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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 has been 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 the left ventricular ejection fraction (LVEF).

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 characterization, 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.

## MYOCARDIAL FIBROSIS IN AORTIC STENOSIS

Early studies focusing on the histopathology of the LV in AS patients showed the presence of fibrosis; 2 types were identified—interstitial fibrosis and replacement fibrosis—with the former believed 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 noninvasively quantify fibrosis earlier and longitudinally in the disease process. Quantification of LV replacement fibrosis is possible using CMR late gadolinium enhancement (LGE), and Azevedo et al. (2) have shown 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. Because interstitial fibrosis is a diffuse disease process affecting the entire LV, and the CMR LGE technique relies on the 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, which is a magnetic property of the tissue and its surroundings, and can directly characterize 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, which is the change in T1 relaxation rates in the myocardium and blood after gadolinium contrast injection. They found an increased gadolinium contrast partition coefficient in patients with dilated cardiomyopathy compared with normal control subjects, which was believed to be due to an 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. Hematocrit is also measured to calculate the extracellular volume (ECV) fraction, a measure that correlates well with the interstitial fibrosis burden as 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 as measured by histology and native T1 values ($r = 0.66$). Significant differences in native T1 values were shown between

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normal control subjects and those with severe AS, although there appeared to be a degree of overlap in native T1 values between normal subjects and those with moderate AS (7). Although prognostic data were lacking in these early studies, a 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 *iJACC*, Chin et al. (9) studied a group of 166 heterogeneous AS patients and 37 healthy control subjects, and reported that the state of the myocardium, as assessed by T1 mapping techniques, was of prognostic significance.

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Their study makes a significant contribution to the field by exploring the prognostic value of the novel CMR T1 measures, including native T1, post-contrast T1, the gadolinium contrast partition coefficient, and ECV, as surrogate markers for LV interstitial fibrosis in AS and correlates these measures to histology. They also proposed a new measurement, the indexed extracellular volume (iECV), which was 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 ($R = 0.87$) of all techniques. Correlation with native T1 values and interstitial fibrosis ($r = 0.76$) was stronger than with ECV alone ($r = 0.7$).

The investigators also proposed a new classification system for AS, independent of valve parameters; a system that is based purely on assessment of the myocardium, dividing subjects into those with normal myocardium, extracellular expansion (based on an increased iECV), and replacement fibrosis (as measured by the presence of LGE).

There were no statistically significant differences ($p = 0.08$) in the 6-min walk test between these patient groups, despite the gross differences in LV fibrosis, which reinforced 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, because prognostic T1 data has 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 mortality in those with replacement fibrosis.

Although there is much to commend this study, it has a number of important limitations, in part acknowledged by the investigators. 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).

Although 166 patients with AS is a large number for a single-center study, large multicenter studies with longer follow-up are required to determine whether native or post-contrast T1, the gadolinium contrast partition coefficient, ECV, or 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 biopsies, native T1 values were the next strongest discriminator among the 3 groups ($p = 0.0002$) after iECV ($p < 0.0001$) of all the techniques examined. Further exploration of native T1 data would be an opportunity, because there are clear practical advantages to adopting a noncontrast 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 with ECV quantification.

Finally, as the group acknowledged, what precisely are being measured with native T1 and ECV values is still hotly debated. Correlation is not causation, and although 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 noncontrast 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. Randomized, prospective, multicenter studies that incorporate native T1 and ECV mapping techniques using different sequences with long-term outcome data may answer these questions. The noninvasive and reproducible nature of CMR, together with its superior capability for myocardial tissue characterization, including

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novel mapping techniques, make it an ideal tool to assess the biological response of the myocardium to antifibrotic agents in AS and other disease states. By demonstrating the prognostic value of myocardial characterization in AS with CMR, Chin et al. (9) have achieved an important enabling step toward this future.

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## REFERENCES

**1.** Krayenbuehl HP, Hess OM, Monrad ES, Schneider J, Mall G, Turina M. Left ventricular myocardial structure in aortic valve disease before, intermediate, and late after aortic valve replacement. Circulation 1989;79:744–55.

**2.** Azevedo CF, Nigri M, Higuchi ML, et al. Prognostic significance of myocardial fibrosis quantification by histopathology and magnetic resonance imaging in patients with severe aortic valve disease. J Am Coll Cardiol 2010;56:278–87.

**3.** Shriani J, Pick R, Roberts WC, Maron BJ. Morphology and significance of the left ventricular collagen network in young patients with hypertrophic cardiomyopathy and sudden cardiac death. J Am Coll Cardiol 2000;35:36–44.

**4.** Messroghli DR, Radjenovic A, Kozerke S, Higgins DM, Sivananthan MU, Ridgway JP. Modified Look-Locker inversion recovery (MOLLI) for high-resolution T1 mapping of the heart. Magn Reson Med 2004;52:141–6.

**5.** Jerosch-Herold M, Sheridan DC, Kushner JD, et al. Cardiac magnetic resonance imaging of myocardial contrast uptake and blood flow affected with idiopathic or familial dilated cardiomyopathy. Am J Physiol Heart Circ Physiol 2008;295:H1234–42.

**6.** Flett AS, Hayward MP, Ashworth MT, et al. Equilibrium contrast cardiovascular magnetic resonance for the measurement of diffuse myocardial fibrosis: preliminary validation in humans. Circulation 2010;122:138–44.

**7.** Bull S, White SK, Piechnik SK, et al. Human non-contrast T1 values and correlation with histology in diffuse fibrosis. Heart 2013;99:932–7.

**8.** Nadjiri J, Nieberler H, Hendrich E, et al. Prognostic value of T1-mapping in TAVR patients: extra-cellular volume as a possible predictor for peri- and post-TAVR adverse events. Int J Cardiovasc Imaging 2016;32:1625–33.

**9.** Chin CWL, Everett RJ, Kwiecinski J, et al. Myocardial fibrosis and cardiac decompensation in aortic stenosis. J Am Coll Cardiol Img 2017;10:1320–33.

**10.** Mahmod M, Piechnik SK, Levelt E, et al. Adenosine stress native T1 mapping in severe aortic stenosis: evidence for a role of the intravascular compartment on myocardial T1 values. J Cardiovasc Magn Reson 2014;16:92.

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