EDITORIAL COMMENT

Why Is Aortic Sclerosis Associated With Adverse Clinical Outcomes?*

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Calcific aortic valve disease encompasses a range of disease severity from mild leaflet thickening without valve obstruction, called "aortic sclerosis," to severe aortic stenosis. It is intuitive that severe obstruction in blood flow at the valve level results in poor clinical outcomes and that relief from the obstruction by valve replacement corrects the problem. However, we now recognize that milder degrees of calcific valve disease are also associated with adverse clinical outcomes. In the absence of altered valve hemodynamics, the mechanism of this association is not obvious.

Aortic sclerosis is diagnosed on echocardiography as focal areas of increased echogenicity on the valve leaflets with normal valve motion and a normal, or only mildly increased, antegrade velocity across the valve. Definitions vary slightly, but typically an outflow velocity <2.5 or <2.0 m/s is used to separate sclerosis from mild stenosis. Aortic valve sclerosis is a common finding on echocardiography; in population-based studies, aortic sclerosis is present in about 25% of adults over 65 years of age (1–3). Aortic valve sclerosis is associated with many of the same "risk factors" as coronary artery disease (CAD). Clinical factors associated with aortic sclerosis include age, male gender, hypertension, elevated serum levels of lipoprotein(a) and low-density lipoprotein (LDL), smoking, and diabetes (1,3–5).

At the tissue level, aortic sclerosis is characterized by focal areas of subendothelial thickening on the aortic side of the valve leaflet. The normal aortic valve leaflet consists of three well-defined layers: the fibrosa is the central dense collagen layer that provides tensile strength to the leaflet; the ventricularis is an elastin-rich layer on the ventricular side of the leaflet; and the spongiosa is a layer of loose connective tissue typically confined to the basal one-third of the leaflet. The lesions of aortic sclerosis displace the subendothelial elastic lamina on the aortic side of the leaflet and extend into the adjacent fibrosa. It is presumed that endothelial disruption related to altered shear stress on the aortic side of the leaflet may initiate the disease process, although there is no direct evidence for this hypothesis.

The early lesions of aortic sclerosis have many similarities with atherosclerosis. There is prominent accumulation of LDL and lipoprotein(a), with evidence of LDL oxidation (6–8). An inflammatory cell infiltrate is present, composed of macrophages, with some foam cells, and T-lymphocytes. The lipids and inflammatory cells co-localize with areas of microscopic calcification, and a subset of macrophages produces proteins, such as osteopontin, that are involved in tissue calcification. Phenotypic cellular changes occur, including evidence of calcifying vascular cells and demonstration of an osteoblast phenotype (9,10). Aortic sclerosis lesions also contain angiotensin-converting enzyme with local production of angiotensin II (11). Other components of the lesion include overexpression of tenascin C and alterations in the expression of matrix metalloproteinases (12–14). Animal models of calcific aortic valve disease suggest that both cell proliferation and apoptosis are involved in the disease process (15,16).

The presence of aortic sclerosis is associated with adverse clinical outcomes, and this association is present even when baseline factors such as cardiac risk factors and known atherosclerotic disease are taken into account (17). In the Cardiovascular Health Study of over 5,000 adults over age 65 years followed up for approximately five years, aortic sclerosis was associated with a 40% increase in the risk of myocardial infarction and a trend toward an increased risk of angina, heart failure, and stroke in patients without known cardiovascular disease at study entry. In patients with no known CAD at study entry, there was a 50% increase in the risk of cardiovascular death (17). The association between mild valve disease and adverse clinical outcomes has been observed in other studies (18), and this association is not specific to the aortic valve, with adverse outcomes also associated with mitral annular calcification at a similar risk level (19–21).

Unfortunately, although epidemiologic studies are the best approach for establishing associations, they provide little insight into the mechanism of these associations. There are several possible causes of adverse outcomes in adults with aortic valve sclerosis. First, disease progression in the valve leaflets may lead to increased leaflet stiffness with valve obstruction (e.g., aortic stenosis). In a study of over 2,000 patients with aortic sclerosis, progression to aortic stenosis occurred in 16% (22). However, most developed only mild stenosis, and in the 2.5% of patients who developed severe stenosis, the average time interval from diagnosis of aortic sclerosis to severe aortic stenosis was eight years, a longer time frame than encompassed by the epidemiologic studies showing the association between aortic sclerosis and clinical outcome. The rate of hemodynamic progression of aortic stenosis in prospective studies also suggests that valve obstruction is unlikely to be the cause of adverse outcomes in patients with aortic sclerosis (23,24).

The second hypothesis is that aortic sclerosis is simply a
marker of subclinical CAD. Support for this mechanism includes the association between aortic sclerosis and atherosclerosis of the aorta (3,20) and the observation that about 50% of adults undergoing aortic valve replacement for severe aortic stenosis also have concurrent significant CAD.

The third hypothesis is that both aortic sclerosis and atherosclerosis are the result of a common underlying pathophysiologic mechanism such as inflammation. In this issue of the Journal, Chandra et al. (25) tested this hypothesis by comparing inflammatory markers and CAD in patients with and without aortic sclerosis who presented to the emergency department with chest pain. Aortic sclerosis was present in 49% of these 415 patients, a higher prevalence than seen in population-based studies, most likely due to the selection of patients with cardiac symptoms. Even with this relatively small number of patients, there was an increased rate of cardiovascular events, defined as cardiovascular death or CAD, at one year in those with aortic sclerosis compared with those with a normal valve (16.8% vs. 7.1%, p = 0.002), supporting the association seen in population-based studies. Coronary artery disease was present in 76% of all patients, with a similar prevalence in those with and without aortic sclerosis.

Aortic sclerosis was also associated with increased serum levels of C-reactive protein and fibrinogen, with the risk of cardiovascular death or CAD increasing with each tertile of C-reactive protein. On multivariate analysis, clinical outcome was predicted by the presence of CAD, myocardial infarction at the index admission, C-reactive protein levels, congestive heart failure, and age but not by the presence of aortic sclerosis. The authors conclude that adverse outcomes in patients with aortic sclerosis are related to the presence of CAD and systemic inflammation.

The observation that aortic sclerosis predicts clinical outcome in a group of symptomatic patients with a high prevalence of CAD is of particular interest because in the Cardiovascular Health Study, the association between aortic sclerosis and clinical outcome was observed only in those subjects without known CAD. The association of aortic sclerosis with elevated inflammatory markers is consistent with other studies and suggests that inflammation may play a role in the disease process (26). However, these data still do not unequivocally prove that inflammation is the cause of adverse clinical outcomes in patients with aortic sclerosis.

Another potential underlying mechanism that might explain adverse outcomes in aortic sclerosis patients includes endothelial dysfunction, as suggested by the finding of reduced brachial artery flow-mediated dilation in patients with aortic sclerosis (27). Other proposed mechanisms include genetic polymorphisms of the vitamin D receptor, leading to altered tissue calcification (28), and apolipoprotein A1, B, and E polymorphisms (29), leading to increased lipid accumulation in the valve leaflets. The important of lipid accumulation in this disease process is highlighted by several small retrospective studies showing that lower serum LDL levels or treatment with lipid-lowering therapy is associated with a slower rate of disease progression in calcific aortic valve disease (30–33).

Thus, to date it remains unclear whether the mechanism of the association between aortic sclerosis and adverse clinical outcomes is diffuse atherosclerosis, inflammation, endothelial dysfunction, altered calcium metabolism, lipid accumulation, genetic polymorphisms, or other, as-yet-undefined, factors. Ultimately, proof of a cause-effect relationship will require a prospective randomized intervention trial in which blocking the proposed pathway results in a reduction in adverse clinical outcomes.

Despite the similarities between calcific aortic valve disease and atherosclerosis, there are distinct differences in these disease processes. Many patients with significant CAD do not have aortic valve disease and vice versa. In patients with CAD, clinical events often are due to plaque rupture, whereas there is little evidence for plaque instability or thrombus formation on the sclerotic aortic valve leaflets. Exploring the differences between these similar, but not identical, disease processes may enhance our understanding of both conditions.

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REFERENCES


