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TISSUE CHARACTERIZATION OF THE MYOCARDIUM : STATE OF THE ART CHARACTERIZATION BY MR AND CT IMAGING

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INTRODUCTION

Fibrosis is a feature of many cardiomyopathies and the failing heart and is a major independent predictor of adverse cardiac outcomes. Replacement fibrosis is typically the result of myocardial infarction. Diffuse interstitial fibrosis results from common cardiovascular risk factors; interstitial fibrosis has been shown to be reversible and treatable with early intervention. Non –invasive imaging methods to detect fibrosis are in development. Recent advances have been made in the fields of cardiac magnetic resonance imaging (CMR), computed tomography (CT) and nuclear medicine. Our review particularly focuses on the field of CMR and the techniques of Late Gadolinium Enhancement (LGE) and T1 mapping, useful in the detection of myocardial scar and diffuse myocardial fibrosis respectively.

PATHOLOGICAL BASIS OF FIBROSIS

The extracellular matrix (ECM) is a dynamic molecular network that is essential in giving strength to the heart and coordinated signaling between cells in the tissue. It anchors cardiac muscle cells (myocytes), regulates tissue mechanics, and stores growth factors. [1–3] The ECM is composed of collagens and elastic fibers buried in a gel of proteoglycans, polysaccharides and glycoproteins. Aberrant healing processes result in the common pathological feature called fibrosis. Fibrosis forms from an increased amount of collagen (fibrosis) resulting from altered collagen turnover, in which net collagen deposition exceeds net collagen breakdown. Diffuse myocardial fibrosis is known to increase with age and other cardiovascular risk factors [4]. At a molecular level, matrix metalloproteinases also play a key role in the development of myocardial fibrosis.

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Increased myocardial collagen deposition is the common endpoint for a wide variety of cardiomyopathies. Collagen deposition results in abnormal myocardial stiffness and contractility, which leads to progression of heart failure and disruption of the intercellular signaling. These disruptive processes may lead to malignant arrhythmias and sudden death. Indeed, multiple clinical studies have shown fibrosis to be a major independent predictor of adverse cardiac outcomes [5–8]. It is always present in end-stage heart failure [9]. Diastolic function is initially affected and followed by deterioration of systolic function [10].

The two distinct types of fibrosis in the heart are replacement fibrosis and interstitial fibrosis. Replacement fibrosis is focal development of scar that replaces dead cardiomyocytes from injury and is only seen when the integrity of the cell wall is affected [11]. Depending on the etiology, both regional and diffuse patterns can be seen. Scarring from myocardial infarction is the most common cause of replacement fibrosis. Hypertrophic cardiomyopathy, sarcoidosis, myocarditis, chronic renal insufficiency, and toxic cardiomyopathies are other conditions associated this type of fibrosis [12, 13].

Interstitial fibrosis is generally a diffuse process. It has two subtypes, reactive and infiltrative interstitial. Reactive fibrosis is present in a variety of common conditions, including aging and hypertension. It is caused by an increase in collagen production and deposition by stimulated myofibroblasts. Infiltrative interstitial fibrosis is much rarer and is caused by progressive deposition of insoluble proteins or glycosphingolipids in the interstitium. Examples of infiltrative fibrosis include amyloidosis and Anderson-Fabry disease [14, 15]. Eventually, both interstitial and infiltrative fibrosis lead to cardiomyocyte apoptosis and replacement fibrosis [10]. Unlike replacement fibrosis, interstitial fibrosis may be reversible and is a target for treatment [16, 17].

The ability to noninvasively image fibrosis could be very useful for diagnostic and therapeutic purposes in cardiomyopathy treatment. Tissue biopsy has been the gold standard for fibrosis assessment, but it is invasive in nature and prone to sampling error. The emergence of noninvasive imaging modalities like cardiovascular magnetic resonance (CMR) imaging and computed tomography (CT), have led to development of novel imaging methods for a range of cardiomyopathies.

DETECTION OF FIBROSIS WITH ENDOMYOCARDIAL BIOPSY

The gold standard for the detection of myocardial fibrosis is endomyocardial fibrosis. A small ($<1\text{mm}^3$) sample is taken, typically from the right ventricular side of the distal myocardial septum. The sample is assessed using Masson trichome staining. Quantitative absolute assessment of the collagen volume fraction in tissue samples is measured by quantitative morphometry with picrosirius red.

Being an invasive technique, this carries a risk of complications. In cases of localized fibrosis, sampling error restricts the accuracy. It is also not possible to determine fibrotic involvement of the whole LV.

DETECTION OF REPLACEMENT/ FOCAL FIBROSIS WITH LATE GADOLINIUM ENHANCEMENT (LGE) CARDIAC MAGNETIC RESONANCE (CMR)

CMR imaging demonstrates safe, high resolution imaging without ionizing radiation. CMR is well established as a standard of reference for the evaluation of myocardial structure and function. Pixel signal intensity of CMR images is based on the magnetic properties of hydrogen nuclei in the magnetic field. The two most common parameters from CMR are longitudinal relaxation time, T1, and transverse relaxation time, T2.

A unique clinical role of CMR (in comparison to echocardiography) is the use of late gadolinium enhancement (LGE) to define the presence of focal fibrosis or myocardial scar. For the evaluation of focal fibrosis, for example, from myocardial infarction (MI), late gadolinium enhancement (LGE) imaging has been a gold standard for visualization and quantification of scar. Figure 1 below shows scar from an inferior wall MI.

Myocardial scar is most commonly observed in fact as a result of MI. However, nonischemic cardiomyopathies are also frequently associated with LGE. CMR can be used to classify patients with myocardial dysfunction as ischemic versus nonischemic etiology based on LGE images. This distinction is very meaningful for clinical treatment. Figure 2 below shows LGE at the inferior right ventricular insertion point, a typical location for scar in hypertrophic cardiomyopathy patients.

The physiological basis of the LGE of myocardial fibrosis is based on the combination of an increased volume of distribution for the contrast agent and a prolonged wash-out related to the decreased capillary density within the myocardial fibrotic tissue [18, 19].

LGE CMR TECHNIQUE

The LGE technique to detect myocardial scar has a major advantage in its simplicity and robustness: an inversion pulse is used to suppress normal myocardium, followed by a standard gated T1-weighted gradient echo acquisition.

LGE sequences are based on distribution difference of the gadolinium based contrast agent in normal and fibrotic tissue. In areas of higher gadolinium chelate concentration, T1 time is shorter than in adjacent issue and shows high signal intensity on LGE image.

The discrimination between scarred/fibrotic myocardium and normal myocardium relies on contrast concentration differences combined with the chosen setting of the inversion-recovery sequence parameters. These parameters are set to “null” the normal myocardial signal that appears dark in the final image relative to the bright signal of the scarred/fibrotic myocardium.

Given various specific properties of the tissue, the T1 shortening induced by the gadolinium contrast agent generates specific differences in signal intensity. The major tissue parameters that influence the final voxel signal intensity in the contrast-enhanced images are local perfusion; extracellular volume of distribution; water exchange rates among the vascular;

interstitial, and cellular spaces; and wash-in and wash-out kinetics of the contrast agent [18, 20].

The myocardial “gray zone” is increasingly being defined on LGE clinical studies. The “gray zone” has been conceptually defined as myocardium with intermediate signal intensity enhancement between normal and scarred/fibrotic myocardium [21]. This area reflects tissue heterogeneity within the infarct periphery and has been shown to strongly correlate with ventricular arrhythmia inducibility and postmyocardial infarction mortality in ischemic cardiomyopathy [21, 22].

LGE CMR: CLINICAL APPLICATIONS

LGE-CMR has become a first-line noninvasive exam for the etiologic assessment of new-onset myocardial dysfunction [13, 23]. LGE with CMR came to the clinical forefront in the setting of ischemic cardiomyopathy. Subendocardial or transmural LGE is the typical pattern seen in myocardial infarcts using LGE-CMR.

Kim et al. [24] showed that regional differences in signal intensity were correlated to the extent and severity of myocardial injury. Subsequently they reported in experimental studies that the spatial extent of hyperenhancement was the same as the spatial extent of the collagenous scar at 8 weeks with highly significant correlations. In ischemic cardiomyopathy, the transmural extent of LGE is predictive of myocardial wall recovery after revascularization, but it is also predictive of adverse LV remodeling [25, 26].

LGE-CMR also provides prognostic information in nonischemic cardiomyopathies. LGE is significantly and independently associated with adverse cardiac events in patients with cardiac amyloidosis [27] and in patients undergoing aortic valve replacement [28]. In hypertrophic cardiomyopathy, Rubinshtein et al. [29] and Kwon et al. [30] reported that LGE was strongly associated with arrhythmia and subsequent sudden cardiac death.

Different patterns of enhancement have been reported according to the underlying etiology, whether ischemic or non-ischemic. Typical LGE enhancement patterns [31] for different cardiomyopathies are summarized in Table 1.

LGE CMR LIMITATIONS

Recently the CMR community has come to realize a disadvantage of the LGE method: the “normal” myocardium that is suppressed by the inversion pulse may actually contain low levels of diffuse fibrotic tissue in many diseases. Although LGE CMR is well validated and clinically accepted for the evaluation of focal myocardial scar, it has inherent disadvantages for assessment of diffuse myocardial fibrosis. LGE relies on the differences in signal intensity between scarred and adjacent normal myocardium to generate image contrast. As this method needs a normal myocardium reference value, the LGE CMR method is unlikely to detect the presence of fibrosis in diffuse cases where there is no clear distinction between fibrotic tissue and normal myocardium.

There are limitations of the LGE CMR method in its precise classification of myocardial fibrosis as present or absent. With conventional LGE imaging sequences, signal intensity is

expressed on an arbitrary scale that differs from one imaging study to another and therefore is challenging to assess for direct signal quantification in cross-sectional or longitudinal comparisons. The late gadolinium-enhanced myocardial fibrotic tissue is influenced not only by technical parameters set during image acquisition (inversion time [32], slice thickness, and so on), but also according to the intensity threshold that is arbitrarily set during post-processing to differentiate normal from fibrotic myocardium [33]. Presently, there is no single consensus on the intensity threshold settings to use for clinical assessment of myocardial fibrosis.

Various methods have been reported to define late enhanced myocardium, with significantly different results [33], perhaps explaining the variation in frequency of myocardial fibrosis by LGE CMR in different studies [34]. Thus while the LGE CMR method has been widely adopted in the clinical setting, wide variation in quantification of focal fibrosis and lack of detection of diffuse myocardial fibrosis have led to additional CMR approaches.

DETECTION OF DIFFUSE FIBROSIS WITH CMR BY T1 MAPPING

T1 mapping is an imaging method which can provide a quantitative assessment of tissue characterization on CMR [35]. T1 mapping enables identification of early myocardial fibrosis at a treatable stage, when it cannot be otherwise detected by circulating biomarkers [36]. There is now a growing body of evidence that T1 mapping can detect early fibrosis that is not otherwise detectable by LGE method. [37]

In comparison to LGE images, T1 mapping reduces the influences of windowing and variations in signal enhancement by directly measuring the underlying T1 relaxation times. T1 relaxation time is measured in milliseconds, and represents a magnetic property of the tissue, also referred to as longitudinal or spin lattice relaxation. The T1 relaxation time of the normal myocardium is on the order of 1000 msec. In the presence of an MRI contrast agent, the T1 relaxation time can be substantially reduced and thus the T1 time is reflective of the concentration of the MRI contrast agent in the tissue. The actual T1 times of each element of myocardium are determined on a pixel by pixel basis.

Before gadolinium contrast agent administration (“native” T1 values), areas of diffuse myocardial fibrosis have greater T1 values (by about 10–20%) than normal tissue. After gadolinium administration, T1 values are lower than normal in diffuse myocardial fibrosis. The expanded extracellular space in diffuse fibrosis accumulates more gadolinium-based contrast than healthy tissue which is compact with myocytes. Reduction in T1 values is not specific for diffuse myocardial fibrosis, however. T1 time reduction may also occur with cardiomyopathies where the extracellular space is expanded, such as with amyloid depositions. [38]

T1 MAPPING TECHNIQUE

By reconstructing a sequence of images, T1 maps are generated in which every pixel represents T1 relaxation time of the corresponding section of myocardium. The Modified Look-Locker Inversion-recovery (MOLLI) sequence, described by Messroghli et al. [39–42] is a frequently used T1 mapping sequence. A currently favored approach to T1 mapping is a

short MOLLI (modified Look-Locker inversion recovery) sequence. Using the ShMOLLI sequence, the average breath hold decreases from 18 to 9.1 seconds, and the number of required heartbeats decreases from 17 to nine [43]. This is particularly useful for dyspneic patients.

High-resolution native and post-contrast T1 maps may be obtained within a single breath hold. This MOLLI sequence has been thoroughly described, optimized, and tested in phantom studies, on healthy volunteers, and ischemic cardiomyopathy patients. ECG gated images are acquired at end-diastole. Images from multiple consecutive inversion-recovery acquisitions are then merged into one data set. A T1 map of the myocardium is created which is a parametric reconstructed image.

T1 maps can be obtained before or after gadolinium contrast administration. The pre-contrast T1 map is a baseline reference. The post-contrast T1 maps are assessed at different time points after contrast administration. A T1 distribution histogram may be created to analyze the composition of each myocardial slice. A curve of myocardial T1 recovery which reflects the contrast agent wash-out can be obtained using post contrast maps [44]. The MOLLI technique is sensitive to heart rate extreme values. It may also underestimate T1 times before gadolinium (native t1) and is best used for post gadolinium images. It does, however, produce a highly reproducible and fast T1 map of the heart. Intra and inter-observer agreement levels range is on the order of approximately 10% [44].

Besides MOLLI and shMOLLI T1 mapping, other CMR techniques are also available to obtain CMR T1 maps. [39, 42, 45–47]. These T1 mapping variants have been designed to have varying sensitivities to motion artifacts, heart rate, and intrinsic T1 value ranges [42]. The accuracy and reproducibility of the final T1 measurements is directly affected by the acquisition sequence. When comparing results of different studies it is thus important to note the particular technique used. Figure 3 below shows grey scale images of pre-contrast and 25 min post contrast T1 maps in a healthy volunteer acquired using the SMOLLI technique.

QUANTIFYING T1 MAPPING RESULTS: PARAMETERS AVAILABLE FROM T1 MAPS

There are three general approaches to obtaining T1 values to describe the tissue composition of the myocardium: “native” T1 values (no gadolinium contrast administered), post-gadolinium T1 time and normalized values (such as extracellular volume fraction or partition coefficient). Post gadolinium T1 times vary, depending on renal excretion of the contrast agent and delay time in measurement after gadolinium administration. The impact of those confounding variables might be reduced by calculating relative T1 mapping indices including the partition coefficient (λ) and extracellular volume fraction (ECV); both parameters are derived from the ratio of T1 change in blood and myocardium [45, 48] and are expressed as percentages. Calculation of ECV requires concurrent measurement of hematocrit (HCT). The ECV and λ are calculated using the following formulas [49]:

$$\begin{aligned}\Delta R1_{\text{myo}} &= 1/T1_{\text{myo-post}} - 1/T1_{\text{myo-pre}} \\ \Delta R1_{\text{blood}} &= 1/T1_{\text{blood-post}} - 1/T1_{\text{blood-pre}} \\ \lambda &= \Delta R1_{\text{myo}} / \Delta R1_{\text{blood}} \\ \text{ECV} &= \lambda \times (1 - \text{HCT})\end{aligned}$$

The ECV expresses the proportion of the myocardium representing interstitial space versus cellular space. With greater fibrosis, the interstitial component increases relatively to the cellular space. Gadolinium distributes only to the extracellular space and appears to be retained preferentially in areas of collagen/ scar. Thus in the presence of disease, native T1 is increased, post gadolinium T1 is decreased and ECV is increased. ‘ECV maps’ can be created from co-registration of T1 maps to locate the diffuse fibrosis [50, 51].

A relatively small number of studies are available to identify the ‘best’ T1 parameter (e.g., native T1, post gadolinium T1 or ECV) to detect various disease states. ECV has been a particularly attractive variable to quantify myocardial fibrosis since it normalizes for blood pool and hematocrit. However, ECV incorporates five different variables into its computation, each with an associated measurement error. If the errors in these variables accumulate, ECV could be insensitive for disease detection.

T1 MAPPING CLINICAL APPLICATIONS

Patient studies using T1 mapping have varied in study and design. The acquisition sequences have varied. Some studies have evaluated both native and post contrast T1 maps whereas others have only evaluated native T1 maps. Despite the differences in technique, a clear pattern that has been seen is that in cardiac disease post contrast T1 times are shorter. Table 2 summarizes ten key articles where cardiovascular diseases have been assessed with T1 mapping.

Multiple studies have also examined the use of ECV and cardiovascular diseases. A concern is that ECV has a wide range of normal values, ranging from about 23% to 30%. [37] This range may overlap with ECV values in early disease. Although ECV is less likely to be useful as a single cut-off value to identify abnormal versus normal patients, change in ECV within an individual may be a more promising approach to assess, for example, a therapeutic response.

The accuracy of myocardial T1 mapping has been recorded in a few studies. Bauner et al [52] and Messroghli [42] et al found sensitivities and specificities to be greater than 95% for detection of chronic myocardial infarction using contrast enhanced T1 mapping. Ferreira et al [53] reported that, in 21 patients with acute regional myocardial edema and no infarction and 21 healthy patients, unenhanced T1 mapping had sensitivity and specificity of 92%.

T1 MAPPING VALIDATION

Relatively few validation studies have been carried out comparing histology to T1 mapping values. Iles et al [47] studied a symptomatic heterogeneous heart failure population using post contrast MOLLI. On myocardial biopsy of transplanted hearts, they demonstrated an

inverse correlation of T1 values with percentage fibrosis. They also found a reduction in T1 time with worsening diastolic function. Sibley et al. used a post-contrast Look-Locker technique. They also demonstrated an inverse correlation between T1 time and histological fibrosis on biopsy in patients with a broad range of cardiomyopathies [54].

A few other studies using post contrast Look-Locker, MOLLI and other T1 techniques have shown a correlation between T1 values and percentage myocardial fibrosis. Non-contrast T1 mapping techniques has been less well validated.

T1 mapping can accurately differentiate both interstitial and replacement fibrosis from normal myocardium, as demonstrated by Kehr et al. [55] They carried out an in vitro magnetic resonance study of selected human myocardium samples, and documented post-contrast T1 values for both diffuse and replacement fibrosis to be significantly different from T1 values for normal myocardium. There was no significant difference between the diffuse fibrosis and replacement fibrosis T1 values, however.

T1 MAPPING LIMITATIONS

T1 mapping of the heart is technically demanding and standardization of the methodology is required.

The accuracy is sensitive to several confounding factors [35]. These include the gadolinium myocardial washout rate (affected by glomerular filtration rate) and the properties of the gadolinium contrast agent (dose, concentration, injection rate, relaxivity, water exchange rate). The time delay after gadolinium administration which post contrast times are measured and the type of acquisition sequence used should be recorded as they significantly affect the final T1 value. Areas of LGE significantly affect the mean slice T1 value and interfere with diagnosing diffuse fibrosis. These areas therefore need to be accounted for. Myocardial T1 distribution can be significantly scattered, and this might limit its sensitivity for disease states with less severe fibrosis. T1 maps are usually created at the mid-ventricular level. If the fibrosis is not homogenous, areas of disease may not be measured.

COMPUTED TOMOGRAPHY (CT)

CT scanning is increasingly having widespread clinical application for evaluation of coronary artery disease. The utility of cardiac CT for the evaluation of coronary artery stenosis has already been demonstrated in large, multi-center clinical trials [56–59]. Given the significant clinical advantages of CCTA for coronary artery lesion evaluation, it would be highly desirable if CT would also be useful for characterization of myocardial tissue abnormalities as well as myocardial function.

CT thus far has demonstrated initial utility primarily for the evaluation of myocardial scar. Lardo et al [60] demonstrated in an animal study that the spatial extent of acute and healed myocardial infarction could be determined and quantified accurately with contrast-enhanced CT. The CT findings were compared to histology. In a cohort of patients with intermediate-high pre test probability, Bettencourt et al found that CT delayed enhancement had good

accuracy (90%) for ischemic scar detection with low sensitivity (53%) but excellent specificity (98%).

The use of MDCT for diffuse abnormalities of myocardial tissue is significantly more challenging than the evaluation of focal myocardial scar due to the low contrast resolution of CT scanning. The distribution of iodinated contrast agent in the myocardium may be used to assess the degree of fibrosis. Several new studies highlight the potential of MDCT in this regard.

ECV measured with cardiac CT represents a new approach toward the clinical assessment of diffuse myocardial fibrosis. Nacif et al found [61] good correlation between myocardial ECV measured at cardiac CT and that measured at T1 mapping cardiac MR imaging in 24 subjects. A combination of healthy subjects and heart failure patients were studied. ECV was higher in patients with heart failure than in healthy control subjects for both cardiac CT and cardiac MR imaging, as expected. For both cardiac MR imaging and cardiac CT, ECV was positively associated with end diastolic and end systolic volume and inversely related to ejection fraction. Figure 4 below shows pre and post contrast MR and CT images. The antero-lateral segment was used as this segment was most reliably identified on the pre contrast CT.

The results of Nacif et al were confirmed in a subsequent study by Bandula et al [62] who demonstrated that ECV measured using an equilibrium CT technique in twenty four patients with aortic stenosis correlated well with histologic quantification of myocardial fibrosis and with ECV derived by using equilibrium MR imaging.

In terms of clinical application, Langer et al [63] studied patients with hypertrophic cardiomyopathy with MDCT. In that study, CT was able to reliably detect myocardial fibrosis as evident by late enhancement. Patient- and segment-based sensitivity was 100% and 68 % respectively compared to LGE-CMR. This technique could therefore be potentially used in cases with CMR contra-indications.

SUMMARY AND FUTURE PERSPECTIVES

CMR methods to noninvasively identify diffuse myocardial fibrosis have great potential to characterize and quantify early disease. Myocardial fibrosis is a common endpoint of many chronic myocardial and systemic diseases and is not available by other noninvasive tests. T1 mapping adds to the information provided by LGE-CMR and further improves our knowledge and the clinical assessment of myocardial diffuse fibrosis. This technique might help us to better stratify much larger and lower cardiovascular risk patient populations (diabetics, hypertensive), detecting subclinical myocardial changes before the onset of diastolic and systolic dysfunction.

The clinical value of T1 mapping remains to be seen, however. Two especially interesting applications for T1 mapping are amyloidosis and hypertrophic cardiomyopathy. In both cases, the extent of disease is otherwise difficult to quantify.

Further work in the field is ongoing to determine which disease processes may benefit by T1 mapping, and which parameter (s) (e.g., native T1, post gadolinium T1, ECV) are most sensitive and specific to identify the presence or absence of disease and its extent. Studies with large groups of patients and prospective studies are needed using standardized imaging protocols.

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KEY POINTS

1. LGE is a simple, robust, well validated method for the assessment of scar in acute and chronic myocardial infarction.
2. LGE is useful for distinguishing between ischemic and nonischemic cardiomyopathy. Specific LGE patterns are seen in nonischemic cardiomyopathy.
3. Patient studies using T1 mapping have varied in study, design and acquisition sequences.
4. Despite the differences in technique, a clear pattern that has been seen is that in cardiac disease post contrast T1 times are shorter.
5. ECV measured with cardiac CT represents a new approach toward the clinical assessment of diffuse myocardial fibrosis by evaluating the distribution of iodinated contrast.

Figure 1.
Inferior wall MI (black arrow). Wall thinning and Late Gadolinium Enhancement is seen.

Figure 2.
Delayed post contrast image showing LGE (black arrow) at the inferior right ventricular insertion point in a patient with hypertrophic cardiomyopathy.

Figure 3.
 Grey scale images of pre-contrast (left) and 25 min post contrast (right) T1 maps in a healthy volunteer acquired using the SMOLLI technique.

Cardiac MR imaging region of interest measurements obtained, *A*, before and, *B*, after gadolinium chelate administration and reformatted cardiac CT region of interest measurements obtained, *C*, before and, *D*, after administration of an iodinated contrast agent. Orange outline = myocardium, white circle = blood pool.

From: Nacif et al (2012) Interstitial myocardial fibrosis assessed as extracellular volume fraction with low-radiation-dose cardiac CT.

Table 1

CMR LGE enhancement patterns for different cardiomyopathies [31]

Mid myocardial : Hypertrophic cardiomyopathy, Dilated cardiomyopathy, Pulmonary hypertension
Patchy: Sarcoid, Amyloid, Myocarditis
Transmural: Infarction (most common), Sarcoid (chronic), Myocarditis (Severe)
Subendocardial: Infarction, Amyloid, Hypereosinophilic syndrome, Cardiac Transplant
Subepicardial: Myocarditis (most common), Sarcoid

Table 2

Clinical studies using T1 mapping to evaluate myocardial fibrosis

Author and Date	Disease	Technique	Sample size (Cases/ Controls)	Conclusions
Messroghli 2007 [42]	Acute or chronic	MOLLI	24/24	In acute and chronic infarction, pre contrast T1 values were higher than T1 values in remote myocardium
Maceira 2005 [46]	Amyloidosis	LL	22/16	Subepicardial post contrast T1 values were significantly reduced in amyloid compared with controls
Broberg 2010 [64]	Adult congenital heart disease	LL	50/14	Cases of adult congenital heart disease had elevated fibrosis index
Flett 2010 [65]	Aortic stenosis/HCM	LL	18/8 (aortic stenosis). 8/8 (HCM)	A high correlation was seen between T1 mapping with equilibrium contrast cardiac imaging and histologic samples of aortic stenosis and HCM
Gai 2011 [66]	Type 1 Diabetes	LL	19/13	A significant difference was seen in post contrast T1 values between those at low risk for diabetes compared with those at high risk
Ugander 2012 [49]	NICM/ prior MI	MOLLI	30/11, 36/11	ECV is increased in those with prior MI and NICM
Bauner 2012 [52]	Chronic MI	MOLLI	26/26	A significant difference is seen in post contrast T1 values in chronically infarcted myocardium compared to healthy myocardium
Turkbey 2012 [67]	Myotonic muscular dystrophy	LL	33/13	Lower post contrast T values were seen in myotonic muscular dystrophy than in controls
Dass 2012 [68]	HCM/DCM	ShMOLLI	28/12 (HCM), 18/12 (DCM)	Cases with HCM or DCM had higher pre contrast T1 times than controls
Messroghli 2003 [41]	Acute MI	LL	8/8	Post contrast T1 values in acute MI were significantly reduced compared to normal myocardium

Note: MOLLI = modified look locker inversion, LL = look locker, ShMOLLI – short modified look locker version, MI = myocardial infarction, HCM = hypertrophic cardiomyopathy, DCM – dilated cardiomyopathy, NICM = non ischemic cardiomyopathy.