JACC: CARDIOVASCULAR IMAGING
VOL. 6, NO. 4, 2013

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcmg.2013.02.002

iVIEW

EDITOR'S PAGE

# T1 Mapping by CMR in Cardiomyopathy: A Noninvasive Myocardial Biopsy?

Christopher M. Kramer, MD,* Y. Chandrashekhar, MD,† Jagat Narula, MD, PhD‡

Cardiac magnetic resonance (CMR) is evolving to be the imaging modality of choice for differentiating the etiology of cardiomyopathies. Its inherent 3-dimensional nature enables accurate measurement of left ventricular (LV) volumes, mass, and ejection fraction (1). Late gadolinium enhancement (LGE) is used to aid in the differentiation of ischemic from nonischemic cardiomyopathies, and in the setting of the latter, can usually distinguish myocarditis, sarcoidosis, amyloidosis, and other infiltrative cardiomyopathies based upon their distinct pattern of enhancement (2). In addition, the newer technique of T1 mapping (3), typically performed after gadolinium-based contrast agent administration, has proved useful in demonstrating increased extracellular volume in conditions such as hypertrophic cardiomyopathy and aortic stenosis, and in these particular settings has been shown to correlate well with histological markers of myocardial fibrosis (4). Newer tissue mapping strategies, both T1 and T2, are quantitative techniques that offer the promise of standardizing CMR measurements of myocardial tissue properties, no longer leaving the interpretation to the eye of the beholder (5).

A subset of cardiomyopathy patients, especially those with amyloidosis, often suffer from concomitant renal dysfunction and may not be candidates for gadolinium due to concerns over nephrogenic systemic fibrosis (6). Thus, the ability to characterize myocardial tissue without contrast would be of substantial importance. T1 mapping is one such quantitative CMR technique and can be performed with or without contrast; the pulse sequence for T1 mapping has been recently improved with shortened breath-hold duration. The ability to measure differences in T1 without contrast would also obviate issues raised by the contrast kinetics due to variable renal function, contrast agent relaxivity, and pulse sequence differences. In this issue of *iJACC*, 2 papers demonstrate data in support of *native* or *noncontrast* T1 mapping for tissue characterization in various clinical conditions.

In the first, Puntmann et al. (7) compared hypertrophic cardiomyopathy (HCM) and nonischemic dilated cardiomyopathy (DCM) patients with control subjects. T1 mapping was performed prior to and sequentially at 10-min intervals after contrast infusion to calculate extracellular volume (ECV) fraction. These authors found that native T1 was significantly longer in cardiomyopathy patients (HCM 1,254 ± 43 ms, and DCM 1,239 ± 57 ms) than in controls (1,070 ± 55 ms); the accuracy was high with an area under the receiver operating curve of 0.99. In fact, native T1 performed better than post-contrast T1 and ECV measurements. Thus, in a case of diagnostic dilemma in which both morphologic imaging and LGE were unclear or the patient had stage 4/5 chronic kidney disease, native T1 mapping could clarify the diagnosis. Although, larger multicenter studies will be useful it is a significantly important finding.

The second paper by Karamitsos et al. (8) is a study of patients with amyloidosis; approximately one-half with a definitive diagnosis of cardiac involvement, one-quarter without, and another quarter with *possible* involvement. In addition to healthy control subjects they also included pa-

From the *University of Virginia, Charlottesville, Virginia; †University of Minnesota School of Medicine, Minneapolis, Minnesota; and the ‡Icahn School of Medicine at Mount Sinai, New York, New York. Dr. Kramer is supported by NIH R01 HL075792. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

tients with aortic stenosis (AS) as a set of hypertrophic controls. They found that native myocardial T1 was higher in cardiac amyloidosis compared to normal subjects and AS patients. Interestingly, their normal values were 958 ± 20 ms, over 100 ms shorter than the values in the previously discussed paper of Puntmann et al. (7). This also points to some of the limitations of the T1 mapping technique, e.g., variations dependent on pulse sequence used, scanner manufacturer, and field strength used. However, a native T1 value of 1,020 ms was 92% accurate for demonstrating possible or definite cardiac involvement in amyloid patients. This offers promise for the ability to identify cardiac amyloid without using contrast in CMR, a considerable advantage given the relatively high incidence of chronic kidney disease in this population.

The pathophysiologic basis of the elevated T1 values in these clinical conditions is not well understood. The link between post-contrast T1 shortening and fibrosis is fairly well-established in fibrotic diseases as mentioned above (4). As hypothesized by Puntmann et al. (7), the increase in native T1 may be due to increased extracellular volume due to expansion of the interstitial space from fibrosis in HCM or fibrillar deposits in amyloidosis. However, it is concerning as to why *native* T1 was not elevated in AS, which is also associated with fibrosis (8)? Is it specific for certain disorders? Was fibrosis in the AS not severe enough? Many such concerns would need clarification.

Furthermore, significant limitations remain to the application of T1 mapping in a broad manner. The pulse sequence varies between manufacturers, is not presently a product sequence, and is currently available only at selected centers; T1 values also differ at 1.5-T and 3.0-T field strengths. Moreover, whereas some laboratories report T1 values, others measure ECV. Thus, the pulse sequences and rules of measurement need to be standardized. A subcommittee of the Society for Cardiovascular Magnetic Resonance has recently been charged with this responsibility.

These 2 papers (7,8) nicely illustrate the agony and the ecstasy in cutting edge research and also the difficult road ahead. The Indian parable of 3 blind men and the elephant is highly applicable—what the results mean depends on the perspective used. Much appears to be a true breakthrough at first glance including the ability to characterize cardiac tissue with a simple CMR sequence and to do so without contrast in patients with renal dysfunction. The disease could be detected very early (8), even before current gold standards have indicated cardiac involvement. However, these very findings also raise other clinically loaded questions. Is differentiation between *normal* and *abnormal* (as in the Puntmann paper [7]) using a sophisticated and costly technique the major need of the hour in either HCM or DCM? In any case, these patients already had self evident disease recognized through other cheaper and widely used methods. Would the ability of T1 mapping to distinguish between *normal* and *abnormal* then be called a *screening* technique subject to the rigid rules? Should the future premium be placed on differentiating between type of pathology rather than normal versus abnormal in the myocardium? Finally, while eventual studies will clarify this part, the *so what* question would need to be answered. What would it mean for therapy and outcome? Just documenting that something is abnormal, even if detected early on, would have little benefit unless that information had direct clinical consequence. Although at least at this time such a goal seems far off for noncontrast T1 mapping, it needs to be the immediate focus of future research. The Karamitsos et al. (8) paper raises another interesting aspect. How do we decide what is true if the test parameter turns out better than the gold standard? In patients with amyloidosis, but no evidence for cardiac involvement, noncontrast T1 values were higher than normal, nearing those seen with moderate to severe AS. Is T1 mapping a determinant of an early disease not detectable by current approach, or is it just false positive? In the absence of a histological correlate we are only left to speculate. Editors have to often deal with really nascent science. Waiting for a histologic proof may be very difficult or even impossible to obtain in a robust manner and may delay publication of potentially important findings. On the other hand, rapid publication leaves a nagging feeling that the story is incomplete.

These 2 papers illustrate another important issue for investigators working on the edge of re-

JACC: CARDIOVASCULAR IMAGING, VOL. 6, NO. 4, 2013
APRIL 2013:532–4

search, as to how to interpret the mechanisms for what we find in a world without other guideposts, and when the thinking is juiced with optimism. Not surprisingly, the most common path is to extrapolate from other similar tests and conditions. It may be implied that noncontrast T1 mapping might be an even more sensitive alternative to LGE. Probably, LGE detects different fibrosis than that by increased T1 times; the coarse fibrosis seen with LGE most certainly also influences T1 times. Future studies will clarify this and it is a bit premature to conclude that one is a substitute for another. The second leap of faith common to many papers in this area is that native T1 increase implies fibrosis. Although there is a strong association, could one exclude the possibility of something totally unrelated to fibrosis, or common to both fibrosis and an altered extracellular matrix (including volume, edema, or unknown parameters that may influence T1 relaxivity)? Thus, while we may conclude that the patients with amyloidosis without clear cardiac involvement do have CMR suggested cardiac involvement, one is not any wiser about what this involvement means. Finally, these papers also illustrate the *cardiac biopsy* nature of these early findings. Logistical reasons and convenience limit these studies to focal slices and similar to a regular biopsy this may be hit or miss for a patchy pathology. Additional studies may clarify if these findings still hold true in the whole heart.

Regardless, T1 mapping comprises an important part of the imager's armamentarium for differentiating cardiomyopathies. It remains to be determined whether it would supersede the use of LGE or evolve as an additive approach. It is with confidence that we state that the age of noninvasive myocardial biopsy is upon us. We, however, also are acutely aware that we would need to know what this all means and how best to use it in clinical practice. We at *JACC: Cardiovascular Imaging* promise to help you ride along on this cutting edge journey.

## REFERENCES

1. Hundley WG, Bluemke DA, Finn JP, et al. ACCF/ACR/AHA/NASCI/SCMR 2010 expert consensus document on cardiovascular magnetic resonance: a report of the american college of cardiology foundation task force on expert consensus documents. J Am Coll Cardiol 2010;55:2614–62.
2. Parsai C, O'Hanlon R, Prasad SK, Mohiaddin RH. Diagnostic and prognostic value of cardiovascular magnetic resonance in non-ischaemic cardiomyopathies. J Cardiovasc Magn Reson 2012;14:54.
3. Iles L, Pfluger H, Phrommintikul A, et al. Evaluation of diffuse myocardial fibrosis in heart failure with cardiac magnetic resonance contrast-enhanced T1 mapping. J Am Coll Cardiol 2008;52:1574–80.
4. Flett AS, Hayward MP, Ashworth MT, et al. Equilibrium contrast cardiovascular magnetic resonance for the measurement of diffuse myocardial fibrosis: preliminary validation in humans. Circulation 2010;122:138–44.
5. Kramer CM, Narula J. Viability is in the eye of the beholder . . .. J Am Coll Cardiol Img 2012;5:574–5.
6. Zou Z, Zhang HL, Roditi GH, Leiner T, Kucharczyk W, Prince MR. Nephrogenic systemic fibrosis: review of 370 biopsy-confirmed cases. J Am Coll Cardiol Img 2011;4:1206–16.
7. Puntmann VO, Voigt T, Chen Z, et al. Native T1 mapping in differentiation of normal myocardium from diffuse disease in hypertrophic and dilated cardiomyopathy. J Am Coll Cardiol Img 2013;6:475–84.
8. Karamitsos TD, Piechnik SK, Banypersad SM, et al. Noncontrast T1 mapping for the diagnosis of cardiac amyloidosis. J Am Coll Cardiol Img 2013;6:488–97.