Myocardial Tissue Characterization by Magnetic Resonance Imaging

Novel Applications of T1 and T2 Mapping

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Abstract: Cardiac magnetic resonance (CMR) imaging is a well-established noninvasive imaging modality in clinical cardiology. Its unsurpassed accuracy in defining cardiac morphology and function and its ability to provide tissue characterization make it well suited for the study of patients with cardiac diseases. Late gadolinium enhancement was a major advancement in the development of tissue characterization techniques, allowing the unique ability of CMR to differentiate ischemic heart disease from nonischemic cardiomyopathies. Using T2-weighted techniques, areas of edema and inflammation can be identified in the myocardium. A new generation of myocardial mapping techniques are emerging, enabling direct quantitative assessment of myocardial tissue properties in absolute terms. This review will summarize recent developments involving T1-mapping and T2-mapping techniques and focus on the clinical applications and future potential of these evolving CMR methodologies.

Key Words: diffuse fibrosis, scarring, edema, inflammation, parametric mapping

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Cardiac magnetic resonance (CMR) is an imaging technique that has substantially evolved over the last 15 years to become a valuable clinical and research tool in cardiology.1-2 With the development of the late gadolinium enhancement (LGE) technique using an inversion-recovery (ShMOLLI) cardiac gated mapping of T1. September 29, 2010. All rights sold exclusively to Siemens Medical Solutions. US patent pending 61/689,067: Stefan K. Piechnik and Matthew D. Robson. Color map design method for immediate assessment of the deviation from established normal population statistics and its application to cardiovascular T1 mapping images. The remaining authors declare no conflicts of interest.

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US patent pending 61/387,591: Stefan K. Piechnik and Matthew D. Robson. Systems and methods for shortened look-locker inversion recovery (Sh-MOLLI) cardiac gated mapping of T1. 2004. A new frontier for CMR to explore tissue characteristics in more quantitative terms. To estimate T1, an inversion recovery sequence is used independent of field strength or the presence of off-resonance effects. The remaining authors declare no conflicts of interest.

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T1-weighted (T1W) sequence in 1999, the identification of the patterns and distribution of scar and fibrosis became possible for differentiating ischemic from nonischemic cardiomyopathies.1,3,4 Similarly, the refinement of T2W techniques enabled the detection of myocardial edema and inflammation, further establishing the role of CMR in myocardial tissue characterization.5 Recently, parametric T1-mapping and T2-mapping techniques opened a new frontier for CMR to explore tissue characteristics in more quantitative terms.6,7 These novel mapping strategies offer the promise of objective assessment of myocardial tissue properties, providing an absolute quantitative measure rather than just a qualitative (visual) or semiquantitative evaluation (on the basis of comparisons of relative signals), which can be subjective and may underestimate or overestimate disease.

This review will focus on the clinical applications of T1 and T2 mapping with particular focus on recent developments in this rapidly evolving field.

MYOCARDIAL T1 AND T1 MAPPING

T1 is the longitudinal (or spin-lattice) relaxation time of a tissue. T1 mapping refers to parametric maps that are generated from a series of images acquired with different T1 weighting so that each pixel can be assigned a T1 value. T1 maps can be displayed using color or thresholded scales to enable quantitative visual interpretation.8,9 Each tissue type exhibits a characteristic range of normal T1 relaxation times at a particular field strength, deviation from which may be indicative of disease. Measured myocardial T1 values are also influenced by various physiological and technical factors, including temperature, disease, age, sex, heart rate, and the pulse sequence used.10-12

The Modified Look-Locker Inversion Recovery (MOLLI) method developed by Messroghli et al13 in 2004 opened a new frontier of clinical applications for myocardial T1 mapping. Newer variants, based on inversion-recovery, saturation-recovery, or hybrid approaches, continue to emerge, enabling faster acquisition times and minimizing sources of error such as heart-rate dependency, motion, off-resonance, and partial volume effects.14-20 Although MOLLI-based sequences are the most used and most extensively validated,11,13,20,21 the saturation-recovery single-shot acquisition sequence is a very promising novel approach demonstrating good T1 measurement accuracy in phantoms.14 This contrasts with MOLLI techniques, which are known to underestimate...
Myocardial T1-mapping methods are used for native (ie, without the use of gadolinium-based contrast agents) and also for postcontrast T1 measurements. In combination with hematocrit levels, these enable the quantification of extracellular volume fraction (ECV). Native myocardial T1 reflects a composite signal from both the intracellular (predominantly myocytes) and the extracellular compartment. Gadolinium-based contrast agents shorten T1 times, and the physiological differences in redistribution after administration directly affect tissue T1. However, isolated postcontrast T1 values are influenced by a number of factors, including native T1, the type and dosage of gadolinium contrast used, and the postcontrast acquisition time within the contrast pharmacodynamics redistribution process. The latter depends on numerous systemic variables, such as body fat percentage, hematocrit levels, and glomerular filtration rate. Therefore, currently preferred outputs for myocardial T1 quantification are native T1 and ECV.

There is increasing interest in the study of the myocardial interstitium as a determinant of disease course and as a therapeutic target in a number of cardiac conditions. ECV measures the extracellular space, and, in the absence of myocardial edema or other factors that could expand the interstitial space (such as amyloid), expansion of the myocardial collagen volume fraction is responsible for most of the extracellular matrix expansion. ECV can act as a surrogate for (but not as a direct measure of) myocardial interstitial fibrosis. It is possible to quantify myocardial ECV in vivo using the equilibrium CMR technique, which showed good correlation with histologic collagen volume fraction. Equilibrium CMR assumes an equilibrium steady state between the intravascular and interstitial spaces as a strict, 2-compartment model and requires a constant infusion of contrast to achieve a steady state. This protocol may be abbreviated by using the bolus contrast technique with delayed (15 min) postcontrast measurement, known as dynamic-equilibrium CMR, which closely approximates the steady state and is sufficient for most myocardial ECV applications. ECV calculation can correct for some of the variables confounding isolated postcontrast T1 values, but its accuracy also relies on the assumption that the effect of contrast is equal in the 2 compartments, which is subject to debate. Additional confounders include incomplete dynamic equilibrium, contrast transfer into other compartments, and a faster renal clearance than exchange rate.

Clinical Applications of T1 Mapping

The clinical utility of native T1 mapping relies on a normal range with small variability and high sensitivity to disease. Elevated T1 times in the myocardium have been reported in a number of commonly encountered cardiac conditions including myocardial infarction, myocarditis, hypertrophic and dilated cardiomyopathy (DCM), cardiac amyloidosis, cardiac involvement in systemic diseases, and diffuse fibrosis in patients with aortic stenosis.

FIGURE 1. T1 mapping in acute myocardial infarction. Edema T2W images (left column), acute LGE images (center), and ShMOLLI T1 mapping (right column) are displayed. Two sets of images (A and B) corresponding to 2 separate patients are shown. A, A case of transmural inferior STEMI. Both edema (T2W) and LGE depict an area of increased signal intensity; in the same region T1 mapping depicts significantly increased T1 values (shown in red) compared with the remote unaffected myocardium (normal T1 values shown in green). B, A case of subendocardial NSTEMI. Although the T2W images show only a mild increase in brightness, there is an area of increased T1 values exceeding the area of LGE enhancement. It is noteworthy that the peak troponin I level was significantly different in the 2 patients (peak troponin I 50 mg/mL in the STEMI patient vs. 7 mg/mL in the NSTEMI patient). NSTEMI indicates non-ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction (modified from Dall’Armellina et al, figure 1). Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
FIGURE 2. T1 mapping in acute myocarditis. A, Dark-blood T2W imaging demonstrating increased signal intensity in the mid-lateral wall (arrows). B, Bright-blood T2W imaging demonstrating increased signal intensity in the mid-lateral wall (arrows). C, Shortened MOLLI (ShMOLLI) T1 map demonstrating increased T1 values (1100 to 1200 ms) in the lateral wall (arrows). D, LGE imaging demonstrating mid-wall enhancement in the lateral wall (arrows) (modified from Ferreira et al,37 figure 1). Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

FIGURE 3. T1-mapping in amyloidosis. CMR end-diastolic frame from cine (left panel), ShMOLLI noncontrast T1 map (middle panel), and LGE images (right panel) in a normal volunteer, a cardiac amyloid patient, and an aortic stenosis patient. Note the markedly elevated myocardial T1 time in the cardiac amyloid patient (1170 ms, into the red range of the color scale) compared with the normal control (955 ms) and the patient with aortic stenosis and left ventricular hypertrophy (998 ms). ED indicates end diastolic (modified from Karamitsos40). Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
In particular, native myocardial T1 is prolonged by excess free water content,\textsuperscript{45–47} such as that due to acute edema, inflammation, or pooling within an expanded interstitial space. Ferreira et al\textsuperscript{9} demonstrated for the first time that native T1 mapping detects acute myocardial edema in patients with Tako-tsubo cardiomyopathy and regional stunning with high diagnostic accuracy compared with conventional T2W techniques. Dall’Armellina et al\textsuperscript{48} found that the diagnostic performance of T1 mapping for detecting acute myocardial injury was at least as good as that of T2W CMR in patients with ST elevation myocardial infarction and superior to T2W imaging in patients with non-ST elevation myocardial infarction (Fig. 1). For determining the area at risk after acute myocardial infarction, native T1 mapping and T2 mapping yield similar quantitative results and good agreement with microspheres in animal models.\textsuperscript{49} Recently, native T1 mapping was shown to have superior sensitivity compared with T2W and LGE techniques in detecting acute myocarditis (Fig. 2), which may be especially useful in detecting subtle focal disease and when gadolinium-based contrast imaging is not feasible.\textsuperscript{37} Furthermore, native myocardial T1 values are significantly elevated in patients with DCM and hypertrophic cardiomyopathy compared with normal controls\textsuperscript{38,50}, T1 values are also increased in apparently normal regions without LGE in both conditions. These findings suggest that native T1 mapping provides information on myocardial tissue characteristics beyond that achieved by standard CMR techniques. The clinical utility of native T1 mapping was also shown in patients with cardiac amyloidosis (Fig. 3) who have significantly elevated T1 values compared with normal subjects and patients with aortic stenosis.\textsuperscript{40} Native T1 mapping may be particularly useful for identifying amyloid patients with possible or definite cardiac involvement given its high diagnostic accuracy and the difficulty in applying conventional LGE in this cohort.\textsuperscript{40} Increased native T1 values have been reported in patients with human immunodeficiency virus\textsuperscript{51} and patients with systemic lupus erythematosus and cardiac involvement.\textsuperscript{52} In patients with severe aortic stenosis, native T1 values are increased and correlate with the degree of biopsy-quantified collagen volume fraction.\textsuperscript{45} Native myocardial T1 values may be lowered by water-protein interactions and fat or iron content and thus can also serve as a diagnostic tool in

**FIGURE 4.** Examples illustrating excellent agreement between LGE and ECV in cases of focal abnormalities in myocardial ECV. Pre-contrast T1 maps (top row), postcontrast T1 maps (second row), LGE (third row), and ECV maps (bottom row) for patients with: (A) chronic MI, (B) acute myocarditis, and (C) HCM. HCM indicates hypertrophic cardiomyopathy; MI, myocardial infarction (modified from Kellman\textsuperscript{57}). Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
characterizing Anderson-Fabry disease, fat in cardiac masses, and myocardial siderosis. ECV may serve as a marker for myocardial fibrosis in a number of myocardial diseases. The ECV of the normal myocardium has been reported to be in the range of 24% to 28%. ECV expansion has been demonstrated in a number of cardiac conditions including myocardial infarction, myocarditis, hypertrophic cardiomyopathy and DCM, cardiac amyloidosis, diabetes, obesity, congenital heart disease with myocardial dysfunction, and other cardiac conditions characterized by diffuse myocardial fibrosis (Fig. 4). The detection of interstitial myocardial fibrosis may allow early therapeutic intervention before irreversible changes occur.

**MYOCARDIAL T2 AND T2 MAPPING**

T2 (or spin-spin) relaxation time is the time constant governing the exponential decay of transverse magnetization. The fractional increase in T2 is substantially larger than the fractional increase in T1 when water content is increased, and this relationship was demonstrated in a canine model of acute myocardial infarction 30 years ago. Various technical improvements since then have enabled the wide clinical use of T2W CMR for the qualitative or semiquantitative detection of myocardial edema and inflammation. However, there are a few well-recognized limitations of conventional T2W techniques, including the need for a “normal” reference region of interest, either in remote myocardium or skeletal muscle.
muscle, which can lead to false-negative results when these reference areas are also affected in systemic processes.\textsuperscript{37,80,69}

Quantification of T2 myocardial relaxation times promises to circumvent these limitations and is achieved by collecting multiple images with different T2-weighting, providing multiple points along the T2 decay curve for fitting of an exponential signal decay model.\textsuperscript{6} Initial T2-mapping techniques based on dark-blood turbo spin echo sequences were sensitive to ghosting and motion artifacts.\textsuperscript{6}

Recently, bright-blood T2 prep-based pulse sequences showed improved results.\textsuperscript{70} These T2-mapping techniques exhibit heart-rate dependency, sensitivity to the order of acquisition,\textsuperscript{71} and flip angle, with incomplete T1 recovery resulting in T1 weighting and errors in the T2 relaxation time measurements, although increasing the sampling interval can reduce this effect.\textsuperscript{72} Currently, normal measured T2 times exhibit larger interindividual variability compared with measured T1 times\textsuperscript{70,72,73} but nevertheless have been shown to be useful in detecting disease.

Clinical Applications of T2 Mapping

T2 mapping can detect edematous myocardial territories in a variety of cardiac pathologies, including acute myocardial infarction, myocarditis, Tako-tsubo cardiomyopathy, and heart transplant rejection.\textsuperscript{72,74–77} Verhaert et al\textsuperscript{77} assessed T2 mapping in patients with acute myocardial infarction and found that myocardial segments characterized by recent ischemic injury can be quantitatively differentiated from remote myocardium by their higher T2 value (Fig. 5). Another study from the same group showed the usefulness of T2 mapping in suspected myocarditis or Tako-tsubo cardiomyopathy, demonstrating that T2 mapping can identify myocardial involvement beyond conventional CMR techniques such as T2W and LGE imaging. T2 mapping has also been used as a non-invasive tool for cardiac transplant monitoring with promising preliminary findings in small cohorts.\textsuperscript{74,78}

FUTURE DIRECTIONS

T1-mapping and T2-mapping techniques have already demonstrated clinical usefulness as quantitative tissue characterization MR techniques in a variety of common cardiac conditions. Further technical improvements are expected to advance their clinical application in the detection of acute, subacute, and subclinical pathologies. Consensus within the CMR community regarding methodological issues and standardization is needed to facilitate wider clinical utility. Multicenter studies should be performed to assess not only the diagnostic value of these techniques but also their utility in therapeutic monitoring and prognostication.

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