

Diffuse Interstitial Myocardial Fibrosis by T1 Myocardial Mapping: Review

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Abstract

Diffuse interstitial myocardial fibrosis has been described in various cardiac pathologies. Late gadolinium enhancement by cardiac magnetic resonance can detect the presence of focal myocardial fibrosis, but is limited for the assessment of diffuse interstitial fibrosis. T1 myocardial mapping is a noninvasive imaging technique which enables visualization and quantification of diffuse interstitial myocardial fibrosis. In this article, we review the T1 mapping technique and its utility in various cardiovascular disorders associated with presence of diffuse interstitial fibrosis.

Keywords: T1 mapping; Interstitial myocardial fibrosis; Cardiac magnetic resonance

Introduction

The Extracellular Matrix (ECM) in a normal human heart is composed of collagen fibers, proteoglycans, glycosaminoglycans and fibroblasts. Myocardial fibrosis, defined as a significant increase in collagen volume fraction of myocardial tissue, is a common histological feature in various cardiomyopathies [1]. The distribution of this myocardial fibrosis varies according to the underlying pathological process. Replacement myocardial fibrosis corresponds to the replacement of myocytes due to cardiomyocyte necrosis and apoptosis resulting from underlying pathologies including ischemia, infarction, and myocarditis. Infiltrative myocardial fibrosis is seen in conditions like Amyloidosis, Anderson-Fabry disease. Diffuse interstitial myocardial fibrosis has been described in various conditions including hypertension [2], diabetes, valvular disorders, aging heart and idiopathic dilated cardiomyopathy [3]. Diffuse interstitial fibrosis results from progressive increase in collagen synthesis by myofibroblasts. Interstitial fibrosis and infiltrative fibrosis ultimately lead to irreversible replacement fibrosis. Several therapeutic strategies aimed at regression of this reversible interstitial fibrosis are available. Therefore, early diagnosis of this reversible interstitial myocardial fibrosis is essential to identify patients at risk for subsequent development of symptomatic heart failure. Though endomyocardial biopsy enables qualitative and quantitative assessment of myocardial fibrosis [4], it is invasive, prone for sampling errors and cannot detect the fibrotic involvement of whole ventricle. Cardiac Magnetic Resonance (CMR) imaging allows noninvasive assessment of myocardial structure and function with great level of accuracy and reproducibility [5]. The assessment of myocardial fibrosis is best performed after injection of gadolinium contrast agents that are employed to reduce the T1 relaxation time of myocardial tissue [6].

Late Gadolinium Enhanced (LGE) CMR enables visualization and quantification of focal myocardial scar. The infarcted regions have a slower washout rate of gadolinium contrast than the healthy myocardium leading to lower T1 times in these areas. LGE CMR depends on the difference in this signal contrast between the myocardial scar and the normal myocardium [7]. Although LGE CMR allows qualitative assessment of myocardial scar, it is limited for absolute quantification of myocardial scar and also for assessment of diffuse interstitial myocardial fibrosis. This limitation is overcome by the myocardial T1 mapping which enables direct signal quantification and characterization of myocardial tissue on a standardized scale [8]. In this review, we discuss in detail the assessment of diffuse interstitial myocardial fibrosis by T1 mapping technique.

T1 mapping Techniques

A T1 map is a parametric reconstructed map in which individual pixel's intensity represents the T1 relaxation time of corresponding myocardial voxel. The original sequence to measure T1 relaxation times was developed by Look-Locker using free breathing, multi-point approach; which has been shown to be highly efficient and has been widely used for T1 measurements of brain. Different CMR acquisition sequences have been further developed to obtain a myocardial T1 map including VAST [9] and inversion recovery TrueFISP [10]. Currently, the most widely used sequence is the Modified Look-Locker Inversionrecovery (MOLLI) technique described by Messroghli et al. [8]. MOLLI sequence allows accurate and reproducible in vivo measurement and T1 mapping of myocardium with high spatial resolution within a single breath-hold [11]. MOLLI sequence uses a balanced Steady-State Free Precision (SSFP) readout to obtain a higher signal-noise ratio. MOLLI sequence uses ECG gated image acquisition at end-diastole over 17 heart beats to reconstruct 11 images. All source images have identical voxel sizes, image position and phase of cardiac cycle except for different inversion times. These 11 images are merged to generate one final T1 map, from which T1 time for global or segmental left ventricle can be assessed. (Figure 1) demonstrates LGE sequence, pre- and post-contrast T1 mapping sequence using MOLLI sequence in a normal healthy volunteer. MOLLI sequence however has certain limitations. MOLLI is heart rate dependant, especially T1 values less than 200 or more than 750 ms. A heart rate correction of these obtained T1 values as described by Messroghli et al. should increase the sensitivity and specificity of this technique for assessment of myocardial fibrosis [11]. To overcome this limitation of heart rate correction, an optimized MOLLI sequence was described by Messroghli et al. [12]. Also, MOLLI requires 17 heart beats to obtain one T1 map leading to a long breath hold, thus prone for breathing motion artifacts. A recent introduction of Shortened MOLLI sequence (ShMOLLI) enables generation of accurate and precise high-resolution myocardial T1 maps in a short breath-hold, using 9 heartbeats across a

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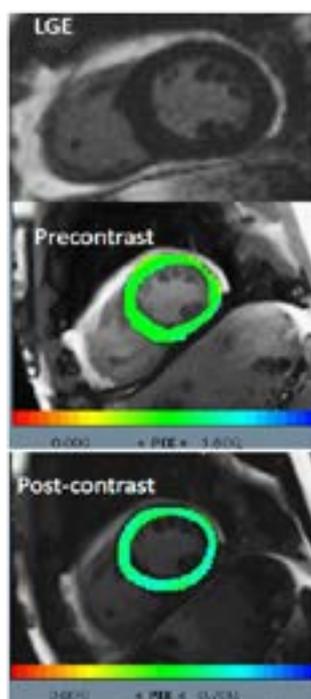


Figure 1: T1 mapping using MOLLI sequence in a normal healthy volunteer: LGE sequence (top); Precontrast (middle) and post-contrast (bottom). T1 mapping analysis yielded a precontrast T1 of 948ms and a 12 minute post-contrast T1 of 455 ms.

wide range of heart rates and T1 values [13]. T1 maps can be obtained at different slice levels before and after contrast administration. T1 values are computed for every pixel with three parameter curve fitting using Levenberg-Marquardt fitting algorithm [8]. More recently, ECV mapping has been introduced which includes generating an automatic ECV map from the acquired pre and post contrast T1 maps calibrated by blood hematocrit. ECV mapping incorporates the algorithm for (1) correction of respiratory motion due to insufficient breath-holding, (2) correction of misregistration between breath-holds and (3) automated identification of blood pool. ECV mapping has been used for quantification of both focal and diffuse myocardial abnormalities of ischemic and non-ischemic origin [14,15].

T1 Parameters

The parameters measured from the T1 mapping include pre- and post contrast myocardial and blood T1 times. Myocardial post contrast T1 values are affected by a variety of technical and physiological factors including the type and amount of contrast agent, magnetic field strength, precontrast T1 time, body composition, renal function and hematocrit. To avoid these limitations, normalization of myocardial T1 values in relation to the blood T1 values has been proposed [16,17]. The normalized T1 parameters calculated from these measured variables include partition coefficient and extracellular volume fraction (ECV). Several studies have used these integrated and raw T1 parameters as markers of diffuse interstitial myocardial fibrosis. Partition coefficient is defined as the ratio of tissue gadolinium concentration to the blood gadolinium concentration at equilibrium and is calculated as the slope of the linear relationship between R1 (reciprocal of T1) of myocardium versus the blood before and after gadolinium administration [18]. ECV fraction is calculated by multiplying the partition coefficient with (1-hematocrit/100) [19]. Precontrast T1 time, partition coefficient and

ECV are positively associated, while post-contrast T1 time is negatively associated with presence of diffuse interstitial myocardial fibrosis.

Histological validation

The T1 values obtained from myocardial T1 mapping have been histologically validated in few studies. Myocardial collagen content progressively increased as post contrast T1 times shortened with a correlation coefficient (r) of -0.7 as described by Iles et al [9]. Myocardial post-contrast T1 times have been correlated with biopsy detected interstitial fibrosis in patients evaluated for nonischemic cardiomyopathy [20]. A significant positive correlation ($r=0.73$) has been demonstrated between the partition coefficient of gadolinium and histological collagen volume fraction in interstitial and replacement fibrosis [21]. A strong correlation between histological CVF % and ECV by ShMOLLI ($r=0.685$) has been described by Fontana et al [22]. In patients with severe aortic stenosis, precontrast T1 values correlated with CVF % ($r=0.65$) [23].

Advantage

T1 mapping enables better visualization and characterization of myocardial tissue both on a global and a regional level. Myocardial T1 mapping can detect and quantify diffuse interstitial myocardial fibrosis, thus assist in monitoring the effectiveness of therapy aimed at regression of myocardial fibrosis and altering ventricular remodeling. Furthermore, early identification of diffuse interstitial fibrosis may aid in identification of patients at risk for subsequent development of heart failure. As a noninvasive imaging technique to assess diffuse interstitial myocardial fibrosis, T1 mapping has a potential to follow serial changes in myocardium over time. Whereas Endomyocardial biopsy can be prone to sampling errors and is limited by its accessibility to certain regions of heart, T1 mapping allows sampling of entire myocardium.

Limitations

Despite the advantages of T1 mapping by MOLLI sequence, being a single-shot acquisition sequence, the accuracy of pixel by pixel T1 estimation may be compromised. Also, the range of the raw and integrated T1 measurements for patients and normal volunteers is lacking. The exponential increase in T1 times after gadolinium administration depends on the gadolinium wash-out kinetics. Thus, the post-contrast T1 value varies with the timing of post contrast T1 image acquisition. To overcome this limitation, equilibrium contrast CMR has been proposed which involves a bolus administration of gadolinium contrast followed by a continuous infusion to measure the ECV fraction [24]. However, the work by Schelbert et al. demonstrates that there is no significant difference in the ECV fraction measured by constant infusion and bolus administration [25].

T1 mapping in Animal Models

The T1 mapping techniques described above are adequate for image acquisition for heart rates up to 100 beats per minute. These techniques are not suitable for use in small animals where heart rates of 200-600 beats per minute are expected. Several different T1 mapping techniques have been described to assess T1 relaxation times in small animals. Small Animal Look-Locker Inversion recovery (SALLI) as described by Messroghli et al. enables time efficient generation of cardiac T1 maps at high heart rates [26]. ECV fraction quantified by T1 mapping using SALLI correlated with collagen volume fraction by histology [27]. Li et al., described fast cardiac T1 mapping in mice using compressed sensing method which allows T1 image acquisition in less than 80 seconds at high spatial resolution [28]. Further research work with larger number of animals is necessary to evaluate the accuracy of these modalities.

T1 myocardial mapping in specific cardiovascular diseases

Ischemic heart disease: The first clinical use of T1 mapping technique was done by Messroghli et al in patients with acute myocardial infarction (MI). Precontrast T1 times were $18 \pm 7\%$ higher and post contrast T1 times were $27 \pm 4\%$ lower in the area of myocardial infarction compared to non-infarcted areas [29]. In patients with acute MI, incremental increase in precontrast T1 values identified the severity of myocardial injury and predicted the functional recovery at follow-up [30]. There was a marked difference in post-contrast T1 time between the LGE positive and negative areas (333 ± 30 ms vs. 429 ± 22 ms) in patients with ischemic cardiomyopathy [9]. Partition coefficient of gadolinium in patients with acute and chronic MI was significantly higher compared to controls [18]. In patients with prior MI, infarct region demonstrated a higher ECV fraction ($51 \pm 8\%$) compared to remote normal myocardium ($27 \pm 3\%$) [14]. (Figure 2) demonstrates a LGE sequence and pre- and post-contrast T1 mapping images using MOLLI sequence in a patient with ischemic cardiomyopathy.

Non-ischemic cardiomyopathy: Collagen deposition in non-ischemic cardiomyopathy is diffuse, and not commonly detected by LGE CMR. In LGE negative areas of myocardium, a significant difference in the post-contrast T1 time has been demonstrated in patients compared to controls (429 ± 22 ms vs. 564 ± 23 ms) [14]. Precontrast T1 time has been demonstrated to differentiate between diseased and normal myocardium with 100% sensitivity, 96% specificity and 98% diagnostic accuracy. Further, in patients with Non-Ischemic Dilated Cardiomyopathy (NIDCM), higher precontrast T1 times were associated with a lower LV ejection fraction [31]. Partition coefficient of gadolinium and ECV fraction were significantly higher in patients with NIDCM than in controls (partition coefficient of 0.56 ± 0.15 vs. 0.41 ± 0.06 ; ECV of $31 \pm 5\%$ vs. $24 \pm 3\%$). This expansion of extracellular matrix was also associated with a reduced myocardial blood flow and reduced ejection fraction [32]. In another study, in patients with NIDCM, ECV was elevated at $38.1 \pm 1.9\%$ compared to controls, despite the absence of LGE in these patients [15]. (Figure 3) demonstrates LGE sequence and pre- and post-contrast T1 mapping images using MOLLI sequence in a patient with Non-ischemic cardiomyopathy.

Hypertrophic cardiomyopathy: In patients with Hypertrophic Cardiomyopathy (HCM), post contrast T1 times were significantly shorter compared to controls and were associated with abnormal diastolic function [33]. In HCM, precontrast T1 values correlated with disease severity, and were higher in areas with increased wall thickness [34]. Another study has demonstrated that precontrast T1 times were positively associated with LV mass [31]. Also, the mean ECV values in HCM ($35.7 \pm 2.9\%$) were more heterogenous but lower than the ECV values for MI [15]. In a recent study, it has been demonstrated that compared to controls, ECV is increased in patients with overt HCM as well as sarcomere mutation carriers even in the absence of LV hypertrophy [35]. (Figure 4) demonstrates LGE sequence and pre- and post-contrast T1 mapping images using MOLLI sequence in a patient with HCM.

Myocarditis: Although endomyocardial biopsy remains the gold standard for diagnosis of myocarditis, combined T1 and T2 weighted imaging techniques enable noninvasive diagnosis of myocarditis with high specificity [36]. Precontrast T1 times greater than 990 ms optimally differentiated segments affected by myocardial edema from normal segments with high sensitivity and specificity [37]. Precontrast T1 times were elevated in patients with acute myocarditis, while ECV values in patients with myocarditis were focally elevated ($44 \pm 6\%$) compared to remote regions ($26.4 \pm 3\%$) [15].

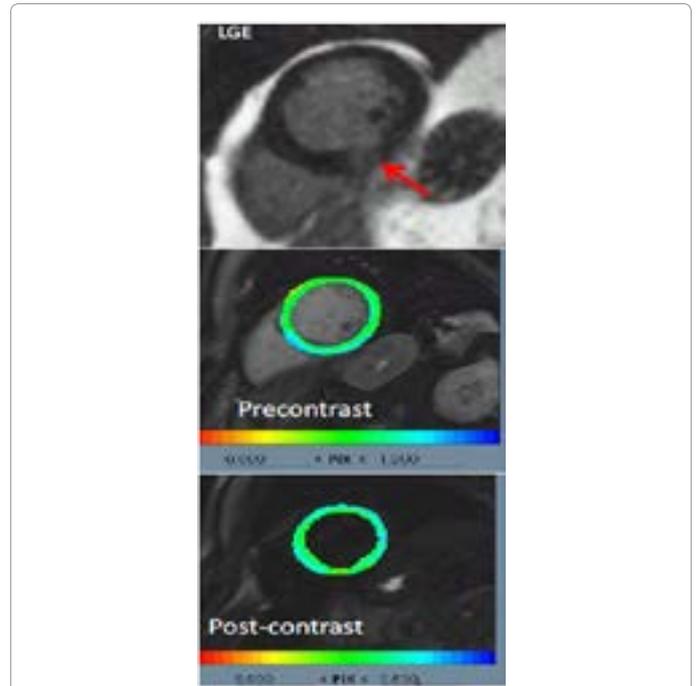


Figure 2: T1 mapping using MOLLI sequence in a participant with ischemic scar (red arrow) LGE sequence (top) and corresponding precontrast (middle) and post-contrast (bottom) T1 images. T1 mapping analysis yielded a precontrast T1 of 1047ms and a 12 minute postcontrast T1 of 286ms.

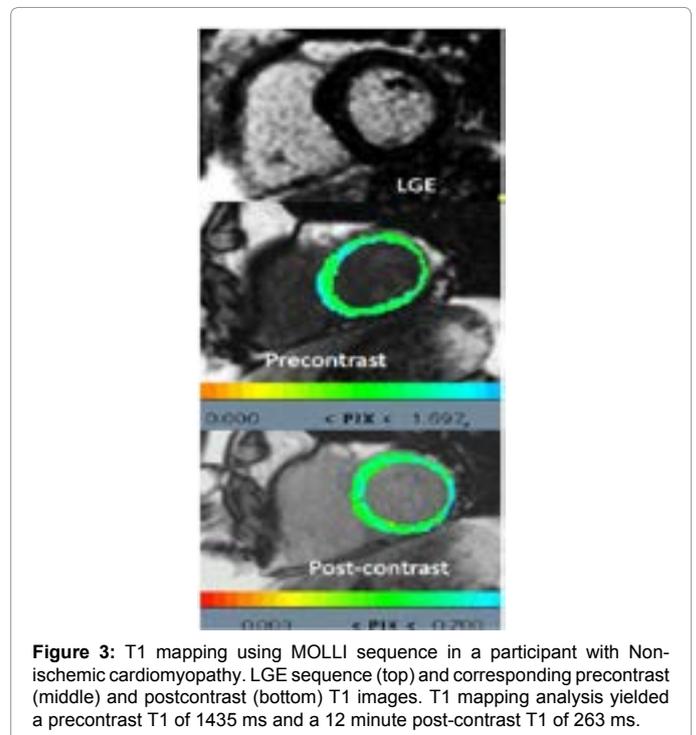


Figure 3: T1 mapping using MOLLI sequence in a participant with Non-ischemic cardiomyopathy. LGE sequence (top) and corresponding precontrast (middle) and postcontrast (bottom) T1 images. T1 mapping analysis yielded a precontrast T1 of 1435 ms and a 12 minute post-contrast T1 of 263 ms.

Amyloidosis: Cardiac amyloidosis is characterized by amyloid deposition leading to expansion of interstitial space. Precontrast T1 time was significantly elevated in patients with amyloidosis compared to controls (1140 ± 61 ms vs. 9799 ± 51 ms) [38]. Both partition coefficient of gadolinium and ECV fraction were 1.8 fold higher in amyloidosis compared to controls. The ECV values in amyloidosis

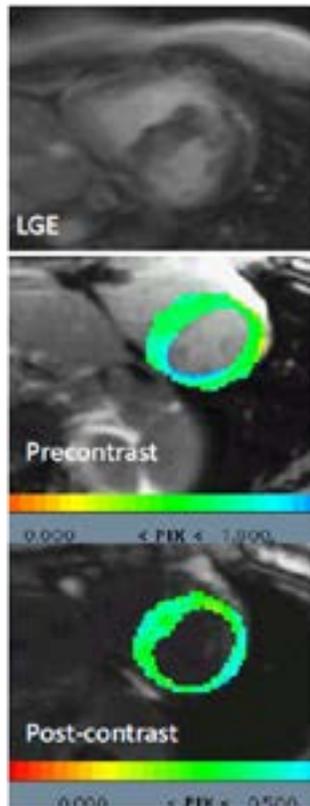


Figure 4: T1 mapping using MOLLI sequence in a participant with Hypertrophic cardiomyopathy. LGE sequence (top) and corresponding precontrast (middle) and postcontrast (bottom) T1 images. T1 mapping analysis yielded a precontrast T1 of 1215 ms and a 12 minute post-contrast T1 of 248 ms.

ranges from 32 to 60% with a mean of $46 \pm 12\%$ [15]. Furthermore, T1 mapping in amyloidosis has been demonstrated to be useful in prognostic assessment and provide information relating mortality risk prediction [39].

Others: Patients with type 2 diabetes mellitus compared to normal controls had a shorter global post contrast T1 time indicating the presence of diffuse interstitial myocardial fibrosis and more impaired longitudinal systolic and diastolic function [40,41]. Patients with adult congenital heart disease had significantly higher ECV fraction compared to normal controls ($31.9 \pm 4.9\%$ vs. $24.8 \pm 2\%$) and an associated systolic dysfunction [19].

Future directions

Myocardial T1 mapping is a noninvasive imaging method to visualize extracellular matrix and quantify diffuse interstitial myocardial fibrosis. T1 mapping with MOLLI sequence offers early detection of this extracellular matrix expansion. T1 mapping technique has been investigated in different clinical scenarios, but standardization of normal values in normal individuals is necessary. Also, most of these studies have been conducted in a single center in very small cohorts; large multi-center studies are required before this technique can be more widely used in a clinical setting. Further, racial/ ethnicity differences exist LV remodeling and cardiovascular disease, further research is required to investigate the utilization of this technique in different ethnic groups. Also, longitudinal studies are necessary to examine the serial changes in LV remodeling, monitor the

therapeutic strategies aimed at regression of myocardial fibrosis and thus improving clinical outcomes.

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