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EDITORIAL COMMENT

On Fibrosis, Prognosis, and the Unique Role of CMR

A Paradigm Shift From "Bright Is Dead" to "Bright Is Bad"*

Chiara Bucciarelli-Ducci, MD, PhD,†‡ Clerio F. Azevedo, MD, PhD§‖

"Learning never exhausts the mind."
—Leonardo da Vinci (1)

With an increasingly aging population, aortic stenosis (AS) has become the most frequent valvular heart disease in North America and Europe. It is a progressive condition characterized by a long latent asymptomatic period, followed by a shorter symptomatic stage associated with increased morbidity and higher mortality. Surgical aortic valve replacement (AVR) and transcatheter aortic valve replacement (TAVR) are the only effective treatments for severe AS. Currently, the timing for AVR and TAVR is based on the severity of AS, the presence of symptoms, and/or the presence of left ventricular (LV) systolic dysfunction (LV ejection fraction <50%). Asymptomatic patients tend to be treated conservatively.

Nevertheless, despite these well-established criteria on the appropriateness of AVR intervention, the management of asymptomatic patients with preserved LV systolic function continues to be controversial (2). Registry data indicate that 15% of patients undergoing AVR are asymptomatic at the time of surgery (3). Novel markers to improve risk stratification would be valuable in identifying asymptomatic patients who would benefit from AVR.

Over the past 2 decades, cardiovascular magnetic resonance (CMR) has been increasingly adopted in clinical practice in the work-up of ischemic and nonischemic cardiomyopathies (4,5). CMR is used as an advanced diagnostic tool to accurately assess biventricular anatomy and function, but its unique application is in vivo myocardial tissue characterization. Indeed, it has been widely demonstrated that the late gadolinium enhancement (LGE) technique allows the accurate assessment of myocardial replacement fibrosis in both ischemic and nonischemic cardiomyopathies. Importantly, replacement fibrosis by LGE has been found to represent a ubiquitous marker of adverse prognosis in ischemic heart disease, nonischemic dilated cardiomyopathy, hypertrophic cardiomyopathy, cardiac sarcoidosis, cardiac amyloidosis, and biopsy-proven myocarditis (6–11). This suggests that the time has come for a paradigm shift from "bright is dead" to "bright is bad." Myocardial enhancement is not only a marker of myocardial scarring/necrosis, as seen in ischemic heart disease, as it represents a broader spectrum of myocardial damage in a variety of cardiomyopathies.

In the context of severe AS, the degree of myocardial fibrosis plays an important role in the transition from well-compensated hypertrophy to overt heart failure and risk of sudden cardiac death (12), suggesting that LGE is a marker of more advanced disease (13).

SEE PAGE 144

In this issue of the *Journal*, Barone-Rochette et al. (14) report the prognostic significance of LGE in 154 patients undergoing AVR for severe AS (aortic valve area 0.71 ± 0.17 cm^2, mean gradient 49 ± 17 mm Hg). Overall, they evaluated a low-risk population with no previous myocardial infarction, normal ejection fraction (84% of patients), and low surgical risk

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From the †NIHR Bristol Cardiovascular Research Unit, Bristol Heart Institute, University of Bristol, Bristol, United Kingdom; ‡CMR Unit, Royal Brompton Hospital, National Heart & Lung Institute, Imperial College London, United Kingdom; §Department of Cardiovascular MRI and CT, Clínica de Diagnóstico por Imagem, Rio de Janeiro, Brazil; and the ‖Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose. Both authors contributed equally to this work.

scores. Symptoms were relatively mild; only 20% of patients had chest pain, 27% were in New York Heart Association functional class III/IV, and 7% had a history of syncope. They also excluded patients with previous AVR or coronary artery bypass surgery and those with coexisting severe aortic regurgitation and/or other severe valve disease—all factors that would have otherwise impacted assessment of prognosis.

Replacement myocardial fibrosis by LGE was identified in nearly one-third of the patients (28%), with either an ischemic (9%) or nonischemic pattern (19%). One might speculate, as patients with previous myocardial infarctions were excluded, that the ischemic patterns could represent either small asymptomatic infarctions (perhaps distal embolization, given the mean infarct size of 3.5%) or myocardial damage related to subendocardial ischemia from the increased LV pressure/wall stress of severe AS. Notably, the presence of both ischemic and nonischemic LGE in patients with severe AS has also been previously reported (15,16). During a median follow-up of 2.9 years, 21 patients died (11 cardiovascular deaths, 55% of which were sudden deaths). On both univariable and multivariable analyses, patients with pre-operative LGE had a 2.8-fold increase in all-cause mortality compared with those with no LGE. This is the first study to demonstrate that the prognostic value of LGE in patients with severe AS also applies to those undergoing TAVR. This is particularly relevant, because TAVR candidates represent a much higher risk population in whom the indications and the timing of intervention are still being defined.

The study nicely complements previous prognostic CMR studies in patients with aortic valve disease, but it focuses on a larger, more homogenous population with severe degenerative AS undergoing AVR. Azevedo et al. (15) demonstrated in a cohort of patients (28 with AS and 24 with aortic regurgitation) that LGE was associated with less LV functional improvement late after AVR and higher all-cause mortality. In that study, the mortality rate (6.8%/year) was higher than in the current study (4.7%/year), which may reflect the more heterogeneous population with higher baseline risk in the earlier study. Dweck et al. (16) studied 143 patients with moderate and severe AS and reported 8- and 6-fold higher rates of all-cause mortality in patients with nonischemic and ischemic LGE, respectively, compared with those without LGE. However, in that study, only 50% of the patients underwent AVR, and the remaining 50% received medical treatment.

The major limitation of the current study is the small number of events, which is not surprising considering the low-risk population. Unfortunately, the low number of patients with LGE and the low number of events prevent a full analysis of the association between different LGE patterns and patient outcome. Considering that 55% of the cardiovascular deaths were sudden, it is possible that myocardial fibrosis as identified by LGE creates the substrate for ventricular arrhythmia (17).

More recently, novel technical developments in CMR have introduced T1 mapping for assessment of extracellular volume, a biomarker of reactive myocardial interstitial fibrosis and a promising pre-clinical marker of disease (18). T1 mapping and extracellular volume were not performed in the present study. However, initial experience suggests that native (noncontrast) T1 values are increased in patients with severe AS and to a greater extent in symptomatic versus asymptomatic patients (19). Flett et al. (20) confirmed that diffuse interstitial myocardial fibrosis measured with equilibrium-contrast CMR (a technique validated histologically) is elevated in severe AS compared with normal individuals, although there is considerable overlap between normal control subjects and AS patients. At 6 months after AVR, diffuse myocardial fibrosis was not reversible, and the regression of LV hypertrophy was the result of reduced cellular mass. Further investigation is necessary to clarify the role of diffuse myocardial fibrosis in the natural history of AS.

An ongoing, prospective, observational cohort study (The Role of Myocardial Fibrosis in Patients with Aortic Stenosis; NCT01755936), is investigating the prognostic implications of myocardial fibrosis (by LGE and T1 mapping) in patients with mild, moderate, and severe AS. This study is seeking to address the potential roles of LGE and T1 mapping as new markers for risk assessment in patients with severe AS. Whether the results of this study will translate into more objective risk stratification of asymptomatic patients with severe AS, which could trigger earlier referrals for AVR, remains to be seen.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Chiara Bucciarelli-Ducci, Bristol Heart Institute, University Hospitals Bristol NHS Foundation Trust, Marlborough Street, BS2 8HW Bristol, United Kingdom. E-mail: c.bucciarelli-ducci@bristol.ac.uk.

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