Myocardial T1 Mapping – Comparison of Techniques

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Introduction

Diffuse myocardial fibrosis and other remodeling of the myocardial extracellular space are common pathological features of many cardiac diseases [1]. These changes can be measured non-invasively using magnetic resonance imaging (MRI) through changes in native (non-contrast) myocardial T1 relaxation times, post-contrast T1 times, and derived estimates of extracellular volume (ECV) using both native and post-contrast T1 values. Numerous clinical studies have found correlations between both myocardial T1 and ECV measurements and various metrics of disease severity in patient populations including heart failure [2], dilated cardiomyopathy [3], and amyloidosis [4]. These findings have also been further validated by histological correlations to MRI fibrosis measurements in human studies of aortic stenosis and hypertrophic cardiomyopathy [5-8]. A large single-centre study of myocardial ECV in consecutive patients showed increased ECV to be an independent predictor of short-term mortality [9], demonstrating its prognostic importance.

The ability to quickly and reliably assess diffuse myocardial fibrosis using MRI makes T1 and ECV promising surrogate biomarkers with the potential for widespread clinical utility [10-12]. This optimism has led to the development of a multitude of techniques for their measurement, each with unique properties, advantages, and disadvantages. Three major classes of T1 measurement techniques are reviewed here in order to provide insight into differences in reported T1 and ECV values and determine the most appropriate technique for potential new studies.

T1 mapping techniques

Continuous Look-Locker techniques

The classic Look-Locker experiment consists of a series of measurements using a train of radiofrequency (RF) pulses with a short repetition time (TR) to more efficiently sample the T1 recovery curve [13]. This is commonly implemented using an inversion pulse followed by a continuous spoiled gradient recalled echo (GRE) readout [14] (Fig. 1A). Magnetization perturbation caused by the repeated RF excitations causes a shortening of the apparent relaxation time (T1*) and a reduction in the equilibrium magnetization. However, assuming that the TR << T1 and a flip angle <10° is used, the true T1 value can be calculated when using a standard 3-parameter exponential recovery model by applying the commonly termed “Look-Locker correction factor” [15] (Fig. 2A):

\[ \text{Signal} = A - B \times \exp(-TI/T1^*) \]  
\[ T1 = (B/A - 1)T1^* \]

Cardiac Look-Locker implementations typically use gated-segmented imaging readouts, with between 15-30 images acquired at different effective inversion recovery (TI) times and cardiac phases in a single breath-hold (Table 1). This k-space segmentation results in images with less temporal blurring compared to single-shot images, but with increased sensitivity to artifacts from poor breath-holding.

### Table 1

<table>
<thead>
<tr>
<th>Continuous Look-Locker [3, 50]</th>
<th>MOLLJ (Intermittent Look-Locker) [6, 18, 23, 29, 30, 49]</th>
<th>SASHA (Independently magnetization-preparation) [37, 44, 45]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Readout</td>
<td>GRE</td>
<td>bSSFP</td>
</tr>
<tr>
<td>k-space acquisition</td>
<td>segmented</td>
<td>single-shot</td>
</tr>
<tr>
<td>Preparation pulse</td>
<td>inversion</td>
<td>inversion</td>
</tr>
<tr>
<td>Number of images</td>
<td>15-30</td>
<td>7-11</td>
</tr>
<tr>
<td>Duration</td>
<td>1 breath-hold</td>
<td>9-18 heartbeats</td>
</tr>
<tr>
<td>Base matrix size</td>
<td>176-192</td>
<td>192-256</td>
</tr>
<tr>
<td>Flip angle</td>
<td>10-12°</td>
<td>35°</td>
</tr>
<tr>
<td>Myocardial T1 (1.5T)</td>
<td>Not reported</td>
<td>939-1011 ms</td>
</tr>
<tr>
<td>Normal ECV (1.5T)</td>
<td>25%</td>
<td>25-27%</td>
</tr>
</tbody>
</table>

Comparison of typical pulse sequence parameters between three major classes of myocardial T1 mapping sequences.
Look-Locker sequences with a continuous balanced steady-state free precession (bSSFP) imaging readout such as the Small Animal Look-Locker Inversion recovery (SALLI) [16] and Multi-Contrast Late Enhancement (MCLE) sequences [17] have been used to improve blood-tissue contrast and overall signal yield compared to GRE. These sequences also utilize the cardiac phase information to generate a cine-like time series for analysis of cardiac function.

Continuous Look-Locker sequences provide excellent sampling of the inversion recovery curve, but the cardiac motion between images that is intrinsic to the sequence design can be problematic for T1 quantification. Continuous through-plane cardiac motion in a typical short-axis slice results in signal enhancement as unexcited spins move into the imaging plane, modulating the shape of the recovery curve and potentially confounding calculated T1 values. Additionally, data analysis is time consuming because the myocardium must be manually contoured for each image separately and parametric T1 pixel maps cannot be readily generated.

Intermittent Look-Locker techniques

The MOdified Look-Locker Inversion recovery (MOLLI) technique overcomes many of the challenges associated with cardiac and respiratory motion by using ‘intermittent’ cardiac-gated single-shot readouts instead of continuous readouts [18]. The sequence consists of multiple ‘Look-Locker sets’, each of which contains an inversion pulse followed by gated single-shot images at a consistent heart rate. As sampling of the recovery curve in each set is limited and also determined by the heart rate, Look-Locker sets are repeated with slightly incremented TI values and separated by several heartbeats to allow magnetization recovery. MOLLI images also generally use bSSFP readouts to improve blood-tissue contrast as well.
Implementation varies in the number of Look-Locker sets and the number of images in each set, which are commonly indicated with a series of numbers such as 3(3)3(3). In this naming convention, the parentheses indicate the number of recovery heartbeat segments between sets and all other numbers indicate the number of images in each set. This example, 3(3)3(3), describes the original MOLLI implementation with three Look-Locker sets containing 3, 3, and 5 images and each set separated by 3 heartbeats for recovery. The choice of sampling pattern affects not only the total breath-hold duration, but also the variability of calculated T1 values and potential heart rate dependent T1 errors.

With good breath-holding, the consistent cardiac phase between MOLLI images simplifies data analysis by allowing regions of interest (ROIs) to be drawn for all images simultaneously. Consistent spatial positions between images allows parametric T1 maps to be generated, which provide an invaluable visual tool for identifying spatial patterns of T1 abnormalities. While myocardial T1 mapping was feasible with other techniques prior to MOLLI, the simplicity of a single breath-hold acquisition and straightforward analysis contributed to its success and helped to spur the growth of the T1 mapping field as a whole.

Similar to the continuous Look-Locker techniques, the measured apparent T1 time, termed T1*, from MOLLI data is generally shorter than the true T1 time due to magnetization perturbation by the image readouts. Conventional MOLLI analysis uses the standard Look-Locker correction factor (Eq. 2) to estimate the true T1 value. However, MOLLI’s intermittent bSSFP readouts result in notable differences in the magnetization time-course compared to the continuous GRE readouts for which the correction factor was derived. This difference in magnetization progression gives rise to errors in MOLLI T1 values that are systematically dependent on multiple factors and well characterized [20]. Briefly, MOLLI T1 values are generally systematically underestimated with reduced T2 values [21, 22], increased T1 values [18, 23, 24], high heart rates [18, 23], increased off-resonance [25], poor inversion efficiency [26, 27], and magnetization transfer (MT) effects [28]. The magnitude of T1 errors from these factors is dependent on various aspects on the sequence implementation, resulting in a wide range of calculated MOLLI T1 values. For example, various studies of healthy subjects using 3(3)3(3)5 MOLLI at 1.5T have reported average myocardial T1 values of 939±24 ms (n=20) [29], 1011±41 ms (n=10) [30], and 950±21 ms (n=102) [31]. Despite moderate differences in mean T1 values between studies, the coefficient of variation within a given study is 2.2-4.0%, suggesting that healthy myocardial MOLLI T1 values are stable and consistent within a specific sequence implementation.

While a number of MOLLI’s systematic dependencies are deeply rooted in the use of the Look-Locker correction factor for an intermittent bSSFP Look-Locker readout, other dependencies have been mitigated through a combination of sequence modifications and alternative image reconstruction algorithms. For example, heart rate dependence in certain MOLLI implementations is largely due to incomplete magnetization recovery between Look-Locker sets. By ordering the Look-Locker sets from longest to shortest, such as the 5(3), 4(1)3(1), 2, and 5(1)1(1)1 patterns, and defining the recovery durations in seconds instead of heartbeats [32], heart rate dependence is significantly reduced. A conditional fitting algorithm used in the shortened MOLLI (ShMOLLI) sequence, where images from later Look-Locker sets are discarded when fitting long T1 values or if the residual fit error is too great, further improves heart rate insensitivity [23]. An optimized adiabatic inversion pulse was also found to increase the accuracy of the MOLLI sequence [27], and more complex MOLLI T1 calculation techniques utilizing Bloch equation simulations [33] have also been developed to account for other dependencies. However, as these improvements bring MOLLI T1 values closer to the true T1 value, it is important to be mindful that newer implementations are no longer directly comparable to reported literature values from previous, less accurate implementations.

Although systematic errors in MOLLI T1 values are conceptually undesirable when trying to accurately quantify true T1 values, the primary goal of most T1 mapping is to reliably quantify myocardial fibrosis. This more pragmatic view asserts that well characterized systematic errors are tolerable, provided that MOLLI T1 values are a reproducible biomarker that is sensitive to fibrosis. This perspective is supported by extensive published literature using the MOLLI techniques in a wide variety of cardiomyopathies. Furthermore, the influence of T2 values and MT on native MOLLI T1 values may actually increase its sensitivity to overall cardiac disease, as common pathologic changes in T2 and MT also increase native MOLLI T1 values. However, variability in factors such as flip angle and off-resonance is dependent on MRI system design and shimming, but still cause artifactual changes in MOLLI T1 values. Thus MOLLI’s systematic dependencies are simultaneously an advantage and a disadvantage. While they may increase sensitivity of MOLLI T1 values as a biomarker for overall cardiac disease, there is the potential for misinterpretation because it may be difficult to rule out non-pathological confounders as the underlying cause of MOLLI T1 derived ECV abnormalities.

Intermittent Look-Locker can also be performed using a saturation recovery preparation, such as in the MLLSR sequence [34]. As an ideal saturation pulse nullifies longitudinal magnetization regardless of the magnetization before it, recovery periods between Look-Locker sets are no longer required and thus more images can be acquired in the same total duration. However, as MLLSR still fundamentally uses an intermittent Look-Locker acquisition, it has similar characteristics to the MOLLI sequences, with underestimated
apparent T1* values that cannot be accurately corrected with direct application of the Look-Locker correction factor in Eq. 2.

**Independently magnetization-preparation techniques**

Both continuous and intermittent Look-Locker sequences acquire multiple images after a single magnetization preparation (inversion or saturation) pulse as a means of reducing the total scan time and providing a wide range of sampled recovery times. In comparison, the SR-TFL [35], SAP-T1 [36], and SATuration-recovery single-SHot Acquisition (SASHA) sequences [37] acquire only a single image after each saturation pulse. As ideal saturation pulses reset the longitudinal magnetization regardless of the initial state, each image is independently magnetization prepared, and thus the magnetization time-course in each image readout is independent of other image readouts. The SASHA sequence consists of a non-prepared ‘anchor’ image, followed by a series of saturation recovery images in sequential heartbeats (Fig. 1C). Images are gated single-shot bSSFP readouts, similar to the MOLLI sequence (Table 1), but have significantly poorer blood-tissue contrast. SASHA images and analysis from a subject with myocarditis are shown in Fig. 3.

T1 values calculated from SASHA data using a 3-parameter model (Eq. 1) have been shown to be highly accurate and robust over a wide range of T1, T2, flip angles, heart rates, off-resonance values, and magnetization transfer effects [20, 28, 37]. However, the dynamic range of signal intensities in SASHA is nearly half that of MOLLI due to its saturation recovery preparation, resulting in significantly higher SASHA T1 variability [20]. SASHA data acquired using a variable flip angle (VFA) readout and using a 2-parameter model for T1 calculation has been recently shown to have coefficients of variation similar to MOLLI measurements while maintaining SASHA’s accuracy [38]. VFA images were also shown to consistently reduce image artifacts associated with off-resonance effects. However, VFA readouts further reduce blood tissue-contrast in the anchor image, potentially reducing the effectiveness of motion correction algorithms and impairing visual identification of the myocardial boundaries when contouring on raw images.

The number of acquired SASHA images is flexible and can be reduced in subjects with diminished breath-hold capabilities at the expense of increased variability. The original SASHA sequence used saturation recovery times (TS) linearly spanning the range of values possible while keeping the saturation and imaging in the same heartbeat to maximize the number of acquired images in a fixed duration. Longer TS times may better sample the recovery curve for long T1 values and can be achieved by imaging in a separate heartbeat from the saturation pulse, such as in the SR-TFL sequence [35] and the recent SMART-Map sequence [39]. Recent work numerically optimizing saturation recovery times for 3-parameter [40] and 2-parameter [41] models found clustered sampling patterns with repeated TS times result in moderate reductions in T1 variability.

The robustness of the SASHA sequence to systematic confounders makes it an attractive candidate for T1 mapping in new study protocols. While SASHA is a relatively new sequence with less clinical and histological validation compared to more established techniques, studies with SASHA in patients with heart failure [37], anthracycline cardiotoxicity remodelling [42], and Fabry disease [43] have findings consistent with established literature. Nevertheless, the lack of established values and difficulty comparing values between techniques make SASHA a difficult choice for sites where data has already been acquired with another technique.
Discussion

Absolute native myocardial T1 values vary significantly between imaging sequences, with 15-20% lower values with MOLLI compared to SASHA [44, 45] due to MOLLI’s systematic underestimation [20]. ECV values are derived using both native and post-contrast T1 measurements in the blood and myocardium and thus systematic T1 errors, which may be different between each of these measurements, result in even larger differences between sequences (Table 1). Therefore, caution must be exercised when comparing literature values, and a recent consensus statement on T1 mapping recommends that site-specific normative values be established for any given T1 mapping sequence implementation [46].

In clinical practice, breath-hold motion commonly causes errors in T1 maps as signal intensity changes between images are caused by spatial misalignment instead of magnetization recovery. Although manually adjusting ROIs between images can overcome some motion effects, this process increases analysis time and effort. A robust non-rigid image registration algorithm designed for the large changes in image contrast in MOLLI data was found to significantly reduce apparent motion between images and improve T1 map quality [47]. In the Siemens implementation found in the MyoMaps package, T1 maps are generated from motion corrected images on the scanner console directly. This immediate feedback allows the operator to easily detect poor quality data sets and repeat the acquisition and enables focused investigations within the same study, as T1 abnormalities can be detected in real-time.

By extending the image registration algorithm to co-register native (non-contrast) and post-contrast T1 maps and using hematocrit values with automated blood pool segmentation, parametric ECV maps can also be generated [48, 49]. ECV image maps are more easily interpretable than T1 maps because they represent a physiologically relevant parameter and the ability to generate these in a semi-automated manner greatly improves analysis workflow. The uncertainty in T1 values from fitting measured data to the exponential recovery model can be quantified by converting fit residuals into a standard deviation with the same units as T1 values [32]. This approach can be further extended to calculating uncertainties in derived ECV values. These uncertainty maps provide valuable context in interpreting the likelihood of whether T1 and ECV abnormalities are simply due to measurement noise.

Conclusions

Myocardial T1 mapping is an active and exciting field of research, driven by a strong clinical motivation to detect diffuse myocardial fibrosis that is so ubiquitous in cardiac disease. A number of techniques are commonly used for T1 mapping, each with unique advantages and disadvantages. While direct comparison of values between these techniques is complicated by different systematic dependencies between sequences, the ability of each technique described here to detect fibrosis is supported by clinical evidence and literature. The most appropriate technique for any given study depends on considerations such as the image quality of single-shot images in subjects with smaller or thinner hearts and fast heart rates, the likelihood of variations in known confounders, and the need to compare values to existing literature. Commercial availability of a T1 mapping sequence in MyoMaps provides broad clinical access to this technology, and is a significant step towards the adoption of T1 mapping as a clinical standard for quantifying myocardial fibrosis.

References


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1 The product is still under development and not commercially available yet. Its future availability cannot be ensured.

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