Myocardial T1 Mapping

– Hope or Hype? –

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Cardiovascular magnetic resonance is a well-established tool for the quantification of focal fibrosis. With the introduction of T1 mapping, diffuse myocardial processes can be detected and quantified. In particular, infiltration and storage disorders with large disease-related changes, and diffuse fibrosis where measurement is harder but the potential impact larger. This has added a new dimension to the understanding and assessment of various myocardial diseases. T1 mapping promises to detect early disease, quantify disease severity and provide prognostic insights into certain conditions. It also has the potential to be a robust surrogate marker in drug development trials to monitor therapeutic response and be a prognostic marker in certain diseases. T1 mapping is an evolving field and numerous factors currently preclude its standardization. In this review, we describe the current status of T1 mapping and its potential promises and pitfalls. (*Circ J* 2015; **79**: 487–494)

Key Words: Biomarkers; Cardiovascular MRI; Diffuse fibrosis; Imaging; T1 mapping

The Need for T1 Mapping

Cardiovascular magnetic resonance (CMR) is the gold standard for noninvasive detection of focal fibrosis using gadolinium-based contrast agents (GBCA).^{1–4} This technique cannot be used to quantify diffuse fibrosis and for that, endomyocardial biopsy (EMB) remains the gold standard despite being prone to sampling error. Biopsy also carries with it inherent procedural risk and provides no information on the extent of ventricular involvement.^{5,6} With the introduction of T1 mapping, diffuse processes can now be detected and quantified, particularly for infiltrative and storage processes where the signal is high and for quantification of diffuse fibrosis, which is difficult to perform, but potentially has greater impact. This is reflected by the exponential rise in the number of myocardial T1 mapping-related publications referenced on Pubmed (**Figure 1**), and the swift progress made towards delivery of T1 mapping as a commercially available clinical test. It offers numerous promises, such as early detection of specific conditions; a surrogate marker in drug development trials, and as a prognostic marker in certain diseases. However, this is a still rapidly evolving field and numerous factors are currently precluding its standardization.⁷ This review describes the status quo of T1 mapping and its potential promises and pitfalls.

T1 Mapping: Past and Present

Late gadolinium enhancement (LGE) imaging was an advance on T1-weighted imaging because the operator could select a tissue that was “normal” and null it; that is, exaggerating the signal from any tissue with a different T1, thus identifying focally abnormal regions such as scar (eg, infarction), edema or amyloid. T1 mapping requires quantification of the exact T1 of a particular tissue and can be performed without GBCA. Different tissues have specific ranges of T1 (milliseconds) at a particular magnetic field strength⁸ and can be used to detect pathology.

Native T1 or Native Myocardial T1

The native T1, or noncontrast myocardial T1, is the longitudinal relaxation time (T1) of a given tissue without GBCA. This provides an intrinsic signal from both the myocytes and the interstitium.⁹ Our current understanding is that T1 is prolonged with fibrosis,¹⁰ edema¹¹ and amyloid¹² (**Figure 2**) and reduced in lipid accumulation (Anderson-Fabry disease [AFD]),¹³ cardiac siderosis,¹⁴ (**Figure 3**) and hemorrhage in acute infarction (**Figure 4**).¹⁵ However, as techniques advance, potentially other trends may be found. It does appear that pseudo-normalization of native T1 values also occurs when 2 processes cancel out coexisting fibrosis and iron (eg, sickle cell disease) or lipid (eg, AFD).¹⁶

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Post-Contrast T1 for Extracellular Volume (ECV) Quantification

The extracellular matrix (ECM) is a complex architectural network made up of structural and nonstructural proteins contributing to strength and plasticity.¹⁷ The matrix is hydrated with extracellular fluid; measurement of this, the ECV, approximates the ECM. The ECM and ECV may expand with fibrosis, edema or amyloid (**Figure 2**).

GBCAs do not cross cell membranes. Post-contrast T1 mapping therefore partly measures the extracellular space. However, factors such as renal excretion rate, altered wash-in and

wash-out kinetics of GBCAs in diseased myocardium,¹⁸ the volume of distribution and the acquisition time¹⁹ are influential. The ECV technique intrinsically corrects for this. ECV measurement is done when the concentration of contrast is equal in the water between cells in the myocardium and in blood; a sufficient equilibrium exists, either by a primed infusion or after a bolus and sufficient time (15 minutes is adequate for all but massive interstitial expansion).²⁰ The ratio of a pre- to post-contrast signal change in the myocardium and blood reflects the relative ECV of the blood and myocardium (ie, the partition coefficient). As the blood ECV is one minus the hematocrit (from a simple blood test, **Figure 5**), this can be substituted to obtain the myocardial ECV,²⁰ which is $(1 - \text{hematocrit}) \times \Delta R1_{\text{myocardium}} / \Delta R1_{\text{blood}}$, where $R1 = 1/T1$.

There is no real need to use an infusion; the bolus-only method²¹ works for conditions with ECV <0.4, but progressively reads a higher ECV in high interstitial expansion diseases. An alternative approach is to perform multiple T1 measurements during contrast wash-out rather than awaiting equilibrium.²² The accuracy and relative precision of these approaches are unknown, and currently most centers do a single pre- and post-contrast measurement. Newer approaches are to automatically register the pre- and post-contrast T1 maps to create ECV maps (**Figure 5**).²³

Measuring the T1: Techniques and Sequences

Initial methods of T1 measurement involved multiple breath-holds to obtain the recovery curve from different time points. The Look-Locker sequence was introduced²⁴ to measure the T1 relaxation time at multiple time points after an initial excitation pulse and then subsequently adapted as the modified Look-Locker inversion recovery (MOLLI)²⁵ sequence. Color pixel-wise “T1 maps”, whereby each pixel carries the measured value of T1 (**Figure 6**), can now be generated. Since the introduction of the MOLLI method, multiple incremental improvements have been made, including better inversion

Figure 3. Short-axis ShMOLLI color maps of a normal myocardium and conditions with low native T1 values (green: normal T1, blue: low T1). ShMOLLI, shortened modified Look-Locker inversion recovery sequence.

Figure 4. Basal short-axis view of a patient with an acute inferior myocardial infarction. The white arrow on the MOLLI image shows the area of low T1 denoting hemorrhage within the area of edema in the inferior and inferoseptal walls. The red arrow on the corresponding LGE image shows the dark core of microvascular obstruction within a full-thickness infarct in the same territory. LGE, late gadolinium enhancement; MOLLI, modified Look-Locker inversion recovery sequence.

Figure 5. ECV maps derived by acquiring hematocrit, native T1 and post-contrast T1 values (MOLLI) from the short-axis view of a healthy volunteer. ECV, extracellular volume; MOLLI, modified Look-Locker inversion recovery sequence.

pulses, sampling schemes, image reconstruction (eg, motion correction),^{18,25} curve fitting (making shorter breath-holds) and the introduction of error maps to provide confidence in measured results.²⁶ New techniques have also been developed, including the saturation recovery single-shot acquisition (SASHA) sequence²⁷ and hybrid schemes (eg, SAPHIRE), which is heart rate independent and uses a combination of saturation and inversion pulses.^{28,29} Each technique is

implemented differently by different scanner manufacturers^{30–32} and there is currently a lack of clarity on which improvements are valuable or even how to measure this value. Intuitively, the best sequence would be the one that most accurately measures T1, but even this is difficult and it is likely that precision (compared to the disease signal) and robustness across a healthcare system (which is not yet done) may be more important than accuracy. Reflecting this, current advice is to have a

Figure 6. Results from 3 T1 mapping sequences (MOLLI, ShMOLLI and SASHA) of the 4 chambers of the heart of a healthy volunteer. Each technique has a different normal range and color display (color look-up tables are not currently standardized). Development is rapid and it may not yet be the time to standardize these, but at some stage, methodology should come second to clinical utility and standardization. MOLLI, modified Look-Locker inversion recovery sequence; SASHA, saturation recovery single-shot acquisition sequence; ShMOLLI, shortened MOLLI.

locally produced reference range from healthy volunteers, although quality control and standardization systems are being constructed.

T1 Mapping in the Clinical Context

Cardiac Amyloidosis

Amyloid in ventricular muscle is either light-chain (AL) or transthyretin (ATTR) in origin. Massive deposition of amyloid can occur in the heart, causing heart failure (HF) and a poor prognosis.³³ Diagnosing cardiac amyloid using conventional CMR measures is easy in advanced disease, but harder in early disease (when treatment will improve survival). Late gadolinium imaging appearances are variable and renal failure precluding gadolinium administration use is not uncommon. T1 mapping techniques may have a higher sensitivity for detecting early disease,¹² are able to quantify the amyloid and can be used in the context of renal failure. In addition, the ECV elevation in amyloidosis is beyond that of any other disease, making it pathognomonic. AL may have a higher native T1 and ATTR has a higher ECV, which hints at the underlying biology and may help predict the underlying subtype.^{34,35} Both native T1 and ECV are linked to prognosis^{36,37} and are currently being used as surrogate markers in 2 clinical trials of novel therapeutic agents for the treatment of amyloidosis (NCT 01981837 and 01777243).

AFD

AFD is a rare but treatable X-linked disorder resulting in sphingolipid deposition in a number of different organs. Its cardiac manifestations are left ventricular (LV) hypertrophy, arrhythmias and valvular disease.³⁸ Early treatment with enzyme replacement therapy may reverse or slow disease progression. Native T1 mapping can identify patients early, potentially helping target the costly enzyme therapy. Two groups have independently demonstrated lower myocardial T1 values in AFD patients compared with healthy controls.^{13,39} Furthermore, T1 mapping can discriminate against other diseases with hypertrophy with no overlap in T1 values¹³ and has excellent reproducibility.⁴⁰ Pseudo-normalization in T1 values (mixed extracellular fibrosis and lipid) and subsequent prolongation

of T1 (burnt-out fibrosis) may provide an insight into disease progression.

Iron Overload

Hemochromatosis (primary and secondary) is characterized by a progressive increase in total body iron stores and abnormal iron deposition in several organs, including the heart and liver. Aggressive chelation therapy can prevent death, but is not without side effects.⁴¹ Development of the T2* imaging technique for the quantification of cardiac iron deposition led to a shift in the survival of patients with cardiac siderosis,⁴² but it requires a long breath-hold, and post-processing can be complex. Iron shortens the native T1 and Sado et al recently showed T1 mapping had a good correlation with T2*, was more reproducible and could potentially improve the detection of mild iron overload.¹⁴ This will inevitably have implications for future clinical trial design and therapeutic monitoring.

Ischemic Heart Disease

The role of T1 mapping in understanding LV remodeling following myocardial infarction has also been explored. Dall'Armellina et al noted that the higher the acute native T1 value, the lower the likelihood of segmental recovery at 6 months.⁴³ Chan et al⁴⁴ showed reduced post-contrast T1 in the remote myocardium of acute and chronic infarct patients when compared with controls. In that group of patients, there was also a correlation between the post-contrast T1 value and LV ejection fraction (EF). However, other studies failed to show a difference in post-contrast T1 and ECV between the remote myocardium of infarct patients and controls.^{45,46} More work remains to be done. T1 mapping have been shown to correlate with the area at risk when compared with SPECT⁴⁷ and more validation studies are needed to establish its role with reference to T2 mapping.

HF

T1 mapping adds a new dimension to improving our understanding of the changes to the ECM, which plays a role in the pathogenesis of HF. There is a correlation between post-contrast T1 values and diffuse fibrosis on EMB⁴⁸ and whole-heart histology (heart transplant)⁴⁹ in patients with symptomatic HF.

A strong correlation has also been shown between ECV and diastolic dysfunction in patients with HF and preserved EF,⁵⁰ and a post-contrast T1 less than 388 ms (using their particular scanner and sequence) has been linked with an increased risk of cardiac events.⁵¹ Diabetic patients have been shown to have higher ECV values, and at a higher risk of death and hospitalization for HF.⁵² Of note, renin-angiotensin-aldosterone blockade was associated with lower ECV values.⁵²

Aortic Stenosis (AS)

Despite existing guidelines for surgical treatment,^{53–55} the pathophysiology underlying AS is incompletely defined. Diffuse fibrosis may appear prior to symptom manifestation and architectural changes, so there is potential to improve diagnosis and treatment. Mild to moderate diffuse fibrosis at baseline has been linked to better symptomatic improvement through marked reduction of LV hypertrophy (LVH) postoperatively compared with those with severe fibrosis.^{56–58} Increased native T1 values have been shown to correlate with histology,¹⁰ and this increase was more pronounced in symptomatic patients. In a group of asymptomatic patients,⁵⁹ native T1 values also correlated significantly with global longitudinal strain. ECV was found to be persistently elevated 6 months after aortic valve replacement for severe AS, despite LVH regression, indicating early LVH regression is predominantly a cellular process.²⁰ Interest in T1 mapping as a biomarker in AS is growing and prospective cohort studies (NCT 01658345, 02174471, 01755936)⁶⁰ are currently underway.

Cardiomyopathy

In a small cohort of dilated cardiomyopathy (DCM) patients,⁶¹ the native T1 values and ECV were increased in DCM patients when compared with normal volunteers, and a prolonged native T1 correlated with histological fibrosis.^{62–64} Likewise, native T1 values and ECV have been validated for hypertrophic cardiomyopathy (HCM) against normal cohorts.^{21,32,64,65} Puntmann et al also showed that native T1 mapping had higher sensitivity and specificity compared with post-contrast T1 and ECV to differentiate between DCM/HCM patients and

normal volunteers.⁶⁴ More work is being done on an international scale to explore the role of T1 mapping as a prognostic biomarker in HCM (HCMR study, NCT 01915615). In patients with muscular dystrophy and cardiac involvement, global and regional myocardial ECV values were significantly higher compared with patients without cardiac involvement and controls,⁶⁶ and therefore may play a role in risk stratification of these patients. There is also growing interest in exploring the role of T1 mapping in the early detection of rejection following heart transplantation,⁶⁷ in those at risk of uremic cardiomyopathy in chronic kidney disease,⁶⁸ and in the detection of early diffuse fibrosis in systemic sclerosis^{69,70} and systemic lupus erythematosus.⁷¹ However, more validation work is required to establish which disease process will benefit the most from this technique.

Myocarditis

The clinical spectrum of acute myocarditis can range from subtle to catastrophic. Biopsy remains the gold standard for diagnosis but has limitations and CMR with LGE was a major advance. Existing techniques such as LGE imaging may be negative in cases with minimal areas of global rather than focal abnormality;⁷² detecting edema by conventional T2 imaging may be challenging.^{73,74} Native T1 mapping has been shown to have superior diagnostic performance and higher sensitivity for detection of acute myocarditis than T2-weighted and LGE imaging^{75,76} and was able to display typical non-ischemic patterns without the need for contrast agents when the patients were imaged within 3 days of presentation.⁷⁷ ECV has not yet been well studied.

Atrial Fibrillation (AF)

AF⁷⁸ is linked to diffuse atrial and ventricular fibrosis.⁷⁹ Ling et al showed reduced post-contrast atrial T1 in AF predictive of outcome post ablation,⁸⁰ and AF (persistent or paroxysmal) has reduced post-contrast T1 values,⁸¹ whereas tachycardia-induced cardiomyopathy has persistently lower post-contrast T1 values post ablation.⁸² However, it is our opinion that the technology for routinely quantifying diffuse atrial fibrosis does

not exist at this stage.

Pitfalls and Challenges

There are several challenges before T1 mapping can be routinely implemented in clinical practice and the T1 Consensus Statement⁷ lays out some of these. Currently, it recommends the need for local normal values for every scanner, consistent parameters across pre- and post-contrast maps, quality control by use of parametric error maps, avoidance of partial voluming of blood when drawing regions of interest during analysis, and systematic testing of the accuracy, precision and stability of techniques over time. Other challenges remain, such as an overlap in T1 values between different disease states and normal (Figure 7), with the exceptions of large changes with fat, iron, amyloid and edema. Much work is ongoing to reduce the measurement error contributing to variability, including all aspects from sequence design and outputs, analysis methodology and quality control systems.

Future Prospects

The T1 mapping field is progressing rapidly on all fronts. New clinical developments, such as large, multicenter collaborations and Biobank studies, are underway. In the near future, T1 mapping could potentially change clinical practice and help develop new therapies for amyloid, AFD and iron overload. It will extend the spectrum of recognized disease in rheumatologic conditions affecting the heart, improve our understanding of myocarditis, may increase detection of infiltration in elderly HF (eg, ATTR amyloidosis) and explore new avenues such as monitoring of chemotherapy-induced cardiotoxicity (NCT 01719562) and cardiac involvement in HIV (NCT 02054494). These platforms should help develop tighter methodologies for diffuse fibrosis quantification. Integration of T1 mapping with other technologies (eg, genetics, proteomics, hybrid PET/MR imaging) may reinvigorate our understanding of the nature of myocardium and its components and transform our day-to-day management of disease processes.

Conclusions

Although T1 mapping is currently impeded by restricted accessibility, nonstandardized reference values for normal and abnormal myocardium, and non-uniformity of technique among vendors, it promises to play a fundamental role in a variety of clinical settings in the near future. We anticipate this will start for rare diseases, where there are high disease-related changes and clinical need and a drug development imperative will catalyze its standardization. This should subsequently provide the development platform for more robust methods for detection of diffuse fibrosis. Combined, the potential is for better mechanistic insights into disease processes, which should eventually lead to improved diagnostic pathways, prognostication and monitoring of therapy.

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