

The Tissue Issue

T1 Mapping and the Myocardium



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Cardiac magnetic resonance (CMR) has made major inroads in the past 2 decades thanks to its ability to characterize myocardial tissue noninvasively (1). It began with late gadolinium enhancement as a means to assess myocardial infarct size (2), for which it is now the gold standard. Over time, it was recognized that other nonischemic causes of myocardial fibrosis visible on pathology, such as hypertrophic cardiomyopathy, sarcoidosis, and so on, could be visualized with late gadolinium enhancement (3). More than a decade ago, a new pulse sequence called modified Look-Locker inversion recovery was developed for T1 mapping (4) that enables the quantitative evaluation of myocardial T1 either without contrast, so-called native T1, or post-contrast. A Society for Cardiovascular Magnetic Resonance consensus document has been published regarding the optimal approaches to T1 mapping (5). Native T1 is especially useful in patients who cannot receive gadolinium-based contrast agents because of stage 4 or 5 chronic kidney disease. Native T1 is highest in patients with amyloidosis, many of whom have chronic kidney disease (6). It is elevated to an intermediate degree in hypertrophic cardiomyopathy and other nonischemic cardiomyopathies (7). Post-contrast T1 mapping is used to calculate extracellular volume (ECV), which is elevated in the setting of interstitial fibrosis or other causes of increased

extracellular space such as edema and/or inflammation (1). Elevated ECV has been documented in hypertensive heart disease (8), hypertrophic cardiomyopathy (9), and heart failure with preserved ejection fraction (10). Increased ECV has been associated with adverse short-term cardiac prognosis in a diverse patient population (11).

T1 mapping is an extremely versatile technique. This issue of *iJACC* is dedicated to a variety of applications and potential uses of T1 mapping in cardiovascular disease. The promise is remarkable and increasingly tangible. For example, the group at Oxford has studied native T1 at rest and with adenosine stress, showing that native T1 is sensitive to changes in myocardial blood volume, which may be a sensitive marker of ischemia (12). They found that normal myocardium increased native T1 with adenosine by more than 6%, whereas infarcted myocardium showed essentially no increase. Ischemic myocardium showed an intermediate increase of approximately 4%. This was a pilot study with only 10 patients with coronary artery disease included, and thus larger studies are clearly needed to further examine this hypothesis. A major advance here is the ability to perform stress CMR studies without using gadolinium. Because the T1 changes with stress are small, reproducibility and reliability must be established so as to know whether such studies could be useful in individual patients. Sensitivity to blood volume changes offers exciting possibilities in other myocardial diseases.

The paper by Treibel et al. (13) represents a potential major advance in the ease of measuring ECV using post-contrast T1 mapping. Typically, ECV requires measurement of the hematocrit (Hct) for accurate assessment, which can be problematic in outpatients coming for routine CMR, who may not have other reasons for a blood draw. This

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multicenter group of investigators demonstrates a method for estimating Hct using the T1 of the blood pool. Substituting the estimated Hct into the formula for calculating ECV enables the measurement of a “synthetic” ECV that correlates closely with the standard ECV measure ($r^2 = 0.97$). The investigators demonstrate excellent performance in a validation cohort of 213 patients. Using synthetic ECV would preclude the need to draw Hct in patients who otherwise do not need to have blood drawn.

Two pieces in this issue examine the utility of T1 mapping in congenital heart disease. The Boston Children’s group measured ECV in both the left and right ventricles in 84 patients with repaired tetralogy of Fallot (14). They found increased left ventricular (LV) ECV in 11 of the patients and right ventricular (RV) ECV in 9 patients. LV and RV ECV correlated reasonably well with each other. Interestingly, increased RV ECV was associated more with volume rather than pressure overload. The investigators explain this by noting that cell volume as well as ECV increases with pressure overload. In addition, with myocardial atrophy in volume overload, ECV, which is a relative value, increases. Increased LV ECV was associated with arrhythmias. This is the first study to systematically compare LV and RV ECV and thus adds important information to the understanding of the potential use of T1 mapping in RV diseases. The research correspondence by Broberg et al. (15) also examines T1 mapping in 52 adults with repaired tetralogy of Fallot compared with 22 controls, but their analysis was limited to the left ventricle. This group found that 15 of the patients had ECVs ≥ 30 , and 1 in 3 of these had atrial arrhythmias or cardiovascular death, compared with 6% of the remaining 30 patients. Although the numbers are small, the study adds weight to the concept that elevated ECV is associated with adverse prognosis.

The prognostic power of T1 mapping was studied by Kammerlander et al. (16) in 473 patients referred for CMR, but excluding patients with amyloidosis, hypertrophic cardiomyopathy, and Anderson-Fabry disease. They demonstrate a good correlation with ECV by tissue FAXS analysis and ECV on CMR, further validating the measure. They also found that higher ECV by tertile was associated with cardiovascular hospitalization and cardiac death among imaging values, although when adjusted for clinical parameters, it was no longer statistically significant. However, ECV has been shown to

have independent prognostic power in larger patient groups (11).

Puntmann et al. (17) performed another prognostic study, but specifically in nonischemic dilated cardiomyopathy. They studied 637 patients and followed them for 22 months and observed 28 deaths, of which 22 were cardiac. Because Hct was not measured concurrently, ECV could not be measured in every patient. Interestingly, native T1 was an independent predictor of mortality, as well as heart failure mortality and hospitalizations, which constituted a secondary endpoint. However, we cannot be sure that ECV isn’t as good as native T1 in this particular population, because they were not directly compared. That being said, this study demonstrates that T1 mapping has prognostic utility in all comers referred for CMR as well as those particularly referred for evaluation of nonischemic dilated cardiomyopathy.

Finally, Taylor et al. (18) review the technical background and potential clinical applications of T1 mapping in a comprehensive look at the field by innovators in this area (18). Where does the field go from here? The initial validation studies are in the books, but further research is clearly needed to fully flesh out the clinical utility of both native T1 and ECV. We are at the very early stages of understanding the prognostic utility of these measures, and this needs to be compared with the prognostic utility of LV function and/or late gadolinium enhancement in the various myocardial diseases in which it has been studied. In addition, little is known presently about the change over time in any of these measures. Understanding the latter is essential to consider using native T1 or ECV as endpoints for clinical trials of novel therapeutics aimed at improving clinical outcomes. In that regard, studies are now beginning of novel agents to remove amyloid protein from patients with amyloidosis using T1 mapping as surrogate endpoints in addition to clinical endpoints. Such studies will help to validate the utility of these techniques. In summary, we at *JACC* hope that we have brought to the reader important insights into a rapidly evolving and novel area that promises exciting developments and new applications over the next few years for cardiovascular imagers.

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