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Introduction to the Compendium on Calcific Aortic Valve Disease

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Once symptoms arise, stenotic aortic valve disease leads rapidly to death unless surgical or interventional replacement is performed. Already the most prevalent form of valvular heart disease in the Western world, fibrocalcific aortic valve disease affects 25% of those over age 65 (1), and its incidence is growing inevitably as our population ages. Valve replacement is second only to coronary bypass surgery, among operations on the heart. FDA approval of percutaneous transcatheter aortic valve replacement this past year has sparked growing interest in the underlying pathophysiology of the disease. According to many of our textbooks, aortic valve stenosis results from an inevitable, degenerative disorder of aging, due solely to mechanical "wear and tear." However, with advances in experimental models, and based on pioneering work by Mohler (2), Otto (3), and Rajamannan (4), recent research findings are now converging on a major shift in paradigm, with inflammation and atherogenic phenomena as the emerging mechanisms.

The goal of this Compendium, -- the first of its category in *Circulation Research* -- is to update investigators and clinicians on the dramatic changes in our understanding of aortic valve disease, through a series of reports covering the spectrum of research, from basic science in valvular interstitial cells, and molecular mechanisms in animal models, to epidemiology of populations and clinical trials in patients.

Carabello (5) opens the series with an historical perspective on the "new" disease of aortic valve stenosis. With rheumatic fever no longer a major cause of aortic stenosis in developed countries, patients now present at older ages resulting in changes in the natural history, clinical signs, and co-morbidities. He addresses mechanisms such as hemodynamic stress and inflammation that account for the new clinical manifestations. He also comments on the team-based, interventional option, now available for advanced stages of disease, in which a mechanical valve is inserted via a catheter within and, like a stent, expanded over the diseased valve.

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In their contribution on hemodynamic and cellular response feedback, Gould, Srigunapalan, Simmons and Anseth (6) report on the mechanically hostile environment facing valves, including shear, bending, tensile, and compressive forces, and how the effects of these stresses depend on the intrinsic mechanical properties of the extracellular matrix. They describe how the growth of calcific nodules on the aortic faces of the cusps in fibrocalcific aortic stenosis depends on the degree to which stress is transferred to the cytoskeleton, which, in turn, depends on extracellular matrix compliance. Based on results from computational, finite element models, and ex vivo and in vitro experiments, they describe properties and responses specific to the aortic vs. ventricular surfaces of the cusps, paying particular attention to differential endothelial cell adaptation to shear stress which could account for differences in disease manifestation. They also describe interactions between mechanical events and paracrine signaling, focusing on the role of transforming growth factor-β in modulating normal and pathological responses of valvular interstitial cells.

Towler (7) details the molecular and cellular signaling events that promote mineralization and ectopic bone formation in the valve, with an emphasis on similarities to, and distinctions from, bone mineralization; the potential roles of circulating osteoprogenitor cells, morphogens, and endothelial-mesenchymal transformation; the complexity, heterogeneity, and multiple cells involved; as well as spatial and mechanical differences favoring almost exclusive expression of disease on the aortic surface of the cusps. Like Gould, Srigunapalan, Simmons and Anseth (6), he makes the intriguing point that the rigid plastic substrate in conventional tissue culture is a better model for the mineralized matrix in calcific aortic valves than for the compliant matrix of normal valves.

In their discussion of mouse models, Weiss, Miller, and Heistad (8) review current techniques for assessing aortic valve function in mice, and point out how errors in echocardiography may lead to misdiagnosis of presence and severity of aortic stenosis in this animal model. They emphasize that fibrocalcific changes in the aortic valve may be associated with aortic regurgitation as well as stenosis. They further describe genetic mechanisms that result in bicuspid aortic valves and in postnatal predisposition to development of aortic stenosis. They address mechanisms by which oxidative stress, epigenetic modification, inflammation and angiogenesis may contribute to the pathogenesis of valve disease in the context of ageing, hypertension and genetic causes.

Lindman, Bonow, and Otto (9) incorporate these considerations into state-of-the-art clinical management of aortic stenosis, including risk assessment based on blood tests, calcium mass, and stress testing; explanations for how the classification of severity depends on functional and hemodynamic context; the approach to concomitant hypertension and its effect on left ventricular hypertrophic remodeling, with a focus on the renin-angiotensin system; as well as indications for surgical and percutaneous transcatheter interventions, and their limitations in the face of ventricular fibrosis or hypertrophy.

Altogether, this Compendium builds a comprehensive new picture of aortic valve disease, from different expert perspectives all converging on the view that the process is regulated, rather than degenerative, with emerging opportunities for new forms of treatment, intervention, and, potentially, prevention.

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