Aortic stenosis (AS) is perhaps the most common and most often cause of sudden death among valvular heart diseases. In a remarkable way, its natural history has changed over the past 50 years because its pathogenesis has changed and our management strategies, on the basis of better understanding of its pathophysiology, have altered its outcome. The following is an attempt to alert the reader to this new disease in preparation for the in-depth examinations of both basic and clinical science that are presented in this compendium.

Evolution of the Pathogenesis of AS

By 1970, rheumatic fever as a cause of AS already had begun to wane in developed countries and was replaced pathogenetically by degenerative calcific disease. The ambiguous term “degenerative” suggested that AS stemmed from wear and tear on the valve over time, perhaps explaining its greater incidence in older patients. It was known that AS developed earlier in patients born with a bicuspid rather than a previously normal tricuspid aortic valve, suggesting that hemodynamic stress on the valve might play a role. In a seminal group of observations, Otto et al examined the pathology in early disease and noted that the initial AS plaque resembled the plaque of coronary artery disease (CAD; Figure 1). Subsequent investigations also found that CAD and AS had similar risk factors in common. Additional evidence amassed that AS, like CAD, was an active inflammatory process with active inflammatory cells present in the lesions, with increased heat in some AS plaques and increased circulatory C-reactive protein present in AS patients. Inflammation marked by increased valve calcification also suggested rapid progression to severe disease. However, there are significant differences between the atherosclerosis of CAD and the process of aortic valve calcification. With CAD, plaque rupture is the major event leading to clinically important events, whereas in AS it is progressive calcification, even with lamellar bone formation that causes immobility of the valve. Further, statins, which are so effective in reducing CAD mortality, did

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not decrease AS progression. Nonetheless, our understanding that AS is an active rather than a degenerative process presents potentially new targets for inhibiting or even preventing AS development. It is known that the valve cusps in AS are usually heterogeneous in size and shape, potentiating shear stress differences among the leaflets. A reasonable hypothesis of the pathology of AS is that hemodynamic stress leads to inflammation that, in turn, allows for lipid infiltration and that these factors together result in calcification and leaflet immobility.

Natural and Unnatural History of AS
Figure 2A is probably one of the most famous in valvular heart disease. Compiled by Ross and Braunwald and published in 1968, it demonstrated that patients with AS sustained a long asymptomatic latent period during which survival was close to that of an otherwise healthy population. Once symptoms developed at the age of ≈60 years, survival decreased precipitously. Today, the onset of symptoms still portends as poor prognosis without valve replacement, but the age of onset of symptoms has increased by ≈15 years, reflecting a change in pathogenesis from rheumatic and congenital AS to that of atherosclerotic AS as noted (Figure 2B). With aging also comes a host of age-related comorbidities complicating assessment of symptoms of AS. Some patients may fail to recognize the symptoms of AS, whereas symptoms not attributable to AS may be misinterpreted.

Roles of Aging and Echo Doppler
Echocardiography in Changing the Disease
During this same period of pathogenic change, AS diagnosis also changed from invasive heart catheterization, which was cumbersome and difficult to perform serially, to a noninvasive and easily repeated echocardiographic strategy. Figure 3 depicts AS as 3 resistors in series. The first (R₁) is the resistance to pulmonary flow that may increase reversibly in AS. The second resistor (R₂) is the stenotic aortic valve, whereas the third resistor (R₃) is the total peripheral resistance. Before the advent of echo Doppler interrogation, AS severity was assessed in symptomatic advanced disease with very severe obstruction for the first time in the catheterization laboratory. It was not uncommon to discover a transvalvular mean gradient of >100 mmHg. Today, serial echo examinations allow for much earlier detection at less severe stages of the disease, and very severe AS (aortic valve area [AVA] <0.6 cm²) is rarer today than it was 40 years ago, so that R₂ is less. However, as the population has aged, hypertension that increases in incidence with age has become a major hemodynamic factor. Decades ago, a common clinical theory was that severe AS and hypertension did not coexist. However, today, their coincidence is commonplace. Thus, in evaluating the patient with AS today, total resistance to outflow (R₁+R₂) must be considered and hypertension, which should be no less deadly in patients with AS than in those without, must be treated effectively but with caution in the presence of nearly fixed outflow obstruction at the aortic valve.

Hypertrophic Compensation and Ejection Performance
In 1973, Grossman et al postulated that pressure overload acting through wall stress in some way informed the myocardium to lay down sarcomeres in parallel, increasing left ventricular (LV) wall thickness. Because Laplacian systolic wall stress, \(\sigma = \frac{P \times r}{2Th}\), where \(P\) is systolic pressure, \(r\) is the LV radius, and \(Th\) is wall thickness, an increase in wall thickness in the denominator of the Laplace equation offset the increased pressure in the numerator, normalizing stress in a feedback loop. It is clear that this concept is operative, but perfect hypertrophic compensation often does not occur. In some cases, especially in older women, the amount of hypertrophy that develops seems excessive, afterload is reduced to subnormal levels, and ejection performance is normal or supernormal. In some cases, hypertrophy is inadequate to normalize wall stress and ejection fraction is decreased. In other cases, there is concentric remodeling with little hypertrophy, a pattern in which LV wall thickness is increased but chamber size is decreased. Although ejection fraction is normal, the fact that the LV is ejecting from a small end-diastolic volume means that stroke volume is reduced, in...
turn reducing the transvalvular gradient. Because it is often thought that severe AS is attended by a transvalvular gradient of ≥40 mm Hg when LV function is normal, this latter circumstance could cause the clinician to underestimate AS severity, a pathophysiology not well-recognized until recently.

**Understanding the Symptoms of AS**

As noted, the onset of the classic symptoms of AS represents a crucial demarcation in the natural history of the disease and is associated with a precipitous decline in survival. Thus, understanding the pathophysiology of the classic symptoms of AS, angina, syncope, and those of heart failure (primarily dyspnea) is a key to understanding the disease process.

**Angina**

Approximately 35% of AS patients have angina as their presenting symptom. In the broadest sense, angina occurs when myocardial oxygen demand exceeds oxygen supply. Both sides of this equation are affected in AS. Oxygen demand is approximated clinically as the product of systolic wall stress...
and heart rate. As noted, in some AS cases, hypertrophy is inadequate to normalize stress and, thus, increased systolic wall stress leads to increased myocardial oxygen demands, predisposing the patient to angina.21 Concurrently, oxygen supply in AS also may be reduced. Normally, coronary blood flow can increase by ≤20-fold because of vasodilatory autoregulation. Increased flow accommodates the increased myocardial oxygen demands of exercise. However, in AS, coronary flow reserve may be limited to less than half of normal.22 Reduced reserve is probably predicated on increased LV diastolic pressure that compresses the endocardium, limiting endocardial reserve is probably predicated on increased LV diastolic pressure that compresses the endocardium, limiting endocardial reserve which might prevent output from increasing, but R 3 still decreases in causing the symptom of angina, most patients with AS have LVH and reduced coronary flow reserve but do not have angina. Further, the presence and magnitude of LVH does not correlate with the symptom.25 Thus, the definitive cause of angina in AS remains uncertain. No specific LV mass or wall thickness presages the onset of angina, whereas aortic valve area predicts coronary flow reserve, as does the ratio of systolic ejection time (the period of oxygen debt) to diastolic filling time (the period of oxygen repayment), and seems to correlate best with the occurrence of angina in AS.25,26 It is probable that the elusiveness of the mechanism of angina in AS resides in not a single cause but rather a blend of multiple anatomic and pathophysiologic variables.

**Syncope**

Syncope is the brief reversible loss of consciousness and usually occurs from interruption of cerebral blood flow. In AS, syncope is caused by hypotension, but the exact cause of this decline in blood pressure remains uncertain. It is clear, however, that when syncope does occur, it almost always happens during exercise. Ohm’s law as it applies to the heart states that blood pressure = cardiac output × total peripheral resistance. Thus, hypotension occurs when there are abnormalities in cardiac output or total peripheral resistance or both. One theory for exercise-induced syncope in AS is embodied by the resistances shown in Figure 3. Exercise leads to peripheral vasodilatation (a decline in R 3). In normal subjects, increased cardiac output more than compensates for the decline in resistance and blood pressure increases. However, in AS, the high resistance at the aortic valve (R a) might prevent output from increasing, but R a still decreases so that blood pressure declines, leading to syncope. Cardiac output also may be limited by the cardiac remodeling that attends AS. In some patients, remodeling results in small ventricles capable of generating less stroke volume, and such patients are predisposed to syncpe.27 However, there are strong data to support inadequate total peripheral resistance as the culprit. In dogs, high LV pressure induced by aortic outflow obstruction led to a vasodepressor reflex.28 Because the transvalvular gradient increases by the square of the output,29 a doubling of cardiac output would increase a 40-mm Hg gradient to 160 mm Hg, a pressure that could easily affect myocardial pressure sensors, leading to inappropriate vasodilatation. In humans, AS is associated with a failure of appropriate forearm vasoconstriction with exercise.30 Thus, inappropriate vasodilatation may be implicated in the syncope of AS. Finally, exercise-induced arrhythmia likely accounts for some cases of syncope in AS. As with angina, there is probably no single cause of syncope in AS, but rather many factors act in concert to cause this symptom.

**Dyspnea**

It is remarkable that with the advanced technology of today, the exact cause of cardiac dyspnea is still unknown. However, the symptom seems to correlate best with elevated left atrial pressure. It is likely that impaired cardiac output also plays a role in causing the symptom. In turn, these pathophysiologic consequences have many causes in patients with AS and stem from systolic dysfunction, diastolic function, or both.

**Systolic Dysfunction**

Systolic dysfunction accrues from afterload mismatch, myocardial contractile dysfunction, or both. As noted, the amount of concentric hypertrophy that develops in AS may or may not be sufficient to normalize afterload.31 In cases of inadequate hypertrophy, afterload mismatch reduces ejection fraction and cardiac output, forcing an increased reliance on preload reserve and its attendant increase in filling pressure, in turn leading to dyspnea.32 In other AS patients, myocardial damage from persistent pressure overload leads to reduced contractility and heart failure. The mechanisms by which pressure overload causes myocardial damage are unclear. Intermittent ischemia, abnormalities in calcium handling, densification myocardial microtubules, and apoptosis all have been implicated.33-35

**Diastolic Dysfunction**

Concentric hypertrophy in pathological states is almost invariably associated with diastolic dysfunction. Diastole is usually divided into 2 parts: isovolumic active relaxation followed by passive filling.36 In patients with concentric LVH, isovolumic relaxation is prolonged, increasing the time to mitral valve opening, and, in turn, shortening filling time. With regard to passive filling, in general, it requires greater filling pressure to distend a thickened LV; therefore, for any given LV diastolic volume, greater filling pressure is required. Abnormal diastolic filling, in turn, accrues from thickened myocytes and also from increased stiffness imparted by increased collagen content of the extracellular matrix.39

**Bicuspid Aortic Valve**

In the past, it was recognized that some patients with AS also had dilatation of the proximal aorta, a condition referred to as postsenotic dilatation. The term was meant to suggest that, in some way, the aorta was responding to the hemodynamics of the AS by compensatory dilatation. However, it is now recognized that such patients (at least most of them) have a bicuspid rather than a tricuspid aortic valve.40 Approximately 1% to 2% of the population is born with a bicuspid aortic valve. Aortic dilatation is more common with fusion of the noncoronary cusp with either the left cusp or the right cusp and is rarer with fusion of the left and right cusps.41 Rather than some form of
compensation, it is clear that aortic dilatation with bicuspid valvular AS is a genetic disease. Aortic dilatation may lead to aortic dissection and concomitant aortic root surgery may be necessary when the valve itself is addressed surgically.

**Evolution in Management**

Although the current management of AS is addressed by Lindman et al. elsewhere in this compendium, it is fascinating to explore how we arrived at the current therapy. Thirty-five years ago it was often thought that asymptomatic patients with severe AS rarely died suddenly. Mortality for aortic valve replacement (AVR) was approximately 5%, doubling if it was accompanied by coronary revascularization. Thus, there was a strong belief that AVR should not be undertaken in truly asymptomatic patients because the risk/benefit ratio favored watchful waiting. However, in those >35 years of age, surgical mortality has steadily decreased and is approximately 2.5% overall today.

Importantly, the estimated Society of Thoracic Surgeons risk of AVR in an asymptomatic 70-year-old patient without other comorbidities is <1%. At the same time, it is clear that asymptomatic patients with severe AS do die suddenly, albeit rarely. The estimated risk of sudden death in asymptomatic severe AS patients is approximately 0.5% to 1.0% per year. Thus, surgical risk approaches the risk of watchful waiting for symptoms to develop, leading to reconsideration of AVR in asymptomatic patients. Further, there are asymptomatic patients at higher than average risk. These include those patients with transaortic jet velocities >4.0 m/s, those with heavy valve calcification (who have rapid progression in their disease), those with abnormal exercise test results, those with severe LVH, and those with increasing B-type natriuretic peptide. Thus, today, AVR may be undertaken in asymptomatic patients with ≥1 of those risk factors when surgery is performed by surgeons in centers with excellent surgical outcomes. At the other end of the AS spectrum is the patient with far-advanced disease, severe symptoms, and decreased LV function. Key in addressing this group of patients is an enhanced understanding of the hemodynamics and pathophysiology of AS. Once taken as a sacrosanct measure of AS severity, there is now recognition that AVA is only one such measure and that AVA may vary directly with cardiac output. Thus, in some patients, resting AVA suggests severe disease; however, with increased cardiac output generated by inotrope infusion, valve area increases dramatically, a condition termed pseudo AS. Such patients do not have severe AS and do reasonably well with medical management, but they inevitably have advanced heart failure and the poor prognosis that accompanies it. Conversely, other patients with truly severe AS also have severe contractile dysfunction and are unable to generate a stroke volume, and thus are unable to generate a transvalvular gradient. Once thought to be inoperable, such patients may benefit from AVR, especially if they demonstrate improved cardiac output during inotropic challenge. Thus, time has witnessed changes in AS management at both ends of the spectrum. Both asymptomatic patients with severe disease and patients with far-advanced disease now may be referred for surgery and benefit from it, an unlikely scenario 35 years ago.

**Transcatheter AVR**

The changes in AS management noted evolved gradually over time. However, the recent advent of transcatheter AVR (TAVR) was a discontinuous change, an abrupt departure from previous therapy. Although it took a decade to reach fruition, TAVR now offers hemodynamically superb relief of outflow obstruction without surgery. In turn, TAVR provides improvement in both longevity and, importantly, quality of life for inoperable patients. TAVR also offers a less invasive avenue of therapy for high-risk but operable patients. An important collateral benefit to TAVR is that approval in the United States was facilitated by the successful completion of an elegant randomized trial in an area of clinical cardiology in which such trials have been conspicuously absent, proving that evidence-based medicine can be derived in the field of valvular heart disease. A second outgrowth of TAVR is the reaffirmation of the importance of a Heart Team. In this approach, cardiologists, heart surgeons, imagers, and other key personnel view the patient, bringing a wide variety of expertise and judgment to the management decision. This process improves care and promotes teamwork among the professionals providing the care.

**What the Future May Hold**

Currently, management of AS relies on AVR and is predicated largely on symptomatic status and our assessment of severity. Although our tools of severity assessment have become sophisticated, the concepts are 100 years old. This is likely to change radically in the coming decades. Two obvious targets loom, understanding and preventing valve calcification and understanding what biological processes lead from obstruction to flow to hypertrophy to heart failure to death. Surely the occurrence of symptoms lies at the end of this sequence. There must be the activation of a host of systems that presage symptom development long before there is severe LVH and fibrosis. If these could be detected, then it might lead to the prevention of AS all together or to early valve replacement. In turn, early therapy could be facilitated by the almost certain evolution of TAVR into a more easily applied less invasive technique. Thus, although the evolution of AS in the past 50 years has been striking, this evolution is not over and will likely accelerate in an exciting array of new understanding and new technology in the future.

**Disclosures**

None.

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