Case presentation: A 66-year-old man is referred to a cardiologist for the evaluation of a heart murmur. The patient claims to be entirely asymptomatic, although his wife notes that he has decreased his physical activity over the past two years because he is “getting old.” At physical examination, his blood pressure was 120/70 mm Hg; pulse, 80 bpm; respiration, 13 breaths per minute; and temperature, 99.0°F. Cardiovascular examination revealed normal central venous pressure. His carotid upstrokes were reduced in volume and delayed in upstroke. Cardiac examination revealed a forceful sustained apical impulse in its normal position. There was a 3/6 late-peaking systolic ejection murmur heard at the right upper sternal border radiating to the neck. The rest of the physical examination was unremarkable.

Echo-Doppler evaluation revealed an ejection fraction of 0.60, a left ventricular free wall thickness of 1.3 cm, and a peak transaortic flow velocity of 4.5 m/s. How should this patient be managed? Should he undergo aortic valve replacement now? Should he undergo longitudinal follow-up to monitor progression of his aortic stenosis?

Over the past 40 years, diagnostic techniques, substitute cardiac valves, and valve implantation surgery have undergone continued improvement, reducing the risk of the valve replacement and enhancing its benefits. Thus, the risk-benefit analysis of valve surgery has tilted in favor of increasingly early intervention for valve disease. The following is a summary incorporating this concept into the current strategy for managing patients with aortic stenosis such as the one described above.

Patients With Severe Symptomatic Aortic Stenosis

The patient with severe aortic stenosis who presents with symptoms represents the most straightforward management strategy for the disease. Survival is nearly normal until the classic symptoms of angina, syncope, or dyspnea develop. However, only 50% of patients who present with angina survive 5 years, whereas 50% survival is 3 years for patients who present with syncope and 2 years for patients who present with dyspnea or other manifestation of congestive heart failure. In all, 75% of symptomatic patients with severe aortic stenosis succumb unless the aortic valve is replaced. On average, symptoms develop once the aortic valve area has become <1.0 cm², although there is extraordinary case-to-case variation in valve area at the time symptoms first develop. Thus, some patients may become symptomatic at valve areas >1.0 cm², and other patients do not develop symptoms until the aortic valve orifice area is <0.5 cm².

Once surgery has been performed, age-corrected survival is nearly normal after surgery. The large contrast between a 75%, 3-year mortality for symptomatic patients who do not undergo surgery versus a nearly normal postoperative survival rate makes the decision to perform aortic valve replacement in symptomatic patients with severe aortic stenosis an obvious choice in the absence of surgical contraindications.

Asymptomatic Patients With Severe Aortic Stenosis

The asymptomatic patient with aortic stenosis has an excellent prognosis despite severe left ventricular outflow obstruction. Nonetheless, the outcome for such patients is not perfect, and there is a small risk of sudden death or of rapid advancement from the asymptomatic phase to symptoms to sudden death. Several studies have attempted to ascertain the risk of sudden death in the population of asymptomatic patients with severe aortic stenosis. Table 1 tabulates many of these studies and demonstrates that the overall risk of sudden death in this group of patients is ~2%.

One strategy advocated to circumvent this risk is to operate on all patients with severe aortic stenosis. Unfortunately, there are several difficulties with this approach. First, it is not clear what constitutes severe aortic stenosis. Whereas some authorities have used a valve area of 1.0 cm², others have used a value of 0.75 cm². The Figure shows the extreme
TABLE 1. Studies of the Natural History of Asymptomatic Patients With Aortic Stenosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Mean Follow-Up, years</th>
<th>Severity of Aortic Stenosis</th>
<th>Sudden Death Without Symptoms, No. of Patients</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chizner et al, 1980</td>
<td>3</td>
<td>2</td>
<td>AVA &lt;1.1 cm²</td>
<td>0</td>
<td>Retrospective study</td>
</tr>
<tr>
<td>Turina et al, 1987</td>
<td>16</td>
<td>4</td>
<td>AVA &lt;0.9 cm²</td>
<td>0</td>
<td>Retrospective study</td>
</tr>
<tr>
<td>Horstkotte and Loogen, 1988</td>
<td>35</td>
<td>“years”</td>
<td>AVA=0.4–0.8 cm²</td>
<td>3</td>
<td>Retrospective study</td>
</tr>
<tr>
<td>Kelly et al, 1988</td>
<td>51</td>
<td>0.5</td>
<td>PV=3.5–5.8 m/s</td>
<td>0</td>
<td>Prospective study</td>
</tr>
<tr>
<td>Pellikka et al, 1990</td>
<td>113</td>
<td>1.7</td>
<td>PV &gt;4.0 m/s</td>
<td>0</td>
<td>Prospective study</td>
</tr>
<tr>
<td>Faggiano et al, 1992</td>
<td>37</td>
<td>2.0</td>
<td>AVA=0.85±0.15 cm²</td>
<td>0</td>
<td>Prospective study</td>
</tr>
<tr>
<td>Otto et al, 1992</td>
<td>114</td>
<td>2.5</td>
<td>PV=3.6±0.6 m/s</td>
<td>0</td>
<td>Prospective study</td>
</tr>
<tr>
<td>Pellikka, 2001</td>
<td>610</td>
<td>5.1</td>
<td>PV=4.0</td>
<td>12</td>
<td>Prospective study</td>
</tr>
<tr>
<td>Total</td>
<td>985</td>
<td>4.0</td>
<td></td>
<td>15</td>
<td>Average risk of sudden death&lt;0.4%/y</td>
</tr>
</tbody>
</table>

AVA indicates aortic valve area; PV, peak instantaneous velocity.

A more practical approach is to identify that group of asymptomatic patients at highest risk for sudden death and to consider aortic valve replacement in them. Otto and colleagues demonstrated that transaortic flow velocity, a guide to aortic stenosis severity, was a useful predictor of the eventual development of symptoms. When the initial flow velocity was <3 m/s, there was 70% chance that an aortic valve replacement was required in the next 5 years. However, when initial flow velocity exceeded 4 m/s, there was 15% in the next 5 years. Thus, transaortic flow velocity helped to define a high-risk group of patients.

A second strategy used to screen for high-risk patients is exercise testing. Although exercising symptomatic patients with aortic stenosis has increased risk and should be avoided, exercise testing in patients with asymptomatic aortic stenosis seems to be safe and is a logical extension of the patient’s natural activities. That is, if patients are asymptomatic, they are going to exercise anyway, and it seems wise to have at least one such episode observed by a physician. In the study by Otto et al, each patient underwent exercise testing every 6 months, and there were no cardiac deaths in asymptomatic patients.

A second problem with surgery for all patients with severe disease is that in adult acquired aortic stenosis, valve repair is virtually impossible; thus aortic valve replacement is almost inevitable. Even if replacement is performed using a pulmonary autograft, a substitute valve must be placed in the pulmonary position. Therefore, the strategy of operating on all asymptomatic patients with aortic stenosis exposes 100% of patients to the operative risk, plus the risk of living with a prosthetic valve, in order to benefit the 2% who are at risk of sudden death. The risk of living with a prosthesis, tabulated from several studies, is at least 1% per year.

hit heterogeneity of valve areas at which patients become symptomatic (and therefore, more liable to sudden death). Thus, in my view, it is impossible to define a single critical valve area. Even if a critical valve area could be defined, to use it, valve area would have to be calculated accurately. It should be noted that although one formula for calculating valve area was validated for the mitral valve, it has never been well validated for the aortic valve. Indeed, the discharge coefficients for the Gorlin formula for the aortic valve were never noted that although one formula for calculating valve area would have to be calculated accurately. It should be highlighted that the development of aortic valve replacement (AVR) is compared with valve area before surgery was 0.93 ± 0.32 cm². Reproduced with permission from Otto et al.
Patients With Severely Reduced Ejection Fraction and Aortic Stenosis

At the opposite end of the spectrum from the asymptomatic patient is that patient with advanced heart failure and depressed ejection fraction. Depressed ejection fraction in aortic stenosis has two basic causes: afterload mismatch and contractile dysfunction. \(^1\) Huber and colleagues\(^2\) have demonstrated that afterload mismatch is at least partially responsible for left ventricular dysfunction in approximately three quarters of the patients who have it. The greater the role of afterload mismatch for reduced ejection fraction, the better the response to surgery. In other words, if excessive afterload has primarily caused a reduction in ejection fraction, then relief of the valve obstruction will cause a sudden fall in afterload with a substantial rise in ejection fraction. Although wall stress is usually used as a measure of afterload, its calculation is tedious and not often applied clinically. However, mean transvalvular gradient forms a reasonable surrogate for afterload mismatch. The higher the gradient, the greater the afterload and usually the better the response to surgery. \(^3\)

Most problematic in the group of aortic stenosis patients with heart failure and reduced ejection fraction are those with low transvalvular gradient and low ejection fraction. In general, reports of outcome for these patients have demonstrated a poor prognosis after surgery. \(^4\,5\,6\) In this group, irreversible left ventricular dysfunction rather than afterload mismatch is the primary cause for reduced ejection performance and poor outcome. A study by Connolly and colleagues\(^7\) demonstrated a 21% operative mortality for this group, with only 50% surviving for 4 years. Despite such poor results, some patients do improve with aortic valve replacement. At issue is the need for the clinician to decide preoperatively which patients with low gradient, low ejection fraction, and low output might benefit from an aortic valve replacement versus those patients who will not. Currently, the mainstay in making this distinction is to identify patients who have truly severe aortic stenosis versus those patients who have a small calculated valve area without true aortic stenosis, a condition that I refer to as aortic pseudostenosis. In the first situation, severe valve disease has led to severe left ventricular dysfunction, and therefore, correction of the valve disease (which was the primary defect) might lead to improvement in left ventricular function and in outcome. In the second condition (aortic pseudostenosis), a left ventricle weakened from another process, such as coronary disease or idiopathic cardiomyopathy, is unable to open a mildly but not severely stenotic aortic valve. In both conditions, the calculated valve area may lie in the range considered to indicate severe aortic stenosis, but only in the first condition is there truly severe valve disease. The current standard for divorcing these two conditions is to increase cardiac output either by using positive inotropic agents such as dobutamine or to reduce total peripheral resistance with a vasodilator. \(^8\,9\) These two interventions can lead to the same conclusion through somewhat different mechanisms. As shown in Table 2, when cardiac output is increased through the use of dobutamine in a patient with a severely stenotic valve, output and gradient increase in tandem, and calculated valve area increases only slightly. On the other hand, in aortic pseudostenosis, when output increases substantially, gradient increases only slightly or not at all, leading to a large increase (\(\geq0.3 \text{ cm}^2\)) in calculated valve area.

If a vasodilator is used, the same changes occur in calculated valve area through somewhat different mechanisms. In principle, if the most severe resistance to outflow is the stenotic aortic valve itself, then a decrease in total peripheral resistance does not permit an increase in cardiac output; thus, a vasodilator causes downstream pressure to fall and gradient to increase, demonstrating that the aortic stenosis is severe. On the other hand, if valve resistance is small and it is total peripheral resistance that is the resistance most limiting to flow, then decreasing total peripheral resistance permits increased forward output, reducing the gradient in some cases and producing a dramatic rise in calculated valve area.

Although the need to separate true aortic stenosis from aortic pseudostenosis is now generally accepted, it is not clear what the result would be if surgery were performed on only those patients in whom pharmacological manipulation had been used preoperatively to divorce the two groups. It is likely that the prognosis would not be as good as that for patients with aortic stenosis with preserved left ventricular function, but it probably would be better than the prognosis for a mixed group of patients with true and pseudoaortic stenosis undergoing aortic valve replacement.

**Pathophysiology of the Valve Lesion and Its Management**

In developed countries, rheumatic fever has become a rare cause of aortic stenosis. Instead, calcific disease most often

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**TABLE 2. Hemodynamic Manipulation of Aortic Stenosis Patients With Low Gradient and Low Output**

<table>
<thead>
<tr>
<th>Condition</th>
<th>True Aortic Stenosis</th>
<th>Aortic Pseudostenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Dobutamine</td>
</tr>
<tr>
<td><strong>CO, L/min</strong></td>
<td>3.0</td>
<td>5.0</td>
</tr>
<tr>
<td><strong>LVP, mm Hg</strong></td>
<td>130/20</td>
<td>160/20</td>
</tr>
<tr>
<td><strong>AoP, mm Hg</strong></td>
<td>90/60</td>
<td>100/60</td>
</tr>
<tr>
<td><strong>G, mm Hg</strong></td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td><strong>AVA, cm²</strong></td>
<td>0.6 cm²</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*AoP indicates aortic pressure; AVA, aortic valve area; CO, cardiac output; G, mean gradient; and LVP, left ventricular pressure.*
affects patients born with a bicuspid valve, a condition that affects 1% to 2% of the population and predominates in men. When stenosis develops on a bicuspid valve, it usually occurs relatively early in life (ie, in the fifth and sixth decades). When aortic stenosis develops in a previously normal tricuspid valve, it typically develops later in life (ie, in the sixth, seventh and eight decades). Until recently, the process of developing aortic stenosis was considered degenerative, in some way reflecting the concept of “wear and tear” on the aortic valve. In the past decade, the concept of degenerative disease has given way to that of an active inflammatory process related in some ways to coronary artery disease. Supporting this concept are the following data: (1) The early lesion of aortic stenosis resembles that of the initial plaque of coronary disease. (2) Studies have demonstrated that some risk factors for coronary disease, such as elevated serum cholesterol, are also related to the development of aortic stenosis. (3) There is a close correlation between calcification found in the coronary arteries, which is indicative of the development of coronary disease, to the amount of the calcification found in the aortic valve. Most intriguing is evidence that HMG CoA reductase inhibitors (statins) retard the progression of both coronary disease and of aortic stenosis. In some studies, this retardation is related to a fall in cholesterol, but in others, retardation has occurred without a consistent relationship to cholesterol, suggesting that statin agents may have effects other than simple cholesterol lowering to account for their effects on the aortic valve. Although aortic valve replacement and its timing have been the major foci of the therapy of aortic stenosis, it is possible that in the future, aggressive therapy with statins and other agents might block or slow the progression of the valve lesion, forestalling or even preventing the need for aortic valve replacement.

Disease in Elderly Patients
Aortic stenosis occurs as a process of aging, and therefore, severe symptomatic disease often occurs in elderly patients. Although advanced age has been a risk factor for operative mortality in patients with aortic stenosis, these data must be interpreted with caution because increasing age is a risk factor for death in everyone. In other words, the life expectancy of an 80-year-old patient is ~6 years, whether or not the patient has aortic stenosis. Several studies examining outcome in very elderly patients with aortic stenosis have been performed. Lindblom et al found that age-corrected survivorship for patients over the age of 65 was not different from that of a normal population. In general, most studies come to the same conclusion: that there is almost no age limit for aortic valve surgery in patients with aortic stenosis in the absence of comorbid conditions. However, once coronary disease, other valvular heart disease, neurological deficits, and renal failure are added to the clinical setting, outcome worsens, and these factors must be taken into consideration when deciding whether to correct aortic stenosis in elderly patients.

Summary
In patients with aortic stenosis who develop the classic symptoms of angina, syncope, or dyspnea, prompt aortic valve surgery should be performed to prevent sudden death. In view of the known risk of sudden death in this group, delay for even a month or two is likely to incur some mortality. Thus, I believe aortic valve replacement should be performed within 30 days after symptoms develop.

Asymptomatic patients with severe aortic stenosis can be managed medically, but such management has taken on a more active investigative strategy. In my view, all such patients should undergo exercise testing if they can exercise. If unexpectedly poor exercise tolerance is demonstrated or if there is exercise-induced hypotension or ventricular arrhythmia, aortic valve replacement seems wise, although benefit in this group is not absolutely proven.

In the case of patients with poor left ventricular function because of excess afterload (high gradient), aortic valve replacement leads to improved ejection performance and a good outcome. In the group of patients with low gradient and low ejection fraction, the distinction should be made preoperatively between true and pseudoaortic stenosis. In patients with true aortic stenosis who respond to dobutamine, aortic valve replacement should be offered with the advice that postoperative prognosis is likely to be reduced.

Finally, the possibility of retarding the progression of aortic stenosis or even preventing severe obstruction with statin drugs and other agents is a new and exciting prospect for the management of this disease.

With regard to the patient presented above, I would recommend a physician-performed exercise study. If, during exercise, there was earlier-than-predicted fatigue or dyspnea or if ventricular tachycardia or hypotension was induced, I would refer the patient for aortic valve replacement.

References

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