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G3 – 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.

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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 tear¹ 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 Monckeberg³ 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

Pomerance¹ and Roberts⁵ 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 others⁶ 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 1¹² 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 trials¹⁷ with statin therapy have shown 50% reduction in the progression of CAVD. However, prospective clinical trials such as SALTIRE¹⁸ (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 Ezetimibe and Simvastatin failed to alter clinical outcomes in 1800 patients with AS. THE ASTRONOMER study²⁰ (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 RAAVE²¹ (Rosuvastatin affecting Aortic Valve Endothelium) study demonstrated that rosuvastatin slowed progression of CAVD.

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