Editorial Comment:

Myocardial Fibrosis in Aortic Stenosis

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Traditionally, aortic stenosis (AS) has been an easy disease for clinicians to understand and treat. It was seen primarily as a disease of the valve, which would be replaced when the stenosis became severe, and the patient symptomatic; the myocardium was largely ignored with assessment focused on measurement of left ventricular (LV) ejection fraction (EF).

Advanced cardiovascular imaging techniques have put an end to the simplicity of the old days. In particular, with cardiac magnetic resonance (CMR) imaging and myocardial tissue characterisation, it has become apparent that the LV response to pressure overload is complex, and may be as important as the degree of valve stenosis itself in determining patient prognosis and onset of symptoms.

LV Myocardial fibrosis in AS

Early studies focusing on the histopathology of the LV of AS patients showed the presence of LV fibrosis; two types were identified - interstitial fibrosis and replacement fibrosis - with the former thought to be the reversible stage preceding irreversible replacement fibrosis (1). The presence of LV fibrosis adversely predicts prognosis both in AS and other cardiac pathologies (2, 3). Traditionally, LV fibrosis burden is quantified on histology from endomyocardial biopsy, an invasive technique with potentially serious complications.

CMR has opened a window as the only imaging modality in clinical practice with the capacity to non-invasively quantify fibrosis earlier and longitudinally in the disease process. Quantification of LV replacement fibrosis is possible using CMR late gadolinium enhancement (LGE), and Azevedo at al (2) showed that replacement fibrosis as measured by CMR LGE (validated by histology) is associated with a poorer prognosis in severe AS.

Finding a reliable technique for quantification of the potentially reversible LV interstitial fibrosis in AS was more challenging. As interstitial fibrosis is a diffuse disease process affecting the entire LV, and the CMR LGE technique relies on presence of normal myocardium to contrast with the diseased myocardium, it is not suitable for quantification of interstitial fibrosis. CMR T1-mapping showed early promise (4); it generates a pixel-by-pixel map of the heart based on T1 relaxation time - a magnetic property of the tissue and its surroundings - and can directly characterise the myocardium without relying on relative signal differences. In 2008, Jerosch-Herold et al (5) used T1 mapping to calculate the gadolinium contrast partition coefficient (λGd) – the change in T1 relaxation rates in myocardium and blood after gadolinium contrast injection once equilibrium distribution between blood and myocardium was obtained. They found increased λGd in patients with dilated cardiomyopathy compared to normal controls, thought to be due to increased extracellular matrix, perhaps reflecting interstitial fibrosis. In 2010, Flett et al (6) built on this technique, describing 'equilibrium contrast CMR' based on similar principles. Equilibrium CMR assumes an equilibrium steady state between the intravascular and interstitial spaces as a 2-compartment model and requires a constant infusion of contrast to achieve a steady state; haematocrit is also measured to calculate the extracellular volume fraction (ECV), a measure which correlates well with interstitial fibrosis burden measured by histology from endomyocardial biopsies in patients with AS and hypertrophic cardiomyopathy (6).

Other groups investigated whether native T1 values could provide a surrogate measure of interstitial fibrosis in AS; good correlation was shown between interstitial fibrosis measured by histology and native T1 values (r=0.66) and significant differences in native T1 values were shown between normal controls and those with

severe AS, although there appeared to be a degree of overlap in native T1 values between normals and those with moderate AS (7). Although prognostic data were lacking in these early studies, a very recent study suggested that ECV may be a predictor of adverse events peri- and post-transcatheter aortic valve replacement (8).

Contribution of this paper to the field

In this issue of the journal, Chin et al (9) studied a group of 166 heterogeneous AS patients and 37 healthy controls, and report that the state of the myocardium, as assessed by T1 mapping techniques, is of prognostic significance.

The paper makes a significant contribution to the field by exploring the prognostic value of the novel CMR T1 measures, including native T1, post-contrast T1, λGd and ECV, as surrogate markers for LV interstitial fibrosis in AS and correlates these to histology. They also propose a new measurement – the indexed extracellular volume (IECV), derived from the product of ECV and LV end-diastolic volume indexed to body surface area, which showed the strongest correlation with interstitial fibrosis on histology (R=0.87) out of all techniques.

Correlation with native T1 values and interstitial fibrosis (r=0.76) was stronger than with ECV alone (r=0.7). The group also proposed a new classification system for AS, independent of valve parameters and based purely on assessment of the myocardium, dividing subjects into those with: normal myocardium, extracellular expansion (based on increased IECV), and replacement fibrosis (as measured by presence of LGE).

Interestingly, there were no statistically significant differences (p=0.08) in the six minute walk test between these patient groups, despite the gross differences in LV

fibrosis, reinforcing the idea that symptoms appear late in the disease process, once irreversible damage to the LV has already occurred.

The 2.9 years of follow up data presented in this paper is particularly relevant, as prognostic T1 data has, to date, been lacking in this AS population. Their data showed clear stepwise increases in all-cause mortality across these groups, with the lowest mortality in those with normal myocardium and the highest in those with replacement fibrosis.

Although there is much to commend this paper, it has a number of important limitations, in part acknowledged by the authors. One critique is that the techniques were validated against only a small number of biopsies (n=11), leaving margin for error; similar studies in the area presented biopsy data in 19 and 18 AS patients, respectively (6,7).

Whilst 166 AS patients is a large number for a single center study, large multi-center studies with longer follow-up are required to determine whether native or post-contrast T1, λGd, ECV or indeed the newly proposed IECV are of independent prognostic value.

No clear comment was made about the prognostic value of the native T1 data in this study; from the patients with biopsy, native T1 values were the next stongest discriminator between the three groups ($p=0.0002$) after ICEV ($p<0.0001$) of all the techniques examined. Further exploration of native T1 data would be an opportunity, as there are clear practical advantages to adopting a non-contrast technique; the scan time is shorter, it can be applied in patients with significant renal dysfunction, it is independent of gadolinium kinetics and processing of the data is less cumbersome compared to ECV quantification.

Finally, as the group acknowledged, what precisely is/are being measured with native T1 and ECV values is still hotly debated; correlation is of course not causation, and whilst the signal may in part reflect interstitial fibrosis, it is also subject to confounders such as extracellular edema and expansion of the intravascular space (10). Nevertheless it remains an attractive potential future biomarker for interstitial fibrosis.

The Future

To date, the prognostic data in the field are not yet sufficiently strong to warrant inclusion of CMR assessment of LV fibrosis into international guidelines for management of valve disease. For any technique to be incorporated into routine clinical practice it needs to be simple, quick, robust and reproducible; the jury remains out about whether contrast or non-contrast T1-mapping techniques are the superior surrogate markers of interstitial fibrosis. Published work in the field used different T1 mapping sequences; consensus is needed about which sequence is the most effective. Randomised, prospective, multicentre studies incorporating native T1 and ECV mapping techniques using different sequences with long-term outcome data may answer these questions. The non-invasive and reproducible nature of CMR, together with its superior capability for myocardial tissue characterisation, including novel mapping techniques, make it an ideal tool to assess the biological response of the myocardium to anti-fibrotic agents in AS and other disease states. By demonstrating the prognostic value of myocardial characterisation in AS with CMR, Chin et al (9) have achieved an important enabling step towards this future.

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