Changing the paradigm in the management of valvular heart disease

Fortuni, F.; Bax, J.J.; Delgado, V.

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PERSPECTIVE

Changing the Paradigm in the Management of Valvular Heart Disease

In Addition to Left Ventricular Ejection Fraction, Focus on the Myocardium

Federico Fortuni, MD
Jeroen J. Bax, MD, PhD
Victoria Delgado, MD, PhD

Valvular heart disease (VHD) is a major health problem that affects >2% of the general population.[1] In 2017, the prevalence of calcific aortic stenosis was 12.6 million and caused 102 700 deaths while the number of prevalent cases for degenerative mitral valve disease was 18.1 million and led to 35 700 deaths.[1] Timely diagnosis and risk stratification are pivotal in the decision-making of patients with aortic stenosis and mitral regurgitation. According to current recommendations for these 2 specific diseases, left ventricular ejection fraction (LVEF) is the first parameter to detect the cardiac damage on which further decision making is based. However, calcific aortic stenosis and degenerative mitral regurgitation impose to the left ventricle (LV) a pressure and volume overload respectively, leading to different LV remodeling (the starting point of cardiac damage) to maintain LVEF. In aortic stenosis, the obstruction that the calcified aortic valve poses to the LV outflow, triggers hypertrophic LV remodeling to reduce wall tension and maintain cardiac output. Accordingly, LVEF remains preserved but does not reflect the cardiac damage which is already taking place. In mitral regurgitation, an important fraction of the volume ejected by the LV is directed to the left atrium, which in turn dilates to accommodate the volume overload that eventually flows back into the LV in diastole. As a consequence, the LV dilates to normalize stroke volume and peripheral perfusion, so that LVEF can appear falsely preserved or supranormal for a long time while cardiac damage has already started. When these compensatory mechanisms exhaust, the LVEF starts to reduce and recovery of LV systolic function after valve intervention may not be complete. The development of symptoms and deterioration of LV systolic function do not always coincide and deciding whether the symptoms are caused by the severe VHD is often challenging, particularly in patients with comorbidities (ie, pulmonary disease, chronic kidney disease, obesity). Therefore, it would be very valuable to identify early markers of myocardial damage in severe VHD that can prompt an early referral for intervention.

Myocardial mechanics based on strain imaging and tissue characterization using cardiovascular magnetic resonance (CMR) have provided a large body of evidence on the prognostic importance of assessing the LV myocardial changes that precede the reduction in LVEF and the onset of symptoms in patients with calcific aortic stenosis or mitral regurgitation (Figure).

LV global longitudinal strain derived from tissue Doppler imaging or 2-dimensional speckle-tracking echocardiography measures the LV myocardial shortening and is a more sensitive parameter of LV systolic dysfunction than LVEF. In a recent patient-level meta-analysis, Magne et al demonstrated that a LV global longitudinal strain <14.7% was related with 2.5-fold higher risk of all-cause mortality in 1067 patients with asymptomatic severe aortic stenosis and preserved LVEF.[2] It is important to note that this association remained consistent also in patients with LVEF ≥60%. Similarly, in patients with severe degenerative mitral regurgitation, LV

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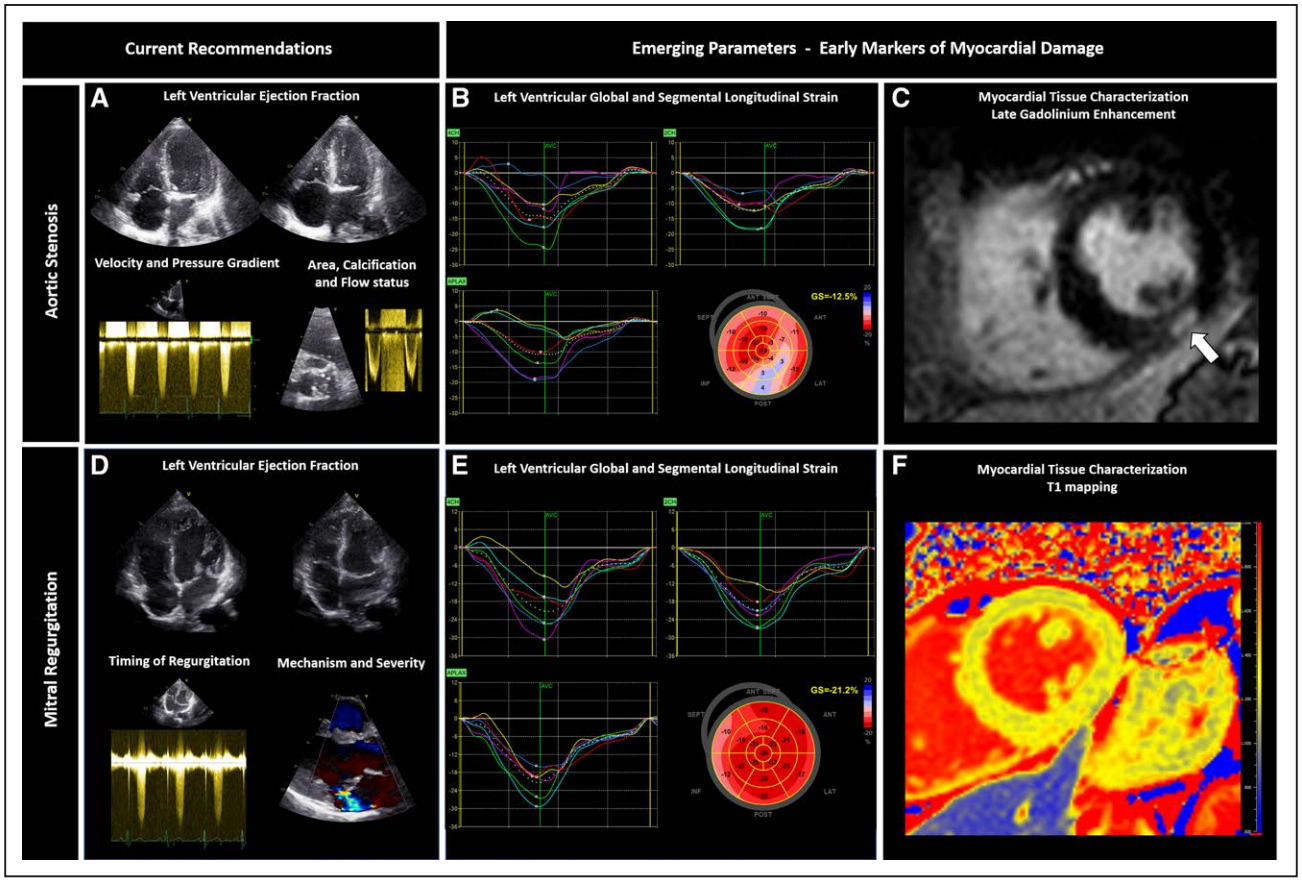

Figure. Imaging markers of cardiac damage in valvular heart disease.
Left, Illustration of a summary of the conventional imaging parameters recommended by current guidelines to evaluate patients with aortic stenosis (**A**) and mitral regurgitation (**D**). **Right** and **center**, Illustrations of the emerging imaging markers of cardiac damage. The center (**B** and **E**) shows the segmental longitudinal strain curves derived from the apical 4-, 2-, and 3-chambers views with the bull's eye displaying the global longitudinal strain and the strain values for the 17 myocardial segments of the left ventricle. The right (**C** and **F**) shows 2 short axis views of the heart acquired with cardiovascular magnetic resonance. **C**, Demonstration of the presence of focal late gadolinium enhancement (white arrow) in the midposterior wall of the left ventricle corresponding to fibrosis. **F,** In contrast, a diffuse increase in the T1 mapping values indicates diffuse nonischemic fibrosis.

global longitudinal strain may be impaired while LVEF is ≥60%. Technological advances have permitted the assessment of LV global longitudinal strain with feature tracking applied to full-cardiac cycle multidetector-row computed tomography and CMR. These changes in myocardial mechanics are partly driven and accompanied by changes in the myocardial tissue.

Tissue characterization with late gadolinium enhancement (LGE) CMR detects the presence of replacement fibrosis and may help to differentiate the LV remodeling due to VHD from the presence of concomitant cardiomyopathies. In a multicenter observational study including 674 patients with severe aortic stenosis undergoing aortic valve replacement, Musa et al showed that the presence of LGE was associated with all-cause mortality independently of LVEF.[3] Each 1% increase in LV myocardial scar (detected with LGE CMR) increased the risk of all-cause mortality by 11% and the risk of cardiovascular mortality by 8%, making LGE a very useful marker for risk stratification. The presence of LGE in patients with degenerative mitral regurgitation has been also associated with poor survival, increased risk of malignant ventricular arrhythmias, and sudden cardiac death.[4] However, before replacement fibrosis occurs, changes in the extracellular matrix with increase of collagen deposition and myofibroblasts (reactive fibrosis) can be detected with T1 mapping and extracellular volume quantification. In a prospective study including 440 patients with severe aortic stenosis from 10 centers across Europe, North America, and Asia, Everett et al demonstrated that each percent increase in extracellular volume was independently associated with a 10% increase in the risk of all-cause mortality.[5]

The cumulative evidence showing that early markers of cardiac damage have incremental prognostic value over LVEF has the potential to change the paradigm in the management of VHD. Although speckle tracking echocardiography and CMR have several theoretical advantages over the sole use of LVEF, it must be acknowledged that they are still underused in clinical practice because of lack of prospective validation, expertise, and availability. The integration of large datasets, machine learning, and ongoing randomized trials incorporating these new technologies in the diagnostic

and therapeutic algorithms of patients with VHD, such as the EVOLVED (Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients With Severe AS) trial (URL: http://www.clinicaltrials.gov. Unique identifier: NCT03094143), will help to establish their role in clinical practice, individualize risk stratification and possibly add on the use of LVEF which represents an unspecific late marker of LV damage.

ARTICLE INFORMATION

Correspondence

Victoria Delgado, MD, PhD, Department of Cardiology, Heart Lung Center, Albinusdreef 2 2300 RC Leiden, the Netherlands. Email v.delgado@lumc.nl

Affiliations

Department of Cardiology, Leiden University Medical Center, 2300RC Leiden, The Netherlands (F.F., J.J.B., V.D.). Department of Molecular Medicine, University of Pavia, Pavia, Italy (F.F.).

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