T1 Mapping in Heart Failure
From Technique to Prognosis, Toward Altering Outcome

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Cardiovascular magnetic resonance (CMR) is increasingly used in the assessment of heart failure and cardiomyopathy because it offers uniquely precise noninvasive phenotypic characterization. Beyond enabling highly accurate and reproducible quantification of ventricular volumes and ejection fraction, the power of this technique was further established by the application of late gadolinium enhancement to identify scar, which has both diagnostic and prognostic use. Although this regional replacement fibrosis can be identified by late gadolinium enhancement and is clearly associated with adverse outcome in several cardiomyopathies, it is mostly irreversible. In contrast, reactive interstitial fibrosis, generally a precursor of replacement fibrosis, is potentially reversible. In reality, reactive fibrosis and replacement fibrosis are on a continuum. It is appreciated that a significant myocardial process is not identified by conventional late gadolinium enhancement CMR (in the absence of adequate expansion of the extracellular space) in a variety of cardiac conditions and that this undetected common pathology is diffuse interstitial fibrosis.

T1 mapping to assess extracellular volume (ECV) as a biomarker for diffuse myocardial fibrosis is currently a hot topic in the literature because this technique has emerged from its infancy and developed during the past decade, proliferating during the past 3 years. T1 maps can be produced of the native T1 value of tissue (informing with regard to both the myocyte and the interstitium) or after gadolinium contrast administration (enabling quantification of the extracellular space). The current gold standard technique for ECV quantification is equilibrium contrast CMR as described by Flett et al, with continuing development. T1 mapping may be sensitive to myocardial involvement under several conditions long before other changes are evident by biochemical, imaging or clinical indices. There are growing data correlating T1 time as a marker of extracellular matrix with tissue samples. Currently, numerous techniques for T1 mapping exist, and this heterogeneity adds to the challenges of data interpretation. To generate a T1 map, numerous coregistered image samples are taken during T1 recovery, which describes the recovery of the longitudinal component of nuclear spin after application of a radiofrequency pulse. A curve is fitted to the signal intensity plots at successive inversion times from which the T1 value at each pixel is derived, and ultimately a spatial representation (parametric map) of myocardial T1 values is produced. A modified look-locker inversion recovery sequence was the first clinically viable approach to T1 mapping of the heart. These early protocols have evolved to improve patient compliance and image quality but are still undergoing refinement. Although there is much interest in T1 mapping, close attention must be paid to minimizing errors resulting from either the technique or other sources or noise. Partial voluming of the blood pool can be problematic. Modified look-locker inversion recovery is precise and reproducible but has some accuracy issues. Saturation recovery techniques have improved accuracy but are less precise and less evaluated. There are numerous variations of methods and protocol. The CMR community is working to establish reference values for these, and ideally will agree a common validated method that is standardized across institutions, vendors and scanners. A forum has been established within the Society for Cardiovascular Magnetic Resonance to tackle these issues.

In systolic heart failure and, in particular, in heart failure with preserved ejection fraction (HFPEF or diastolic heart failure), it is likely that the global myocardial burden of diffuse fibrosis is of central relevance. Targeting the disease process earlier may be fundamentally important, and it is hoped that T1 mapping will offer a noninvasive early biomarker, free of the issues inherent in myocardial biopsy. There remains a lack of evidence-based therapy for HFPEF. Furthermore, there have been limited advances in the pharmacotherapy of chronic heart failure during recent years. Greater understanding of the molecular and cellular abnormalities underlying the disease process is required.

In this issue of Circulation: Cardiovascular Imaging, Mascherbauer et al report a timely preliminary study involving postcontrast CMR T1 mapping to explore the relationship between extracellular matrix accumulation and outcome in patients with suspected HFPEF. They enrolled 100 patients with suspected HFPEF, of whom 63 had HFPEF confirmed by transthoracic echocardiography, B-type natriuretic peptide, and right heart catheterization. Among the 61 subjects with confirmed HFPEF who also had interpretable T1 images, 16 combined cardiac outcome events (3 deaths from cardiovascular cause and 13 hospitalizations for heart failure) were identified during a mean follow-up period of 22.9±5.0 months. No events were recorded among those not confirmed to have HFPEF. There was a significant difference in T1 time...
hypertension, diabetes mellitus, and obesity, it is interesting

Given that the varied risk factors for HFPEF include old age,

particular toward the extremes of groups. But there seems

to be an overlap in T1 values between normal and disease

states that may challenge the specificity of the technique.13,14

The recently published studies by Liu et al15 and Piechnik et

al16 offer some insight into normal variation of T1 values, and

these data complement the study by Mascherbauer et al.11

Given that the varied risk factors for HFPEF include old age,

hypertension, diabetes mellitus, and obesity, it is interesting

that Liu et al15 found only weak correlation between ECV and

age (R²=0.021).

In addition to adding to the understanding of the pathobiol-
gy in HFPEF, the study by Mascherbauer et al11 found signif-

icant association between postcontrast CMR T1 time and

outcome in patients with HFPEF (hazard ratio, 0.99 [95% confidence interval: 0.98–0.99]; P=0.046), and from this the authors postulate its potential role as a prognostic biomarker in this setting. They present an impressive R value of 0.98 (P=0.046) for the correlation of T1 time with extracellular

(albumin range mapping and haematocrit.5 Left atrial area was

also significantly associated with outcome (hazard ratio, 1.08

[1.03–1.13]; P<0.01). The authors also incorporated invasive

assessment of the right heart, providing interesting correlation

of T1 time with pulmonary hemodynamics.

CMR can provide information with regard to several estab-

lished and emerging biomarkers, but new imaging techniques

must yield a change in outcome, not just information.18 The goal

is a ubiquitous T1 mapping technique to identify diffuse fibrosis

at a stage in the disease process to trigger an intervention that alters prognosis in a timely manner for maximum benefit in a similar way that T2* imaging of cardiac iron loading19 has transformed the outcome in β-thalassemia major.20

The application of T1 mapping to study the myocardium has the potential for another significant advance in the power and use of CMR, with clinical benefit from the identification of myocardial derangement that it is not possible to be identified currently. It is encouraging that articles such as the one in this issue provide data supporting the use of this technique in pro-

dviding diagnostic and prognostic information. However, CMR itself will not provide an improvement in outcome without proven interventions but may offer the tool to evaluate these and identify in whom and when maximum benefit is derived. Considerable work is required to consolidate T1 mapping methods and further establish the clinical use of the output, but as data continue to emerge it is possible to be optimistic as to the enormous potential of this technique. If with T1 mapping we can robustly measure diffuse fibrosis, guide therapy, and provide input to risk stratification models, perhaps most powerfully in combination with clinical, imaging, and genetic parameters, this will have far-reaching implications for cardiology. At present, we remain some way from this.

Disclosures

D.J. Pennell is a consultant to Siemens, Novartis, APOPharma, AMAG, and Shire and is a director and shareholder in Cardiovascular Imaging Solutions Limited. The other author reports no conflicts.

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