EDITORIAL COMMENT

Usefulness of advanced cardiovascular imaging in aortic valve replacement. Ready for prime time?

Utilidade da imagiologia cardiovascular avançada na substituição valvular aórtica. Pronta para o horário nobre

Luís M. Moura

Centro de Investigação em Tecnologias e Serviços de Saúde (CINTESIS), Faculty of Medicine, Department of Medicine, University of Porto, Porto, Portugal

Over the last decade, research into left ventricular (LV) structure and function in patients with aortic stenosis (AS) has increased, due to improvements in imaging modalities and potential therapies. This has prompted a focus on sub-clinical changes in LV function, as well as the degree of reversibility of LV structural changes in advanced stages of AS. These factors may influence the optimal timing of valve intervention.

In this issue of the Portuguese Cardiology Journal, Azevedo et al. sought to compare cardiac magnetic resonance (CMR) assessed global radial strain (GRS), global circumferential strain (GCS), and global longitudinal strain (GLS) in AS patients with preserved LVEF before and after aortic valve replacement and to explore its clinical utility for detecting LV systolic function changes in LV reverse remodeling.[1]

Assessing the consequence of aortic stenosis for the left ventricle

The magnitude of LV hypertrophy (LVH) is poorly linked to AS severity,[2] suggesting that other factors are also involved in its development. Age, gender, angiotensin-converting enzyme I/D polymorphism, co-existing coronary artery disease and hypertension are additional factors influencing LV response to AS.[3] Histopathological studies have shown that myocardial fibrosis in particular is an integral part of myocardial disease progression in AS.[4] The mechanisms governing the development and progression of myocardial fibrosis (MF) are not fully understood. Myocardial fibrosis has traditionally been categorized as diffuse interstitial fibrosis (appears to be reversible with afterload relief) or replacement fibrosis (myocyte necrosis).

LV remodeling characterization

Echocardiography is the first line and the most commonly used imaging technique to assess patients with AS. Linear LV dimensions must be measured to calculate the LV mass and LV mass index for LV remodeling classification,[5] however it has several limitations relative to CMR (poor acoustic windows, misaligned LVs, difficulties in delineating the posterior wall, inaccurate estimation of the LV mass in the presence of asymmetrical hypertrophy, etc.).

Certain remodeling patterns are associated with a worse outcome, and there may be sexual dimorphism in the myocardial response to AS.[6]

Left ventricular fibrosis, left ventricular diastolic and systolic function

Left ventricular fibrosis in AS was first described in histopathologic studies as part of the hypertrophic response:

E-mail address: luismoura@med.up.pt

increasing myocyte size eventually leads to myocyte apoptosis and subsequent replacement fibrosis, possibly explaining the transition from hypertrophy to heart failure.[7] In AS, MF, defined as a significant increase in the collagen volume fraction of myocardial tissue, is a complex process involving at least three main alterations: endocardial thickening, subendocardial microscars, and diffuse interstitial fibrosis.[8]

Although myocardial biopsy is the gold standard to diagnose MF, it is invasive and has some limitations (mainly sampling errors and the inability to assess MF globally). Cardiac magnetic resonance is the only non-invasive alternative that enables direct global assessment of MF,[9] using two approaches: late gadolinium enhancement (LGE) and myocardial T1 mapping. LGE enables the quantification of focal interstitial expansion, with direct visualization of focal replacement fibrosis, whereas myocardial T1 mapping assesses the diffuse interstitial expansion of fibrosis.

Replacement fibrosis is detected with CMR using LGE. Beta gadolinium-based contrast agents partition into extracellular space and wash out of areas of focal fibrosis slower than healthy tissue. Multiple studies have consistently shown strong independent associations between ischemic and non-ischemic LGE and both cardiovascular and all-cause mortality. Furthermore, the development of non-ischemic LGE in AS appears to serve as an objective marker of LV decompensation and portends further rapid progression of fibrosis burden.[10] Importantly, this fibrosis does not regress after aortic valve replacement (AVR);[8,10] the burden of scarring that develops while awaiting surgery persists in patients for life. This is important because the greater the MF, the worse the long-term prognosis is.[11]

The detection of LGE in AS may therefore offer incremental prognostic information. Clinical implementation of LGE to optimize the timing of aortic valve intervention is being tested in the randomized EVOLVED-AS trial (Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients with Severe AS, Clinical Trials.gov 03094143).[12]

Unlike LGE, which is insensitive for the detection of diffuse interstitial fibrosis, T1 mapping techniques can provide overall assessments of the extracellular compartment. While providing a close surrogate assessment of myocardial fibrosis,[12] these markers are also affected by other extracellular factors including edema and capillary volume. The most studied methods are native T1, which does not require gadolinium contrast, and extracellular volume fraction (ECV%).[13] T1 mapping has provided important insight into the myocardium in AS, most notably the potential for diffuse fibrosis to reverse post-AVR, with an increasing body of evidence demonstrating its prognostic power in AS with other conditions (cardiomyopathies).[14]

LV diastolic function is one of the earliest consequences of LVH and MF in AS. LV diastolic dysfunction is associated with increased mortality, worsens with progressive myocardial remodeling before AVR, and gradually improves with reverse remodeling after AVR.

The improvement in diastolic dysfunction in AS takes longer than the reversal of LV systolic dysfunction (the former is mainly related to longstanding LV structural changes while the latter also reflects afterload mismatch).[15]

Although LVEF provides important information and guides therapy, it is load-dependent and not an index of myocardial contractility.

Global longitudinal strain assessment of LV deformation detects earlier changes in myocardial function and enables a better understanding of progression to heart failure in AS.[16] Speckle-tracking echocardiography allows for a multidirectional assessment of myocardial deformation. In AS, LV longitudinal strain is impaired, especially in the basal segments, and is a predictor of clinical events in asymptomatic AS (the primary mechanism involved in the alteration of LV longitudinal strain in AS is LV fibrosis).[17]

Moreover, GLS also depends on the pattern of LV remodeling, with lower values in patients with significant concentric LVH.[18]

Recent studies have shown that GLS predicts postoperative LV dysfunction and outcomes better than ejection fraction.[19]

Although this technique has high levels of acceptance and is widely available, it exhibits several inherent limitations such as poor inter-reader reproducibility and need for an appropriate ''acoustic window''. Cardiac magnetic resonance feature tracking gives us the possibility of deriving deformation parameters from standard cine sequences and thus combine the advantages of both imaging modalities.[20] However, comparability between different vendors, imaging modalities and post-processing software needs to be further assessed and proven.

Assessment of left ventricular reverse remodeling - EPICHEART Study

Ideally, surgery should be performed before irreversible changes occur in the myocardium. Indeed, rather than an isolated valve disease, AS is a more global disease, potentially affecting the entire myocardium. Ejection fraction is the only LV parameter currently recommended to guide intervention in asymptomatic patients with AS, with a cut-off value of 50% for referral for AVR.[21]

Future trials to establish clear thresholds and incorporating GLS into decision-making for asymptomatic patients with AS will be needed to establish its role as a marker of subclinical LV decompensation. The traditional criteria for AVR are now being questioned based on our current understanding of pre-clinical myocardial disease in asymptomatic AS. Echocardiographic and CMR assessment of myocardial deformation and myocardial fibrosis offer clear prognostic information above and beyond valve hemodynamic and LVEF alone.

Azevedo et al. assessed the relationship between global and regional left ventricular strain, strain rate, displacement and velocity using CMR-FT and LVEF before and after AVR in a prospective cohort of AS patients. One objective of this study was to assess reverse remodeling using CMR with standard functional and innovative deformation parameters in patients after six months of AVR (EPICHEART Study) and assess the prognostic impact.

In this study, they found that there is a significant reduction in GLS and GCS CMR parameters after AVR, with unchanged LVEF compared to baseline.[1] The authors reported similar findings in several recent echocardiographic

studies as well as some studies recently published with CMR-FT within three months of a successful transcatheter valve replacement (TAVR) in comparison to a healthy control group.[22]

As it was demonstrated that positive response after AVR (surgical valve replacement or TAVR) could be predicted by analyzing longitudinal strain and velocity, it has been suggested that the assessment of cardiac mechanics could be useful for the right timing of AVR. Nevertheless, the prognostic implication of persistent subtle functional abnormalities after AVR remains poorly investigated and thus unclear.[23] A correlation between deformation parameters and outcomes has not as yet been reported.

Randomized trials are needed to determine whether the use of fibrosis imaging biomarkers (LGE), T1 mapping and GLS can improve outcomes of asymptomatic patients with AS. The EVOLVED-AS study[12] is an ongoing trial that should answer these crucial questions.

Conflicts of interest

The authors have no conflicts of interest to declare.

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