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EDITORIAL COMMENT

Is it Time for a New Paradigm in Calcific Aortic Valve Disease?*

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At an average heart rate of 70 beats/min, the aortic valve in a 70-year-old patient will have opened and closed, incessantly, over 25 million times. It is not surprising then that calcific aortic valve disease (CAVD), which becomes clinically apparent only late in life, was previously considered a degenerative process. Now, CAVD is known to be—on the basis of research over the past 2 decades, including histopathologic, epidemiologic, and animal studies—a complex, biologically active process with many mechanistic similarities to atherosclerosis but also with key differences. Yet despite this recent understanding, valve replacement surgery remains the only proven therapy for this disease.

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It is not coincidental that advances in CAVD biology paralleled advances in noninvasive imaging. Two-dimensional echocardiography enables direct, in vivo visualization of valve anatomy and provides semiquantitative measures of calcification severity. Doppler echocardiography is clinically indispensible in determining the hemodynamic consequences of late stage disease (aortic stenosis) and optimal timing of operative interventions. However, as important as echocardiography has been for understanding CAVD, it is limited in its ability to monitor the progression of early-stage, preobstructive CAVD (aortic sclerosis). Fortunately, complementary imaging modalities are starting to arise. For example, computed tomography is a well-validated tool for quantifying early-stage calcification and measuring progression, although at the expense of radiation exposure.

Large population-based studies such as the echocardiography-based CHS (Cardiovascular Health Study) study (1) and the computed tomography-based MESA (Multi-Ethnic Study of Atherosclerosis) study (2) have identified risk associations between CAVD and several clinical factors, although it is notable that CAVD was not a pre-specified end point for these trials. Many of these risk associations are also coronary artery disease risk factors: age, male sex, hypertension, hypercholesterolemia, the metabolic syndrome, and smoking. Strengthening the paradigm that CAVD is due to an atherosclerosis-like mechanism are histopathologic studies showing cellular inflammation and lipoprotein deposition and hypercholesterolemic animal models of aortic sclerosis.

A natural corollary of the paradigm that CAVD is an atherosclerosis variant was the hypothesis, supported by retrospective analyses, that CAVD progression could be slowed by the same interventions that slow coronary artery disease progression. Yet 2 large randomized clinical trials of statin medications—SALTIRE (Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression) (3) and SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) (4)—failed to slow CAVD progression or delay the clinical sequelae of CAVD in older adults with mild to moderate or more advanced CAVD. It is possible that these trials targeted patients whose disease was too advanced for therapy to be effective, but identifying patients in earlier stages is challenging and would require treating many patients who would never develop clinical disease. In light of the negative results of these large, well designed studies, a new paradigm for CAVD might be needed.

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Although there are mechanistic similarities between atherosclerosis and CAVD, CAVD is not simply atherosclerosis of the valve. Clinicians see many patients with severe aortic stenosis that have little coronary atherosclerosis at the time of valve replacement. Whereas the hallmark of atherosclerosis is the unstable lipid-rich plaque, the hallmark of CAVD is severe, progressive calcification that stiffens leaflets and leads to hemodynamic obstruction. More detailed explorations of the nonatherosclerotic mechanisms that contribute to CAVD—such as shear forces, genetic factors, and regulators of myofibroblast differentiation and osteoblastic calcium deposition—are clearly needed. This need was highlighted in a recent study by Miller et al. (5) showing that not only are reactive oxygen species (ROS) increased in calcifying aortic valve leaflets but the primary mechanism of ROS production, uncoupled nitric oxide (NO) synthase activity, might be distinct from that seen in vascular atherosclerotic lesions.

The study by Ngo et al. (6) in the current issue of *iJACC* represents a welcome departure from studying only traditional CAVD risk associations. Two aspects of this study merit special comment. First, the use of integrated backscatter of the aortic valve leaflet as a quantitative measure of aortic sclerosis severity is novel. It is somewhat difficult to interpret the apparent lack of association between CAVD and atherosclerotic risk factors, given the use of this newer echocardiographic approach, the small sample size, and high degree of disease misclassification. However, although this method needs additional validation, it offers potential for a new means of quantifying CAVD in its early stages.

Second, they explore the relationship between CAVD and several indirect measures of NO responsiveness, including asymmetric dimethylarginine (ADMA) concentration—a marker of endothelial dysfunction—and platelet NO resistance. Valvular calcification is a complex interplay between local paracrine factors and systemic regulators of calcium homeostasis. Oxidative stress seems to play a central role in this process, with ROS mediating transcriptional upregulation of the Wnt/β-catenin, Runx2/Cbfa1, and Msx2 pathways that promote osteochondrogenic matrix remodeling and myofibroblast transformation toward osteoblastic phenotypes. As the Miller et al. study (5) highlights, the principle mechanisms of ROS production might be

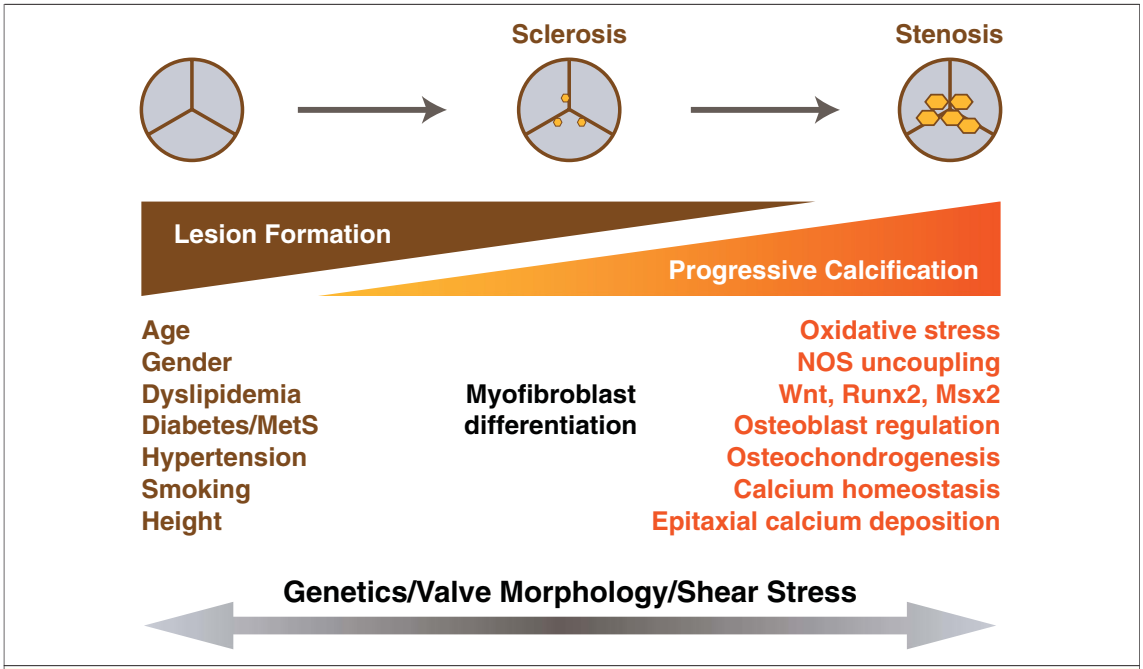

Figure 1. A Potential Paradigm for Understanding CAVD Progression

In early stage calcific aortic valve disease (CAVD), traditional cardiovascular risk factors promote valvular lesions via atherosclerosis-like mechanisms. Increased valvular oxidative injury causes transcriptional upregulation of the Wnt/β-catenin, Runx2/Cbfa1, and Msx2 pathways, promoting myofibroblast transdifferentiation into osteogenic phenotypes. Systemic and paracrine regulators of osteoblast function, calcium homeostasis, and dystrophic epitaxial calcification play an increasing role as calcification progresses. Genetic factors, valve morphology (e.g., bicuspid valves), and shear stress likely contribute to disease progression across the full spectrum of disease. MetS = metabolic syndrome; NOS = nitric oxide synthase.

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tissue-specific, with uncoupled NO synthase activity playing a central role in the production of valvular ROS. But calcification can also occur through noncellular mechanisms by means of epitaxial calcification, and both osteopontin and fetuin—local and systemic inhibitors of calcification—might be important regulators of this process.

The positive finding of an association between aortic valve integrated backscatter intensity and platelet NO resistance is intriguing. It is possible that the systemic or genetic mechanisms underlying platelet NO resistance (e.g., scavenging of NO by superoxide species) are associated with increased ROS within the aortic valve leaflets. Additionally, platelet NO serves as an inhibitor of platelet aggregation, and NO resistance implies a pro-thrombotic milieu for CAVD patients. It has been previously shown that aortic sclerosis is associated with a 50% increased risk for cardiovascular morbidity and mortality (7), a finding that has been attributed to subclinical atherosclerosis, inflammation, or other mechanisms. This current study points toward another potential mechanism: underlying NO resistance might predispose to both valvular calcification and thrombotic events. Additional confirmatory and mechanistic studies are clearly needed.

Over the next several decades, as the population of the U.S. and the world ages, CAVD will become increasingly prevalent and clinically manifest. Although we now know that CAVD is a biologically active process with many similarities to atherosclerosis, the atherosclerosis paradigm has failed to identify effective medical therapies to slow or prevent CAVD progression. If such therapies are to be developed, it is time for a new paradigm (Fig. 1) to stimulate new thinking and new insights into the varied and overlapping mechanisms that regulate lesion formation, myofibroblastic transformation, and calcification progression.

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