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Reviews

Aortic Sclerosis—A Marker of Coronary Atherosclerosis

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Summary: Aortic valve sclerosis is defined as calcification and thickening of a trileaflet aortic valve in the absence of obstruction of ventricular outflow. Its frequency increases with age, making it a major geriatric problem. Of adults aged > 65 years, 21–29% exhibit aortic valve sclerosis. Incidence of aortic sclerosis increases with age, male gender, smoking, hypertension, high lipoprotein (Lp) (a), high low-density lipoprotein (LDL), and diabetes mellitus. Aortic valves affected by aortic sclerosis contain a higher amount of oxidized LDL cholesterol and show increased expression of metalloproteinases. Clinically, it can be suspected in the presence of soft ejection systolic murmur at the aortic area, normal split of the second heart sound, and normal volume carotid pulse, but it can be best detected by echocardiography. Aortic sclerosis may be accompanied by mitral annulus calcification up to 50% of cases. It is associated with an increase of approximately 50% in the risk of death from cardiovascular causes and the risk of myocardial infarction. The mechanism by which aortic sclerosis contributes to or is associated with increased cardiovascular risk is not known. Aortic sclerosis is associated with systemic endothelial dysfunction, and a small percentage of cases may progress to aortic stenosis. Lowering of LDL cholesterol by 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have been shown to decrease progression of aortic valve calcification. Aortic sclerosis is not a mere benign finding. Once diagnosis of aortic sclerosis has been made, it should be considered a potential marker of coexisting coronary disease. Aggressive management of modifiable risk factors, especially LDL cholesterol lowering, may slow progression of the disease.

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Introduction

Aortic valve sclerosis is defined as calcification and thickening of a trileaflet aortic valve in the absence of ventricular outflow obstruction. Calcific aortic valve disease was recognized as early as the 1600s. As recently as early in the twentieth century, valve calcification was believed to occur due to rheumatic disease or degeneration. The prevalence of calcific valve disease of rheumatic etiology in the developed world has declined due to a decline in rheumatic fever, whereas aortic valve disease of degenerative etiology has increased due to increased longevity. It is common in the elderly, affecting 21 to 26% of adults aged > 65 years. The prevalence of aortic sclerosis increases with age and is present in 37% of adults aged > 75 years.[1] In a population-based echocardiographic study, in patients aged > 65 years, 29% exhibited age-related aortic valve sclerosis.[2]

Independent clinical factors associated with aortic sclerosis include age (two-fold increased risk for each 10-year increase in age), male gender (two-fold excess risk), present smoking (35% risk increase), and a history of hypertension (20% risk increase).[3] Other significant associated factors include height, high lipoprotein (LP) (a) level, high low-density lipoprotein (LDL) level, and diabetes mellitus.[4,5] Secondary hyperthyroidism, Paget's disease, as well as elevated creatinine and calcium are also linked to progression of valve calcification.[6]

Pathophysiology

Many pathophysiologic factors relate to valve calcification and include both genetic and environmental influences.

Until recently, it was believed that in the absence of commissural fusion, progressive thickening and calcification of the aortic valve was due to a nonspecific degenerative process related to aging. Instead, current studies suggest that although the initiating factor may be related to mechanical and shear stress forces, leaflet changes are due to an active disease process characterized by subendothelial lesions on the aortic side of the

leaflets. This consists of intracellular and extracellular lipid accumulation [apolipoprotein (apo) E, apo (a), apo B]; inflammatory cells (foam cell macrophages, nonfoam cells, occasional T cells); and fine, stippled mineralization associated with active production of osteopontin by a subset of lesion macrophages.[7] Matrix metalloproteinases induce remodeling of the extracellular matrix via cytokine stimulation, which may enhance the calcific process. There is evidence of chronic inflammation and active synthesis of osteopontin protein, similar to atherosclerotic plaque, by macrophages in the aortic valve area.[8] There is also an accumulation of T-cells (with expression of interleukin [IL]-2 receptors), fibroblasts (with expression of smooth muscle cell characteristics), and human leukocyte antigen (HLA)-DR in the abnormal region of the aortic valve.[9, 10]

Diagnosis

Clinically, aortic valve sclerosis can be suspected on cardiac auscultation during physical examination by the presence of a soft ejection systolic murmur in the aortic area, a normal split of the second heart sound, and a normal volume carotid pulse; it can be best confirmed by echocardiography. Some have suggested that aortic valve sclerosis severity can be graded as follows: grade 1 = increased echo density; grade 2 = thickening or calcific deposits ≥ 3 mm; and grade 3 = same as grade 2 with mildly restricted motion of aortic leaflets and pressure gradient < 16 mmHg across the aortic valve.[5]

Aortic sclerosis may be accompanied by mitral annulus calcification (up to 50%), and calcification of coronary arteries, but rarely by aortic regurgitation.[11]

Although echocardiography is the standard test for aortic valve sclerosis, it does not quantify calcium. Electron-beam tomography may be the appropriate imaging modality; quantification of aortic valve calcification can be achieved and sequentially monitored by this technique. The significance of aortic valve bioprosthesis calcification and its relation to cardiovascular events remain uncertain.

Prognosis and Course

Two studies have demonstrated an association between aortic sclerosis and cardiovascular mortality and morbidity.[13, 14]

The Cardiovascular Health Study[12] was a prospective health study of 5,888 men and women aged ≥ 65 years, with a mean follow-up of 5 years. All-cause mortality and cardiovascular mortality, per 1,000 person-years of follow-up among subjects with aortic sclerosis, was approximately twice that of subjects with normal aortic valves. Persons with aortic sclerosis demonstrated an independent increased risk of death from any cause and from cardiovascular causes even after adjusting for baseline variables. Aortic sclerosis was associated with a relative risk of myocardial infarction of 1.40 (95% confidence interval [CI] 1.07–1.83) and congestive heart failure (relative risk, 1.28; 95% CI 1.01–1.63). There was also a trend toward an increased risk of angina pectoris and stroke among subjects with sclerotic aortic valves. It is surprising that the increase in risk associated with aortic sclerosis was most evident in subjects without clinically evident coronary artery disease (CAD).[13]

Similarly, Teerlink *et al.*[14] reported that aortic sclerosis carried an increased mortality risk (hazard ratio, 1.5, CI 1.4–1.7; p 0.0001) among 997 patients who had echocardiographic evidence of aortic sclerosis. Previous studies have also shown that patients with aortic valve sclerosis undergoing coronary angiography have a higher prevalence of CAD.[15]

The reason for increased cardiovascular events associated with aortic sclerosis is not known, but can be best explained by assuming that aortic sclerosis is an objective marker of other forms of cardiovascular disease, especially CAD, as aortic sclerosis and CAD share many risk factors.[16]

Poggianti *et al.*[17] reported that aortic sclerosis was associated with significantly lower endothelium-dependent, flow-mediated dilation of the brachial artery (a marker of systemic endothelial dysfunction) compared with morphologically normal aortic valves. Endothelial dysfunction associated with aortic sclerosis may be one of the proposed mechanisms for cardiovascular events; another is myocardial ischemia secondary to endothelial dysfunction, even in the absence of obstructive CAD. Another possible mechanism by which coronary endothelial dysfunction may contribute to cardiac events is through acceleration of coronary atherosclerosis, as evidenced by development of obstructive CAD.[17]

Adler *et al.*[18] reported a highly significant association of mitral annular calcification (MAC) with atherosclerosis of the vascular system, including CAD, similar to aortic valve sclerosis.

Based on the Framingham Heart Study, Fox *et al.*[19] reported that MAC assessed by M-mode echocardiography has an independent association with CVD death and all-cause death, which underscores the calcification at other sites, that is, mitral valve as a marker of cardiovascular events similar to aortic valve calcification.

In a small percentage of persons with aortic sclerosis, disease progresses, calcification and fibrosis increase, and leaflet stiffness increases, all of which leads to a reduced systolic opening and an increase in forward velocity causing hemodynamic abnormality. Despite the fact that clinical factors such as hypertension, diabetes mellitus, smoking, and hyperlipidemia are shared by both aortic sclerosis and aortic stenosis, these factors did not predict the rate of hemodynamic progression or clinical outcome;[20, 21] the extent of valve calcification was the only independent predictor of clinical outcome. A study by Rosenhek *et al.*[22] showed that once aortic stenosis develops, even in asymptomatic patients, aortic jet velocity increased by 0.3 m/s and valve area decreased by 0.1 cm^2 per year; however, there was wide variation in the rate of progression.

Serum LDL cholesterol levels significantly influence the progression of aortic valve calcification. Studies have shown a significant decrease in progression of aortic valve calcification detected by electron-beam tomography if the LDL level was kept < 130 mg/dl by 3-hydroxy-3-methylglutaryl coenzyme A (HMG-coA) reductase inhibitors.[23] Similarly, Shavelle *et al.*[24] reported that patients treated with statins had a 62–63%

lower median rate of aortic valve calcium accumulation and a 44–49% reduction in definite aortic valve calcium progression assessed by electron beam tomography. Therefore, it seems possible that risk-factor modification that has proven to have a beneficial influence on the progression and outcomes of CAD, such as the reduction of LDL cholesterol, may also be able to slow the progression of aortic sclerosis.

Conclusion

Much coronary disease is silent and not identified by the standard screening techniques of history taking, electrocardiography at rest, and physical examination; many subjects have occult coronary disease. Therefore, it is likely that once echocardiography is added to the standard evaluation, pathologic processes that may occur in the coronary arteries may be identified more easily in the aortic valve. Once the diagnosis of aortic sclerosis has been made by echocardiography, it should be considered a potential marker for CAD, and those diagnosed should undergo intensive screening for CAD. Aggressive management of modifiable risk-factor reduction should be undertaken in such cases.

Prospective, large scale, randomized trials are needed to determine whether atherosclerotic risk-factor modification is effective in retarding progression of aortic valve calcification and reducing or preventing cardiovascular events such as myocardial infarction, strokes, and progression to aortic stenosis. Studies are also needed to evaluate whether aortic sclerosis is associated with increased risk of endocarditis.

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