

Myocardial T1 mapping: modalities and clinical applications

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Abstract: Myocardial fibrosis appears to be linked to myocardial dysfunction in a multitude of non-ischemic cardiomyopathies. Accurate non-invasive quantitation of this extra-cellular matrix has the potential for widespread clinical benefit in both diagnosis and guiding therapeutic intervention. T1 mapping is a cardiac magnetic resonance (CMR) imaging technique, which shows early clinical promise particularly in the setting of diffuse fibrosis. This review will outline the evolution of T1 mapping and the various techniques available with their inherent advantages and limitations. Histological validation of this technique remains somewhat limited, however clinical application in a range of pathologies suggests strong potential for future development.

Keywords: T1 mapping; modified Look Locker inversion recovery (MOLL); extracellular volume; myocardial fibrosis

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Introduction

There is increasing evidence that the underlying, pathological basis for a variety of non-ischemic cardiomyopathies is myocardial fibrosis. This pathological process of extracellular matrix (ECM) remodeling results in multiple functional consequences including impaired relaxation (1), precipitation of arrhythmias (2) and impaired contractile reserve (3). Traditionally, myocardial fibrosis has been recognized in conditions such as hypertensive heart disease, hypertrophic cardiomyopathy (HCM) and idiopathic dilated cardiomyopathy (DCM). However, there is increasing identification of myocardial fibrosis as the common causative factor of myocardial dysfunction in many other, particularly metabolic, processes such as obesity, diabetes and aging. Early identification of this underlying, often diffuse, interstitial myocardial fibrosis is important for diagnosis and essential for optimization of reversibility with intervention. Multiple non-invasive diagnostic strategies have been trialed as an alternative to endomyocardial biopsy for fibrosis assessment including: echocardiographic backscatter (4), nuclear imaging (5), peripheral collagen biomarkers (6) and molecular labeling techniques (7).

Their clinical application has remained limited. The rapid development of cardiac magnetic resonance (CMR) imaging heralds a new era of promising techniques for identification of ECM accumulation within the heart and surrounding structures. Delayed gadolinium enhancement (DE-CMR) imaging has become the new gold standard for identification of focal fibrosis. T1 mapping has the potential to provide a similar quantitative assessment of diffuse myocardial fibrosis.

Evolution of fibrosis quantification by CMR

The ability to achieve high resolution, 3-dimensional imaging without the use of ionizing radiation has ushered in an age of safer and superior tissue characterization. Magnetic resonance imaging exploits the magnetic properties of hydrogen nuclei protons within a determined magnetic field. Longitudinal relaxation time (T1) and transverse relaxation time (T2) are central properties. T1 and T2 are determined by the molecular make-up of tissue, which is primarily determined by the proportion of water content. The T1 value is specifically defined as the time when longitudinal proton magnetization recovers

approximately 63% of its equilibrium value (8).

DE-CMR imaging has been widely used to detect and assess myocardial scar and perfusion. It is the non-invasive gold standard for quantification of focal myocardial fibrosis as small as 0.16 g (9) and is based on the premise that there is a distribution difference of contrast between normal and fibrotic myocardium. Areas of fibrosis demonstrate greater gadolinium accumulation which is represented as a region of high intensity signal with a shorter T1 time than adjacent normal tissue (10). This is clinically useful for assessment of infarction and other regional processes such as the mid-myocardial fibrosis of HCM (11). Conventionally this method is performed using inversion recovery gradient-echo sequences 10-15 minutes after gadolinium infusion. Retention of contrast within the extracellular space results in shortening of the inversion time (T1) and hyperenhancement relative to normal myocardium. Ischemic scar usually results in delayed enhancement (DE) in a subendocardial or transmural distribution consistent with the perfusion territories of epicardial coronary arteries, while non-ischemic fibrosis tends to be irregular and intramural or subepicardial in distribution (12).

The main limiting factor with using DE-CMR in non-ischemic cardiomyopathies is that the fibrotic process is often diffuse, thereby lacking the presence of normal non-fibrotic myocardium as a frame of reference. This can result in underestimation of the true expanded ECM burden due to interstitial fibrosis. To ameliorate this issue, contrast enhanced T1 mapping has been developed to quantify diffuse, non-ischemic myocardial fibrosis, as it does not rely on contrasting signal intensity. It is an evolving technique, which has also needed to overcome the inherent technical issues associated with physiological cardiac and respiratory motion.

T1 mapping techniques

Multiple CMR T1 based techniques have been employed for quantitation of diffuse fibrosis. Currently all have inherent advantages and limitations. Messroghli *et al.* have been at the forefront of T1 mapping sequence development (13). Their modified Look Locker inversion recovery (MOLLI) technique was designed to overcome the limitations of motion and prolonged acquisition time. Specifics included an ability to acquire data within one breath-hold at a designated time within the cardiac cycle and the capability of merging images from multiple Look Locker experiments at different consecutive inversion

times into one data set. MOLLI sequencing employs a balanced steady-state free precession (SSFP) readout to achieve a higher signal to noise ratio with a narrow image acquisition period of less than 200 msec in end-diastole to minimize motion artifact (13). Reproducibility of this technique is high (14). Even faster acquisition times have been achieved by Piechnik *et al.* who developed a shortened MOLLI sequence (ShMOLLI) which requires a short breath-hold of only nine heart beats duration (15). Both sequences are similar but ShMOLLI does not require full recovery of magnetization on sequential inversion pulses and has less heart rate (HR) dependency, which may improve accuracy (16). Other prototype vendor specific sequences are in development including a modified Look-Locker FIESTA technique using saturation-recovery imaging (17), saturation-recovery single shot acquisition (SASHA) (18), and saturation pulse prepared heart-rate-independent inversion recovery, which consists of a combination of saturation and inversion pulses (19).

T1 mapping methodology

There are variations on the exact methodology employed by the various rapid T1 mapping sequences to determine T1 time. Current protocols are increasingly using both pre- and post-contrast imaging (*Figure 1*). Typically a series of short-axis images are acquired pre- and approximately 12 minutes after gadolinium-based contrast with between 6 and 12 consecutively longer inversion times depending on the protocol. Image acquisition is best performed with vectorcardiogram (VCG) gating and the use of inspiratory breath holds. Offline, standard basal, mid-ventricular and/or apical slices are then selected and can be further divided into conventional myocardial segments (or discrete regions of interest) and blood-pool for analysis if desired. A curve fitting technique is employed to reconstruct the consecutively acquired images into one data set from which a T1 map of voxels is generated. The signal intensity of each mapped voxel directly represents the T1 relaxation time of the corresponding myocardial tissue. An exponential recovery curve of signal intensities at the different inversion times is then created for each designated region of interest (slice or segment) to determine the myocardial T1 relaxation time. These can be averaged to extrapolate T1 as an index of diffuse fibrosis, where shorter T1 time and higher signal intensity correspond to increased gadolinium contrast accumulation within the ECM (*Figure 2*).

Standardization of myocardial T1 values to non-

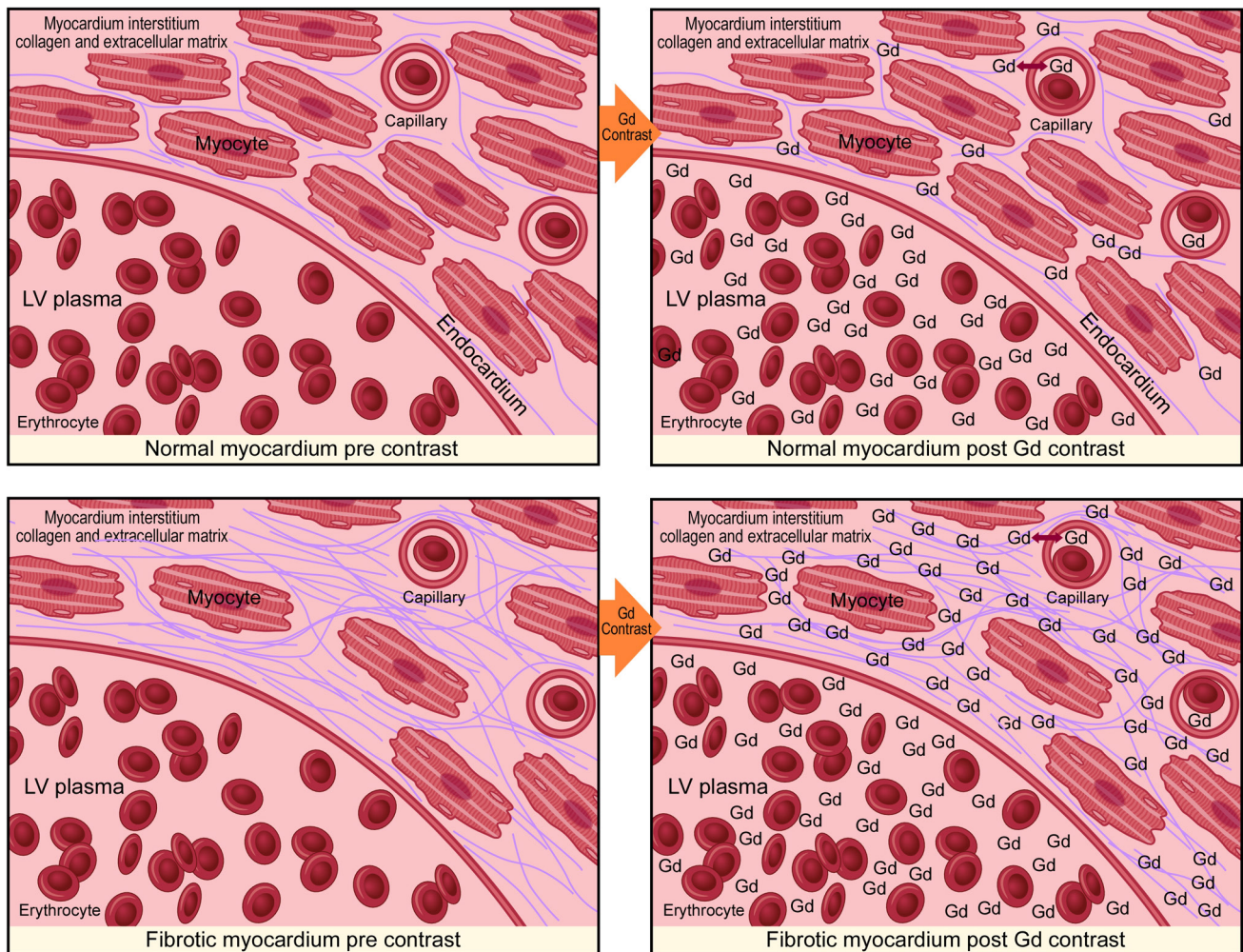


Figure 1 Pre- and post-gadolinium (Gd) contrast dispersion in normal versus fibrotic myocardium.

myocardial tissue (blood) assists in minimizing the dynamic features of gadolinium contrast. The ratio of myocardial to blood post-contrast T1 values is expressed as the partition coefficient. By preceding post-contrast T1 mapping with pre-contrast T1 mapping, myocardial extra-cellular volume (ECV) can similarly be derived. This pseudo-equilibrium technique employs the reciprocals of myocardial and blood T1 values pre- and post-contrast and then adjusts for hematocrit to correct for the blood contrast volume of distribution (20,21). This ECV is expressed as a percentage of the total myocardial extracellular space. Gadolinium equilibrium between blood and myocardium must be achieved prior to image acquisition to enable accurate estimation of ECV. Typically this occurs from 8.5 minutes post contrast injection, after which ECV differences between

time-points are minimal (22). A larger ECV represents increased contrast accumulation in an expanded ECM.

T1 mapping advantages and limitations

Pre-contrast/native T1 mapping

Pre-contrast techniques measure the intrinsic or native myocardial T1. They have an inherent advantage for subjects with significant renal impairment who may be at increased risk of nephrogenic systemic sclerosis. However, non-contrast T1 mapping is limited by an inability to clearly distinguish interstitial from myocyte signal intensity. This may be of clinical consequence in early disease processes when there is minimal difference in T1 values between healthy and disease states. Accuracy

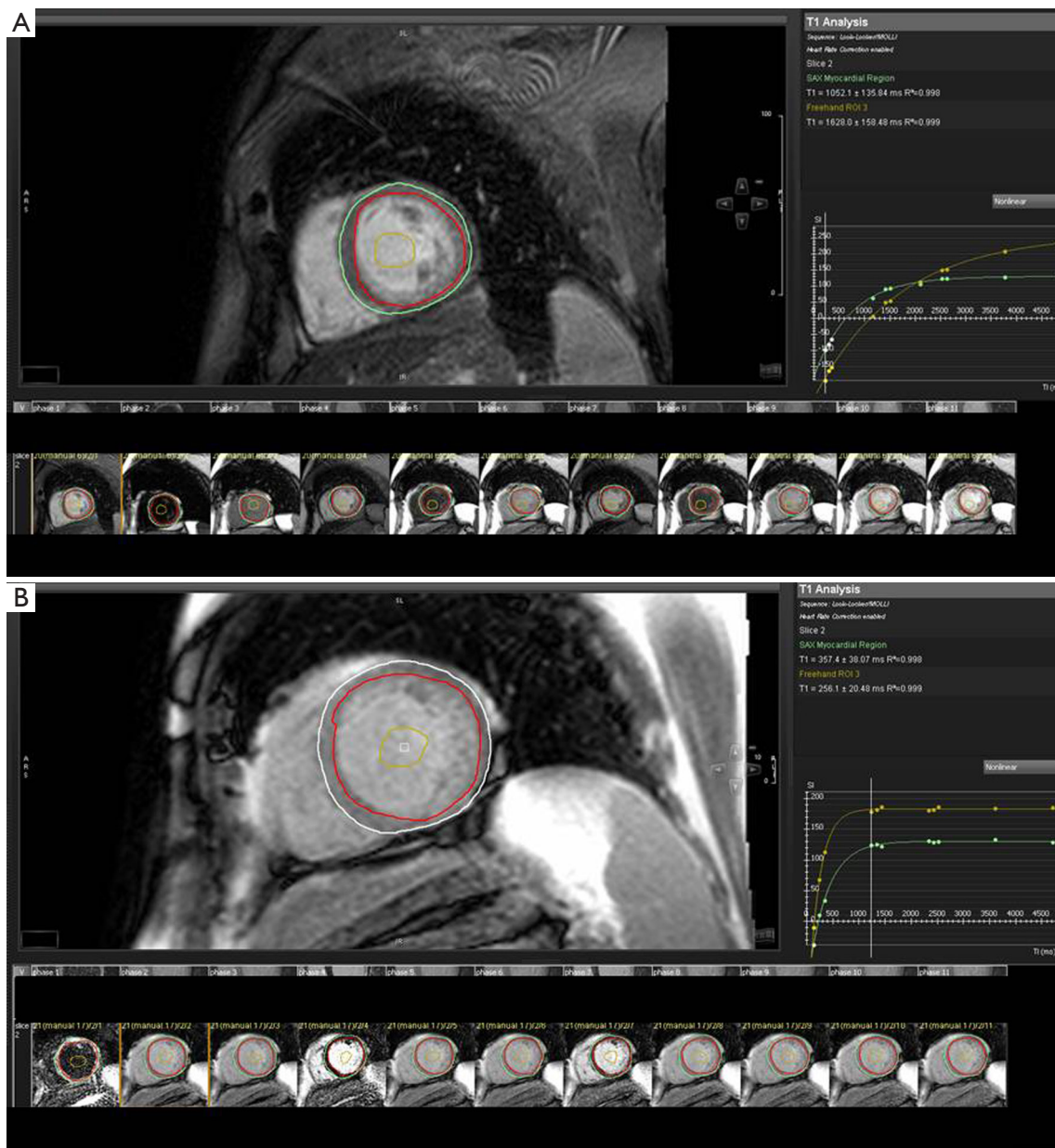


Figure 2 MOLLI technique: pre-contrast (A) and post-contrast (B) T1 maps of the mid left ventricle left ventricle in short-axis view with the epicardium (white circle), endocardium (large red circle) and blood-pool (small red circle) outlined. An exponential recovery curve of signal intensities at different inversion times (TI) determines the myocardial (green line) and blood-pool (red line) T1 values which can then be used (with hematocrit) to determine the extracellular volume.

is also reduced at longer T1 values. As noted above, HR is a documented physiologic covariate of T1 values due to imaging dependency on VCG triggering (14). This is especially problematic when imaging at high magnetic field strengths (3T). Currently, standard Look-Locker and rapid T1 mapping sequences do not have in-built features for HR

correction. However, some of the newer techniques such as ShMOLLI have faster acquisition times and are inherently less HR dependent. Standardization of the acquisition phase in the cardiac cycle within and between studies remains an important consideration as acquisition timing can impact on T1 value and ECV due to fluctuation of the myocardial

blood volume (23). A reduction in T1 time of 43-70% has been observed from diastole to systole (24). Clinical feasibility of T1 mapping markedly increased with the advent of non-contrast MOLLI imaging due to increased reproducibility, higher spatial resolution and reduced motion artifact. However, this technique remains prone to frequency-dependent errors in T1-measurement (25), which has limited its practical utility.

Post-contrast

Post-contrast T1 mapping sequences are relatively intuitive for those familiar with CMR and can be readily incorporated into standard DE-CMR protocols without significant prolongation of study duration. In addition to HR and acquisition related confounders, there are several established physiological covariates related to contrast administration, which must be considered. These include: body fat percentage, renal function, delay time in measurement after contrast administration and gadolinium characteristics (such as dose, concentration and water exchange rate). Contrast dispersion may be influenced by higher percentage body fat composition in some individuals, leading to increased contrast dose relative to extra-cellular water content. Contrast administration is relatively contraindicated in subjects with an estimated glomerular filtration rate of <30 mL/min/1.73 m². Ideally, all confounding factors should be screened as predictors of post-contrast T1 values using linear regression analysis to enable appropriate data correction prior to analysis (26).

Although acquisition of pre- and post-contrast T1 mapping images can be performed in a timely fashion using the current rapid protocols, offline post-processing still remains laborious. Due to the time consuming nature of analysis of T1 values in multiple segments, some studies have also limited assessment to single mid-ventricular regions of interest and assumed these to be representative of the whole myocardium. Segmental analysis can also be problematic due to ventricular motion artifacts which occur most frequently in the infero-postero-lateral region (17). These regions may need to be deemed non-evaluable and excluded from analysis.

Partition coefficient and ECV mapping

Estimation of partition coefficient and ECV fraction from T1 mapping reduce the effect of confounding variables as they are calculated from the ratio of change in myocardial

T1 relative to blood-pool T1 pre and post-contrast (27). The advantage of this type of methodology is that it minimizes systematic errors in technique, enables better comparison of scans at different time points and results in less variability at different field strengths and across different vendor platforms. This could be of significant clinic benefit for monitoring of interval change within individuals, assessing treatment effect and allowing comparison of disease patterns within the general community. The main confounding factor affecting the partition coefficient is hematocrit. However, it can be easily corrected using blood volume of distribution (1-hematocrit) to give the ECV. Although the ECV is a more reliable measure of interstitial space, it remains based on the assumption of contrast equilibrium between blood and myocardium. Theoretically this may be problematic in certain disease states, although practically this does not appear to be an issue provided there is an adequate time period allowed for adequate contrast dispersion (22). Clinically, there is a wide spread of ECV values with overlap of values between normal and diseased myocardium (23). This makes it problematic for diagnostic purposes and more suited to measurement of interval change within individuals or assessment of more end-stage disease. Controversy persists regarding the influence of magnetic field strength (1.5 *vs.* 3 T) on myocardial ECV (22,23).

Alternative volume of distribution T1 mapping techniques

In an attempt to negate the inherent limitations of T1 mapping described above, alternative CMR techniques using volume of distribution methodology have been developed to estimate myocardial ECM burden. Equilibrium contrast cardiovascular magnetic resonance imaging (EQ-CMR) relies on a primed continuous infusion of contrast to achieve blood: myocardial equilibrium and thereby negate the effects of kinetic confounders (28). The three pronged method involves a contrast bolus followed by infusion, a blood sample to measure blood volume of distribution (1-hematocrit) and T1 measures pre- and post-equilibrium (with HR correction) to calculate the myocardial volume of distribution as a measure of diffuse myocardial fibrosis (28). Results are promising, however, widespread adoption of this technique outside research protocols has been limited due to its time and labor consuming methodology. Attempts have been made to simplify this technique with bolus contrast administration,

however, this results in a disparity with infusion ECV results when ECV levels are >0.4 (29). Volume of distribution has also been estimated via mathematical modeling. Jerosh-Herold *et al.* describe a technique whereby they perform multiple T1 measures during contrast washout and use complex mathematical modeling to minimize the effects of kinetic confounders and establish the ECV (27). The practical aspects of this technique are much simpler than EQ-CMR, meaning that it could be more easily integrated into a busy CMR lab. However, due to the multiple (and often exponential) factors, which determine contrast washout, mathematical modeling is complex and potentially liable to multiple predictable and unpredictable limitations. This may reduce its accuracy in ECV quantification as small calculation errors may be multiplied by several factors of magnitude in complex equations.

Technique validation

ECM is synthesized and degraded in a dynamic process of continual tissue growth and repair. This structural scaffolding is constituted in part from fibrillar collagen [predominantly types I (30) and III (31)], which provides both strength and elasticity. However, certain factors predispose to detrimental myocardial ECM remodeling, including: activation of inflammatory cytokines (32), potentiation of neurohormonal cascades (33), and upregulation of the renin-angiotensin-aldosterone system (34). Initial clinical T1 mapping studies examined advanced disease states where fibrosis had a known underlying pathological role. Iles *et al.* studied a symptomatic heterogeneous heart failure population, which included transplant recipients. They used post-contrast MOLLI to demonstrate an inverse correlation of T1 values with percentage fibrosis on myocardial biopsy of transplanted hearts, as well as a reduction in T1 time with worsening diastolic function (35). These results were corroborated by Sibley *et al.* who used a post-contrast Look-Locker technique to document an inverse correlation between T1 time and histological fibrosis on biopsy in patients with a broad range of cardiomyopathies, regardless of the degree of DE-CMR (36). However, in both these studies, endomyocardial biopsy samples were taken from the right ventricle, whilst T1 values were taken from left ventricular maps on the assumption that the pathological process was one of diffuse fibrosis.

A small number of other studies employing post-contrast Look-Locker, MOLLI and other T1 techniques

have demonstrated a correlation between T1 values and percentage myocardial fibrosis in a variety of pathologies. Non-contrast T1 mapping techniques have been less comprehensively compared against histological samples. ShMOLLI is the best validated and has demonstrated a relationship between T1 values and ECV fraction in severe aortic stenosis (37). Histological validation of the volume of distribution method EQ-CMR has been performed in small numbers of patients with aortic stenosis (28). Histological validation of T1 mapping techniques in early disease states is lacking due to the obvious ethical issues associated with performing invasive biopsies on relatively well subjects. Correlation of T1 values with collagen volume fraction in small animal models (20) has provided some indirect methodological validation (*Table 1*). While validation with histopathology is of considerable importance, the use of histopathology as the gold standard may also have its limitations. Significant desiccation of tissue samples frequently occurs during the fixation process, which can alter ECV, which may explain why many groups have not been able to demonstrate r values >0.7 . Therefore, validation with hard clinical endpoints and the demonstration of T1 mapping to predict response to various treatments will be necessary to launch T1 mapping into mainstream clinical use.

Clinical applications

T1 values have been correlated with echocardiographic functional and structural parameters, as well as pathological processes, which are known to be associated with increased myocardial fibrosis. T1 mapping has also been employed in subclinical myocardial disease to determine if underlying functional disturbance detected on echocardiographic parameters correlates with reduced T1 values in asymptomatic subjects in whom myocardial biopsy cannot be ethically justified. Markers of both systolic (58) and diastolic dysfunction (17) have been found to correlate with reduced T1 values in early non-ischemic diabetic heart disease suggesting a possible pathological role of fibrosis even in early disease states. This is reinforced by the study by Rao *et al.*, which found aldosterone excess to be associated with ECM expansion in T2DM (55) (*Table 1*). Thus, further studies are needed to determine if treating patients with early disease states can prevent progression to more advanced disease. In addition, T1 mapping has the potential to risk stratify patients with advanced cardiac disease and identify patients who may not respond to

Table 1 Examples of histopathological validation and clinical application of T1 mapping techniques

CMR technique		Histopathological validation	Clinical application
Pre-contrast	ShMOLLI	Correlation with biopsy-quantified fibrosis pre aortic valve replacement (38)	Detection of cardiac amyloidosis (39); Identification and assessment of Anderson-Fabry disease (40); Detection of underlying disease processes in HCM and DCM beyond those assessed by DE-CMR (41)
Post-contrast	Look-Locker	Right ventricular biopsy in a heterogeneous cardiomyopathy population (36); small-animal model of left ventricular hypertrophy (20)	Left ventricular fibrosis in HCM (42); Reduced T1 time in myotonic dystrophy (43); Predicts positive left ventricular remodeling in non-ischemic cardiomyopathy (44)
	MOLLI	Right ventricular biopsy in cardiac transplant recipients (35)	Left atrial fibrosis in atrial fibrillation (45); Extracellular space expansion in cardiac amyloidosis (46); Discrimination of normal and diffusely diseased myocardium (HCM/DCM) (47); Persistent left ventricular structural and function abnormalities in tachycardia-mediated cardiomyopathy post ablation (48); Detection of subclinical myocardial involvement in patients with systemic lupus erythematosus (49)
	Modified Look-Locker saturation recovery		Relationship between T1 values and diastolic dysfunction in early T2DM (17)
	Saturation-recovery single-shot acquisition (SASHA)		Identification of Fabry's disease independent of LVH (50); Marker of ventricular remodeling suggestive of fibrosis in anthracycline cardiotoxicity (51)
	ECV mapping	Correlation with histological CVF in explanted hearts (52)	Quantification of ECV in myocardial infarction, non-ischemic cardiomyopathy, remote remodeling and increased age (21); ECV doubled in ischemic scar compared with normal myocardium (53)
Volume of distribution	EQ-CMR	Correlation with CVF on biopsy in severe AS (37)	Variability in ECV with gender and a number of cardiac diseases (Anderson-Fabry, HT, DCM, HCM, AS, amyloidosis, MI) (40)
	Mathematical modeling	ECV increases with age and extent of myocardial fibrosis in mice hearts (54)	Aldosterone is associated with myocardial extracellular matrix expansion in T2DM (55); Myocardial ECV is increased in HCM sarcomere mutation carriers even in the absence of LVH (56); Quantification of ECM expansion in infiltrative heart disease (57)

AS, aortic stenosis; CVF, collagen volume fraction; DCM, dilated cardiomyopathy; DE-CMR, delayed gadolinium enhancement imaging; ECM, extracellular matrix; ECV, extracellular volume; EQ-CMR, Equilibrium contrast cardiovascular magnetic resonance imaging; HCM, hypertrophic cardiomyopathy; HT, hypertension; LGE, late gadolinium enhancement; LVH, left ventricular hypertrophy; MOLLI, modified Look Locker inversion recovery; MI, myocardial infarction; ShMOLLI, shortened modified Look Locker inversion recovery; T2DM, type 2 diabetes mellitus.

medical therapy and should be treated with more aggressive interventions such as device therapies.

Broberg *et al.* demonstrated a relationship between increased ECV and worsening of volumetric parameters in subjects with adult congenital heart disease compared to controls (59). Myocardial ECV has also been shown to correlate with short-term mortality (60) and histological collagen burden with low variability between scans (61). It has recently been found to be proportionally increased with advancement of age (21) and female gender (62). It must always be remembered that a reduction in T1 values is not specific for fibrosis and can be noted in alternative infiltrative pathologies, which cause increased myocardial signal intensity such as cardiac amyloid (63). However, these processes often demonstrate characteristic patterns of distribution, which can already be appreciated and differentiated using DE-CMR. The impact of myofibril disarray on T1 mapping in HCM remains controversial but may result in overestimation of ECV (64).

Although T1 mapping is typically employed for assessment of diffuse, non-ischemic fibrosis, it has been conversely used for characterization of myocardial infarction including Tako-tsubo cardiomyopathy (65). Acutely, prolongation of T1 and T2 values occurs in the setting of increased free water molecules (66). Increased pre-contrast T1 values not only reflect greater edema suggestive of more severe cellular injury (65), but also suggest a reduced likelihood of improvement in myocardial function long-term (67). This same premise shows promise for detection of non-ischemic acute edema in conditions such as myocarditis (65). Chronically, reduced T1 values have been demonstrated in regional infarcted tissue compared with normal myocardium (16).

Future directions

Assessment of ECM expansion in the setting of valve disease with T1 mapping has remained restricted to small cohorts with aortic valve disease (37,38,40,68). However, the potential clinical applications are immense, especially given the increasing body of evidence demonstrating a direct relationship between fibrosis burden and adverse outcomes (69). Quantification of diffuse fibrosis may assist with timing of surgery and predicting response to and recovery from surgical interventions (i.e., valve replacement/repair) in a similar way to the use of contractile reserve with stress echocardiography. Current research studies exploring T1 mapping in these areas will hopefully further add to the

potential clinical applications of this evolving technique.

As the technique of T1 mapping matures, serial monitoring of other non-valvular disease states such as HCM will hopefully also clarify the natural history of fibrosis progression. This may assist in the timing of targeted interventions. Patterns of diffuse fibrosis may also become more evident in a similar way to the characteristic changes observed on DE-CMR. Although, achieving similar diagnostic sensitivities to DE-CMR will be difficult. T1 mapping should also be well suited to identification of more focal regions of diffuse fibrosis. In real world clinical practice, it is likely that many subjects will present with concurrent manifestations of both diffuse and focal fibrosis. A common anticipated example would be ischemic cardiomyopathy in the setting of diabetes or obesity. This overlap may prove challenging for T1 quantification, as the degree of regional contrast accumulation will significantly impact upon the global T1 value (70). Accounting for these regions of focal enhancement by excluding them from T1 maps may assist, but would be technically difficult using current manual techniques. Future development of graded maps of signal intensity may enable automatic exclusion of regions with T1 values outside nominated ranges from global T1 calculations.

Accuracy of T1 values remains to be conclusively established. Currently, this is limiting its widespread use as a clinical application for diagnosis and guiding treatment. Histopathological validation remains limited and needs to be significantly improved across all T1 modalities. This is crucial for determination of accuracy as well as establishing the relationship of T1 values from different sequences, vendors and field strengths. Thus far, this type of multimodality testing has been largely limited to phantom studies (71). Overall, test-retest reproducibility appears to be good (54), especially with the newer single breath-hold ShMOLLI technique (37,72). However, larger, multicenter trials will be important to establish inter-observer variability between institutions and different T1 mapping techniques. Similarly, reliability of documented normal valves for both T1 and ECV remains suboptimal due to limited studies with small subject numbers (54). Once definitive normal valves are established, diagnostic valves in disease states will be more reliable and clinically meaningful. The recently described method of predicting T1 mapping and ECV measurement error may enable more confident identification of early disease as well as facilitate sequence optimization and allow more direct comparison of different T1 mapping protocols (25). Lastly, even the most

rapid T1 sequences are limited by lengthy post-processing. Development of reliable tissue tracking and automated border detection software for delineation of regions of interest would significantly improve the functionality and clinical applicability of the technique.

Conclusions

T1 mapping has the potential to be a useful technique for quantification of diffuse myocardial fibrosis in a variety of clinical settings. Currently, limited accessibility, accuracy, clear reference values for normal and abnormal myocardium and uniformity of technique amongst vendor specific sequences impede its practical applicability. Until currently, multiple research groups are actively addressing these issues, as the number of publications with T1 mapping has exponentially increased over the past few years, and the field is rapidly expanding. Multiple centers continue to apply various T1 mapping techniques to characterize various disease states which will undoubtedly provide the basis for more widespread clinical applicability. While our ability to interpret and compare meaningful data regarding true fibrosis burden from T1 values is currently limited, the advent of rapid T1 mapping for mainstream clinical use is likely to arrive in the not to distant future.

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