Cardiac Magnetic Resonance Assessment of Myocardial Fibrosis
Honing New Clinical Tools

Victor A. Ferrari, MD; Walter R.T. Witschey, PhD; Rong Zhou, PhD

I do not seek. I find.
—Pablo Picasso

Diffuse interstitial myocardial fibrosis (DMF) and replacement myocardial fibrosis (or scar) are common features of a wide variety of pathological conditions of the heart and play an important role in the progression of heart failure. Recent advances in cardiac magnetic resonance (CMR) techniques now permit assessment of DMF as well as the commonly used scar imaging, or late gadolinium enhancement (LGE) methods.

Recent work has shown the prognostic value of detecting DMF in patients with valvular heart disease and early diabetic cardiomyopathy. Although conventional LGE techniques can successfully identify replacement fibrosis in conditions such as acute and chronic myocardial infarction and hypertrophic cardiomyopathy, they are less suitable imaging methods for detecting DMF because there may be little normal myocardium available to compare with affected areas. Fibrosis shortens the postcontrast longitudinal relaxation time (T1) properties of myocardium, and this feature may be exploited in DMF because T1 can be directly measured by CMR, using specific pulse sequences in a strategy known as T1 mapping. Among them, the modified Look-Locker inversion recovery (MOLLI) sequence has been used extensively by Messroghli et al. In their article published in this issue of Circulation: Cardiovascular Imaging, Messroghli and colleagues applied a custom MOLLI technique in a rat model of DMF to better account for potential weaknesses in the technique such as sensitivity to motion and heart rate. In addition to comparing T1 relaxation times before and after a 2-week infusion of angiotensin II to induce DMF, they also derived myocardial extracellular volume from hematocrit and T1 of blood and myocardium. The authors found a very good correlation between extracellular volume and fraction of collagen volume estimated by histology, and the method is relatively straightforward to implement on conventional clinical 3-T scanners. This allows for more investigators to perform fibrosis imaging research on presently available equipment with little modification. The applicability of this technique for higher heart rate applications allows for widening its potential use to the younger pediatric population or even fetal imaging.

There has been great interest recently in MRI pulse sequence methods designed for myocardial T1 quantification, which are somewhat different from those used in standard clinical practice and deserve mention. Clinical LGE MRI typically uses two types of inversion recovery (IR)-prepared pulse sequences, but neither is optimal for accurate and reproducible visualization of diffuse myocardial fibrosis. The first is the inversion time (TI) scout, which rapidly acquires multiple images at varying TI, using a segmented or single-shot Look-Locker pulse sequence to determine the optimal TI to maximize late enhancing tissue contrast. The TI scout is much like the modified Look-Locker method proposed several years ago by Messroghli et al for cardiac T1 mapping. The second approach uses T1-weighted images obtained at the chosen TI with a segmented IR-prepared pulse sequence.

From an engineering perspective, there are small differences between the Look-Locker methods and T1-weighted methods. Signal-to-noise ratio, spatial resolution, and spatial coverage may be compromised with the TI scout to rapidly obtain multiple contrast images across a range of TIs. The segmented IR-prepared pulse sequence obtains high contrast-to-noise ratio (CNR) images at a single inversion time to maximize contrast between late enhancing tissue and myocardium, but is time-consuming relative to the TI scout.

Newer strategies for DMF imaging have combined the fast acquisition time and multiple contrast capabilities of the TI scout with the improved CNR, spatial resolution, and spatial coverage of the segmented IR LGE scans. The combination is useful because it reduces the total imaging time, enables T1 quantification, and does not compromise image quality. Several studies have already explored the use of these fast methods for rapid myocardial T1 relaxation time mapping or multicontrast imaging.

What additional advancements must take place to further reduce scan time, enable T1 quantification, yet not sacrifice...
the sensitivity for detecting DMF? One approach uses multiple receivers and reconstruction methods (parallel imaging) to reduce scan time. Another strategy favors undersampling of image data, using radial or spiral k-space trajectories to achieve these goals. These two methods have different signal aliasing properties from Cartesian trajectories and may tolerate k-space undersampling without major reductions in image quality. Alternatively, balanced steady-state free precession pulse sequences, which may have intrinsically greater steady-state signal-to-noise ratio, provide shorter repetition times and quantify T1 more accurately than spoiled gradient echo methods. A recent technique uses view-sharing acquisitions to combine k-space data obtained from multiple views at multiple inversion times to enhance signal-to-noise efficiency.

Unfortunately, many of these methods may reduce scan time at the cost of CNR, and therefore further investigation into contrast detectability is required. In other approaches, advances have been made in reducing the sensitivity to motion artifacts of conventional segmented IR scans over a long scan time using free-breathing acquisitions. The proposed method by Messroghli et al in this article could be translated to humans using such a strategy. In several applications, free-breathing acquisitions have already been combined with undersampled radial trajectories with golden angle view ordering, using view sharing, temporal filtering, or parallel reconstruction. These methods could deliver high CNR and high spatial resolution and coverage without motion artifacts. Nevertheless, work must still be done to compare how increasing scan efficiency and decreasing scan time affects the detectability of lesions.

Where will the major breakthroughs be in the field of myocardial fibrosis detection? One innovative strategy is the use of equilibrium contrast imaging by continuous infusion of contrast. This method reduces the effect of contrast agent washout during T1 measurement and minimizes the confounding effects of heart rate variability and body composition. In a selected population of patients undergoing surgery for aortic stenosis and hypertrophic cardiomyopathy, Elliott et al found a very strong correlation between the T1 measurement of DMF and histological fibrosis. However, the applicability of this technique must be evaluated in a larger patient population and with different cardiomyopathies. Another area that may provide new advances is the use of endogenous contrast agent mechanisms. Although endogenous MR contrast agents such as noncontrast T2 or T1 quantification, magnetization transfer, or spin-lock imaging have been used for detection of focal fibrosis, it has been observed that their ability to detect DMF is not as great as LGE MRI. Therefore, it may be advantageous to use methods of combined relaxometric mapping to validate endogenous contrast with reduced scan time. The advantages of these techniques are clear in that they improve patient comfort and tolerance of CMR, require no exogenous contrast agents nor coordination of timing between contrast injection and scanning, and permit assessment of DMF in patients with reduced glomerular filtration rates, in whom conventional MRI contrast agent use would not be possible.

Characterization of myocardial tissue abnormalities with CMR represents a valuable tool to define the presence and stage of a disorder at a point in time, and to serially and noninvasively monitor both animal models and patients for progression of disease or therapeutic efficacy. While we may not yet have proven treatments for DMF, honing the tools now for its assessment and quantification is of vital importance. We currently face an abundance of riches with respect to the number and diversity of techniques available to measure DMF. Assessing the performance of various approaches for detecting and measuring DMF will permit the selection of optimal pulse sequences for specific disorders. Standardization of protocols and techniques is necessary to allow more rigorous comparisons between methodologies since it is likely that more than one technique may prove to be accurate and efficacious.

The true tipping point for these new tools will be their performance in clinical trials. As we have frequently observed, the true prognostic value of imaging-based surrogate markers is best revealed when rigorously tested in large, randomized, clinical studies. These data are accumulating for other CMR methods, and will likewise follow for DMF techniques once the strongest contenders prove themselves. As in art, change in medical science often comes quickly from disruptive forces; appreciating the value of these forces and preparing for their inevitable impact will aid us in finding what we presently seek.

Disclosures
Dr Ferrari is a member of the Board of Trustees of the Society for Cardiovascular Magnetic Resonance and serves on the Editorial Board for the Journal of Cardiovascular Magnetic Resonance.

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