Myocardial T1-Mapping: Techniques and Clinical Applications

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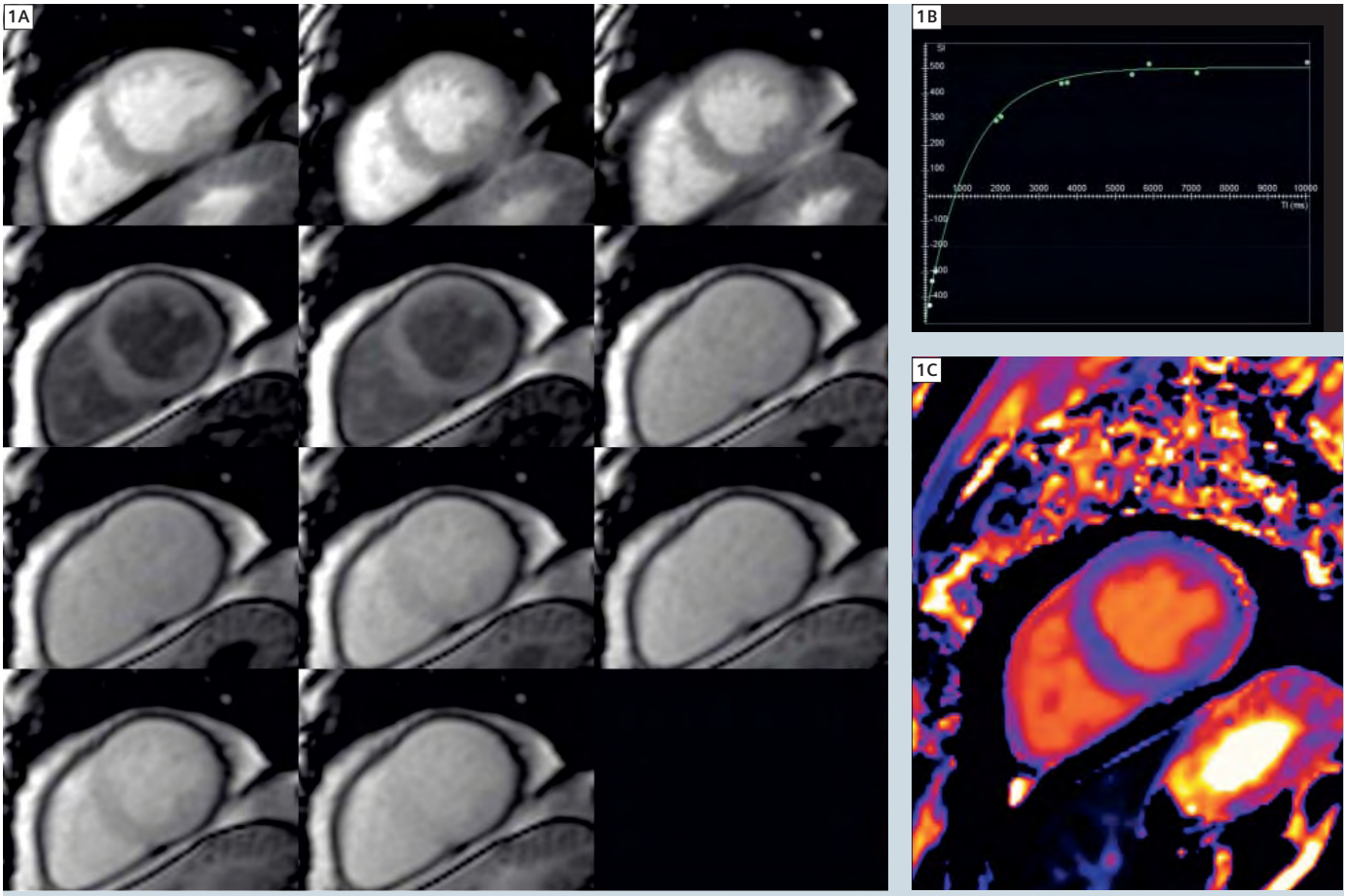
Introduction

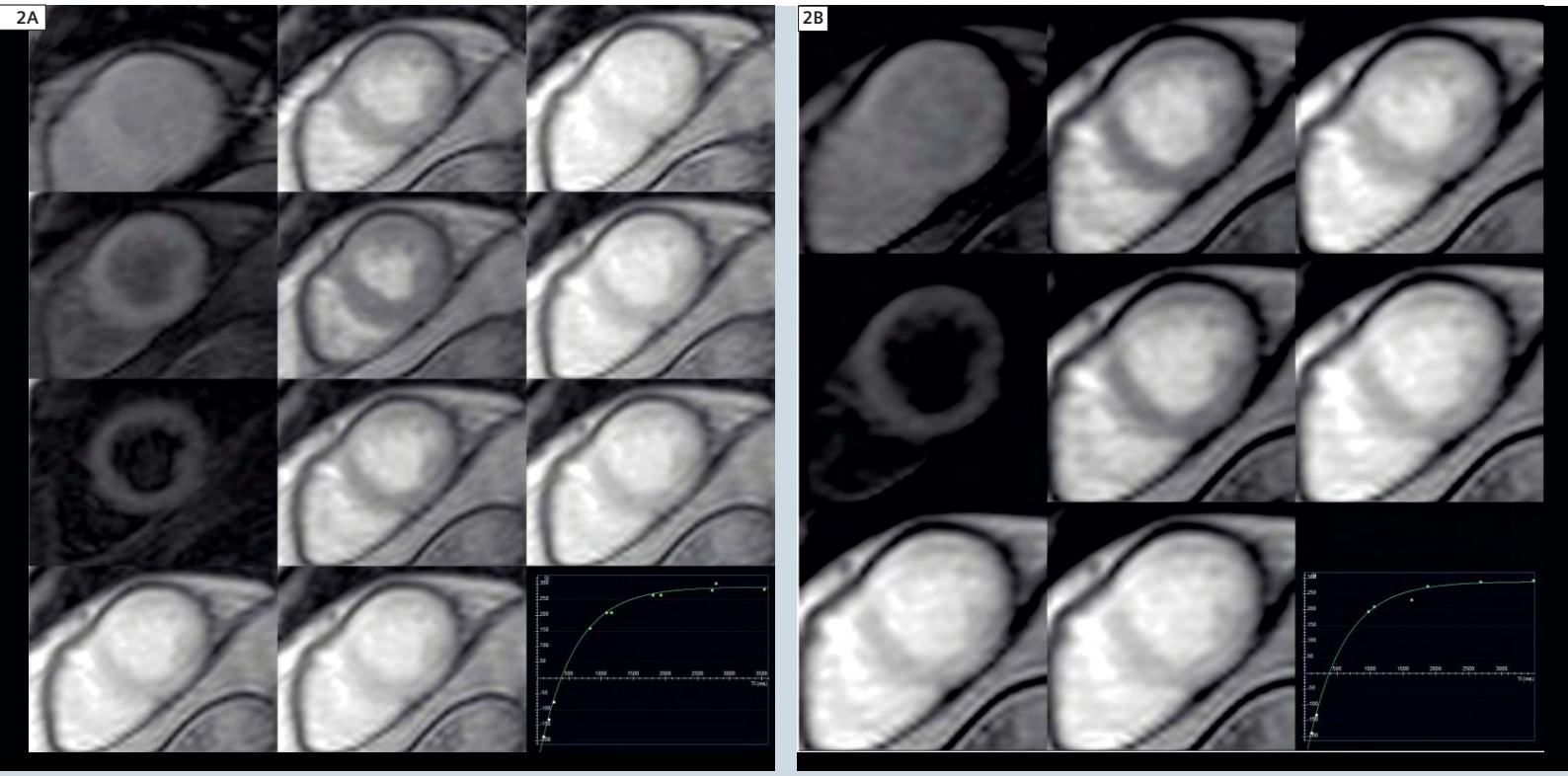
Cardiovascular magnetic resonance (CMR) has been an increasingly used imaging modality which has experienced significant advancements in the last years [1]. One of the most used techniques that have made CMR so important is late gadolinium enhancement (LGE) and the demonstration of localized areas of infarct and scar tissue [2–4]. However, despite being very sensitive to small areas of regional fibrosis, LGE techniques are mostly dependent on the comparison to supposedly normal reference areas of myocardium, thus not being able to depict more diffuse disease.



1 MOLLI images **(1A)** with respective signal-time curves **(1B)** and reconstructed T1 map **(1C)** at 3T. The mean T1 time for this patient was 1152 ms (pre-contrast).

Table 1: Comparison of the MOLLI sequences available for T1-mapping:

Sequence	Original MOLLI T1 sequence [15]	Optimized MOLLI sequence [17]	Shortened MOLLI sequence [18]
Preparation	Non-selective inversion recovery	Non-selective inversion recovery	Non-selective inversion recovery
Bandwidth	1090 Hz/px	1090 Hz/px	1090 Hz/px
Flip angle	50°	35°	35°
Base matrix	240	192	192
Phase resolution	151	128	144
FOV x % phase	380 x 342	256 x 100	340 x 75
TI	100 ms	100 ms	100 ms
Slice thickness	8 mm	8 mm	8 mm
Acquisition window	191.1 ms	202 ms	206 ms
Trigger delay	300 ms	300 ms	500 ms
Inversions	3	3	3
Acquisition heartbeats	3,3,5	3,3,5	5,5,1
Recovery heartbeats	3,3,1	3,3,1	1,1,1
TI increment	100–150 ms	80 ms	80 ms
Scan time	17 heartbeats	17 heartbeats	9 heartbeats
Spatial resolution	2.26 x 1.58 x 8 mm	2.1 x 1.8 x 8 mm	1.8 x 1.8 x 8 mm



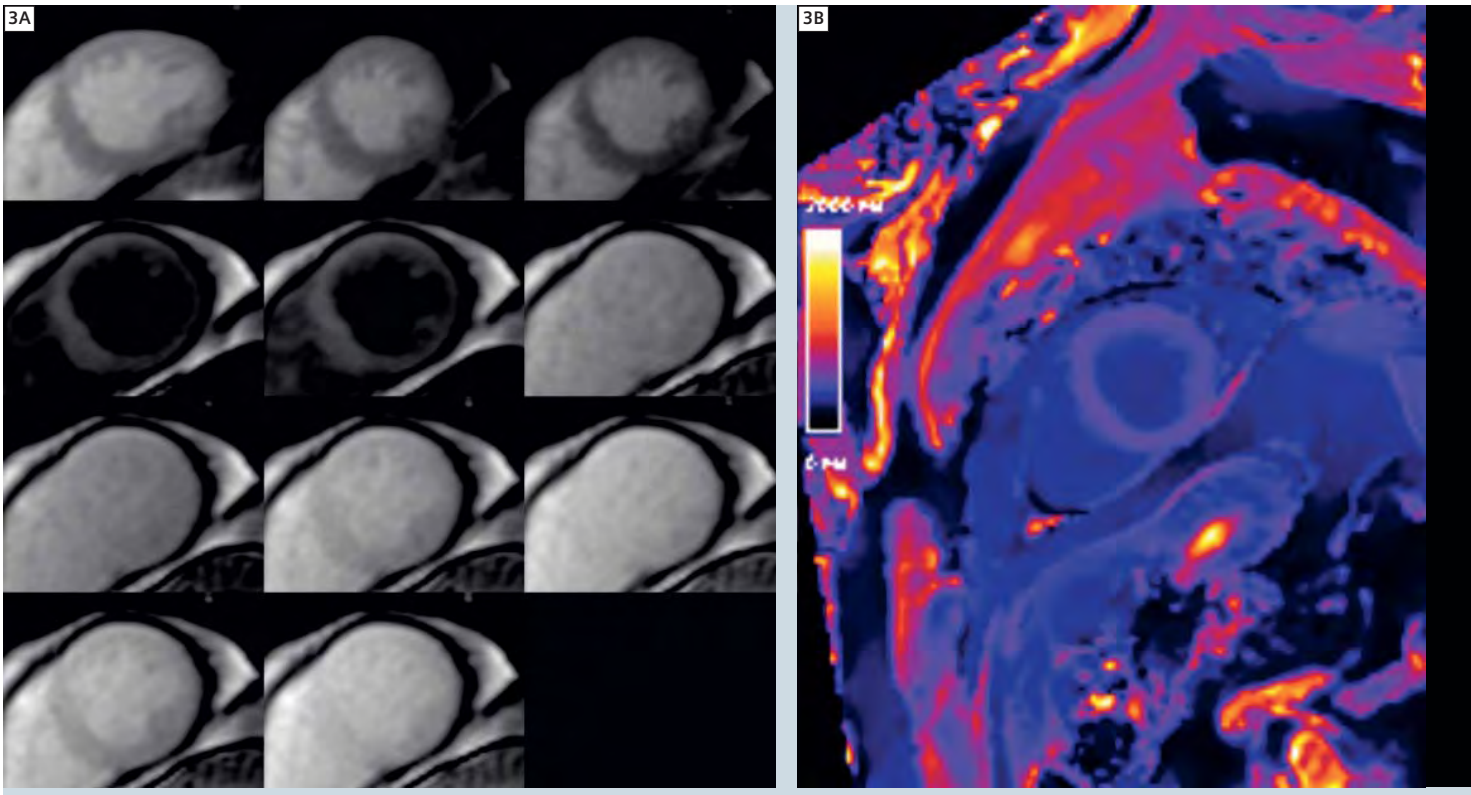
2 MOLLI **(2A)** versus ShMOLLI **(2B)** in a single patient at 3T post-contrast. The calculated values for the 11 MOLLI images were 551 ms versus 544 ms for the 8 images of the shMOLLI set. The time to acquire the MOLLI images were 21 seconds versus 14 seconds for the shMOLLI sequence (with a patient heart rate of 61 bpm).

Myocardial interstitial fibrosis, with a diffuse increase in collagen content in myocardial volume, develops as a result of many different stimuli including pressure overload, volume overload, aging, oxidative stress and activation of the sympathetic and renin-angiotensin-aldosterone system [5]. Different from replacement fibrosis, where regional collagen deposits appear in areas of myocyte injury, LGE has a limited sensitivity for interstitial diffuse fibrosis [6]. Therefore, if one wants to image diffuse interstitial fibrosis within the myocardium other techniques might be more suitable. While echocardiogram backscatter and nuclear imaging techniques may be applied for that purpose [7, 8], myocardial tissue characterization is definitely an area where CMR plays a large role. While equilibrium contrast CMR and myocardial tagging have been shown to reflect diffuse myocardial fibrosis, T1-mapping techniques have been most widely used. In the following, we describe the developments in T1-mapping as well as their possible current and future uses.

T1-mapping

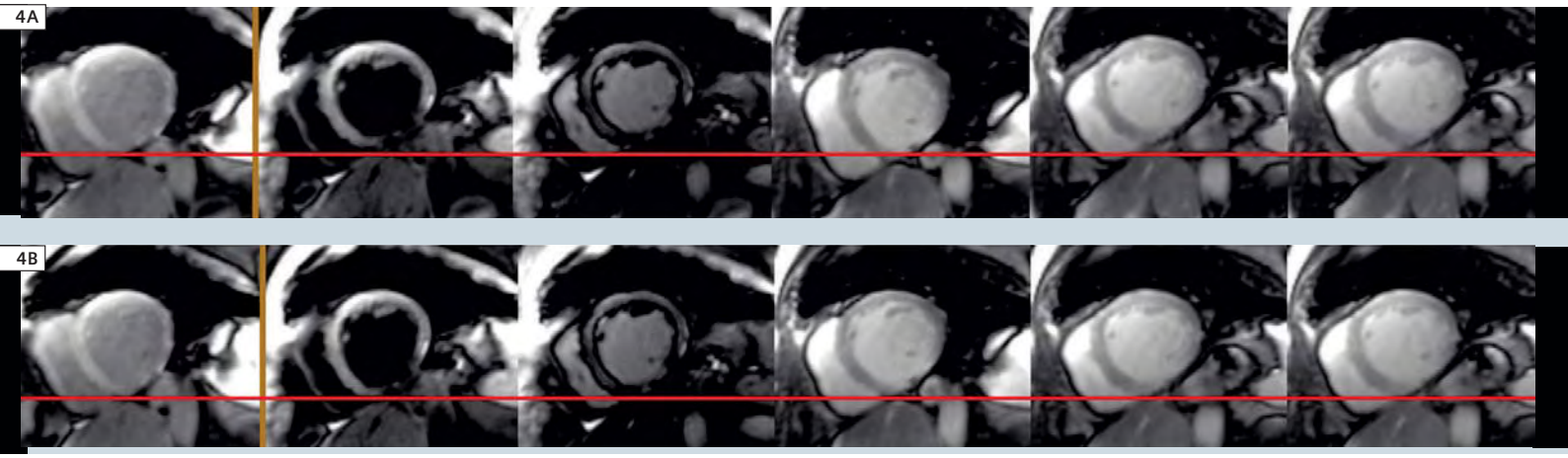
By directly quantifying T1 values for each voxel in the myocardium, a parametric map can be generated representing the T1 relaxation times of any region of the heart without the need to compare it to a normal reference standard before or after the use of a contrast agent. The first attempts to measure T1 times in the myocardium used the original Look-Locker sequence and were done using free breathing with acquisition times of over 1 minute per image [9, 10], not allowing for pixel-based-mapping but only for regions-of-interest analysis. Another implementation of T1-mapping used variable sampling of the k-space in time (VAST), acquiring images in three to four breath-holds and correlating that data to invasive biopsy [11]. Other sequences have been used for quantification of T1 as well using inversion recovery TrueFISP [12, 13] or multishot saturation recovery images [14] but their reproducibility and accuracy have not been extensively validated.

The most widely used T1-mapping sequence is based on the Modified Look-Locker Inversion-recovery (MOLLI) technique. Described originally by Messroghli et al. [15] it consists of a single shot TrueFISP image with acquisitions over different inversion time readouts allowing for magnetization recovery of a few seconds after 3 to 5 readouts. The parameters for the original MOLLI sequence are described in Table 1. The advantages of this sequence over previous methods are its acquisition in only



3 An example of an automated T1-map generated on the fly with inline processing after acquisition of a MOLLI sequence at 3T. In **(3A)** the original images acquired and in **(3B)** the inline map. The T1 for this patient was calculated at 525 ms post-contrast.

one relatively short breath-hold, the higher spatial resolution (1.6 x 2.3 x 8 mm) and increased dynamic signal. Reproducibility studies using this sequence have shown that the method is very accurate with a coefficient of variation of 5.4% [16] although an underestimation of 8% should be expected based on phantom data. An example of MOLLI images and its respective signal-time curves and map are shown in Figure 1. One disadvantage of this implementation of MOLLI is its dependence on heart rate, mostly true for T1 values less than 200 msec or greater than 750 msec. However, because the deviation is systematic, raw values can be corrected using the formula $T1_{corrected} = T1_{raw} - (2.7 \times [\text{heart rate} - 70])$, bringing the coefficient of variation down to 4.6% after applying the correction. An optimized MOLLI sequence was subsequently described where heart rate correction might not be even necessary [17]. In the optimized sequence, the authors tested variations in readout flip angle, minimum inversion time, inversion time increments and number of pauses between each readout sequence. The conclusion from these experiments showed that a flip angle of 35°, a minimum inversion time of 100 msec, increments of 80 msec and three heart cycle pauses allowed for the most accurate measurement of myocardial T1 (Table 1). Because T1 assessment may be sensitive to motion artifacts and not all patients might be able to hold their breaths throughout all the necessary cardiac cycles used in MOLLI's sequence implementation, more recently a shortened version sequence (ShMOLLI) using only 9 heart beats was presented to account for those limitations [18]. Using incomplete recovery of the longitudinal magnetization that is corrected directly in the scanner by conditional interpretation, ShMOLLI was directly compared to MOLLI in patients over a wide range of T1 times and heart rates both at 1.5 and 3T. The results showed that despite an increase in noise and slight increase in the coefficient of variation (especially at 1.5T), T1 times were not significantly different using ShMOLLI with the advantage of much shorter acquisition times (9.0 ± 1.1 sec versus 17.6 ± 2.9 sec). An example of MOLLI and ShMOLLI images from the same patient is presented in Figure 2. Up to now, after acquiring images for T1-mapping, one had to analyze them using in-house developed software, dedicated commercial programs or open-source solutions [19], not always a simple and routine task, leading to difficulty in post-processing the data and generating T1 values. Recent advances have provided new inline processing



techniques that will generate the T1-maps automatically after image acquisition with MOLLI, without the need for further post-processing, accelerating the whole process. An example of such automated T1-map is presented in Figure 3. At the same time, inline application of motion correction permits more accurate pixel-wise maps, avoiding errors due to respiratory deviations. An example of an image with and without motion correction is presented in Figure 4.

Clinical applications

Potentially, T1-mapping can be used to assess any disease that affects the myocardium promoting diffuse fibrosis. However, because of its recent development, the technique has only been evaluated on a small number of patients although the clinical scenarios are varied.

The first clinical description of direct T1-mapping in pathological situations was done in patients with acute myocardial infarction [20]. While the authors did not use the described MOLLI sequence, they did note that pre-contrast infarct areas had an 18 ± 7% increase in T1 times compared to normal myocardium and that after contrast the same areas showed a 27 ± 4% reduction compared to non-infarcted areas ($P < 0.05$ for both). In chronic myocardial infarction, where LGE has proven so useful, these changes were also observed although differences were not as pronounced as in the acute setting [21].

In amyloidosis, post-contrast T1 times were also detected to be shorter in the subendocardial regions compared to other myocardium areas [22]. The combination of both LGE identification and T1 times < 191 msec in the subendocardium at 4 minutes provided a 97% concordance in diagnosis of cardiac amyloidosis and T1 values significantly correlated to markers of amyloid load such as left ventricular mass, wall thickness, interatrial thickness and diastolic function.

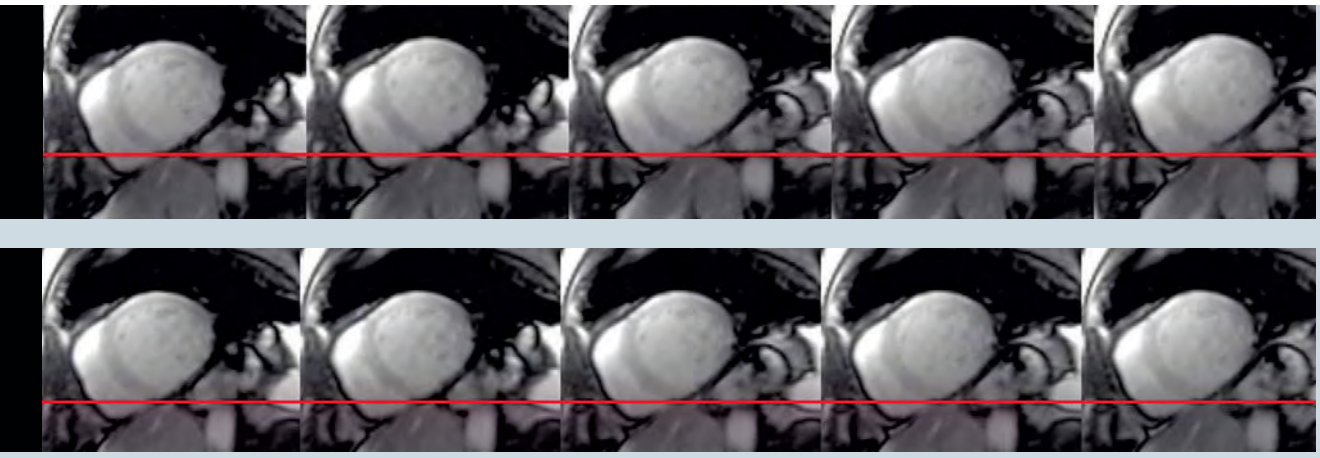
In valve disease, an attempt to show differences in T1 values in patients with chronic aortic regurgitation using MOLLI sequence did not find any changes in the overall group before or after contrast [23]. However, the authors did notice that differences were observed regionally in segments that demonstrated impaired wall motion in cine images. The small number of patients (n = 8) in the study might have affected the conclusions and further evaluation of similar data might yield other conclusions.

A more recent study showed that, using equilibrium contrast CMR, diffuse fibrosis measured in aortic stenosis patients provided significant correlations to quantification on histology [24].

In heart failure, the use of T1-mapping has been more widely studied and directly correlated to histology evaluation [11]. In this paper, the authors evaluated patients with ischemic, idiopathic and restrictive cardiomyopathies showing that post-contrast T1 times at 1.5T were significantly shorter than controls even after exclusion of areas of LGE (429 ± 22 versus 564 ± 23 msec, $P < 0.0001$).

We have investigated a similar group of patients on a 3T MAGNETOM Verio scanner and have found that both dilated and hypertrophic cardiomyopathy patients have lower post-contrast T1 times compared to controls, but non-infarcted areas from ischemic cardiomyopathy patients do not show significant differences (unpublished data). Examples of a myocardial T1-map at 3T from a patient with dilated cardiomyopathy and suspected hypertrophic cardiomyopathy are seen in Figure 5 and 6 respectively.

Finally, in patients with both type 1 and 2 diabetes melitus, T1-mapping using CMR was able to show that these patients may have increased interstitial fibrosis compared to controls as T1 times were significantly shorter (425 ± 72 msec versus 504 ± 34 msec, $P < 0.001$) and correlated to global longitudinal strain by echocardiography, demonstrating impaired myocardial systolic function.



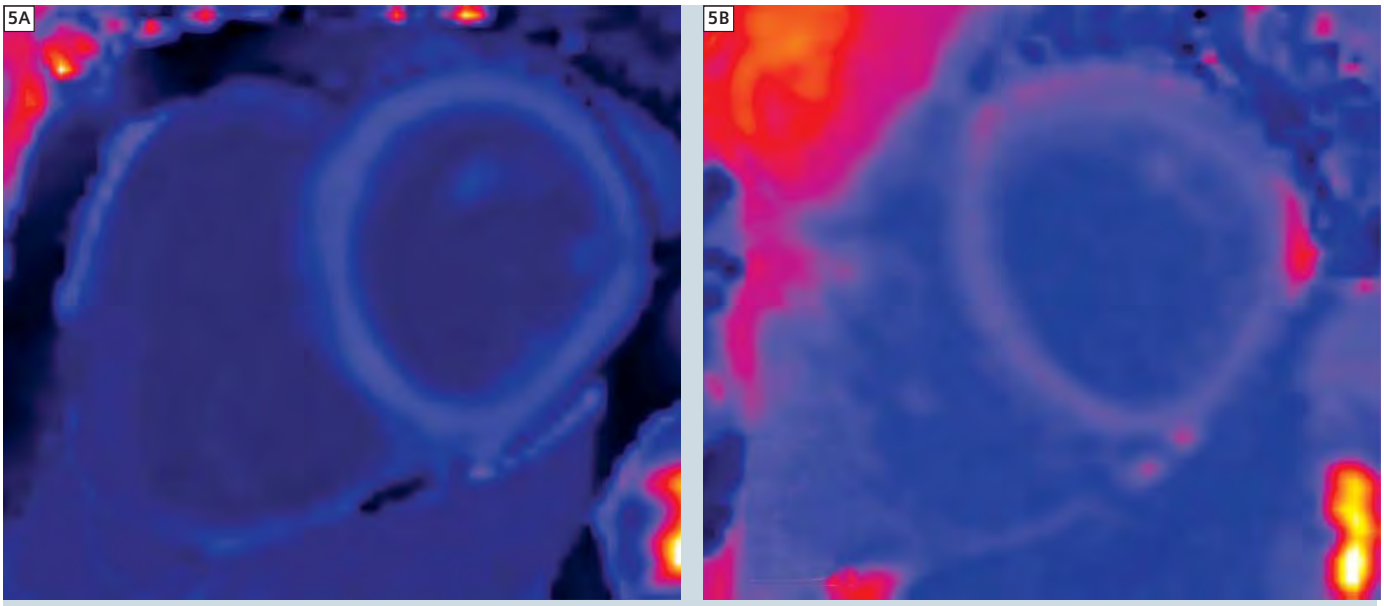
4 Example of a MOLLI sequence obtained without **(4A)** and with **(4B)** motion correction. Notice the deviation from baseline of the left ventricle during the image acquisition cycle, fully corrected in **(4B)**.

Future directions

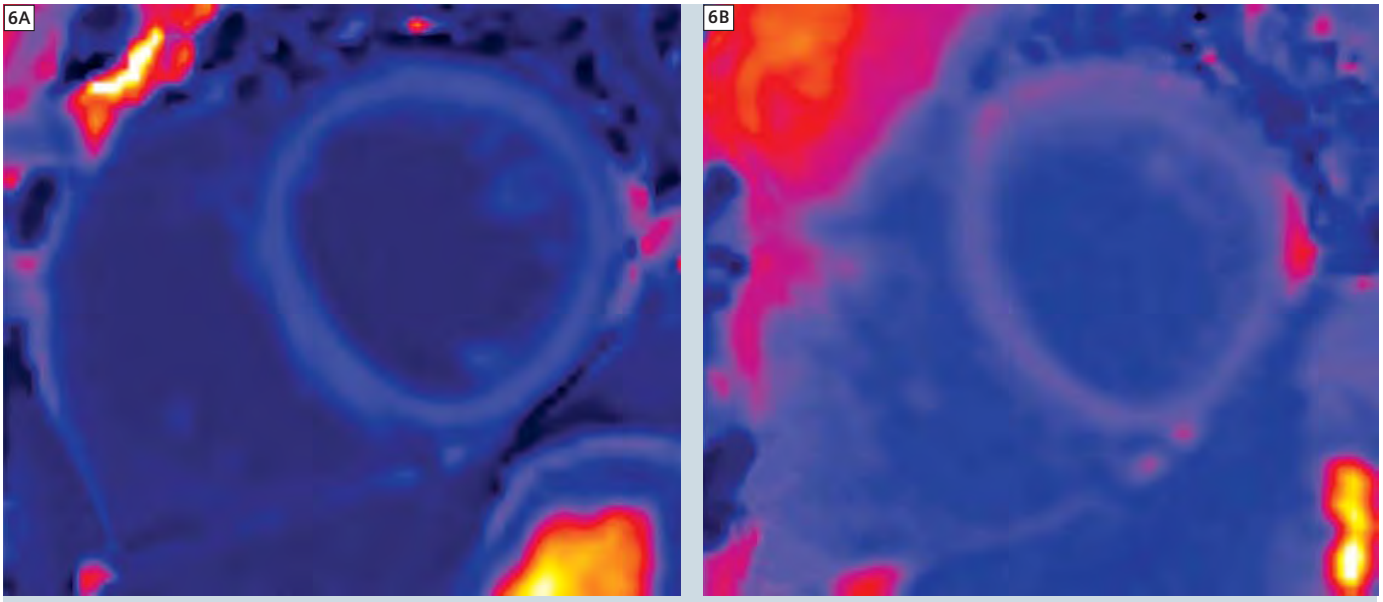
Certainly with the research of T1-mapping in different clinical scenarios the applicability of the method will increase substantially. In the meantime, more effort has been made to further standardize values across different patients and time points. As T1 time, especially after injection of contrast, depends on both physiologic and scan acquisitions, methods have been described to account for these factors, with normalization of T1 values [25]. More than that, standardization of normal values across a larger number of normal individuals is also necessary since most papers provide data on much reduced cohorts, mostly limited to single center data. In that regard, a large multicenter registry is already collecting data at 3T in patients from 20 to 80 years of age in Latin America [Fernandes JL et al. – www.clinicaltrials.gov – NCT01030549]. Besides that, other techniques are under development that might allow T1 measurement with larger coverage of the heart using 3D methods [26]. Nevertheless, with the current techniques available there are already much more clinical applications to explore and certainly quantitative T1-mapping will become one of the key applications in CMR in the near future.

References

1 Fernandes JL, Pohost GM. Recent advances in cardiovascular magnetic resonance. Rev Cardiovasc Med 2011;12:e107-12.
2 Kim RJ, Wu E, Rafael A, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med 2000;343:1445-53.
3 Assomull RG, Prasad SK, Lyne J, et al. Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy. J Am Coll Cardiol 2006;48:1977-85.
4 Ordovas KG, Higgins CB. Delayed contrast enhancement on MR images of myocardium: past, present, future. Radiology 2011;261:358-74.
5 Jellis C, Martin J, Narula J, Marwick TH. Assessment of nonischemic myocardial fibrosis. J Am Coll Cardiol 2010;56:89-97.
6 Mewton N, Liu CY, Croisille P, Bluemke D, Lima JA. Assessment of myocardial fibrosis with cardiovascular magnetic resonance. J Am Coll Cardiol 2011;57:891-903.
7 Picano E, Pelosi G, Marzilli M, et al. In vivo quantitative ultrasonic evaluation of myocardial fibrosis in humans. Circulation 1990;81:58-64.
8 van den Borne SW, Isobe S, Verjans JW, et al. Molecular imaging of interstitial alterations in remodeling myocardium after myocardial infarction. J Am Coll Cardiol 2008;52:2017-28.
9 Flacke SJ, Fischer SE, Lorenz CH. Measurement of the gadopentetate dimeglumine partition coefficient in human myocardium in vivo: normal distribution and elevation in acute and chronic infarction. Radiology 2001;218:703-10.
10 Brix G, Schad LR, Deimling M, Lorenz WJ. Fast and precise T1 imaging using a TOMROP sequence. Magn Reson Imaging 1990;8:351-6.
11 Iles L, Pfluger H, Phrommintikul A, et al. Evaluation of diffuse myocardial fibrosis in heart failure with cardiac magnetic resonance contrast-enhanced T1 mapping. J Am Coll Cardiol 2008;52:1574-80.
12 Schmitt P, Griswold MA, Jakob PM, et al. Inversion recovery TrueFISP: quantification of T(1), T(2), and spin density. Magn Reson Med 2004;51:661-7.
13 Bokacheva L, Huang AJ, Chen Q, et al. Single breath-hold T1 measurement using low flip angle TrueFISP. Magn Reson Med 2006;55:1186-90.
14 Wacker CM, Bock M, Hartlep AW, et al. Changes in myocardial oxygenation and perfusion under pharmacological stress with dipyridamole: assessment using T*2 and T1 measurements. Magn Reson Med 1999;41:686-95.
15 Messroghli DR, Radjenovic A, Kozerke S, Higgins DM, Sivananthan MU, Ridgway JP. Modified Look-Locker inversion recovery (MOLLI) for high-resolution T1 mapping of the heart. Magn Reson Med 2004;52:141-6.
16 Messroghli DR, Plein S, Higgins DM, et al. Human myocardium: single-breath-hold MR T1 mapping with high spatial resolution--reproducibility study. Radiology 2006;238:1004-12.
17 Messroghli DR, Greiser A, Frohlich M, Dietz R, Schulz-Menger J. Optimization and validation of a fully-integrated pulse sequence for modified look-locker inversion-recovery (MOLLI) T1 mapping of the heart. J Magn Reson Imaging 2007;26:1081-6.
18 Piechnik SK, Ferreira VM, Dall'Armellina E, et al. Shortened Modified Look-Locker Inversion recovery (ShMOLLI) for clinical myocardial T1-mapping at 1.5 and 3 T within a 9 heartbeat breathhold. J Cardiovasc Magn Reson 2010;12:69.
19 Messroghli DR, Rudolph A, Abdel-Aty H, et al. An open-source software tool for the generation of relaxation time maps in magnetic resonance imaging. BMC Med Imaging 2010;10:16.
20 Messroghli DR, Niendorf T, Schulz-Menger J, Dietz R, Friedrich MG. T1 mapping in patients with acute myocardial infarction. J Cardiovasc Magn Reson 2003;5:353-9.
21 Messroghli DR, Walters K, Plein S, et al. Myocardial T1 mapping: application to patients with acute and chronic myocardial infarction. Magn Reson Med 2007;58:34-40.
22 Maceira AM, Joshi J, Prasad SK, et al. Cardiovascular magnetic resonance in cardiac amyloidosis. Circulation 2005;111:186-93.
23 Sparrow P, Messroghli DR, Reid S, Ridgway JP,



5 T1-mapping at 3T after contrast of a patient with **(5A)** dilated cardiomyopathy (T1 of 507 ms) in comparison to **(5B)** a control patient (T1 of 615 ms).



6 T1-mapping of a patient with **(6A)** suspected hypertrophic cardiomyopathy (T1 of 466 ms) in comparison to **(6B)** a control patient (with a T1 of 615 ms).

Bainbridge G, Sivananthan MU. Myocardial T1 mapping for detection of left ventricular myocardial fibrosis in chronic aortic regurgitation: pilot study. AJR Am J Roentgenol 2006;187:W630-5.

24 Flett AS, Hayward MP, Ashworth MT, et al. Equilibrium contrast cardiovascular magnetic resonance for the measurement of diffuse myocardial fibrosis: preliminary validation in humans. Circulation 2010;122:138-44.

25 Gai N, Turkbey EB, Nazarian S, et al. T1 mapping of the gadolinium-enhanced myocardium: adjustment for factors affecting interpatient comparison. Magn Reson Med 2011;65:1407-15.

26 Coolen BF, Geelen T, Paulis LE, Nauerth A, Nicolay K, Strijkers GJ. Three-dimensional T1 mapping of the mouse heart using variable flip angle steady-state MR imaging. NMR Biomed 2011;24:154-62.

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