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Commentary: Closing in on aortic stenosis

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CENTRAL MESSAGE

Continued characterization of the interactions between the biomechanical and molecular mechanisms behind degenerative calcific aortic stenosis may lead to effective preventative treatment strategies.

Jarrett and colleagues[1] have methodically contributed to a better understanding of the complex processes underlying degenerative calcific aortic stenosis (AS). In this most recent investigation, they build upon previous work, which established (1) a differential response of aortic valve interstitial cells (AVICs) to Toll-like receptor 4 stimulation, inducing an inflammatory osteogenic phenotype characteristic of degenerative AS,[2] and (2) the downregulation of this process by simvastatin.[3] In rigorously demonstrating the anti-inflammatory effect of simvastatin on mechanistic pathways leading to Toll-like receptor 4–induced osteogenic activity and corresponding calcium deposition in human AVICs in vitro, the group of Jarret and colleagues adds degenerative AS to the growing list of pathologies associated with aging and frailty resulting from chronic inflammatory states.

However, the significance of these findings goes well beyond the notion of prophylactically treating degenerative AS with statins. The processes identified experimentally with calcific degenerative AS are multiple and variegated, including endothelial dysfunction, inflammation, endothelial–mesenchymal-transition, angiogenesis, apoptosis, extracellular matrix remodeling, fibrosis, and osteogenesis.[4] Although the premise that degenerative AS could be prevented simply with the early use of statins is plausible, this "magic bullet" would seem improbable, particularly since there is no convincing evidence that a lower incidence of AS has been observed among the vast number of individuals taking statins for cardiovascular risk reduction.

Although the relative prevalence of AS among cardiovascular disease is significant and growing with the aging population, it presently only comprises 2.8% of those aged 75 years or older,[5] rendering impractical the notion of broadly prescribing statins solely to prevent degenerative

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AS. Obtaining a more granular view of the metabolic processes behind degenerative AS is essential in identifying potential metabolic marker profiles associated with an increased inflammatory propensity for AS and developing new anti-inflammatory agents more specific to the osteogenic processes linked to AS and other degenerative disease states.

Although the notion that degenerative AS is simply the result of mechanical wear and tear is generally accepted as overly simplistic, more refined investigation of the complex biomechanical forces sustained by the aortic valve supports the notion that mechanical stresses, particularly abnormal ones such as observed in bicuspid aortic valve disease, may act to trigger and sustain inflammatory degradative processes. For example, Carrion, Patel, and others have reported that the increased biomechanical cyclic strain experienced by bicuspid aortic valve leaflets is associated with decreased expression of specific microRNAs, a class of short noncoding RNAs, leading to increased expression of inflammatory and calcification-associated genes in human AVICs.[6,7] One might speculate that further characterization of structural characteristics and conformations of aortic valve leaflets associated with abnormal cyclic shear stresses and strain may lead to the early identification of patients at risk for developing degenerative AS using advanced imaging techniques (eg, echocardiography, computed tomography).

Jarrett and colleagues should be commended for conducting high-quality, translational research addressing a growing segment of heretofore unpreventable cardiovascular disease. The larger challenge, however, will be elucidating the specific interactions between the biomechanical and molecular mechanisms behind degenerative AS and the relative contributions and amelioration of predisposing risk factors.

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