

The Pathogenesis of Aortic Stenosis
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Aortic valve disease is the third most common cardiovascular disease in the United States, exceeded only by hypertension and coronary artery disease. Approximately 2% to 7% of the population older than 65 years has aortic stenosis, and calcific aortic stenosis is the most common indication for valve replacement. Despite its prevalence, the pathogenesis of calcific aortic stenosis is not well understood. In particular, the cellular mechanisms by which the aortic valve leaflets become calcified are unclear.

Calcific aortic stenosis has traditionally been considered a “degenerative” process with passive accumulation of calcium on the aortic valve leaflets. Recently, however, separate lines of investigation have begun to coalesce, suggesting that the pathogenesis of calcific aortic stenosis may be an active biologic process.

One such line of investigation includes epidemiologic studies which have identified several clinical risk factors for the development of aortic stenosis including hypertension, hyperlipidemia and diabetes mellitus. Importantly, these same clinical risk factors are also associated with atherosclerosis. It is now appreciated that inflammatory mechanisms initiate and perpetuate atherosclerosis on a cellular level. Hence, it is logical to postulate that given the similarity of clinical risk factors for the development of aortic stenosis and atherosclerosis, the cellular mechanisms of the two disease states may have common features as well (i.e.: mechanisms of inflammation). It is therefore noteworthy that patients with aortic stenosis have circulating evidence of systemic inflammation such as elevated C-reactive protein and elevated levels of circulating soluble adhesion molecules.

Such clinical investigations are supported by studies in which histological evidence of inflammation has been found in calcified aortic valve leaflets removed at the time of aortic valve replacement. Early aortic valvular lesions demonstrate lipid accumulation as well as an infiltrate of chronic inflammatory cells such as macrophages, mast cells and T lymphocytes. Histological data such as these provide circumstantial evidence that mechanisms of inflammation may play an important role in the pathogenesis of aortic stenosis.

In another line of investigation, histological evidence of active bone formation has been found in aortic valves removed at the time of aortic valve replacement. The calcified aortic leaflets have features which resemble the osteogenic bone formation found in skeletal bone. Skeletal bone formation is dependent upon osteoblasts which create a mineralized extracellular matrix. Osteoblast cells are phenotypically characterized by several proteins associated with bone formation including osteopontin, osteocalcin and bone sialoprotein. Using RT-PCR, increased mRNA levels for all of these have been found in calcified aortic valves. Such data indicate that bone-forming cells (osteoblasts or osteoblast-like cells) are present in calcified aortic valve leaflets, and in fact, are responsible for the calcification. The origin of the bone-forming cells is not known.

Taken together, these background studies strongly suggest that calcific aortic stenosis is (1) an inflammatory disease and (2) the process of calcification results from active bone-like formation. The fact that calcified aortic valve leaflets have a histological appearance consistent with bone formation suggests that calcific aortic stenosis is a process of active bone formation rather than a passive degenerative process. This implies that bone-forming cells (osteoblasts or osteoblast-like

cells) may be responsible for the calcification, and that some cells within the valve may have the potential to become osteoblast-like. However, the origin of such cells is unknown.

The normal human aortic valve leaflet is a gossamer structure. It is primarily comprised of a single layer of endothelial cells on both the aortic surface and the ventricular surface overlying a very thin matrix of collagen and elastin fibrils. Interspersed among the collagen and elastin fibrils are cells. Some of these cells are fibroblasts, but the predominant cell type has a phenotype with features of both myoblasts and fibroblasts, hence it is called a myofibroblast. These myofibroblasts are referred to as aortic valve interstitial cells (AVICs).

The AVIC is a biologically active cell, and has been implicated in the pathogenesis of aortic stenosis. These cells have been shown to express toll-like receptors (TLRs) 2 and 4. Toll-like receptors are phylogenetically preserved components of the innate immune system, and mediate many mechanisms of inflammation; the central role of TLRs, specifically TLR2 and TLR4, in the mediation of inflammatory stimuli is well recognized. Toll-like receptor signaling induces gene transcription and its downstream effects, which include cytokine, chemokine and adhesion molecule production, are mediated through NF- κ B. While the role of TLRs in atherosclerotic mineralization has been investigated, insight into the inflammatory TLR signaling in heart valves has only recently emerged. To this end, it is important to note that NF- κ B also has a central role in controlling the expression of genes associated with bone mineralization.

Our laboratory utilizes isolated human AVICs from normal and stenotic aortic valves to study the pathogenesis of aortic stenosis. Our work to date suggests that these cells may change their phenotype to one consistent with a bone-forming cell in response to pro-inflammatory stimulation. We hypothesize that these cells play an important role in the pathogenesis of aortic stenosis.