An overview of aortic stenosis (AS): what we know and when should we intervene?

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Abstract

Introduction: A condition in which there is a continuous state of fibrosis, thickening as well as calcification of the leaflets that'll eventually impede the amount of blood reaching the heart, which, if left untreated/maltreated, will eventually lead to death (1). AS does not only have an impact on the aforementioned valve, but on the LV and the entirety of the systemic vasculature (2). The most commonly encountered heart valve lesion, AS is believed to affect 2-5% of older adults (3). It is estimated that 4-7% of individuals aged 65 years or older have been diagnosed with severe AS (3). **Etiology of AS:** It is believed that there are 3 major causes of AS, these are: 1) Degenerative (Calcific), 2) Rheumatic (4,5), and 3) Congenital **Clinical Manifestations & Underlying Etiology:** First articulated in 1968 by Ross and Braunwald (8), it is now commonly accepted amongst professionals that the development of symptoms (such as exertional dyspnea, angina, and syncope) is a poor prognostic sign as it clearly signifies left ventricular decompensation (1,8). **Diagnosis:** The diagnosis of calcific aortic stenosis is initially suspected if a systolic ejection murmur is present; be that as it may, the clinically significant question is normally whether the aortic stenosis is to be classified as 'severe' (5). The three most useful signs when it comes to diagnosing severe aortic stenosis are: 1) Late peaking systolic murmur, 2) Single second heart sound or paradoxical splitting of S2, and 3) 'cooing' murmur (5). **Current guideline-recommended treatment strategies and their limitations:** In a general sense, contemporary clinical rules suggest aortic valve intervention when stenosis seriousness is considered extreme and there is confirmation of left ventricular decompensation, via the direct even-handed or proxy representative measures (1). **Conclusion:** Aortic stenosis is a common cardiac disease that is of the upmost importance, deserves our undivided attention, and a crucial part in decreasing any morbidity and mortality is generally through a very careful follow-up. The gold standard investigation for suspected cases is echocardiography (5), currently the only treatment available would be a valve replacement therapy which is proven to have a good outcome and increases the patient's life span (4). In asymptomatic patients on the other hand aortic valve replacement is considered only after symptoms have developed or if the exercise test results are worrying (4,14). We are hoping that in the future there'll be more treatment options available that would suit the different ages and health statuses of the patients. **Recommendations:** 1) The initiation, funding, and publication of further studies on AS, ergo permitting for decreased morbidity and mortality**,** 2)The initiation of awareness programs amongst the public that would result in a decreased likelihood of lifestyle-caused AS, 3) The initiation of awareness programs amongst the public that would result in patients being overall better surgical candidates if it must take place, 4) The initiation of nation-wide (in Sudan and elsewhere around the world) geriatric services that would result in the monitoring of those most likely to fall ill with AS.

Keywords: *Echocardiography; Cardiology; Cardiothoracic surgery; Medicine; HHE; Surgery; Aortic Stenosis*

Abbreviations:

AS = Aortic Stenosis

LV = Left Ventricle

CT = Computed Tomography

ECG = Electrocardiogram

AVR= Aortic Valve Replacement

AVB= Atrioventricular Block

LBBB= Left bundle branch block

EOA= Effective Orifice Area

HHE= Hand-Held-Echocardiography

MAVD= Mixed aortic valve illness

AR = Aortic Regurgitation

Introduction:

A condition in which there is a continuous state of fibrosis, thickening as well as calcification of the leaflets that'll eventually impede the amount of blood reaching the heart, which, if left untreated/maltreated, will eventually lead to death (1). AS does not only have an impact on the aortic valve, but on the LV and the entirety of the systemic vasculature (2). The most commonly encountered heart valve lesion, AS is believed to affect 2-5% of older adults (3). It is estimated that 4-7% of individuals aged 65 years or older have been diagnosed with severe AS (3). Furthermore, there exists the dismal possibility that a significant number of individuals exhibiting AS are either not recognized or are not followed-up by their respective clinicians in the most precise/accurate of manners (3). It seems as if there is a rather modest amount of predominance towards males (4).

Etiology of AS:

It is believed that there are 3 major causes of AS, these are:

1) Degenerative (Calcific),
2) Rheumatic (4,5), and
3) Congenital

1) Degenerative (Calcific):

For numerous years, rheumatic coronary illness was the fundamental driver of aortic valve illness (5).

In the course of the last 50+ years, nonetheless, there has been a change from a rheumatic etiology to a 'degenerative' instrument in view of the increment in admittance to medical services in created nations and the expanding age of the populace in the US and Europe (5).

For a long time, 'degenerative' aortic stenosis was believed to be brought about by the detached collection of calcium on the outside of the aortic valve (5). Recent researches have illustrated, notwithstanding, that the etiology of aortic valve infection has a comparative pathophysiology to that of vascular atherosclerosis, and that the therapy of this illness could be like that of constant vascular atherosclerosis (5)

The underlying plaque of aortic stenosis is corresponding to that of CAD. The risk factors such as male sex, hyperlipidemia, evidence of active inflammation and age are held in like manner by the two disorders (4). Furthermore, there is a high occurrence of the two disorders in the same patient (4).

Calcific aortic stenosis is, for the most part, brought about by solid calcium accumulation inside the valve cusps and less by combination of the commissures. The area of these accumulations assists with understanding orifice variability in calcific aortic stenosis when cardiac output is raised via the use of inotropic agents or vasodilators (4).

2) Rheumatic

While rheumatic heart disease is not as common in developed countries, it is still very important to mention that when the aortic valve is affected by rheumatic heart disease that the mitral valve is generally affected as well. (4)

Accordingly, the finding of rheumatic aortic stenosis ought not to be made without the typical echocardiographic proof of rheumatic mitral valve distortion (4).

Furthermore, in rheumatic aortic stenosis commissural combination is typically present, by contrast in relation to calcific aortic stenosis (4).

A study of 250 cases of aortic stenosis has been made, and 196 were rheumatic and 54 were congenital (6).

3) Congenital:

Most cases of extreme congenital aortic stenosis are distinguished and treated in early childhood and puberty (4).

First and foremost, anatomically, congenital aortic stenosis frequently includes a unicuspid, unicommissural valve and is essentially never related with asymptomatic endurance into adulthood (4).

Another pertinent point is that, angina and heart failure are unusual in congenital aortic stenosis, while abrupt demise in individuals without manifestations of aortic stenosis is by all accounts more common (4).
The shortfall of heart failure could be inferable to some degree to the way that ejection performance is generally supranormal and wall stress is odd on the grounds that concentric hypertrophy appears to overcompensate for the existing pressure factor overload (4).

Of note, congenital cases were more likely to be subvalvular than initially expected (6).

In summary, patients at risk of AS, like those with a congenitally bicuspid valve or childhood rheumatic fever, experience a long, inactive phase during which progressive valve hindrance happens, but clinical occasions, including sudden heart demise (assessed yearly danger at 1%) are inconsistent to such an extent that the mortality hazard of intervention with AVR during this asymptomatic period is believed to exceed that related with dynamic observation (3).

Pathophysiology of valvular stenosis

Beginning of serious indications of aortic stenosis—angina, syncope, and cardiovascular breakdown—stays the major outline point in the sickness' course.

The asymptomatic patient has a decent viewpoint even with extreme check, while a person with indications has a death pace of about 25% each year (4). For a relatively significant proportion of our understanding of AS, fibrocalcific AS was believed to be a degenerative sickness in which ongoing 'erosion' elicited underlying harm and, ergo, inactive valvular calcification. Nevertheless, contemporary believing is that fibrocalcific AS manifests as part of a progression of multifaceted and profoundly directed inflammatory, fibrotic, as well as osteogenic measures. The pathophysiological measures driving aortic valve stenosis can be categorized into two stages (1,7):

i) The ‘initiation’ phase, and
ii) The ‘propagation’ phase

The initiation phase, characterized by valvular lipid deposition, endothelial injury, and proinflammatory response, as well as infiltration of lipids, lipid oxidation and exhibits a number of similarities to atherosclerosis (1,7). Although this is the case, at least 3 RCTs have determined there to be no association between the prescription of statins and the improvement of the disease in any way, shape, or form (1).

The propagation phase is signaled by the appearance of osteoblast- like cells that synchronize continuous valvular calcium and bone matrix deposition. This osteogenic phenotype involves many gesticulating molecules involved in

bone formation and is both self-perpetuating and highly regulated. Advances in imaging now permit for non-invasive evaluation of both the load and activity of calcification in the valve; with that being said, the seriousness of aortic valve obstruction is still greater assessed using echocardiography (1,7).

Clinical Manifestations & Underlying Etiology

First articulated in 1968 by Ross and Braunwald (8), it is now commonly accepted amongst professionals that the development of symptoms (such as exertional dyspnea, angina, and syncope) is a poor prognostic sign as it clearly signifies left ventricular decompensation (1,8).

In clinical scenarios, these symptoms might manifest themselves in the following manner:

Angina will manifest itself as chest pain following activity (as a general rule, the less rigorous the activity, the further the angina is in severity). This occurs as a result of a 'supply-demand imbalance' (1).

As for dyspnea, this manifests itself as an inability to carry out activities that were formerly 'easy' for the patient to conduct. This occurs due to a dysfunction of the left ventricle (1).

Syncope occurs due to cerebral hypoperfusion (1). This, logically enough, results in a feeling of dizziness and 'light-headedness' (1).

Supraventricular/Ventricular Arrhythmias & Conduction malfunctions, which is brought to light when asking the patient if 'they're able to feel their heart racing' has been linked to AS multiple times during studies due to the following reasons (9):

For starters, the settlement of calcium on the conduction system as a consequence of its closeness to the aortic valve complex and the development of left ventricular malfunction, both of which have been linked to the occurrence of LBBB and progressed AVB in patients with aortic stenosis.

Secondarily, the elevated pressure in the left ventricle leading to, as mentioned multiple times throughout this paper, left ventricular hypertrophy as well as left atrium overload (9).

Diagnosis

The diagnosis of calcific aortic stenosis is initially suspected if a systolic ejection murmur is present; be that as it may, the clinically significant question is normally whether the aortic stenosis is to be classified as 'severe' (5). The three most useful signs when it comes to diagnosing severe aortic stenosis are:

1) Late peaking systolic murmur,
2) Single second heart sound or paradoxical splitting of S2, and
3) 'cooing' murmur (5)

A late peaking systolic murmur, as assessed by Effective Orifice Area (EOA) has suggested that stenotic aortic valves require a longer duration of time to wholly open than normal valves (5,10). This further strengthens the hypothesis that a stenotic valve possibly, in consequence of its stenosis, further adds to the pressure applied upon a ventricle, ergo causing hypertrophy of the associated ventricle.

Consequently, this will most likely result in delaying of the aortic aspect of the 2nd heart sound. This could, in theory, result in a single second heart sound or an abnormal splitting of S2 (5). Although this may occur, it is important that we note that it is possible for this sign to be faint in nature and, ergo, undetectable (5).

Although relatively uncommon, a 'cooing' murmur could be highly indicative (5). Of course, it is well established by now that the systolic murmur of aortic stenosis could possibly be boisterous in the mitral area as opposed to the area of concern (11). In fact, it could possibly even be louder (11). From an echoic standpoint, the murmur is usually of similar intensity in both areas (11). When a systolic murmur can be heard at the mitral area and is of greater

intensity than it is in the aortic area, it is important to suspect mitral valve disease; cardiac imaging may be decisive in differentiating the scenarios (11).

The seriousness of aortic stenosis is evaluated via authentication from clinical evaluation, echo-cardiography and Doppler studies, and cardiac catheterization (5).
Although it is usually accepted that echo-cardiography usually refers to the ultrasound device found in cardiac units in hospital-settings, it is important that we note that technological advancements mean that Hand-Held-Echocardiography (HHE) has manifested itself as accurate and useful in the detection of valvular pathologies (12) and that the accuracy of these HHE devices is 'comparable to the standard ultrasound machine used for a comprehensive echocardiographic exam' (12). As the authors of a 2018 paper beautifully articulated 'integrating HHE as part of the physical examination can lead to more rapid bedside diagnosis, triage, and treatment of valvular heart disease'.

Furthermore, in so far as patients with substantially calcified aortic valves are concerned, especially those with severe aortic valve stenosis, cardiac CT scans with ECG gating seem to manifest value in the assessment of the situation (13).

Current guideline-recommended treatment strategies and their limitations

In a general sense, contemporary clinical rules suggest aortic valve intervention when stenosis seriousness is considered extreme and there is confirmation of left ventricular decompensation, via the direct even-handed or proxy representative measures (1).

As mentioned further in this article, the intensity of aortic valve is best assessed through the use of echocardiography, but has its own limitations when severity is grating or low-stream states exist (1).

The updated (as of 2017) ESC/EACTS guideline for assessing AS severity (14) states the following:

"1) The evaluation of aortic regurgitation requires consideration of valve morphology and the mechanism and severity of regurgitation, including careful assessment of aortic dilatation.

2) In asymptomatic patients with severe aortic regurgitation, careful follow-up of symptomatic status and LV size and function is mandatory.

3) The strongest indication for valve surgery is the presence of symptoms (spontaneous or on exercise testing) and/or the documentation of LVEF 50 mm.

4) In patients with a dilated aorta, definition of the aortic pathology and accurate measurements of aortic diameters are crucial to guide the timing and type of surgery.

5) Aortic valve repair and valve-sparing aortic surgery instead of aortic valve replacement should be considered in selected cases in experienced centers." (14)

In summary, the guidelines are based on the famous medical principle 'First, do no harm'.

Evaluation of Disease Severity

An agreed upon approach towards assessing the severity of valvular AS is through the use of echocardiography.

Anatomical photos show the pathogenesis of AS, the degree of maintenance, valve calcification, leaflet displacement, and the fundamental construction of the aortic root (2). It is additionally conceivable to survey the LV reaction to extreme distress from pressure overload of a chronic nature, just as other hemodynamic manifestations of AS (2). Hemodynamic boundaries include maximum aortic velocity, mean transvalvular gradient, and continuity equation valve area (2). In so far as we have been able to conclude, the entirety of the aforementioned

hemodynamic parameters have been meticulously analyzed in comparison to rather invasive data and are rather reliable predictors of clinical prognosis (2).
Of these parameters, aortic speed is the most reproducible, and, furthermore, is the best indicator of clinical prognosis (2). Aortic speed permits us to classify AS as mild (2.6 to 3.0 m/s), moderate (3 to 4 m/s), or severe (>4 m/s) (2). Leaflet thickening, plus calcification with sufficient leaflet displacement, and a speed of ≤2.5 m/s is to be identified as aortic sclerosis (2) (aortic sclerosis is when leaflet thickening takes place, but without alteration of cardiac function). Based on the simplified Bernoulli equation, the maximum transaortic pressure gradient (ΔP) is calculated using velocity (V) as a variable (2):

$$\Delta P\text{max} = 4V^2\text{max}$$

The mean gradient is calculated in the following manner (2):

1) Tracing the continuous-wave Doppler curve
2) Averaging the instantaneous gradients over the ejection period.

The calculations associated with the aforementioned echo-cardiographic findings are beyond the scope of this article. However, the information is available throughout a myriad sources. We highly recommend the paper by Otto (2).

Clinical Scenarios Requiring Further Interpretation

1) Hypertension

The long-term elevated blood pressure which is common in adults is considered one of the scenarios requiring further interpretation.

Hypertension causes expanded shear pressure across the aortic valve. Shear pressure across endothelial cells in vitro incites inflammation, which has been exhibited on stenosed valve leaflets in vivo (15).

Theoretically speaking, longstanding hypertension could bring about aortic stenosis (15).

Another point is that the presence of hypertension influences the treatment options in patients with AS in two proportional ways: hypertension may cover the seriousness of stenosis, and the presence of stenosis may influence the ideal treatment of hypertension (2).

2) **Aortic root disease**
The fundamental etiology of AS is a bicuspid valve in more than half of grown-ups including about 60% of those introducing at age 50 to 70 years and about 40% of those 70 years old. Patients with a bicuspid aortic valve have an unusual aorta with an expanded risk for aortic expansion and analyzation. After aortic valve replacement, the most grounded risk factor for aortic analyzation is a bicuspid aortic valve (2).
3) **Combined stenosis and regurgitation**

Mixed aortic valve illness (MAVD) alludes to the conjunction of aortic stenosis (AS) and aortic regurgitation (AR) (16).

Notwithstanding the generally high pervasiveness of MAVD, there is a clear lack in information on the result and the board of this entity. Nonetheless, a number of ongoing studies have detailed that the anticipation of patients with joined moderate AS and moderate AR is comparable or more problematic than those with secluded extreme AS or AR. The restorative administration of MAVD is relatively perplexing and is found on the guideline recommendations for the predominant lesion, AS or AR (16).

4) Diabetes

The well-known metabolic disease that causes high blood sugar has been related with an expanded predominance of AS and adds to the increasing AS progression (17).

While further information from substantial epidemiological and well-controlled studies is required. In this way, having both of the illnesses conveys a higher risk of morbidity and mortality. In patients being thought of for intervention, conversation within a heart valve team and along with other specialists (diabetologist/ anesthesiologist) is unequivocally suggested. This applies to both suggestive and asymptomatic diabetic patients with significant AS (17).

Conclusion

Aortic stenosis is a common cardiac disease that is of the upmost importance, deserves our undivided attention, and a crucial part in decreasing any morbidity and mortality is generally through a very careful follow-up. The gold standard investigation for suspected cases is echocardiography (5), currently the only treatment available would be a valve replacement therapy which is proven to have a good outcome and increases the patient's life span (4).

In asymptomatic patients on the other hand aortic valve replacement is considered only after symptoms have developed or if the exercise test results are worrying (4,14).

We are hoping that in the future there'll be more treatment options available that would suit the different ages and health statuses of the patients.

Recommendations

1) The initiation, funding, and publication of further studies on AS, ergo permitting for decreased morbidity and mortality.
2) The initiation of awareness programs amongst the public that would result in a decreased likelihood of lifestyle-caused AS.
3) The initiation of awareness programs amongst the public that would result in patients being overall better surgical candidates if it must take place.
4) The initiation of nation-wide (in Sudan and elsewhere around the world) geriatric services that would result in the monitoring of those most likely to fall ill with AS.

Ethical considerations:

The authors hereby declare no conflicts of interest. The authors contributed equally to the data collection, writing, and editing of this paper.

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