Calcific Aortic Stenosis: Current Concepts and Management Options

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Citation


Abstract

Calcific aortic stenosis is the most commonly encountered valvular disease in the western countries that needs surgical attention. It affects approximately 2-3% of the elderly population above 65 years and it is associated with significant morbidity and mortality. The most common etiology of acquired aortic stenosis is calcific degeneration. The natural history of aortic stenosis is well known. Patients with mild to moderate AS can be asymptomatic for several years even with the presence of obstruction. Senile degenerative AS is the most common cause for aortic valvular replacement. Aortic stenosis can be diagnosed with good physical examination, Doppler echocardiogram and cardiac catheterization. Management of symptomatic aortic stenosis is replacement of aortic valve. Recent data suggest that statins may be helpful in slowing the hemodynamic progression of calcific aortic stenosis. This review will focus on etiology, pathophysiology, diagnostic evaluation and therapeutic options of acquired aortic stenosis.

ETIOLOGY AND PATHOPHYSIOLOGY

Calcific aortic stenosis is caused by progressive fibrosis and calcification of valve cusps. The process of calcification appear to be mediated by acute inflammation, lipid deposition and mechanical stress, ultimately valve cusps heavily calcify and cause severe aortic stenosis. This disease process shares similar risk factors as atherosclerosis such as smoking, hypercholesterolemia and hypertension and diabetes mellitus. Lp(a) raised serum creatinine and raised serum calcium. Thus, modification of these risk factors may slow the progression of aortic valve calcification. Rheumatic valvular disease is common in the developing countries, but it is rarely seen in the developed countries. Gerber et al, reported inflammatory markers like plasma C reactive protein levels are elevated in patients with tricuspid and Bicuspid AS than normal aortic valves. Study by Sanchez et al, reported that there was high rate of progression of AS in patients with CRP levels greater than 0.3mg/dl. These findings suggest that CRP might help in predicting the hemodynamic progression of AS. Calcific aortic stenosis develops gradually and the cardiac output is maintained initially despite increasing gradient across the aortic valve. As a result, left ventricle becomes hypertrophic, and the patient may develop angina, with out any coronary artery disease. Eventually left ventricle no longer accommodates the outflow tract obstruction and ultimately starts failing.

Gender and age are important factors; Females tend to develop increased concentric wall thickness and small chamber size compared with men. Progression of AS with increase in the wall stress and afterload leads to a decrease in the ejection fraction and left ventricular systolic dysfunction. Elderly patients tend to have pronounced diastolic dysfunction.

Figure 1

Table 1

<table>
<thead>
<tr>
<th>Risk factors for calcification of aortic valve</th>
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</thead>
<tbody>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>HTN</td>
</tr>
<tr>
<td>Renal failure</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Raised serum calcium [Hypercalcemia]</td>
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<tr>
<td>Raised serum creatinine</td>
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</table>
CLINICAL DIAGNOSIS

On physical examination common signs and symptoms are harsh systolic, crescendo-decrescendo murmur, at the left upper sternal border and it is transmitted to the carotids. The ejection systolic murmur is loudest at right second intercostal space. Loudness of murmur correlates to the severity of stenosis, except in patients in with left ventricular dysfunction. Delayed and diminished carotid artery pulses are better indicator of the severity of the aortic stenosis. Systolic thrill can be palpated at the base of the heart. A palpable S4 is felt in patients with left ventricular hypertrophy due to left atrial contraction in the setting of a hypertrophied ventricle with impaired relaxation. As the AS becomes severe, angina may occur due to increased myocardial oxygen demand. Most likely cause of syncope is multifactorial such as, neurocardiogenic, ventricular arrhythmias and inability to augment an appropriate cardiac output with exercise. In these patients congestive heart failure can occur with the normal ejection fraction, most likely due to diastolic dysfunction. Presence of angina, heart failure and syncope in AS has to be monitored very closely and it may be an indication for AV replacement. Patients with AS have to be followed periodically in the clinic for the development of the symptoms. Echocardiogram with Doppler is helpful in monitoring progression of AS and has to done periodically to monitor progression of AS. Progression of the AS is related to various factors as mentioned (please refer table No 1).

Strongest predictors of aortic stenosis progression are degree of the stenosis and the degree of aortic valve calcification. Aortic stenosis can be diagnosed with good physical examination and Doppler echocardiogram, cardiac catheterization. Measurement of aortic valve area by echocardiography is the best non invasive imaging modality and the important parameters to measure are mean transvalvular gradient, maximum aortic velocity, valve area. These parameters are important predictors of clinical follow up of the patient. Aortic stenosis can be classified based on aortic velocity mild (2.6 to 3.0m/s), moderate (3 to 4m/s) and severe more than 4m/s of aortic velocity. Among these aortic velocity area is most reproducible and is the strongest predictor of the clinical outcome. Aortic valve area can be calculated using continuity of flow equation. Aortic valve area (AVA) is calculated based on utilizing the principle that volume flow proximal to the valve equals volume flow through the valve.
NATRIURETIC PEPTIDES AS MARKERS IN AORTIC VALVE DISEASE.

Numerous studies have reported that natriuretic peptides correlate with the severity of aortic stenosis, expressed either as transvalvular gradient or valve area. Correlations are generally closer with BNP and NT-proBNP than with ANP. Gerber et al reported that in aortic stenosis patients with a transvalvular gradient of at least 25 mm Hg, concentrations of natriuretic peptides (BNP, NT-proBNP, and ANP) correlated extensively with measures of the severity of stenosis and measures of LV chamber size, wall thickness and stress, ejection fraction, left atrial size, and right ventricular pressures. Natriuretic peptide concentrations increased steadily with decreasing valve area and increased greatly when ejection fraction fell below 50%.

Low gradient, Low flow aortic stenosis. Recently lot of attention has been given to low –flow, low-gradient AS. It is defined in the literature as, aortic valve area <1.0 cm² and mean gradient <30 mm of HG and LVEF <40% calculated by both the Gorlin’s and continuity equation. This group comprises 5% of the patients of the patients with significant AS. Dobutamine stress ECHO helps in grading the aortic stenosis and also tests the left ventricle contractile reserve. Commonly used doses are in the range of 5-20µg/kg/min. Some times there may be a risk of arrhythmia with higher doses and it has to be done in a controlled setting. In severe AS there will relatively large rise in the mean pressure difference and a small rise in the orifice area. However moderate stenosis is associated with a small rise in mean pressure difference and larger rise in effective orifice area. In the severe AS patients surgical risk increases significantly if the stroke volume does not increase by more than 20% during the Dobutamine infusion. Presence of the left ventricular contractile reserve determines outcomes after the surgery than the markers of AS. Final decision will depend on the urgent necessity of the surgery and other co morbid conditions.

ROLE OF STATINS

Several studies have shown beneficial effects of statins, stating that they may slow the progression of aortic stenosis. Since AS and CAD share similar risk factors, statins may play an important role as pleitropic and anti inflammatory agents. Interestingly this effect is independent of cholesterol lowering effect. Results of the retrospective studies showed that statins may slow the progression of the aortic stenosis by their anti-inflammatory and lipid lowering effects.

Four recently published retrospective studies suggested that statins may decrease the progression of aortic stenosis. But on the contrary in contrary recently published SALTIRE (Scottish aortic stenosis and lipid lowering therapy, impact on regression) Double blind randomized controlled trial did not show any effect on slowing of the progression of disease. There is an argument that SALTIRE trial is not powered to assess the benefits of lipid lowering treatment on cardiovascular end points, such as fatal and non fatal myocardial infarction, but there was a favorable trend in reducing clinical events. Newby et al acknowledged that the timing of therapy for aortic valve stenosis may play the key role in the future treatment of this condition disease. The important issue may be treating this disease earlier in its process to slow the progression of bone formation in the aortic valve. Ongoing larger prospective randomized trials like SEAS (Simvastatin and the Ezetimibe in Aortic Stenosis) and ASTRONOMER ((Aortic Stenosis Progression Observation Measuring Effects of Rosuvastatin ) RAAVE ((Rosuvastatin Affecting Aortic Valve Endothelium) STOP-AS (Stop Aortic Stenosis ) may give us definitive answer in the near future.

In the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis)
Calcific Aortic Stenosis: Current Concepts and Management Options

study, (Rossebo and Pedersen 2004) is an event driven 4-year study in which treatment with the combination of simvastatin 40 mg plus Ezetimibe 10 mg daily is being compared with placebo in 1870 subjects with moderate, asymptomatic, aortic stenosis. Expected completion is in 2008.

RAS INHIBITION AND ROLE OF ACE INHIBITORS.

Conventionally angiotensin-converting enzyme (ACE) inhibitors were considered to be contraindicated in patients with aortic stenosis. These concerns which are primarily regarding safety and tolerability of these agents in patients with aortic stenosis are based on the misclassification of ACE inhibitors as vasodilators rather than being founded on their results of clinical research. (30) ACE inhibitors are [I is well] tolerated in symptomatic patients with severe AS. Patients with congestive heart failure with LV dysfunction and low normal blood pressure patients are prone to have hypotension. ACE inhibitors may have an important role in the treatment of AS, because it can decrease the pressure over load of the left ventricle and also stress and strain on the aortic valves (12). It is well known that sclerotic aortic valves tissues expresses angiotensin II and ACE which may contribute to the disease progression and inflammation. (14) Various studies in animal models have shown that long term blockade of the renin-angiotensin system arrested cardiac growth and even resulted in regression of established LVH in aortic stenosis. (13) There are two observational studies which showed mixed results, O Brien et al, reported that in 123 patients who were treated with ACE inhibitors there was 71% decrease in AS calcification. In contrast Rosenhek et al reported that progression of AS was not delayed by the ace ACE inhibitors. Larger clinical trials need to be done to address this issue, till than it can be used cautiously in patients with CAD, HTN, Heart failure and also who can tolerate this medication. However, there is already evidence that ACE inhibitors can be started in patients for hypertension associated with moderate aortic stenosis and these drugs do not need to be stopped in a patient who remains well despite more severe aortic stenosis (30).

MEDICAL AND SURGICAL MANAGEMENT OF AORTIC STENOSIS.

Currently, the only definitive therapy for AS is aortic valve replacement (AVR). Management of the asymptomatic patients include good history taking, physical examination and other investigations include such as EKG, Echo with Doppler. Baloon valvuloplasty is done occasionally in severely ill patients with AS if they have any contraindications for aortic valve replacement. Percutaneous replacement of aortic valve is an emerging technique, this may be an option for patients with limited life expectancy. Accurate diagnosis and efficient treatment are increasingly becoming more important as aortic valve replacement is the treatment of choice for severe aortic stenosis (26). There is evidence that once AS becomes severe, ischemia and fibrosis occur rapidly, setting up the possibility of heart failure and sudden death even after successful valve replacement (30). Therefore aortic valve replacement should be performed before extensive fibrosis occurs (30). The favorable long-term outcome following aortic valve replacement and the relatively low operative risk from previous studies emphasize the importance of an accurate and timely diagnosis. (27-29) Sharma et al in systematic review reported that in AS patients with LV (left ventricle) dysfunction show a clear functional improvement after AVR. Ventricles regress rapidly and reach their final size within first 6 months of surgery. (30) Maillet et al reported in patients with severe AS and reduced LVEF (left ventricular ejection fraction) can undergo valve replacement with low perioperative mortality and moderate postoperative morbidity. (31) Chiappinni et al in a retrospective study noted that, the outcome after AVR in octogenarians is excellent, with an acceptable operative risk and the late survival rate is good. They concluded that cardiac surgery can not be withheld on the basis of age alone. (30). Please Refer to table no 3 for the indications of aortic valve replacement.
Calcific Aortic Stenosis: Current Concepts and Management Options

Figure 5

Table 3

<table>
<thead>
<tr>
<th>Indications for Aortic Valve Replacement</th>
</tr>
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<tbody>
<tr>
<td>Class I</td>
</tr>
<tr>
<td>1. AVR is indicated for asymptomatic patients with severe AS* (Level of Evidence: B).</td>
</tr>
<tr>
<td>2. AVR is indicated for patients with severe AS* undergoing coronary artery bypass graft surgery (CABG) (Level of Evidence: C).</td>
</tr>
<tr>
<td>3. AVR is indicated for patients with severe AS* on the aorta or other heart valves (see Section 5.7 of the original guideline document). (Level of Evidence: C).</td>
</tr>
<tr>
<td>4. AVR is recommended for patients with severe AS* and LV systolic dysfunction (ejection fraction less than 0.50) (Level of Evidence: C).</td>
</tr>
</tbody>
</table>

Class IIa

AVR is reasonable for patients with moderate AS* undergoing CABG or surgery on the aorta or other heart valves (see Section 5.7 of the original guideline document). (Level of Evidence: B).

Class IIb

1. AVR may be considered for asymptomatic patients with severe AS* and abnormal response to exercise (e.g., development of symptoms or asymptomatic hyper trophy). (Level of Evidence: C).

2. AVR may be considered for adults with severe asymptomatic AS* if there is a high likelihood of rapid progression (age, calcification, and CAD) or if surgery might be delayed at the time of symptoms onset. (Level of Evidence: C).

3. AVR may be considered in patients undergoing CABG who have mild AS* when there is evidence, such as moderate to severe valve calcification, that progression may be rapid. (Level of Evidence: C).

4. AVR may be considered for asymptomatic patients with extremely severe AS (aortic valve area less than 0.5 cm², mean gradient greater than 50 mm Hg, and jet velocity greater than 5 m/s) per second when the patient’s expected operative morbidity is 15% or less. (Level of Evidence: C).

Class III

AVR is not useful for the prevention of sudden death in asymptomatic patients with AS who have none of the findings listed under the class Ia/IIa recommendations. (Level of Evidence: B).

Figure 6

Indications for Aortic Balloon Valvotomy

<table>
<thead>
<tr>
<th>Indications for Aortic Balloon Valvotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class Ia</td>
</tr>
<tr>
<td>1. Aortic balloon valvotomy might be reasonable as a bridge to surgery in hemodynamically unstable adult patients with AS who are at high risk for AVR. (Level of Evidence: C).</td>
</tr>
</tbody>
</table>

2. Aortic balloon valvotomy might be reasonable for palliation in adult patients with AS who cannot be performed because of severe concomitant conditions (Level of Evidence: C).

Class III

Aortic balloon valvotomy is not recommended as an alternative to AVR in adult patients with AS; children younger children without valve calcification may be an exception (see Section 5.1.3 of the original guideline document). (Level of Evidence: B).

Figure 7

Figure 3: Severe Aortic Stenosis Management Strategy.

References


Author Information

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