Unexpected persistence into adulthood of low wall stress in patients with congenital aortic stenosis: Is there a fundamental difference in the hypertrophic response to a pressure overload present from birth?

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ABSTRACT Congenital aortic stenosis in children is characterized by low left ventricular systolic wall stress allowing for supernormal ejection performance. In contrast, adults with acquired aortic stenosis have normal or excessive systolic wall stress resulting in either normal or subnormal ejection performance. In this study young children with congenital aortic stenosis, older children and adults with congenital aortic stenosis, and adults with acquired aortic stenosis were evaluated to test the hypothesis that the childhood pattern of low wall stress would convert to the adult pattern with advancing age. Left ventricular end systolic wall stress was lower in both congenital aortic stenosis groups when compared with that in age-matched normal subjects or adults with acquired aortic stenosis. Ejection fraction was higher in both groups of patients with congenital aortic stenosis than in age-matched controls. There was no tendency in the 16 patients with congenital aortic stenosis, some of whom were followed to the age of 33, for the congenital pattern of wall stress and ventricular performance to convert to the adult pattern. These results suggest that there is a fundamental difference in the hypertrophic response to a pressure overload present at birth compared with the response to one acquired later in life.


CHILDREN WITH congenital aortic stenosis have abnormal left ventricular systolic wall stress resulting in supernormal ejection performance. Adults with acquired aortic stenosis have normal or subnormal ejection performance. We hypothesized that if patients with congenital aortic stenosis were permitted to mature into adulthood without relief of the stenosis, the adult pattern of stress and ejection performance would develop. Therefore, we analyzed ventricular performance and cardiac mechanics in three groups of patients with aortic stenosis: young children with congenital aortic stenosis, older children and adults with congenital aortic stenosis, and adults with acquired aortic stenosis. If our hypothesis were correct, wall stress would increase with age in patients with congenital aortic stenosis and evolve into the pattern of acquired adult aortic stenosis.

Methods

*Study patients.* Twenty-three consecutive patients with pure aortic stenosis who met our criteria for study (described below) were age-matched with 23 normal subjects. Normal subjects were chosen randomly for study on the basis of age and without any prior knowledge of their hemodynamic and angiographic data. Six groups, including a total of 46 subjects, were studied and compared: group YCAS, young children with congenital aortic stenosis; group YNL, young age-matched normal children; group OCAS, older children and adults with congenital aortic stenosis; group ONL, older age-matched normal subjects; group AAS, adults with acquired aortic stenosis; and group ANL, adult age-matched normal subjects.

Group YNL and seven of nine subjects in group ONL were chosen from those undergoing electrophysiologic testing for arrhythmias in our pediatric catheterization laboratory. Before electrophysiologic testing these patients underwent pressure measurement and ventriculography to rule out structural cardiac disease. Patients free of cardiac anatomic abnormalities were
chosen for study if they met all of these four criteria: (1) they were receiving no drugs known to affect cardiac function, (2) they had two consecutive sinus beats during ventriculography, (3) cardiac chamber and wall thickness silhouettes were clearly visible and could be determined with certainty, and, (4) properly calibrated pressure tracings were available for review for which the dicrotic notch pressure and left ventricular end-diastolic pressure could be clearly discerned.

Fourteen individuals fulfilled these criteria, including eight male and six female subjects. Two group ONL patients and all group ANL patients were chosen from among patients undergoing cardiac catheterization in our adult catheterization laboratory for chest pain atypical of coronary ischemia. All were subsequently found to have normal coronary arteriograms, normal left ventricular end-diastolic pressure, and normal left ventriculograms. None had evidence of mitral valve prolapse. None were receiving β-blockers or calcium channel-blocking agents. All fulfilled the same criteria as group YNL patients.

Group YCAS patients were those with congenital aortic stenosis who were under the age of 10. In addition to fulfilling criteria 1 to 4 as listed for group YNL, group YCAS patients all had a peak transaortic valve gradient of 50 mm Hg or greater. Gradient was chosen as the measure of severity of aortic stenosis instead of valve area since there is no general consensus regarding the critical valve area or area index in small children. Seven patients, three boys and four girls from 4.5 to 10 years old (mean 8.4 ± 1.1) fulfilled these criteria and comprised the group.

Group OCAS consisted of patients with congenital aortic stenosis who were over the age of 15 years. Except for age, groups YCAS and OCAS had identical inclusion criteria. Nine patients ranging in age from 15 to 33 years (mean 21.0 ± 2 years) comprised the group, which included five men and four women.

Group AAS included adults with acquired aortic stenosis who were over the age of 50 and fulfilled the criteria required of the other aortic stenosis groups. Additionally, patients were excluded from this group if they had subnormal left ventricular ejection performance (ejection fraction <0.55), since these patients frequently have high wall stress.5-7 The inclusion of such patients with high wall stress would have biased the study in favor of demonstrating a difference between the adult and childhood groups with aortic stenosis. Seven patients from 58 to 72 years old (mean 63 ± 2) comprised this group. All of these patients had normal coronary arteriograms and were without other valvular lesions.

Of the 23 patients with aortic stenosis, 17 underwent aortography, which demonstrated no more than mild (1+) aortic insufficiency in all 17. Three additional patients underwent noninvasive Doppler studies that demonstrated no significant aortic insufficiency. In the remaining three patients there was no suggestion of significant aortic insufficiency on physical examinations.

Two patients in group YCAS and four in group OCAS underwent cardiac catheterization at the University of Kentucky. The remaining patients were catheterized at the Medical University of South Carolina.

Catheterization procedure. Catheterization was performed in a similar manner at both institutions in subjects in the fasting state. Children were premedicated with 2 mg/kg meperidine and 1 mg/kg promethazine. Cineangiography was performed in the right anterior oblique view at 60 frames/sec. In adults premedication consisted of 5 to 10 mg diazepam and 50 mg diphenhydramine given orally or 50 to 100 mg intramuscular secobarbital given before the procedure. Cineangiograms were obtained in the right anterior oblique view at 30 (11 patients) or 60 (12 patients) frames/sec. Pressures were recorded just before cineangiography through fluid-filled catheters in children and adults. In children, the transvalvular gradient was obtained at the time of left heart catheter pullback. No peripheral catheter was used to obtain simultaneous left ventricular and systemic pressures because of the increased risk of vascular complications in children. In adults, the gradient was obtained from simultaneous recording of left ventricular and peripheral pressures.

Measurements and calculations. Cardiac volumes were calculated by the area-length method.6 The end-diastolic volume was taken as the largest volume and the end-systolic as the smallest volume. Volumes were indexed to body surface area. Wall thickness was measured at the midanterior left ventricular wall at end-diastole and was calculated for end-systole with the assumption that cardiac mass remains constant during the cardiac cycle.7 Echocardiograms were also available for review for 14 of 23 patients with aortic stenosis and for 10 of the 23 control subjects. The echocardiographic measurements of posterior wall thickness, obtained by an observer blinded to the angioraphic results, did not vary by more than 1 mm from the angiographic results in 23 of the 24 cases and varied by 1.5 mm in the twenty-fourth case. End-systolic circumferential wall stress was calculated by Mirsky’s formula and expressed as kilodynamics/square centimeter:

\[
\text{Stress} = \frac{\rho \cdot \frac{1}{h} \left( \frac{1}{h} - \frac{h}{2b} - \frac{b^2}{2a^2} \right)}{1332} \text{ dynes/cm}^2/\text{mm Hg}
\]

where \( \rho \) = dicrotic notch pressure from the aortic pressure tracing just before entering the left ventricle; \( b = \) left ventricular end-systolic semimajor axis; \( \frac{D + h}{2} \); \( a = \) left ventricular end-systolic semimajor axis; \( \frac{L + h}{2} \); \( h = \) end-systolic wall thickness.

End-diastolic stress was calculated by the same formula, where \( p = \) end diastolic left ventricular pressure; \( b = \) left ventricular end-diastolic semimajor axis; \( a = \) left ventricular end-diastolic semimajor axis; \( h = \) end-diastolic wall thickness. Left ventricular mass, expressed in grams, was calculated9 as:

\[
\text{Mass} = \left( \frac{4}{3} \pi \left( \frac{L + 2h}{2} \right) \cdot \left( \frac{M + 2h}{2} \right) \cdot \left( \frac{N + 2h}{2} \right) \right)^{1.05}
\]

where \( \frac{L + 2h}{2} \) = semimajor axis; \( \frac{M + 2h}{2} \) and \( \frac{N + 2h}{2} \) = semiminer axes; \( h = \) end-diastolic wall thickness; \( V = \) left ventricular end-diastolic chamber volume.

Statistics. When each group of patients with aortic stenosis was compared only with its age-matched control group, a paired t test was used to evaluate group differences. When multiple (more than two) group comparisons were made, analysis of variance was used, followed by a Newman-Keuls test if analysis of variance showed a significant difference among the groups. Dispersion from the mean is reported as ± SEM. Linear regression, when performed, was calculated by the least square method.

Results

Hemodynamic variables for subjects in each of the groups are listed in tables 1 and 2. Peak aortic valve gradients, as shown in figure 1, were not significantly different among the three groups of patients with aortic
TABLE 1

Age and angiographic data (group means ± SEM)

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>EDVI (cc/m²)</th>
<th>ESVI (cc/m²)</th>
<th>EF</th>
<th>MI (g/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>YNL</td>
<td>8.4 ± 1.1</td>
<td>70 ± 6</td>
<td>23 ± 3</td>
<td>0.69 ± 0.03</td>
</tr>
<tr>
<td>OCAS</td>
<td>8.4 ± 1.1</td>
<td>74 ± 13</td>
<td>14 ± 2</td>
<td>0.80 ± 0.03</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>&lt;.05</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>ONL</td>
<td>21 ± 2</td>
<td>78 ± 5</td>
<td>31 ± 2</td>
<td>0.61 ± 0.02</td>
</tr>
<tr>
<td>OCAS</td>
<td>21 ± 2</td>
<td>98 ± 8</td>
<td>22 ± 4</td>
<td>0.78 ± 0.03</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>&lt;.05</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ANL</td>
<td>63 ± 2</td>
<td>78 ± 17</td>
<td>18 ± 2</td>
<td>0.76 ± 0.01</td>
</tr>
<tr>
<td>AAS</td>
<td>63 ± 2</td>
<td>90 ± 10</td>
<td>28 ± 7</td>
<td>0.71 ± 0.05</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; MI = mass index.

Groups compared by paired t test.

The importance of finding in this study was the persistent presence of subnormal left ventricular systolic wall stress in older patients with congenital aortic stenosis. No trend toward conversion to the adult pattern of normal or high wall stress occurred in these patients. Our results are consistent with those of Carpenter et al., who examined another congenital pressure overload — coarctation of the aorta — and found persistent hypertrophy and hyperdynamic contraction in normotensive adults up to 27 years after repair.

Our observation that systolic wall stress did not increase with age in patients with congenital aortic stenosis and did not evolve into the pattern of acquired adult aortic stenosis has several possible explanations, including the following:

TABLE 2

Pressure and stress data (group means ± SEM)

<table>
<thead>
<tr>
<th>LVP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>h/r</th>
<th>ESS (kdynes/cm²)</th>
<th>EDS (kdynes/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>YNL</td>
<td>108 ± 4</td>
<td>9 ± 1</td>
<td>0.30 ± 0.01</td>
<td>104.7 ± 11</td>
</tr>
<tr>
<td>YCAS</td>
<td>189 ± 10</td>
<td>14 ± 1</td>
<td>0.52 ± 0.05</td>
<td>63.3 ± 6.7</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;.001</td>
<td>&lt;.05</td>
<td>&lt;.01</td>
<td>NS</td>
</tr>
<tr>
<td>ONL</td>
<td>122 ± 4</td>
<td>9 ± 1</td>
<td>0.28 ± 0.02</td>
<td>157 ± 12</td>
</tr>
<tr>
<td>OCAS</td>
<td>185 ± 8</td>
<td>14 ± 2</td>
<td>0.50 ± 0.05</td>
<td>70.1 ± 8</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;.001</td>
<td>&lt;.05</td>
<td>&lt;.001</td>
<td>NS</td>
</tr>
<tr>
<td>ANL</td>
<td>144 ± 9</td>
<td>12 ± 1</td>
<td>0.32 ± 0.02</td>
<td>116 ± 8</td>
</tr>
<tr>
<td>AAS</td>
<td>205 ± 10</td>
<td>21 ± 3</td>
<td>0.52 ± 0.05</td>
<td>110.9 ± 10</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;.01</td>
<td>&lt;.05</td>
<td>&lt;.01</td>
<td>NS</td>
</tr>
</tbody>
</table>

EDS = end-diastolic stress; ESS = end-systolic stress; h/r = ratio of end-diastolic left ventricular wall thickness to radius; LVP = peak left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure.

Groups compared by paired t test.

Discussion

The most important finding in this study was the persistent presence of subnormal left ventricular systolic wall stress in older patients with congenital aortic stenosis. No trend toward conversion to the adult pattern of normal or high wall stress occurred in these patients. Our results are consistent with those of Carpenter et al., who examined another congenital pressure overload — coarctation of the aorta — and found persistent hypertrophy and hyperdynamic contraction in normotensive adults up to 27 years after repair.

Our observation that systolic wall stress did not increase with age in patients with congenital aortic stenosis and did not evolve into the pattern of acquired adult aortic stenosis has several possible explanations, including the following:
FIGURE 2. Ejection fractions (EFs) for the six groups of patients. Each patient in the groups of those with aortic stenosis is represented by a symbol and the corresponding symbol for each subject in the control group represents the age-matched control for that patient. The comparisons were performed by analysis of variance followed by the Newman–Keuls test.

FIGURE 3. Wall stress for the six groups of patients. Symbols are matched and statistical analysis is as in figure 2.
(1) The stimulus to hypertrophy could have been different among the groups, i.e., there may have been a difference in the severity of obstruction or in the amount of pressure overload among the groups examined, leading to different levels of hypertrophy. This seems unlikely since all groups were chosen with the use of the same criteria. All groups had severe aortic stenosis clinically and the pressure gradients were similar in the three groups of patients with aortic stenosis.

(2) We may have failed to identify the transition between congenital and acquired aortic stenosis because this transition occurs in individuals in the age range between 34 and 55 years and no patients in this age group were available for our study. However, since there was no trend in this direction by age 33, this possibility seems remote. It appears unlikely that a sufficient number of patients between the ages of 34 and 55 will ever be available for study.\(^{11, 12}\)

(3) A likely and intriguing possibility is that there may be a fundamental difference between the myocardial response to a pressure overload that exists from birth and the response to overload that is acquired later on in life. It is possible that hyperplasia, instead of or together with hypertrophy, occurs when pressure overload exists from birth.\(^{13-17}\) In experimental animals subjected to pressure or volume overload in the neonatal period, hyperplasia has been demonstrated to occur, presumably because the young myocyte has retained the capacity to proliferate. On the other hand, pressure or volume overload imposed later in life results in hypertrophy. Myocardial biopsy to provide tissue for cell counting techniques would have been required to distinguish between hypertrophy and hyperplasia in our patients. Alternatively, there may be a fundamental difference between the way the nonterminally differentiated myocardial cell of the neonate responds to afterload stress and the response of the adult myocyte. Many investigators believe that mechanical load (wall stress) is the major determinant of the extent of hypertrophy.\(^{18}\) The presence of subnormal wall stress in children with aortic stenosis indicates that at least at rest the extent of concentric hypertrophy is greater than needed to offset the pressure overload present. Perhaps the hypertrophic response to a given stress is more extensive in the neonate than the adult. Or it may be that the hypertrophic response in the neonate is "normal" and that the response in the adult is limited. The well-known limitation in coronary hyperemic reserve in the adult with extensive pressure overload hypertrophy\(^{19}\) might be an example of a factor that could limit further hypertrophy. Other currently unknown factors, alone or in combination, may determine the amount of hypertrophy in congenital versus acquired aortic stenosis.

End-diastolic stress was not significantly reduced in patients with congenital aortic stenosis nor was it different among the groups of patients. This finding is consistent with Grossman's hypothesis that it is primarily systolic load that affects concentric hypertrophy.\(^{18}\)

**Limitations.** A limitation of this investigation is a lack of linear follow-up of individual patients with congenital aortic stenosis from birth through the sixth decade with repeated measurements of ventricular mechanics. This would have been the best way to examine age-related changes in wall stress. Because such a study is impossible in an era of surgical therapy of an otherwise fatal disease, it was necessary to compare group of patients of different ages but with a similar degree of pressure overload as the stimulus for hypertrophy.

End-systolic circumferential wall stress was calculated and assumed to be representative of a generally

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**Figure 4.** Ejection fraction plotted against end-systolic wall stress for the six groups of subjects. The figure demonstrates that patients with congenital aortic stenosis had higher ejection fractions and lower wall stress than control subjects. There is a linear correlation between ejection fraction and wall stress, as shown throughout the range of the variables.
reduced wall stress throughout systole. Although a frame-by-frame analysis permitting calculation of mean systolic and peak systolic wall stress would have been ideal, we believe that our previous investigation of children with congenital aortic stenosis in which mean, peak, and end-systolic stress were calculated justifies this approach.

Our patient groups were relatively small. However, the data within each group were consistent and large differences in the important area of wall stress existed between patients with congenital aortic stenosis and normal subjects or patients with acquired aortic stenosis. Thus, it is unlikely that group size caused us to come to an erroneous conclusion regarding wall stress.

There may be small errors in our stress measurements attributable to the use of a fluid-filled catheter in most of our patients. The delay in pressure measurement when a fluid-filled system is used causes a slightly lower than actual pressure to be paired with a relatively large volume in early systole. This may cause a pressure slightly higher than the actual pressure to be matched with volume at end-systole and thus overestimation of end-systolic stress. However, pressure and volume were carefully matched for RR intervals, and the time delay in transmission of pressure through well-flushed fluid-filled catheters has been shown to be only about 10 msec, which is less than the time between cine frames. Previous studies demonstrate that no serious error is introduced by these methods.

Our pressure and ventriculographic measurements were not made simultaneously. The end-systolic pressure in all subjects was obtained just before entrance of the catheter into the left ventricle and thus some changes could have occurred in pressure before the ventriculogram was recorded.

In conclusion, children with aortic stenosis have subnormal wall stress and enhanced ejection performance compared with those in normal subjects. With increasing age there is no tendency toward development of the wall stress pattern seen in acquired adult aortic stenosis of normal or increased stress. We suggest that a pressure overload present from birth may yield a fundamentally different pattern of hypertrophy (or possibly hyperplasia) than that seen when the pressure overload is acquired later in life.

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