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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Calcification in Aortic Stenosis

The Skeleton Key

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ABSTRACT

Aortic stenosis is a common, potentially fatal condition that is set to become an increasing public health burden. Once symptoms develop, there is an inexorable deterioration with a poor prognosis. Despite this, there are no medical therapies capable of modifying disease progression, and the only available treatment is aortic valve replacement, to which not all patients are suited. Conventional teaching suggests that aortic stenosis is a degenerative condition whereby "wear and tear" leads to calcium deposition within the valve. Although mechanical stress and injury are important factors, it is becoming increasingly appreciated that aortic stenosis is instead governed by a highly complex, regulated pathological process with similarities to skeletal bone formation. This review discusses the pathophysiology of aortic stenosis with an emphasis on the emerging importance of calcification, how this can be visualized and monitored using noninvasive imaging, and how our improved knowledge may ultimately translate into novel disease-modifying treatments.
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Aortic stenosis is the most common form of valve disease in the Western world and is set to become an ever-increasing public health burden (1,2). Despite this, there are no medical therapies to halt or delay disease progression, and the only available treatment is aortic valve replacement or implantation, to which not all patients are suited. There is, therefore, a major unmet clinical need to identify pharmacological treatments capable of modifying this disease process.

Aortic stenosis was long considered to be a degenerative condition whereby "wear and tear" resulted in progressive calcium formation within the valve. Although mechanical stress and injury remain central to its pathophysiology, emerging evidence has indicated that aortic stenosis develops as part of a highly complex and tightly regulated series of processes, each of which may be amenable to medical intervention (3). In particular, aortic stenosis can be divided into 2 distinct phases: an early *initiation phase* dominated by valvular lipid deposition, injury, and inflammation, with many similarities to atherosclerosis, and a later *propagation phase* where pro-calcific and pro-osteogenic factors take over and ultimately drive disease progression (**Figure 1**) (4). This review discusses the pathophysiology of aortic stenosis, with an emphasis on the emerging importance of calcification, how this can be imaged with modern noninvasive techniques, and how our improved knowledge might ultimately lead to the development of novel therapies.

PATHOLOGY OF AORTIC STENOSIS

INFLAMMATION, LIPIDS, AND THE INITIATION PHASE OF AORTIC STENOSIS. Under normal circumstances, the aortic valve is composed of 3 leaflets, each of which is a thin (<1 mm), smooth, flexible, and

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ABBREVIATIONS AND ACRONYMS

BMP = bone morphogenetic protein

CT = computed tomography

FDG = fluorodeoxyglucose

LDL = low-density lipoprotein

OPG = osteoprotegerin

PET = positron emission tomography

RANK = receptor activator of nuclear factor kappa B

RANKL = receptor activator of nuclear kappa B ligand

TGF = transforming growth factor

VIC = valvular interstitial cell

mobile structure (3). In aortic stenosis, these leaflets become thickened, fibrosed, and calcified, resulting in reduced leaflet mobility and progressive valvular obstruction.

The early stages of aortic stenosis are in many ways similar to atherosclerosis. Indeed, the 2 conditions share many common risk factors, with large longitudinal studies consistently demonstrating that the *incidence* of aortic stenosis is linked to factors such as smoking, age, and hypertension (5–7). As in atherosclerosis, endothelial damage due to increased mechanical stress and reduced shear stress is believed to be the initiating injury, perhaps best illustrated by bicuspid valve disease. The characteristic 2-leaflet structure of these valves results in less efficient dissipation of mechanical stress and accelerated endothelial damage, so that patients almost universally develop aortic stenosis and display more rapid disease progression (8).

Following endothelial damage, the same lipids implicated in atherosclerosis infiltrate the valve, in particular, lipoprotein(a) and oxidized low-density lipoprotein (LDL) cholesterol. Consequently, observational studies have identified cholesterol and its related lipoproteins as independent risk factors for the development of aortic stenosis (5–7,9). Indeed, a strong genome-wide association was recently established between a single-nucleotide polymorphism in the locus of lipoprotein(a) and the incidence of aortic valve calcification (10). Progressive endothelial injury and lipid oxidization then establishes an inflammatory response within the valve that is characterized predominantly by infiltration of macrophages, but also involves T lymphocytes and mast cells (11). At this early stage, regions of stippled microcalcification that colocalize with sites of lipid deposition are observed (11). The formation of these microcalcifications may be mediated by cell death and the release of apoptotic bodies in these areas. Such apoptotic bodies are similar to the matrix vesicles found in bone, which contain the prerequisite components for calcium crystal deposition (including calcium and inorganic phosphate ions) and facilitate the formation of needle-like crystals of hydroxyapatite (4,12). In bone, as these hydroxyapatite crystals expand, they pierce the outer membrane of the vesicle and become exposed to the extracellular environment, thereby forming nucleation sites for further calcium deposition. It is probable that similar processes also occur within the valve (13). Furthermore, hydroxyapatite deposition evokes further proinflammatory responses from macrophages, creating a positive feedback loop of calcification and inflammation in the early stages of disease (14). It seems likely that these mechanisms underlie early calcium formation in aortic stenosis and its association with lipid and inflammation.

The apparent link between lipid, inflammation, and calcification in these early stages and the pathological similarities with atherosclerosis led to the hypothesis that statins might be beneficial in patients with aortic stenosis. This was supported by encouraging nonrandomized human data (15) and studies in hypercholesterolemic animal models demonstrating that lipid deposition and oxidative stress precede the conversion of valvular interstitial cells to those with an osteoblastic phenotype, and that this process is inhibited by atorvastatin (16,17). However, when statins were formally tested in 3 independent randomized controlled trials of patients with aortic stenosis, each demonstrated a failure of this therapy to halt or retard aortic stenosis progression, despite reducing the serum LDL cholesterol concentrations by more than one-half (18–20). This has led investigators to re-examine the pathophysiology underlying aortic stenosis and to the realization that although inflammation and lipid deposition may be important in establishing the disease (the initiation phase), the later stages are instead characterized by an apparently self-perpetuating cycle of calcium formation and valvular injury (the propagation phase) (4). Indeed, once this propagation phase has become established, disease progression is dictated neither by inflammation nor by lipid deposition, but rather by the relentless accumulation of calcium in the valve leaflets. This may explain the failure of statins to modify disease progression in aortic stenosis, which commonly presents beyond the initiation phase. Moreover, there is some data that statins may even be procalcific in the vasculature (21,22).

CALCIFICATION AND THE PROPAGATION PHASE. Skeletal bone formation is characterized by the initial deposition of collagen matrix, which provides a scaffold upon which progressive calcification can develop. With time, this calcium acquires a more ordered crystalline structure until the characteristic features of lamellar bone are finally observed. Similar structural processes are believed to occur in the aortic valve, with many of the same cell mediators and proteins implicated (23). Indeed, in aortic stenosis, collagen is deposited in anticipation of the procalcific processes that subsequently dominate. This fibrotic process within the valve may be mediated, in part, by reduced nitric oxide expression following endothelial injury (24); however, the renin-angiotensin system (RAS) is also believed to play a central

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