

Valvular Aortic Stenosis: An Update

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Introduction

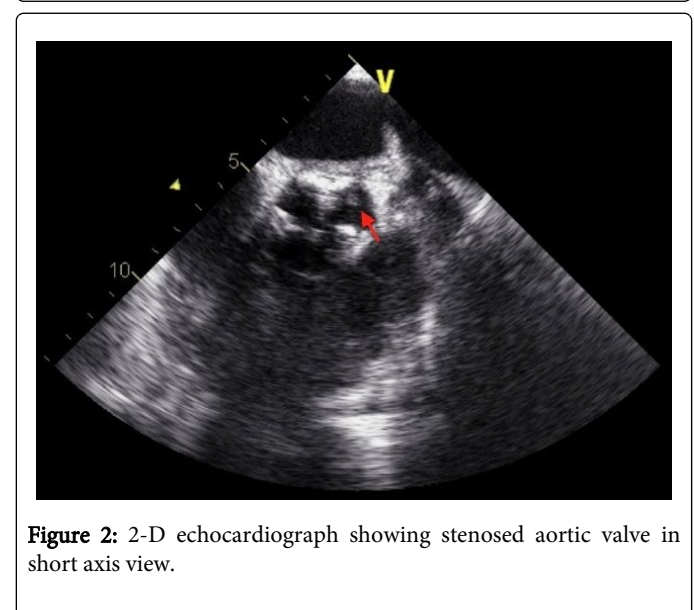
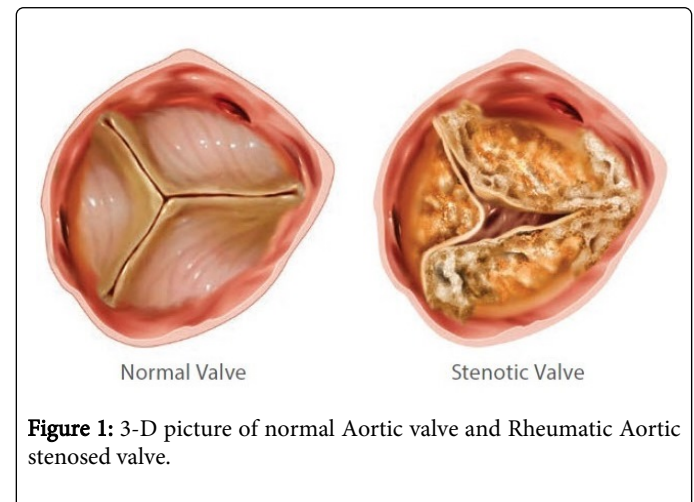
Aortic stenosis (AS) is a narrowing of the aortic valve opening that restricts normal blood flow to the entire body. It is estimated to be prevalent in up to 7% of the population over the age of 65 [1]. It is also more likely to affect men than women as 80% of adults with symptomatic aortic stenosis are male [1]. After the onset of symptoms, patients with severe aortic stenosis have a survival rate as low as 50% at 2 years and 20% at 5 years without aortic valve replacement [1].

Etiology

The valvular aortic stenosis is commonly seen in congenitally bicuspid aortic valve. Approximately 1-2% of population is born with bicuspid aortic valve, which, with aging is prone to get sensed. The bicuspid aortic valve, a genetic disease, is also a risk factor for premature aortic stenosis and ascending aortic aneurysms. The histopathological features of ascending aorta in bicuspid aortic valve and Marfan syndrome are same, such as medial degeneration, decreased fibrillin-1, and enhanced matrix metalloproteinase activity in the aortic wall [1,2]. Among the acquired etiologies of majorities of AS, rheumatic valvular AS (Figure 1) and senile calcific degeneration of aortic valve are the most common causes in developing and developed world respectively [3]. Aortic stenosis is a slow, progressive disorder that starts with aortic sclerosis and progresses to severe calcific aortic stenosis. Other less common causes of acquired AS are atherosclerosis, end-stage renal disease, rheumatoid arthritis and amyloidosis. Several features of calcific AS resembles to that of coronary artery disease (CAD). Both conditions are common in men, older people, and patients with hypercholesterolemia. The major risk factors associated with an increased aortic valve disease are similar to that associated with atherosclerosis like male sex, increasing age, hypertension, smoking, elevated lipoprotein A, elevated LDL cholesterol, cigarette smoking, diabetes mellitus, increased serum calcium and creatinine levels [4]. Heyde's syndrome is a syndrome of aortic valve stenosis associated with gastrointestinal bleeding from colonic angiodysplasia. It is named after Dr. Edward C. Heyde, who first described the association in 1958 [5]. It is due to the induction of von Willebrand disease type IIA by the valvular stenosis [6]. A 2003 study showed how the subtle form of von Willebrand disease present in Heyde syndrome patients resolved rapidly after aortic valve replacement of the stenosed aortic valve. The coagulation abnormality, the study poses, is possibly caused by the increased breakdown of the very large von Willebrand factor molecule by its natural catabolic enzyme (named ADAMTS13) under conditions of high shear stress around the valve [6].

Pathophysiology

The normal aortic valve area (AVA) in adults is 2.6-3.5 cm² (the normal AV index being 2 cm²/m²) with hemodynamically significant obstruction occurring at cross sectional valve areas of 1 cm² or less. The average rate of progression of AVA is 0.1 cm²/ year and peak instantaneous gradient by 10 mm Hg / year [7]. The rate of progression is higher in patients on calcium supplements, increased serum creatinine and patients on hemodialysis [8]. Repeated serial measurements of serum Brain natriuretic peptide (BNP),



Atrial natriuretic peptide (ANP) and the N-terminal part of the propeptides reflect information on the stage of the disease and its hemodynamic impact [9]. According to 2014 AHA/ACC valvular heart disease guidelines, severe AS is said to be present when the mean systolic pressure gradient is more than 40 mmHg with normal cardiac output (CO), a peak velocity greater than 4 m/sec and AVA less than 1 [10]. Simplified Gorlin equation (also known as Hakki equation) can be used to calculate AVA based on CO and peak pressure gradient across the valve.

$$\text{Valve area} = \text{CO} / \sqrt{\text{PG}}$$

Where CO=cardiac output, PG=pressure gradient

It can be concluded from the above equation that critical AS can be seen even with minimal pressure gradient when the CO is significantly decreased. This phenomenon, also known as 'low pressure-low gradient aortic stenosis' is a paradox, and clinically leads to a decline in the intensity of ejection systolic murmur with progressive features of heart failure. Hypertrophied left ventricle (LV) is also hypercontractile to maintain adequate stroke volume and thus the ejection fraction remains normal until very advanced stage of the disease. Also, according to the Laplace's law, the intracavitary systolic pressure generated to overcome the left ventricular outflow tract obstruction in AS directly increases the myocardial wall tension.

$$\text{Wall tension} = P \times R / 2h$$

Where, P=intracavitary pressure, R is the internal radius and h is the wall thickness of LV. The increase in wall tension (chronic pressure overload state) stimulates parallel concentric replication of the sarcomeres leading to concentric left ventricular hypertrophy (LVH). LVH developing as a consequence of ventricular vascular adaptation. So, therapeutic strategies for treatment of hypertension need to consider the impact of drugs on different components of arterial load in order to favour the regression of LVH and improve systolic and diastolic function [11].

The decrease in cavity size limits stroke volume due to decrease in left ventricular filling which, in turn, leads to low cardiac output state at low heart rates. Other consequences of left ventricular hypertrophy include altered diastolic compliance (diastolic dysfunction) of left ventricle, imbalance in the myocardial oxygen supply and demand ratio and deterioration of the intrinsic contractility of left ventricle. Left ventricular diastolic dysfunction (LVDD) develops in late stages and leads to the elevation of LV filling pressures [12]. Therefore, echocardiographic measurements of diastolic function provide important prognostic information. While all Doppler parameters estimate LVDD at moment of the performance, left atrial structural and functional remodeling parameters have been proposed as a barometer of diastolic burden over time and as predictor of common cardiovascular outcomes, such as atrial fibrillation, stroke, congestive heart failure, and cardiovascular death [13,14].

As in any other stenosis lesion, atrial contribution of ventricular filling becomes very important. Atrial kick contributes to 40% of ventricular filling as opposed to 15-20% ventricular filling of normal LV. Thus, normal sinus rhythm is very important in such patients as development of atrial fibrillation (AF) in such patients can lead to acute pulmonary oedema [15,16].

Clinical Features

Angina, syncope and dyspnea are the classic triad of symptoms. Symptomatic patients have poor prognosis, especially, when they present with decompensated heart failure. Such patients have a life expectancy of only 2-5 years, if left untreated [17,18]. Syncope results from inability of patients to increase cardiac output in response to exercise induced peripheral vasodilation. Atrial Fibrillation further worsens the situation due to loss of atrial kick. Clinically, pulsus parvus et tardus (slow rising pulse with narrow pulse pressure) is a typical finding in the carotids due to prolonged ejection phase. Auscultation of chest reveals ejection systolic murmur and soft delayed A₂ leading to narrow splitting of S₂ in mod AS and paradoxical splitting of S₂ in severe aortic stenosis. The loudness of ejection systolic murmur in aortic area is proportional to the severity of aortic stenosis.

Chest X ray is non-specific and may show features of LVH, aortic valve calcification and post-stenotic dilatation. In ECG, there is usually evidence of LVH. The gold standard for diagnosing aortic stenosis is 2-dimensional Doppler echocardiography (Figure 2). The doppler assessment includes the measurement of AVA and trans-valvular pressure gradient by which the severity of aortic stenosis can be estimated [19,20]. Coronary angiography is required to exclude coronary artery disease that co-exists in 50% of patients. Coronary angiogram should be done in such patients irrespective of anginal symptoms as silent myocardial infarction (MI) and physical limitations are common in this age [21]. Cardiac catheterization is rarely done in an isolated aortic stenosis. It becomes necessary when non-invasive data are inconclusive [10].

Current strategy for managing patients with severe AS

The primary management depends on the severity of the disease. If severe AS is present, next step is to decide whether the patient is symptomatic or asymptomatic. The strategy to operate on all asymptomatic patients with severe symptomatic aortic stenosis exposes 100% of patients to operative risk along with the risk of living with prosthetic valve. A more practical approach is to identify the group of asymptomatic patients at highest risk of sudden death and to consider aortic valve replacement in them. Trans aortic flow velocity is a useful predictor of the eventual development of symptoms in patients with severe aortic stenosis [7]. When the initial inflow velocities exceed 4 m/sec there are 70% chances that an aortic valve replacement will be required within the next 2 years. Another strategy used to screen for high risk patients is exercise testing, although it should be avoided in symptomatic patients. Any asymptomatic patient with severe aortic stenosis, if develops symptoms after exercise, should be considered symptomatic [10]. A subset of patients with severe aortic stenosis includes patients with left ventricular dysfunction (low ejection fraction) and low transvalvular pressure gradient. Such patients suffer a high operative mortality rate and poor prognosis. It is difficult to assess accurately the aortic valve area in this low flow low gradient aortic stenosis because the calculated valve area is proportional to the forward stroke volume and because the Gorlin constant varies in low flow states. Some patients with low flow low gradient aortic stenosis have decreased aortic valve areas as a result of inadequate forward stroke volume rather than anatomic stenosis. Surgical therapy is unlikely to benefit such patients because the underlying pathology is weakly contractile myocardium. However, patients with severe anatomic aortic stenosis may benefit from aortic

valve replacement despite the increased operative risk associated with low flow low gradient haemodynamic state.

2014 AHA/ACC valvular heart disease guidelines call for dobutamine stress echocardiography testing to distinguish between patients with fixed anatomic aortic stenosis from those with flow dependent aortic stenosis and with LV dysfunction. Low flow low gradient aortic stenosis is defined as a mean gradient of less than 40 mmHg and a calculated AVA of less than 1 cm². Dobutamine stress echocardiography can reveal three different responses- (i) Increase in transvalvular pressure gradient and cardiac output but no change in AVA. It signifies an anatomically fixed aortic stenosis. (ii) Increase in cardiac output with little or no change in gradient and slight increase in calculated valve area. Such patients are having relative AS and still benefit from surgery. (iii) No increase in cardiac output but increased transvalvular pressure gradient. Such patients have absence of contractile reserve. Patients with good contractile reserve and fixed aortic stenosis have relatively good prognosis with valve replacement. The role of medical therapy in AS is limited but the recent update is as follows:

- Antihypertensive therapy- Medical therapy for hypertension in patient with aortic stenosis should control. There is no specific antihypertensive drug recommended for patients with aortic stenosis. Diuretics should be avoided if the LV chamber is small. Angiotensin Converting Enzyme Inhibitors may be advantageous. Beta blockers are an appropriate choice in patients with concurrent CAD.
- Vasodilator therapy- It can be used in patients with severe AS and NYHA class IV heart failure to reduce afterload and to stabilize the patient before urgent AVR.
- Statin therapy- It is not recommended for prevention of haemodynamic progression of aortic stenosis in patients with mild to moderate calcific aortic valve disease. There is no data to support the use of statins for prevention of progression of aortic stenosis. It can be used in patients with concurrent CAD, hypercholesterolemia and aortic stenosis [10].

The aortic valve replacement (AVR), either surgical or transcatheter, is the best treatment for AS as age-corrected survival is nearly normal after AVR [10].

Timing of intervention

The class I indications for AVR are:

- Patients with severe high grade aortic stenosis who are symptomatic by history or by exercise testing.
- Asymptomatic patients with severe aortic stenosis and LVEF<50%.
- Severe aortic stenosis patients undergoing other cardiac surgery.

AVR is reasonable (Class II indications) in:

- Asymptomatic patients with severe AS and decreased exercise tolerance.
- Low flow-low gradient severe AS with reduced LVEF with a low dose dobutamine stress study that shows an aortic velocity \geq 4 m/sec (or mean PG \geq 40 mmHg with a valve area \leq 1cm² at any dobutamine dose.
- Symptomatic patients with low flow low gradient severe AS who are normotensive and have LVEF \geq 50% if clinical, hemodynamic and anatomic data support valve obstruction as the most likely cause.

Selection of intervention

Before selection of interventional procedure, the surgical risk should be evaluated using logistic Euro SCORE and STS score to categorize the patient into low, intermediate and high risk group. Surgical AVR is the treatment of choice for severe AS with low or intermediate surgical risk but TAVI (Trans Catheter Aortic Valve Implantation) is an alternative for selective high risk surgical (STS score>10% or logistic Euro SCORE>20%) or inoperable patients. Exclusion criteria for TAVI include bicuspid or non-calcified aortic valve, peripheral vascular or aortic disease, coronary artery disease requiring revascularization, severe chronic kidney disease, severe left ventricular hypertrophy, LVEF<20%, severe mitral regurgitation, or significant neurological disease. Procedural complications include death (2-5%), stroke (2-5%), acute kidney injury (1-2%), coronary occlusion (0.6%), major bleeding (15%), vascular site complications (10-15%), need for permanent pacemaker (5-15%), significant perivalvular leak (10%), valve embolization (0.3%), and prolonged hospitalization. Thirty-day mortality is 6% to 10% and 1 year mortality is 20-30% [22]. Transcatheter aortic valve implantation (TAVI) is thought to change the characteristics and outcome of patients with aortic stenosis undergoing surgical aortic valve replacement (SAVR). Rozen GR, et al. investigated the difference in clinical characteristics and outcomes of SAVR patients in the TAVI era and have seen a dramatic decrease in 1-year mortality and adverse perioperative events in patients undergoing SAVR for severe aortic stenosis during recent years [23]. This change is likely related to selection of lower-risk patients for AVR in the TAVI era.

Summary

In patients with aortic stenosis who develop the classic symptoms of angina, syncope, or dyspnoea, prompt aortic valve surgery should be performed to prevent sudden death-ideally within 30 days of onset of symptoms. Asymptomatic patients with severe aortic stenosis can be managed medically, but such management has taken on a more active investigative strategy. All such patients should undergo exercise testing if feasible. If unexpected 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 case of patients with poor left ventricular function because of excess afterload (high gradient), aortic valve replacement leads to an improved ejection performance and a good outcome. In patients with severe aortic stenosis who respond to dobutamine, aortic valve replacement should be presented with the advice that postoperative prognosis is likely to be reduced.

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