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C3 – Core Curriculum in Cardiology

Calcific aortic valve disease: Is it another face of atherosclerosis?

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ABSTRACT

Calcific aortic valve disease (CAVD) is the most common valvular heart disease in the elderly. As life expectancy increases, prevalence of CAVD is expected to rise. CAVD is characterized by progressive dystrophic calcification of aortic cusps. In the initial stages, the pathogenesis is similar to atherosclerosis, characterized by basement membrane disruption, inflammation, cell infiltration, lipid deposition, and calcification. Presence of osteopontin in calcified aortic valves suggests pathological calcification and bone formation in these calcified valves. Historical, experimental, genetic, and clinical evidences suggest that CAVD and atherosclerosis share the same pathological sequences with common risk factors. Understanding the two faces of atherosclerosis, the vascular and valvular, will help us to prevent progression of aortic sclerosis to aortic stenosis, by controlling modifiable risk factors and by initiating statin therapy in them. However, the knowledge about these preventive measures and drugs is scanty. In this review article, an attempt is made to unfurl the relation between atherosclerosis and CAVD.

1. Introduction

Calcific aortic valve disease (CAVD) is the major cause for surgical valve replacement in western countries. Rheumatic fever has waned as cause of aortic stenosis (AS), and CAVD has become the prime cause of AS even in developing countries. The perception that calcific AS is the result of aging and wear and tear[1] of aortic valve is changing. There are similarities between the plaque of coronary atherosclerosis and initial lesions of CAVD, with presence of similar risk factors for both.[2] Monckeberg[3] described the dystrophic calcification of the aortic valve in 1904 as cause of nonrheumatic calcific AS. This article attempts to discuss the insights to debate whether CAVD is another face of atherosclerosis.

2. The risk factors for vascular atherosclerosis and CAVD

Hypertension, smoking, diabetes mellitus, elevated cholesterol, and male gender have been identified as the risk factors shared by CAVD and atherosclerosis, and a concept of atheromatous valvulopathy thus evolved.[4] An active biological

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process similar to atherosclerosis type of pathophysiology involving oxidative stress, inflammation, and endothelial dysfunction in aortic valves was noted in patients with hypercholesterolemia. Hemodynamic stress, genetic dysregulation, and oxidative stress lead to active inflammatory process resulting in severe calcific AS. Conventional treatment of CAVD with severe AS is aortic valve replacement. But with apparent similarities between CAVD and atherosclerosis, pharmacotherapy, designed to retard the process of atherosclerosis, can be considered to slow progression of CAVD if therapy is initiated early.

2.1. *Histological evidences*

Pomerance[1] and Roberts[5] described calcification of the aortic cusps that was preceded by lipid deposition and postulated that CAVD shared the same etiology as coronary atherosclerosis. Otto et al.[2] and others[6] have also delineated the histological features of CAVD. Characteristically, thickening and calcification of aortic valves are seen only on the aortic side on gross inspection. Microscopically, diseased aortic leaflets have disrupted endothelium on the aortic side alone but not on ventricular side, and the disease progresses through stages of sclerosis and stenosis. There is subendothelial accumulation of intra- and extracellular lipids and lipoproteins. Chronic inflammatory cell infiltration made up of foam cells, nonfoam cell macrophages, and 'T' lymphocytes has been noted. The regions with lipoproteins are at the same location as areas of calcification. From the subendocardial region, these lesions extend to the central portion of the leaflets called the fibrosa and most often involve the base of the leaflets. This process is similar to what occurs in vascular atherosclerosis.[7]

2.2. *Experimental evidences*

Experimental models of atherosclerosis are important to understand the disease process of CAVD if the risk factors are common for both. Studies in mice and rabbits have proven that hypercholesterolemia causes both atherosclerosis and valve calcification. Early endothelial abnormalities in the aortic valves have been described in experimental hypercholesterolemia in rabbits.[8] Three months of cholesterol diet induced early mineralization and endothelial nitric oxide synthase mediated modification of the aortic valve. Six months of cholesterol diet induced marked thickening and calcification of the aortic valve leaflets with attenuation on atorvastatin therapy.[9] In experimental rabbit model, when the effect of angiotensin-converting enzyme inhibitors (ACE) was tested, inhibition of atherosclerotic process was noted.[10] Drolet et al.[11] have also shown that a high cholesterol diet and vitamin D treatment resulted in development of AS in rabbits.

2.3. *Genetic evidences*

The pathobiology of aortic valve calcification is closely linked to genetic factors. The NOTCH I[12] transcriptional factor regulates osteogenic differentiation, as well as valve development. Functional mutations in the gene may increase osteoblast formation and calcification and alter structural development of valve. Aortic valve cusps, which are under constant mechanical stress, require constant cell turnover and telomeric changes. Calcification is a distinguishing feature of CAVD and Shetty et al.[13] found that calcified valve allografts expressed bone-specific transcription factor cbfa-1, osteopontin, and osteonectin, which were not found in normal valves. The genotype in the genetic mouse model, which lacks the gene for LDL receptor but expresses the receptor for human apolipoprotein B-100, is known to be associated with human atherogenic lipid abnormalities and induces valvular and vascular atherosclerosis.[14] The mechanism by which calcification develops is activation and upregulation of the LDL receptor 5 (Lrp5) pathway in vascular and valvular interstitial cells. Elevated cholesterol induces a phenotypic switch to bone forming cells within the valve leaflets.[15] Matrix metalloproteinases, interleukin, transforming growth factor beta, purine nucleotides, and tumor necrosis factor alpha have all been identified as signaling pathways along with Lrp5 pathway in the development and progression of vascular atherosclerosis and bone formation. There is also increased expression of elastolytic cathepsins S, K, and V and their inhibitor cystatin C in the stenotic aortic valves.

2.4. *Clinical evidences*

New imaging modalities, like contrast-enhanced molecular imaging as adjunct to cardiac magnetic resonance imaging using nanoparticles, have been shown to penetrate atherosclerotic plaques and delineate the pathology involved in CAVD better.[16] Microcomputerized tomography is helpful to assess mineral levels in explanted human heart valves. Characteristic heavy calcification has been shown to occur near the outer edges of each calcified nodule found on the valve as reported by Rajamannan et al.[15] These new imaging modalities, which characterize underlying pathological processes, may help decide on appropriate treatment targets. It is worthwhile considering randomized controlled trials with and without statins in cases of bicuspid aortic valves to study the progression of aortic stenosis in them.

Statins, by lowering lipid levels, as well as by pleiotropic effects, downregulate expression of inflammatory cytokines and thereby alter the inflammatory milieu in degenerative heart valves. Retrospective clinical trials[17] with statin therapy have shown 50% reduction in the progression of CAVD. However, prospective clinical trials such as SALTIRE[18] (Scottish Aortic Stenosis and Lipid Lowering Therapy) trial did not show any positive result with high-dose atorvastatin in severe AS. In SEAS study,[19] the combination of Ezetemibe and Simvastatin failed to alter clinical outcomes in 1800 patients with AS. THE ASTRONOMER study[20] (AS progression observation, measuring effects of rosuvastatin trial) showed that despite favorable changes in lipid parameters and CRP, progression of AS, as measured by peak aortic gradient, was not altered. Treatment with rosuvastatin did not slow progression of AS in the subgroup analysis based on AS severity, age, and severity of calcification of aortic valve. However, the RAAVE[21] (Rosuvastatin affecting Aortic Valve Endothelium) study demonstrated that rosuvastatin slowed progression of CAVD.

The stage at which statin therapy is initiated matters. Normalization of plasma lipid levels at early stages of AV disease could reverse or halt progression of AS. If this is so, why have prospective studies been negative? The possibilities are:

(1) Statin treatment was initiated far too late in the course of the disease, though mild and moderate AS patients were included. Miller et al.[22] showed that genetic switch for lipid lowering was initiated early in the disease process even before hemodynamic changes were noted.
(2) It is possible that only certain time periods of disease development are susceptible to modulation by lipid lowering drugs.
(3) Other pharmacological tools to alter blood lipid profiles may have a role in treatment of AS besides statins.
(4) Lipid accumulation may not be the only focal point of disease pathogenesis.

Angiotensin-converting enzyme, angiotensin II (AT II), and the profibrotic AT I receptors are present in stenotic aortic valves and their enzymatic activity is augmented in diseased valves. This may cause the profibrotic and proinflammatory milieu to enhance lipid accumulation.[23] Though clinical studies of ACE inhibitors in AS have been discordant as per currently available evidence, for lipid lowering or any pharmacological treatment to be effective, they should be initiated at early stages of disease.

The National Heart, lung, and blood institute conveyed a meeting of keen investigators on CAVD, in September 2009. The executive summary of the proceedings was published by Rajamannan et al.[24] They concluded that CAVD covers spectrum of disease process from initial cellular changes in valve leaflets to development of aortic stenosis and further resulting in bone formation. The structure of the valve leaflets is regulated by valve endothelial cells and valve interstitial cell (VICs). VICs may behave differently at different times due to triggering factors. The triggers for VIC differentiation or dysfunction include factors like hemodynamic sheer stress, solid tissue stresses, inflammatory cytokines, and growth factors. Once activated, VICs can differentiate into a variety of other cell types, including myofibroblasts and osteoblasts.

Progression of disease in bicuspid aortic valves and bioprosthetic valves may represent true model to study VIC activation and calcification to understand the pathobiology of CAVD. Further research is needed to study the signaling pathway between valvular endothelial cells and VICs. Traditional echocardiography may not detect initiation and progression of disease but molecular imaging techniques need to be developed. Rajamannan et al.[24] made recommendations that studying the genetic, anatomic, and clinical risk factors for initiation and progression of CAVD is essential to plan therapeutic strategies.

Hypertension, smoking, diabetes mellitus, and metabolic syndrome have been linked to the development of AS, though the exact disease promoting action is unclear. But not all patients with risk factors for atherosclerosis develop calcific AS and vice versa. Discrepancies exist in both conditions (Table 1).[25] In AS, large contributor of disease progression is prominent calcification with gradual development of outflow obstruction whereas in coronary atherosclerosis, the events are acute, related to plaque rupture and thrombosis. The strategies of plaque stabilization and antithrombotic treatment used for coronary atherosclerosis are not beneficial for CAVD.

Table 1 – Comparison of calcific aortic valve disease and atherosclerosis.[25]

	Calcific aortic valve disease	Atherosclerosis
Histopathologic features		
Lipoprotein accumulation	++++	++++
Lipid oxidation	++++	++++
Calcification	+++++	++
Inflammatory changes	+++	++++
Systemic inflammatory markers	+	++
Chlamydophila pneumoniae and other infectious agents	+	+
Genetic polymorphisms	++	+++
Prominent cell type	Fibroblast	Smooth muscle
Clinical risk factors		
Renal dysfunction	++++	++++
Smoking	+++	++++
Hypertension	++	++++
Elevated serum lipoprotein levels	+++	++++
Diabetes mellitus	+	+++
Endothelial dysfunction	++	++++

3. Conclusions

The pathophysiology of CAVD is now understood to be an active process akin to atherosclerosis and involves initiating factors, endothelial dysfunction, inflammatory responses, oxidative stress leading to remodeling of the valves, and mineralization of valves. The pharmacotherapeutic interventions, which are likely to retard these processes, may potentially delay the disease progression in aortic valves and postpone need for valve replacement. Earlier is the pharmacological intervention, better will be the expected outcomes.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. Pomerance A. Pathogenesis of aortic stenosis and its relation to age. *Br Heart J*. 1972;34:569–574.
2. Otto CM, Kuusisto J, Reichenback DD, et al. Characterisation of the early lesion of degenerative valvular aortic stenosis: histological and immunohistochemical studies. *Circulation*. 1994;90:844–853.

3. Monckeberg JG. Der normale histologische Bau und die Skelerose der. *Virchows Archiv*. 1904;176:472–514.
4. Stewart BF, Siscovick D, Lind BK, et al. Clinical factors associated with calcific aortic valve disease: cardiovascular health study. *J Am Coll Cardiol*. 1997;29:630–634.
5. Roberts WC. The senile cardiac calcification syndrome. *Am J Cardiol*. 1986;58:572–574.
6. Mohler ER, Gannon F, Reynolds C, et al. Bone formation and inflammation in cardiac valves. *Circulation*. 2001;103:1522–1528.
7. Ross R. Atherosclerosis – an inflammatory disease. *N Engl J Med*. 1999;340:115–116.
8. Cimini M, Boughner DR, Ronald JA, et al. Development of aortic valve sclerosis in a rabbit model of atherosclerosis: an immunohistochemical and histological study. *J Heart Valve Dis*. 2005;14:365–375.
9. Rajamannan NM, Subramaniam M, Caira F, et al. Atorvastatin inhibits hypercholesterolemia induced calcification in the aortic valves via the Lrp5 receptor pathway. *Circulation*. 2005;112:1229–1234.
10. Arishiro K, Hoshiga M, Negoro N, et al. Angiotensin receptor-I blocker inhibits atherosclerotic changes and endothelial disruption of the aortic valve in hypercholesterolemic rabbits. *J Am Coll Cardiol*. 2007;49:1482–1489.
11. Drolet MC, Arsenault M, Conet J. Experimental aortic valve stenosis in rabbits. *J Am Coll Cardiol*. 2003;41:1211–1217.
12. Garg V, Muthu AN, Ranson JF, et al. Mutations in NOTCH-1 cause aortic valve disease. *Nature*. 2005;437:270–274.
13. Shetty R, Pepin A, Charest A, et al. Expression of bone regulatory proteins in human valve allografts. *Heart*. 2006;92:1303–1308.
14. Weiss RM, Ohashi M, Miller JD, et al. Calcific aortic valve stenosis in old hypercholesterolemic mice. *Circulation*. 2006;114:2065–2069.
15. Rajamannan NM, Subramaniam M, Richard D, et al. Human aortic valve calcification is associated with an osteoblast phenotype. *Circulation*. 2003;107:2181–2184.
16. Cai JM, Hatsukami TS, Fergusan MS, et al. Classification of human carotid atherosclerotic lesions with in vivo multi contrast magnetic resonance imaging. *Circulation*. 2002;106:1368–1373.
17. Novnio GM, Tiong IY, Pearce GL, et al. Effect of hydroxymethylglutaryl coenzyme a reductase inhibitors on the progression of calcific aortic stenosis. *Circulation*. 2001;104:2205–2209.
18. Cowell SJ, Newby DE, Precolt RJ. A randomized trial on intensive lipid lowering therapy in calcific aortic stenosis. *N Engl J Med*. 2005;352:2389–2397.
19. Moura LM, Ramos SF, Zamorano JL, et al. Rosuvastatin affecting aortic valve endothelium to slow the progression of aortic stenosis. *J Am Coll Cardiol*. 2007;49:554–561.
20. Rossebe AB, Pedersen TR, Allen C, et al. The simvastatin and ezetimibe in aortic stenosis (SEAS). *N Engl J Med*. 2008;359:1343–1356.
21. Chan KL, Teo K, Dumesnil JG, et al. Effect of lipid lowering with rosuvastatin on progression of aortic stenosis – result of the aortic stenosis progression observation: measuring effects of rosuvastatin (ASTRONOMER) trial. *Circulation*. 2010;121:306–314.
22. Miller JD, Weiss RM, Serrano KM, et al. Lowering plasma cholesterol levels halts progression of aortic valve disease in mice. *Circulation*. 2009;119:2693–2701.
23. O'brien KD, Shavelle DM, Caulfield MT, et al. Association of angiotensin converting enzyme with LDL in aortic valvular lesion and in human plasma. *Circulation*. 2002;106:2224–2230.
24. Rajamannan NM, Evans FJ, Aikawa E, et al. Calcific aortic valve disease: not simply a degenerative process. *Circulation*. 2011;124:1783–1791.
25. Freeman RV, Otto CM. Spectrum of calcific aortic valve disease: pathogenesis, disease progression and treatment strategies. *Circulation*. 2005;111:3316–3326.