Patterns of Progression of Aortic Stenosis:  
A Longitudinal Hemodynamic Study  

STEPHEN WAGNER, M.D., AND ARTHUR SELZER, M.D.

SUMMARY To examine factors that might affect progression in valvular aortic stenosis (AS), we reviewed serial hemodynamic studies in 50 adult patients. Seven patients had congenital, 22 rheumatic and 21 degenerative-calcific aortic stenosis. The patients with calcific aortic stenosis were older (62 ± 6 vs 51 ± 9 years, p < 0.001) and had onset of murmur later in life. For all patients average values at first study include age 54 ± 4 years, a peak gradient of 38 ± 27 mm Hg and a calculated aortic valve area of 1.3 ± 0.7 cm². A mean of 3.5 ± 3 years later, the gradient was 57 ± 30 mm Hg and aortic valve area 0.8 ± 0.4 cm². Peak left ventricular pressure increased 9 ± 33 mm Hg and cardiac output decreased 0.5 ± 0.2 l/min. Patients were divided into rapid (n = 21) and slow (n = 29) progressors; the rates of change in aortic valve area were 0.30 ± 0.21 and 0.02 ± 0.08 cm²/yr, respectively. Degenerative-calcific aortic stenosis was present in 76% of the rapid progressors and in 21% of slow progressors (p < 0.001); the groups also differed in that 48% of rapid progressors had a serial decrease in cardiac output of more than 1 l/min compared with 17% of slow progressors (p < 0.05). Furthermore, all patients who progressed into the critical range of severity of aortic stenosis (< 0.05 cm²) and developed left ventricular failure had degenerative-calcific aortic stenosis.

We conclude that aortic stenosis progresses more rapidly in patients with degenerative-calcific than in those with congenital or rheumatic disease. In some patients, calculated aortic valve area is reduced due to an impaired ability of the failing left ventricle to move calcified leaflets rather than to an anatomic reduction in valve orifice.

VALVULAR aortic stenosis is generally recognized as a progressive disease characterized by increasing stenosis of the orifice. Clinical manifestations of aortic stenosis often progress parallel to the increase in valvular obstruction. Hemodynamic studies have shown increases in pressure gradient and decreases in calculated valve areas. The speed of this process varies, yet factors affecting the rate of progression require further clarification. Therefore, we evaluated factors that could influence the rate of progression of aortic stenosis.

Methods

The study was based on a series of 50 patients with aortic stenosis who had undergone two complete hemodynamic evaluations more than 4 months apart and had not had aortic valve surgery or infective endocarditis in the interim. Only patients with pure or predominant aortic stenosis were considered acceptable for the study. Patients who had more than mild aortic regurgitation were excluded. Patients with associated cardiac diseases, such as mitral stenosis and coronary artery disease, were considered acceptable for study.

Cardiac catheterization was performed to evaluate patients with clinically significant aortic stenosis. In patients with milder degrees of aortic stenosis, surgical treatment was not recommended. Some patients with severe aortic stenosis refused to undergo open heart surgery. The second study was performed because of a change in clinical status (physical findings, electrocardiographic or radiographic findings), new symptoms, or worsening of old symptoms. About half of the patients had clinical progression of symptoms thought to relate to progression of aortic stenosis.

One hundred three cardiac catheterizations were performed in the 50 patients. Transvalvular gradients were measured at each study: in 71 by simultaneous left ventricular pressure and aortic pressure recording (transseptal methods in 66, left ventricular puncture in five), in 32 by left ventricular-aortic pull-back. The aortic valve area was calculated using the Gorlin equation. Cardiac output determinations were made by the Fick principle. In 14 of the 103 studies it was necessary to use a derived systolic ejection period based on the heart rate and valvular gradient to calculate the aortic valve area. Twenty-six patients underwent selective coronary arteriography. Luminal narrowing ≥ 70% of a major coronary branch was considered significant. The majority of patients underwent left ventriculography. Those with auscultatory evidence of aortic regurgitation underwent aortic root angiography to evaluate the degree of aortic regurgitation.

Clinical records were reviewed with special reference to symptoms, physical findings, signs of congestive cardiac failure, electrocardiographic signs of left ventricular hypertrophy and radiologic evidence of valvular calcification.

Evaluation of the presumed cause of aortic stenosis was made using the following criteria. Congenital aortic stenosis was considered in patients with murmurs known to be present since birth or early childhood and without a history of rheumatic fever or evidence of rheumatic heart disease. Rheumatic aortic stenosis was considered in patients with a reliable history of acute rheumatic fever or the coexistence of mitral stenosis. Degenerative-calcific aortic stenosis required the discovery of the murmur of aortic stenosis in adult life, absence of a history of rheumatic fever, the presence of valve calcification and the age greater than 50 years at first catheterization. These included cases with late changes on a bicuspid aortic valve as well as those with severe degenerative changes. Patients who had features suggestive of the presence of aortic...
steno sis early in life but did not meet the criteria for inclusion in the rheumatic or congenital groups were included in a "mixed" aortic stenosis category.

Statistical analysis was performed when appropriate. The mean differences between the categories of aortic stenosis were compared by unpaired two-tailed t tests. Relative frequencies of clinical features were compared between subsets using either the chi-square test with Yates corrections or the Fisher exact two-tailed test.1

Results

The present series consisted of 36 male and 14 female patients with aortic stenosis. The mean age at the time of the first study was 56 years (range 32–76 years). Sixteen patients had associated minimal or mild aortic regurgitation. Documented coronary artery disease was present in 14. Rheumatic mitral valve disease was present in 14. Seven patients had congenital aortic stenosis, 15 rheumatic, seven "mixed" category and 21 had degenerative-calcific aortic stenosis. The presence of valve calcification was established by fluoroscopic evaluation in 42 patients.

Serial studies were performed with a mean time interval of 3.5 years and a range from 4 months to 14 years. Figure 1 shows the rate of progression expressed as the aortic valve area plotted against time. Thirty-six patients showed progression of aortic stenosis. Thirteen patients showed no significant change between studies. One patient (mixed etiology) showed an increase in the aortic valve area from 1.4 to 2.1 cm². Arbitrarily, the rate of progression was divided into a rapidly progressive category (group 1) and a slowly progressive category (group 2) with a dividing line characterized by a slope of 0.15 cm² year. Mean values of the principal hemodynamic findings at each study and the change between studies are shown in Table 1. Significant changes were found between studies in peak aortic gradient, aortic valve area and in cardiac output. Peak left ventricular pressure did not change significantly.

Table 2 presents a comparison of hemodynamic findings in group 1 and group 2. The time interval between catheterizations was comparable for both groups. The decrease in cardiac output was significantly greater in the rapid progressors. Further, the majority of patients in group 1 had degenerative-calcific aortic stenosis, which was found in a minority of patients in group 2.

To evaluate this difference further, patients with degenerative-calcific aortic stenosis were compared with patients in the other etiologic categories (Table 3). A highly significant difference in the rate of progression was present between the two groups. The age difference is expected. However, the time interval between studies, the initial valve area and progression of pressure gradient showed no significant difference between the two categories.

A review of clinical features of aortic stenosis in relation to the rate of progression revealed no significant relationships. The initial presentation, or subsequent appearance of angina pectoris, syncope or left ventricular hypertrophy on the ECG was not related to the rapidity of progression of aortic stenosis. The coexistence of mitral valve disease or of coronary artery disease was not associated with rapid progression. Finally, the initial severity of the valve stenosis did not predict subsequent progression. Among the seven patients who had initial valve areas of 0.7 cm² or less, progression occurred in two.

Sixteen patients had critical aortic stenosis, defined as an aortic valve area of 0.5 cm² or less at the second

<table>
<thead>
<tr>
<th>Table 1. Summary of Findings in Two Cardiac Catheterizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cath 1</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Peak gradient (mm Hg)</td>
</tr>
<tr>
<td>Aortic valve area (cm²)</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
</tr>
<tr>
<td>Peak LV pressure (mm Hg)</td>
</tr>
</tbody>
</table>

Abbreviation: Cath = catheterization; LV = left ventricular.
catheterization (table 4). Eight of the 16 patients in this category were in group 1 and eight were in group 2. Six of the eight patients in group 1 had cardiac failure, compared with none in group 2. All patients in group 1 had degenerative-calcific aortic stenosis, compared with one in group 2. Six of eight patients in group 1 had a decrease in cardiac output greater than 1 l/min, compared with only one in group 2.

**Discussion**

The progressive nature of valvular aortic stenosis as judged by increasing clinical symptoms is well known, and several studies of the natural history of aortic stenosis are available. However, the increase in the severity of valvular obstruction as measured by hemodynamic methods is not well understood. In children with congenital aortic stenosis, reduction of aortic valve area shown by longitudinal studies is relatively uncommon and, to a large extent, depends upon body growth in relation to the size of the aortic orifice. Serial hemodynamic studies of adult patients with aortic stenosis by Cheitlin et al. presented evidence, based on measurement of transaortic gradient, that a progressive increase in stenosis occurs in some patients but not in others. Calculation of aortic valve area in 11 patients by Bogart et al. showed the variability in the rate of progression of aortic stenosis, and demonstrated that progression may develop in as short a time as 29 months.

In this study, serial calculations of aortic valve area were done in 50 patients, constituting a large enough series to attempt an evaluation of factors influencing the development and rate of hemodynamic progression of aortic stenosis. The decision to separate the three principal etiologic groups of aortic stenosis was based on the fact that each produces and affects aortic stenosis in populations of different ages and that degenerative-calcific aortic stenosis differs from the rheumatic variety.

Separating nonprogressive and slowly progressive cases from rapidly progressive cases by an arbitrary dividing line, we found that rapid progression occurs preferentially in patients of the degenerative-calcific aortic stenosis. Considering the average advanced age of patients in this category, rapid progression occurs more frequently in older patients; it is, however, not directly related to age. Progression was not related to the initial severity of the lesion or to the presence or absence of symptoms at the time of the first study. The rate of progression may be very fast, as many of our patients showed significant progression earlier than cases reported by Bogart; rapid progression is often associated with a decrease in cardiac output. As a result, the peak left ventricular pressure and the trans-aortic pressure gradient were not reliable indexes of progression of aortic stenosis. Rapid progressors in whom the severity of aortic stenosis became critical presented evidence of congestive cardiac failure, but this was not the case in slow progressors reaching the same severity.

**Table 2. Principal Findings in Rapidly Progressive and Slowly Progressive Aortic Stenosis**

<table>
<thead>
<tr>
<th></th>
<th>Rapid progressors (n = 21)</th>
<th>Slow progressors (n = 29)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age cath 1 (years)</td>
<td>58 ± 8</td>
<td>54 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>AVA change (cm²/yr)</td>
<td>-0.32 ± 0.20</td>
<td>-0.02 ± 0.13</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AVA total change (cm²)</td>
<td>0.9 ± 0.7</td>
<td>0.3 ± 0.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gradient change (mm Hg)</td>
<td>25.6 ± 19.3</td>
<td>15.9 ± 23.6</td>
<td>NS</td>
</tr>
<tr>
<td>Interval (years)</td>
<td>3.2 ± 2.9</td>
<td>3.6 ± 2.4</td>
<td>NS</td>
</tr>
<tr>
<td>Change in CO (l/min)</td>
<td>-0.91 ± 1.3</td>
<td>-0.22 ± 1.1</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Calcific aortic stenosis</td>
<td>14/21</td>
<td>7/29</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Abbreviations: cath = catheterization; AVA = aortic valve area; CO = cardiac output.

**Table 3. Findings in Degenerative-Calcific Aortic Stenosis Contrasted with Findings in Aortic Stenosis of Other Causes**

<table>
<thead>
<tr>
<th></th>
<th>Degenerative-calcific aortic stenosis (n = 21)</th>
<th>Aortic stenosis of other cause (n = 29)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age cath 1 (years)</td>
<td>61 ± 6</td>
<td>52 ± 9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AVA change (cm²/yr)</td>
<td>-0.26 ± 0.25</td>
<td>-0.06 ± 0.15</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AVA total change (cm²)</td>
<td>0.7 ± 0.7</td>
<td>0.4 ± 0.6</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Interval (years)</td>
<td>3.3 ± 2.0</td>
<td>3.6 ± 3.0</td>
<td>NS</td>
</tr>
<tr>
<td>Initial gradient (mm Hg)</td>
<td>37 ± 27</td>
<td>39 ± 28</td>
<td>NS</td>
</tr>
<tr>
<td>Initial AVA (cm²)</td>
<td>1.5 ± 0.8</td>
<td>1.2 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Gradient progression (mm Hg/yr)</td>
<td>10 ± 12</td>
<td>7 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Change in CO (l/min)</td>
<td>-0.85 ± 1.3</td>
<td>-0.24 ± 1.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: see table 2.
In the interpretation of findings of this study two questions arise: Is progression of aortic disease (or lack of it) a predetermined process? Is there a basic difference between degenerative-calcific aortic stenosis and congenital or rheumatic aortic stenosis that accounts for different speed of progression?

The rate of progression is neither uniform nor predetermined in each case. Thus, some factor probably changes nonprogressive aortic stenosis into the progressive variety, or slowly progressive into the rapidly progressive variety.

In evaluating the second question, the pathologic process that leads to aortic valve stenosis must be reviewed. Stenosis of the valve can be produced by commissural fusion, which reduces the size of the aortic orifice beyond a certain critical valve area, or by fibrosis or calcification, which reduces the mobility of the valve. In physiologic terms, a transaortic pressure gradient is produced by resistance to flow through the stenotic valve. This gradient has a constant level (the peak aortic systolic pressure) and a variable level (the peak left ventricular systolic pressure). In fixed-orifice aortic stenosis, outflow resistance is constant; however, if resistance is caused by valvular noncompliance, it varies in relation to the available force (i.e., left ventricular systolic pressure) opening the valve. Inasmuch as the pressure gradient is related to the square of the flow through the orifice, changes in cardiac output have a profound effect on the pressure gradient, which determines the available systolic force. For example, if the left ventricular pressure is 200 mm Hg, aortic pressure 100 mm Hg and the cardiac output 6 l/min, a 30% decrease in cardiac output (to 4.2 l/min) would reduce the gradient by 50%, resulting in peak left ventricular systolic pressure of 150 mm Hg, representing a substantial reduction of the valve-opening force. Thus, onset of cardiac failure leading to a decrease in cardiac output would reduce the size of the aortic orifice by lowering the force available to open the stiff cusps.

On the basis of these considerations, the following hypothesis best explains our findings. In congenital and rheumatic aortic stenosis, the basic process is one of commissural fusion and fixed-orifice stenosis, and progression is very slow, if present at all. Calcium deposition is common, but represents a secondary process. In degenerative-calcific aortic stenosis, valve stiffness and calcification are the primary factors that affect valves with minor deformities (e.g., bicuspid valve). Here, progression of aortic stenosis depends largely or entirely upon increasing immobility of the valve by further deposition of calcium. As the valve stiffness increases to a critical point, afterload mismatch may develop, producing impaired left ventricular function. Decrease in cardiac output further impairs the effective valve area. Thus, a small increment in valve stiffness may increase the severity of aortic stenosis considerably; the onset of cardiac failure automatically increases the severity of aortic stenosis.

The same process can occur in patients with congenital or rheumatic aortic stenosis who show secondary valve calcification. However, in the degeneration group, in which calcification is the primary process, rapid progression occurs preferentially.

Rapid progression — a specific process related to valve calcification — is the likely basis for the precocious state of patients with calcific aortic stenosis who develop cardiac failure. It may explain the rapid clinical deterioration of some such patients as well as the tendency toward sudden death.

References

Patterns of progression of aortic stenosis: a longitudinal hemodynamic study.

S Wagner and A Selzer

Circulation. 1982;65:709-712
doi: 10.1161/01.CIR.65.4.709

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1982 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on
the World Wide Web at:
http://circ.ahajournals.org/content/65/4/709.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally
published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the
Editorial Office. Once the online version of the published article for which permission is being requested is
located, click Request Permissions in the middle column of the Web page under Services. Further
information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/