Native Myocardial T1 Mapping, Are We There Yet?

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SUMMARY

T1 or longitudinal relaxation time is one of the very fundamental magnetic resonance imaging (MRI) time constants and a tissue characterizing parameter. Only during the last decade did it become possible to quantify T1 values of the myocardium through T1 mapping. Evolving from only region of interest analysis and long acquisition times to the pixel-based parametric mapping and short breath-hold sequences, T1 mapping is reaching maturity among cardiac magnetic resonance (CMR) techniques. Both inversion recovery methods such as MODified Look-Locker Inversion (MOLLI) and Shortened MOLLI (ShMOLLI) and saturation recovery methods such as Saturation recovery Single-Shot Acquisition (SASHA) are available for T1 quantification with variable degrees of accuracy, precision, and reproducibility. Native (non-contrast) T1 values increase with edema, amyloid deposition, and fibrosis, while they decrease in fat or iron deposition in the myocardium. These features enabled significant expansion of the clinical applications of native T1 mapping where it provides high sensitivity and specificity and even acts as a disease biomarker or a predictor of prognosis. It is of particular usefulness in diffuse myocardial diseases where conventional CMR techniques might be deceiving. A brighter future for the technique is expected if certain challenges are to be faced, examples of which are the need for standardization of normal values, acquisition techniques, and improving analysis tools. (Int Heart J 2016; 57: 400-407)

Key words: Myocardium, Cardiovascular MRI, Diffuse fibrosis

Over the past few decades, cardiac magnetic resonance (CMR) imaging has proven to be an indispensable diagnostic tool for everyday modern clinical practice. The role of MRI in cardiac imaging includes functional and morphological assessment, yet MRI is genuinely known for its superior tissue characterization. Some clinical examples for this role are the assessment of ischemic cardiac disease, non-ischemic cardiomyopathy, myocarditis, and infiltrative heart diseases. However, the myocardial involvement in these different pathologies is sometimes diffuse and can, on the other hand, have myocardial fibrosis as its final product. Both myocardial fibrosis and diffuse myocardial disease pose some challenges to conventional CMR sequences where fibrosis is exclusively detected by late gadolinium enhancement (LGE) MRI that again may miss a diffuse or early disease and is contraindicated in renal dysfunction. Myocardial T1 mapping emerged as a quantitative analysis tool for myocardial T1 values, avoiding the sole dependence on the observer’s eye. Two types of T1 mapping are available; “native” (ie, non-contrast) and post contrast mapping (for extracellular volume (ECV) fraction quantification). Native T1 mapping is of particular benefit in patients whose kidney dysfunction precludes the contrast material injection. Surprisingly enough, certain studies have shown native mapping to be a superior disease discriminator and adverse outcomes predictor than the ECV fraction quantified from post contrast mapping, as will be discussed later on. Advances in shortened breath-hold, free-breathing pulse sequences, and quantification analysis software have pushed it further to become a potential tool in routine CMR practice. However, challenges still lie ahead. Issues like standardization of imaging protocols, pulse sequences, and normal ranges, understanding the complexity of human tissue which may affect the results quantified by T1 mapping, and developing better tools for image analysis are all challenges that require more multicenter research to resolve. In this review, we will briefly discuss the physical principles and the evolution of the technique, and highlight the clinical applications, controversies, and expected future of the native myocardial T1 mapping.

Basic Physical Principles; First Things First

“All science is either physics or stamp collecting”, Rutherford.

MR imaging depends on the electromagnetic properties of atoms. The positively charged, continuously spinning protons in hydrogen atom nuclei act like billions of tiny magnets. When these protons/tiny magnets in our bodies are exposed to the external magnetic field of the MRI scanner, certain changes in the proton movement (precession) and arrangement (in parallel and antiparallel directions) occur. The cumulative effect of these opposite directions will be the “net
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When a radiofrequency “RF” pulse is sent towards the area to be imaged, the RF excitation induces the protons to reach a higher energy level causing the net magnetization vector to flip by a certain angle, and this produces two magnetization vector components; longitudinal and transverse magnetizations. When the RF excitation is stopped, the net magnetization vector realigns with the axis of the magnetic field through the process called “T1 recovery”, during which the longitudinal magnetization increases in magnitude, or recovers. For this recovery to take place, the currently high energy protons have to give up their energy. One way to lose energy is to release it to the surrounding environment “i.e., spin-lattice recovery” and the duration this process needs depends on the tissue where the hydrogen atoms exist.

At this point, hopefully, it should be less problematic to understand how T1 (the longitudinal relaxation time) defines which type of tissue we are imaging.

Evolution of Myocardial T1 Mapping Techniques; Power of the Pixel

The very first attempts to quantify the T1 values of the myocardium were based on a region of interest (ROI) analysis using the original Look-Locker inversion recovery sequence (LL) where different inversion times were used to acquire inversion images under free or held breathing. Ambitious as they were, the relatively long acquisition times and the lack of pixel-based parametric mapping made them unfeasible in the clinical setting. The introduction of the MOLLI sequence marked a revolutionary turning point of CMR, allowing for the true transition to the pixel-based mapping of the myocardium. As evolution speeds up, an even shorter version of the MOLLI sequence, ShMOLLI, was introduced, followed by research whose aims were breath-hold shortening, image quality optimization, and motion correction. Researchers also developed a T1 mapping sequence that allows for free-breathing, multislice native mapping; Slice-interleaved T1 (STONE). Recently, methods using saturation instead of inversion recovery have been described; Saturation recovery Single-Shot Acquisition (SASHA). Furthermore, sequences combining both inversion and saturation for T1 mapping are now available for patients with arrhythmia. So far, the MOLLI method developed by Messroghli, et al remains the most widely used in clinical practice. They introduced two major modifications of the conventional Look-Locker sequence: 1) selective data acquisition at a given time in the cardiac cycle (late diastole) over successive heartbeats, and 2) merging of data from multiple LL experiments into one data set. It uses a single-shot steady-state free-precession (SSFP) acquisition over different inversion time readouts. A set of 3 consecutive inversion recovery (IR) experiments is performed throughout one breath hold over 17 heartbeats. In each IR experiment, multiple images are acquired; one for each heartbeat, producing a total of 11 images. (Figure 1). In addition to selectivity and the merging of data, the MOLLI method has a higher spatial resolution, allows acquisitions in one relatively short breath-hold, and reduces cardiac motion by using a narrow acquisition window with parallel imaging techniques. The method is reproducible and has a coefficient of variation of 5.4%. MOLLI is influenced by heart rate. However, this influence is systematic and correction formulas can decrease the coefficient of variation further.

The more recent ShMOLLI sequence further decreases the duration of breath hold from 17.6 (± 2.9) seconds to 9.1 (± 1.1) seconds, and the number of required heart beats from 17 to 9 compared with the original MOLLI. Good agreement between the two methods was confirmed. The Table summariz-
Clinical Applications of Native T1 Mapping

Acute myocardial infarction (MI): Cellular edema occurs within 15 minutes of coronary occlusion and reaches a peak after 1 to 2 hours from the onset of the ischemic event. Water has high T1 value and therefore T1 mapping can detect acute MI and assess the extent of myocardial damage with high sensitivity, specificity, and with significantly lower variability of T1 measurements as compared to T2-weighted (T2W) imaging. It was also superior to T2W imaging in non ST-segment elevation MI (NSTEMI). In an animal study, T1 increases were found to be more pronounced in myocardium that was infarcted than in myocardium that was salvaged by reperfusion. Native T1 mapping was also helpful in determining the area at risk (AAR) and yielded similar quantitative results, agreeing well with microspheres. In reperfusion injury, the values at areas of microvascular obstruction (MVO) have been found to be slightly higher than those of remote myocardium, but lower than the surrounding infarcted area (Figure 2). These T1 changes may persist for two months after the onset of the infarction.

Chronic myocardial infarction: Native T1 values are increased in chronic MI regions where the scarred myocardium is re-

Table. Summary of the Points of Strength and Weakness of the Commonest T1 Mapping Techniques where +++ means good, ++ means fair, and + means poor.

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<th>Inversion recovery based</th>
<th>Saturation recovery based</th>
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<tr>
<td></td>
<td>Conventional MOLLI</td>
<td>SiMOLLI</td>
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<tr>
<td>Breath-hold duration (in seconds)</td>
<td>17.6 (± 2.9)</td>
<td>9.1 (± 1.1)</td>
</tr>
<tr>
<td>No. of required heart beats</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>No. of acquired images</td>
<td>11</td>
<td>7</td>
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<tr>
<td>Availability</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Independence from heart rate</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Accuracy</td>
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<td>Precision</td>
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<tr>
<td>Reproducibility</td>
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<td>Low image noise</td>
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Figure 2. Sagittal T2 STIR (A), LGE MRI (B), and native T1 mapping (C) at the same level in acute anteroseptal MI with MVO, intramyocardial hemorrhage, and apical thrombus. High T1 values are seen at the edematous, acutely infarcted myocardium corresponding well with areas of high T2 STIR signal and LGE. Low T1 values are seen at the intramyocardial hemorrhage and apical thrombus.
placed with fibrosis due to accumulation of extracellular collagen. The increases, however, are not as high as in acute MI as the acute phase edema subsides. In areas where lipomatous metaplasia takes place in the chronic infarct, T1 values are shortened. A recent study showed that native T1 maps can detect STEMI and NSTEMI chronic MI with high sensitivity and specificity when using threshold based detection but with high specificity and modest sensitivity when depending on visual assessment of the infarcts as compared to LGE (figure 3).

**Non-ischemic cardiomyopathy:** One of the pioneer studies that investigated the role of native T1 mapping in non-ischemic dilated (DCM) and hypertrophic cardiomyopathy (HCM) demonstrated significant T1 increases in these subjects compared to controls with high sensitivity, specificity, and diagnostic accuracy (Figure 4). These findings were correlated with results from endomyocardial biopsy in other studies.

Approaching a frequent dilemma in clinical practice, a recent study showed that native T1 clearly discriminates between HCM and hypertensive heart disease (HHD), with T1 values being significantly increased at the former. Moreover, the study showed that T1 values were significantly higher in genotype positive-phenotype negative HCM patients when compared to controls and that native T1 was an independent discriminator between HCM and HHD, and was even superior to ECV, left ventricular (LV) wall thickness, and indexed LV mass measurements. Recently, the prognostic relevance of T1 mapping in non-ischemic cardiomyopathy was assessed in a large multicenter study revealing that T1 mapping was signifi-

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**Figure 3.** Short axis LGE MRI (A) and native T1 mapping (B) at the same level in chronic lateral wall MI showing an area of T1 elevation representing replacement fibrosis and corresponding with LGE.

**Figure 4.** Longitudinal and basal short axis LGE MRI (A and C) and native T1 mapping (B and D) at the same level in HCM patient showing patchy areas of T1 elevation being most pronounced at the septal and anterior walls of the left ventricle and matching areas of LGE.
cantly predictive of all-cause mortality and heart failure events in these patients.\textsuperscript{43} Not surprisingly, native T1 was again the sole predictor of the endpoint events. In systemic lupus erythematosus, native T1 may also have the potential to detect subclinical myocardial involvement.\textsuperscript{44}

**Myocarditis:** Classically, CMR detects myocarditis by recognizing areas of edema on T2W sequences and sub-pericardial LGE. However, diffuse myocarditis would be missed with LGE MRI. T2W is no better; being limited by low image quality and interpretation bias. Increases in T1 values in myocarditis owing to the redistribution of free water in the intra- and extracellular compartments associated with edema and inflammation of the myocardium are more readily detectable by T1-mapping than T2W methods (Figure 5). Native T1 mapping emerged as a novel criterion for diagnosis of acute myocarditis after it provided superior diagnostic performance to T2W CMR and higher sensitivity compared to LGE techniques.\textsuperscript{45} Other studies also confirmed T1 mapping to have low inter-observer variability and to be at least equal to other CMR techniques.\textsuperscript{46,47} A recent study took a further step demonstrating the value of T1 mapping in discriminating acute from convalescent stages of myocarditis. It proposed an algorithm where native T1 values in acute myocarditis are set at $>5$ SD above the mean of normal range, whereas convalescence is best defined by either abnormal native T1 ($>2$ SD) or the presence of LGE.\textsuperscript{48}

**Amyloidosis:** Myocardial involvement in amyloidosis is frequently diffuse, rendering its assessment with LGE CMR often problematic because areas of differential LGE are absent. It is also not uncommon for LGE to be absent in early stages of the disease. In addition, many patients with amyloidosis suffer from significant renal impairment that precludes contrast material administration. Native T1 mapping offers a competent alternative. Its role in the diagnosis of cardiac infiltration by light chain (AL) amyloidosis was assessed by Karamitsos, et al who demonstrated high diagnostic accuracy (Figure 6).\textsuperscript{49} The amyloid burden seemed to be in good correlation with markers of systolic and diastolic dysfunction and LV mass index. Another study assessed the role of native T1 mapping in transthyretin (ATTR) amyloidosis and yielded similar diagnostic performance and disease tracking to AL amyloid, but with lower maximal T1 elevation.\textsuperscript{50} In a recent study to evaluate its prognostic value, T1 mapping proved to be a biomarker for cardiac AL amyloidosis and able to predict mortality in systemic amyloidosis.\textsuperscript{51}

**Fabry disease:** Fabry disease is known to lower T1. This is attributed to increased glycosphingolipid concentration in the myocardium, where lipids yield low T1 values. Native T1 mapping is probably the most sensitive and specific CMR parameter in Fabry disease patients irrespective of sex and LV morphology and function with no overlap with other causes of LV hypertrophy; a fact demonstrated by two independent authors.\textsuperscript{52,53} The technique is also highly reproducible and can detect early disease in subjects with no LV hypertrophy yet. In those patients, the T1 lowering had a prevalence rate of 50% and was associated with echocardiographic parameters of cardiac dysfunction, signifying the role of T1 mapping as an early disease biomarker.\textsuperscript{54}

![Figure 5. Short axis T2 STIR (A), LGE MRI (B), and native T1 mapping (C) at the same level in acute myocarditis. High sub-pericardial T1 values are seen at the edematous, inflamed myocardium corresponding with areas of high T2 STIR signal and LGE at the epicardium.](https://example.com/image-url)
Iron overload: T2* CMR is so far the gold standard for detecting cardiac siderosis but it is limited by the long breath-hold techniques, susceptibility artifacts (more common at 3T MRI scanners), and reduced discrimination between both early and very severely iron overloaded hearts.\(^{55,56}\) Iron shortens T2* and T2, and T1 through its paramagnetic influence. Hence, the role of native T1 mapping to detect cardiac siderosis was investigated by researchers who concluded good correlation between low native T1 and T2* values with the added benefit of significantly improved reproducibility and early disease detection.\(^{57,58}\)

Controversies

So, can the magnet (ie, native T1 mapping) be a new biopsy tool? The answer would seem to be not yet. Some challenges do lie ahead of the technique before it is considered as such. The consensus statement of the T1 mapping development group addresses some of these challenges in detail.\(^{11}\)

A very basic controversy has to do with our definition of normal and abnormal. The reader might have been wondering: what are the normal native T1 values? However, the answer is somehow sophisticated. The various MR scanners used (in terms of both field strength and vendor), pulse sequences (whether inversion, saturation recovery or hybrid), differences between the standard and shortened versions of sequences, and even differences in age and sex make definitive normal values very hard to establish. Therefore, it is the duty of each institution to determine its own normal. At our institution for example, normal native T1 values are set at 1314 ± 29 ms.

Another important question is: what are we really measuring with T1 mapping? The current methods for T1 mapping assume a simple model where the pixel consists of a single compartment with a homogeneous single T1 value. This is not true for the more complex biological and molecular structures of the human body. This understanding has a particular impact on accuracy and precision. T1 values derived from the more available and mature inversion recovery techniques are found to be more affected by this complex nature (eg, the magnetization transfer) than are the saturation recovery sequences. The latter on the other hand are noisier, more artifact prone, and more importantly, less reproducible.\(^{59}\)

The choice of the optimal technique for T1 mapping, the level of spatial coverage needed, and then the tool for image analysis are still controversial in the CMR community.\(^{11}\)

![Figure 6. Short axis LGE MRI (A), and native T1 mapping (B) at the same level in cardiac amyloidosis. High myocardial T1 values are seen at the infiltrated myocardium in correspondence with areas of LGE.](image)

The position statement also sets recommendations for quality control (through the use of parametric error maps), analysis (through conservative drawing of regions of interest to avoid the partial volume effect of blood), and technical development (through methodological validation of sequences, unique naming of new sequences, and systematic testing of accuracy and precision).

In clinical practice, the overlap in T1 values among different pathologies and between those and normal individuals under the same conditions poses yet another diagnostic challenge (Figure 7).

Future directions

“The future belongs to those who prepare for it today”, Malcolm X.\(^{60}\)

The ability of native T1 mapping to continue expanding its territory in the CMR field requires more effort towards standardization of the acquisition techniques and establishing normal reference ranges with synchronous developments by MRI vendors and software analysis companies and collaboration between academics and clinicians. Multicenter and
biobank studies are becoming a necessity. More attention has to be paid to histopathological validation of different T1 mapping techniques. Setting concrete reference ranges for the different pathologies that alter T1 values and creating differentiating algorithms for their overlapping values would be a step ahead. Scarcce data are available on the usefulness of native T1 mapping in cardiac masses, cardiac sarcoidosis, post-reperfusion intramyocardial hemorrhage, and right ventricular or atrial pathologies. These, among others, are potential clinical applications for the technique.

Conclusion: Native T1 mapping is one of the most rapidly developing fields in CMR. Recent advances in acquisition sequences have made it possible for short acquisition times, improved accuracy and precision, and robust reproducibility without the need for contrast material. The technique is of particular benefit in certain diffuse or early myocardial diseases where traditional CMR methods such as LGE might fail. Its clinical applications extend from rare diseases such as Fabry disease to more frequent ones like cardiac amyloidosis to conditions encountered in everyday clinical practice like myocardial infarction. Native T1 mapping is expected to make an even greater impact in the clinical field if certain issues are worked out, of which standardization of the technique methodology and normal ranges are the most important.

We might not be there yet, but we are definitely on track.

References

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