Ventricular Performance, Pump Function and Compensatory Mechanisms in Patients with Aortic Stenosis

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SUMMARY The contractile capacity of the human ventricle when chronically pressure-overloaded by aortic stenosis remains a subject of major debate. The compensatory mechanisms used to maintain normal resting cardiac output and ejection fraction, and the relation of compensatory mechanisms to symptoms, have not been fully documented. In this report we examined ventricular performance and the relationship of compensatory mechanisms to symptoms in 11 patients with severe aortic stenosis and congestive heart failure symptoms (AS-CHF group), in 10 patients with significant aortic stenosis but no heart failure symptoms (AS-C group), and in 12 normal subjects. Alterations in afterload, preload and wall thickness in aortic stenosis may adversely affect the validity of indexes of contractile function, so we attempted to account for or avoid the effect of such alterations. The natural variations in ventricular volume were used to estimate group ventricular function relationships relating peak systolic wall stress to end-diastolic volume index (Frank-Starling), and to estimate group relationships of end-systolic pressure or stress to end-systolic volume (Sagawa). The slope of the linear regression lines that estimated the Frank-Starling index and the Sagawa index showed statistically significant depression (p < 0.01) of left ventricular contractile function in the AS-CHF patients, while ventricular contractile function was relatively normal in the AS-C patients. End-diastolic volume index and pressure were significantly increased (p < 0.01) only in the AS-CHF group. Peak systolic left ventricular wall stress, ejection fraction, resting cardiac index, and the ratio of ventricular mass to volume were not statistically different from normal in either group.

ISOLATED cardiac muscle and intact animal hearts have shown decreased contractile function in the severely and acutely pressure-overloaded hypertrophied and failing heart.\textsuperscript{1-5} When the pressure overload is less intense and less acute and when heart failure does not develop, ventricular performance is variable.\textsuperscript{6, 7} In experimental animals, it appears that depression of myocardial function is directly related to the severity of the overload, the presence of congestive failure and, possibly, the duration of the overload.\textsuperscript{1, 3, 6, 7}

Despite these experimental studies, ventricular contractile function in patients with chronic pressure overload caused by aortic stenosis is still debated.\textsuperscript{8-17} From the limited patient studies available, it seems reasonable to postulate that ventricular contractile function is depressed when severe pressure overload has caused congestive failure, but normal when the overload is less severe and failure has not occurred.\textsuperscript{9, 11, 16, 17}

In this study, we tested this hypothesis by determining hemodynamic values and quantitative ventricular function measurements in three groups of patients. Patients with severe aortic stenosis and congestive heart failure symptoms were compared with patients without heart disease and with patients with significant aortic stenosis but no heart failure symptoms. We also studied compensatory mechanisms to determine whether they produce undesirable symptoms while maintaining normal ventricular pump function despite depressed ventricular muscle function.

Methods

Patient Groups

Three patient groups were established: 12 normal patients, 10 patients with significant but less severe aortic stenosis (average valve area 1.00 ± 0.27 cm\(^2\)) and no heart failure symptoms (AS-C group) and 11 patients with more severe aortic stenosis (average valve area 0.54 ± 0.06 cm\(^2\)) and symptoms of congestive heart failure (AS-CHF group). All 33 patients were studied by cardiac catheterization, biplane left ventriculography and selective coronary cinearteriography.

The 12 normal patients underwent cardiac catheterization because of chest pain syndromes. They were considered normal because ejection fraction was greater than 0.50, they showed no regional wall abnormality, end-diastolic pressure was 13 mm Hg or less, and they had no coronary artery, shunt or valve lesion. None of the 10 AS-C patients had symptoms of congestive heart failure. Specifically excluded from the AS-C group were patients with dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea and pulmonary edema. All AS-CHF patients had one or more of the following: dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, or previous acute overt pulmonary edema. A history of pulmonary edema was present in six of the 11 patients in the AS-CHF group.
A history of syncope was present in three AS-C patients and four AS-CHF patients. Angina was present in six AS-C patients and five AS-CHF patients. None of the patients studied had significant coronary artery disease, aortic insufficiency or mitral valve disease. Mitral valve disease was excluded by the absence of a mitral pressure gradient or regurgitation during ventriculography. Aortic regurgitation was excluded by aortic root contrast injection in any patient with a diastolic murmur. The sex distribution was similar in the three groups. The AS-CHF patients (average 64 ± 4 years [SEM]) were older than those in the normal group (45 ± 4 years) and the AS-C group (53 ± 6 years).

Catheterization and Ventricular Function Analysis

Cardiac catheterization was conducted in the fasting state with mild sedation (diazepam or secobarbital) and local anesthesia.18, 19 The brachial or percutaneous femoral technique was used for catheterization of the left ventricle by the retrograde method. Simultaneous brachial artery pressure was determined by percutaneous puncture or simultaneous left ventricular and aortic root pressures were determined by a proximal and distal dual micrometer catheter (Millar). Left ventricular pressure was recorded immediately before angiography by standard catheter techniques in 11 patients, or simultaneously with the angiogram by a catheter-tip manometer incorporated into the injection catheter (Millar) in 22 patients. Nonsimultaneous pressure curves were traced on a digital plotting table and synchronized with the ventriculographic data using electrocardiographic R-wave registration and a specially designed computer program.20 To determine the time difference between the Millar and fluid-coupled catheters, we simultaneously measured pressures with both catheters in 17 randomly chosen cardiac cycles in two dogs. The time delay in peak left ventricular pressure from Millar to fluid-filled catheters was 13.2 ± 3.1 msec, a lag of less than one cine frame. This degree of lag would not significantly alter the determination of pressure relative to left ventricular volume at end-systole. We have demonstrated previously that pressure at end-systole does not change significantly during this period of time at end-systole.20 Therefore, no time lag correction was used. End-systolic pressure was chosen as the pressure that corresponded to the smallest ventricular volume. Biplane 35-mm cineventriculograms of the left ventricle were exposed at 60 frames/sec. Contrast injection rates were 11–15 ml/sec. Recorded simultaneously on the cine film were the ECG and the left ventricular pressure for those whose pressure was measured with a catheter-tip manometer. A timed light pulse was recorded on both biplane films to provide precise synchronization between the films during analysis. All studies were performed in the 60° left anterior oblique and 30° right anterior oblique biplane positions. The aortic valve area was calculated by the formula of Gorlin and Gorlin.21 Cardiac output was determined by the Fick principle.

To calculate left ventricular volume, the ventricular image in each view is divided by computer into 50 diameters. The diameters are calculated in each view as the vector distance between points on opposite sides of the endocardial outline that lie on a line perpendicular to the long axis. To calculate volume, Simpson’s rule is used to sum the product of the left and right anterior oblique diameters at each level.

Ventricular mass is calculated using the formula of Rackley et al.22 where average wall thickness is measured from the region of the anterior left ventricular wall in the right anterior oblique view extending 3 cm from the midventricle toward the apex. When wall thickness is determined, it is doubled and added to the average ventricular diameters calculated with the Dodge formula23 for the two views and to the long axis. The whole ventricular volume minus the chamber volume gives the muscle volume. The mass is calculated by multiplying volume by 1.05, the specific gravity of cardiac muscle.22

To calculate wall stress, a thin-walled model is applied to the ventricle in the region which is half of the distance from the apex to the base. This method incorporates the actual curvature of the ventricle along a midwall line calculated from the endocardial and epicardial coordinates.

The meridian radius of curvature (Rm) is calculated from the formula:

\[ R_m = \frac{(1 + \dot{y}^2)^{3/2}}{\ddot{y}} \]

where \( \dot{y} = \frac{dy}{dx} \) and \( \ddot{y} = \frac{d^2y}{dx^2} \), and \( x \) and \( y \) are the spatial coordinates of points on the midwall axis. This formula is applied to a parabolic curve calculated from 25 points along the ventricular wall in the right anterior oblique view using the least-squares method, with the point of interest at the center of the region of analysis. The hoop radius (Rh) is calculated by a geometric method described previously.22 When the two radii of curvature are known, stress is calculated by the formula:

\[ S_h = \frac{P_Rh}{T} \frac{(2R_m - R_h)}{(2R_m)} \]

where \( T \) is wall thickness and stress (Sh) is in the circumferential (hoop) direction. After stress is found for each frame, a curve of hoop stress vs time is plotted for each cardiac cycle. These calculations have been described.20, 24, 25

Statistical Analysis

One-way analysis of variance was used to examine differences between data for the three groups. Linear regression using the method of least squares was used to find the slopes of the ventricular function curves, and the slopes were compared using a nonpaired t test.
Results

Hemodynamics, Hypertrophy, and Relationship of Hypertrophy to Volume

Left ventricular peak pressure was significantly elevated ($p < 0.01$) above the normal group average (121 ± 5 mm Hg) in both AS-C (184 ± 12) and AS-CHF (201 ± 11) groups. The AS-C group had an average left ventricular end-diastolic pressure of 10 ± 2 mm Hg, not significantly different from the normal group pressure of 9 ± 1, but the AS-CHF group pressure averaged 16 ± 3 and was significantly elevated ($p < 0.05$) above the other two groups. Heart rates were similar in the three groups, averaging 65 ± 3 beats/min in the normal group, 73 ± 5 in the AS-C group and 72 ± 5 in the AS-CHF group. Cardiac index averaged 3.2 ± 0.1 l/min in the normal group and was not significantly different in either the AS-C group (3.5 ± 0.1 l/min) or the AS-CHF group (2.6 ± 0.1 l/min). However, three AS-CHF patients had cardiac indexes below 2.4 l/min, the lower limit of normal in our laboratory. The average ejection fraction was not significantly altered in AS-C patients (0.67 ± 0.03) or AS-CHF patients (0.53 ± 0.04) compared with normal (0.63 ± 0.03). The ejection fraction was greater than 0.50, the lower limit of normal in our laboratory, in each normal and AS-C patient and in eight of the 11 AS-CHF patients. Left ventricular mass in the AS-C group was significantly increased ($p < 0.02$) above the normal value of 86 ± 6 g/m² to a value of 113 ± 9 g/m². The ventricular mass in the AS-CHF group averaged 196 ± 27 g/m² and was significantly elevated ($p < 0.02$) above both normal and AS-C groups. The ratio of left ventricular mass to left ventricular end-diastolic volume was significantly increased above the normal group value of 0.91 ± 0.08 in both the AS-C group (1.22 ± 0.12, $p < 0.05$) and the AS-CHF group (1.30 ± 0.13, $p < 0.03$).

Left Ventricular Wall Stress

Despite the elevation of peak systolic pressure in both AS groups and increased ventricular volume in the AS-CHF group, increased wall thickness tended to reduce peak systolic wall stress in both AS groups (fig. 1). Peak systolic wall stress for seven of 10 AS-C patients and for 10 of 11 AS-CHF patients were normal. There were no significant differences among the average values for any group, although the values for AS-C group (479 ± 52 dyn/cm² × 10⁻³) and the AS-CHF group (450 ± 29 dyn/cm² × 10⁻³) tended to be higher than the value for the normal group (355 ± 33 dyn/cm² × 10⁻³). End-diastolic left ventricular wall stress averaged 39 ± 3 dyn/cm² × 10⁻³ in the normal group, 32 ± 5 dyn/cm² × 10⁻³ in the AS-C group, and 55 ± 8 dyn/cm² × 10⁻³ in the AS-CHF group. The AS-CHF group value was significantly greater ($p < 0.02$) than the normal.

Left Ventricular Volume Index

The end-diastolic volume index was normal in each AS-C patient (fig. 2). However, eight of 11 AS-CHF patients had end-diastolic left ventricular volumes above the normal range, and the AS-CHF average of 147 ± 12 cm³/m² was significantly increased ($p < 0.01$) compared to the normal value of 94 ± 5 cm³/m² and the AS-C group value of 98 ± 9 cm³/m². The end-diastolic left ventricular volume index of the AS-CHF group was significantly elevated ($p < 0.05$) to 71 ± 9 ml/m² compared to the normal value of 38 ± 3 ml/m² and the AS-C group of 32 ± 3 ml/m².

Left Ventricular Performance Indexes

Four indexes were selected to estimate left ventricular function in an attempt to account for or avoid some of the problems caused by altered afterload, preload and wall thickness in aortic stenosis.

In the first such index, a Frank-Starling-type relationship of peak systolic wall stress vs end-diastolic ventricular volume index was plotted for each group (fig. 3). Determination of the peak systolic stress at the naturally occurring variations in end-diastolic volume among the patients in each group provided data for calculation of a linear regression line for each group. These linear regression lines were used as estimates of a segment of the ventricular function relationship for each group and are shown as the sloping lines in figure 3. The slopes of the lines were then compared.

Figure 1. Peak systolic left ventricular wall stress in three patient groups. Wall stress for each patient is shown as a symbol while the horizontal short line through the symbol is the average in each group. The area between the dashed lines is the normal range. AS-C = patients with aortic stenosis and no symptoms of heart failure; AS-CHF = patients with severe aortic stenosis and heart failure symptoms.

Figure 2. End-diastolic left ventricular volume index in three patient groups. Volume index for each patient is shown as a symbol while the horizontal short line through the symbols is the average in each group. The area between the dashed lines is the normal range. Abbreviations: see figure 1.
The relationship of left ventricular peak systolic stress to end-diastolic volume index in each patient group. The individual points are shown for each patient. The sloping solid lines through the points are the linear regression. The slope of these linear regressions and their standard errors are shown below each group. The p value denotes the significant difference of the AS-CHF slope from both AS-C and normal slopes. Abbreviations: see figure 1.

The relationship of end-systolic pressure to end-systolic volume index, recently proposed by Sagawa as a measure of ventricular performance, was plotted for each group (fig. 4).\(^\text{26}\) Determination of the end-systolic pressure at the naturally occurring variations in end-systolic ventricular volume among the patients in each group provided data for calculation of a linear regression line for each group. These linear regression lines were then used as estimates of the E\(_{\text{max}}\) line for each group and are shown as the sloping lines in figure 4. Variance of the slopes was calculated and the lines in each group were compared statistically as described above. A significant reduction (\(p < 0.01\)) in the slope of this line was observed in the AS-CHF group compared with the normal and AS-C groups. The slope for the AS-CHF group was 0.08 ± 0.03, compared with 0.6 ± 0.5 for the AS-C group and 0.9 ± 0.3 for the normal group. The slope of the AS-C group was not significantly different from that of the normal group, although it was lower than normal.

Finally, to correct for variations in wall thickness among the groups, end-systolic stress was calculated and plotted against end-systolic volume index (fig. 5). Naturally occurring variations in the volume were again used to plot the linear regressions, which were used as estimates of the E\(_{\text{max}}\) lines, and the slopes were statistically compared. A significant reduction (\(p < 0.01\)) in the slope of this estimate of the E\(_{\text{max}}\) line was found in the AS-CHF group (0.9 ± 0.5) compared with both normal (5.8 ± 1.3) and AS-C groups (3.9 ± 1.3). Although the AS-C group had a lower slope than the normal, the difference was not statistically significant.

Discussion

This study suggests that contractile function, estimated by group performance vs volume curves and
end-systolic pressure-volume relationships, is reduced in patients with severe aortic stenosis and congestive heart failure. Further, contractile function appears relatively normal in patients with significant but less severe aortic stenosis but without heart failure.

Several studies have evaluated the relationship between ventricular contractile indexes and clinical status in patients with aortic stenosis. Pantely, Morton and Rahimtoola showed decreased mean velocity of circumferential fiber shortening and ejection fraction in 10 patients with pure aortic stenosis. Of their patients were described as functional class III (New York Heart Association). However, it is difficult to evaluate their study because both circumferential fiber shortening and ejection fraction can be altered by changes in afterload. Brunner, Steiger, Goebel and Krayenbuehl studied 41 patients with pure or predominant aortic stenosis and found a bimodal distribution of contractile indexes similar to our current observations. Seventeen of their patients had normal isovolumic and ejection phase contractile indexes. The isovolumic contractile indexes used were \( V_{\text{max}} \) and peak measured isovolumic velocity of shortening, and the ejection phase contractile indexes used were mean velocity of circumferential fiber shortening and mean normalized systolic ejection rate. In 16 of their patients, either the isovolumic or the ejection phase indexes were reduced, and in eight others both indexes were reduced. Their results are difficult to compare with ours because several of their patients had significant aortic insufficiency and because they did not describe any correlation of the ventricular mechanics with clinical symptoms of heart failure even though there was a significant inverse correlation of contractile indexes with end-diastolic pressure. Levine found decreased contractile element velocity during isovolumic systole in four of twelve patients studied with aortic stenosis. Three of the four patients with depressed contractile indexes had congestive heart failure, while none of the eight patients with normal isovolumic contractile indexes had congestive heart failure.

These patient studies appear consistent with observations of experimental animals subjected to ventricular pressure overload. The animals studied had no depression or moderate depression of contractile function in the hypertrophied nonfailing heart and more severe depression of contractile function when heart failure was present. In these experimental studies, the extent of reduction of contractile function also appeared to be related to the severity of ventricular outflow stenosis.

The findings of our investigation differ from those of Gunther and Grossman, who suggest that poor cardiac performance in patients with aortic stenosis may not be related to depression of myocardial contractility, but rather to increased wall stress and inadequate hypertrophy. Our data show no evidence that inadequate hypertrophy accounts for the failure state since, in our AS-CHF group, systolic wall stress was relatively normalized, ventricular mass was highest, and the ratio of left ventricular mass to end-diastolic volume was not depressed. We confirmed previous studies that demonstrate that wall stress is relatively normal despite increased intracavitary pressure in patients with aortic stenosis.

Gunther and Grossman’s conclusions about myocardial contractile performance may be questioned because ejection fraction and mean velocity of fiber shortening, which they used to estimate ventricular function, are sensitive to alterations in afterload. Further, if their data are used to plot stroke work index vs end-diastolic volume as a Frank-Starling relationship, findings that may be contrary to their conclusions become evident. They discussed a group A of five patients with aortic stenosis who seemed to have heart failure because they had significant reduction of cardiac index and average end-diastolic left ventricular pressure of 31 mm Hg, and a second group B of nine patients with aortic stenosis and a normal cardiac output and less elevation of end-diastolic pressure to 21 mm Hg. Stroke work index in their aortic stenosis group A (45 ± 9 g-m/m²) was significantly lower (p < 0.01) than in their aortic stenosis group B (71 ± 9) despite significantly increased (p < 0.01) end-diastolic volume index (111 ± 17 ml/m²) in group A.

**Figure 5.** The relationship of left ventricular end-systolic stress to end-systolic volume index in each patient group. The individual points are shown for each patient. The sloping solid lines through the points are the linear regressions. The slope of these linear regressions and their standard errors are shown below each group. The p value denotes the significant difference of the AS-CHF slope from both AS-C and normal slopes. Abbreviations: see figure 1.
compared with group B (75 ± 6 ml/m²). These data suggest decreased contractile function in their aortic stenosis group A patients, who appear to be operating on a lower Frank-Starling relationship than their aortic stenosis group B patients.

Although our data and other studies suggest that contractile function is decreased in severe aortic stenosis, this suggestion must be interpreted with caution because alterations in afterload, preload and wall thickness in aortic stenosis may adversely affect the validity of several indexes of contractile function.17, 19 We used two techniques in an attempt to account for or avoid these effects. Our first technique was plotting two Frank-Starling-type relationships of peak systolic stress vs preload expressed either as end-diastolic volume or end-diastolic stress. Both incorporate preload variations into the performance analysis so that preload effects are taken into account and the use of stress avoids errors caused by variations in wall thickness. Our second technique was analysis of the relationship between pressure and volume at end-systole. This contractile index, proposed by Sagawa and recently extended to man by Grossman and by Weisfels, is thought to be independent of both preload and afterload.20, 21, 22 End-systolic stress vs end-systolic volume was also plotted to correct for differences in wall thickness.

These techniques also have limitations. Naturally occurring variations in end-diastolic and end-systolic volume within each group of patients were used to calculate linear regression lines that served as estimates of the Frank-Starling relationship and Emax lines for each group. To make group comparisons as objective and reliable as possible, the estimates were obtained by linear regression analysis, and statistical techniques were used to compare the slopes. These relationships would have been better defined if each heart had been manipulated through a range of volumes and individual curves had been obtained, but such manipulation and the necessary multiple ventriculograms were not considered safe in patients with aortic stenosis.

Our data provide some experimental support for the suggestion that compensatory mechanisms maintain cardiac output and ejection fraction in the presence of pressure overload and depressed contractile function, but may lead to symptoms of congestive heart failure.10, 23 There was no significant difference in average resting cardiac index or average ejection fraction between the two groups. The data suggest that an increase in preload, acting as a Frank-Starling compensation, was maintaining cardiac output and ejection fraction in the AS-CHF group despite depression of contractile function. When we divided our patients into two groups, the AS-CHF group had significant decreases in contractile function and significant increases in end-diastolic ventricular volume. Eight of 11 AS-CHF patients had abnormally elevated end-diastolic volume (fig. 2). None of our 10 AS-C patients had end-diastolic volume above normal values. Further, the AS-CHF group had significantly increased end-diastolic pressure of 16 ± 3 mm Hg, while the AS-C group had normal end-diastolic pressure of 10 ± 2 mm Hg, a difference that may account for the dyspnea in the AS-CHF group. It is important to point out that our findings refer only to the resting heart. Reduced cardiac output response to exercise has been demonstrated in such patients.44

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Detection of Dysrhythmia in Pediatric Patients with Mitral Valve Prolapse

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SUMMARY The association of dysrhythmias with mitral valve prolapse in pediatric patients was investigated by graded treadmill exercise testing and 24-hour ambulatory ECG monitoring. Twenty-six unselected patients with a clinical diagnosis of mitral valve prolapse confirmed by echocardiography or angiocardio- graphy or both were studied. On 24-hour ambulatory ECG monitoring, six patients (23%) had potentially serious ventricular dysrhythmias. Five of these patients also manifested ventricular dysrhythmias on treadmill exercise testing. Neither standard ECG abnormalities nor clinical symptoms correlated with detected dysrhythmias. This study shows that potentially serious ventricular arrhythmias are common in pediatric patients with mitral valve prolapse and that ambulatory ECG monitoring and treadmill exercise testing are useful for detecting dysrhythmias.

MITRAL VALVE PROLAPSE is now recognized as a common form of mitral valve dysfunction. Although previous reports suggest that the prognosis for isolated mitral valve prolapse in childhood is excellent,101 syncope and sudden death have been reported and are felt to be related to cardiac arrhythmias.2 The association of mitral valve prolapse with arrhythmias manifested on ambulatory monitoring or stress testing has been well substantiated in adults.104 To date, there have been few reports concerning this association in pediatric patients.1,4 In this paper we report the results of treadmill exercise testing and 24-hour ambulatory ECG monitoring in a group of unselected pediatric patients with mitral valve prolapse.

Methods

Patient Population

The study group consisted of 26 consecutive patients seen during a 1-year period in the Pediatric Cardiology Clinic with an auscultatory diagnosis of isolated mitral valve prolapse. In each patient, the diagnosis of mitral valve prolapse had been confirmed by echocardiography or angiocardio- graphy or both.1918 Nineteen patients had been followed with a diagnosis of mitral valve prolapse; in seven patients the diagnosis was made during the study. All patients...
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