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EDITORIAL COMMENT

Parsing the Shades of Gray of Myocardial Fibrosis in Aortic Stenosis

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Earlier intervention is a shared theme across a wide variety of cardiovascular diseases, and valvular heart disease is no exception. Surgical aortic valve replacements (SAVRs) or transcatheter aortic valve replacements (TAVRs) are well established for treating severe aortic stenosis (AS), although contemporary guidelines suggest asymptomatic severe AS intervention may be considered when there is impaired left ventricular ejection fraction <50%, reduced exercise capacity or blood pressure decrease during exercise testing, very high peak systolic velocity ≥5 m/s, elevated brain natriuretic peptides ≥3× upper reference limit, rapid disease progression (≥0.3 m/s annually), and concomitant with other cardiac surgery.[1,2] Recent randomized trials such as AVATAR (Aortic Valve Replacement Verus Conservative Treatment in Asymptomatic Severe Aortic Stenosis) and RECOVERY (Randomized Comparison of Early Surgery versus Conventional Treatment in Very Severe Aortic Stenosis) found SAVR to reduce composite cardiovascular events in selected asymptomatic severe AS patients, while moderate AS intervention trials are ongoing.[3,4] Given the adverse prognosis associated with both moderate and asymptomatic severe AS, there is an impetus to identifying cardiac biomarkers that indicate which of these AS patients may benefit from earlier intervention.

In this issue of *JACC: Cardiovascular Imaging*, Lee et al[5] examined, in a multicenter prospective cohort of 257 asymptomatic severe AS and moderate AS patients, the relationships between interstitial fibrosis and scar quantification using cardiac magnetic resonance (CMR) and 83 death and/or heart failure admission events over a median of 5.7 years of follow-up. AS severity correlated with diastolic dysfunction and left ventricular mass, but not extracellular volume (ECV) and late gadolinium enhancement (LGE) by CMR. However, higher ECV was independently associated with cardiovascular events (HR: 1.05; 95% CI: 1.02-1.11; $P = 0.017$) in multivariable analysis, whereas higher LGE percentage quantification (and not LGE presence or distribution) and lower aortic valve area (using echocardiography) were also adverse imaging prognosticators. Clinical risk factors associated with higher ECV include female gender, higher NYHA functional class, worse renal function, diastolic dysfunction, and higher N-terminal pro-B-type natriuretic peptide. Based on these findings, the authors concluded that CMR characterization of myocardial damage may help identify higher-risk patients needing closer surveillance.

Although CMR has limited clinical roles in grading AS severity, CMR is noninferior to computed tomography angiography in sizing the aortic annulus for TAVR work-up, so is often used in this setting when computed tomography angiography is contraindicated.[6] There is immense recent interest in the concept of "cardiac damage" from AS being associated with worse prognosis, and left ventricular myocardial damage is "stage 1" in this process.[7] CMR is the best cardiac imaging modality for myocardial tissue characterization and scar or fibrosis quantification, with the key sequences being LGE, T1 and T2 mapping, and ECV, and their reference ranges have been published.[8] Although T1 and T2 parametric mapping have the advantages of not requiring gadolinium contrast administration, ECV value and reference ranges are more comparable across scanners because they are less dependent on magnetic field strength, sequence, and imaging parameters. This can be seen in a cohort study of 440 AS preintervention patients undergoing CMR across 10 sites on both 1.5-T and 3.0-T scanners, which demonstrated significant variability in T1 b values, whereas ECV values were consistent

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regardless of field strength or pulse sequence used, and supports ECV being the more standardized method for quantifying myocardial fibrosis.[9]

Prior studies have also identified the prognostic value of CMR myocardial tissue characterization in AS patients. A meta-analysis of 19 studies and 2,032 AS patients found LGE was present in 49.6%, and was associated with higher all-cause and cardiovascular mortality (pooled OR: 3.26 and 2.89, respectively).[10] Another prospective observational study of 127 moderate or severe AS patients with age- and sex-matched controls using 3.0-T CMR found native T1 values to be higher in AS patients, and was independently associated with poor prognosis, along with and incremental to LGE presence and/or extent and EuroSCORE (European System for Cardiac Operative Risk Evaluation) II.[11] The aforementioned multicenter study of 440 preintervention AS patients by Everett et al[9] found ECV to also be independently associated with all-cause mortality (HR: 1.10; 95% CI: 1.02-1.19; $P = 0.013$) adjusting for age, sex, ejection fraction, and LGE. The current study by Lee et al[5] found similar results, and adds to the literature the prognostic importance of ECV specifically in the asymptomatic severe and moderate AS cohort.

Despite this growing evidence for CMR myocardial fibrosis quantification in AS patients, several questions remain unanswered and warrant further investigation. First, in both Lee et al and Everett et al studies, ECVs were reported at 26.6% (24.4%-29.9%) and 27.7% $\pm$ 3.5%, respectively, which significantly overlap with normal ECV values especially when intrareader and inter-reader measurement variability is considered, and challenges clinical applicability.[5,8,9] Second, the optimal prognostic threshold for ECV needs to be determined, along with evaluation of how ECV may impact the management strategy in patients with asymptomatic severe and moderate AS.[5,9] Third, how CMR is integrated into the risk stratification of AS patients alongside clinical features, laboratory biomarkers, and echocardiography requires larger studies and advanced statistical analyses including machine learning. Critically, whether there is benefit in clinical outcomes when SAVR or TAVR is performed earlier in higher-risk AS patients as determined using CMR myocardial tissue characterization is unknown, but needs to be established for these CMR techniques to impact management. Furthermore, given the known resource constraints for performing CMR, do all or which subgroup(s) asymptomatic severe or moderate AS patients warrant CMR evaluation has yet to be determined. Lastly, it remains unclear if serial CMRs documenting the natural history and progression of myocardial fibrosis has clinical utility.

Overall, the authors Lee et al[5] should be commended for their elegant study to enable further risk stratification using CMR in 2 AS populations where their management remains uncertain. These findings expand the clinical application of CMR myocardial fibrosis quantification into valvular heart disease evaluation, and potentially treatment decisions. Further studies are necessary to validate these findings, and more importantly to determine the optimal multimodality cardiac imaging strategy to identifying not only asymptomatic severe and moderate AS patients at high risk, but also who would benefit from early intervention to improve clinical outcomes.

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