Relationship of contractile state to ejection performance in patients with chronic aortic valve disease

THOMAS WISENBAUGH, M.D., DAVID BOOTH, M.D., ANTHONY DEMARIA, M.D., STEVEN NISSEN, M.D., AND JOHN WATERS, M.D.

ABSTRACT To assess the relative contributions of afterload mismatch and impaired contractility to pump dysfunction in patients with chronic aortic valve disease, simultaneous left ventricular cineangiography and micromanometry were performed in 56 patients: 21 with severe aortic stenosis, 16 with severe aortic regurgitation, and 19 normal control subjects. Left ventricular mass was increased in patients with aortic stenosis and aortic regurgitation (172 ± 52 vs 224 ± 63 g/m², respectively, p < .05) as were end-diastolic volume (101 ± 39 and 167 ± 44 vs 77 ± 16 ml/m²; p < .05) and end-systolic volume (50 ± 40 and 84 ± 43 vs 24 ± 7 ml/m²; p < .05). Although ejection fraction was depressed in both abnormal groups (0.56 ± 0.18 for patients with aortic stenosis and 0.53 ± 0.13 for those with aortic regurgitation vs 0.69 ± 0.05 for control subjects; p < .05), the decrease in ejection fraction was disproportionate to the mild degree of afterload mismatch (end ejection stress 129 ± 17 in patients with aortic stenosis and 154 ± 58 in those with aortic regurgitation vs 117 ± 46 kdyn/cm² in control subjects; p = NS) with 10 of 21 patients with aortic stenosis and 12 of 16 patients with aortic regurgitation falling below the 95% prediction limit of the linear inverse relationship between ejection fraction and end-systolic stress for controls (EF = 0.78 - 0.00074-ESS). The maximum stress-volume index ratio, which is an index of inotropic state that is independent of preload but sensitive to afterload, was also depressed in patients with aortic stenosis and aortic regurgitation (3.8 ± 1.4 and 2.5 ± 0.9 vs 5.0 ± 1.3 kdyn/cm²/m² for control subjects; p < .05), and first-order partial correlation demonstrated that this decrease was inversely related to left ventricular mass index. Thus, although afterload mismatch may adversely affect ventricular performance in patients with aortic valve disease, extensive hypertrophy and contractile dysfunction appear to be the major determinants of pump dysfunction.


AFTERLOAD MISMATCH has been recognized as a cause of impaired pump performance in patients with chronic aortic valve disease. However, separating the effect of myocardial contractile dysfunction from that of afterload mismatch on pump performance has been difficult because of the lack of a load-independent index of contractile function.

Recently, the relationship between end-systolic stress and either ejection fraction or end-systolic volume has been used to estimate myocardial contractile function in chronically overloaded ventricles of animals and man. The present angiographic analysis of ventricular stress and volume was conducted to determine the relationship of contractile function to ejection performance in patients with chronic aortic stenosis or chronic aortic regurgitation. In this study, extensive hypertrophy and contractile dysfunction, rather than inadequate hypertrophy with afterload mismatch, were the major determinants of depressed ejection performance.

Methods

Subjects. From July 1983 through March 1985, 37 patients evaluated for symptomatic aortic valve disease with cardiac catheterization at the University of Kentucky and the Lexington Veterans Administration Medical Centers met the following criteria for inclusion in this study: (1) no coronary stenosis of greater than 50% lumen diameter and no regional area of akinesia or dyskinesis evident on ventriculography, (2) no history of alcohol abuse or other illness associated with cardiomyopathy,
(3) no significant mitral valve disease as defined by a computed mitral valve area less than 1.5 cm² or angiographic mitral regurgitation graded more than 2 + in severity by the criteria of Hunt et al.,14 and (4) catheterization data judged to be adequate based on criteria described below. Twenty-one patients had predominant aortic stenosis (group 1) as determined by a calculated valve area less than 1.2 cm² (mean 0.7 ± 0.2 cm²) and no greater than 2 + aortic regurgitation. Sixteen patients had predominant aortic regurgitation (group 2) graded angiographically as 3 + or greater with an aortic valve area of greater than 1.2 cm² and symptoms of greater than 3 months duration. A control group comprised 19 patients who were catheterized to evaluate chest pain syndromes but who were found to have: (1) normal coronary arteries, (2) a left ventricular ejection fraction of 0.60 or greater, and (3) left ventricular angiographic wall thickness less than 1.1 cm.

All patients were in sinus rhythm, and the QRS duration did not exceed 0.11 sec. Long-term medical therapy consisted of β-blockers (five control, five group 1, one group 2), diuretics (0 control, 10 group 1, six group 2), digoxin (0 control, five group 1, five group 2), calcium-channel blockers (eight control, three group 1, 0 group 2), and other vasodilators such as nitrates, captopril, and hydralazine (eight control, 10 group 1, four group 2). Subjects’ ages averaged 49 ± 10 years (35 to 70) in the control group, 58 ± 13 (28 to 76) in group 1, and 48 ± 17 (24 to 75) in group 2. The mean functional class (NYHA) was 2.8 ± 0.9 for group 1 and 2.9 ± 0.8 for group 2.

**Procedure.** Patients were premedicated with oral diazepam (5 to 10 mg). Right heart catheterization was performed via a femoral vein. Left heart catheterization was performed retrograde via a femoral or brachial artery with a No. 8F micromanometer catheter with a pigtail configuration, except for three patients in group 1 in whom transeptal catheterization was performed and two patients each in group 2 and the control group. In these seven patients pressure was recorded just before left ventricular angiography through well-flushed fluid-filled catheters, during which time there was no change in heart rate. In the other patients, left ventricular pressure was recorded simultaneously with injection of 39 to 54 ml of meglumine diatrizoate into the left ventricle during biplane cine angiography (30 degree right anterior oblique and 60 degree left anterior oblique). Precise synchronization between pressure and cine recordings was achievable with a cine frame marker, which recorded a mark for each film exposure (60/sec) simultaneously with the pressure recording. Immediately after ventriculography, biplane cineangiography of a grid positioned at mid chest was performed to correct for magnification. Coronary angiograms were performed in all patients.

Three patients in the control group gave informed consent to a protocol approved by the Human Investigations Committee for repeat left ventricular cineangiography after augmentation of afterload with ergonovine. In these three patients, coronary angiography was performed first; after a 10 min period of hemodynamic stabilization, left ventricular cineangiography and micromanometry were performed. Ergonovine maleate was then administered intravenously in three doses (0.05, 0.10, and 0.20 mg) over 20 min. After the third dose of ergonovine, left ventricular cineangiography and micromanometry were repeated, followed by repeat coronary angiography. Peak left ventricular systolic pressure was augmented by 27, 30, and 43 mm Hg in these three patients, but none developed evidence of coronary spasm in response to ergonovine.

**Analysis of catheterization data.** Only well-opacified sinus beats not immediately preceded by a premature beat were analyzed. Left ventricular silhouettes for each frame of an entire cardiac cycle were digitized with a hand-held cursor (Summographics). Left ventricular wall thickness was measured at the mid portion of the anterior wall in the right anterior oblique view or at the posterolateral wall as viewed in the left oblique projection. Left ventricular volume was computed by the area-length method and a regression equation. Correction factors for each view were derived from the grids. Because the quality of the left anterior oblique view was not judged to be adequate in all patients and because segmental dysynergy was absent, only single-plane right anterior oblique data are reported in the present study. Left ventricular pressure for the corresponding cardiac cycle was digitized starting from the mid portion of the QRS complex, which was considered to be end-diastole.

Cardiac output was determined by thermodilution and/or the Fick method. Ejection fraction is SV/EDV and regurgitant fraction is (SV - CO/HR)/SV where SV is angiographic stroke volume, EDV is end-diastolic volume, CO is cardiac output, and HR is heart rate during ventriculography. Aortic valve area was computed with the Gorlin equation16; when significant aortic regurgitation and stenosis coexisted, angiographic flow was used to compute valve area. Left ventricular mass was computed as:

\[
LVM = \frac{[(\pi/6) (L + 2h) (D + 2h)^2 - EDV]}{1.05}
\]

where L is the ventricular long axis, D is the diameter as computed from the area-length relationship, and h is wall thickness at end-diastole. Dynamic left ventricular wall thickness was computed from dynamic chamber volume and LVM, which is assumed to be constant, by means of the Newton-Raphson method used by Hugenholtz et al.17 Briefly, iteration of the three equations

\[
g(h) = h^3 + h^2 (L/2 + D) + h (LD/2 + D^2/4) - LVM(3/4pi) \\
g'(h) = 3h^2 + h (L + 2D) + LD/2 + D^2/4 \\
h = 1h - g(h)/g'(h)
\]

is performed until convergence on the solution for h, where g(h) is a function of h, g'(h) is the first derivative of the function, and 1h represents the value of h from the preceding iteration. Circumferential wall stress was computed with Mirsky’s equation18:

\[
S = \frac{(1.33PD/2h)(1-h/D-D^2/2L^2)}{}
\]

Stress and volume, indexed for body surface area, were plotted frame by frame with a computer, which searched the frames for the maximum ratio of stress to volume. We have previously found this ratio to be an index of inotropic state that is independent of myocardial length but sensitive to changes in afterload.19 Mean systolic stress is the stress integrated over the ejection time. Stress at end ejection was located on the stress-volume loop at the point at which volume first fell within 3 ml of absolute minimum. This method was used because a smoothing function was not applied to the data points, and the absolute nadir of the volume-time plot was sometimes at a point when stress was falling most rapidly.

Because the accuracy of wall stress computations is highly dependent on chamber volume and wall thickness measurements, the intraobserver and interobserver variability of these measurements was evaluated by the end-diastolic frames of nine ventriculograms (three from each patient group). The mean variability for the volume measurements between two observers (T. W. and S. N.) was 5.4 ± 3.8%. For the observer who traced the silhouettes for this study (T. W.), the intraobserver variability was 5.5 ± 5.0%. For the wall thickness measurements, the interobserver variability (T. W. vs S. N.) was 10.8 ± 5.5% and
the intraobserver (T. W.) variability was 7.4 ± 5.2%. In 40 patients in whom both right and left anterior oblique views were considered adequate, the variability between the measured anterior and posterior wall thickness was 14.5 ± 11.4%. This was greater than the nonuniformity between septal and posterior wall thickness measured by M mode echocardiography (2.4 ± 8.2%) in 26 of the study patients in whom echocardiography was performed within 2 weeks of cardiac catheterization. The correlation for posterior wall thickness measurements between echocardiography and ventriculography was $h_{\text{vgram}} = 1.040 - h_{\text{echo}} - 0.203$ (r = .78, p < .008).

**Statistical analysis.** A computer program based on multivariate general linear hypothesis (SYSTAT, Inc.) was used for intergroup comparisons by analysis of variance and, when appropriate, analysis of covariance. Significant differences among groups, when found, were isolated with Fisher's protected least significant difference method. Curve fitting was performed by the least-squares method. First-order partial correlations were made by the Pearson correlation matrix.

**Results**

The hemodynamic data are summarized in figure 1. Left ventricular end-diastolic pressure tended to be higher in both group 1 and group 2 compared with control subjects, although cardiac index was maintained in both (figure 1).

The mean value of end-diastolic stress, which was used as a measure of preload, was elevated in group 2 but not in group 1 compared with that in the control group (figure 2). The mean value of mean systolic stress was higher in group 2 than that in the control group, although afterload measured as end-systolic stress was similar among the three groups (figure 2).

Ejection fraction varied widely within groups 1 and 2 but was significantly depressed in both groups compared with that in the control group (figure 3). An inverse relationship between ejection fraction (EF) and end-systolic stress (ESS) was observed in all three groups: control group, $EF = 0.78 - 0.00074 \cdot \text{ESS}, r = -.74, p < .001$; group 1, $EF = 0.77 - 0.00167 \cdot \text{ESS}$.

![FIGURE 1](http://circ.ahajournals.org/)

**FIGURE 1.** The hemodynamic data were recorded simultaneously with left ventricular cineangiographic and micromanometric data during held inspiration except for cardiac index, which was measured just before injection of contrast medium. Values are represented as mean ± SD in this and subsequent figures. C = control group; AS = aortic stenosis (group 1); AR = aortic regurgitation (group 2).

![FIGURE 2](http://circ.ahajournals.org/)

**FIGURE 2.** Preload estimated as end-diastolic stress, afterload estimated as mean systolic stress and end-systolic stress. Abbreviations as in figure 1.
pressure overload. This concept, proposed by Ross, was extended by Gunther and Grossman to patients with aortic stenosis. Because ejection performance was inversely related to afterload, it was proposed that pump failure in patients with aortic stenosis occurred when the degree of hypertrophy was no longer adequate to maintain normal wall stress. When Carabello

FIGURE 3. Angiographic data. Abbreviations as in figure 1.

ESS, $r = - .75, p < .001$; group 2, EF = 0.79 - 0.00167·ESS, $r = - .73, p < .001$. Although ejection fraction extrapolated to a normal value at zero end-systolic stress for both groups 1 and 2, the slopes of the regressions for these two groups differed significantly ($p < .05$) from those of the regressions for the control group by analysis of variance. As shown in figure 4, there was unequivocal impairment of ejection performance that was disproportionate to the degree of afterload mismatch in 10 of the 21 patients with aortic stenosis and in 10 of 16 patients with aortic regurgitation. Interestingly, only one of 11 patients with aortic stenosis with an ejection fraction less than 0.60 fell within the 95% prediction limits of the normal relationship between ejection fraction and end-systolic stress. All 12 patients with aortic regurgitation in whom the ejection fraction was less than 0.60 fell below the 95% prediction limits of the normal ejection fraction–end-systolic stress relationship.

To further clarify the etiology of impaired ejection performance in patients with aortic stenosis, contractile state was estimated in individual patients by the maximum ratio of stress-to-volume as illustrated in figure 5, which has been used by others to estimate contractile state in valvular heart disease. For groups 1 and 2, the maximum stress:volume ratio was depressed ($3.8 \pm 1.4$ for group 1 and $2.5 \pm 0.9$ for group 2 vs $5.0 \pm 1.3$ kdyne/cm²/m² for control subjects; $p < .05$) despite afterload that was comparable to normal. Furthermore, there was a strong inverse correlation between the maximum stress:volume ratio and left ventricular mass (figure 6), indicating that the development of extensive hypertrophy is associated with ventricular contractile dysfunction in aortic valve disease.

 Discussion

Afterload mismatch has been recognized as a cause of impaired pump performance in patients with chronic
et al.\textsuperscript{3} extended the earlier study by Gunther and Grossman,\textsuperscript{2} it was inferred that a myocardial factor might be operative in a small subset of patients with aortic stenosis and congestive heart failure, in whom the pressure gradient was small. However, the small control group comprising six normal subjects in the earlier study\textsuperscript{2} and the lack of controls in the subsequent study\textsuperscript{3} did not permit a statistical comparison of contractile function between normal subjects and patients with aortic stenosis. The inverse relationship between ejection fraction and afterload observed in the present investigation is consistent with the results of these previous studies. However, our results extend previous findings in that they indicate that impaired performance in patients with aortic stenosis is not generally the effect of afterload mismatch on ventricles with inadequate hypertrophy, since impaired performance was found in patients with extensive hypertrophy, normalized afterload, and evidence of contractile dysfunction.

Several other clinical investigations support the conclusion that afterload mismatch is not the principal determinant of depressed ejection performance in chronic pressure overload. Huber et al.\textsuperscript{20} found that more traditional indexes of inotropic state were depressed in a subset of patients with aortic stenosis in whom peak systolic stress was normalized by extensive hypertrophy. In both the study of Huber et al.\textsuperscript{20} and the present investigation (figure 6), evidence of impaired inotropic state was more prominent in patients with greater hypertrophy than in those with moderate hypertrophy. Likewise, Takahashi et al.\textsuperscript{9} identified abnormal end-systolic stress-diameter slopes in hypertensive patients with severe wall thickening but not in those with modestly increased thickness. These findings are consistent with the experimental data in mammals\textsuperscript{7,21} and indicate that hypertrophy in man is a limited adaptation to pressure overload that eventually results in muscle failure and concomitant pump failure.

Although impaired inotropic state has long been postulated as the major cause of ventricular dysfunction in chronic aortic regurgitation,\textsuperscript{22} studies in animals

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Stress-volume loops for a representative patient from each group illustrating the method of obtaining the maximum stress-volume ratio (MSVR). This index of inotropic state underestimates maximal fiber elastance by a degree inversely proportional to the magnitude of the end-systolic stress, since it assumes the volume intercept to be zero.\textsuperscript{19}}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6.png}
\caption{Relationship between contractile function estimated as maximum stress-volume ratio (MSVR) and left ventricular mass index. A strong inverse correlation was noted even after accounting for the mathematical dependence of both stress and mass on wall thickness\textsuperscript{31} by means of a first-order partial correlation.}
\end{figure}
with experimentally induced volume overload have generally demonstrated normal muscle function.\textsuperscript{23, 24} In particular, studies in cats performed by Cooper et al.\textsuperscript{23} have shown convincingly that in volume-induced hypertrophy, contractile dysfunction is absent or takes longer to develop compared with hypertrophy of a comparable amount produced by pressure overload.\textsuperscript{21} These results in animals suggest that myocardium hypertrophied by volume overload may be functionally different from that hypertrophied by a pressure overload. In chronic severe aortic regurgitation in man, it may be that contractile dysfunction is caused less by the volume overload than by the concomitant pressure overload.\textsuperscript{5, 11}

Estimation of contractile function in patients with chronic myocardial overload has been difficult because of the lack of a load-independent index of contractile function.\textsuperscript{25} Maximal elastance,\textsuperscript{26} \(E_{\text{max}}\), has recently gained acceptance as an index that is sensitive to inotropic state and relatively insensitive to loading conditions. Accurate determination of \(E_{\text{max}}\), however, requires repeated measurements of end-systolic ventricular volume over a sufficiently wide range of systolic pressure to allow a meaningful regression. This is difficult in patients in whom hemodynamics are already abnormal, particularly those with critical aortic stenosis.\textsuperscript{10} Preliminary data obtained in our catheterization laboratory indicate also that changes in inotropic state may occur during load manipulation in patients in whom autonomic reflexes have not been blocked pharmacologically. Thus it may not be practical to determine \(E_{\text{max}}\) in patients with severe valvular heart disease.

The maximum stress:volume ratio for a single beat has been recently used as a practical alternative to measuring \(E_{\text{max}}\) in disease states associated with abnormal ventricular size and loading conditions.\textsuperscript{11, 12} The results of recent animal studies demonstrate that, although maximum stress:volume ratio is insensitive to short-term changes in preload and is sensitive to short-term inotropic interventions, this ratio changes in direct proportion to short-term changes in afterload.\textsuperscript{19} Thus reduced maximum stress:volume ratio could be caused by either depressed inotropic state or reduced afterload. In patients with aortic stenosis and preserved pump function in the present study, afterload measured as end-systolic or as mean systolic stress was comparable to that for control subjects. However, afterload was elevated in patients with aortic stenosis and severely impaired ejection performance. Contractile function may thus have been slightly overestimated by maximum stress:volume ratio in some patients with aortic stenosis and also in the group with aortic regurgitation, in which mean systolic stress tended to be higher than normal. However, contractile performance estimated from maximum stress:volume ratio was highly concordant with that estimated from the ejection fraction–end-systolic stress relationship (figure 4). The preload sensitivity of this latter relationship might also have caused overestimation of contractile function in group 2, in which preload was elevated, but not in group 1, in which preload was normal.

**Limitations.** Several technical limitations of this study should be mentioned, one of which is the measurement of afterload. It has been proposed that afterload be described by impedance spectra.\textsuperscript{27} Impedance, however, does not take into account the interrelationship between ventricular wall thickness, chamber dimensions, and pressure that may affect load at the myocardial fiber level.\textsuperscript{19} For this reason, those studying the function of hypertrophied hearts have generally used either mean systolic stress\textsuperscript{2, 3} or, more recently, end-systolic stress\textsuperscript{24} as a measure of the load that limits ejection. Neither of these measurements uniquely describes afterload, since both depend in part on contractile force generated by the ventricle. Although stronger correlations between ejection fraction and end-systolic stress, compared with ejection fraction and mean systolic stress, were observed for all three patient groups, uncertainty remains in regard to the more appropriate descriptor of afterload. In the present study, when ejection fraction–afterload relationships were analyzed with mean rather than end-systolic stress, the results were qualitatively similar in terms of identifying contractile dysfunction in patients with aortic stenosis (EF = 0.82 – 0.00141·MSS vs EF = 0.79 – 0.00057·MSS for control; p < .05) and those with aortic regurgitation (EF = 0.77 – 0.00099·MSS; p = NS vs control).

End-systole has traditionally been defined as the time at which ventricular volume reaches a minimum. However, Sagawa\textsuperscript{26} noted that the coincidence of end ejection, as indicated by minimum ventricular volume or dicrotic notch, with maximal elastance is “circumstantial” and has recently derived \(E_{\text{max}}\) by means of the point in each cardiac cycle where the pressure:volume ratio reached maximum.\textsuperscript{29} Computer analysis of stress-volume loops in our patients usually showed that maximum stress:volume ratio in each cardiac cycle very nearly coincided in time with the time of end ejection (figure 5, left and right panels). However, in some patients, the stress:volume ratio reached maximum well before end ejection (e.g., middle panel of figure 5). For consistency, therefore, the “afterload” for each
patient was measured as the stress at the end of ejection (see Methods). The lack of a uniform definition of end-systole may be one of several methodologic differences responsible for different results in our study of contractile function in patients with aortic stenosis compared with that of Mehmel et al., who used dicrotic notch pressures from 2 beats at different loads to derive $E_{\text{max}}$.

Some concern must be expressed regarding the suitability as a control group patients catheterized because of chest pain syndromes but with normal epicardial coronary arteries. However, it is doubtful that abnormal vasodilator reserve noted in some patients with chest pain and normal coronary arteries rendered our control group abnormal, since the only two patients who were found to have angiographically normal coronary arteries but a left ventricular ejection fraction less than 0.60 during this study were excluded. It is also unlikely that the small age differences among the groups significantly influenced differences in ventricular function noted among the groups. Finally, the clinical importance of the present findings will be tempered if future studies demonstrate full recovery of contractile function after successful aortic valve replacement despite severe preoperative hypertrophy with contractile impairment.

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T Wisenbaugh, D Booth, A DeMaria, S Nissen and J Waters

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