used in a static analysis to evaluate instantaneous stresses throughout the cardiac cycle.26 Left ventricular $\sigma_c$ is the force per unit area acting at the midplane to the heart in the direction of the apex-to-base length. Meridional stress is ideally suited for echocardiographic derivation of stress because it uses only the minor-diameter dimension. Left ventricular $\sigma_c$ is the force acting at the equatorial plane, and uses both major- and minor-diameter dimensions.

We plotted individual stress values as a function of time from end-diastole to end-systole, then calculated the mean systolic meridional stress ($\bar{\sigma}_m$) and the mean systolic circumferential stress ($\bar{\sigma}_c$) during ejection by planimetricing the area under the stress-time curve. Using the value of mean stress for subsequent data analysis allows for cancellation of minor errors inherent in the fluid-filled recording system (15 patients); the stresses early in systole, which are lower because of a slower rise time of left ventricular pressure, are balanced by the stresses at peak systole, which are higher because of overshoot.23

Statistical analysis was by analysis of variance.

Results

To test the hypothesis that cardiac dilatation serves to maintain left ventricular performance during chronic aortic regurgitation, we arbitrarily separated our patients into two groups: those with an end-diastolic volume $< 150$ ml/m² (group 1) and those with an end-diastolic volume $> 150$ ml/m² (group 2). Table 1 contains the data for each patient at both loading conditions. Group 1 was distinguished from group 2 at the lower loading condition by a smaller end-diastolic vol-


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Mean ± SEM  27 ± 4 ± 5  127/19 ± 6/2  183/40 ± 10/3  134 ± 4 ± 6  157 ± 9

p (a vs b) < 0.005 < 0.001 < 0.005

Group 2 (EDV > 150 ml/m²)

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Mean ± SEM  51 ± 3 ± 3 ± 6  159/26 ± 7/3  206/41 ± 9/5  191 ± 9 ± 14  234 ± 17

p (a vs b) NS < 0.001 < 0.02

p (group 1 vs group 2) NS NS < 0.005 NS < 0.001 < 0.001 < 0.05 NS

Abbreviations: a = basal state, lower level of systolic load; b = phenylephrine infusion, higher level of systolic load; HR = heart rate; LVP = left ventricular pressure; ED = end-diastolic; EDV = end-diastolic volume; EF = ejection fraction; SVL = left ventricular stroke volume; Vcf = velocity of circumferential fiber shortening; σm = mean systolic meridional wall stress; σc = mean systolic circumferential midwall stress; RF = regurgitant fraction.

ume (134 ± 4 ml/m² vs 191 ± 9 ml/m² [± SEM], p < 0.001), a lower left ventricular peak systolic pressure (127 ± 6 mm Hg vs 159 ± 7 mm Hg, p < 0.001) and a smaller left ventricular mass (146 ± 9 g/m² vs 234 ± 17 g/m², p < 0.001). Though there was no significant difference in σm or in σ between the groups at lower systolic load, group 1 had a higher average ejection fraction (0.60 ± 0.02 vs 0.51 ± 0.03, p < 0.01) and Vcf (0.92 ± 0.04 sec⁻¹ vs 0.75 ± 0.07 sec⁻¹, p < 0.05) than did group 2. Left ventricular stroke volume was smaller in group 1 than in group 2 (81 ± 3 ml/m² vs 98 ± 7 ml/m², p < 0.05), while forward stroke volume was similar in each group (44 ± 3 ml/m² vs 41 ± 5 ml/m², NS). Regurgitant fraction was significant-ly larger in group 2 than group 1, which supports the pressure, volume and mass data indicating that aortic regurgitation was more severe in group 2. No patient in either group had mitral regurgitation in either ventriculogram, or coronary artery disease.

Figure 1 illustrates the influence of higher systolic loading conditions upon two indexes of preload, left ventricular end-diastolic volume and end-diastolic pressure. In both group 1 and group 2, higher levels of left ventricular systolic pressure were associated with significant increases in end-diastolic volume (p < 0.005, p < 0.02, respectively) and in end-diastolic pressure (p < 0.001, p < 0.005, respectively). The increase in left ventricular systolic pressure at the high-
er loading condition was similar for each group (45% vs 30%, NS), as was the increase in end-diastolic volume (18% vs 14%, NS).

Figures 2 and 3 illustrate the relationship between two stages of afterload, in this case represented by $\sigma_m$, the induced changes in end-diastolic volume and three ejection phase indexes of left ventricular function. Afterload augmentation caused a 12% reduction in Vcf in group 1 (0.92 ± 0.04 sec$^{-1}$ to 0.80 ± 0.04 sec$^{-1}$, $p < 0.02$) and a 27% reduction in group 2 (0.75 ± 0.07 sec$^{-1}$ to 0.55 ± 0.08 sec$^{-1}$, $p < 0.02$); these reductions were not significantly different between the groups. Higher levels of afterload caused significantly different effects upon ejection fraction and left ventricular stroke volume between the groups, however. In group 1, increased afterload resulted in no change in ejection fraction (0.60 ± 0.02 vs 0.60 ± 0.02), whereas in group 2, ejection fraction decreased 22% (0.51 ± 0.03 to 0.42 ± 0.04, $p < 0.005$); the difference between groups was significant ($p < 0.005$). Augmented afterload caused a 17% increase in left ventricular stroke volume (81 ± 3 ml/m$^2$ to 94 ± 5 ml/m$^2$, $p < 0.05$) in group 1 but no change in group 2 ($p < 0.025$). Effective, or forward, stroke volume was maintained in group 1 despite higher afterload (44 ± 3 ml/m$^2$ vs 39 ± 3 ml/m$^2$, NS), whereas forward stroke volume decreased in group 2 (41 ± 5 ml/m$^2$ to 27 ± 2 ml/m$^2$, $p < 0.05$). An average end-diastolic volume in excess of about 150 ml/m$^3$ was associated with a significant reduction in ejection fraction (fig. 3). Vcf decreased gradually with progressive dilatation. In group 1, the increase in end-diastolic volume induced by an increase in afterload was associated with a significant increase in left ventricular stroke volume, whereas in

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FIGURE 1. Influence of two systolic pressure loads on left ventricular (LV) end-diastolic volume and LV end-diastolic pressure in two groups of patients with aortic regurgitation. • = group 1 (basal end-diastolic volume < 150 mL/m²); ○ = group 2 (basal end-diastolic volume > 150 mL/m²). LV end-diastolic volume and pressure were significantly higher at the higher pressure load in each group.

group 2 a similar increase in end-diastolic volume was associated with a decrease in left ventricular stroke volume.

Discussion

Afterload, the force or tension exerted upon the myocardial wall after the onset of ejection, and preload, the wall tension at end-diastole, interact with the contractile state of the myocardium to determine the overall function or performance of the heart. As diastolic volume overload progresses during chronic aortic regurgitation, the initial increase in fiber stretch and sarcomere length stimulates series addition of sarcomeres. End-diastolic wall tension, analogous to preload or fiber stretch of "isolated" muscle, depends on adequacy of series addition of new sarcomeres, which in turn determines the degree of chamber enlargement. We used end-diastolic volume as an approximate measure of preload at the level of individual muscle fibers. Animal studies demonstrate that basic responses of the left ventricle are modified by a large Frank-Starling reserve, by which an increase in afterload is matched by an increase in preload. Ross called this phenomenon "preload reserve." Progressive dilatation occurs at the expense of exhausting preload reserve, in which case an increase in afterload cannot be compensated by the Frank-Starling mechanism, and left ventricular function deteriorates. Wall thickening accompanies chamber enlargement during progressive volume overload, contributing to the development of eccentric hypertrophy and normalizing wall stress. Adequacy of hypertrophy prevents reduction in performance that would be a consequence of afterload mismatch. Alternatively, afterload mismatch may

FIGURE 2. Influence of afterload, \( \sigma_m \), on three ejection-phase indexes of left ventricular (LV) contractility. With a similar increase in afterload, ejection fraction was maintained constant and stroke volume increased significantly in group 1 (•), whereas ejection fraction decreased significantly and stroke volume decreased slightly in group 2 (○). The mean velocity of circumferential fiber shortening (VCF) decreased significantly in response to an increase in afterload in both groups. VCF was significantly less in group 2 than in group 1 at the higher loading condition.
AFTERLOAD MISMATCH IN AORTIC REGURGITATION/Ricci

**Figure 3.** Influence of preload, represented by end-diastolic volume, on three ejection-phase indexes of left ventricular (LV) contractility. Ejection fraction decreased significantly with increasing end-diastolic volume above 160 ml/m², whereas the mean velocity of circumferential fiber shortening (VCF) decreased progressively with increasing end-diastolic volume. Stroke volume rose with increasing end-diastolic volume to 160 ml/m² and decreased slightly at higher levels. ● = group 1; ○ = group 2.

occur when inotropic state becomes depressed, with loading conditions relatively constant, resulting in deterioration of left ventricular performance. Clinical application of the concept of afterload mismatch and preload reserve is ideally suited to chronic aortic regurgitation because of the long natural history of progressive volume overload during which, in addition to progressive hypertrophy that normalizes wall stress, there is theoretically gradual encroachment upon preload reserve. If this conceptual framework truly describes the physiologic adaptations in chronic aortic regurgitation, moderately hypertrophied ventricles would have normal basal function, whereas extensively hypertrophied ventricles that are grossly dilated and at or beyond the limit of preload reserve would have depressed function. Moreover, an acute pressor stress, testing the magnitude of preload reserve to compensate for increased afterload, should be associated with maintenance of left ventricular function in the moderately hypertrophied ventricles that have ample remaining preload reserve, but would significantly depress left ventricular function in the grossly dilated ventricles.

Our data indicate that the concept of afterload mismatch and preload reserve may be applied to patients with volume overload due to chronic aortic regurgitation. In all cases in group 1, ventricular dilatation judged by end-diastolic volume was moderate (average volume 134 ml/m²), and in every case greater than 108 ml/m², which is substantially larger than the normal value of 70 ± 20 ml/m² (± SD). In group 2, dilatation was to more than 2.5 times the normal size. This degree of dilatation is also reflected in the extent of eccentric hypertrophy; the average mass for group 1 was 45% larger than normal (92 ± 16 g/m²) and for group 2 was 150% larger than normal. Thus, we have two groups of patients with aortic regurgitation, each with significant hypertrophy such that afterload is similar, but one with moderate (group 1) and one with severe (group 2) ventricular dilatation.

Both ejection fraction and VCF are valuable indexes of basal left ventricular function and separate groups with normal from those with clearly abnormal function, whereas stroke volume is better suited to characterize an acute change in afterload. With σm and σi, representing afterload, being similar for both groups, and despite preload being greater for group 2 than for group 1, the depressed ejection fraction and VCF in group 2 indicate that reduced left ventricular performance occurred in this group as a result of a depressed inotropic state.

The profound difference between the two groups in their response to an increased level of afterload also indicates that the concept of afterload mismatch and preload reserve is useful for assessing chronic volume overload. In group 1, increased afterload was associated with no significant change in ejection fraction or forward stroke volume, a significant increase in left ventricular stroke volume, and a slight decrease in VCF. In group 2, however, increased afterload produced a significant decrease in ejection fraction and VCF, no change in left ventricular stroke volume, and a profound decrease in forward stroke volume. The increase in left ventricular stroke volume in response to augmented afterload in group 1 is due to the induced increase in end-diastolic volume, in part as a consequence of the increase in regurgitant fraction, and demonstrates the importance of preload reserve. The alterations in stroke volume in group 2 indicate absence of preload reserve. The effect of acute pressure loading on stroke volume and ejection fraction in our
patients was similar to that shown previously as a decrease in stroke volume and ejection fraction in patients with severely depressed left ventricular function and regurgitant fraction greater than 0.5, and an increase or no change in stroke volume or ejection fraction in patients with normal or slightly depressed function or regurgitant fraction less than 0.5. Both ejection fraction and Vcf, as ejection-phase indexes of contractility, are sensitive to changes in afterload.

The decline in Vcf during augmented afterload in group 1 patients deserves further comment. Vcf may be more sensitive to afterload than ejection fraction, and therefore may be a more sensitive indicator of afterload mismatch, in which case the reduction in Vcf with augmented afterload in group 1 would indicate exhaustion of preload reserve in this group as well as in group 2. The significant increase in stroke volume in response to increased afterload in group 1 would be difficult to explain with this alternative formulation, however. Another problem in the use of Vcf is its critical dependence on ejection time, which may be difficult to measure precisely in patients with aortic regurgitation. A minor error in measurement of ejection time would cause a significantly larger error in Vcf than in \( \sigma_m \) or \( \sigma_c \), which are integrated over the entire period of ejection. Finally, since Vcf reflects the state of a theoretical fiber in the middle plane of the ventricle, it is more a measure of regional function than ejection fraction or stroke volume, which reflect global performance. If a regional contraction disorder does exist in aortic regurgitation, as recently suggested, Vcf would be less useful as a measure of overall preload reserve.

Johnson et al. reported that ejection-phase indexes in patients with aortic regurgitation were always higher when obtained from a biplane or left anterior oblique projection than from the right anterior oblique projection. The discrepancy is consistent, however, for end-diastolic volumes of 161–313 mL and for ejection fraction of 0.35–0.77. We do not believe that restriction of our measurements to the right anterior oblique projection weights the results toward one group or the other. Our average values for \( \sigma_m \) are slightly higher than those in one report of normal patients and of those with

![Three-dimensional schematic of the interrelationship of preload, represented by end-diastolic volume (EDV); afterload (AL), expressed as \( \sigma_m \); and ejection fraction (EF), an ejection-phase index of contractility, in patients with chronic aortic regurgitation (AR). Point A represents a typical value from a normal heart. Point B represents the state of moderate aortic regurgitation and is illustrated by the average values for group 1. Point C represents severe aortic regurgitation and is illustrated by the average values for group 2. Line A-B-C, therefore, represents the progression from the normal state to moderate and to severe chronic volume overload due to aortic regurgitation. Lines B-B' and C-C' represent the effect of acute afterload augmentation at each stage in the progression of aortic regurgitation. Patients with moderate left ventricular dilatation and sufficient hypertrophy to normalize afterload have sufficient preload reserve to permit normal left ventricular performance in the basal state as well as during acute increases in afterload (line A-B'-B'). Patients with severe left ventricular dilatation have exhausted preload reserve and depressed left ventricular performance basally, with further profound depression during acute afterload elevation (line B-C-C'). Because afterload is similar for B and C and for B' and C', the reduction in left ventricular performance in severe aortic regurgitation is due to a depressed inotropic state.

FIGURE 4.
chronic volume overload, but similar to values of another report. Our values for \( \sigma \) are similar to those previously reported.

The relationship between afterload and ventricular performance does not appear to depend on whether afterload is represented by \( \sigma_m \) or by \( \sigma_e \). In some respects, \( \sigma_m \) is a more convenient measure because it can be easily derived from echocardiographic data.

An important factor germane to the concept of afterload mismatch is adequacy of venous return. If venous return had been reduced during the higher loading condition, thereby limiting the amount of ventricular dilatation, an artificial mismatch could have been produced. That this potential effect would influence the responses in one group more than in the other group is unlikely; indeed, the magnitude of increased end-diastolic volume induced by the increased afterload was not different between the groups. Phenylephrine, an adrenergic pressor agent, may have a small direct positive inotropic effect upon the myocardium, and at the same time induce a mild reflex negative inotropic effect. Examination of heart rate in our patients may help explain these effects. The mean heart rate decreased in group 1 and increased slightly in group 2, changes that would be expected to produce effects opposite to those observed in terms of the response of left ventricular function to induced changes in afterload in our patients. Moreover, the small differences in heart rate in each condition of afterload (less than 6 beats/min) would not produce major changes in contractility.

Figure 4 shows the average data for each group in the form of a three-dimensional diagram relating afterload, preload and ejection fraction. The average normal coordinates are derived from accepted values for end-diastolic volume and ejection fraction and from \( \sigma_m \) reported in normal patients. As aortic regurgitation becomes established at a moderate level (B), afterload increases only slightly from normal (A-B), while the left ventricle dilates and hypertrophies, and left ventricular performance, measured by ejection fraction, is maintained in the normal range of 0.60. Acute afterload stress at this point (B-B') is compensated for by further dilatation, and left ventricular function remains normal, indicating that preload reserve remains adequate. As aortic regurgitation becomes more severe (C), though hypertrophy increases to prevent all but a slight increase in afterload (B-C) and further dilatation ensues, mismatch occurs as a result of depressed inotropic state, and left ventricular performance deteriorates. Acute afterload stress at this point (C-C') results in profound depression of left ventricular performance. This represents exhaustion of preload reserve; our data suggest that the limit of preload reserve is 160–190 ml/m² of end-diastolic volume.

Whether the depressed inotropic state and exhaustion of preload reserve in group 2, at both low and high levels of systolic loading is irreversible, indicating permanent damage to the contractile machinery, is not established. Similar studies of left ventricular hemo-
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D R Ricci

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