Assessment of Myocardial Fibrosis in Hypertrophic Cardiomyopathy by Cardiac Magnetic Resonance: Modalities and Clinical Applications.

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Abstract

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disease caused by mutations in sarcomeric contractile proteins, characterized by cardiomyocytes disarray, interstitial fibrosis, increased arteriolar wall thickness and scarring. Fibrosis could represent a substrate for the generation of malignant ventricular tachyarrhythmias, which represent the current pathway for sudden cardiac death and is responsible for passive diastolic dysfunction, that is the leading cause of dyspnea.

The aim of this review is to depict the increasingly role of cardiac magnetic resonance (CMR) for assessment of myocardial fibrosis in HCM. This article will briefly review the current status of the novel CMR techniques (the Late Gadolinium Enhancement and the emerging T1 mapping) for identification, characterization and quantization of myocardial fibrosis in HCM.

In addition, this review will discuss the most recent acquisition techniques, the new parameters and their possible clinical utility in diagnosis, therapeutic management and prognosis in HCM.

Keywords: Myocardial fibrosis; Late Gadolinium Enhancement; T1-mapping; Hypertrophic cardiomyopathy

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Introduction

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disease with a prevalence of about 0.2% [1]. It is characterized by unexplained left ventricular (LV) hypertrophy in the absence of other cardiac or systemic diseases that by themselves would be capable of producing the given magnitude of hypertrophy and caused by mutations in sarcomeric contractile proteins [2]. In contrast to ischemic cardiomyopathy, HCM is characterized by diffuse histopathological abnormalities involving the entire LV myocardium, including replacement fibrosis and expanded extracellular matrix due to interstitial fibrosis and/or myocyte disarray [3].

Therefore in HCM, both interstitial fibrosis and reparative fibrosis, secondary to ischemic necrosis of cardiomyocytes, are present [3]. Characteristically, myocardial ischemia is often present even in the absence of atherosclerotic plaques of sub-epicardial coronary arteries because of the increased demand of oxygen, reduced coronary reserve due to constriction and reduced compliance of the intramural vessels and diastolic dysfunction resulting in compression of sub-endocardial vessels [4].

Myocardial fibrosis could represent a substrate for the generation of malignant ventricular tachyarrhythmias, which is the current pathway for sudden cardiac death in HCM [5]. In an autopsy study in patients with HCM who died suddenly, the calculated interstitial collagen volume fraction was about 8 times greater than in control subjects and 3 times higher than in patients with essential hypertension [6], a condition well known to have interstitial fibrosis [7,8]. Fibrosis comprised 15% (up to 27%) of the transmural septal tissue sections [6]. However, currently we do not know which type of fibrosis is more relevant for generating
ventricular tachyarrhythmias in HCM. In HCM there is an increase in the fraction of interstitial collagen, caused by the excessive synthesis of collagen I (increase of peptides released during the synthesis) not sufficiently balanced by its greater degradation for the reduced activity of metallo-proteinase catabolic (or collagenase) 1 and 2 of the matrix (MMP-1 and MMP-2) [9]. The accumulation of collagen, increasing the rigidity of left ventricle, is responsible for passive diastolic dysfunction, that is the leading cause of dyspnea [7,8,10]. In animal models with genetic mutations responsible for human HCM, it has been shown that treatment with an AT1 receptor antagonist, [11] or with simvastatin, [11] or more recently with N-acetylcysteine, [12] a precursor of glutathione, reduces the hypertrophy, the fibrosis, disarray and improves diastolic function.

In addition, recent studies have showed the presence of myocardial fibrosis in subjects with pathogenic sarcomere mutations and no LV hypertrophy, [13,14] supporting the hypothesis that fibrotic remodeling is triggered early in HCM pathogenesis.

Therefore, it is important to identify a sensitive and specific non-invasive method for identifying characterizing and quantifying myocardial fibrosis in HCM, which allows repeated assessments over time.

Assessment of the different types of myocardial fibrosis in HCM by cardiac magnetic resonance

Currently, the non-invasive gold standard for quantification of myocardial fibrosis is cardiac magnetic resonance (CMR). In CMR images, the pixel signal intensity is based on the relaxation of hydrogen nuclei protons in the static magnetic field, of typically 1.5 or 3.0-Tesla scanners. The main CMR techniques for assessment of myocardial fibrosis are Late Gadolinium Enhancement (LGE) and T1-mapping.

LGE

LGE technique by CMR is the gold standard for the assessment of reparative fibrosis [15].

Methodology

The technique is based on the administration of gadolinium contrast agents, paramagnetic metal ions encapsulated in a chelant that prevents toxic effects, reduce the T1 relaxation time of adjacent tissues, such as the blood and myocardium. Thus, the local gadolinium tissue concentration will induce differences in signal intensity in the T1-weighted image. The major tissue parameters that will 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 [16,17]. The increase in gadolinium concentration within fibrotic tissue based upon the combination of an increased volume of distribution for the contrast agent and a prolonged washout related to the decreased capillary density within the myocardial fibrotic tissue [16,18] causes T1 shortening which appears as bright signal intensity in the CMR image based on conventional inversion-recovery gradient echo sequences. The parameters of inversion-recovery gradient echo sequences set to “null” the normal myocardial signal that will appear dark in the final image relative to the bright signal of the scarred/fibrotic myocardium, after 10 to 15 minutes from gadolinium infusion [19]. LGE by CMR highlights regions of scar or fibrosis, as small as 0.16 g, as an area of high intensity signal [20]. Therefore, quantification of late enhancement explores the volume of the extra-cellular matrix, but this volume is increased also in other pathological processes, such as inflammation and edema.

LGE in HCM.

The precise pathophysiological mechanism responsible for LGE in HCM currently remains uncertain. Moon et al [21] demonstrated significant correlation between areas of LGE and scar by histology in a single heart obtained after heart transplantation. Between 50% and 80% of HCM patients show areas of LGE, which can be planimetered and the amount quantified and expressed as percentage of the total LV mass or volume [22-25]. Any pattern of distribution and location of LGE can be observed in HCM, although it never corresponds to a coronary vascular distribution. The most common LGE pattern is patchy with multiple foci in mid-myocardium of both ventricular septum and free wall, especially in the regions with the most hypertrophy [26]. Less commonly, LGE can be confined to free wall, septum, apex, and the areas of right ventricular insertion into ventricular septum and can also occur in RV wall. Transmural LGE occurs in one half of HCM patients [23,27]. Various methods exist to calculate the extent of LGE in HCM. The most widely used techniques have been a variety of semi-automated algorithms which identify high signal intensity LGE pixels after applying a grayscale threshold a number of standard deviations (SD) above the mean signal intensity within a remote region of interest containing normal “null” myocardium (i.e. 2, 4, 5 or 6 [SD]) or peak intensity of scarred myocardium (i.e. full width at half maximum [FWHM]) [28]. In patients with atherosclerotic coronary artery disease and prior myocardial infarction, areas of intermediate LGE signal intensity (i.e. “grey-zone”) correlated histologically to regions of tissue heterogeneity (mixture of isolated myocytes and fibrosis), while regions of higher signal intensity LGE correlate with core infarct zones comprised of only replacement scar [29]. Identification of areas of tissue heterogeneity are of potential importance, as these regions may represent a more arrhythmogenic substrate than the core infarct [30].

The differences in methodology translate into differences in the quantified areas of LGE and can impact on the ability to generalize individual research studies. However, 6SD and FWHM have been found to most closely approximate the extent of fibrosis compared with visual assessment (or the Raleigh curve method) and to be the most reproducible method for quantification of LGE in HCM compared to other grayscale thresholds [28,31-33]. (Figure 1)

Limits

While LGE CMR is the most accurate method to measure myocardial replacement fibrosis, its sensitivity is limited for the assessment of diffuse interstitial fibrosis, because the image contrast relies on the difference in signal intensity between fibrotic and “normal” myocardium, and such differences may not exist if the process is diffuse.

T1-Mapping

Contrast enhancement T1-mapping has been developed to quantify diffuse, non ischemic myocardial fibrosis. Compared to
LGE technique, T1-mapping technique by CMR eliminates the influences of windowing and variations in signal enhancement by directly measuring the underlying T1 relaxation times on a standardized scale of each myocardial voxel to characterize [34].

**Sequences**

In past, T1-mapping with the Look-Locker [35] method employs a continuous acquisition of image data and so it is not suitable for cardiac application, because cardiac motion causes a significant displacement of cardiac structures during image acquisition. Recently, modified Look-Locker inversion recovery (MOLLI) sequence [36] uses electrocardiogram-gated image acquisition, using a single shot steady-state free-precession technique and merges images from three consecutive inversion-recovery sequences into one data set. With MOLLI sequences, image data for single slice T1 mapping of the heart can be acquired at high spatial resolution (approximately 2.0 x 2.0mm in plane) within one breathhold of the subject. It has been shown that T1 maps provide good T1 accuracy and high reproducibility both pre- and post-contrast [37] and spatial resolution reproducibility. This MOLLI prototype sequence [38], uses 17 heart-beats to reconstruct 11 images with different inversion times during mid-diastolic cardiac cycle. An exponential recovery curve is fit to image intensities at different inversion times is then created for each designated segment to determine the pre- and post-contrast myocardial T1 time. All images are combined to generate the final T1 map, applying algorithms to define the best fitting curve over the 11 acquired initial voxels linking for the same location. Those fitting algorithms are very sensitive to motion and image quality/artifacts. The result is a T1 map imaging where the T1 time for the global or segmented LV can be obtained with an average acquisition time of 15 to 20 seconds (one breathhold). T1 maps can be obtained at different slice levels, typically by a series of short axis images at basal, mid ventricular and apical level of left ventricle. (Figure 2)

More recently, the new short MOLLI sequences (Sh MOLLI), [39] that have shorter acquisition times and are less dependent on the heart rate, provide immediate T1 maps with high resolution in less time and with high precision.

An alternative to inversion-recovery technique is the saturation recovery single-shot acquisition (SASHA) technique [40] that consists of 1 image acquired without any saturation recovery preparation in the first heart beat, followed by saturation recovery images with varying saturation time in the next 10 heartbeats, resulting in a total of 11 images for fitting T1. This technique has improved accuracy in T1 determination but has a lower signal to noise ratio than MOLLI technique [40].

**Methodology and Parameters.**

**Native T1** value refers to T1 measurement without the use of gadolinium contrast agents. Native mean T1 value of normal myocardium is of 977±63 ms at 1.5 T [37]. Native T1 values of myocardial fibrosis (infarct scar) are significantly longer than those of normal myocardium (1060 ± 61 vs 987±34 ms) although the range of native T1 value distribution overlaps with that of fibrotic myocardium [41]. There is no correlation between values of native T1 and LGE to identify focal fibrosis because native T1 mapping reflects both the intra- and extracellular compartments while LGE (as the post-contrast t1 mapping ) reflects only the extracellular space [42].

**Post-contrast T1** value refers to T1 measurement at time point after gadolinium administration. The post-contrast T1 values between 10 and 15 minutes of normal myocardium have been reported around 483 ± 20 ms at 1.5 T. Post-contrast T1 values of scarred myocardium are significantly shorter than those of normal myocardium due to the retention of gadolinium contrast in fibrotic tissue. Messroghli et al. 41 reported post-contrast T1 values around 390 ± 20 ms in chronic infarct scar compared to 483 ± 23 ms in normal myocardium for T1 maps obtained between 10 and 15 minutes after contrast administration. In an in vitro magnetic resonance study of human myocardium samples, Keh et al [43], showed that post-contrast T1 values for both diffuse and replacement fibrosis were significantly different from post-contrast T1 values for normal myocardium. Although there was no significant difference between the respective diffuse fibrosis and replacement fibrosis post-contrast T1 values, there was a significant correlation between post-contrast T1 value and myocardial collagen content. It has been shown that the post-contrast T1 time could be employed as an index of diffuse fibrosis, because it was shorter in patients with heart failure and myocardial fibrosis, validated by myocardial biopsy, than controls [44]. However, post-contrast myocardial T1 time measurement can be changed with variations in the precise time of measurement, body weight and corresponding contrast dose, rate of gadolinium clearance.
and hematocrit [45]. Therefore, Flett et al. [46] developed a new technique, equilibrium contrast CMR, to quantify diffuse myocardial fibrosis. The myocardial extracellular contrast volume of distribution (ECV) was calculated using the following equation:

$$ECV = \lambda \times (1 - \text{hematocrit})$$

where hematocrit is the percentage of red blood cell volume in a blood volume sample; \( \lambda \) is given as:

$$\lambda = \frac{\Delta R_{1,\text{myocardium}}}{\Delta R_{1,\text{blood}}}$$

with \( \Delta R_1 = \frac{1}{\Delta T_1} \) and \( \Delta T_1 = T_{1,\text{post}} - T_{1,\text{pre}} \)

where \( T_{1,\text{post}} \) and \( T_{1,\text{pre}} \) represent the T1 values before and after contrast, respectively. 

ECV correlated strongly with histological fibrosis at biopsies in both aortic stenosis and HCM patients [46]. Unlike post-contrast T1 value, ECV directly measures the proportion of myocardium occupied by extracellular space measuring myocardial uptake of contrast relative to plasma since gadolinium and plasma equilibrate during slow renal washout. However, ECV does not inform regarding potential variables such as the state of collagen cross-linking or extent of signal due to myocardial disarray [45].

Afterwards, comparing ECV measurements during a constant infusion and 12-50 min after a bolus of gadolinium, ECV measurements did not differ significantly [47]. Because myocardial ECV can be measured reliably and accurately 12-50 minutes after a simple bolus, its measure can be integrated easily into a CMR exam. However, when ECV is > 0.4, the bolus technique seems to measure ECV higher compared with infusion [47].

**T1 Mapping in HCM**

- **Native T1** value is significantly longer in HCM compared with normal control subjects [48].
- **Native T1** value can be used for non-contrast assessment of myocardial fibrosis in HCM. The 1060 ms threshold of the native T1 relaxation time is characterized by the best balance between agreement and correlation with fibrosis assessed by LGE 6SD method [48].
- **Post-contrast T1** time is shorter and correlate histologically with myocardial diffuse fibrosis in HCM patients [49]. ECV provides quantitative estimates of diffuse myocardial fibrosis in patients with HCM, validated by surgical myocardial biopsy [46,50,51].

Comparing HCM patients with healthy subjects, all T1-mapping parameters (native T1, post-contrast and ECV) prove highly accurate; however, the native T1 value shows the greatest discriminatory power, with a diagnostic accuracy of 98% [52].

**Possible clinical applications of LGE and T1-mapping by CMR in HCM**

**LGE**

LGE by CMR has been linked to outcome in HCM [53]. LGE has prognostic value in predicting adverse cardiovascular events in HCM patients. There are significant relationships between LGE and cardiovascular mortality, heart failure death, and all-cause mortality in HCM [53].

Additionally, several studies have shown that HCM patients with LGE are at greater risk of ventricular tachyarrhythmias on ambulatory monitoring compared with those without LGE [54,55] and small series have suggested relationship between presence of LGE, assessed visually, and adverse clinical events [56,57]. A recent international multicenter prospective study [58] of over 1293 HCM patients followed for a median of 3.3 years showed that the magnitude of LGE, by manual assessment, was an independent predictor of sudden death, with patients with LGE >15% of LV myocardium being at greatest risk. Recently, Ismail et al [59] published a study of 711 HCM patients followed for a median of 3.5 years. The extent of LGE quantified using the FWHM method was a predictor of sudden cardiac death or aborted sudden cardiac death by univariable analysis but it failed to remain predictive by multivariable analysis.
These results imply that quantification of LGE may be an important tool to identify asymptomatic patients at risk of sudden death, who would then be potential candidates for implantable cardioverter-defibrillator implantation and there is the need of a standardized approach to quantify LGE that is objective, reproducible and useful for routine evaluation.

In addition, in HCM, LGE correlates directly with LV wall thickening and inversely LV ejection fraction and in particular LGE at RV insertion points correlates with increased estimated LV filling pressure in HCM (higher E/e’ ratio and greater left atrium) [60]. Therefore, the LGE evaluation could be useful in assessing the grade of heart failure and the therapeutic decision.

In addition, LGE by CMR can have a role to help in differential diagnosis between HCM and other cardiomyopathies. Infiltrative cardiomyopathies such as cardiac amyloidosis, glycogen/lysosomal storage diseases including Fabry, that are considered to be the most common non-sarcomeric diseases in which cardiac phenotypic expression can mimic that of HCM (i.e. “phenocopies”).

Concentric hypertrophy and global homogeneous subendocardial LGE pattern on contrast-enhanced images is highly specific for cardiac amyloidosis, such that the signal from the myocardium cannot be adequately suppressed and differentiated from the adjacent blood pool [61]. A similar pattern of concentric wall thickening with a particular LGE distribution to the basal inferolateral wall has been frequently reported in Fabry disease [62]. In cardiac sarcoidosis, LGE is distributed mostly into the basal and mid-inter-ventricular septum, but also spread into all the LV segments; additionally, LGE can be nodular, circumferential, and subepicardial and subendocardial [63,64].

T1-Mapping
To date, in HCM patients there are no available T1-mapping data about outcome yet. However, it was found an association between ECV and BNP [65], that in its turn has showed to be an independent predictor of morbidity and mortality in HCM patients [66]. Myocardial ECV is increased in HCM sarcomere mutation carriers even in the absence of LV hypertrophy [14] and the quantification of ECV may help characterize the development of myocardial fibrosis in HCM and assist in developing novel disease modifying therapy, targeting interstitial fibrosis.

Both shorter post-contrast myocardial T1 times [49] and increased ECV [14], both indexes of diffuse myocardial fibrosis, correlate with non-invasively estimated LV filling pressure, suggesting a mechanistic link between diffuse myocardial fibrosis and abnormal diastolic function in HCM. A significant correlation found also between peak systolic LV outflow tract pressure gradient and energy loss, due to viscous dissipation (evaluated by the novel 4D-Flow technique by CMR) with ECV, indicating a possible mechanistic link between HCM related flow abnormalities, increased LV afterload, and LV structural remodeling [67]. Developing treatments targeted at interstitial fibrosis may have the potential to change the pathophysiologic substrate, thereby diminishing disease progression and reducing the risk of arrhythmias and heart failure in HCM.

In addition, native T1 value and ECV are significantly higher in HCM compared with patients with hypertension and native T1 is an independent discriminator between HCM and hypertensive heart disease, helping in differential diagnosis between these two heart diseases [68]. However, currently T1-mapping is still an emerging technique and requires further methodological standardization (i.e. uniformity of technique amongst vendor specific sequences) before it can be used for clinical applications [45]. Nevertheless, probably the large number of current studies on T1-mapping and its easy, fast and repeatable over time applicability allow its use in clinical practice in a near future.

Conclusion
In HCM, myocardial fibrosis, both interstitial fibrosis and reparative fibrosis, is present and correlates to malignant ventricular tachyarrhythmias and diastolic dysfunction.

The novel CMR techniques (the LGE and the emerging T1 mapping) seem to be a useful non-invasive method for identifying, characterizing and quantifying myocardial fibrosis in HCM, allowing repeated assessments over time. While LGE by CMR is the most accurate method to measure myocardial replacement fibrosis, contrast enhancement T1-mapping by CMR quantify accurately myocardial diffuse fibrosis, directly measuring the T1 relaxation times. In particular, ECV by T1 mapping seems to give the most accurate assessment of the diffuse fibrosis because it directly measures the proportion of myocardium occupied by extracellular space measuring myocardial uptake of contrast relative to plasma.

The development of treatments targeted at myocardial fibrosis could slow down disease progression and reduce the risk of arrhythmias and heart failure in HCM.

Declarations of Interest
The author declares no conflicts of interest.

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References


20. Piekannik SK, Ferreira VM, D’Ammelin E, Coelho-Filho OR, Neubauer A, Robson MD. Shortened Modified Look-Locker Inversion Recovery (ShMOLLI) for clinical myocardial T1-mapping at 1.5 T and 3 T within a 9 heart breath hold and compared with a 15 minute study. J Cardiovasc Magn Res 2010; 12:16-29.


