Evaluation of Left Ventricular Function in Patients with Aortic Regurgitation Using Afterload Stress

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SUMMARY Left ventricular function was assessed in 14 patients with chronic aortic regurgitation by afterload elevation with angiotensin. Seven of 14 patients maintained their resting ejection fraction with angiotensin (group A), while the remaining seven experienced a decline of greater than 0.10 in ejection fraction (group B). Six of seven group A patients showed an appropriate rise in left ventricular stroke work index in response to the angiotensin-induced rise in left ventricular end-diastolic pressure. In contrast, six of seven group B patients showed abnormal, flat, or declining stroke work indices. Included in the seven group B patients were two patients with left ventricular dysfunction secondary to coronary artery disease. The five other group B patients, who did not have coronary disease, exhibited similar stress-induced ventricular dysfunction, despite the absence of any significant resting hemodynamic differences from patients in group A. These five stress-induced dysfunction patients were distinctive from patients who maintained their ejection fraction level in that the former all had regurgitant fractions of greater than 0.50, whereas all group A patients had regurgitant fractions of less than 0.50. Similarly, these five stress-induced dysfunction patients had significantly larger left ventricular end-diastolic volumes than did the group A patients. These data suggest that patients with pronounced aortic regurgitation measured in terms of regurgitant fraction greater than 0.50 and left ventricular end-diastolic volume of greater than 160 cm$^3$/m$^3$ exhibit impaired ventricular function if appropriately stressed. As most of the patients with stress-induced dysfunction had a normal ejection fraction at rest, it may be that stress-induced dysfunction represents a stage before overt resting dysfunction and cardiac failure.

☐ EVALUATION OF LEFT VENTRICULAR (LV) FUNCTION in patients with aortic regurgitation remains an important clinical problem. There exist no firm physiologic or hemodynamic criteria to indicate at what point in time myocardial dysfunction develops or at what time valve replacement should be performed in order to avert or reverse myocardial dysfunction. Spagnuolo et al. found that the triad of marked radiographic evidence of LV enlargement, electrocardiographic diagnosis of ventricular hypertrophy, and wide pulse pressure identified patients at high risk for the development of congestive heart failure, angina, or death. However, these data are of limited assistance in assessing indications for aortic valve replacement in asymptomatic or mildly symptomatic patients who exhibit some of the features of this triad.

The severity of aortic regurgitation as measured by large regurgitant fractions and markedly elevated end-diastolic volumes, correlates with the severity of clinical symptoms, but has not been correlated with quantitative measures of myocardial dysfunction. Left ventricular end-diastolic pressure has not been found to be a good index of LV dysfunction in that it correlates poorly with end-diastolic volume and ejection fraction in patients with aortic regurgitation, and may be normal in patients with advanced disease. Depression of forward cardiac output in patients with severe regurgitation reflects very advanced disease with severe regurgitation and overt congestive heart failure. Gault et al., in a small number of patients studied pre- and postoperatively, found that a lowered velocity of circumferential fiber shortening ($V_{cf}$), indicative of abnormal myocardial function, was not reversed by aortic valve replacement, suggesting that resting abnormalities might not be reversible by surgery. We have therefore studied left ventricular function during stress induced by increasing afterload with angiotensin in a group of patients who at rest had relatively normal indices of myocardial function. We have examined the resultant hemodynamic and quantitative volumetric responses and found that stress abnormalities of left ventricular function can be detected in some patients, particularly those with the most severe degrees of regurgitation.

Methods

Fourteen consecutive patients fulfilling the clinical criteria of chronic isolated aortic regurgitation and who agreed to participate, with informed consent, comprise the study (table 1). Patients with concurrent mitral valve disease or aortic stenosis (> 10 mm Hg mean left ventricular to aortic gradient) were excluded. Resting cardiac catheterization was performed after premedication with 100 mg secobarbital intramuscularly. Cournand or Birdseye catheters with Statham P23Db transducers were employed for right-sided pressures, and 6.7 French polyethylene end-hole catheters with Micron MP-15 transducers or Millar transducer-tipped catheters were used for the left-sided pressures. Forward cardiac outputs ($CO_f$) were determined either by the direct Fick method or duplicate indocyanine green indicator dilution techniques. Pressures were computer determined and checked manually. Resting single plane angiography was performed using a 6.7 French angiographic catheter or #8

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French Millar angiographic catheter passed retrogradely across the aortic valve with the patient in the 30° right anterior oblique position. End-diastolic and end-systolic LV volumes and ejection fraction were determined by light-pen computer processing of video disc recorded LV images as previously described. Three sinus systolic-diastolic cycles, excluding postextrasytolic beats, were analyzed and averaged. Left ventricular cardiac output (CO
subscript LV
) was determined by multiplying angiographically-determined stroke volume by heart rate. Heart rate at the time of the angiogram and at the measurement of forward cardiac output were within eight beats of one another. Regurgitant fraction (RF) was then calculated according to the formula

\[
\text{RF} = \frac{\text{CO}_{\text{LV}} - \text{CO}_F}{\text{CO}_{\text{LV}}}.
\]

Left ventricular stroke work index (SWI
subscript LV
) was calculated using the formula: SWI
subscript LV
 = (LV stroke index) \times (mean LV systolic pressure during ejection) \times (0.0136).

After resting hemodynamics and LV angiography were performed, LV pressure was monitored until returning to baseline levels. Angiotensin was then infused through a peripheral vein, beginning at a rate of 0.4 \( \mu \)g/min and increasing 0.4 \( \mu \)g/min every three minutes until LV systolic pressure was raised by 20–50 mm Hg. Doses of angiotensin required were 0.4–2.0 \( \mu \)g/min. Hemodynamics were then allowed to stabilize for ten minutes, at which time LV pressure was recorded. In nine of the 14 patients, simultaneous aortic pressure was also measured, and in six, forward cardiac output was determined during angiotensin infusion (table 2). While angiotensin infusion was maintained, the LV angiogram was repeated and quantitative volumetric data, ejection fraction, and SWI
subscript LV
 were calculated for angiotensin (table 2). At least 30 minutes separated this angiogram from the first. There were no complications in performing this second angiogram. Data analysis was performed by computation of mean and standard error of the mean (±SEM). Analysis of paired data and statistical significance was evaluated by means of the paired Student's t-test.

**Results**

**Clinical Data**

Clinical data are presented in table 1, and hemodynamic data in table 2. Patient ages ranged from 27 to 63 years (mean 45 years). Clinical disease severity, as assessed by New York Heart Association (NYHA) classifications, was Class I or II for eight patients, and Class III for six patients. Five of the patients had had rheumatic fever in the past, and two of these had had subacute bacterial endocarditis at some time remote from the present study. One patient had ankylosing spondylitis, and one syphilis, as probable etiologies for their valvular disease. Thirteen of the 14 patients had left ventricular hypertrophy by radiographic and electrocardiographic criteria (table 1). Patient 14 died suddenly six months after study and was found to have aortic valve scarring and severe arteriosclerotic coronary disease with diffuse myocardial fibrosis. Five patients had coronary arteriography because of either chest pain or age. Three showed coronary narrowings, and only one had significant multivessel disease (patient 13). All patients except 4, 6, and 14 had aortic valve replacement; the coronary arteries were inspected and palpated at this time and, excluding patient 13, were judged to be free of major disease.

**Response to Afterload Elevation**

Left ventricular systolic pressure was raised for all patients by an average of 24% (148 to 183 mm Hg) and LV end-diastolic pressure by 65% (24.1 to 39.6 mm Hg) (table 2). There was, however, no direct correlation between peak LV systolic pressure elevation and the rise in LV end-diastolic pressure. Forward cardiac index was depressed by angiotensin in each of the six patients in whom this was determined. Regurgitant volume and regurgitant fraction in-
### Table 2. Hemodynamic and Angiographic Data for Control and Angiotensin Interaction

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<th>Ao pressure (s/d, mm Hg)</th>
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<th>LV CI (L/min/m²)</th>
<th>Forward CI (L/min/m²)</th>
<th>LV SWI (g-m²)</th>
<th>ed vol (cm³)</th>
<th>LV SV vol (cm³)</th>
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Abbreviations: C = control; A = angiotensin; BSA = body surface area (m²); LV = left ventricular; s/d = systolic/diastolic; Ao = aortic; HR = heart rate; CI = cardiac index; SWI = stroke work index; Vol = volume; SV = stroke volume; EF = ejection fraction; RF = regurgitant fraction.
creased in four patients, was unchanged in one, and fell in one, due to a decrease in total LV cardiac output (table 2).

Seven of the 14 patients experienced little change in ejection fraction with angiotensin (three had virtually no change, three had decreases of less than 0.10, and one increased ejection fraction by 0.10). The remaining seven patients experienced declines in ejection fraction of more than 0.10 with afterload elevation. The average of the ejection fraction drop in these seven patients was 0.19, with a range of 0.13 to 0.28 (fig. 1). This differential response to angiotensin was used to divide patients arbitrarily into two groups: those seven patients who maintained their ejection fraction with angiotensin were termed group A and the seven patients who experienced a greater than 0.10 decline in ejection fraction were designated group B.

Striking differences in the response of SWI_{LV} to stress were found between these two groups (fig. 2). Six of seven group A patients showed a rise in SWI_{LV} in response to angiotensin-induced elevation of LV end-diastolic pressures. In contrast, six of seven group B patients manifested flat or declining SWI_{LV}. There were no substantial differences in the angiotensin-induced rises in LV systolic pressures or end-diastolic pressures between the patients of groups A and B (fig. 3). This response of SWI_{LV} to angiotensin largely reflected a significant fall in stroke volume in group B patients (157 to 115 ml, \( P < 0.01 \)) compared to no change in group A patients (146 to 152 ml, not significant NS) (fig. 4).

Patients in both A and B groups increased their end-diastolic volumes with angiotensin, although the magnitude of the changes was relatively small. For all patients, LV end-diastolic volume increased 7.7% (271 to 292 ml, \( P < 0.05 \)). Left ventricular cardiac index tended to rise in group A patients with angiotensin (5.6 to 6.3 L/min/m²) and fall slightly with group B patients (6.6 to 5.9 L/min/m²) despite similar resting values. The difference in these changes between groups A and B was significant (\( P < 0.05 \)). Heart rate was virtually unchanged in group A patients given angiotensin (79 to 81 beats/min, NS) but rose slightly in group B patients (72–86 beats/min, \( P < 0.01 \)).

Two of the group B patients (patients 13 and 14) differed from the remaining five in having small regurgitant fractions and normal resting end-diastolic volumes (table 2). Both of these patients had severe coronary artery disease, and one (no. 14) had a histopathologically-proven severe myocardial fibrosis. The remaining five of seven group B patients had regurgitant fractions greater than 0.50 (mean 0.66, range 0.53–0.78), whereas all of group A patients had regurgitant fractions less than 0.50 (mean 0.37, range 0.19–0.49) (fig. 4). These five patients with stress-induced dysfunction had significantly larger LV end-diastolic volumes at rest than did those who maintained function with stress (357 ± 31 cm³ and 251 ± 26 cm³, respectively; \( P < 0.05 \)) (fig. 5). Despite these stress-induced differences, control hemodynamics were markedly similar. Left ventricular end-diastolic pressure

**FIGURE 1** This graph plots the ejection fraction for the control and angiotensin states. Seven patients, shown on the left, either increased ejection fraction with angiotensin (one patient), had an unchanged ejection fraction (three patients), or exhibited less than a 0.10 fractional ejection fraction fall (three patients). Over-all ejection fraction in this group of patients (A) declined 0.03. In contrast, ejection fraction in seven patients deteriorated markedly, from a range of −0.13 to −0.28 (mean, −0.19 ± 0.03). These patients comprise group B, shown on the right. Over-all resting ejection fraction for the two groups was quite similar (0.58 ± 0.02 for group A; 0.56 ± 0.03 for group B).

**FIGURE 2** Left) Ventricular function curves plotting left ventricular stroke work index (SWI_{LV}) vs left ventricular end-diastolic pressure (LVEDP) for control and angiotensin. In six of seven group A patients SWI_{LV} increased with augmentation of LVEDP. Right) Similar ventricular function curves for group B patients. Note the declining values for SWI_{LV} with increased LVEDP in five of seven patients.
and ejection fraction were virtually identical (fig. 6). Forward cardiac index in the group A patients was significantly higher than in patients with stress-induced dysfunction.

Discussion

Previous studies have shown that, despite large regurgitant fractions, both clinical symptoms and standard measures of LV dysfunction may remain relatively normal in patients with aortic regurgitation.\textsuperscript{1,5,6} Several studies, including the present one, document the lack of correlation of LV end-diastolic pressure with the severity of regurgitation, end-diastolic volume, or ejection fraction.\textsuperscript{5} Almost paradoxically, one study found that preservation of exercise capacity was associated with higher LV end-diastolic pressures than in subjects with abnormal exercise capacity.\textsuperscript{6} Left ventricular end-diastolic pressure in patients with chronic aortic regurgitation is related not only to myocardial function, but also to the amount of aortic regurgitation per beat, heart rate, afterload, and ventricular compliance, and thus, cannot be used alone as a reliable index of LV function.\textsuperscript{6}

Resting ejection fraction is well maintained despite increasingly severe degrees of aortic regurgitation and symptomatic deterioration.\textsuperscript{6} Tyrell et al.,\textsuperscript{2} in 27 patients with aortic regurgitation, found no clear association between ejection fraction and NYHA functional classification. In 38 patients with isolated aortic regurgitation, with a wide spectrum of severity (end-diastolic volumes from 100–400 cm\(^3\)/m\(^2\)), the over-all ejection fraction was normal.\textsuperscript{3} In aortic regurgitation ejection fraction was found to have no correlation with end-diastolic volume, an observation felt to emphasize the "physiologic" independence of the resting ejection fraction.\textsuperscript{3}

Forward cardiac index is quite variable in patients with aortic regurgitation and dependent upon the interaction of left ventricular output, regurgitation, heart rate, and myocardial function. Subnormal resting forward cardiac index is generally seen only with severe disease and advanced symptoms.\textsuperscript{4,9}

The response of cardiac output to exercise in patients with aortic regurgitation is also complex. In patients with significant aortic regurgitation left ventricular cardiac output does not increase with exercise, but regurgitant fraction falls markedly, thus allowing a significant rise in forward cardiac output.\textsuperscript{4,9} Lewis, Bristow, and Griswold\textsuperscript{10} found that those patients with aortic regurgitation who exhibited a blunted rise in forward cardiac output to exercise had an abnormal

\textbf{Figure 3} The response of left ventricular stroke volume to afterload stress of groups A and B is illustrated. Left ventricular stroke volume is little affected in group A (146 to 152 cm\(^3\), NS), but a precipitous drop occurs in group B patients (151 to 115 cm\(^3\), P < 0.01).

\textbf{Figure 4} Regurgitant fractions for the seven "normal function" patients (group A) and for the five stress-induced dysfunction patients with pure aortic regurgitation are shown. Normal function patients have regurgitant fractions < 0.50 (mean, 0.37) and all stress-induced dysfunction patients have regurgitant fractions > 0.50 (mean, 0.66).

\textbf{Figure 5} End-diastolic volumes for the patients with "pure" aortic regurgitation who maintained normal function with afterload stress, and for the five "stress-induced dysfunction" patients. The stress-induced dysfunction patients' end-diastolic volumes are significantly greater than those of the patients who maintained normal function (194 cm\(^3\)/m\(^2\) vs 130 cm\(^3\)/m\(^2\), P < 0.05).
exercise factor. No differentiation between their “normal” and “abnormal” groups could be made on the basis of resting cardiac index, frontal heart area, stroke index, or clinical severity; however, regurgitant fractions were not directly measured.

The applicability of constructing ventricular function curves by increasing afterload has been well demonstrated in animals and humans. We have applied these principles in patients with aortic regurgitation and used angiotensin to elevate afterload because of its marked peripheral hemodynamic effects and relatively minimal cardiac effects.

Although the patterns of ventricular response to increased afterload were arbitrarily divided into two groups, it is recognized that a continuum of ventricular functional reserve exists. In one group (A) the ejection fraction remained relatively constant and LV stroke work index rose with higher LV end-diastolic pressures, while in the abnormal group (B), ejection fraction fell and LV stroke work index generally fell or remained flat, characteristics associated with the failing ventricle. Since systolic pressure was elevated to equal degrees in both groups, the fall of LV stroke work index in group B patients was largely the result of the rather dramatic decline in stroke volume. These findings of flat or declining SWLV in some patients with aortic regurgitation are quite similar to the behavior of patients with other types of cardiac lesions who had clear-cut left ventricular dysfunction following angiotensin.

It is recognized that the extent of the stress imposed upon the left ventricle may alter the response. Wall stress may be increased by both the elevation of aortic pressure and the increased end-diastolic volumes reflecting accentuated regurgitation. Although the increments in aortic pressure and end-diastolic volume were similar in both patient groups, no decrease in LV cardiac index occurred in group A patients, whereas in group B patients the LV cardiac index fell significantly. Similarly, Ross and Braunwald, in giving from 1.25 to 0.75 µg/min of angiotensin, observed no consistent change in cardiac index in patients with normal LV function, but a modest fall in patients with LV dysfunction. Nolan et al. also found that doses of angiotensin sufficient to elevate mean arterial pressure up to 30% in normal individuals yielded no change in cardiac index; however, still higher afterload elevations did diminish cardiac index. It is also conceivable that afterload elevation affected greater regurgitation in group B than in group A patients. Although angiotensin regurgitant fractions were available in only six of 14 patients, such a difference was not found. In fact, in one group B patient, regurgitant volume and fraction fell, due to a decrease in LV output.

Thus, evidence for LV dysfunction in some patients with aortic regurgitation is given by the conjunction of falling ejection fraction, distinctly abnormal ventricular function curve, and diminished stroke volume, when the ventricle is stressed by increased afterload. Two patients (13 and 14) had only trivial aortic regurgitation and exhibited features of an associated cardiomyopathy which, in both cases, was felt to be ischemic in origin. Their dysfunction was felt to be related to this condition rather than their modest aortic regurgitation. The other five patients exhibiting LV dysfunction had no evidence of coronary disease and had larger end-diastolic volumes and larger regurgitant fractions than did the more normal patients. No patient who maintained normal function with stress had a regurgitant fraction greater than 0.49, and no patient with stress-induced dysfunction without coronary disease had a regurgitant fraction of less than 0.53. All patients with stress-induced dysfunction without coronary disease had an end-diastolic volume index in excess of 160 cm³/m². The resting forward cardiac index tended to be lower in these patients, but there was considerable overlap.

These data strongly suggest that patients free of coronary artery disease, with pronounced aortic regurgitation, measured in terms of regurgitant fractions greater than 50% and LV end-diastolic volumes greater than 160 cm³/m², are likely to have impaired ventricular function if appropriately stressed. This dysfunction may occur at a time when resting LV end-diastolic pressure and ejection fraction are quite normal. We surmise that significant depression of the resting ejection fraction and resting forward cardiac index in patients with aortic regurgitation reflects a much more ad-
advanced stage of ventricular impairment. Our data are consistent with the other reports suggesting that regurgitant fractions of greater than 60% are associated with more severe clinical symptoms. The fact that the end-diastolic volume also differed between patients with stress-induced dysfunction and patients with normal stress function undoubtedly reflects the differences in regurgitant fractions.

It is likely that left ventricular dysfunction which is provoked only by stress precedes development of rest abnormalities and represents an intermediate stage in the natural history of aortic regurgitation. The fact that there was substantial correlation between ventricular dysfunction and the severity of the aortic regurgitation suggests that clinical deterioration may depend primarily upon progressive increases in valvular regurgitation rather than upon an independently progressive "myocardial factor." It should be recognized that patients with concomitant aortic stenosis were excluded from this study in order to provide a homogeneous patient group. It is likely that for many patients, concomitant aortic stenosis introduces an additional factor which may strongly influence myocardial function. Only careful longitudinal studies with pre- and postoperative hemodynamics and angiography will fully answer the questions of reversibility of ventricular size and performance and the optimal time for aortic valve replacement. Our data do suggest that quantitatively severe regurgitation is consistently found in association with stress-provoked ventricular dysfunction.

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