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EDITORIAL

Aortic stenosis: An update

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Abstract

Aortic stenosis (AS) is the most common valvular heart disease in the world. It is a disease of the elderly and as our population is getting older in both the developed and the developing world, there has been an increase in the prevalence of AS. It is impacting the mortality and morbidity of our elderly population. It is also causing a huge burden on the healthcare system. There has been tremendous progress in our understanding of AS in recent years. Lately, studies have shown that AS is not just a disease of the aortic valve but it affects the entire systemic vasculature. There are studies looking at more sophisticated measures of disease severity that might better predict the optimal timing of valve replacement. The improvement in our understanding in etiology and pathophysiology of the disease process has led to a number of trials with possible treatment options for AS. In this review, we talk about our understanding of the disease and latest developments in disease assessment and management. We look forward to a time when there will be medical treatment for AS.

INTRODUCTION

Aortic stenosis (AS) is the most common valvular heart disease and the third most common cardiovascular disease after hypertension and coronary artery disease in the western world[1]. The prevalence of AS increases from 2% in adults over 65 years to 4% in adults over 85 years of age[2]. AS is a progressive condition and after the onset of heart failure, survival is < 2 years without valve replacement[3]. 50% of patients with AS presenting with angina, syncope or heart failure survive for 5, 3 or 2 years respectively without aortic valve replacement (AVR). As life spans increase, the burden of senile AS on the health care system is expected to increase. Close monitoring and use of AVR when the disease becomes significant remains the standard of care[4,5]. AS is the most common reason for AVR in the developed world. Though the disease has been known for decades, little has been known about the pathophysiology, and a lot of work is going into the understanding of possible etio-pathogenesis. New innovative techniques and management have been studied to stop or reduce the progression of AS. To date though, no medical therapy has been proven to alter the natural history of patients with AS. In this review, we talk about our understanding of the disease and latest developments in its management.

ETIOLOGY OF CALCIFIC AS

AS was always thought to be due to a passive, degenerative process leading to accumulation of calcium and causing narrowing of the valve. The pathogenesis of AS, however, is still not well understood. The risk factors for calcific aortic valve disease are similar to the risk factors for atherosclerosis, which includes male sex, hypertension, elevated levels of low density lipoprotein (LDL) cholesterol, and smoking[2,6-8]. The incidence of AS is higher in patients with chronic kidney disease and patients who have had radiotherapy in the past. It has been shown from the valve specimens taken during surgery for AS that there are increased levels of inflammation, which might lead to calcification[9-12]. There are also increased levels of LDL, which might lead to inflammation and calcification[13,14].

Recent studies have shown specific bone-cell phenotypes are present in calcifying human valves[15,16]. Specific markers of bone formation have been identified in calcified aortic valves; it includes the bone matrix proteins osteopontin, osteocalcin and bone sialoprotein[17-22], and the osteoblast transcription factor Runx2[18,23,24]. Genetic studies are also evolving, which point towards genetic factors that predispose individuals to developing calcific AS.

DIAGNOSIS

Patients may present with symptoms of exertional chest pain, breathlessness or syncope but the majority of patients are asymptomatic. AS is suspected when an ejection systolic murmur (ESM) is heard in the precordium in symptomatic or asymptomatic patients. Diagnosis of AS is by detailed history and physical examination, echocardiography and confirmation with cardiac catheterization.

Clinical evaluation

History and physical examination is very important in patients with AS. It helps not only for the diagnosis but also to assess severity. Patients with AS usually have ESM in the precordium. Patients with exertional symptoms have hemodynamically significant valvular stenosis and hence need treatment. The severity of AS in asymptomatic patients can be assessed by other clinical findings - poorly palpable pulse, late peaking of ESM and reversal of S2 split.

Echocardiography

Echocardiography is the most commonly used noninvasive test of choice for patients with suspected AS. The severity of AS is determined by echocardiography by the mean and peak aortic valve gradients (AVG), aortic valve area (AVA) and aortic valve velocity. Echocardiography does not measure the pressures directly and the AVA is also a derived value[25]. The AVG is also dependent on stroke volume and systolic ejection time. Hence the hemodynamic measurements and calculations change rapidly. There is a possibility of underestimation of AVA if the ejection fraction is reduced. AS is a systemic vascular disease affecting not only the valve but also the systemic vasculature. More sophisticated measures of disease severity are needed to explain the overlap in hemodynamic severity between symptomatic and asymptomatic patients. In this way we might be able to better predict the optimal timing of AVR. New mathematical models are being studied to look at ventricular-vascular coupling in the accurate assessment of severity of AS[26]. The other role of echocardiography is the use of stress echocardiography in moderate stenosis to see if the patient might benefit from AVR.

Cardiac catheterization

Cardiac catheterization is essential in almost all patients with AS. It is useful in confirming the severity of disease and it is also useful if there is discordance between clinical examination and Doppler measurements. Cardiac catheterization allows for actual measurement of the AVG and cardiac output, and calculation of the AVA. We can also measure the atrial and ventricular volumes, cardiac output and right heart pressures. Cardiac catheterization with selective coronary arteriography is necessary to diagnose the presence, location and severity of associated coronary artery disease.

Multidetector computed tomographic and cine magnetic resonance

Multidetector computed tomography (CT) has become far more than a simple anatomic technique dedicated to coronary imaging. Cine magnetic resonance (MR) use in the diagnosis of cardiac diseases has been expanding. Both multidetector CT and cine MR have been used in the assessment of contractile function and for characterization of myocardial infarction. They may also provide important information pertaining to valve morphology, accurately measuring the AVA and in the assessment of severity of stenosis[27].

MANAGEMENT

The AVA normally ranges from 3.0 to 4.0 cm^2 in adults and a transvalvular gradient usually develops when the orifice area is < 50% of normal. In patients with normal left ventricular systolic function, severe AS is defined as a peak AS velocity > 4 m/s, a mean transaortic pressure gradient > 40 mmHg, or an AVA < 1 cm^2. A valve area index < 0.6 cm^2/m^2 is also indicative of severe AS[4,5]. The management of severe AS has historically been surgery, but other treatment options have been looked at.

Hydroxymethylglutaryl-coenzyme A reductase inhibitors

Lipids are known to be the key in the development of fibrosis and then calcification of aortic valves leading to stenosis. Hence lipid lowering agents, hydroxymethylglutaryl-coenzyme A reductase inhibitors, or statins, may be a potential agent for halting the progression of AS. Studies have shown variable results.

The Rosuvastatin Affecting Aortic Valve Endothelium study was a prospective study looking at 121 patients with asymptomatic moderate to severe AS with AVA of 1.0 to 1.5 cm^2 and followed them by echocardiogram. Patients with a LDL cholesterol > 3.4 mmol/L were treated with rosuvastatin while those with an LDL < 3.4 mmol/L received no lipid lowering therapy. Over a mean follow-up of 73 wk there was reduced progression of AS in the rosuvastatin group compared to the control group (increase in AS velocity of 0.04 m/s per year in the rosuvastatin group *vs* 0.24 m/s per year in the control group, $P = 0.007$; decrease in AVA of 0.05 cm^2 per year in the rosuvastatin group *vs* 0.10 cm^2 per year in the control group, $P = 0.041$). This study showed promise for statins in reducing progression of AS[28].

The Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression study was a randomized trial on 155 patients who received either atorvastatin 80 mg daily or placebo. Patients with increased peak AS velocity and aortic valve calcification on echocardiography were enrolled. The average peak AS velocity was 3.43 m/s, the average AVA was 1.03 cm^2, and aortic valve calcium score was 5920 log arbitrary units. Thirty-six patients had severe AS based on a peak AS velocity. Patients were followed for a median of 25 mo. Despite a significant change in the mean LDL cholesterol between the two groups following treatment ($P < 0.001$), there was no difference in measures of AS progression between the two groups (increase in peak aortic jet velocity of 0.20 m/s in both groups, $P = 0.95$; increase in valvular calcification 22.3% per year in the atorvastatin group *vs* 21.7% per year in the placebo group, $P = 0.93$)[29].

Simvastatin and Ezetimibe in Aortic Stenosis was a randomized, double-blind trial involving 1873 patients with mild-to-moderate asymptomatic AS. The patients received either 40 mg of simvastatin plus 10 mg of ezetimibe or placebo daily. The primary outcome was a composite of major cardiovascular events, including death from cardiovascular causes, AVR, nonfatal myocardial infarction, and hospitalization for unstable angina pectoris, heart failure, coronary artery bypass grafting, percutaneous coronary intervention, and nonhemorrhagic stroke. During a median follow-up of 52.2 mo, the primary outcome occurred in 333 patients (35.3%) in the simvastatin-ezetimibe group and in 355 patients (38.2%) in the placebo group [hazard ratio in the simvastatin-ezetimibe group, 0.96; 95% confidence interval (CI): 0.83-1.12, $P = 0.59$]. AVR was performed in 267 patients (28.3%) in the simvastatin-ezetimibe group and in 278 patients (29.9%) in the placebo group (hazard ratio, 1.00; 95% CI: 0.84-1.18, $P = 0.97$)[30]. This study showed that cholesterol lowering medications, simvastatin and ezetimibe did not reduce the composite outcome of combined aortic valve events. This therapy reduced the incidence of ischemic cardiovascular events but not events related to aortic valve stenosis.

The Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin trial is a randomized, double-blind, placebo-controlled trial in asymptomatic patients with mild to moderate AS and no clinical indications for cholesterol lowering. The patients were randomized to receive either placebo or rosuvastatin. A total of 269 patients were randomized: 134 patients to rosuvastatin 40 mg daily and 135 patients to placebo. The median follow-up was 3.5 years. The annualized increase in the peak AS gradient was 6.3 mmHg in the rosuvastatin group and 6.1 mmHg in the placebo group ($P = 0.83$)[31]. Hence this was again a negative study for use of statins in AS.

The effect of statins on the progression of AS is still not clear. The latest trials do not show any benefit in established AS. We may have to look at high risk patients like possible gene linkage or patients with end-stage renal disease and trying to prevent AS. We might also have to look at patients with mild disease and see if it reduces the disease progression. Further studies are required to answer our questions.

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) and angiotensin Ⅱ receptors have been found in stenotic aortic valves. This leads to the hypothesis that the renin-angiotensin system may play a role in disease progression. This led to trials with ACE inhibitors (ACEi) looking for their effect in AS. Two hundred and eleven patients with asymptomatic AS and a peak AS velocity of > 2.5 m/s (average peak AS velocity 3.96 m/s; mean AVA 0.84 cm^2) were retrospectively identified and the rates of hemodynamic progression of AS were compared between patients who were taking an ACEi *vs* those who were not[32]. No difference was found (increase in peak AS velocity of 0.29 m/s per year *vs* 0.35 m/s per year, respectively, $P = 0.29$). To date, there is no randomized trial looking at the effect of ACEi in AS.

Bisphosphonates

Rajamannan *et al*[15] showed that the mechanism for aortic valve calcification is similar to that for skeletal bone formation and that this process is mediated by an osteoblast-like phenotype. Innasimuthu *et al*[33,34] did a retrospective study on patients > 70 years, who had transthoracic echocardiograms (TTE) > 1 year apart and an initial AVA of 0.6-2.0 cm^2. Patients were excluded if they had an ejection fraction < 40%, other significant valvular or congenital heart disease, end-stage renal disease or heart transplant. The cohort was divided depending on the use of bisphosphonates. AVA, peak and mean aortic valve gradient, and the change between the studies were calculated. Seventy six patients fit study criteria with 8 in the bisphosphonate group and 68 in the non-bisphosphonate group. The period between the TTEs was 23 ± 5 mo in both the groups. AVA in the non-bisphosphonate group worsened by 0.2 cm^2 and in the bisphosphonate group it improved by 0.1 cm^2 ($P = 0.001$)[33,34].

Skolnick *et al*[35] did an observational study of patients with AS from the echocardiographic database comparing

18 patients on treatment for osteoporosis (bisphosphonates, calcitonin, or estrogen receptor modulators) with 37 patients not on the treatment. AVA was calculated using the continuity equation. Mean baseline AVA was 1.33 cm^2 and not significantly different between groups. After a mean of 2.4 years, mean annual changes in AVA were reduction by 0.22 cm^2 in those not on treatment for osteoporosis and 0.10 cm^2 in patients receiving osteoporosis treatment ($P = 0.025$). In a multivariable analysis including age, gender, and statin use, only the treatment group was associated with a change in AVA[35]. There has recently been increased interest in bisphosphonates as a medication in reducing the disease progression. These two studies are retrospective and used observational data and hence randomized trials are required to assess its effect on AS.

Transcatheter aortic valve implantation

In 2002, the first patient underwent transcatheter aortic valve implantation (AVI) for the treatment of severe symptomatic AS. There have been studies looking at the feasibility of percutaneous transvenous, transarterial, and transapical placement of the aortic valve. There were several single-center trials, which demonstrated that this new approach was a reasonable treatment option for patients who were inoperable or at a very high risk for surgery. The results of recent multicenter trials have shown that the procedure is safe and effective. These were associated with success rates of > 90% and 30-d procedural mortality rates of < 10% even though the trials involved very high-risk patients[36,37]. The prospective randomized PARTNER study, whose results will be available towards the end of 2010, will make a significant contribution to clearly establishing the safety and efficacy of percutaneous placement of the aortic valve in patients who are inoperable or at a high surgical risk.

Surgery

AVR is the definitive therapy for severe AS. Over time, the operative risk has dramatically decreased; currently operative mortality of isolated AVR is 2%-5% in patients over 70 years and 5%-15% in older adults. After valve replacement, symptoms diminish, quality of life improves, and long-term survival is similar to that expected for an age-matched population[38,39]. Patient-prosthesis mismatch could result in significant mortality and morbidity in patients after AVR. Hence careful selection of prostheses is important for the longevity of the replaced valve[40,41].

CONCLUSION

AS is a very common valvular heart disease and it can lead to significant mortality and morbidity in the elderly population. Severity of the disease is estimated by symptoms, clinical evaluation, echocardiography and cardiac catheterization. We need more studies looking at new techniques to assess the severity of AS more accurately and to predict the optimal timing of surgery. The only known effective treatment with documented benefits is AVR. There are a number of studies looking at the possible benefit of medications in reducing the progression of AS and transcatheter AVI in inoperable patients. We need more randomized controlled trials looking at the effective use of medications and minimally invasive procedures.

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