Circulation: Cardiovascular Imaging

EDITORIAL

Myocardial Hypertrophy, Matrix Expansion, and Focal Scar

Progression and Regression in Aortic Stenosis

See Article by Everett et al

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Severe aortic stenosis (AS) is common. Once symptomatic or left ventricular (LV) impairment develops, current guidelines recommend aortic valve replacement (AVR) to improve survival and symptom status.[1] But the pathogenesis of symptoms may be difficult to ascertain in the elderly with multiple comorbidities, and indeed, LV impairment may be late—occurring potentially after irreversible changes have occurred in the heart, which in turn may result in residual risk to patients even after AVR. The current focus of AS management remains the valve itself; however, during the last decade, there has been increasing recognition of the importance of the myocardium. The stenosed valve is the insult—necessary but perhaps not sufficient to cause the adverse consequences of AS. How the myocardium responds is equally important and may determine the urgency of intervention. The myocardium itself is adaptable but there are limits. In response to afterload, early changes are benign and physiologically appropriate with myocardial cellular hypertrophy and proportionate extracellular matrix expansion to maintain wall stress. However, the afterload of AS is proximal to the coronary origins so reduction of microvascular function starts with reduced capillary density, compensatory vasodilation, and impaired myocardial blood flow—so even if myocytes were infinitely adaptable, compensation through adaptation cannot be indefinite.[2,3] Further, increasingly maladaptive changes occur with cell death by apoptosis or autophagy, microvascular ischemia, alterations of extracellular matrix components (eg, increased collagen I and III deposition),[4] and the development of irreversible microscars particularly in the subendocardium. The combination of an increasingly precarious systemic circulation with its physiological autonomic adaptability lost, and myocardium that is now heterogeneous, ischemic, and arrhythmogenic is dangerous. Arrhythmia becomes increasingly likely and intolerable because of hypoperfusion-related positive feedback. Many of the processes leading to these scenarios are detectable. Transvalvular gradients and by inference myocardial perfusion pressures, LV hypertrophy, and cardiac function have long been measurable. Cardiovascular magnetic resonance (CMR) adds extra information with late gadolinium enhancement (LGE) detecting focal fibrosis and T1 mapping for the derived parameter, that is extracellular volume fraction (ECV), which reflects fibrosis burden and its reciprocal (1–ECV=ICV) reflecting the cell (mainly myocyte) volume.[5,6] These can be expressed either as proportions (ECV in percentage) or as absolute volumes if the ECVs or ICVs are multiplied by the myocardial volume; this matrix volume or iECV is, therefore, obtained by the simple equation of LVM/1.05×ECV (1.05 being the specific gravity of the myocardium). With this armamentarium at our disposal, we can now better interrogate the biology of LV hypertrophy.[7,8]

Key Words: Editorials ■ aged ■ aortic valve stenosis ■ fibrosis ■ humans ■ magnetic resonance imaging

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In the current issue, Everett et al[9] report serial imaging using the above methods in 2 cohorts of patients with AS—1 asymptomatic group (mild, moderate, or severe AS) under a watchful waiting regimen, and 1 symptomatic group undergoing surgical AVR. What they found was that without intervention, the AS severity progressed (by peak velocity and valve area), with increased filling pressures. Myocardial changes were a decrease in longitudinal function, increased hypertrophy (wall thickness, mass), and, importantly, increased amounts of focal fibrosis (LGE). Indeed, there seemed to be an acceleration in AS progression, coupled with scar number and extent. Diffuse fibrosis remained in proportion to cell volume during this phase, however. In the cohort of patients undergoing AVR, LV mass regression did occur because of a reduction in both myocyte and interstitial volume (by the ECV technique)—both parameters demonstrating plasticity and reversibility but with the cellular hypertrophy regression, more (so the ECV rose post-AVR). Scar, however, did not reverse.

The authors should be lauded for delivering a well-conducted cross-sectional, 2-center CMR AS study, with all the challenges of using different MRI field strengths and sequence parameters. The multiparametric approach (LGE and ECV imaging) in the current study provides important pathophysiological insight into the natural history of LV remodeling in AS. The postoperative data confirm the results of the RELIEF-AS study (Regression of Myocardial Fibrosis After Aortic Valve Replacement; NCT02174471) demonstrating in 116 patients at 1-year post-AVR a 19% regression in indexed LV mass, 16% reduction in matrix volume, and a proportionally greater 22% reduction in cell volume with focal fibrosis being irreversible.[8] What is new is the insights into the accumulation over time of LGE—with its near absence in mild AS (with minimal annual change) but increasing accumulation with moderate and severe AS. We know that small amounts of LGE in AS reflect much larger changes in the myocardium—indeed patients with severe AS and LGE on CMR have thousands of microscars, with a subendocardial preponderance and marked thickening of the endocardium[4,10,11] coupled with alterations in the qualitative nature of the fibrosis, its maturity, tensile properties, and collagen subtypes. There may in addition be other processes at play. LGE represents focal interstitial water, usually fibrosis, but it can also be inflammation or amyloid. One recent AVR study showed a 6% prevalence of wild-type transthyretin amyloidosis amyloidosis at biopsy,[12] and 2 recent studies have shown a prevalence of 1 in 7 using bone scintigraphy in (older) patients undergoing transcatheter AVR.[13,14]

Does this matter, and how can we use these insights to improve patient care? Judicious timing of surgical or transcatheter intervention is likely to lead to better outcomes. Intervening too early front-load procedural risk, in some cases, may be unnecessary and may expose patients to ongoing risk (anticoagulation, endocarditis, and valve failure). Conversely, watchful waiting risks the loss of some patients from sudden death, the conversion of elective surgery in stable patients to salvage surgery in decompensation, and, importantly, the potential accrual by patients of risk or limitation that persists postprocedure. There is emerging evidence for this concept of residual risk and of the consequences of delay. Some patients without overt symptoms may be reluctant to undergo surgery, but we need to be careful and look at long-term outcomes. In the CURRENT-AS registry (Contemporary Outcomes After Surgery and Medical Treatment in Patients with Severe Aortic Stenosis), 3-year mortality was 9% in patients who had early AVR compared with 17.9% in propensity-matched patients who were initially managed conservatively.[15] Acute decompensation in watchful waiting strategies is increasingly recognized,[16] and the recently presented AS700 multicenter study suggested that the presence of myocardial scar (present in half of patients with severe AS undergoing AVR) was associated with a doubling of death rates and 3.5 years—the full article is awaited. New approaches are being explored.[17] The EVOLVED-AS study (Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients With Severe Aortic Stenosis; NCT03094143) is currently recruiting to investigate whether we can reduce the incidence of heart failure and death by timing intervention based on the presence of scar by MRI, troponin elevation, or adverse ECG changes before the development of symptoms.

Finally, we remind that although the CMR cell-versus-matrix approach seems relatively new, we acknowledge the pioneering work of Schwarz et al[10] in 1978 who used invasive biopsy to divide LV hypertrophy into cellular and fibrotic components in AS—in the era of CMR, we can now reveal the dynamic changes and track response to therapy. But really, this is not about CMR or techniques—it is about patients. We need to think about AS as a disease of the myocardium where we should be seeking to avoid irreversible AS cardiomyopathy and, if that is unavoidable (first presentation being late in many patients), consider strategies after valve replacement to mitigate residual risk. These approaches may, given how common AS is, yield great improvements in patient outcomes.

ARTICLE INFORMATION

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