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SECONDARY PREVENTION AND INTERVENTION (D. STEINBERG, SECTION EDITOR)

Aortic Stenosis

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Abstract
Purpose of Review Aortic stenosis is the most prevalent valvular heart disease. The purpose of this paper is to review the epidemiology, pathophysiology, and diagnosis of aortic valve stenosis.
Recent Findings The diagnosis of aortic stenosis has evolved over time. Originally diagnosed with cardiac catheterization and echocardiography, more advance imaging techniques including computed tomography, magnetic resonance imaging, and 3D printing have improved our understanding of the physiology and hemodynamic effects of aortic stenosis.
Summary Valvular heart disease affects a broad patient population, and the most common form of severe valve dysfunction is aortic valve stenosis. It is important to understand the prevalence of the disease and the pathophysiology of aortic stenosis. Both traditional and modern imaging modalities are used to accurately identify aortic stenosis, to define the severity, and to select patients best suited for valve replacement therapy.

Keywords Aortic stenosis · Cardiac CT · Cardiac MRI · 3D printing · Low-flow low-gradient AS · Multi-modality imaging of aortic stenosis · Prognostic tools for severe aortic stenosis · Low-flow, low-gradient aortic stenosis as a well-recognized entity

Introduction

Aortic stenosis is a well-established valvular heart disease which effects a broad population. Once predominately caused by rheumatic fever, primary prevention of the disease in developed countries has seen calcific aortic stenosis arise as the predominant etiology although rheumatic aortic stenosis is still prevalent in underdeveloped countries. As the health and longevity of the general population increases, so does the incidence of valvular heart disease, specifically calcific aortic stenosis [1•]. Certain populations have an increased risk of developing aortic stenosis which include familial hyperlipidemia, renal failure, mediastinal radiation, and metabolic disorders of calcium [2]. This increase in disease prevalence has been mirrored by improvements in not only the diagnosis and understanding of the disease process but also great strides have been made in surgical outcomes as well as novel therapeutic techniques such as transcatheter aortic valve replacement [3].

Epidemiology

Aortic stenosis, irrespective of its underlying etiology, is a progressive disease that ultimately reaches a threshold of severe stenosis and symptom development. Historically, rheumatic aortic stenosis was the predominate etiology. Over time, this paradigm has shifted and now, the most common reason for the development of severe aortic stenosis and surgical referral is calcific (degenerative) aortic stenosis. The age of presentation is closely related to the underlying structure of the aortic valve. A prospective study evaluating valve morphology of 932 patients referred for aortic valve replacement showed that 6% were unicuspid, 54% congenital bicuspid, and 40% tricuspid [4•]. Stenosis with unicuspid valves usually presents earlier in life, congenital bicuspid valves usually in the 4th–6th decades of life, and calcific tricuspid valve stenosis in the 6th–8th decades. Although these are generalized tertiles, patients that present with severe aortic stenosis before the 6th decade of life should undergo thorough evaluation for a bicuspid etiology to allow for proper screening of its associated aortopathies.

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Patterns of calcification differ between the different etiologies of aortic stenosis (AS). Rheumatic aortic stenosis is associated with commissural fusion with resultant leaflet immobility and retraction. This leads to progressive stenosis and commonly a component of aortic insufficiency. Calcific AS affects both tri-leaflet and congenital bicuspid valves with calcium deposition predominately at the leaflet bases along the flexion point.

Not all flow acceleration across the left ventricular outflow tract (LVOT) can be attributed to a valvular pathology. Subvalvular stenosis caused by muscular ridges, webs, hypertrophic obstructive cardiomyopathy, or systolic anterior motion of the mitral valve apparatus can all "mimic" valvular stenosis, and careful evaluation is needed to exclude these different etiologies.

The natural history of aortic stenosis has been well established and studied over the past five decades originally proposed by Ross and Braunwald in their seminal 1968 paper on aortic stenosis [5]. The population studied was post-mortem evaluation of patients with severe aortic stenosis of predominately rheumatic or congenitally bicuspid etiology. A retrospective review showed a relatively stable period of symptom quiescence followed by a rapid decline in survival after the development of symptoms. Survival time varied based on presentation with average survival ranging from 5 years with angina, 3 years with syncope, and 2 years with signs of left ventricular dysfunction or heart failure. More recent analyses of patients with severe aortic stenosis who were considered prohibitive surgical risk show a much more precipitous decline in survival with just over 50% mortality at 1 year [6, 7]. It is difficult to compare such diverse (different) patient populations, but these trials consistently show that once symptoms develop, there is a consistent decline in survival unless the mechanical obstruction is corrected.

Not every patient with severe aortic stenosis is created equal and some patients may remain asymptomatic for a long period of time. Previous studies have compared patients with severe symptomatic aortic stenosis with those with severe stenosis who are asymptomatic [8]. This showed that the absence of symptoms was rarely associated with death from a cardiac cause compared with patients who were symptomatic 3.9% vs 38%, respectively. Further studies have evaluated asymptomatic severe AS patients and found that aortic valve calcium is an independent predictor of adverse clinical outcomes in asymptomatic patients. Moderate to severe aortic valve calcification has been shown to be associated with a significant increase in cardiovascular endpoints defined as death or aortic valve replacement due to the onset of symptoms [9]. Some asymptomatic patients require further risk stratification to determine the most appropriate time for intervention. Das et al. [10] showed that it was not only safe to exercise asymptomatic patients with aortic stenosis but also exercised induced symptoms were predictive of spontaneous symptom development over the next 12 months. Subgroup analysis of patients with severe AS (effective orifice area (EOA) ≤ 0.8 cm^2) showed that the development of limiting symptoms on exercise testing has a positive predictive accuracy of 63% of symptom development during the following year.

Pathophysiology

Aortic valve pathology can range from focal leaflet thickening and mild calcification, aortic sclerosis, to a severely calcified aortic valve with immobility of leaflets, to critical AS. It is estimated that only 10–15% of patients progress from aortic sclerosis to valve obstruction over a period of 2 to 5 years [2]. The degree of valvular stenosis is based on echocardiographic assessment of peak velocity across the aortic valve, mean gradient utilizing the modified Bernoulli equation, and calculated valve area by continuity equation (Fig. 1). Current guidelines support echocardiographic assessment as the standard of care in stratifying severity of aortic stenosis [11••, 12]. Both the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) have similar definitions of severe aortic stenosis (peak velocity > 4 m/s, mean gradient > 40 mmHg, AVA < 1 cm^2). Minners et al. [13] sought to validate these echocardiographic parameters by retrospective analysis of 6152 patients referred for echocardiography. Comparing aortic valve area with both mean pressure gradient and peak flow velocity showed that a valve area of 0.8 cm^2 correlated with a mean pressure gradient of 40 mmHg and peak flow velocity of 4 m/s. These inconsistencies in the guidelines mean that AVA < 1 cm^2 is a more sensitive definition compared to a mean gradient > 40 mmHg or peak velocity > 4 m/s which would be a more specific definition of severe aortic stenosis. A staging system has also been developed to help stratify patients who are at risk of aortic stenosis (stage A), mild to moderate obstruction (stage B), severe obstruction without symptoms (stage C), and severe symptomatic aortic stenosis (stage D) [9].

Degenerative AS is a progressive process that occurs over decades. It is postulated that mechanical stress leads to injury of the valve with resultant inflammatory changes and cusp thickening. Histologic studies of aortic valve cusps at different stages of disease progression have shown increased cusp thickness with lesions located predominately on the aortic side and at the base of the cusp [14, 15]. Examination of these subendothelial lesions showed abnormal accumulation of lipids, extracellular mineralization, and inflammatory cell infiltrate with macrophages and T lymphocytes. Further studies

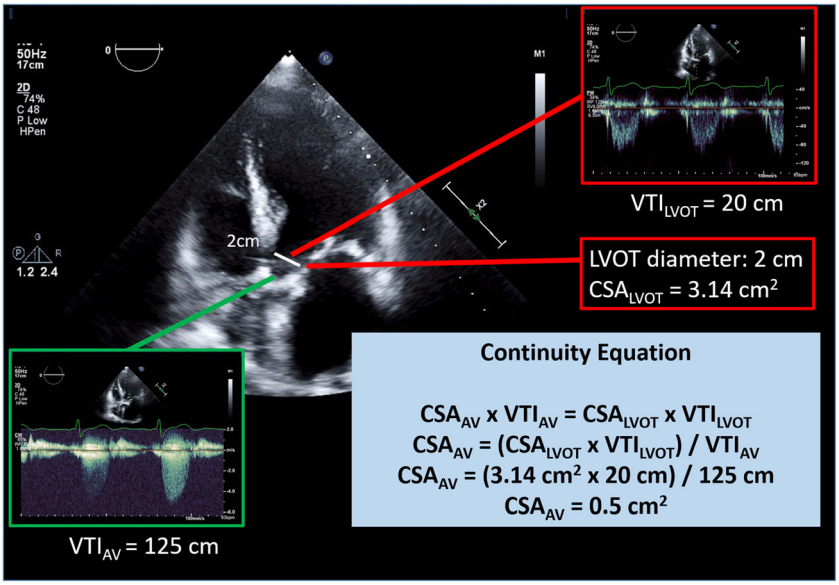

Fig. 1 Doppler echocardiographic determination of aortic stenosis severity. The continuity equation is used to derive the cross-sectional area (CSA) of the aortic valve (AV). A valve area less than 1.0 cm^2 is severe. LVOT, left ventricle outflow tract; VTI, time velocity integral

have demonstrated that the predominate component of lipid accumulation is derived from LDL as demonstrated by apoB and apoA immunoreactivity [16, 17]. The previously described mechanism of valve injury and progression spurred interest in different ways of modifying disease progression. It was postulated that, much like coronary atherosclerotic disease, LDL modification with HMG-CoA reductase inhibitors would result in a slowing of disease progression. Cowell et al. [18] performed a prospective, randomized placebo-controlled trial evaluating the effect of high-intensity atorvastatin on the progression of aortic valve stenosis. Patients were followed for over 2 years with a significant reduction (53%) in LDL levels, but no effect on the progression of aortic stenosis as determined by aortic jet velocity or valvular calcification.

Progressive left ventricular outflow obstruction results in chronic left ventricular (LV) pressure overload and adverse LV remodeling. Increasing LV pressures cause increases in wall stress. To mitigate these changes, the left ventricle will increase wall thickness and overall LV mass with resultant changes in LV filling parameters. While these morphologic changes allow the heart to adapt to the chronic pressure overload, studies have shown that concentric hypertrophy, concentric remodeling, and relative wall thickness (RWT) > 0.66 (normal 0.24–0.42) are associated with early post-operative morbidity and mortality after valve replacement [19, 20].

Increased LV wall thickness leads to impaired relaxation of the left ventricle and resultant diastolic dysfunction. Previous studies have shown that elevated filling pressures (E/e′ > 12) as a surrogate for diastolic dysfunction is independently associated with both increased early and late mortality after AVR [21, 22]. Elevations in LV filling pressure has backstream effects, more specifically leading to increased pulmonary artery pressures. Over time, secondary pulmonary hypertension from LV dysfunction can lead to irreversible changes in the pulmonary vasculature with resultant sustained pulmonary hypertension (PH) which may persist even after aortic valve surgery. Melby et al. [23] performed a retrospective analysis evaluating the impact of PH on early and late outcomes after AVR. They found an associated risk of increased mortality both in the peri-operative setting and long-term survival.

Increases in LV mass and intracavitary pressures also has an impact on coronary blood flow. Coronary perfusion does not increase substantially enough to account for the increased myocardial mass which results in a relative supply demand mismatch. Elevated intracavitary pressures also cause a decrease in the coronary perfusion pressure gradient which can lead to subendocardial ischemia, fibrosis, and worsening diastolic dysfunction.

Aortic stenosis can cause manifestations beyond the heart, specifically gastrointestinal bleeding. This was first observed by Dr. E.C. Heyde in 1958 where he described an increased prevalence of GI bleeding in patients with calcific aortic stenosis [24]. Over the next 5 decades, our understanding of the disease process has improved significantly. Von Willebrand factor is a large protein monomer that forms high-molecular-weight multimers when combined together. These structures help achieve hemostasis in high shear stress conditions. The high stress flow through a stenotic aortic valve causes the unfolding of these multimers and allows ADAMSTS13 to cleave them, reducing their size, and making them less effective at hemostasis. It is hypothesized that vascular aging results in angiodysplastic lesions. This combined with less effective von Willebrand factors can result in an increased incidence of GI bleeding in patients with aortic stenosis. This association is now known today as Heyde's syndrome.

Assessment

Physical Exam

Initial assessment of a patient with aortic stenosis should begin with a physical exam. Cardiac auscultation will reveal a systolic ejection murmur in a sash-like distribution with radiation to the carotid arteries. Murmurs of severe aortic stenosis are typically late peaking owing to the increased pressure required to open the stenotic valve. Careful appreciation of the second heart sound (A_2) can also help identify significant stenoses as its absence can signify a valve that is so calcified; it is unable to close normally and produce an audible sound. Provocative maneuvers can help differentiate the murmurs of aortic stenosis from mitral regurgitation. The murmur of AS is less intense with the Valsalva maneuver or on going from a seated to standing position.

Carotid pulses should also be palpated to assess the amplitude and timing of the carotid upstroke. Severe AS is associated with a carotid upstroke that has a lower amplitude (parvus) and is delayed at its peak intensity (tardus).

Electrocardiography

Electrocardiographic (ECG) assessment of patients with severe AS typically show some amount of left ventricular hypertrophy (LVH). This is associated with reciprocal T wave inversions or ST depressions typically seen in the precordial or lateral leads. Left atrial enlargement is a sequelae of chronic elevations in LVEDP and can be seen on ECG evaluation.

Chest X-ray

Radiographic evaluation of the chest is typically non-specific for aortic stenosis. Aortic valve calcification is rarely seen and the heart is classically of normal size. Certainly, if severe AS has caused LV dysfunction, the left heart border will become enlarged. Left atrial enlargement can occasionally be seen as well as pulmonary vascular congestion, both of which are not specific for aortic stenosis. Careful attention should also be directed to the thoracic aorta for any signs of aortic dilatation or coarctation that can accompany congenital bicuspid aortic valves.

Cardiac Catheterization

Valvular assessment by invasive hemodynamics has been well established and was once the gold standard for the assessment of aortic stenosis prior to the advent of Doppler echocardiography. Invasive hemodynamic evaluation is rarely needed unless there is discordance between the severity of stenosis by echocardiography and the patient's symptom burden [25]. The principle for invasive assessment of valvular area relies on the relation between flow (F) and the velocity (V) of fluids moving across an orifice. The flow equation can be rearranged to solve for area (A) = F/V. The Gorlins [26••] were able to apply this formula to assess valvular stenosis with the addition of coefficients for orifice contraction (C_c) and velocity loss (C_v). The velocity of blood cannot be directly measured invasively, but utilization of Torricelli's law allows for determination of blood velocity by measuring the transvalvular pressure gradient $V = \sqrt{2gh}$ where g represents the velocity of acceleration due to gravity and h is the measured pressure gradient [27]. The final Gorlin formula used to calculate valve area is as follows: $A = F/(C_c \times C_v \times \sqrt{2gh})$. Flow (F) is calculated by either the Fick equation or by thermodilution (TD). Clinicians must know the potential sources of error for both Fick and TD assessments of cardiac output, and best practice usually involves obtaining both to compare for accuracy. Measurement using the Gorlin formula can be cumbersome and difficult to calculate without computer assistance. Dr. Hakki et al. [28•] were able to show excellent concordance between the Gorlin formula and a simplified formula for the assessment of aortic stenosis, the Hakki equation: AVA = cardiac output (CO)/$\sqrt{\Delta P}$. They were able to show very close correlation using both mean gradients ($r = 0.96$) and peak to peak gradients ($r = 0.96$). This simplified formula is now widely used during invasive assessment of aortic stenosis.

Echocardiography

Echocardiography has now become the clinical test of choice to assess for aortic stenosis. The ability to assess both pulsed- and continuous-wave Doppler signals has allowed the calculation of valvular area and mean gradients for aortic stenosis. Valve area is calculated using the continuity equation which requires measurement of the left ventricular outflow tract (LVOT) cross-sectional area (CSA) and the velocity time integral (VTI) of blood at the same location, $CSA_{LVOT} = \pi(D/2)^2$. The continuity equation solving for aortic valve area (AVA) = $(CSA_{LVOT} \times VTI_{LVOT})/VTI_{AV}$ (Fig. 1). Mean pressure gradients are assessed utilizing the modified Bernoulli equation ($\Delta P = 4V^2$) to assess instantaneous pressure gradients across the aortic valve and then averaging the gradients across the ejection period. Galan et al. [29] performed a retrospective analysis comparing stenosis severity by Doppler echocardiography and invasive hemodynamic assessment. They were able to accurately obtain continuous-wave Doppler signals in 98% of patients and show significant agreement 96% between invasive and non-invasive assessment of critical AS (AVA 0.75 cm^2). This study, along with others [30, 31], has validated echocardiography as the preferred method for the assessment of aortic stenosis.

There are a few potential sources of error in echocardiography which can result in an under-/over-estimation of valvular stenosis that need to be addressed. Adequate Doppler

interrogation of the aortic valve is essential. The optimal intercept angle for Doppler assessment is parallel to the flow of blood (0°). Deviations up to 15° result in small underestimations of true velocity, but more obtuse intercept angles can result in gross underestimation of peak velocity and stenosis severity [31]. Apical windows typically provide the best interrogation of aortic valve velocities, but occasionally multiple windows must be assessed to find the highest fidelity continuous-wave (CW) Doppler signal across the aortic valve to ensure accurate assessment of stenosis severity. Pressure recovery is a phenomenon that occurs distal to a stenotic orifice. The law of conservation of energy states that in an isolated system, total energy remains constant. This applies to flow through a stenotic valve as velocity (kinetic energy) increases, pressure (potential energy) must decrease. The inverse occurs in the ascending aorta as blood velocity decreases, pressure will rise resulting in pressure recovery. The net result is an echocardiographic overestimation of invasive catheter gradients. Laskey and Kussmaul [32] studied this in vivo confirming underestimation of true stenosis severity if pressure recovery was not recognized. Further in vitro studies showed that the predictors of significant pressure recovery were associated with smaller aorta size, larger orifice area, and a central jet [33].

Careful attention by both the sonographer and interpreting physician can help avoid the majority of these pitfalls. On occasion, when clinical symptoms are not concordant with echocardiographic data, invasive assessment is still utilized to confirm the degree of valvular stenosis.

Cardiac CT

Multidetector computed tomography (MDCT) imaging is well established in cardiovascular disease, particularly in the assessment of subclinical coronary artery disease. The MESA study group also investigated the incidence and progression of aortic valve calcium in the study population [34]. Across the total population of 5880 participants, they showed only a 13% prevalence of aortic valve calcification at baseline. Patients developed calcification of the AV at a rate of 1.7%/year, most notably in males with diabetes, hypertension, and older age groups. Clavel et al. [35] compared aortic valve calcification (AVC) with degree of stenosis as determined by echocardiography. They found that AVC ≥ 1275 Agatston units (AU) in women and 2065 AU in men correlated very well with two-dimensional (2D) echo Doppler defined as severe AS. Density measurements have also shown a strong correlation with $AVC_{density} \geq 292$ AU/cm^2 in women and 476 AU/cm^2 in men consistent with severe aortic stenosis. These previously mentioned AU calcification threshold have also been shown to be predictive of mortality in patients receiving medical therapy [36•]. Cueff et al. [37] were also able to show that AVC was predictive of true severe AS in patient with low-flow, low-gradient physiology in the setting of a depressed LVEF. Progression of CT technology and the use of cardiac CT angiography prior to transcatheter aortic valve replacement (TAVR) allows for full assessment of the aortic valve, from morphology (tricuspid vs bicuspid), calcification patterns, stenosis severity and subvalvular calcification which could be a risk factor for paravalvular leak after valve implant.

Cardiac MRI

Over the past three decades, cardiovascular magnetic resonance (CMR) has grown as a very robust imaging modality for cardiovascular diseases. CMR allows not only for assessment of valvular anatomy and function but also for the accurate volumetric assessment of left ventricular function as a consequence of the aortic valve stenosis [38]. It has previously been shown on endomyocardial biopsy that aortic stenosis is associated with left ventricular wall interstitial fibrosis [39]. The advent of gadolinium as a contrast agent for CMR has allowed for a non-invasive assessment of LV interstitial fibrosis. Gadolinium distributes out of the circulation and accumulates in the extracellular matrix in the area of scar formation. This late gadolinium enhancement (LGE) allows for scar imaging which can provide prognostic information. Dweck et al. [40] evaluated LGE patterns in AS patients, both CAD and non-CAD mid-wall fibrosis patterns. This prospective study showed that mid-wall fibrosis was an independent risk factor for the primary endpoint of all-cause mortality. There was also a quantitative value with respect to the primary endpoint as every 1% increase in the percent LGE mass was associated with a 5% increase in the risk of mortality. Not surprisingly, aortic valve replacement conferred a survival advantage to medical therapy, but patients with mid-wall fibrosis still showed increased mortality rates compared with patients who underwent AVR and had no evidence of LGE on CMR.

3D Printing

Three-dimensional (3D) printing is a relatively new technology that has shown promise in the medical field. Advancements with printing materials has allowed for replication of the aortic valve apparatus to help with understanding valvular anatomy, function, and potential complications from device implantation. Maragiannis et al. [41] showed that with the use of ECG-gated high-resolution multidetector CT data sets, they were not only able to recreate with multimaterial 3D printing an anatomically correct valve but also able to show a strong correlation of functional assessment between the 3D-printed echo and the clinical Doppler echo study of valve stenosis severity. Advancements like this help us may help us all to better understand patient-specific valve flow dynamics and may potentially impact therapeutic treatment options.

Special Populations

Low-Flow, Low-Gradient Aortic Stenosis

Low-flow, low-gradient (LF-LG) aortic stenosis is a well-recognized clinical entity that manifests with both depressed and preserved systolic function. Severe aortic stenosis is defined by a mean gradient > 40 mmHg, peak velocity > 4 m/s, and an AVA < 1 cm^2. However, these parameters of valve function are all flow dependent and rely on the left ventricle to generate the pressure needed to facilitate valve opening. This clinical scenario of LF-LG AS can be caused by both systolic dysfunction (traditional LF-LG AS) and in the setting of preserved systolic function (paradoxical LF-LG AS) [42].

Traditional LF-LG AS is characterized by an LVEF < 40% and a depressed stroke volume index (SVi) < 35 ml/m^2 [42]. Echocardiography-derived parameters of aortic stenosis will show an AVA < 1 cm^2 in the setting of a mean gradient < 40 mmHg. The clinical question that arises is that whether the aortic stenosis is truly severe, or a product of the depressed LV systolic function (pseudo-severe AS). DeFilippi et al. [43] nicely showed that not only was a dobutamine stress echo (DSE) protocol safe in severe AS patients but also was able to stratify patients based on their contractile reserve as well as the changes in their Doppler-derived AS parameters. Contractile reserve was defined as ≥ 20% improvement in wall motion score. Patients who had contractile reserve were further stratified by their valvular parameters under the stress of dobutamine infusion. True severe AS showed increases in both cardiac output and mean gradient, but little/no change in valve area. Conversely, patients with pseudo-severe AS showed increases in cardiac output and aortic valve area ≥ 0.3 cm^2 with no significant change in pressure gradients. The lack of contractile reserve has also been well established as an independent predictor of peri-operative mortality (22–32%) compared with patients with contractile reserve (5%) [44, 45]. Despite this high operative mortality in patients without contractile reserve, Tribouilloy et al.[51] showed that even this population benefited from AVR with 5-year survival rates of 54% in the surgical AVR group compared with 13% in patients managed medically.

Paradoxical LF-LG AS is a relatively new clinical entity that has become better recognized over the past 10 years. Hachicha et al. [46] initially described a subgroup of patients with severe aortic stenosis defined as indexed AVA 0.6 cm^2/m^2 with associated low mean gradients (< 30 mmHg) in the setting of preserved systolic function (LVEF > 50%). They were further classified as paradoxical low-flow (PLF) if SVi < 35 ml/m^2 or normal-flow (NF) if SVi > 35 ml/m^2. At its base, this condition is caused by a reduced aortic transvalvular flow rate which could result from a myriad of reasons. Anatomic abnormalities such as reduced LV cavity size, significant concentric remodeling, and other pathologic conditions (mitral regurgitation/stenosis, diastolic dysfunction, RV failure, and arrhythmias) can all lead to decreased forward flow and the condition of paradoxical LF-LG AS. Hachicha et al. [46] followed these patients prospectively and showed that the primary endpoint of mortality was not only increased when comparing NF (11%) vs PLF (19%) but also showed worsened survival if PLF subjects were treated medically (58%) vs surgical AVR (93%) at 3 years. Prospective analysis of the PARTNER A/B data looking at paradoxical LF-LG patients also showed a significant increase in 2-year mortality of cohort B medical therapy patients (76.9%) vs TAVR recipients (56.5%) [47]. A recent meta-analysis [48] summarized mortality data over the past 10 years confirming the mortality benefit for surgical AVR in this patient population.

Conclusion

Aortic stenosis is a heterogeneous disease process with multiple different etiologies including rheumatic, congenital bicuspid, and calcific aortic stenosis. Irrespective of the etiology, the end result is progressive valvular stenosis and pressure overload affecting the left ventricle. The scope of this review article was to discuss the epidemiology, pathophysiology, natural history, and the assessment of aortic stenosis. Once a catheter-derived evaluation, Doppler echocardiography has supplanted invasive assessment as the diagnostic modality of choice. New and exciting imaging modalities including cardiac CT and CMR have helped prognosticate patient outcomes, but the assessment of severity continues to rely heavily on echo-derived parameters.

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Compliance with Ethical Standards

Conflict of Interest Jeff Parker declares that he has no potential conflict of interest. Stephen H. Little declares that he has received research support from Medtronic and Abbott, and consulting fees from BayLabs.

Human and Animal Right and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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