

Editor's Note

Can Calcific Aortic Stenosis Be Prevented?



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During my fellowship training I was taught that calcification of the aortic valve was related to aging and was a degenerative process. No one talked very much about aortic sclerosis. Of course, we did not have the benefit of cardiac ultrasound in those days, so this

diagnosis was not made with any degree of assurance unless cardiac catheterization and angiography were performed. Aortic sclerosis was diagnosed when a systolic ejection murmur was heard and the aortic valve appeared “angiographically abnormal” and the pressure difference across the valve was zero or trivial. The murmur was passed off as an innocent systolic ejection murmur and not much thought was given to progression of this lesion.

As cardiac ultrasound became quite sophisticated, more patients were diagnosed with abnormal aortic valves termed “sclerotic,” since there was no significant aortic valve gradient. In recent years much thought has been given to progression of this lesion, because Americans and others throughout the world are living longer lives and significant calcific aortic stenosis is diagnosed commonly in the older patient.

Several lines of evidence relating multiple abnormalities to progression of aortic valve disease have been published in the past several years. For example, Palta *et al.* reported that cigarette smoking, hypercholesterolemia, elevated serum creatinine, and calcium levels are associated with reduction in aortic valve area per year in patients with mild degrees of aortic stenosis.¹

Otto and colleagues² performed histologic and immunohistochemical studies on aortic valve leaflets or on frozen sections obtained at autopsy from 27 patients. Six patients had normal leaflets, 15 had mild microscopic leaflet thickening, and six had clinical aortic stenosis. The group with microscopic leaflet thickening had these features:

1. subendocardial thickening on the aortic side of the leaflets, between the basement membrane and elastic lamina;
2. large amounts of intracellular and extracellular neutral lipids and fine, stippled mineralization;
3. disruption of the basement membrane overlying the lesion.

Control valves showed none of these abnormalities.

The early lesions are characterized by the presence of an inflammatory infiltrate composed of non-foam cells and foam-cell macrophages, occasional T-cells, and, in rare instances, alpha-actin positive cells. The investigators concluded that the early lesion of aortic stenosis is an active inflammatory process with some similarities to atherosclerosis.

Deutscher and colleagues reported findings in 54 patients with isolated aortic stenosis undergoing cardiac catheterization compared with patients without aortic stenosis undergoing angiography for other reasons. Their observations suggest that diabetes and hypercholesterolemia may play a role in aortic stenosis.³

Gotoh and colleagues, using echocardiography, evaluated the relationship of lipoprotein(a) [Lp(a)] to aortic valve sclerosis.⁴ Lipoprotein(a) levels were measured in 347 men and 437 women aged 35 to 90 years. The prevalence of aortic valve sclerosis increased significantly with age and was present in 36.1% of 180 subjects with Lp(a) levels ≥ 30 mg/dl and in 12.7% of 604 subjects with Lp(a) levels < 30 mg/dl ($p \leq 0.001$). They also observed that gender, blood pressure, levels of total cholesterol, high-density lipoprotein cholesterol, triglycerides, and blood sugar did not seem to influence the prevalence of aortic valve sclerosis.

In the Cardiovascular Health Study, Stewart and colleagues, using cardiac ultrasound, reported on the clinical risk factors associated with calcific aortic valve disease.⁵ In a cohort of 5,201 subjects ≥ 65 years of age, aortic valve sclerosis was present in 26%. In subjects ≥ 75 years of age, aortic valve sclerosis was present in 37%. They noted a twofold increase in risk for each ten-year increase in age, a twofold excess risk for male gender, 35% increase in risk in those who continued to smoke cigarettes, and 20% increase in risk in patients with hypertension. They noted that height, high Lp(a), and elevated low-density lipoprotein cholesterol levels were also significant factors. Their conclusions were that clinical factors for aortic sclerosis and aortic stenosis are similar to risk factors for atherosclerosis.

Wilmshurst and colleagues reported a case control study in 20 patients with severe calcific aortic stenosis and 20 controls. They found that the presence of a calcific stenosis in a tricuspid aortic valve was associated with a significant increase in plasma cholesterol; this increase was less in patients who had bicuspid aortic valves.⁶

With this as background supporting the hypothesis that calcific aortic stenosis is associated with an inflammatory process similar to atherosclerosis, Novaro and colleagues⁷ designed a study to test whether statin treatment of patients might slow

the progression of aortic stenosis. This was a retrospective study of 174 patients with mild to moderate calcific aortic stenosis, normal left ventricular function, and minimal aortic regurgitation. Treatment with statins was accomplished in 33% of patients; 67% did not receive the statin. Patients were followed for 21 months. According to cardiac ultrasound, the statin-treated patients had a smaller increase in peak and mean gradient and a smaller decrease in aortic valve area than the untreated patients. The statin-treated patients were older and had a higher prevalence of hypertension, diabetes mellitus, and coronary disease. The investigators concluded that this retrospective analysis is highly suggestive that treatment with the statin reduced aortic stenosis progression compared with those not treated with the statin.

All the findings discussed above suggest to me that once aortic sclerosis is identified, with or without calcification, patients should be aggressively treated with an HMG CoA reductase inhibitor. I doubt that aortic stenosis can be prevented by a single therapy, but perhaps statins, plus other "risk factor" modifications, can slow the process. Of course, a randomized prospective clinical trial would provide much stronger evidence for or against that recommendation.

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