CALCIFIC AORTIC STENOSIS: FROM BENCH TO THE BEDSIDE—EMERGING CLINICAL AND CELLULAR CONCEPTS

801

Nalini M Rajamannan, Bernard Gersh, Robert O Bonow

Heart 2003;89:801–805

Calcific aortic stenosis is the third most common cause of aortic valve disease in developed countries. This condition increases in prevalence with advancing age, afflicting 2–3% of the population by the age of 65 years.¹ The aging US population has led to a burgeoning number of valve replacements per year, which in turn costs the USA approximately \$1 billion. The natural history, as described by Ross and Braunwald, shows that severe symptomatic aortic stenosis is associated with a life expectancy less than five years.² Despite the high prevalence of this condition and the increasing morbidity and mortality, very little is known regarding the cellular basis of calcific aortic stenosis.

Pathologically, progressive aortic stenosis may produce left ventricular hypertrophy, left ventricular diastolic and systolic dysfunction, congestive heart failure, angina, arrhythmias, and syncope. Recent studies demonstrate an association between atherosclerosis and its risk factors and aortic valve disease. Although a unifying hypothesis for the role of atherosclerotic risk factors in the mechanism of vascular and aortic valve disease is emerging, progress in studying the cell biology of this disease has been limited by the paucity of experimental models available. A crucial question to ask is whether the same risk factors for vascular disease that initiate an atherosclerotic type injury in the coronary arteries initiate a similar injury in the aortic valve. If this is the case, it raises the possibility that the treatments used in slowing the progression of vascular atherosclerosis may be effective in patients with aortic sclerosis. Current management of calcific aortic valve disease focuses on defining patients with valvar disease and the development of symptoms to determine the timing of surgical valve replacement. This article will review the pathogenesis, natural history, evaluation, and management of patients with calcific aortic stenosis, taking into account emerging studies important in the understanding of the cellular mechanisms of calcific aortic stenosis. It will also address diagnostic studies for the detection and diagnosis of aortic valve calcium and summarise the current standard of treatment for calcific aortic stenosis and the potential for cholesterol lowering treatment to prevent progression or aortic valve calcification.

AETIOLOGY AND PATHOGENESIS

In 1854 William Stokes described in his textbook, *The diseases of the heart and the aorta*, specific pathological descriptions of calcific aortic valve disease, including: (1) permanent patency of the valve in which the diameter may be increased or diminished; (2) an extreme ossific growth along the valve surrounding the ventricle, at which the valves are often destroyed; and (3) an atheromatous deposit on the ventricular surface of the valve which is often seen in the context of fatty degeneration of the heart.³ In 2003, the aetiologies of calcific aortic stenosis (table 1) include bicuspid aortic valves, degeneration, familial hypercholesterolemia, hyperuricaemia, hyperparathyroidism, Paget's disease, ochronosis, Fabry's disease, systemic lupus erythematosus, and drug induced valvar disease. Currently, there are many proposed theories for the cellular causation of this disease: (1) mechanical shear stress leading to calcific injury as in bicuspid aortic valves; (2) autoimmune phenomena causing degeneration; and (3) cardiovascular risk factors initiating a "response to injury" similar to that seen in atherosclerosis. Other modifying factors that are associated with an increased prevalence of aortic stenosis include conditions with a chronically raised stroke volume and altered calcium metabolism (for example, Paget's disease, renal failure associated with arteriovenous fistula). Figure 1 shows an aortic valve removed at the time of surgical valve replacement, demonstrating valve leaflet nodule formation and thickening. These gross pathologic findings are responsible for the classic symptoms of chest pain, dyspnoea, and syncope in patients who have symptomatic severe aortic stenosis.

NATURAL HISTORY

Asymptomatic patients

Patients with severe calcific aortic stenosis develop left ventricular obstruction that occurs gradually over several years. Over time the left ventricle compensates for the persistent gradient between the left ventricle and the aorta, resulting in left ventricular hypertrophy and an increase in left

See end of article for authors' affiliations

Correspondence to:
Nalini M Rajamannan, MD,
303E Chicago Ave, Tarry
12-703, Chicago, IL 60611,
USA;
n-rajamannan@northwestern.edu

Table 1 Aetiologies of calcific aortic stenosis, including primary valve disease and also diseases that cause secondary valve disease

► Congenital	► HLA B27 valvulitis
► Degenerative	► Alkaptonuria
► Rheumatic	► Gaucher
► Endocarditis	► Hyperparathyroidism
► Hyperuricaemia	► Calciphylaxis
► Inflammatory: secondary to chronic infection	► Fabry's disease
► Homozygous type II	► Drug induced
► Hypercholesterolaemia	► Incontinentii pigmentii
► Pseudoxanthoma elasticum	► Paget's disease
	► Cardiac valve tumours
	► Carcinoid heart diseases

Figure 1 Calcified human aortic valve removed at the time of valve replacement. The arrow points to the bone-like nodules on the aortic surface of the valve. The leaflets also demonstrate increase in thickening.

ventricular mass. Eventually as the aortic stenosis becomes more severe the left ventricle begins to fail. When the preload reserve is diminished and no further compensatory mechanisms are unavailable then heart failure ensues, leading to death within approximately one year.

Predictors of progression of aortic valve disease

There are a number of studies demonstrating the haemodynamic progression of this valvar lesion. Defining the rate of progression of aortic stenosis before to the onset of symptoms

provides the optimal window for intervention for these patients. Doppler echocardiography has provided an accurate, non-invasive measurement of the stenosis severity, which has replaced invasive cardiac catheterisation in the majority of cases.⁴ The incidence of the development of symptoms in asymptomatic patients is as high as 38% in patients with Doppler outflow velocities > 4 m/s after two years and 79% after three years.⁵ Therefore patients with severe aortic stenosis should be monitored closely for the development of symptoms and progression of disease.

MANAGEMENT

Currently, no medical treatment is required for the asymptomatic patient with valvar aortic stenosis. Management of patients with symptomatic aortic stenosis would include selected laboratory examinations, including an ECG, chest radiograph, and an echocardiogram. The echocardiogram will confirm the presence of aortic valve disease and delineate left ventricular (LV) size and function. The American College of Cardiology and American Heart Association (ACC/AHA) guidelines have defined severe aortic stenosis as an aortic valve area of < 1.0 cm² and a mean gradient of > 50 mm Hg.⁶ The decision to replace the valve is dependent on the presence or absence of symptoms with unequivocal evidence of severe stenosis, but this is a complex issue and needs to be individualised, particularly in younger active patients. Recommendations for the use of echocardiography, cardiac catheterisation, and indication for aortic valve replacement in aortic stenosis have been described in the ACC/AHA guidelines (table 2).⁶

EMERGING CLINICAL AND EXPERIMENTAL DATA FOR THE ATHEROSCLEROTIC HYPOTHESIS

Clinical risk factors for the atherosclerosis hypothesis

Emerging epidemiological studies are revealing convincing clinical evidence towards an atherosclerotic hypothesis for the cellular mechanism of this valvar lesion. There is an increasing amount of information demonstrating the association between clinical risk factors for atherosclerosis and the development of aortic stenosis (see box). Homozygous familial hypercholesterolemia (FH) produces a particularly severe form of aortic stenosis often with supra-aortic narrowing in children.⁷ In this specific condition extremely high low density lipoprotein cholesterol (LDL-c) concentrations are seen without the other traditional risk factors for coronary artery disease. Stewart and others from the cardiovascular health study identified several risk factors for calcific aortic valve disease:

Table 2 Management of severe asymptomatic aortic stenosis (AS): current ACC/AHA guidelines

Indication	Class
1. Symptomatic patients with severe AS	I
2. Patients with severe AS before undergoing coronary artery bypass surgery	I
3. Patients with severe AS undergoing surgery on the aorta or other heart valves	I
4. Patients with moderate AS undergoing coronary artery bypass surgery or surgery on the aorta or other heart valves	IIa
5. Asymptomatic patients with severe AS and:	
► left ventricular (LV) systolic dysfunction	IIa
► abnormal response to exercise (for example, hypotension)	IIa
► ventricular tachycardia	IIb
► pronounced or excessive LV hypertrophy (≥ 15 mm)	IIb
► valve area <0.6 cm ²	IIb
6. Prevention of sudden death in asymptomatic patients with none of the findings listed under indication 5	III

Risk factors for calcific aortic valve disease

- ▶ Raised lipoprotein(a)
- ▶ Raised low density lipoprotein cholesterol
- ▶ Cigarette smoking
- ▶ Hypertension
- ▶ Male sex
- ▶ Diabetes mellitus
- ▶ Raised serum calcium
- ▶ Raised serum creatinine

male sex, hypertension, raised LDL-c, and smoking.⁸ Furthermore, Palta and colleagues correlated the progression of aortic valve disease with smoking, raised serum creatinine, cholesterol, and calcium concentrations.⁹ These studies demonstrate that many of the same risk factors initiating vascular atherosclerosis are also implicated in aortic valve disease. Recently, Otto and colleagues reported that aortic sclerosis, which is described as focal areas of increased echogenicity and thickening of aortic valve leaflets without restricted leaflets, is found in 29% of subjects in the cardiovascular health study. In a five year follow up, aortic sclerosis was associated with an increase of approximately 50% in the risk of death from cardiovascular causes and the risk of myocardial infarction, even in the absence of haemodynamically significant obstruction to left ventricular outflow.¹⁰ These findings provide further evidence that the early lesion of aortic valve sclerosis may be associated with coronary artery disease and vascular atherosclerosis. Galante and co-workers have also demonstrated an increase in C reactive protein concentrations in patients with aortic valve stenosis.¹¹ Finally, the extent of aortic valve calcification has been noted as an important predictor of poor outcome in patients with aortic stenosis.¹² Together, these clinical studies suggest that aortic valve calcification is an inflammatory process promoted by atherosclerotic risk factors.

Histologic evidence for atherosclerosis

Many surgical pathological studies of human aortic valves demonstrate the presence of LDL and atherosclerosis in calcified valves, suggesting that there may be a common cellular basis for the genesis of valvar and vascular disease. O'Brien and colleagues have characterised early degenerative valve lesions in human valves and demonstrated an associated inflammatory infiltrate composed of non-foam cell and foam cell macrophages, occasional T cells, and rare α actin positive cells.¹³ A prominent feature of degenerative valvar aortic stenosis is the accumulation of lipid, particularly in the fibrosa, the anatomic layer of the valve located immediately below the endothelium on the aortic side of the valve.¹³ Co-localisation of neutral lipid with immunohistochemical staining for LDL and other proteins implicated in atherogenesis such as lipoprotein(a), and apoE containing lipoproteins might be present in aortic valvar lesions.¹⁴ These histologic studies support the hypothesis that degenerative valvar aortic stenosis is the result of an active inflammatory disease process with some similarities to atherosclerosis. These similar findings are also found in more advanced lesions but in this setting smaller amounts of α actin smooth muscles cells and more advanced calcification is present. Emerging experimental models in vitro and in vivo have demonstrated that atherosclerosis and bone-like features are also present in experimental valve calcification.¹⁵⁻¹⁶ Figure 2 compares a normal aortic valve with an experimental hypercholesterolaemic aortic valve

Figure 2 Normal versus hypercholesterolaemic aortic valve. The valve leaflet of the normal aortic valve (panel A1) has a clear glistening appearance, which is attached to the aorta. The hypercholesterolaemic aortic valve (panel A2) shows atherosclerotic lipid deposition on the valve leaflet as well as the vascular aorta.

Figure 3 Possible mechanism for the development of aortic valve calcification. The cell within the valve develops osteoblast-like features which synthesise important bone matrix proteins involved in the calcification process in the valve.

in an animal model of hypercholesterolaemic diet.¹⁶ The normal aortic valve shows the presence of a normal clear glistening valve leaflet attached to the vascular aorta. The hypercholesterolaemic aortic valve shows atherosclerotic lipid deposition on the valve leaflet as well as the aorta. The combination of clinical findings and experimental observations support the hypothesis that degenerative valvar aortic stenosis is the result of an active inflammatory cellular process similar to atherosclerosis.

Mechanisms of calcification

Although calcification and ossification in aortic valves has been described in the literature for over 100 years, little is known about the synthesis of bone matrix proteins in calcific aortic valve stenosis. Until recently, only descriptive histologic and protein expression studies delineating the development of calcification in the aortic valve existed. Demer and colleagues have defined cardiovascular calcification as being composed of hydroxyapatite deposited on a bone-like matrix of collagen, osteopontin, and other minor bone matrix proteins.¹⁷ Osteopontin expression has been demonstrated in the mineralisation zones of heavily calcified aortic valves obtained at

Table 3 Retrospective studies of statin treatment in calcific aortic valve stenosis

Author	Year	Number of patients	Radiological assessment	Degree of regression
Aronow <i>et al</i> ²³	2001	180	Echo	Statin treatment Change in peak systolic gradient across the aortic valve (−0.370 mm Hg/year)
Novaro <i>et al</i> ²¹	2001	174	Echo	Aortic valve area Non-statin 0.11 (0.18) cm ² /year Statin 0.06 (0.16) cm ² /year
Shavelle <i>et al</i> ²²	2002	65	EBCT	Aortic valve calcium accumulation Non-statin 32.0%/year Statin 10.6%/year
Bellamy <i>et al</i> ²⁴	2001	156	Echo	Aortic valve area Non-statin −3 (10)%/year Statin −7 (13)%/year

EBCT, electron beam computed tomography.

necropsy and surgery.¹⁸ However, the mechanism by which this calcification occurs is not well understood. Histopathologic evidence suggests that the early lesions in aortic valves are not just a disease process secondary to aging, but an active cellular process that follows the classical “response to injury” similar to atherosclerosis.¹⁶ Comparable studies have been performed in aortic valve tissue to determine if these processes are similar. The growing body of literature suggests that hypercholesterolaemia may play a role in aortic valve calcification. Dr Rajamannan’s laboratory has studied the hypothesis that experimental hypercholesterolaemia may play a key role in the initiation and development of bone formation in valvar tissue.¹⁶ Figure 3 shows a potential mechanism for the development of aortic valve calcification. This experimental finding further substantiates the hypothesis that raised cholesterol contributes to the early injury in cardiac valves.

Emerging diagnostic studies for the detection and diagnosis of aortic valve calcium

Currently the “non-invasive gold standard” for diagnosis of aortic valve stenosis is two dimensional Doppler echocardiography.⁵ It is the test of choice to quantify the severity of valve stenosis and pressure differential across the aortic valve. However, there is growing evidence that electron beam computed tomography (EBCT) may be the most accurate non-invasive means of measuring calcification, in the coronary arteries.¹⁹ Several studies have demonstrated the utility of calculating the volume of calcium and the rate of progression of the disease process in the aortic valve.²⁰ These are still preliminary studies which require validation in larger numbers of patients. The utilisation of EBCT may prove more sensitive in the accuracy of measuring the volume of calcification in the valve.

FUTURE MEDICAL TREATMENTS

The natural history studies of valvar aortic stenosis, as defined by clinical and histopathologic parameters, have provided landmark developments towards the understanding of this disease. Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) may allow innovative therapeutic approaches employing both lipid lowering and possibly non-lipid lowering effects to forestall critical stenosis in the aortic valve. These agents have potent LDL lowering effects via inhibition of the rate limiting step in cholesterol synthesis. The evidence to date suggested that three putative non-lipid lowering mechanisms may contribute to the beneficial effects of

HMG-CoA reductase inhibitors in coronary artery disease. These include modification of (1) endothelial function, (2) inflammatory responses, and (3) thrombus formation. Valve replacement is, and will remain, the treatment of choice for severe critical aortic stenosis. Future insights into the mechanisms of calcification and its progression may indicate a role for lipid lowering treatment in halting or modifying the rate of progression of stenosis, and the potential for such an approach is intriguing. Circumstantial, preliminary evidence suggests that aggressive treatment with lipid lowering agents may have a positive impact on the progression of valvar calcification. Novaro and colleagues have published a retrospective study showing less progression of aortic stenosis in patients on statin treatment as assessed by a decrease in the peak and mean gradient of the treated patients.²¹ Shavelle and colleagues also evaluated the effects of statin treatment on the amount of calcium present as measured by EBCT; retrospective analysis showed that statin treatment was associated with a 62–63% lower rate of aortic valve calcium accumulation as assessed by percentage change per year in the scoring system developed for the assessment of the amount of calcium present in the cardiovascular system.²² Table 3 summarises the retrospective data for the use of statins in the treatment of calcific aortic valve stenosis.^{23–24} These retrospective studies, combined with the experimental data, suggest that statin treatment may have a role in the inhibition of bone matrix production and end stage calcification, as proven in the regression of coronary artery calcification.

SUMMARY

This new evidence agrees with the original descriptions of Dr Stokes in that there is an atherosclerotic ossified lesion contributing to the pathogenesis of this disease.³ Recent epidemiological clinical studies have revealed that the risk factors for arterial atherosclerosis—male sex, smoking, and raised serum cholesterol—are similar to the risk factors associated with development of aortic valve stenosis.⁸ Experimental studies *in vitro* and *in vivo* support the hypothesis that the development of aortic valve calcification is similar to that of vascular calcification.^{15–16} Preliminary data are also emerging towards the potential possibility of primary and/or secondary prevention of aortic stenosis. Moreover, future clinical studies using statins in the treatment of aortic valve disease are also necessary to determine their potential for slowing this disease process in patients.

.....

Authors' affiliations

N M Rajamannan, R O Bonow, Division of Cardiology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA
B Gersh, Department of Cardiology, Mayo Clinic, Rochester, Minnesota, USA

REFERENCES

- 1 **Lindroos M**, Kupari M, Heikkilä J, *et al*. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. *J Am Coll Cardiol*. 1993;**21**:1220–5.
- 2 **Ross J**, Braunwald E. Aortic stenosis. *Circulation* 1968;**38**(1 suppl):61–7.
- ▶ **The first study indicating the natural progression of patients with severe aortic stenosis.**
- 3 **Stokes W**. *The diseases of the heart and aorta*. Dublin: Hodges & Smith, 1845:211–12.
- 4 **Otto CM**, Pearlman AS, Gardner CL. Hemodynamic progression of aortic stenosis in adults assessed by Doppler echocardiography. *J Am Coll Cardiol* 1989;**13**:545–50.
- ▶ **Important echo study defining the echo parameters important in the development of severe aortic stenosis.**
- 5 **Oh JK**, Taliercio CP, Holmes DR Jr, *et al*. Prediction of the severity of aortic stenosis by Doppler aortic valve area determination: prospective Doppler-catheterization correlation in 100 patients. *J Am Coll Cardiol* 1988;**11**:1277–24.
- 6 **Bonow RO**, Carabello B, de Leon AC Jr, *et al*. Guidelines for the management of patients with valvular heart disease. *Circulation* 1998;**98**:1949–84.
- ▶ **Current ACC/AHA guidelines for cardiac evaluation for patients with valvar heart disease. Contains a very thorough review of the entire English language literature.**
- 7 **Sprecher DL**, Schaefer EJ, Kent KM, *et al*. Cardiovascular features of homozygous familial hypercholesterolemia: analysis of 16 patients. *Am J Cardiol* 1984;**54**:20–30.
- 8 **Stewart BF**, Siscovick D, Lind BK, *et al*. Clinical factors associated with calcific aortic valve disease: cardiovascular health study. *J Am Coll Cardiol* 1997;**29**:630–4.
- 9 **Palta S**, Pai AM, Gill KS, *et al*. New insights into the progression of aortic stenosis: implications for secondary prevention. *Circulation* 2000;**101**:2497–502.
- 10 **Otto CM**, Lind BK, Kitzman DW, *et al*. Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. *N Engl J Med* 1999;**341**:142–7.
- 11 **Galante A**, Pietroiusti A, Vellini M, *et al*. C-Reactive protein is increased in patients with degenerative aortic valvular stenosis. *J Am Coll Cardiol* 2001;**34**:1078–81.
- 12 **Rosenhek R**, Binder T, Porenta G, *et al*. Predictors of outcome in severe asymptomatic aortic stenosis. *N Engl J Med* 2000;**343**:611–7.
- 13 **O'Brien KD**, Reichenbach DD, Marcovina SM, *et al*. Apolipoproteins B, (a), and E accumulate in the morphologically early lesion of 'degenerative' valvular aortic stenosis. *Arterioscler Thromb* 1996;**16**:523–32.
- 14 **Olsson M**, Thyberg J, Nilsson J. Presence of oxidized low density lipoprotein in nonrheumatic stenotic aortic valves. *Arterioscler Thromb Vasc Biol* 1999;**19**:1218–22.
- 15 **Mohler ER III**, Chawla MK, Chang AW, *et al*. Identification and characterization of calcifying valve cells from human and canine aortic valves. *Heart Valve Dis* 1999;**8**:254–60.
- 16 **Rajamannan NM**, Subramaniam M, Springett M, *et al*. Atorvastatin inhibits hypercholesterolemia-induced cellular proliferation and bone matrix production in the rabbit aortic valve. *Circulation* 2002;**105**:2660–5.
- ▶ **First in vivo model of valve atherosclerosis demonstrating the effects of cholesterol and statins in the aortic valve.**
- 17 **Bostrom K**, Watson KE, Stanford WP, Demer LL. Atherosclerotic calcification: relation to developmental osteogenesis. *Am J Cardiol* 1995;**75**:88B–91B.
- 18 **O'Brien KD**, Kuusisto J, Reichenbach DD, *et al*. Osteopontin is expressed in human aortic valvular lesions. *Circulation* 1995;**92**:2163–8.
- 19 **Sutton-Tyrell K**, Kuller LH, Edmundowicz D, *et al*. Usefulness of electron beam tomography to detect progression of coronary and aortic calcium in middle-aged women. *Am J Cardiol* 2001;**87**:560–5.
- 20 **Kizer JR**, Geffter WB, deLemos AS. Electron beam computerized tomography for the quantification of aortic valvular calcification. *J Heart Valve Dis* 2001;**10**:361–6.
- 21 **Novaro GM**, Tiong TY, Pearce GL, *et al*. Effect of hydroxymethylglutaryl coenzyme A reductase inhibitors on the progression of calcific aortic stenosis. *Circulation* 2001;**104**:2205–9.
- 22 **Shavelle DM**, Takasu J, Budoff MJ, *et al*. HMG CoA reductase inhibitor (statin) and aortic valve calcium. *Lancet* 2002;**359**:1125–6.
- 23 **Aronow WS**, Ahn C, Kronzon I, *et al*. Association of coronary risk factors and use of statins with progression of mild valvular aortic stenosis in older persons. *Am J Cardiol* 2001;**88**:693–5.
- ▶ **First study to evaluate retrospectively the progression of aortic stenosis in patients who are taking statin agents.**
- 24 **Bellamy MF**, Pellikka PA, Klarich KW, *et al*. Association of cholesterol levels, hydroxymethylglutaryl coenzyme-A reductase treatment, and progression of aortic stenosis in the community. *J Am Coll Cardiol* 2002;**40**:1723–30.