Calcific Aortic Valve Stenosis with Aging and Current Development in its Pathophysiology

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Abstract

Aortic stenosis is the most common valvular heart disease affecting the elderly. While most patients have a prolonged asymptomatic phase, the development of symptoms ushers in a phase clinical deterioration that often leads to sudden death without an intervention. Treatment of aortic stenosis with valve replacement often relieves the symptoms but still leaves behind a remodeled left ventricle which may not recover. Understanding the pathophysiology of aortic stenosis and realizing that the disease process may be a more active biological entity rather than a passive degenerative process will help us prevent it. This review serves to summarize the latest literature on the pathophysiology of aortic stenosis in the elderly.

Keywords

- advanced glycosylation end product
- aortic valve disease
- atherosclerosis
- biomarkers
- valvular heart disease
- cardiovascular risk factors

aortic stenosis Aortic stenosis (AS) is the most common valvular heart disease with a prevalence of 10% for severe AS in adults $\geq$80 years.[1] Degenerative, calcific, valvular disease, due to aging, represents the most common etiology of AS in the elderly population, affecting >25% of all patients over the age of 65 years. Most patients have only aortic sclerosis with mild thickening and normal valve function. However, approximately 5% of these patients have significant AS.[2] There is usually a variable asymptomatic phase before the development of symptoms and severe AS. The prognosis changes dramatically with the onset of symptoms such as angina, shortness of breath, or syncope. Older adults may also present with decreased activity levels, a delayed onset of symptoms, or relate their symptoms to other coexisting conditions.[3,4]

In aortic valve disease, mild fibrocalcific changes to the leaflets progress to active bone formation on the aortic valve. Disorganized collagen fibers, presence of inflammatory cells, proteins of extracellular bone matrix, and bone minerals suggest that this is a chronic inflammatory process.[5] Calcification of the valve cusps causes increased valvular stiffness and narrowing with associated increased aortic gradient leading to left ventricular wall thickening and hypertrophy. Sustained hypertrophy and pressure over time contribute to diastolic dysfunction and ventricular strain, resulting in left ventricular failure.[6]

The Cardiovascular Health Study and the Multi-Ethnic Study of Atherosclerosis have shown that clinical risk factors for degenerative aortic valve stenosis may mirror those associated with coronary atherosclerosis.[7] Traditional cardiovascular risk factors such as age, male gender, smoking, high cholesterol, hypertension, and metabolic syndrome have been associated with the development and progression of AS.[8] However, these have been mere associations but have not been determined to be causative factors. Furthermore, treatment with medications such as β blockers or statins to reduce aortic calcification and thereby to prevent the progression of AS has been disappointing.[9] While initial studies showed some benefits, a recent meta-analysis showed that statins had no effect on aortic valve structure, calcification, or clinical outcomes in severe AS.[9] There is some promise for other medications such as angiotensin-converting enzyme inhibitors as some studies have shown changes in hemodynamics due to improved left

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ventricular unloading, although this requires further investigation.[10,11]

The cardiovascular risk factors only account for a third of the population-attributable risk for AS for the aging population.[12] Congenital calcific AS, which primarily results from the disturbed expression of genes that are involved in normal heart valve development, is another powerful risk factor. However, advances in the identification of these defects and in the associated care for infants suffering from congenital AS have helped to recognize these conditions early on. Accordingly, a large knowledge gap exists, which has important implications for our ability to understand the pathophysiology of AS, as well as for our ability to prevent it. The pathogenesis of calcific aortic valve disease, whether acquired or congenital, is likely due to the interplay of genetic and environmental influences, even though the precise mechanisms are not known.

The aortic valve consists of an outer layer of valve endothelial cells, surrounding three layers of extracellular matrix each peppered with valve interstitial cells.[13] Changes in the functionality of the matrix components can potentially lead to AS, since the proper organization of extracellular matrix is essential in maintaining valve morphology and normal function. Any derangement in the extracellular matrix can have detrimental effects on valve function.[14]

The histopathologic heterogeneity of AS indicates the involvement of diverse cell-dependent mechanisms that regulate calcium load on the valve leaflets.[15] For example, woven and lamellar bone with osteoblast matrix production and vascularization has been noted in calcified aortic valves.[16] Endothelial dysfunction at the valve leads to lipid deposition in the subendothelium where they are oxidized and factors such as oxidized low-density lipoprotein are formed. Inflammatory cells, such as monocytes, infiltrate the valve tissue and form foam cells by lipid phagocytosis.[17] Inflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin 1-β, advanced glycosylation end products, and oxidized low-density lipoprotein further promote remodeling of the extracellular matrix.[18,19] On the contrary, healthy valves are devoid of macrophages and the expression of TNF-α is low. Furthermore, in severe calcific AS, fibroblasts differentiate into myofibroblasts with an osteoblast-like phenotype and cause valvular calcification.[20] Reactive oxygen species, specifically hydrogen peroxide, also have a pro-osteogenic role in AS, and several enzymatic mechanisms that counteract oxidative stress are downregulated in valves during the pathogenesis of calcific AS.[21] Additionally, one of the earliest events in AS, following endothelial cell dysfunction, is the accumulation of lipids and subendothelial matrix at the ventricular surface of the valve with the displacement of the elastic lamina while plaque-like subendothelial deposits settle on the aortic surface of the valve.[22]

Another pathway that influences calcium deposition on the aortic valve is the osteoprotegerin/RANKL pathway.[23] RANKL is highly expressed in AS, while it is not expressed at relevant levels in healthy valves, whereas osteoprotegerin is present in normal valves but levels decrease with the progression of AS. Osteoprotegerin profoundly attenuates valve calcification by decreasing levels of proteins such as osterix, osteocalcin, and monocyte-chemoattractant protein-1 which are involved in the osteogenic transformation. The balance of matrix proteins that promote or inhibit calcifications is altered during the disease continuum from healthy valves to calcified ones due to the progressive increase in the gene expression of osteopontin (OPN) and bone sialoprotein II with a progressive decrease of osteoprotegerin.[24]

Moreover, abnormalities in genes that contribute to the development and function of heart valves are known to contribute to congenital calcific AS. This occurs most often in patients with bicuspid aortic valves. One of the most common abnormalities involves the Notch and Wnt pathways. Crosstalk between these two signaling pathways plays an important role in preventing valvular calcification. A heterozygous loss of function mutation of NOTCH1 leads to expression bone morphogenic protein-2 and β-catenin stabilization and signaling, promoting valvular calcification.[25]

Numerous biomarkers have been suggested for following the pathogenesis of aortic valve disease. Fetuin-A, an inhibitor of soft tissue calcification, seems to be a good candidate as its serum levels show a strong inverse correlation with the extent of valve degeneration and calcification.[26] Fetuin-A is believed to suppress the release of TNF-α. Serum level of fetuin-A decreases with aging in AS.[27] Thus, lower circulating levels may mark valve degeneration and subsequent calcification in the elderly.[28] Levels of asymmetric dimethylarginine are also important markers of disease progression in the elderly with higher concentrations and activity levels found in patients with severe AS.[29] Recently, levels of matrix metalloproteinase-10 (MMP-10) or stromelysin-2 have been proposed as another marker of disease progression. MMP-10 is involved in vascular atherosclerosis through Akt protein kinase B proliferation and is hypothesized to play a pathophysiologic role in calcific AS.[30]

Another marker, osteopontin, is directly associated with the ectopic calcification process which occurs during the latter stages of calcific AS. OPN is an extracellular matrix protein that also plays an integral role in myocardial remodeling. Thus, it is also of interest in patients who undergo valve replacement as higher levels of OPN have been associated with adverse outcomes after transcatheter aortic valve replacement.[31] There appears to be a correlation between high levels of OPN and worsening concentric myocardial hypertrophy in AS patients which in turn could complicate post-replacement care.

In conclusion, the pathophysiologic insult in AS is an active cellular process, which includes lipoprotein deposition, chronic inflammation, and fibrocalcific tissue remodeling. Changes to calcium homeostasis further affect calcium deposition on the valve which eventually leads to AS with age. Therefore, aortic valve calcification is a highly active and regulated process of biomineralization, sharing similarities with bone formation. Recently, our focus has been on fixing the severely calcified valve: a mechanical solution for a mechanical problem. There has been a steady reduction in the risk of aortic valve replacement and the introduction of

less invasive transcatheter options has further improved outcomes. However, as we shift from thinking of calcific AS as a passive degenerative process to one characterized by active biology, we have yet to identify interventions that are effective at preventing its initiation or progression. As we continue to learn more about the pathophysiology of this ancient disease process, we need to identify processes and interventions to slow it down.

Conflict of Interest
None declared.

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