Cardiac Magnetic Resonance Imaging Perspectives - T1 and T2 Maps: Fundamentals and Clinical Utility

Juliano Lara Fernandes

Instituto de Ensino e Pesquisa Jose Michel Kalaf; Radiologia Clínica de Campinas, Campinas, São Paulo - Brasil

Abstract

Cardiovascular magnetic resonance imaging has the tissue characterization of various structures and heart diseases as one of its major advantages. In recent years, this characterization is no longer just qualitative and began to be objectively measured by parametric maps of T1, T2 and T2* values. These maps allowed the measurement of areas of edema, inflammation, scarring and, above all, the evaluation of systemic myocardial changes that occur in the extracellular space, whose identification had not yet been possible by other resonance techniques or other imaging acquisition methods. Clinical applications that followed this technical development were extremely fast and have significantly increased 'the capacity of clinical cardiologists to diagnose and prognosticate a number of diseases.

This update sought to review the general technical aspect of the examination, focusing chiefly on practical implications of the method, especially which types of sequence to be used, which critical parameters and how to report native T1, T2, post-contrast T1 and extracellular volume generated values. Regarding the clinical aspect, we sought to identify and rank in a practical manner in which diseases parametric maps are better established and how to apply this knowledge to clinical decisions.

This particular field is subject to rapid and constant changes, with an exponential growth in the number of publications on the subject in recent years. This review attempts to ponder on current pieces of evidence so that we can continue to follow this method evolution in a solid and conscious manner.

Keywords

Magnetic Resonance Imaging / trends; Magnetic Resonance Spectroscopy / heart; Cardiomyopathies.

Mailing Address: Juliano Lara Fernandes •
Avenida José de Souza Campos, 840, Postal Code13092-020, Campinas, SP - Brasil
E-mail: rcccardio@mpc.com.br
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Cardiovascular magnetic resonance imaging (CMRI) is an examination increasingly used in cardiologists' clinical routine, with its rather broad indications for both morphological and functional assessment of the heart as to ischemia research and myocardial scars[1]. Tissue characterization and differentiation by CMRI was always one of the factors in the method having the most impacting diagnostics and has been widely used for the differentiation of tumors, thrombi or location and quantification of areas of focal fibrosis versus normal myocardium[2].

However, tissue differentiation promoted by CMRI has always been based on largely qualitative distinction between a considered pathological tissue versus normal tissue. Even in situations in which more quantitative measures were used - as in the diagnostic criteria of myocarditis by Lake Louise[3], the predominant tissue characterization was obtained with ratios between pathological sign over the normal sign.

The last three years revealed a conceptual change in the way of conducting these assessments by means of CMRI using new techniques that jointly known as parametric maps[4]. In this type of quantitative assessment, a given myocardial segment can be examined by obtaining the same image with different variable modulations that enable to achieve several points and adjust the appropriate curve in order to obtain an objective value. The parameters measured by parametric maps include T1, T2 and T2* values. The latter is actually the most practical evaluation of all three, whose clinical development was also the earliest occurring since 2001[5]. However, as the current use of T2* is limited to the quantification of myocardial iron, we recommend the reading of publications complementary to the subject[6], limiting this review to aspects of T1 and T2.

Thus, we review in this manuscript the fundamentals and clinical applications of myocardial T1 and T2 mapping using cardiovascular magnetic resonance imaging: in the first part of the manuscript, we highlight the evolution and state of the art of techniques to obtain both parameters; in the second part, how it can be used in current daily clinical routine, as well as in potential future applications.

Acquisition of T1 and T2 maps

For parametric maps of these two parameters to be obtained, it is necessary to obtain both the sequences themselves as an item of software capable of either fitting curves or processing them automatically, as well as generating maps without the need for further calculations (Figure 1). Unfortunately sequences of acquisition vary greatly, not only on the same machine, but also as to the way those are implemented by different manufacturers, generating a variation between the numbers that must be controlled, particularly in cases of longitudinal follow-up of patients[7,8]. This is perhaps one of the still existing major limiting factors for this type of imaging in clinical practice, but, if well understood, it can be bypassed in an appropriate manner.

T1 maps

For T1 images, the first sequence that enabled the production of maps in reasonable breath-hold times was known as Modified Look-Locker Inversion Recovery (MOLLI), in 2004[9]. This technique is based on inversion of longitudinal magnetization pulses, which are repeatedly

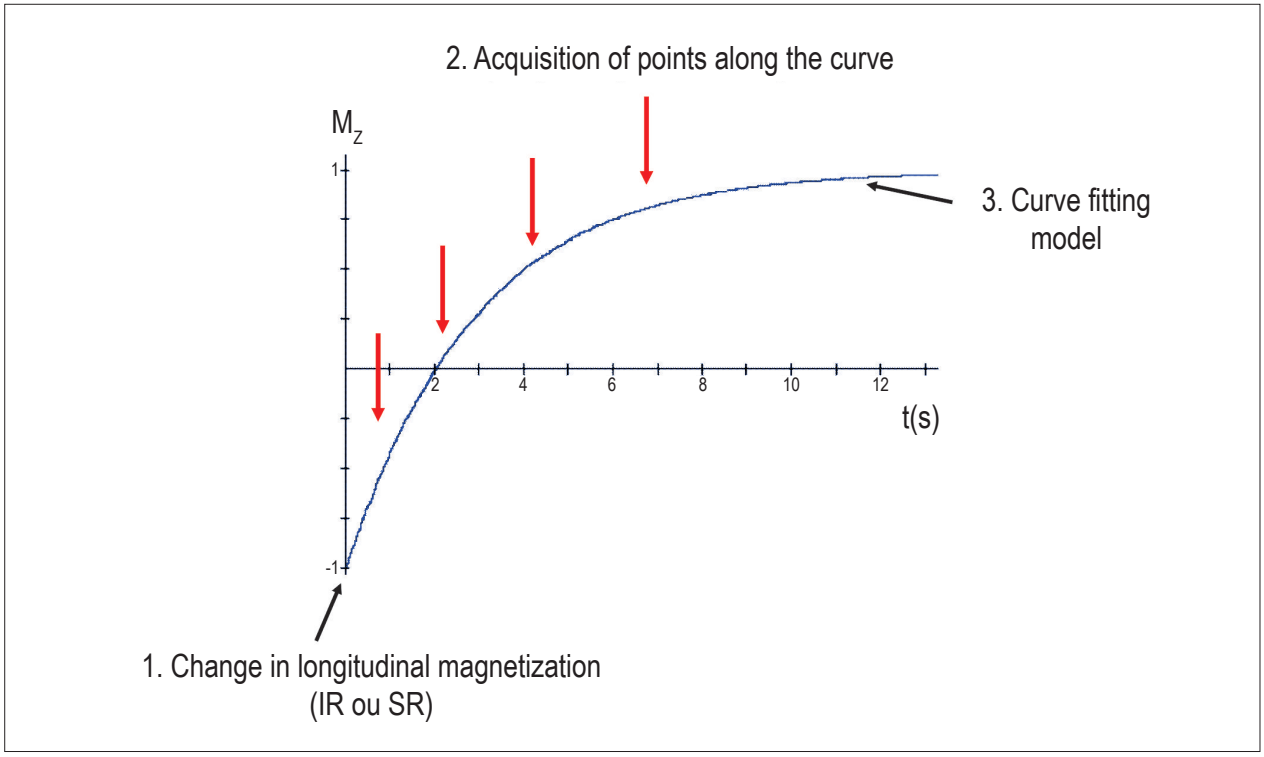

Figure 1 – *Obtaining T1 maps depends on a pulse to change the initial longitudinal magnetization, followed by several experiments acquiring points along the recovery curve, and finally, a curve fitting model.*

applied over a number of heartbeats in a 3(3)3(3)5-type sequence, representing three acquired images, followed by three imageless heartbeats within breath-hold, then more three images, three heartbeats within breath-hold, and five images at the end. For the first time, this sequence allowed to obtain a myocardial T1 map with seventeen heartbeats, whose image was generated at the same phase of the cardiac cycle. Sequences before this one had produced prior images with multiple inversion times, but were acquired at different phases of the myocardial cycle with different thicknesses of wall[10]. After the first experiences with the original MOLLI sequence, it was noticed that it had some problems that limited their use and reproducibility: it depended heavily on the heart rate, acquisitions had a still insufficient spatial resolution and required multiple breath-holds to be carried out. Thus, a new sequence was implemented, whose main modifications consisted in the possibility to make the whole acquisition in a single breath-hold time, reduce the flip angle to 35º so that the magnetization transfer would be less important, fix the minimum reversal time to 100ms, and increments to 80ms[11]. This new implementation of MOLLI technique allowed images to be less dependent on heart rate and more accurate, when compared to the original technique. Based on this experience, MOLLI sequences in 3(3)3(3)5 format should be used. Check that the parameters used for its optimization are being correctly applied.

Despite those implemented changes, the technique using 17 heartbeats still seemed to be long to many patients who could not maintain a single breath-hold over the entire acquisition. In view of this observation, some variations to MOLLI techniques began to be suggested, by modifying the number of heartbeats used to form T1 curve or the number of breath-holds between them. Hence, several variations of the original sequence have been suggested: 3(3)5, 5(3)3, 4(1)3(1)2 and 2(2)2(2)4[12]. The main advantage of all these new suggestions has always been to reduce breath-hold times, with an offset loss of part of the pixels required to reconstruct the signal recovery curve T1 or a higher magnetization transfer between inversion times, causing underestimation of T1 real-time . Another important point about these new implementations is that, in many cases in which T1 is long, especially in the native T1 (without contrast), very high heart rates with very short breath-holds within one or two heartbeats, further intensify these effects. Hence, a slight change in MOLLI sequences was suggested: breath-holds and acquisitions should be measured by time, rather than by number of heartbeats, thus eliminating the heart-rate dependence at once, using formats such as 5s(3s)3s and 4(1s)3(1s)2[13]. Since the native T1 is relatively long (around 1000-1100ms) and post-contrast T1 is much shorter (around 300-400ms), the influence of magnetization transfer is more important in the first case and, therefore, requires more time for recovery between pulses. Thus, when assessing a native T1, a sequence such as 5(3s)3 can be used, while in case of post-contrast T1, the 4(1s)3(1s)2 sequence is preferable and faster. Anyway, the need to use the same type of sequence with the same parameters is reinforced herein, if it is desired to compare the longitudinal follow-up of patients and the exchange between the sequences is not recommended [14].

A variation of MOLLI sequence developed in Oxford was presented in 2010. It was named Shortened MOLLI (shMOLLI)[15]. In shMOLLI technique, pulse inversion are also used in acquisitions, but these are performed in the 5(1)1(1)1 format, with only nine heartbeats and therefore more quickly than the other previous combinations. Figure 2 makes a comparison between the different types of MOLLI and shMOLLI acquisition in terms of required number of heartbeats. As it is quite short, there is no sufficient time available for full recovery of the longitudinal magnetization, but the algorithm makes a conditional interpretation using the last two points of acquisition only in cases in which T1 is shorter. The technique showed to be as accurate as the original MOLLI, albeit the absolute results presented should not be interchangeable either [16].

This manuscript has by now described T1 mapping techniques that use inversion pulse to obtain recovery of the longitudinal magnetization. More recently, new techniques for obtaining the maps have been suggested using saturation recovery methods in place of the inversion pulses, the most known technique so far being referred to as "Saturation Recovery Single-Shot Acquisition" (SASHA)[17]. In MOLLI and shMOLLI techniques, there is a known underestimation of the actual values of T1 due mainly to the transfer of magnetization between different continuous pulses and the influence of T2. In the saturation recovery techniques, this problem is eliminated since each heartbeat has its own pulse saturation, and there is no influence between them. This advantage is complemented by the lower signal to noise ratio (SNR) obtained from these sequences, something partially offset by new forms of readout using steady-state free precession (SSFP) rather than the original techniques with gradient-echo sequences found in the first saturation recovery sequences. Thus, this new type of acquisition can be used for the acquisition of T1 maps, but care should be taken in order to reduce part of the SNR. The SASHA acquisition technique requires ten heartbeats and is also faster than the original MOLLI (Figure 2).

Finally, the process for development of new T1 map sequences remains quite fast with the introduction of new proposals, including hybrid inversion pulse methods with saturation recovery (IR/SR) like SAPPHIRE[18]. In addition to these, other techniques that include new k-space acquisition methods within a shorter time, allowing for spatial resolutions much higher than those currently obtained, are already being implemented, such as ANGIE[19]. These techniques allow not only an assessment of the left ventricle, but also of finer structures such as the right ventricle or atrial walls, and can be acquired under free breathing, also improving the magnetization recovery limitations of MOLLI sequences.

Which sequence should we use?

In the current condition, which sequence should we use in clinical practice? Unfortunately, the answer to this question is not yet fully established and an assessment of accuracy and precision should be performed[7]. MOLLI and shMOLLI sequences are known to determine a T1 value lower than the actual, but have coefficient of variability lower than that of the saturation recovery techniques or IR/SR combined. At the same time, SASHA and SAPPHIRE techniques have higher accuracy, compensating for the lower accuracy[16]. Hence, the selection of choice depends somewhat on the clinical main objective: if it is desired to follow up a patient over time, MOLLI shMOLLI techniques will offer higher reading accuracy, although it should be known that the final absolute value given by the sequences will be less accurate than those given by any other technique. Similarly, if it is desired to obtain more accurate values to the detriment of greater variability among

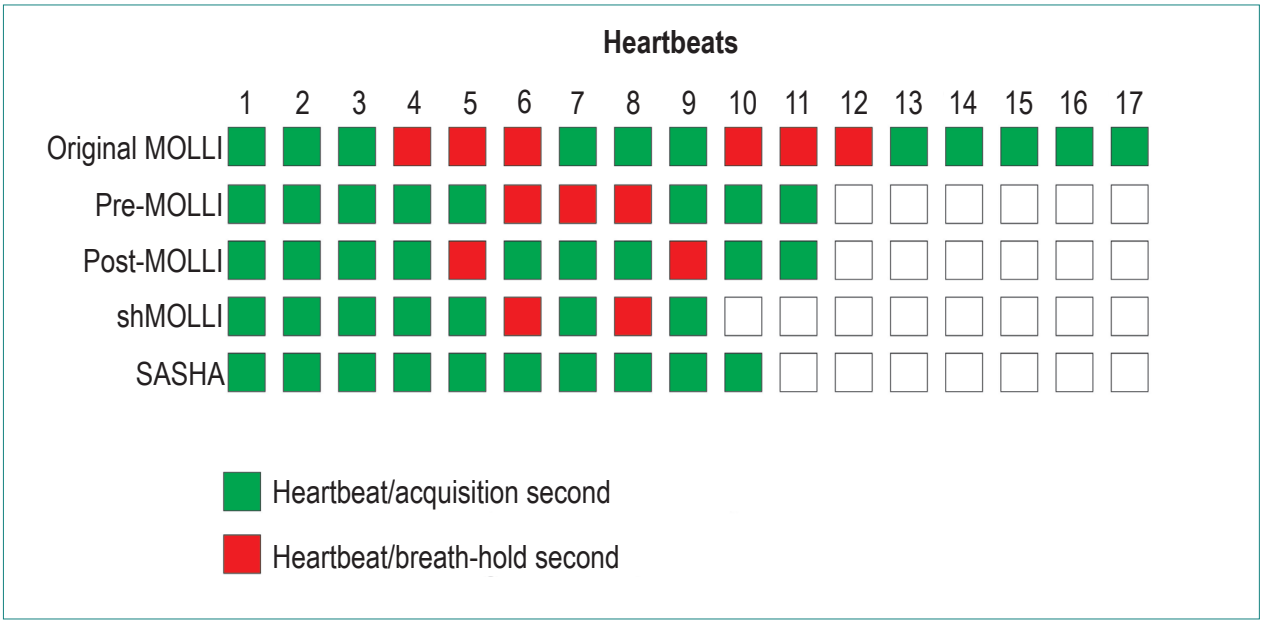

Figure 2 - *Graphical Model representing the various techniques of T1 mapping in relation to the number of heartbeats used and what is happening in each of the heartbeats. Adapted from Higgins and collaborators[32].*

measurements, SR or SR/IR techniques should be sought. Due to this, one should imagine that an absolute value described by myocardial T1 is not enough to fully understand its meaning, including for normal references, as this must be accompanied by the technique used to obtain it and the parameters used. A comparison of the various T1 sequences is listed in Table 1.

Native T1, post-contrast T1, diffusion coefficient and extracellular matrix

Another fairly common technical question in these situations relates to which T1 related parameter should be used for clinical application: native values, post-contrast T1 or calculations derived from these two measures, such as the partition coefficient and the extracellular volume (ECV)[20].

Native T1 refers to the simplest myocardial T1 value, measured by any of the techniques; pre-contrast. The second value to be obtained is myocardial T1 post-certain amount of contrast injected. Some considerations should be made at this point, as the type of contrast, the form of infusion, and the waiting time for assessment of the amount of contrast injected can influence this value. As for the type of contrast used, it was found that small differences exist between at least two types tested (gadobenate dimeglumine and gadopentetate dimeglumine), but these differences are minimal and their clinical importance is probably irrelevant[21]. In the form of infusion, the main discussion is whether to use a continuous injection method of gadolinium in order to obtain a steady state, or bolus injection, similar to what is done in clinical routine examination of CMRI[22]. Current recommendations are that bolus techniques seem to be sufficient for obtaining the T1 value, although for ECV values above 0.4, this technique can overestimate the values if compared to continuous injection[14]. As for the waiting time after which post-contrast T1 measurement should be made, several studies have shown that the T1 value has a steady increase over time, with less variation after 15 minutes of injection[23]. This should therefore be the minimum time for determination of myocardial T1. It should be known, however, that small variations after this time can still occur. Anyway, in serial studies, it is also recommended that comparisons be performed with post-contrast T1 obtained after the same observation period. Finally, regarding the amount injected, a number of publications used amounts ranged from 0.1, 0.15 to 0.2 mmol/kg[24-26], although values of 0.15mmol/kg are more common. Once again, due care should be taken when comparing isolated values of post-contrast T1 as this variable has a huge impact on this value.

The other two variables in connection with T1 related measures refer to the distribution of the contrast in the myocardium, potentially not being influenced by all these variables when only the T1 value is analyzed individually, especially the post-contrast value. For these values to be calculated, one should also have the blood T1 values, usually measured in the left ventricle in the same image of myocardial T1. The first measure, the partition coefficient λ is obtained as follows: the difference between myocardial post-contrast R1 (1/T1) and native R1 is calculated, and the $\Delta R1^{mioc}$is obtained. Then, the same is done with blood R1 values and the $\Delta R1^{blood}$ is obtained. The partition coefficient λ is given by the ratio between $\Delta R1^{mioc}/\Delta R1^{blood}$. Once the patient's hematocrit value is known, the ECV is calculated using the formula ECV=λ.(1-hematocrite)[27]. Some pulse sequences are capable of, if the hematocrit value is added at the time of acquisition, automatically generating the ECV maps, including motion correction, facilitating the process and making it simpler[20]. The analysis of the T1 maps, and its post-processing, if they are not automatically made inline on the device, should be done in proper items of software that enable the interpretation of the various acquisition methods. An alternative can be used from the validation of an item of software obtained not only to this purpose, but also to calculate other parametric maps[28].

T2 maps

Up until recently, if someone talked about assessment of T2 images, the thought that would automatically come to mind was not the parametric maps, but the T2-weighted sequences, such as the black blood turbo spin echo (TSE) imaging. Although widely used in some clinical situations, these images generated much heated debate about what really was being measured, especially due to the overlap caused by interference of the T1 effect[29].

However, this discussion is perhaps outdated, as it is now possible to directly measure T2 with parametric maps obtained in a manner similar to T2* using a signal decay curve from the acquisition of various points of the curve, with different echo times. Two types of sequence may be used to this purpose. The first type is a traditional TSE-type sequence with varied echo times, obtaining the curve from isolated images[4]. This type of acquisition is not as common as it used to be, as it carries all known TSE imaging limitations, in addition to requiring acquisitions in several breath-holds. More recently, to obtain images within one single breath-hold or through free breathing,

Table 1 - Comparison between the various common types of T1 mapping sequences

	MOLLI (original)	MOLLI (optimized)	shMOLLI	SASHA
Short breath-hold	-	+	+	+
Heart rate independent	-	+	+	+
Absolute accuracy	-	-	-	+
Precision	+	+	+-	+-
Image artifacts	+-	+	+	-

an SSFP technique has been employed with the so-called T2-prep, a preparation module before readout that enables the generation of three images from varied TEs in the same acquisition[30,31]. From these images, one decay curve can be generated and T2 calculated (Figure 3). Due care should be taken with these sequences, especially when the heart rate is raised due to potential contamination of the T1 component by incomplete relaxation, something that can be corrected by increasing intervals between acquisitions of the different images.

Clinical Applications

The use of T1 and T2 maps in clinical practice is still relatively limited due to the technical evolutionary process that these methods have rapidly suffered in recent years. So, the most common clinical situations in the use of both methods will be listed below, following an order in which the first items represent cases of greater scientific evidence, and solid data for cases in which these limits have not been well defined. With respect to T1 maps, the current consensus recommends that clinical studies seek to use the native T1 values for usual applications or, in cases in which contrast is used, ECV values, as these are closer to the pathophysiological understanding and as they present a lower variability than the absolute post-contrast T1 or partition coefficient[14]. As to normal values used as a guide for both T1 and T2, these are still system-specific, as previously mentioned here. Thus, they should be established locally so that each service can make use of the comparison with their own standard reference, there including differences in gender, age, myocardial segment and phase of the cardiac cycle[32].

Amyloidosis

Amyloidosis is one of the three situations in which the native T1 is changed in a consistent and reproducible manner in comparison with the normal reference values (the other two situations are iron overload and Fabry disease)[33]. Using the shMOLLI technique, the authors of this manuscript showed that native myocardial T1 is significantly increased when compared with control patients or patients with aortic stenosis, with a cutoff value of 1020ms used to detect, with 92% accuracy, patients with light chain type amyloidosis. This use of the T1 map is particularly important, as patients with amyloidosis may have significant renal failure, which limits the use of gadolinium based contrast and, in such situations, even without this resource, an accurate diagnosis can be established. Figure 4 gives an example of a T1 map of a patient with amyloidosis.

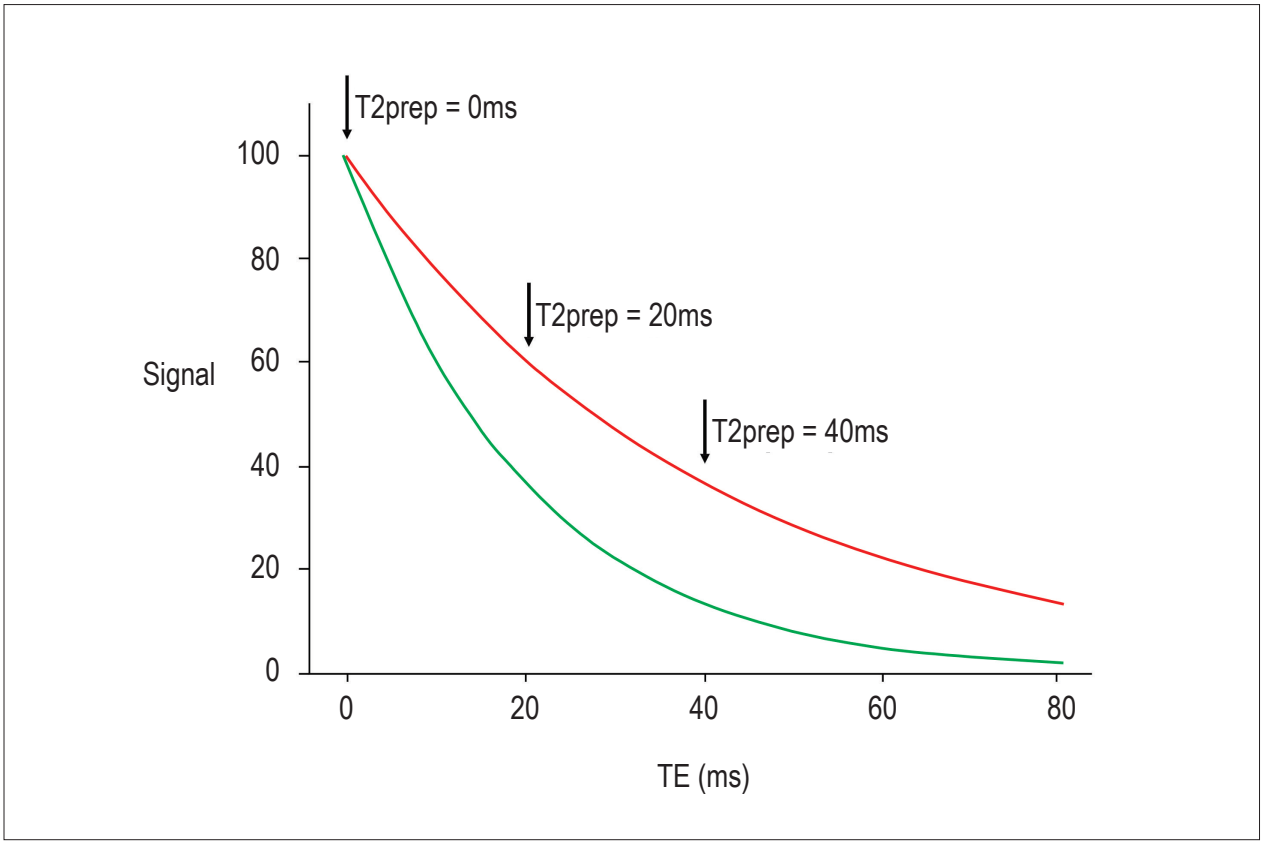

Figure 3 – *Acquisition model and T2 signal based on three acquisitions with curve fitting, with T2prep of 0.20 and 40 ms. The curve in red indicates a tissue that has slower signal decay, with a higher T2 compared to the curve in green, with faster signal decay.*

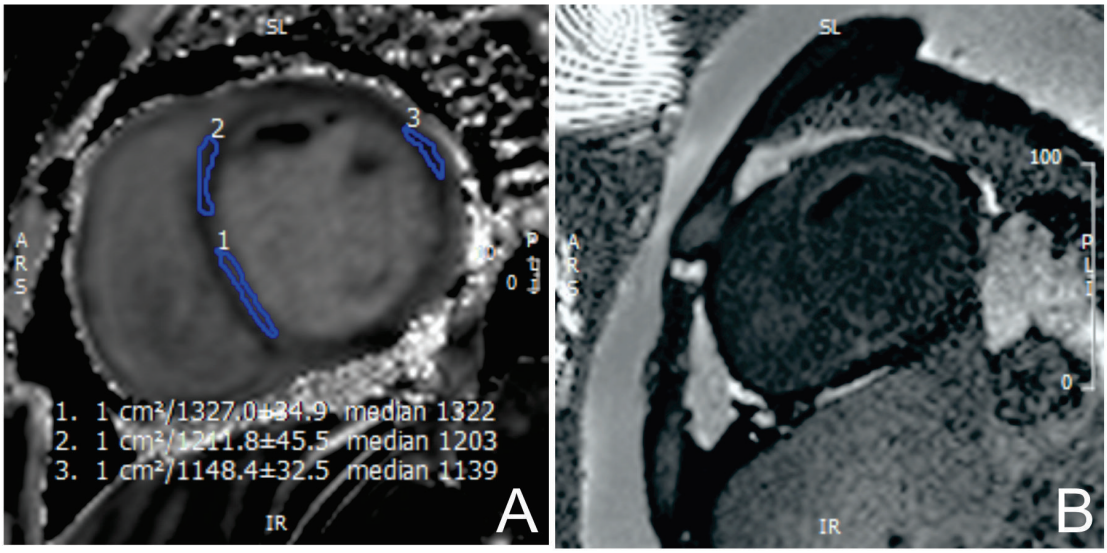

Figure 4 – *myocardial T1 map of a patient with clinical evidence of cardiac amyloidosis at 3T(A), showing an increased septal subendocardial myocardial native T1 compared to myocardium remote areas. In (B) the traditional late post-contrast enhancement imaging showing the difficulty in fitting T1, quick attenuation of cavity contrast and presence of subendocardial enhancement predominantly in the anterior, septal and inferior wall.*

Anderson-Fabry Disease

In this rare disease characterized by the intracellular storage of lipids with concomitant ventricular hypertrophy, the use of native T1 was also critical because it was shown to be significantly lower than that of normal individuals[34]. In this work, native T1 values were also obtained using shMOLLI technique, and in patients with Anderson-Fabry there was absolute discrimination from normal patients, from the interventricular septum measures with T1 values consistently below the normal value. In this case, the use of native T1 is also particularly important in the differential diagnosis of left ventricular hypertrophy causes, as in all other situations, such as hypertrophic cardiomyopathy, amyloidosis, aortic disease or hypertension, the T1 value is increased compared to normal.

Myocarditis and Takotsubo

As myocarditis is characterized by regional myocardial tissue changes, CMRI is considered one of the best tests for diagnosis and prognostic determination. Although the traditional criteria include the use of signal intensity ratio on T1- and T2-weighted images, several studies have more recently shown that the parametric maps can replace these criteria with better accuracy (Figure 5)[35].In the case of T1 values being used, one of the major advantages over the previous criterion is that the contrast injection is not necessary[36], with native T1 having the same area over the curve as the Late Enhancement (LE), with sensitivity higher than that of traditional T2-weighted images[37]. Similarly to the T1 map, T2 maps have also been found to be able to locate areas associated with myocarditis with better sensitivity than T2-weighted images alone, with the use of values > 59 ms at 1.5T having sensitivity and specificity of 94% and 97%, respectively, for identification of these areas[38].

Just as myocarditis, Takotsubo suspected conditions appear to have part of their physiopathology explained by inflammatory changes and regional edema. In such cases, the use of T2 maps has also proven to be important in identifying the disease, showing an increase in the T2 absolute values in the apical portion of the LV, as compared to other regions, without the presence of LE (whose absence is a characteristic of the disease)[38].

Cardiomyopathies

In various cardiomyopathies, the study of T1 maps has shown that the native value, as well as ECV, is usually high[39]. Diseases in which this was characterized include hypertrophic and dilated cardiomyopathies, secondary changes to the aortic valve abnormalities and even in evolution of chronic diseases such as systemic hypertension and diabetes[40-43]. The major current problem of the clinical application of this technique for routine use in such cardiomyopathies relates especially to the great interposition between the normal values and diffuse values found due to an increase in the ECV[44]. Hence, rather than only determining the diagnosis itself, the use of longitudinally measured T1 values can perhaps provide some prognostic clues in these patients, something recently demonstrated by the finding that ECV expansion was associated with an increased risk ratio 1:55 times the overall mortality for every 3% increase in this value[45]. Moreover, perhaps myocardial T1 values may serve as a therapeutic follow-up markers or surrogate endpoints in

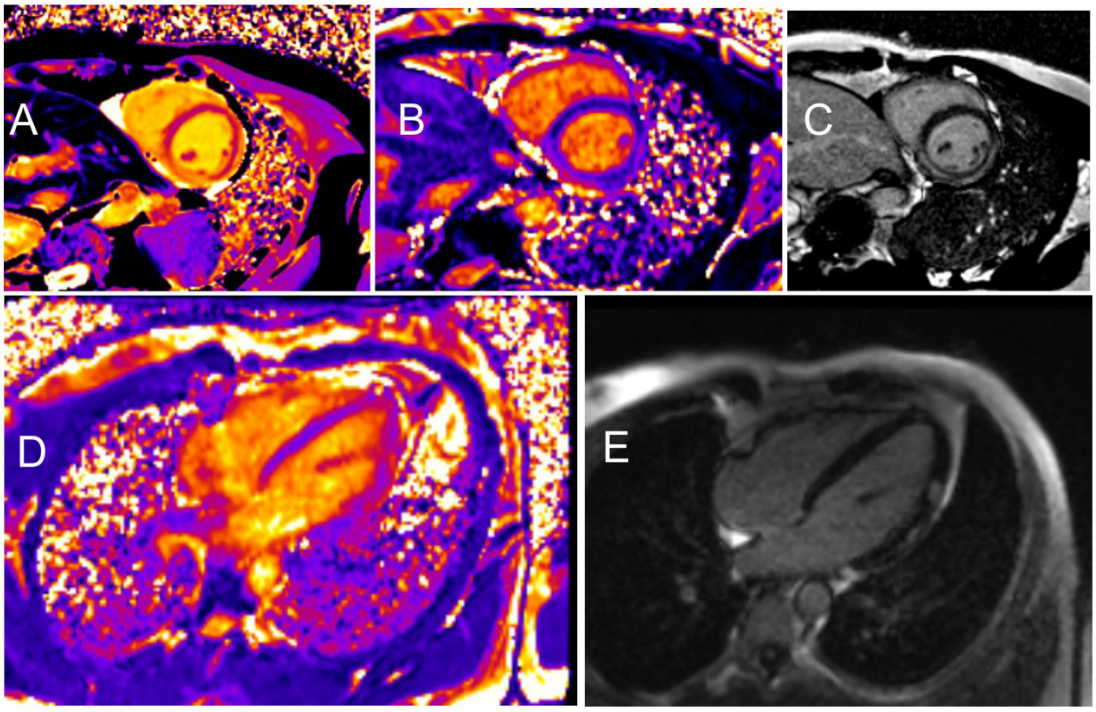

Figure 5 - *Images patients with acute myocarditis 3T: in (A) the native T1 map short axis images corresponding to the map of T2 (B) and late enhancement (C). It is observed that, in the non-contrast T1 and T2 mapping is already possible to see an increase in their two respective values at the bottom and the sidewall of the LV. In (D) T2 map is observed on 4 chambers with scar areas seen in delayed enhancement in (E), previously observed, in this image, in the sidewall.*

clinical trials, as is already being discussed by some studies and as has already been applied in our institution in a clinical study with aliskiren in hypertensive and diabetic patients[46,47].

Other clinical applications

In addition to the situations listed here, we mention some other clinical conditions in which T1 and T2 maps were also investigated, but whose practice migration is still a bit more limited due to the few studies or small number of individuals. Nonetheless, this in no way invalidates its immediate use for these applications, but they should only be placed in a context where the level of evidence is higher for the other diseases. Among these conditions, we highlight the use of T1 and T2 maps in the investigation of the acute and chronic infarction, with both values used not only for identification of the infarcted areas per se, but also of the adjacent area-at-risk, edema and microvascular obstruction[48]. In addition, T2 maps are also found to be sensitive to local oxygen levels, allowing the identification of ischemic and hyperemic areas due to profusion changes observed locally by using techniques known as BOLD-contrast imaging (blood-oxygen-level dependent contrast imaging)[49](Figure 6).

Other conditions in which the use of T1 maps have also proven to be useful involve systemic diseases that affect the myocardium. In addition to amyloidosis, already characterized above, investigation using T1 map also revealed myocardial changes in patients with lupus and systemic sclerosis, in addition to those determined by traditional methods[50,51]. The clinical application of these findings, however, still deserves better characterization.

Finally, an application in which T2 maps deserve special attention refers to the monitoring of post-chemotherapy cardiomyopathy. The fields of cardiology and oncology have recently been shown to have very close interfaces and cardiotoxic effects of chemotherapy are potentially severe, particularly in older individuals[52]. T2 maps appear to be useful in the identification of acute myocardial lesions and their application is being investigated in clinical trials for this purpose[53].

Conclusions

Technical developments of parametric maps in cardiology were rapid and continuing. Several efforts have been made for the maximum standardization of their clinical application, and these efforts were critical for their progressive technical development on a solid base of scientific evidence. As this is one of those unique applications of a method, the T1 and T2 maps are able to introduce into clinical practice new and complementary information to all the other already known to us by using resonance itself and other methods. As all scientific knowledge, this is a moving target, and, in this specific case, mobility is extremely fast. Thus, professionals who conduct

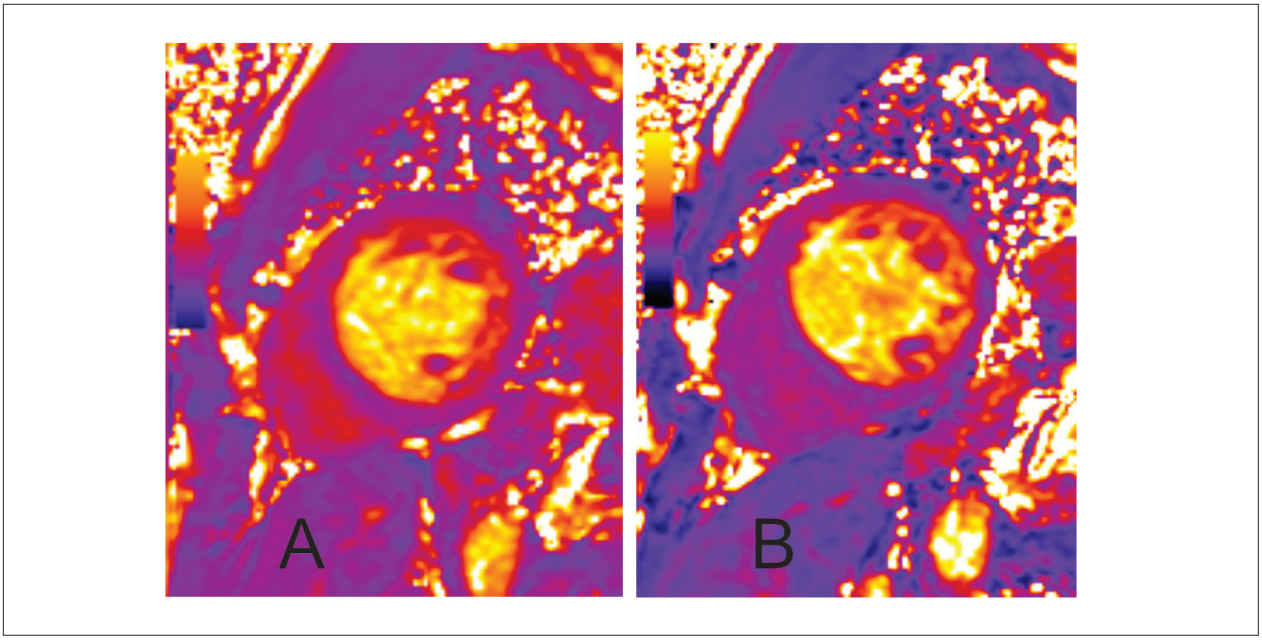

Figure 6 – *T2 Map at 3T application pre- (A) and post (B), 0.56mg/kg of dipyridamole infused for ischemia search. The quantitative evaluation showed increased global LV T2 in this cut-off value of 48ms-58ms, compatible with normal response to vasodilator with no associated ischemia indicated by the BOLD technique.*

examinations shall update themselves from a technical point of view, making sure to be conscious of their methods, current applications and limitations; clinicians, at this moment, shall be aware of these new tools so they can use them under the conditions described herein, in which these tools can offer a unique opportunity for a better use with their patients.

Authors' contributions

Research conception and design: Fernandes, JL; Manuscript writing: Fernandes, JL; Critical revision of the manuscript's major intellectual content: Fernandes, JL.

Potential Conflicts of Interest

Dr. Juliano Lara Fernandes has conflict of interests: Research agreements with Siemens AG, participation in Sanofi-Aventis' medical committee, Novartis AG's paid lessons and advisory committee.

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Academic Association

This study is not associated to graduate programs.

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