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EDITORIAL COMMENT

Cardiac Magnetic Resonance Imaging Identification of Myocardial Fibrosis

The Need for Standardization and Therapies*

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Investigators in the 1980s observed increased signal in infarcted myocardium after infusion of gadolinium-chelate in animal models using cardiac magnetic resonance (CMR) (1), but the pulse sequence used was suboptimal for clinical application. With the improved pulse sequence developed by Simonetti et al. (2), imaging of scar associated with myocardial infarction (MI) (3) and identification of its transmurality was shown to be clinically relevant (4). Soon thereafter, it was recognized that late gadolinium enhancement (LGE), also called delayed-enhanced CMR, was not specific for infarction but was a marker of myocardial fibrosis of any etiology. In the past decade, the use of LGE has rapidly expanded for imaging of myocardial fibrosis in a myriad of cardiac conditions, including dilated cardiomyopathy (5), hypertensive and hypertrophic cardiomyopathy (HCM) (6), infiltrative cardiomyopathies (7,8), and end-stage renal disease (9) (before the recognition of the association of nephrogenic systemic fibrosis and gadolinium chelates).

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The presence of LGE is a marker of adverse cardiac outcome in coronary artery disease. Kwong et al. (10) demonstrated in patients presenting for evaluation for ischemic heart disease that the presence of any LGE was a marker of an increased risk of major adverse cardiac events (MACE). The same was true in diabetic patients without a known history of CAD (11). In patients referred to the catheterization laboratory, the presence of previously unrecognized MI as identified by LGE is also associated with a markedly worse prognosis (12). The presence of a gray zone of intermediate signal at the border zone of MI has also been associated with adverse prognosis, thought to be due to an increased risk of ventricular arrhythmias originating in this region of admixture of infarcted and normal myocardium (13–15).

The adverse prognosis associated with LGE has now been extended to a diverse array of cardiomyopathies. In dilated nonischemic cardiomyopathy, the presence of a midwall stripe of LGE is associated with inducibility of ventricular arrhythmias (16) and a worse cardiac prognosis, especially ventricular arrhythmias and hospital stay for congestive heart failure (17). In HCM, the presence of LGE is associated with increased risk of ventricular arrhythmias (18), and there are emerging data that it is associated with an increased risk of death and other adverse cardiac events.

In this issue of the *Journal*, Azevedo et al. (19) present the results of a study of 54 patients scheduled for aortic valve replacement (AVR) for either aortic stenosis or regurgitation. They performed LGE in standard fashion, and macroscopic fibrosis was noted in 65% of the patients. However, they went beyond standard qualitative analysis and examined the images quantitatively by measuring the increased signal within the myocardium over a certain threshold based on an algorithm defined by their laboratory. They found that quantitatively 3.7% of the myocardium demonstrated increased signal intensity, and this correlated well with quantitative analysis of fibrosis by histopathology from the septal biopsies of these patients during AVR. The amount of fibrosis was a multivariate predictor of all-cause mortality and, in a subset of these patients, predicted lack of improvement of ejection fraction after AVR. Another recent study has shown that the absence of fibrosis was associated with good prognosis after AVR for AS and that the extent of LGE did not change after AVR (20). These are important reports that demonstrate the clinical significance of myocardial fibrosis in aortic valve disease.

However, a problem in the field is the lack of standardization of methodologies to measure increased myocardial signal after gadolinium administration. There are 3 published studies, each with their own methodology to measure the size of the gray border zone after MI (13–15). The present study presents yet another technique for quantification of increased signal. The field could be improved by the institution of T1-mapping, a technique introduced clinically in patients with congestive heart failure by Iles et al. (21). These authors presented a novel T1-mapping method to demonstrate the diffuse increase in signal associated with myocardial fibrosis, which in many conditions might not be identified as focal LGE. In a small subset of 9 patients who underwent biopsy, the signal intensity measured by CMR correlated with the presence of fibrosis. Because fibrosis is more commonly microscopic in many of these conditions,

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the application of a method to measure it such as T1-mapping would be a major advance in the field.

The present study extends the list of cardiac conditions for which the presence of fibrosis is associated with adverse outcome. Now that these associations have been defined, the next step is to identify therapies based upon these findings that might alter outcomes. For example, in HCM, it might be that the presence and/or extent of LGE might define the need for an implantable cardioverter-defibrillator. In valvular heart disease or hypertensive heart disease, the presence and/or extent of fibrosis might be an indication for particular medical therapies that have been shown to have antifibrotic properties (e.g., inhibitors of the rennin-angiotensin/aldosterone system).

Thus, as the list of conditions associated with fibrosis that can be imaged by CMR grows, the imaging community must look toward ways of fine-tuning the imaging to delineate microscopic fibrosis. Once that is finalized, turning the identification of fibrosis into therapeutic advances is an essential next step.

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