The Natural History and Rate of Progression of Aortic Stenosis*

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One of the challenges in clinical cardiology is to determine the optimal time of valve replacement surgery in patients with aortic stenosis. To meet this challenge, one requires an accurate knowledge of the natural history and rate of progression of the disease. This review will summarize the natural history of aortic stenosis in terms of symptoms, mortality, and stenosis progression.

(CHEST 1998; 113:1109-14)

Key words: aortic stenosis; natural history; rate of progression

Surgical therapy, although important and effective therapy for aortic stenosis, has its own inherent risks.1-3 In addition to operative morbidity and mortality, surgery in essence replaces one disease process with another. The burden of aortic stenosis is removed, but the patient is left with "prosthetic heart valve disease." This latter disease is associated with a risk of thromboembolism, endocarditis, prosthetic valve failure, and hemorrhage if anticoagulation is required. On average, the risk of a serious prosthetic valve-related complication is estimated to be 1 to 2% per year.4 The challenge is to determine the inflection point at which surgical therapy will portend a better prognosis compared with medical therapy. To meet this challenge, one requires an accurate knowledge of the natural history of aortic stenosis treated medically vs the risks and long-term outcome of operative treatment. This review will summarize the natural history of aortic stenosis in terms of symptoms, mortality, and stenosis progression.

The Natural History of Aortic Stenosis

Much of our understanding of the natural history of aortic stenosis is derived from clinical studies performed in the era prior to the development of cardiac catheterization and hence lacks hemodynamic information.5-10 In studies done subsequent to our ability to derive invasive hemodynamic data and replace valves, the clinical course of aortic stenosis was often interrupted by valve replacement.11-16 As a result, our view of the natural history of aortic stenosis is largely retrospective, introducing inherent biases to patient selection into these studies. Over time, the primary etiology of aortic stenosis has changed from rheumatic to senile degeneration and calcification and our patient population is older and has more associated coronary artery disease.13,17,18 Thus, the external validity (patient generalizability) of earlier studies must be questioned.

The hemodynamic burden of aortic stenosis is primarily a pressure load to the left ventricle. In accordance to the law of Laplace (wall stress = [pressure × radius]/2 × wall thickness), as left ventricular pressure increases, in order to maintain wall stress, ventricular wall thickness must increase. If the increase in wall thickness is unable to match the rise in left ventricular pressure, wall stress (afterload) increases, which impairs ventricular performance. This phenomenon is referred to as afterload mismatch. Systolic dysfunction in aortic stenosis is largely a result of afterload mismatch.19,20 Transvalvular flow has two determinants: pressure gradient and orifice area. Therefore, one must interpret with caution literature that defines the severity of aortic stenosis solely on the basis of a high pressure gradient as a proportion of patients with poor left ventricular systolic function, and thus low gradients may be missed. The prognosis of these patients is worse than those with preserved left ventricular systolic function.21-23

Recognizing some of its limitations, what can one discern from the literature?

Symptoms and Survival

Symptomatic Aortic Stenosis: The cardinal manifestations of aortic stenosis include syncope, angina pectoris, and dysnea. Once these symptoms de-
velop, the prognosis is poor. The onset of angina, syncope, and dyspnea has been shown to correlate with an average time to death of 5, 3, and 2 years, respectively. This clinical course has been derived primarily from postmortem studies on adults with acquired aortic stenosis\textsuperscript{5,7,9,10} (Fig 1). The average age at death of these patients was 63 years.

**Minimally Symptomatic or Asymptomatic Aortic Stenosis:** As technology advances so, too, do our clinical tools of observation. The routine use of cardiac catheterization and the availability of Doppler echocardiography facilitates the diagnosis of aortic stenosis. Clinical findings suggestive of aortic stenosis can be confirmed easily. As a result, many patients with limited or no symptoms yet hemodynamically significant aortic stenosis are being identified. The dilemma is how best to treat these patients.

The debate concerning the treatment of asymptomatic patients with significant aortic stenosis has largely been settled through the following lines of evidence: In 1937, Contratto and Levine\textsuperscript{5} followed up 180 patients with valvular aortic stenosis over a 25-year period. They reported that sudden death occurred “rarely” in totally asymptomatic patients and was often preceded by the development of symptoms. In 1968, Ross and Braunwald,\textsuperscript{24} in their classic review of the natural history of aortic stenosis, reemphasized that sudden death occurred predominantly in symptomatic patients. In asymptomatic patients with acquired aortic stenosis, the risk of sudden death was reported to be between 3% and 5%. At this time, it was proposed that patients with acquired valvular aortic stenosis have surgery deferred until the onset of symptoms.

Now, three decades later, despite technological advancement allowing us to identify more occult valvular heart disease, the evidence continues to support this proposed conservative treatment of patients with asymptomatic acquired valvular aortic stenosis.

Turina et al\textsuperscript{13} retrospectively reviewed 73 patients with aortic stenosis in whom cardiac catheterization had been performed between 1963 and 1983. The severity of stenosis was primarily determined by the Gorlin-derived aortic valve area (<0.9 cm\textsuperscript{2} severe; 0.95 to 1.4 cm\textsuperscript{2} moderate; >1.5 cm\textsuperscript{2} mild). In 15 patients, the aortic valve area was not calculated. In these patients, mean pressure gradient was used to define the hemodynamic severity of the disease (>50 mm Hg severe, <20 mm Hg mild). In a group of 17 asymptomatic or mildly symptomatic patients with severe aortic stenosis or combined aortic stenosis and aortic regurgitation, none of the patients died or required valve surgery during the first 2 years. At 5 years, 75% were event free (alive and not had surgery) and 94% survived. In the group with moderate aortic disease, none of the asymptomatic or mildly symptomatic patients died, but 27% underwent valve surgery within 5 years. The actuarial survival in relation to New York Heart Association classification was 99% and 76% at 2 and 5 years, respectively, for patients with functional class I to II. In patients with functional class III to IV, the actuarial survival was 31% and 22% at 2 and 5 years, respectively. They concluded that asymptomatic or minimally symptomatic patients with severe aortic stenosis are at low risk of death and that surgical treatment can be postponed until “marked symptoms” appear.\textsuperscript{10}

A cohort of 51 asymptomatic patients with severe aortic stenosis were followed up by Kelly and co-workers\textsuperscript{25} for a mean of 17 months. A Doppler-derived peak systolic pressure gradient of ≥50 mm Hg was used to define severe aortic stenosis. The aortic valve area was not calculated in this study. Twenty-one (41%) of the patients became symptomatic. Only two died of cardiac causes, but both had become symptomatic for at least 3 months prior to their deaths. The conclusion was, again, that patients be followed up until symptoms develop.

The conclusion that asymptomatic patients with acquired valvular aortic stenosis be followed up closely until symptoms develop was echoed by Pellicka et al.\textsuperscript{26} They followed up 113 asymptomatic patients with significant aortic stenosis as determined by a Doppler-derived peak instantaneous systolic pressure gradient of ≥64 mm Hg. The average mean gradient was 47 mm Hg. The mean duration of follow-up was 20 months. The death of three patients was ascribed to aortic stenosis (two, sudden death; one, congestive heart failure). In each case, the development of symptoms preceded death by at least 3 months. The actuarial probability of

![Figure 1. Average course of valvular aortic stenosis in adults. Data assembled from postmortem studies. Reprinted with permission from Ross and Braunwald.\textsuperscript{24}](image-url)
survival was 96%, 94%, and 90% at 6, 12, and 24 months, respectively. The survival did not differ from that predicted for age- and gender-matched control subjects.

Another review of 66 patients with moderate aortic stenosis again identified that symptoms predict adverse outcomes. Mortality was significantly greater (p<0.05) among symptomatic (New York Heart Association functional class III to IV) vs minimally symptomatic patients (23% vs 4%). Moderate aortic stenosis was defined as an aortic valve area of 0.7 to 1.2 cm$^2$ derived by the formula of Hakki. The mean duration of follow-up was 35 months (maximum 7.2 years).

Despite the limitations of the studies, the consensus is that asymptomatic patients are at low risk for complications or mortality. However, following the onset of symptoms, the prognosis worsens dramatically. Surgical therapy should be considered as soon as the patient develops symptoms ascribed to aortic stenosis and if considered a viable option should be performed without delay.

**Stenosis Progression**

A concern, identified in the studies cited above, is that a small proportion of asymptomatic patients may progress very rapidly to develop symptoms and then die suddenly. If, however, one could identify reliable predictors to the rate of progression of aortic stenosis, then surgical consideration may be given to these high-risk, yet asymptomatic patients. In addition, a common clinical scenario is that of a patient with documented aortic stenosis, not of a severity that would routinely result in a surgical intervention, in whom cardiac surgery is planned for other reasons. The question is whether the aortic valve should be replaced at the time of this surgery? Knowledge of reliable predictors to stenosis progression would greatly aid in clinical decision making.

Table 1 summarizes a review of the literature on the progression of aortic stenosis. Doppler echocardiography records the maximal difference between the instantaneous left ventricular and aortic pressures at any point during the systolic ejection period. Catheter-derived peak-to-peak gradient is a noninvasive measurement determined by the difference between the peak left ventricular and aortic systolic pressures. The Doppler-derived peak instantaneous gradient is thus always higher than the peak-to-peak gradient. The difference in these values decreases as the absolute gradient increases. The mean gradient, which is the average gradient throughout systole, should theoretically be equivalent, and studies have shown this to be true.

When cardiac catheterization is used as the tool of observation to follow the rate of progression of aortic stenosis, there will be inherent biases as to the patients selected for follow-up. Only patients who have progressed symptomatically would be subjected to the risk of a second cardiac catheterization. Doppler echocardiography is a noninvasive, reliable tool, ideally suited to follow up asymptomatic patients with aortic stenosis and thus allow a more accurate reflection of the natural progression.

Otto et al prospectively followed up 42 adults with valvular aortic stenosis for a mean duration of 20 months. The average Doppler-derived peak systolic gradient was 54 mm Hg (range, 27 to 108 mm Hg). The peak transaortic pressure gradient changed by +12 mm Hg/yr (−10 to +34 mm Hg) and the mean gradient changed by +8 mm Hg/yr (−7 to +23 mm Hg). Data for the calculation of aortic valve area were available in 25 of the 42 patients, and revealed a mean reduction in aortic valve area of −0.1 cm$^2$/yr (0.0 to −0.5 cm$^2$). Those patients who subsequently required valve replacement as a result of progressive symptoms had a more rapid rate of hemodynamically determined deterioration. How-

### Table 1—Rate of Progression of Aortic Stenosis: A Review

<table>
<thead>
<tr>
<th>Source</th>
<th>Year</th>
<th>No.</th>
<th>Method</th>
<th>Follow-up, yr</th>
<th>Initial ΔP, mm Hg</th>
<th>↑ ΔP per Year</th>
<th>↓ ΔAVA per Year</th>
<th>Faster Rate of Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wagner and Selzer</td>
<td>1982</td>
<td>50</td>
<td>Catheter</td>
<td>3.5</td>
<td>38</td>
<td>5.4</td>
<td>—</td>
<td>Older age, calcific valve</td>
</tr>
<tr>
<td>Nitta et al</td>
<td>1987</td>
<td>11</td>
<td>Catheter</td>
<td>3</td>
<td>23</td>
<td>7.7</td>
<td>—</td>
<td>Older age</td>
</tr>
<tr>
<td>Turina et al</td>
<td>1987</td>
<td>29</td>
<td>Catheter</td>
<td>7</td>
<td>50</td>
<td>3.4</td>
<td>—</td>
<td>None</td>
</tr>
<tr>
<td>Schuler et al</td>
<td>1991</td>
<td>11</td>
<td>Catheter</td>
<td>3.4</td>
<td>56</td>
<td>8.4</td>
<td>—</td>
<td>None</td>
</tr>
<tr>
<td>Davies et al</td>
<td>1991</td>
<td>65</td>
<td>Catheter</td>
<td>7</td>
<td>10</td>
<td>6.5</td>
<td>—</td>
<td>Calcific valve</td>
</tr>
<tr>
<td>Otto et al</td>
<td>1989</td>
<td>42</td>
<td>Doppler</td>
<td>1.7</td>
<td>54</td>
<td>12</td>
<td>0.1</td>
<td>Progressive symptoms</td>
</tr>
<tr>
<td>Roger et al</td>
<td>1990</td>
<td>112</td>
<td>Doppler</td>
<td>2.1</td>
<td>35</td>
<td>4.8</td>
<td>0.1</td>
<td>Progressive symptoms</td>
</tr>
<tr>
<td>Faggiano et al</td>
<td>1992</td>
<td>45</td>
<td>Doppler</td>
<td>1.5</td>
<td>64</td>
<td>15</td>
<td>0.1</td>
<td>Lower LV systolic function</td>
</tr>
<tr>
<td>Peter et al</td>
<td>1993</td>
<td>49</td>
<td>Doppler</td>
<td>2.6</td>
<td>38</td>
<td>7.2</td>
<td>—</td>
<td>Older age, coronary artery disease</td>
</tr>
</tbody>
</table>

*Adapted from Peter et al. ΔP=pressure gradient; LV=left ventricle; ΔAVA=aortic valve area. 
1Peak to peak ΔP. 
Mean ΔP. 
3Peak instantaneous ΔP.
ever, they were unable to identify variables to predict who these “fast progressors” would be.

Roger and colleagues\textsuperscript{30} reviewed 112 adult patients with aortic stenosis who underwent at least three echocardiographic evaluations during a mean 25-month period. At entry, the peak instantaneous gradient was 35±18 mm Hg (6 to 100 mm Hg). After a mean interval of 25 months, the peak instantaneous gradient increased to 44±16 mm Hg, corresponding to an average increase of 4.8 mm Hg/yr. It was also recognized that those who progressed symptomatically had a significantly more rapid rate of hemodynamic progression. Again, no variables were identified that could predict the “fast progressors.”

A cohort of 45 adults with aortic stenosis was followed up by Faggiano and coworkers\textsuperscript{31} for a mean duration of 18 months. At entry, the peak instantaneous gradient varied from 25 to 174 mm Hg and valve area ranged between 0.35 and 1.6 cm\textsuperscript{2}. The peak transaortic pressure gradient changed on average 15±10 mm Hg/yr (range, 8 to +38 mm Hg/yr). The change in calculated aortic valve area was, on average, −0.1±0.13 cm\textsuperscript{2}/yr (range, −0.72 to +0.14 cm\textsuperscript{2}/yr). Once again it should be noted that the rate of progression was variable among patients and that in general, no parameters could be identified to help differentiate “rapid” from “slow progressors.” One caveat to this was that those with a reduction in left ventricular systolic function had a faster rate of progression than did those with normal systolic function. This finding has not been consistently duplicated in other series.

Peter et al\textsuperscript{32} prospectively followed up 49 adults with aortic stenosis. At entry, the average peak instantaneous gradient was 38±15 mm Hg (range, 16 to 78 mm Hg). Patients were followed up for a mean duration of 32 months. The peak transaortic pressure gradient changed by +16 to +93 mm Hg, corresponding to a mean increase of 10.6±11 mm Hg/yr. Of the 49 patients, 21 were identified as “rapid progressors” as defined by a ≥10 mm Hg/yr increase in the peak gradient. These patients were older (64 vs 53 years, p<0.01) and coronary artery disease was more prevalent (38% vs 7%, p=0.01). The rate of progression was not found to correlate with either age or the extent of coronary artery disease when evaluated in other studies.\textsuperscript{25,26,39}

When 123 adults were followed up prospectively for a mean duration of 2.5±1.4 years, once again, marked individual variability in the rate of hemodynamic progression was seen.\textsuperscript{33} The Doppler-derived mean gradient increased by 7±7 mm Hg/yr (−5 to 31 mm Hg) and the valve area decreased by 0.12±0.19 cm\textsuperscript{2}/yr (−0.35 to 1.16). Clinical factors to predict the rate of hemodynamic progression were not found. However, the echocardiographic severity of aortic stenosis at baseline along with the rate of change over time were predictors of clinical outcome—death or need for valve surgery.

Overall, with respect to the rate of progression of acquired valvular aortic stenosis, on average, the aortic valve area decreases by approximately 0.1 cm\textsuperscript{2}/yr and the peak instantaneous gradient increases by 10 mm Hg/yr. However, in any individual patient, at best we can say that it is highly variable. There can be identified two distinct types of patients: those whose conditions progress slowly and others whose conditions progress rapidly. Unfortunately, unless privy to knowledge of prior hemodynamic data, there are no reliable clinical predictors to help us identify into which subgroup an individual patient will fall.

Although it is generally accepted that patients presenting for coronary artery bypass grafting with moderate or severe aortic stenosis (regardless of symptom status) undergo concomitant aortic valve replacement, the treatment of patients presenting for myocardial revascularization with coexisting asymptomatic mild aortic stenosis remains challenging. Given the bimodal rate of progression, it is no wonder that there is no consensus on how to deal with such patients.

Proponents of prophylactic aortic valve replacement at the time of myocardial revascularization argue that repeated surgery is technically more challenging and carries a higher operative mortality.\textsuperscript{34} Fiore and colleagues\textsuperscript{35} reviewed 28 patients who had aortic valve replacement surgery subsequent to coronary bypass surgery and found an operative mortality rate of 18%, compared with 9.1% in those undergoing combined valve and coronary surgery. This is very similar to the 18.2% perioperative mortality in a review of 44 patients requiring aortic valve replacement who had previously undergone coronary bypass surgery.\textsuperscript{36}

If one elects to be conservative and initially perform coronary bypass surgery alone, retrospective studies suggest that the average time to subsequent aortic valve replacement is between 5 and 7.6 years.\textsuperscript{34,36,37} Otto and her colleagues\textsuperscript{38} suggest that when patients are prospectively followed up, those patients with a baseline Doppler jet velocity of <3.0 m/s (peak instantaneous gradient of <36 mm Hg) are “unlikely to develop symptoms due to aortic stenosis over the next 5 years.” Assuming an annual risk of serious prosthetic valve-related complication to be 2\%,\textsuperscript{3} then the 5-year risk would be approximately 10\%. Others have estimated the 5-year risk for serious valve-related complications to be higher at approximately 15 to 20\%.\textsuperscript{38,39}

In the review of 28 patients mentioned above,\textsuperscript{35} the actuarial survival at 1 and 5 years was no different in patients who had combined coronary and valve surgery. However, those with aortic valve replacement in addition to coronary bypass surgery had a significantly lower risk of valve-related complications at 5 years (0.5\% vs 6\%, p=0.04) and a lower risk of late valve-related complications overall (1\% vs 13\%, p=0.02).
surgery vs those who had valve surgery subsequent to coronary bypass. At 10 years, there was a trend toward a greater survival advantage in those patients in whom valve surgery had been delayed. These data along with the increased operative risk of combined surgery and the subsequent risk of valve-related complications make it hard to justify routine prophylactic aortic valve replacement surgery.

THOUGHTS FOR THE FUTURE

Torricelli’s law, the first hydraulic formula that the Gorlin’s used to develop their formula for the calculation of valve area, states that flow is directly proportional to orifice area and flow velocity. Measurements of aortic valve area are made at a single point in time, and thus are based on the assumption that orifice area remains constant throughout ejection. During each ejection, transvalvular flow and pressure gradient increase from zero, reach a peak, and then decrease back to zero. Effective orifice area should thus be constantly changing throughout ventricular systole. Doppler echocardiography will allow one to measure instantaneous aortic valve area at different times during ejection.\(^40\)

When 26 patients with valvular aortic stenosis were evaluated, significant changes in effective aortic orifice area were identified during ejection.\(^41\) The peak and mean transvalvular gradients were 82±24 mm Hg and 50±19 mm Hg, respectively, and the valve area calculated was 0.7±0.3 cm\(^2\). When valve area was calculated at the mid-acceleration point of the flow velocity, it was 84±15% of the valve area at peak velocity (p<0.0001) and 113±17% (p<0.01) of the valve area at peak velocity when calculated at mid-deceleration. In normal subjects, the valve area remained constant during ejection. This indicates that the stenotic valve opens slowly and continues to open during ejection where the normal valve opens rapidly to its full effective orifice size. As well, the magnitude of change in effective orifice area did not correlate with the usual indexes of hemodynamic severity such as valve area at peak velocity and pressure gradient.

When Doppler echocardiography was used to assess the physiologic response to exercise in 28 asymptomatic patients with aortic stenosis, a subgroup of patients showed an increase in aortic flow velocity during exercise that was less than expected should their orifice area be fixed.\(^42\)

The concept of a dynamic aortic valve orifice area needs validation. If verifiable, an assessment of valve pliability derived by Doppler-determined changes in the instantaneous orifice area may provide important clinical information with respect to the relationship of hemodynamic severity and clinical symptoms. In addition, it may prove to be a more sensitive marker of disease progression and one could speculate that a deterioration in the dynamic change in orifice area be a marker of impending “classically” determined hemodynamic deterioration.

CONCLUSION

It has been well established that in patients with acquired valvular aortic stenosis, the development of symptoms portends a poor prognosis. Therefore, it is unlikely that there will be another true natural history study as once a patient develops symptoms, surgical treatment will interrupt the natural course of the disease.

The decision of when to operate on patients with hemodynamically significant yet asymptomatic acquired valvular aortic stenosis is based on less than perfect data. Until the ideal prosthetic valve is developed, there will always be some debate on when to intervene surgically. The risks and benefits of conservative vs surgical therapy must be weighed in each individual patient. Unfortunately, our ability to predict the rate of progression in an individual patient is insufficient. The clinician, therefore, is faced with making a decision under some uncertainty, which is often very difficult. What evidence we do have tends to support a conservative approach to the asymptomatic patient. The greatest risk to the patient with asymptomatic or minimally symptomatic acquired valvular aortic stenosis may well be aortic valve surgery. Only with further experimentation will we be able to develop new conceptual models to enhance our clinical decision making.

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