Assessment of Myocardial Fibrosis With Cardiovascular Magnetic Resonance

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Diffuse interstitial or replacement myocardial fibrosis is a common feature of a broad variety of cardiomyopathies. Myocardial fibrosis leads to impaired cardiac diastolic and systolic function and is related to adverse cardiovascular events. Cardiovascular magnetic resonance (CMR) may uniquely characterize the extent of replacement fibrosis and may have prognostic value in various cardiomyopathies. Myocardial longitudinal relaxation time mapping is an emerging technique that could improve CMR’s diagnostic accuracy, especially for interstitial diffuse myocardial fibrosis. As such, CMR could be integrated in the monitoring and therapeutic management of a large number of patients. This review summarizes the advantages and limitations of CMR for the assessment of myocardial fibrosis.

One of the most common histological features of the failing heart is myocardial fibrosis. Replacement fibrosis, often present in the terminal stages of heart failure, has been reported in histopathological autopsy studies (1,2). The pathophysiological mechanisms that lead to this fibrosis are various, with some being acute, as in myocardial infarction (3), and others being progressive and potentially reversible, as in hypertensive cardiomyopathy (4). Myocardial fibrosis in animal and patient studies is associated with worsening ventricular systolic function, abnormal cardiac remodeling, and increased ventricular stiffness (5–7). In recent clinical studies, fibrosis has also been shown to be a major independent predictive factor of adverse cardiac outcome (8–12).

In therapeutic guidelines for heart failure due to various cardiomyopathies, there are no specific therapeutic strategies based on the tissue composition of the myocardial wall, either in the early or more advanced stages of disease. This lack of specific treatment might result in inappropriate therapies, which can lead to increased morbidity and additional burden to health care services (13). Lack of personalized treatment is also secondary to the absence of accurate clinical tools to precisely phenotype patients with heart disease.

Recent reports have demonstrated the advantages of using cardiovascular magnetic resonance (CMR) for the noninvasive imaging of heart failure patients (14,15). CMR has been established as the reference imaging method for the assessment of cardiac anatomy and function by providing highly accurate and reproducible measures of both the left and right ventricles and also for the assessment of myocardial viability (16–18). The field of CMR is rapidly evolving with continuing technological progress and the recent development of applications that have further enhanced its capacity to characterize myocardial tissue. In this review, we focus on CMR characterization of the different types of myocardial fibrosis and its etiology through late gadolinium enhancement and myocardial longitudinal relaxation time (T1) mapping.

Myocardial Fibrosis: Pathogenesis and Consequences

Fibrosis pathophysiology. In physiological conditions, the fibrillar collagen network is in intimate contact with all the different cell types of the myocardium and plays a critical role in the maintenance of ventricular shape, size, and function (Fig. 1).

Myocardial fibrosis, defined by a significant increase in the collagen volume fraction of myocardial tissue, is always present in end-stage heart failure (19). The distribution of myocardial fibrosis, however, varies according to the underlying pathology and accounts for discrepancies among different pathological reports in which only qualitative as opposed to quantitative measurements were made (19–22). The progressive accumulation of collagen accounts for a spectrum of ventricular dysfunctional processes that com-
monly affect diastole first and subsequently involve systolic performance (5).

**Subtypes of myocardial fibrosis.**
Different types of myocardial fibrosis have been reported according to the cardiomyopathic process (Fig. 1).

**REACTIVE INTERSTITIAL FIBROSIS.**
The first type of fibrosis is interstitial reactive fibrosis with a diffuse distribution within the interstitium, but it can also be more specifically perivascular (23). This type of fibrosis has a progressive onset and follows the increase in collagen synthesis by myofibroblasts under the influence of different stimuli. It has mostly been described in hypertension and diabetes mellitus, where the activation of the renin-angiotensin aldosterone system, beta-adrenergic system, the excess of reactive oxygen species, and metabolic disturbances induced by hyperglycemia are major contributors (23–28) (Fig. 2). But this type of fibrosis is also present in the aging heart, in idiopathic dilated cardiomyopathy (2,21), and in left ventricular (LV) pressure-overload and volume-overload states induced by chronic aortic valve regurgitation and stenosis (29,30). It has

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**Figure 1 Etiophysiopathology of Myocardial Fibrosis**

Myocardial fibrosis is a complex process that involves each cellular component of the myocardial tissue. The myocardial fibroblast has a central position in this process by increasing the production of collagen and other extracellular matrix components under the influence of various factors (renin-angiotensin system, myocyte apoptosis, pro-inflammatory cytokines, reactive oxygen species).
also been reported in the remote noninfarcted myocardium after infarction (31).

Interstitial fibrosis is an intermediate marker of disease severity, as has been shown in hypertensive cardiomyopathy, and it precedes irreversible replacement fibrosis (27,32). It is reversible under specific therapy (4,33,34). Therefore, there is some clinical interest in its assessment for the management of patients with hypertension, diabetes, primary dilated cardiomyopathy, and valvular disease.

INFILTRATIVE INTERSTITIAL FIBROSIS. This subtype of fibrosis is induced by the progressive deposit of insoluble proteins (amyloidosis) or glycosphingolipids (Anderson-Fabry disease) (35,36) in the cardiac interstitium. Although this subject is not the primary focus of this review, their pathophysiology follows similar patterns, and the early detection of cardiac involvement is of critical importance to therapeutic management.

REPLACEMENT FIBROSIS. This replacement or scarring fibrosis corresponds to the replacement of myocytes after cell damage or necrosis by plexiform fibrosis, mainly type I collagen (37). Replacement fibrosis appears as soon as the myocyte integrity is affected. It can have a localized distribution (ischemic cardiomyopathy, myocarditis, hypertrophic cardiomyopathy, sarcoidosis) or a diffuse distribution (chronic renal insufficiency, toxic cardiomyopathies, miscellaneous inflammatory disease) according to the underlying etiology (14,15,38).

Interstitial fibrosis and infiltrative fibrosis ultimately lead to replacement fibrosis in the later stages of disease, where cellular damage and cardiomyocyte necrosis/apoptosis appear (27).

Detection of Myocardial Fibrosis

Endomyocardial Biopsies

Previously, the only methodology available to assess myocardial fibrosis was the histopathological assessment of endomyocardial tissue biopsies or of autopsy pieces. This methodology enables qualitative macroscopic assessment after Masson Trichrome staining (22) and quantitative absolute assessment of the collagen volume fraction in tissue samples by quantitative morphometry with picrosirius red, which specifically stains fibrillar collagen under polarized light (1,21,39). Although this technique offers an absolute quantification of fibrosis in myocardial samples (3), it has 3 evident drawbacks: 1) invasive biopsies are required; 2) sampling error restricts the accuracy of biopsy in the case of localized fibrosis (7,40); and 3) fibrotic involvement of the whole LV cannot be determined.

CMR

In the last 10 years, CMR has emerged as a noninvasive imaging method that allows a comprehensive assessment of myocardial anatomy and function with unequalled levels of accuracy and reproducibility. The use of gadolinium extracellular contrast agents with CMR using late post-gadolinium myocardial enhancement (LGE) sequences have further pushed our ability to accurately and precisely analyze myocardial tissue composition, especially myocardial fibrosis content. Physical basis of CMR tissue characterization. T₁, T₂ relaxation times, proton density. 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-T scanners. The relaxation of the hydrogen nucleus proton is specifically characterized by 2 distinct magnetic resonance relaxation parameters: 1) the T₁ or spin-lattice relaxation time, which corresponds to the specific time decay constant when the proton recovers approximately 63% of its longitudinal magnetization equilibrium value; and 2) the transverse relaxation time (T₂) or spin-spin relaxation time, which corresponds to the specific time when the proton transverse magnetization drops to approximately 37% of its original value. Both of those times...
are measured in milliseconds. Another constitutional parameter that needs to be added to explain the pixel signal intensity is the density of mobile hydrogen atoms within the tissue voxel or proton density.

Both the $T_1$ and $T_2$ relaxation times depend on the molecular environment of the water molecules in the tissue and therefore characterize each tissue very specifically. $T_1$ and $T_2$ relaxation times vary significantly from one type of tissue to another, but also within the same tissue depending on its physiopathological status (inflammation, edema, fibrosis). The CMR imaging techniques used also result in different contrast images. Specific CMR sequences can be used to selectively reveal certain molecular environments within the tissue. Those differences are further enhanced with the use of gadolinium extracellular magnetic resonance contrast agents.

**GADOLINIUM CMR ENHANCEMENT.** Gadolinium contrast agents reduce the $T_1$ relaxation time of adjacent tissue. Thus, the local gadolinium tissue concentration will induce differences in signal intensity in the $T_1$-weighted image. Given various specific properties of the tissue, the $T_1$ 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 (41,42).

**GADOLINIUM CMR OF MYOCARDIAL FIBROSIS ENHANCED.** 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 (41,43). The increase in gadolinium concentration within fibrotic tissue causes $T_1$ shortening, which appears as bright signal intensity in the CMR image based on conventional inversion-recovery gradient echo sequences. Thus, 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.

Of note, gadolinium contrast agents are not specific markers for myocardial fibrosis. Late gadolinium enhancement is caused by modifications of the contrast distribution space as well as wash-in and wash-out kinetics of the contrast into interstitial space or extracellular matrix. Therefore, quantification of late enhancement (e.g., $T_1$ mapping) explores the volume of the extracellular matrix. This volume is increased in myocardial fibrosis but can also be increased in other pathophysiological processes, such as inflammation and edema.

**Measuring myocardial fibrosis with LGE. CLINICAL APPLICATIONS.** The clinical application of myocardial LGE with CMR started with the assessment of experimental acute myocardial infarction followed by measurements in chronic infarct experimental models and patients (44–46). After having shown that the regional differences in signal intensity were correlated to the extent and severity of myocardial injury, Kim et al. (47) 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. The clinical impact of LGE extent in patients with chronic ischemic cardiomyopathy was further demonstrated with the clinical study in 50 patients undergoing revascularization showing that the degree of improvement in the global mean wall-motion score and the ejection fraction was significantly related to the transmural extent of LGE (46).

During the chronic phase of infarction, when a dense fibrotic scar replaces the infarcted myocardium, Mahrholdt et al. (17) showed the accuracy and the clinical reproducibility of delayed enhancement for infarct size determination. Moreover, Ricciardi et al. (48) and Wu et al. (49) showed the higher sensitivity for infarct detection by LGE-CMR as compared with single-photon emission computed tomography, and other studies have confirmed the ability of CMR to detect microinfarctions.

The number of studies assessing myocardial fibrosis by LGE in other types of cardiomyopathies has dramatically increased in the last 10 years (Table 1) (12,40,50–80). Different patterns of enhancement have been reported according to the underlying etiology, and LGE-CMR has become a first-line noninvasive exam for the etiologic assessment of new-onset myocardial dysfunction (14,15,50).

LGE-CMR also provides prognostic information that could be used to define more appropriate therapeutic strategies. 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 (46,81). At the clinical level, infarct size is an independent prognostic factor for heart failure, arrhythmic events, and cardiac mortality (9,11,82). In nonischemic dilated cardiomyopathy, Assomull et al. (8) showed that the presence of myocardial LGE was associated with a 3-fold increase of hospitalization for heart failure or cardiac death and a 5-fold increase of sudden cardiac death or ventricular arrhythmias. In hypertrophic cardiomyopathy, Rubinstein et al. (56) and Kwon et al. (57) reported that LGE was strongly associated with arrhythmia and remained significantly associated with subsequent sudden cardiac death after adjustment for other risk factors. In the same way, LGE is significantly and independently associated with adverse cardiac events in patients with cardiac amyloidosis (74) and in patients undergoing aortic valve replacement (83). Recently, the additional prognostic value of LGE was demonstrated in hypertensive (76) and diabetic (12) patients free of any cardiac symptoms and with preserved ejection fraction. Finally, the clinical significance of LGE also offers potential targets for new therapeutic strategies designed for the purpose of personalizing medical management, although such paradigm requires further development and testing. In this regard, there is a crucial need for LGE-CMR assessment standardization in clinical practice (84).

LGE LIMITATIONS. If LGE allows a sensitive and reproducible qualitative assessment of myocardial replacement fibrosis, it is limited in its accuracy for absolute quantification of myocardial fibrosis, and the assessment of diffuse fibrosis is restricted by technical and physiopathological characteristics. First, with conventional LGE imaging sequences, signal intensity is expressed on an arbitrary scale that differs from one imaging study to another and therefore is unsuitable for direct signal quantification in cross-sectional or longitudinal comparisons. The late gadolinium-enhanced myocardial fibrotic tissue is defined on the basis of the difference in signal intensity between fibrotic and normal myocardium, and this difference generates the image contrast. In addition, LGE is influenced not only by technical parameters set during image acquisition (inversion time [85], 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 (86).

Presently, there is no clear 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 (86–89). This is one of the factors explaining the variability in the frequency of myocardial fibrosis found by LGE in various cardiomyopathies from different studies (Table 1). This questions the reliability and reproducibility of LGE for myocardial fibrosis quantification in a clinical setting.

Another concern with the use of myocardial LGE has emerged with its increasing use to define the myocardial “gray zone” in clinical studies. The “gray zone” has been arbitrarily defined on late enhancement CMR images as myocardium with intermediate signal intensity enhancement between normal and scarred/fibrotic myocardium (90). This area reflects tissue heterogeneity within the infarct periphery and has been shown to strongly correlate with ventricular arrhythmia inducibility and post-myocardial infarction mortality in ischemic cardiomyopathy (90,91). The use of this “gray zone” in ischemic cardiomyopathy and other types of cardiomyopathies further expands the assessment and the quantification of hyperenhanced myocardium for purposes that go beyond pure quantification of myocardial fibrosis.

Finally, although LGE-CMR is the most accurate method to measure myocardial replacement fibrosis, its sensitivity is limited for the assessment of diffuse interstitial fibrosis. In LGE-CMR, 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.

Measuring myocardial fibrosis with T1 mapping. T1 MAPPING BASICS. The recent technical improvements in acquisition sequences now enable us to perform myocardial T1 mapping with high spatial resolution by using 1.5-T magnetic resonance imaging scanners within a single breath hold (92). Compared with LGE images, T1-mapping CMR techniques allow us to eliminate the influences of windowing and variations in signal enhancement by directly mea-
Figure 3  
T1 Map Construction and T1 Recovery Graph After Contrast Administration

(A) T1 map after 15 min of gadolinium administration in an inferior infarct case. This is the Modified Look-Locker Inversion Recovery Sequence that uses 17 heart-beats to reconstruct 11 images with different inversion times during mid-diastole. It is necessary to combine all images to generate the final T1 map. For that, it is necessary to apply 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 left ventricle can be assessed. (B) Graph showing the recovery of absolute myocardial T1 value in a healthy heart (short axis, mid-ventricle) at different time points before and after contrast administration (0, 2, 4, 6, 8, 10, 15, and 20 min). T1 values are expressed as mean ± SD. The global and regional mean T1 values will vary significantly with the time of assessment. The SD of T1 value is more significant before contrast administration. Reprinted with permission from Messroghli et al. (93).
suring the underlying $T_1$ relaxation times. Therefore, it allows signal quantification (in milliseconds) on a standardized scale of each myocardial voxel to characterize myocardial tissue.

**$T_1$ MAPPING METHODOLOGY.** A $T_1$ map of the myocardium is a parametric reconstructed image, where each pixel's intensity directly corresponds to the $T_1$ relaxation time of the corresponding myocardial voxel. Signal recovery from each myocardial voxel is sampled with multiple measurements after a specific preparation pulse sequence, and the associated $T_1$ relaxation time is calculated from these measurements by the combination of all acquisitions. $T_1$ maps can be obtained any time before or after gadolinium contrast administration. The pre-contrast $T_1$ map is a baseline reference. The post-contrast $T_1$ maps are assessed at different time points after contrast administration and could be used to obtain the curve of myocardial $T_1$ recovery reflecting the contrast agent wash-out (Fig. 3) (93).

Different CMR acquisition sequences have been used to obtain myocardial $T_1$ maps (6,75,92,94,95). This is an essential point to consider before performing myocardial $T_1$ maps, because it directly influences the accuracy and reproducibility of the final $T_1$ measurements. This should also be considered when comparing results between different studies. Different $T_1$ mapping strategies will have varying sensitivities to motion artifacts, heart rate, and intrinsic $T_1$ value ranges (94).

The most assessed $T_1$ mapping sequence has been described by Messroghli et al. (92,94,96,97) and is the Modified Look-Locker Inversion-recovery (MOLLI) sequence. MOLLI provides high-resolution $T_1$ maps of human myocardium in native and post-contrast situations within a single breath hold.

This sequence has been thoroughly described, optimized, and tested in phantom studies, on healthy volunteers, and ischemic cardiomyopathy patients. Although it is sensitive to heart rate extreme values and tends to slightly underestimate the true heart $T_1$ value, the method allows a rapid and highly reproducible $T_1$ map of the heart with high levels of intra and inter-observer agreement (93). However, in the only report on the clinical validation of $T_1$ mapping against histology for the assessment of myocardial fibrosis, Iles et al. (6) used a different type of sequence (VAST [Variable Sampling of the k-space in Time] inversion-recovery prepared 2D fast gradient echo sequence with variable sampling of k-space). This sequence, which is very similar to the MOLLI sequence, has been less well validated in the literature.

$T_1$ maps can be obtained at different slice levels, with an average acquisition time of 15 to 20 s (1 breath hold) for 1 $T_1$ map (93). Figure 4 demonstrates $T_1$ maps at the mid-ventricle level.

**THE ADVANTAGES OF $T_1$ MAPPING.** $T_1$ mapping enables direct myocardial signal quantification (in milliseconds) on a standardized scale. This allows a better characterization of myocardial tissue composition on a global or regional level. Myocardial areas of delayed enhancement can be measured in terms of their spatial extent, but also in terms of the magnitude of their signal intensity: The composition of each myocardial slice can be analyzed as a $T_1$ distribution histogram, which gives a more accurate description of the myocardial tissue composition (Fig. 5). One hypothesis would be to use this $T_1$ distribution (mean $T_1$ peak value, distribution scatter) to identify specific myocardial patterns such as myocardial diffuse fibrosis, specific myopathies, or the peri-infarction or “gray zone.”

The pre-contrast mean $T_1$ value of normal myocardium is of $977 \pm 63$ ms, and the post-contrast values between 10 and 15 min of normal myocardium have been reported to be approximately $483 \pm 20$ ms (93) at 1.5-T. Pre-contrast $T_1$ values of myocardial fibrosis (infarct scar) are significantly longer than those of normal myocardium ($1,060 \pm 61$ ms vs. **Figure 4**

**$T_1$ Maps of the Myocardium at the Mid-Ventricular Short-Axis Level in a Healthy Volunteer**

(A) Pre-contrast, (B) post-gadolinium contrast (0.15 mmol/kg) at 12 min, and (C) at 25 min acquired with the MOLLI sequence. The mean $T_1$ value for the left ventricle (LV) can be obtained at each time after tracing the endocardial and epicardial countours of the LV (A).
although the range of pre-contrast $T_1$ value distribution overlaps with that of fibrotic myocardium (97).

Post-contrast $T_1$ values of scarred myocardium (replacement fibrosis) are significantly shorter than those of normal myocardium due to the retention of gadolinium contrast in fibrotic tissue. Messroghli et al. (97) reported $T_1$ values of approximately $390 \pm 20$ ms in chronic infarct scar compared with $483 \pm 23$ ms in normal myocardium for $T_1$ maps obtained after MOLLI acquisitions. From those $T_1$ maps, a mean left-ventricular (LV) $T_1$ value can be obtained. This information can also be processed more precisely through the analysis of the distribution histogram of the LV $T_1$ values. Very distinct patterns of distributions can be seen on those examples, but this has to be shown in further larger clinical studies. This might also be a new way to assess and quantify myocardial fibrosis.

REPORTED CLINICAL APPLICATIONS OF $T_1$ MAPPING. There are very few studies published using $T_1$ mapping in the clinical setting. They are reported in Table 2 (6,75,96,98,99).

$T_1$ MAPPING LIMITATIONS. To date, all of the published clinical studies using $T_1$ mapping have been realized on small groups of selected patients, with different types of $T_1$ acquisition sequences. Although there was no significant difference between the respective diffuse fibrosis and replacement fibrosis $T_1$ values, there was a significant correlation between $T_1$ value and myocardial collagen content. However, the real clinical benefit of $T_1$ mapping remains to be shown. When applied with rigorous methodology, $T_1$ mapping could be the ideal tool to assess and quantify diffuse myocardial fibrosis. It could also improve the accuracy of delayed enhancement and myocardial scar characterization.
when combined with LGE imaging, its accuracy is sensitive to many confounding factors. Those factors are as follows:

1. The physical properties of gadolinium contrast agents (dose, concentration, relaxivity, rate of injection, and water exchange rate) significantly affect the final myocardial voxel $T_1$ value.
2. The time delay of the $T_1$ mapping measurement after gadolinium administration also significantly affects the resulting $T_1$ values. Because the $T_1$ value exponentially increases with the wash-out of gadolinium contrast from the myocardium, the time of $T_1$ mapping acquisition will have a significant influence on the final myocardial voxel $T_1$ value (93). Therefore, in clinical studies, when performing $T_1$ mapping acquisition, the acquisition time after contrast administration should be carefully measured and reported. Solutions to this problem may include normalization to noncardiac tissue (e.g., muscle, blood) or characterization of the time as a $T_1$ curve.
3. The types of $T_1$ mapping acquisition sequence that will affect the sensitivity to motion artifacts (arrrhythmia), heart rate, and $T_1$ extreme values (92,94). Recently, various acquisition protocols with shorter acquisition times have been reported with good levels of accuracy (100,101).
4. The gadolinium myocardial wash-out rate, which mainly depends on each patient’s individual glomerular filtration rate, should be carefully accounted for when performing $T_1$ mapping. Although the influence of renal dysfunction on myocardial $T_1$ mapping remains incompletely understood, Maceira et al. (75) proposed a correction model of myocardial $T_1$ value by blood $T_1$ value in their study of cardiac amyloid patients that significantly improved $T_1$ mapping sensitivity.
5. The presence of LGE areas will have to be accounted for in order to assess the true $T_1$ value of nonaffected myocardial areas. Those areas have been shown to significantly influence global myocardial slice mean $T_1$ value and therefore interfere with the diagnosis of diffuse interstitial fibrosis (6).
6. The hematocrit level will affect the partition coefficient of the gadolinium contrast agent to be considered for the clinical use of $T_1$ mapping.

### Table 2 Clinical Studies Using $T_1$ Mapping

<table>
<thead>
<tr>
<th>First Author (Ref. #)</th>
<th>Cardiac Disease Category</th>
<th>Patient Sample Size (n)</th>
<th>$T_1$ Mapping Method</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Messroghli et al. (96)</td>
<td>Acute myocardial infarction</td>
<td>8</td>
<td>NA</td>
<td>- $T_1$ pre-contrast value of the infarcted myocardium was significantly prolonged (+18 ± 7%) compared with noninfarcted normal myocardium.</td>
</tr>
<tr>
<td>Messroghli et al. (98)</td>
<td>Chronic myocardial infarction</td>
<td>24</td>
<td>MOLLI</td>
<td>- $T_1$ pre-contrast value of the infarcted myocardium was significantly prolonged compared with noninfarcted normal myocardium (1,060 ± 61 ms vs. 987 ± 34 ms).</td>
</tr>
<tr>
<td>Sparrow et al. (99)</td>
<td>Chronic aortic regurgitation</td>
<td>8</td>
<td>MOLLI</td>
<td>- No significant difference in slice averaged myocardial $T_1$ pre- and post-contrast values in the patient group compared with controls.</td>
</tr>
<tr>
<td>Maceira et al. (75)</td>
<td>Cardiac amyloidosis</td>
<td>22</td>
<td>NA</td>
<td>- Subendocardial $T_1$ post-contrast value at 4 min was significantly shorter in amyloid patients than in controls (427 ± 73 ms vs. 579 ± 75 ms).</td>
</tr>
<tr>
<td>Iles et al. (6)</td>
<td>Chronic heart failure</td>
<td>25</td>
<td>VAST</td>
<td>- $T_1$ 15-min post-contrast values correlated significantly with collagen volume fraction on myocardial biopsies ($R = -0.7$).</td>
</tr>
</tbody>
</table>

LGE = late gadolinium enhancement; MOLLI = Modified Look-Locker Inversion Recovery; NA = not applicable; VAST = inversion recovery gradient echo sequence with Variable Sampling of the k-space in Time.
7. Even if myocardial T<sub>1</sub> values have been shown to be the same between basal, mid-cavity, and apical sections of the LV in healthy volunteers, it is unknown whether all sections are affected equally by diffuse interstitial fibrosis. For practical reasons, T<sub>1</sub> maps in patients are performed at a single-section level of the LV (usually mid-ventricle). Therefore, this sampling limitation might affect the final T<sub>1</sub> values in a myocardium in which the fibrosis process is not homogenous.

T<sub>1</sub> mapping is a very sensitive technique that needs to be performed in rigorous conditions in order to enhance its accuracy for fibrosis assessment and allow cross-sectional comparisons (102). Although the post-contrast T<sub>1</sub> value of myocardial fibrosis is significantly different from that of normal myocardium, myocardial T<sub>1</sub> distribution can be significantly scattered, and this might limit its sensitivity for disease states with less severe fibrosis.

T<sub>1</sub> mapping is still an emerging technique. Before it can be used for clinical applications, a more standardized histologically validated technique needs to be identified and assessed in clinical studies on various and larger groups of patients and in multicenter settings.

**Equilibrium contrast CMR.** Recently Flett et al. (103) reported a new CMR method to assess diffuse myocardial fibrosis: equilibrium contrast CMR. This was implemented to improve myocardial T<sub>1</sub> mapping by excluding confounding factors such as heart rate, body composition, and renal clearance variability. It is based on 3 elements: 1) a bolus of gadolinium followed by continuous infusion to achieve blood/myocardium equilibrium; 2) a measurement of the blood volume of distribution (1-hematocrit); and 3) a pre- and post-equilibrium T<sub>1</sub> measurement by CMR. This method allows a precise calculation of the gadolinium myocardial volume distribution that reflects diffuse myocardial fibrosis.

In a selected population of pre-surgical aortic stenosis and hypertrophic cardiomyopathy patients undergoing myectomy, Flett et al. (103) validated this method against fibrosis quantification by histology on selective surgical biopsies. They showed that equilibrium contrast CMR correlated strongly with biopsy histological fibrosis. These data are preliminary and, as for T<sub>1</sub> mapping, have to be confirmed in larger and different cardiomyopathy populations. Also, this method imposes a more complex image acquisition protocol that questions its clinical applicability at the time when CMR availability is still a major limitation in comparison with other cardiac imaging techniques.

**Other Methods to Explore Myocardial Fibrosis**

This review focuses on CMR as the most promising accessible and accurate noninvasive imaging tool to assess myocardial fibrosis in a routine clinical practice. Other noninvasive methods have been used to characterize myocardial fibrosis (perfusable tissue index with positron emission tomography, procollagen-derived pro-peptides and matrix metalloproteinases as serum fibrosis biomarkers, single-photon emission computed tomography imaging with specific radiolabeled agents) or its functional consequences (tissue Doppler echocardiography, CMR tissue tagging) and have been reported in the literature (104) but do not constitute the focus of this review. The cross-sectional combination of different imaging modalities might increase the diagnostic accuracy for myocardial fibrosis, but this still needs to be established.

**Future Perspective**

CMR has recently been proposed as a comprehensive tool in the clinical arena for the diagnosis and management of patients with heart failure (14). LGE-CMR, after showing its prognostic power to predict myocardial recovery in ischemic cardiomyopathy, has also shown its diagnostic accuracy for myocardial replacement fibrosis assessment in different types of cardiomyopathies. LGE presence has a powerful independent clinical prognostic value not only in ischemic cardiomyopathy (9,11,81,82), but also in all other types of cardiomyopathies (8,69,74,105). This knowledge is now being converted into efficient methods to monitor therapeutic applications through new studies designed to improve our therapeutic options.

The emergence of T<sub>1</sub> mapping further improves our knowledge and the clinical assessment of myocardial diffuse fibrosis and further refines the information provided by LGE-CMR. It 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. For the moment, clinical data are scarce, and the clinical value of this technique remains to be shown, specifically in larger groups of patients and in prospective studies. T<sub>1</sub> mapping using standardized imaging protocols combined with LGE will be of great help for a more precise myocardial tissue characterization. This combination of tissue information might help the clinician to better understand and diagnose sooner the underlying cardiomyopathic process. This information will also help to improve therapeutic strategies and enable a more direct monitoring of their effect, thus improving clinical outcomes (4,32).

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Key Words: cardiac magnetic resonance, late gadolinium enhancement, myocardial fibrosis, T1 mapping.