T1 mapping in cardiac MRI

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Published online: 16 June 2017
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Abstract Quantitative myocardial and blood T1 have recently achieved clinical utility in numerous pathologies, as they provide non-invasive tissue characterization with the potential to replace invasive biopsy. Native T1 time (no contrast agent), changes with myocardial extracellular water (edema, focal or diffuse fibrosis), fat, iron, and amyloid protein content. After contrast, the extracellular volume fraction (ECV) estimates the size of the extracellular space and identifies interstitial disease. Spatially resolved quantification of these biomarkers (so-called T1 mapping and ECV mapping) are steadily becoming diagnostic and prognostically useful tests for several heart muscle diseases, influencing clinical decision-making with a pending second consensus statement due mid-2017. This review outlines the physics involved in estimating T1 times and summarizes the disease-specific clinical and research impacts of T1 and ECV to date. We conclude by highlighting some of the remaining challenges such as their community-wide delivery, quality control, and standardization for clinical practice.

Keywords T1 mapping · Extracellular volume · Myocardial disease

Introduction

In magnetic resonance imaging, the longitudinal (spin-lattice) relaxation time (T1) is a fundamental tissue property, now measurable in the myocardium using cardiac T1 mapping sequences. Cardiovascular magnetic resonance (CMR) research data accrued in both animals and humans convincingly demonstrate that native T1, in the absence of gadolinium-based contrast agents (GBCA), lengthens with interstitial expansion caused by edema, infarction, amyloid infiltration, and fibrosis [1]. Conversely, native T1 shortens in the presence of fat and iron accumulation. The left ventricular (LV) myocardial native T1 signal, from a single region of interest on a T1 map, could therefore serve as a simple, on-the-fly, non-invasive discriminator of heart muscle health and disease.

T1-weighted signal also forms the basis of the late gadolinium enhancement (LGE) imaging technique. This technique was the most disruptive tissue characterization method. LGE can quantify focal scar and fibrosis in both ischemic and non-ischemic cardiomyopathies. It works by the principle that scarred tissue passively accumulates more GBCA which shortens its T1 compared to adjacent normal healthy myocardium, and this is visible with a particular imaging sequence (inversion recovery) [2]. T1 mapping adds to this. It has evolved from T1-weighted imaging, to native T1 measurement alone, to post-GBCA T1 measurement in isolation, or through
the partition coefficient to measurement of the extracellular volume (ECV) [3]. The latter is when \( T_1 \) is measured before and after GBCA using a correction for the hematocrit (measured separately or in-line automated) [4, 5]. Native \( T_1 \) and ECV permit earlier diagnosis and quantitative assessment of focal as well as diffuse myocardial disease (Fig. 1). \( T_1 \) mapping by CMR describes the pixel-wise quantification of the spin-lattice relaxation time in order to provide a quantitative tissue characterization that is commonly viewed as a color-coded map of the heart. \( T_1 \) maps are most commonly derived from a series of \( T_1 \)-weighted images, sampling the \( T_1 \) recovery curve after one or more initial preparation pulses.

This review outlines the basic physics of \( T_1 \) mapping and discusses disease-specific clinical and research impacts of \( T_1 \) and ECV to date. We conclude by highlighting the challenges of community-wide delivery, quality control, and standardization in clinical practice.

**Essential physics and evolution of \( T_1 \) mapping sequences**

Broadly, \( T_1 \) mapping sequences have three parts: (1) the \( T_1 \) magnetization preparation pulse, (2) a single image acquisition (readout) after a variable delay, and (3) variable repetitions of (1) and (2) to sample the longitudinal magnetization recovery curve after the magnetization preparation. Raw images are then reconstructed by post-processing into a single \( T_1 \) map using a theoretical model of the expected signal intensity [3] and with the help of various refinements such as respiratory motion compensation (Table 1 and Fig. 2).

A \( T_1 \) map is a two-dimensional (usually brightly colored) slice image where each image pixel displays the \( T_1 \) relaxation time (ms) using a color look-up table to facilitate visual assessment [17]. Imaging at identical time points of the cardiac cycle is needed to yield co-registered images for curve-fitting and spatially resolved quantification of \( T_1 \) [6]. Earlier \( T_1 \) measurement approaches did not do this and became obsolete [18]. When combining raw images, some errors may therefore stem from RR-interval variability (arrhythmia, mistriggering), through-plane cardiac motion that is a normal part of longitudinal cardiac function, and diaphragmatic motion due to respiration. Automated non-rigid registration algorithms can correct for the position of source images to avoid some of this [19, 20]. Acquisition recommendations are now made to minimize other potential sources of errors in sequences and scan planning. For example, operators must aim to minimize partial volume effects by optimal slice orientation relative to the tissue, which is preferably orthogonal to the imaging plane to minimize obliquity. Proper adjustment of the shim volume and center frequency should be ensured to minimize off-resonance artifacts [21]. A typical scan protocol is provided in the 2013 SCMR consensus statement [18].

\( T_1 \) mapping is complex as different approaches are taken with different names. The original Look-Locker sequence developed in the 1970s [22] applied multiple inversion recovery pulses with different times-to-inversion, generating 20 distinct \( T_1 \)-weighted images. The inversion pulse inverted the net magnetization by 180° and was followed by multiple readout pulses interspersed with longitudinal magnetization recovery periods. However, as the relaxation curve was repeatedly perturbed by radiofrequency (RF) pulses of the imaging readout, an “apparent” \( T_1 (T_1^*) \) was assessed and it required further correction for relaxation time measurement [23, 24]. The original Look-Locker was impractical for generating \( T_1 \) maps, as acquisition, lasting 20 min, spanned multiple phases of the cardiac cycle [22]. Use of a new single-shot balanced steady-state free precession (SSFP) readout during diastole [25] permitted better signal-to-noise ratio and efficiency, intrinsic flow compensation [3], and consequently the development of the first MODified Look-Locker Inversion Recovery (MOLLI) [6] approach in a single breath-hold of 17 heartbeats [26]. New MOLLI variants manipulate the prepulses and pauses between them. For example, the original MOLLIIs used a 3(3b)3(3b)5 protocol, with numbers outside of parentheses indicating the number of images acquired after each magnetization preparation pulse, and numbers in parentheses indicating the length of the pause separating image acquisition and any subsequent magnetization preparation pulse, defined either in terms of number of recovery beats \( b \) or number of seconds \( s \). MOLLI’s bSSFP readout also estimates an “apparent” \( T_1 (T_1^*) \) which is influenced by imaging RF pulses, so a Look-Locker correction is still needed to correct for it and deliver a more accurate \( T_1 \) estimate [25]. Later versions, like the 5(3 s)3 variant [11], which shifts the bulk of image acquisition to the “beginning,” allow more time for recovery of longitudinal magnetization. Counting rest periods in seconds instead of recovery beats makes sequences more heart rate independent. Another approach, Shortened MOLLI [8] (ShMOLLI), uses a 5(1b)(1b)1 scheme to acquire images over nine heartbeats making it more suitable for breathless patients [25]. The resultant dataset is however sparser and the one-beat pauses are insufficient to maintain compatibility with the theoretical model used in subsequent \( T_1 \) estimation, for large \( T_1 \) values [3]. ShMOLLI, therefore, employs a conditional fitting algorithm that includes the final two image acquisitions in the curve fitting routine only when the \( T_1 \) estimate tends toward a smaller value [3]. The same Look-Locker correction as for MOLLI is applied. SAtturation Recovery Single SHot Acquisition [11] (SASHA) uses a saturation recovery instead of an inversion recovery preparation. Dephasing the whole imaging volume leads to depletion of the entire magnetization, alleviating the need for any rest periods. Because only one image is acquired after each magnetization preparation, the Look-Locker correction is not required and \( T_1 \) can be estimated directly from pixel-wise curve fitting [3]. Unlike MOLLI,
SASHA does not demonstrate heart rate dependence [26], but it can be less precise on account of the reduced dynamic range (90° vs. 180°). SASHA acquires 10 images in 10 heartbeats with the initial image lacking a saturation preparation [11]. Saturation Pulse Prepared Heart-Rate Independent Inversion Recovery Sequence (SAPPHIRE) uses a hybrid combination of both inversion and saturation pulses that increases the dynamic range (a hybrid of MOLLI and SASHA, trying to get the best of both). Additional comparator sequences are elaborated in Table 1.

**Biological basis of ECV**

The myocardium can be considered as two main compartments: the “intracellular cellular volume” (ICV, 1 − ECV), dominated by myocytes but also including all other cells (fibroblasts, circulating red blood cells, etc.); and the “extracellular volume,” dominated water associated with the extracellular matrix but also including the intracapillary plasma volume [18]. The normal myocardial ECV value is around 25.3 ± 3.5% in health [27]. This is much higher than, for
| Sequence                | Building plan: 3 integral parts | Strength                                                                 | Limitation                                                                 | Reference |
|------------------------|--------------------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------|-----------|
| Original MOLLI         | IR pulse over multiple heartbeats | Single breath-hold                                                        | - High-quality $T_1$ maps                                                  | [6]       |
|                        |                                |                                                                          | - Good precision (noise resilience)                                        |           |
|                        |                                |                                                                          | - Widely available                                                         |           |
|                        |                                |                                                                          | - High inter-center reproducibility                                        |           |
| Fixed-recovery MOLLI   | IR pulse over multiple heartbeats | Single breath-hold                                                        | - Little HR variability                                                    | [7]       |
|                        |                                |                                                                          | - Separate optimization allows precision for both native and post-GBCA regimes |           |
| ShMOLLI                | IR pulse over multiple heartbeats | Single short 9-s breath-hold                                              | - Short breath-holds via short rest periods of 1 heartbeat                 | [8]       |
|                        |                                |                                                                          | - Incomplete magnetization recovery compensated for by conditional data fit |           |
|                        |                                |                                                                          | - Unified sequence for pre-/post-GBCA scanning                            |           |
|                        |                                |                                                                          | - Little HR variability                                                    |           |
| FLASH-MOLLI            | IR pulse over multiple heartbeats | Single 11-s breath-hold                                                   | - Avoids off-resonance artifacts (good for high-field strengths)           | [9]       |
|                        |                                |                                                                          | - No $T_2$ dependence                                                      |           |
|                        |                                |                                                                          | - Tailored fitting compensates for disruption of relaxation by FLASH pulses improving accuracy compared to original MOLLI |           |
| TRASSI                 | IR pulse over multiple heartbeats | Single short 5-s breath-hold                                              | - Inherent properties of the radial acquisition, short breath-hold, and HR-adaptable acquisition window provide high resilience to motion artifacts | [10]      |
|                        |                                |                                                                          | - Tailored fit improves accuracy                                           |           |
|                        | Radial golden-angle FLASH      |                                                                          | - Potential blurring due to view-sharing across heartbeats                |           |
|                        |                                |                                                                          | - Little baseline data                                                     |           |
|                        |                                |                                                                          | - Elaborate post-processing limits availability                            |           |
| SASHA                  | SR preparation over multiple heartbeats | Single 10-s breath-hold                                                  | - Excellent accuracy as invariant to $T_2$, MT, and inversion efficiency  | [11]      |
|                        |                                |                                                                          | - Alternative reconstruction scheme has been proposed to trade off accuracy against precision |           |
|                        |                                |                                                                          | - High-contrast imaging scheme available for free-breathing applications |           |
|                        |                                |                                                                          | - Still low precision compared to MOLLI                                   |           |
| SMART$_1$ MAP          | A series of single-point SR experiments | Single breath-hold (13 heartbeats)                                         | - Low SNR baseline images more prone to artifacts                          | [12, 13] |
|                        |                                |                                                                          | - Low blood-myocardial imaging contrast makes post-processing with image registration challenging |           |
|                        |                                |                                                                          | - Limited data on in vivo clinical                                         |           |
Table 1 (continued)

| Sequence     | Building plan: 3 integral parts | Strength                                              | Limitation                                      | Reference |
|--------------|---------------------------------|-------------------------------------------------------|-------------------------------------------------|-----------|
| SAPPHIRE     | Hybrid SR/IR over multiple heartbeats | Single-shot bSSFP | Single 10-s breath-hold | – Intra-scan heart rate insensitivity by adapting recovery time to changing heart rates by measuring heartbeats in real time | applicability; has yet to be validated at scale and on other vendor platforms | [14] |
| STONE        | IR pulse over multiple heartbeats | Single-shot bSSFP | Interleaved multi (5)-slice 55 s free-breathing + registration + real-time slice tracking | – No rest periods between breath-holds as free-breathing improves patient comfort | Lower precision compared to MOLLI | [15] |
| ANGIE        | IR pulse over multiple heartbeats | Segmented bSSFP | 41 s free-breathing + diaphragmatic navigator gating | – No rest periods between breath-holds as free-breathing improves patient comfort | Potential for slice-tracking failure in heavy breathing patients | [16] |

**ANGIE** Accelerated and Navigator-Gated Look-Locker Imaging for cardiac T<sub>1</sub> Estimation, bSSFP balanced steady-state free precession, FLASH fast low-angle shot, GBCA gadolinium-based contrast agents, HR heart rate, IR inversion recovery, MOLLI MOdified Look-Locker Inversion Recovery, MT magnetization transfer, s second(s), SAPPHIRE SAturation Pulse Prepared Heart-Rate Independent Inversion REcovery Sequence, SASHA SAturation Recovery Single SHot Acquisition, ShMOLLI shortened MOLLI, SNR signal-to-noise ratio, SR saturation recovery, STONE’s slice-interleaved T<sub>1</sub> mapping

* List of T<sub>1</sub> mapping sequences is not exhaustive—more variants exist in the published literature that may not be recapitulated here
example, skeletal muscle, where the ECV may be 10%—myocardium has a lot more collagen (Tables 2 and 3). Various pathophysiological processes alter the ECV and ICV. We now know that athletic adaptation inducing left ventricular hypertrophy reduces the myocardial ECV, meaning that cellular hypertrophy is outweighing fibrosis increases [40]. The ECV may increase with fibrosis, edema, or other protein deposition (amyloid) [46]—or a combination [47]. However, increased capillary density or vasodilatation would also increase ECV, although to a smaller extent [48]. Therefore, ECV changes in isolation require interpretation.

Mathematical derivation of the ECV (Eq. 1) relies on (1) a number of assumptions (including the fast-exchange limit as reviewed elsewhere) [3], (2) measurement of the partition coefficient (the bold right half of Eq. 1, also known as \( \lambda \)), and (3) the patient’s hematocrit (\( Hct \)) representing the cellular fraction of blood [2].

\[
ECV = (1-Hct) \times \left( \frac{1}{T1 \text{ myocardium post-GBCA}} - \frac{1}{T1 \text{ myocardium native}} \right) \left( \frac{1}{T1 \text{ blood post-GBCA}} - \frac{1}{T1 \text{ blood native}} \right) \lambda
\]

**T1 mapping and ECV in selected high signal diseases**

**Lipid storage disease**

Fabry disease (FD) is an intracellular lysosomal storage disease caused by the accumulation of globotriaosylceramide in tissues due to a deficiency in the enzyme \( \alpha \)-galactosidase A [49]. Cardiac involvement causes concentric LVH, arrhythmias, and heart failure, and it is the major cause of mortality [50]. This lipid (in classic lamellar bodies) probably causes the native myocardial T1 to be low, and the result is that T1 mapping can reliably differentiate between FD, other forms of LVH, and healthy controls [51]. T1 lowering is seen in 50–60% of subjects before LVH (Fig. 3c), so it is a biomarker of early cardiac involvement [51], correlating with reduced global longitudinal strain by echocardiography [33]. Because ECV primarily reflects extracellular interstitial disease, it misses the intracellular lysosomal storage, but there may be future roles for late phenotype development as diffuse fibrosis starts [41]. In the infero-lateral wall, where FD has LGE, segmental T1 and T2 elevation may occur (where the pseudo-normalized or elevated T1 is likely due to the effects of replacement fibrosis dominating the fatty-related T1 decrease) and these correlate with blood troponin suggesting that chronic inflammation may be contributing [52]. Enzyme replacement therapy (ERT) for FD may be most beneficial if started sufficiently early, before the establishment of permanent changes [53], but ERT is expensive and early initiation carries societal implications. T1 mapping, capable of detecting early cardiac involvement in FD, could therefore have a major role in guiding timing of commencement of ERT and drug monitoring [33].

**Myocarditis**

Myocardial inflammation is a key step in the development of multiple cardiac diseases. CMR tissue characterization has major potential in its diagnosis. The 2009 “Lake Louise” myocarditis criteria, drafted before mapping was widespread, require the presence of two out of the following three findings: increased myocardial edema by T2-weighted imaging, non-ischemic mid-wall LGE, and hyperemia/capillary leak on early gadolinium enhancement imaging [54]. These are known to be insensitive [55]. Mapping helps. Combining ECV (ECV cut-off \( \geq 27\% \)) with LGE data significantly improves the diagnostic accuracy (90% compared with 79% [54]), and normal ECV has been shown to rule out myocardial damage with a high degree of certainty [56]. Native T1 detects both intracellular and diffuse myocardial change (Fig. 3b), so it has a role in grading the severity and stage of myocardial inflammation [35, 57]. The MyoRacer trial suggests that the most useful imaging tools for confirming or refuting a diagnosis of acute myocarditis are native T1 mapping, followed by T2 mapping, ECV, and Lake Louise criteria in this descending order. By contrast, only T2 mapping showed diagnostic utility in chronic myocarditis [58]. A multiparametric CMR approach toward myocarditis is envisaged: one which exploits T1 mapping and ECV as well as T2 mapping, T2-weighted imaging, early gadolinium enhancement, LGE, and Lake Louise criteria to quantifying the extent of inflammation and distinguish between acute and chronic myocardial injury [59].

**Myocardial infarction**

Acute and chronic infarct imaging is done by standard LGE techniques, but T1 mapping and ECV provide complementary information, both diagnostically and prognostically. In acute myocardial infarction (MI), myocardial edema elevates the native T1 signal and the ECV. Native T1 in the infarct core can predict 6-month post-ST-elevation myocardial infarction (STEMI) mortality even after adjustment for LV ejection fraction [60], and in the remote myocardium, native T1 is
Table 2  Typical ranges of native myocardial $T_1$ in myocardial disease

| Condition                      | Native $T_1^a$ [ms; sequence; $n$] | $Z$ value$^b$ | Reference                     |
|--------------------------------|-------------------------------------|---------------|-------------------------------|
| Aortic stenosis                | 1191 ± 34 [3 T; MOLLI; 20]          | +0.4          | Chin et al. 2014 [28]         |
| Essential hypertension         | 955 ± 30 [1.5 T; SiMOLLI; 40]       | −0.3          | Treibel et al. 2015 [29]      |
| Hypertrophic cardiomyopathy    | 1026 ± 64 [1.5 T; SiMOLLI; 46]      | +1.7          | Fontana et al. 2014 [30]      |
| Dilated cardiomyopathy         | 1056 ± 62 [1.5 T; MOLLI; 29]        | +0.9          | aus dem Siepen et al. 2015 [31]|
| Acute myocardial infarction    | 1248 ± 75 [1.5 T; MOLLI; 40]        | +9.8♦         | Bulluck et al. 2016 [32]      |
| Fabry disease                  | 853 ± 59 [1.5 T; SiMOLLI; 38]       | −3.6♦         | Pica et al. 2014 [33]         |
| Iron overload                  | 863 ± 138 [1.5 T; SiMOLLI; 53]      | −4.1♦         | Sado et al. 2015 [34]         |
| Light chain amyloidosis        | 1130 ± 68 [1.5 T; SiMOLLI; 79]      | +4.8♦         | Fontana et al. 2014 [30]      |
| Transthyretin amyloidosis      | 1097 ± 43 [1.5 T; SiMOLLI; 85]      | +3.8♦         | Fontana et al. 2014 [30]      |
| Acute myocarditis              | 1064 ± 37 [1.5 T; MOLLI; 61]        | +6.2♦         | Hinojar et al. 2015 [35]      |
| Convalescent myocarditis       | 992 ± 19 [1.5 T; MOLLI; 67]         | +2.8♦         | Hinojar et al. 2015 [35]      |

$T_1$ values per disease were derived from at least one representative work in the published literature (other relevant works exist that have not been referenced here). Reported ranges are only applicable to the sequence, imaging protocol, field strength, and scanner configuration used by the group and are not necessarily immediately generalizable across centers [18]. The native $T_1$ signal in some diseases (annotated by ♦ & ♣ shows a large deviation (multiple SDs) from normality, so $T_1$ mapping is bound to be more robust here as the pathology-related $T_1$ change trumps any “normal” biases that confound $T_1$ estimates. In other heart muscle diseases, however (e.g., hypertensive heart disease, aortic stenosis), where $T_1$ changes are less dramatic, biases in $T_1$ estimates may become major signal pollutants, so pathology-related $T_1$ differences may not be realistically resolvable except through large, standardized studies.

$SD$ standard deviation, $T$ Tesla. Other abbreviations as in Table 1.

$^a$Reported in milliseconds as mean ± SD. Defines field-strength (T), sequence used, and sample size ($n$) of the diseased cohort.

$^b$Number of SDs by which a particular disease’s mean $T_1$ value lies above or below the healthy control mean $T_1$ reported by the group in the same study.
independently associated with LV systolic dysfunction [61]. In reperfused acute MI, acute infarct ECV, unlike standard LGE, is independently associated with ejection fraction and convalescent infarct global strain, suggesting it is a better predictor of LV functional recovery [36, 62]. Native T1 may also identify the area at risk and salvaged myocardium [63] better than T2-weighted imaging can. In chronic MI, native T1 and ECV are increased, but values are lower than those observed in acute MI [64]. Native T1 values in chronic MI by widely used bSSFP mapping methods should be interpreted with caution as T1 values may be subject to additive or subtractive bias when water and fat coexist in the myocardium—intramyocardial fat due to lipomatous metaplasia in chronic myocardial scar potentially predisposes to such T1 biases [66]. In the field of stress perfusion CMR for ischemia, T1 mapping of the spleen is being explored as a surrogate indicator of adequacy of vasodilator stress with adenosine [67]. The splenic blood flow paradoxically reduces during the course of adenosine myocardial vasodilatation and native splenic T1 decreases as a result. This makes native splenic T1 in the course of the adenosine infusion (and before GBCA administration) a potential surrogate marker of stress adequacy [67].

### Cardiac amyloidosis

The ventricular myocardium is affected by immunoglobulin light chain (AL) and transthyretin (ATTR) amyloidosis, which has two subtypes, wildtype and mutant [68]. Amyloid deposits and infiltrates the myocardial interstitium and is the major determinant of outcome [43]. Amyloidosis on LGE has characteristic appearances, particularly with the phase-sensitive inversion recovery technique. In early disease, the LGE may be normal. Later, global subendocardial LGE (but more prevalent

| Table 3 Measured ECV relationship in some heart muscle disease |
|------------------|------------------|------------------|
| Condition | ECV<sup>a</sup> (%) [T; n] | Reference |
|------------------|------------------|------------------|
| Acute myocardial infarction | ↑ 56 ± 1.4 [1.5 T; 39] | Kidambi et al. 2016 [36] |
| Aortic stenosis<sup>†</sup> | ↔ 24.3 ± 1.9 [3 T; 50] | Singh et al. 2015 [37] |
| Hypertrophic cardiomyopathy | ↑ 37.1 ± 10.1 [3 T; 20] | Swoboda et al. 2017 [38] |
| Dilated cardiomyopathy | ↑ 27 ± 4 [3 T; 50] | aus dem Siepen et al. 2015 [31] |
| Systolic heart failure | ↑ 31.2, 29.0–34.1<sup>–</sup> [3 T; 40] | Su et al. 2014 [39] |
| Heart failure preserved ejection fraction | ↑ 28.9, 27.8–31.3<sup>–</sup> [3 T; 62] | Su et al. 2014 [39] |
| Athletic adaptation | ↓ 22.5 ± 2.6 [1.5 T; 30] | McDiarmid et al. 2016 [40] |
| Fabry disease | ↔ 21.7 ± 2.4 [1.5 T; 31] | Thompson et al. 2013 [41] |
| Iron overload | ↑ 31.3 ± 2.8 [1.5 T; 19] | Hanneman et al. 2016 [42] |
| Light chain amyloidosis | ↑ 54 ± 7 [1.5 T; 92] | Fontana et al. 2015 [43] |
| Transthyretin amyloidosis | ↑ 60 ± 7 [1.5 T; 44] | Fontana et al. 2015 [44] |
| Acute myocarditis | ↑ 30, 27–32§ [1.5 T; 48] | Bohnen et al. 2017 [45] |

ECV extracellular volume. Other abbreviations as in Table 2
↑ increase, ↓ decrease, † marked increase, ↔ static
<sup>a</sup> Cited ECV values (%) are as mean ± SD except where otherwise stated. Field-strength (T) and sample size (n) are additionally provided. ECV ranges per disease were derived from at least one representative work in the published literature (other relevant works exist that have not been referenced here)
<sup>†</sup> Conflicting data currently
§Median, first, and third quartiles
~Mean, interquartile range
at the base) may occur, associated with blood and myocardium nulling together. Later still, transmural LGE appears [69]. However, native myocardial T1 and ECV may have more discriminatory and predictive power than LGE [46, 70], and they change before LGE [71]. The current working hypothesis is that the ECV can be higher in ATTR due to higher cell volume (derived as $1 - ECV \times$ myocardial mass), indicating concomitant myocyte hypertrophy [44]. Conversely, native T1 (Fig. 3a) can be higher in AL due to the influence of myocardial inflammation [30]. As treatment options differ between AL and ATTR, differentiating between the two by T1 mapping and ECV is clinically important [72].

**Iron overload**

Iron shortens all three CMR relaxation times—T1, T2, and $T_2^*$ [73] (Fig. 3d). $T_2^*$ at 1.5 Tesla (T) (but not at 3 T [74]) is the gold standard for myocardial iron overload assessment and has transformed clinical outcomes when it is used as it can target chelation therapy to where it is needed most [75]. T1 mapping has potential here as well and can serve as a complementary tool [76]. Native myocardial T1 correlates well with $T_2^*$ but has the added advantage of greater reproducibility and sensitivity, and it can detect lower myocardial iron levels potentially missed by $T_2^*$ [34, 42, 77–79]. In thalassemia major, for example, native T1 detected cardiac iron overload in a third of cases missed by $T_2^*$ [76].

Challenges facing the roll-out of native myocardial T1 for cardiac iron assessment include the known variation of absolute T1 between sequences and scanners [78] and its non-specificity—its susceptibility to alter in a large number of heart muscle diseases. In this respect, $T_2^*$ is more disease specific [80]. This advantage should not be overstated—the T1 changes of significant iron completely swamp all other pathologies—the T1 can lower by an impressive 25 standard deviations in severe iron overload, for example. The ECV can be used in iron overload, although there are concerns when iron loading is significant. The ECV can be increased in thalassemia major patients with documented cardiac iron overload, and it correlates with $T_2^*$ but not with LV systolic function and global longitudinal strain [42]. The impression is that
cardiac iron could be transitioning to a fibrotic phenotype, although there is little autopsy evidence for this [81].

**T<sub>1</sub> mapping and ECV in selected modest signal diseases**

**Dilated cardiomyopathy**

In dilated cardiomyopathy (DCM), diffuse myocardial fibrosis may be a prominent feature during disease progression and cardiac remodeling, which eludes depiction by LGE imaging. Early myocardial fibrosis detected by native T<sub>1</sub> mapping in DCM [31] can predict adverse outcomes [82] allowing for risk stratification and for the initiation of timely and appropriate management. However, the T<sub>1</sub> signal change in DCM is not large and conventional T<sub>1</sub> mapping approaches have in-plane resolution limitations when applied to thin-walled hearts (a prevalent phenotype in DCM [83]). Native T<sub>1</sub> is prolonged in DCM and inversely correlated with wall thickness [84, 85] where confounding by partial volume effects may play a part. During the early (subclinical) stages, hearts may have normal LV wall thickness values (~10 mm), so a conventional T<sub>1</sub> mapping sequence could potentially be used, but once the DCM phenotype manifests (often with an increase in overall LV mass), wall thickness may or may not decline with significant partial volume implications. ECV was shown to correlate with clinical prognosis in DCM [86] and with LV systolic dysfunction [87], and although it is recommended in the 2013 T<sub>1</sub> mapping consensus document [18], it is still not accurate enough to be of proven utility for early diagnosis and risk stratification in DCM [18, 31, 88]. T<sub>2</sub> mapping can detect myocardial inflammation that appears to play an important role in non-ischemic DCM [89].

**Hypertrophic cardiomyopathy**

Myocardial disarray, small vessel disease, and fibrosis are histopathological hallmarks of familial sarcomeric HCM. In HCM, LGE is a risk factor for heart failure and an additional risk factor for SCD [90]. T<sub>1</sub> mapping can have additive value [91]. Native T<sub>1</sub> is modestly elevated in HCM as compared to healthy controls and highest in the areas of maximal hypertrophy [90]. T<sub>1</sub> may also be elevated in HCM patients without overt LV hypertrophy, suggesting potential clinical utility as an early disease biomarker [84]. Native T<sub>1</sub> was better than ECV at discriminating HCM from hypertensive heart disease [92] and it identified subclinical HCM in sarcomere gene mutation carriers [92], although some of these have rather thin walls and crypts that could lead to partial volume effects and native T<sub>1</sub> correlated with LV remodeling and global systolic function [85]. ECV cannot discriminate between overt HCM and DCM being similarly elevated in both, suggesting a final common pathway of interstitial change [93], but it can differentiate between sarcomeric HCM and athletic heart as the latter exhibits reduced ECV in the hypertrophied segments [94].

**Valvular heart disease**

Most T<sub>1</sub> mapping studies for valvular heart disease have focused on aortic stenosis (AS). AS is associated with two forms of myocardial fibrosis: diffuse (interstitial) fibrosis that may appear prior to symptom manifestation and architectural change, and the more focal, late irreversible replacement fibrosis. Our understanding of fibrosis in AS is incomplete. Some fibrosis is clearly advantageous, but maladaptive fibrosis also occurs and the myocardial adaptation to the narrowed valve is key to the clinical impact [95]. T<sub>1</sub> mapping can quantify the diffuse myocardial fibrosis in AS providing an indication of AS severity and cardiac function [37, 96] and histopathological correlation has been achieved [74, 97]. Mild to moderate diffuse fibrosis in AS has been linked to postoperative LVH reduction and better symptomatic improvement compared to severe fibrosis at baseline [98]. Native T<sub>1</sub> and ECV were shown to be increased in AS [28] especially in patients with more abnormal patterns of LV remodeling, and they tracked the prognostic biomarker n-terminal pro-brain natriuretic peptide [29], but in another study of asymptomatic moderate/severe AS patients, native T<sub>1</sub> and ECV did not differ significantly from those in age-matched controls at 3 T [37].

Current guidelines classify AS severity mostly by echocardiography via trans-valvular pressure and aortic valve area measurements, and intervention is recommended based on LV ejection fraction and the presence of symptoms, ignoring the myocardial state, in spite of myocardial fibrosis having been shown to determine outcomes in AS patients [99] and ECV demonstrating prognostic value post-tissue aortic valve replacement [100]. The prognostic value of ECV in AS has recently been demonstrated [101] and the “iECV,” derived from the product of ECV and body surface area-indexed LV end-diastolic volume, showed good correlation with histology [101]. Diffuse fibrosis assessment by T<sub>1</sub> mapping in chronic mitral regurgitation may also have clinical utility to guide timing of intervention [102].

**Biomarker roadmap for T<sub>1</sub> mapping**

Familiar imaging biomarkers used daily in cardiac imaging include LV ejection fraction, wall thickness, and left atrial size. New imaging biomarkers such as T<sub>1</sub> mapping and ECV are typically first established as useful complementary tools for new biological insights before becoming surrogate secondary endpoints in clinical studies. They must then cross the “translational gap” before they can become clinical decision-making tools [103] (Fig. 4). Therefore, for T<sub>1</sub> mapping and
Overview of the Imaging Biomarker Development in CMR

- Discovery
- Technical Validation and Early Clinical Evaluation
- Practicality, Availability of Scanners and Cost-Assessment
- Robust Clinical Validation with Long-Term Outcomes

**Fig. 4** Overview of imaging biomarker roadmap for T1 mapping. The technical and early clinical validation of imaging biomarkers often occur in tandem. Cost-effectiveness and usability must be assessed for the biomarker to have the potential of full translational application. In parallel, prognostic assessment with hard outcomes must occur before routine integration into patient care.

ECV, three parallel, not entirely sequential processes, are needed: technical validation (e.g., through the use of phantoms [103, 104]), biological/clinical validation, and cost-effectiveness analysis. We are still missing cost-effectiveness studies for T1 mapping and ECV—not every T1 mapping sequence will have commercial viability as a diagnostic product in healthcare systems, although some sequences certainly will. T1 mapping cost-effectiveness studies are needed to inform on this dichotomy. The funded research agendas of individual centers make it easier to carry on with adding layers of T1 mapping innovation rather than halt the advancement, and scrutinize old work for cost-effectiveness, that may well end up generating unwelcome results. Even those T1 mapping sequences found to lack commercial viability as products may still have niche roles in the research setting, justifying the development of new models to oversee their continued research and development funding, and regulation. Large-scale health-economic considerations and cost-effectiveness studies in T1 mapping, when they happen, will also need to consider the broader portfolio of competitor tests that include other CMR (e.g., LGE, T2 mapping) and non-CMR imaging biomarkers, as well as biospecimen-derived biomarkers (e.g., troponin, N-terminal pro-brain natriuretic peptide, etc.) [105].

Furthermore, we need standardization and centrally coordinated accreditation systems for T1 mapping sites [105]. The issues of standardization and inter-operability is important for T1 mapping as measurements differ between CMR scanners, manufacturers, field strengths, protocols, pulse sequences [106], patient characteristics [107], and other factors. Depending on the sequence used, T1 mapping has specific limitations (see Table 1) that innovative approaches keep trying to address with encouraging results. Partial-volume effects at the interface between myocardium and blood-pool result in reduced accuracy and reproducibility [83, 108] and dark-blood preparation as well as systolic T1 mapping have been proposed as potential solutions to overcome these issues [108, 109]. Elaborate post-processing using improved modeling of the perturbed inversion curve has been studied to increase the accuracy of inversion-recovery-based T1 times [9, 110]. Saturation recovery methods were shown to improve the accuracy of T1 measurements compared to MOLLI, albeit at the expense of precision. Reconstructions with a reduced number of fit parameters have been proposed to trade off some of the precision loss against a slight drop in accuracy [83, 111]. Alternatively, SAPHIRE can be employed, which through the use of a combined inversion/saturation recovery approach allows accurate T1 estimation without sacrificing as much of the precision as SASHA [107, 112]. Other efforts have addressed the RR-interval sensitivity of T1 mapping to improve its performance in the presence of arrhythmias such as atrial fibrillation [113]. Free-breathing T1 mapping sequences are being proposed to overcome motion artifact in sicker patients unable to breath-hold [111] coupled with advances in motion-correction algorithms [20, 114]. Lastly, to increase imaging efficiency and improve specificity beyond conventional T1 mapping, several methods for joint estimation of parameters have recently been explored [115, 116].

**Conclusion**

T1 mapping and ECV of the heart are transforming contemporary CMR through their research and potential clinical applications. These biomarkers have potential to accurately inform clinical decision-making, but like all other biomarkers, they must first survive rigorous scrutiny, validation, and qualification. In spite of the research outputs and excitement within the CMR community, to date, although there has been a first consensus statement [18] with a second one pending, T1 mapping has yet to enter disease-specific guidelines (this may be pending for myocarditis). Still clinical utilization is proceeding with the use of these tools daily in many centers, so more is needed including a wider range of research (technical, translational, standardization) and further consensus/summary processes [117] to illuminate the T1 mapping field. Roadmapping these excellent biomarkers into healthcare for evidence-based patient management is an arduous, time-consuming, but important task. The CMR community needs such guidance.

**Compliance with ethical standards**

**Funding information** G.C. is supported by the UK National Institute for Health Research Rare Diseases Translational Research Collaboration (NIHR RD-TRC, #171603) and by the 2017 Society of Cardiovascular Magnetic Resonance Seed Grant Program. J.C.M. is supported by the NIHR University College London Hospitals Biomedical Research Centre and the Biomedical Research Unit at Barts Hospital, respectively.
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