T1 and T2 Mapping in Cardiology: “Mapping the Obscure Object of Desire”

Sophie Mavrogeni^a Dimitris Apostolou^b Panayiotis Argyriou^b
Stella Velitsista^b Lilika Papa^b Stelios Efentakis^b Evangelos Vernardos^b
Mikela Kanoupaki^b George Kanoupakis^b Athanassios Manginas^b

^aOnassis Cardiac Surgery Center, and ^bMediterraneo Hospital, Athens, Greece

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Abstract

The increasing use of cardiovascular magnetic resonance (CMR) is based on its capability to perform biventricular function assessment and tissue characterization without radiation and with high reproducibility. The use of late gadolinium enhancement (LGE) gave the potential of non-invasive biopsy for fibrosis quantification. However, LGE is unable to detect diffuse myocardial disease. Native T1 mapping and extracellular volume fraction (ECV) provide knowledge about pathologies affecting both the myocardium and interstitium that is otherwise difficult to identify. Changes of myocardial native T1 reflect cardiac diseases (acute coronary syndromes, infarction, myocarditis, and diffuse fibrosis, all with high T1) and systemic diseases such as cardiac amyloid (high T1), Anderson-Fabry disease (low T1), and siderosis (low T1). The ECV, an index generated by native and post-contrast T1 mapping, measures the cellular and extracellular interstitial matrix (ECM) compartments. This myocyte-ECM dichotomy has important implications for identifying specific therapeutic targets of great value for heart failure treatment. On the other hand, T2 mapping is superior compared

with myocardial T1 and ECM for assessing the activity of myocarditis in recent-onset heart failure. Although these indices can significantly affect the clinical decision making, multicentre studies and a community-wide approach (including MRI vendors, funding, software, contrast agent manufacturers, and clinicians) are still missing.

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Introduction

The increasing use of cardiovascular magnetic resonance (CMR) in clinical practice is based on the accurate and highly reproducible measurements. CMR, through the assessment of late gadolinium enhancement (LGE), gave to cardiology the great opportunity of non-invasive biopsy for fibrosis quantification. Details provided by LGE give information about the underlying pathophysiology and are related to prognosis and response to treatment [1–5]. However, LGE requires regional relative differences in the signal intensity between normal and abnormal myocardium and is unable to detect diffuse myocardial disease [6]. Therefore, a more detailed tissue characterization remains the “obscure object of desire” in cardiology.

Recent advances in CMR allow reliable tissue characterization, based on the absolute quantifiable differences in recovery rates of longitudinal magnetization by T1 mapping [7]. T1 mapping is a robust and highly reproducible index that provides meaningful measurements reflecting important myocardial properties [8]. The proposed T1-based indices include native T1, which reflects myocardial disease involving the myocyte and interstitium without the need for gadolinium, and T1 post-contrast that reflects diffuse myocardial fibrosis. Extracellular volume fraction (ECV) is a direct gadolinium-based measurement of the size of the extracellular space, reflecting only interstitial disease [9]. ECV attempts to dichotomize the myocardium into a cellular and an interstitial component, expressed as volume fractions. Current advances in T1 measurement allow the routine non-invasive measurement of ECV.

Clinical Implications of New CMR Indices

Native (Non-Contrast) T1

The native (non-contrast) T1 measurement of myocardium allows the non-invasive detection of biologically important phenomena and promises to improve our diagnostic capability, measures the disease severity, and potentially influences the prognosis. It can detect important pathophysiologic processes, related to excess of water as in oedema [9, 10], protein deposition [11, 12], and other T1-altering substances, such as lipid [13, 14] or iron (haemorrhage, siderosis) [15], without the use of gadolinium, and therefore it can also be applied in patients with severe renal failure.

Changes of myocardial native T1 mapping reflect cardiac diseases, such as acute coronary syndromes, infarction, myocarditis, and diffuse fibrosis (that are presented with high T1) [16], and systemic diseases, such as cardiac amyloid (high T1) [16] Anderson-Fabry disease (low T1) [17], and siderosis (low T1). By including native T1 mapping in a CMR scan, we can reveal various pathologies, such as area at risk in acute coronary syndromes [9, 10, 18], global myocarditis without LGE and preclinical cardiac involvement, due to iron overload, Fabry disease, cardiac amyloid, etc. [11, 13, 19].

Native T1 mapping can be influenced by various pathologic processes and therefore it should be interpreted cautiously with consideration of the clinical background. Ferreira et al. [10] reported that, in 21 patients with acute regional myocardial oedema and no infarction and 21 healthy patients, native T1 mapping with a thresh-

old of 990 ms had a sensitivity and specificity of 92% compared with T2 ratio using STIR2 and ACUT2E. However, the receiver operator characteristics analysis showed that T1 mapping had a significantly larger area under the curve (AUC = 0.94) compared with T2-weighted (T2W) methods, whether the reference ROI was skeletal muscle or remote myocardium (AUC = 0.58–0.89; $p < 0.03$). Messroghli et al. [20] evaluated 24 patients with acute infarction and reported that native T1 mapping with a threshold of 1,120 ms or more (mean plus 3 standard deviations) had a sensitivity and specificity of 96 and 91%, respectively, compared with LGE that served as the reference.

Post-Contrast T1 Mapping and ECV

After administration of a contrast agent, myocardium-containing fibrosis demonstrates prolonged washout of gadolinium, related to decreased density of capillaries within the scar tissue and an increased distribution of extracellular volume [21]. An increased concentration of gadolinium relaxes the adjacent protons much faster than usual, causing T1 shortening, expressed as an area of high signal intensity on LGE images [22]. The extent of collagen deposition within the myocardium varies depending on the type and severity of the cardiac disease. Focal scarring refers to an area of replacement fibrosis that is detected by LGE. However, diffuse, interstitial fibrosis at histopathologic analysis cannot be detected by LGE. The use of LGE to depict focal scarring depends on the visual differences in signal intensity between regions of scarring and adjacent normal myocardium. On standard LGE images, diffuse fibrosis lacks these differences in signal intensity and may not be visually distinguished from normal myocardium. In contrast, in diffuse, interstitial fibrosis, the application of inversion pulses with standard delayed contrast-enhanced CMR techniques uniformly suppresses the entire myocardium, despite the presence of retained gadolinium, due to fibrosis, and therefore LGE cannot be detected.

T1 mapping overcomes these limitations by measuring the intrinsic T1 time of the evaluated tissue. As expected, non-contrast T1 time in normal myocardium is longer compared with post-contrast T1 time. This is due to the small amount of residual gadolinium in the interstitium, which has a relaxing effect [23] and is amplified by the increased volume of retained gadolinium in patients with diffuse fibrosis and even more in patients with regional scarring. In controls, normal post-contrast myocardial T1 times are reported to be 340–579 ms, while in patients with cardiac disease they are reported to be 250–

580 ms. Post-contrast T1 mapping with a threshold of 392 ms or less (mean plus 3 standard deviations) was reported to have a sensitivity and specificity of 100 and 95%, respectively, in patients with chronic myocardial infarction [20]. The ECV in the myocardium may be estimated from the concentration of extracellular contrast agent in the myocardium relative to the blood in a dynamic steady state. The change in relaxation rate $\Delta R1$ (where $R1 = 1/T1$) between pre- and post-contrast is directly proportional to the Gd-DTPA concentration: $\Delta R1 = \gamma [\text{Gd-DTPA}]$ ($\gamma = 4.5 \text{ L mmol}^{-1} \text{ s}^{-1}$). A dynamic steady state exists for tissues that have a contrast exchange rate with the blood which is faster than the net clearance of contrast from the blood. A dynamic steady state between the plasma and interstitium may be achieved by slow intravenous infusion, or by imaging 15 min following an intravenous bolus administration for normally perfused myocardium, while 15 min may not be adequate for recently infarcted myocardium [24].

$$\text{ECV} = (1 - \text{hematocrit}) \frac{(1/T1 \text{ myopost} - T1 \text{ myopre})}{(1/T1 \text{ bloodpost} - T1 \text{ bloodpre})}.$$

The ECV technique introduces an important new method sensitive to the distribution of the cellular (dominated by myocyte mass) and extracellular interstitial matrix (ECM) compartments. Alterations in these compartments occur during various pathophysiologic processes [10]. Early data proved that ECV measures are of prognostic value equal to left ventricular ejection fraction (LVEF) [20, 21]. However, LVEF underscores the biologic importance of the interstitial matrix. This myocyte-ECM expansion dichotomy may have important implications for identifying distinct therapeutic targets, such as the fibroblasts versus the myocytes that are of great value for heart failure [22]. The extent to which primary ECM expansion from fibroblast activation drives myocyte dysfunction or the extent to which primary myocyte disease leads to ECM expansion in heart failure remains poorly understood, but at least now cardiology has a promising tool to quantify the expansion of interstitial matrix.

In the absence of amyloid or oedema, expansion of the myocardial collagen volume fraction is responsible for most ECM expansion [25] that leads to mechanical [26–28], electrical [29–32], and vasomotor dysfunction [33]; these represent key parameters of cardiac vulnerability [34] and diminish tolerance to ischaemic insults [35–37]. Other studies introduced the idea of “vulnerable interstitium” in sudden cardiac death [37], and described band-like fibrosis in the myocardium resembling hepatic cirrhosis [38]. Fibrosis is considered as a final common

Fig. 1. Inversion recovery sequence showing extensive anteroseptal transmural myocardial infarction.

pathway of many myocardial diseases [39, 40]. Although LGE provides important diagnostic and prognostic information [41–47], T1 mapping and ECV may have an advantage over LGE for quantifying the degree of ECM or interstitial expansion. Furthermore, LGE is less suitable for quantifying the extent of ECM expansion [48–54], due to pathologic processes, where the differences between normal and affected myocardium are less distinct. ECV has better correlation with outcomes than LGE in non-ischaemic cardiomyopathy, due to either primary myocardial or systemic diseases, and may provide additive value beyond age, gender, renal function, myocardial infarction extent, ejection fraction, and heart failure stage [55–60]. Furthermore, ECV, a marker of interstitial fibrosis, and tic , a cell size-dependent parameter, can detect myocardial tissue remodelling from pressure overload [61].

This model has also been used to identify the attenuation of interstitial fibrosis and cardiomyocyte hypertrophy in hypertensive heart disease after treatment with spironolactone [62].

Currently, the application of these new indices opens new horizons in both the diagnosis and treatment of all

Fig. 2. Post-contrast T1 mapping from the same patient.

Fig. 3. Inversion recovery sequence showing extensive subepicardial fibrosis in the lateral wall of the left ventricle, due to myocarditis.

patients in whom oedema and microfibrosis assessment is needed, including aortic stenosis, hypertrophic cardiomyopathy (HCM), myocarditis, ischaemic and non-ischaemic cardiomyopathy, heart failure of any aetiology, and rheumatic, neuromuscular, and endocrine diseases with cardiac involvement (Fig. 1–6). Specifically, shortened post-contrast T1 times in non-ischaemic and ischaemic cardiomyopathy [63, 64] were detected, even after exclusion of LGE areas, consistent with autopsy studies [65, 66]. Additionally, shortened post-contrast T1 times and increased ECV have also been documented in HCM [67, 68], mirroring the myocardial disarray and interstitial fibrosis observed at autopsy [69]. Studies evaluating the interaction between genotypic and phenotypic expression in HCM, with expansion of ECV reported in gene-positive but phenotype-negative HCM patients [68], supporting that subclinical myocardial alterations precede the progression of phenotypic HCM in gene-positive patients. Furthermore, comparison of patients with HCM based on the presence or absence of a known HCM gene revealed differences in the 2 groups regarding the extent of interstitial fibrosis [70], leading to a better understanding of the heterogeneous nature of this disease.

Finally, this new approach offers the great opportunity to reliably and reproducibly validate the effect on the myocardium of various medications including new drugs for heart failure, as well as rheumatic and oncologic medications.

Fig. 4. Post-contrast T1 mapping from the same patient.

Color version available online

T2 Mapping

T2W magnetic resonance imaging pulse sequences have been used to detect oedema in patients with acute myocardial infarction, differentiate acute from chronic infarction, and identify acute myocarditis. However, T2W sequences have suffered from various problems including (a) signal intensity variability caused by phased array coils, (b) high signal from slow-moving ventricular blood that can mimic and mask elevated T2 in subendocardium, (c) motion artefacts, and (d) the subjective nature of T2W image interpretation, unless it is expressed as T2 signal of myocardium versus T2 signal intensity of skeletal muscle (normal value <1.9).

The T2 mapping technique can accurately and reliably detect areas of myocardial oedema without the limitations of qualitative T2W imaging. T2 mapping sequences are useful for the detection of myocardial oedema due to acute myocardial infarction [71], myocarditis [72, 73], stress cardiomyopathy [72, 64], sarcoidosis [74], and cardiac allograft rejection [75]. Normal myocardial T2 values acquired using steady-state free precession MRI have been reported to be 52.18 ± 3.4 ms at 1.5T [76] and 45.1 ms at 3T [77].

T2 mapping is considered superior compared with standard CMR parameters, global myocardial T1 mapping, and ECV for assessing the activity of myocarditis in patients with recent-onset heart failure and reduced left ventricular function (Fig. 6) [78]. Furthermore, T2 map-

Fig. 5. Inversion recovery sequence showing extensive intramyocardial fibrosis in a patient with Sjogren syndrome.

Fig. 6. Post-contrast T1 mapping from the same patient.

ping was proven to be a novel non-invasive tool for transplant monitoring, and initial findings support its potential role in rejection detection [79].

Clinical Implications of T1 and T2 Mapping in Internal Medicine and Neurology

T1 and T2 mapping are of important value for various diseases in internal medicine and neurology.

Internal Medicine Diseases where the Value of T1 and T2 Mapping Is Currently Proven

Amyloidosis

Amyloid deposition in the myocardium can be detected as patchy or subendocardial LGE with early blood pool darkening on Look Locker scout images. However, the amyloid deposition makes nulling of normal myocardium particularly difficult and may lead to difficulties in image interpretation [80]. Native T1 mapping overcomes the limitations of myocardial nulling, provides a quantitative assessment of diffuse extracellular expansion, and can also be applied in patients with renal failure, com-

monly found in amyloidosis. It can also be used for serial evaluation of treatment [81].

Autoimmune Rheumatic Diseases

Cardiovascular disease is the main cause of increased mortality/morbidity in autoimmune rheumatic diseases, due to its silent presentation and the limitations of the currently used techniques that cannot perform tissue characterization [82]. Occult cardiovascular disease is common in rheumatoid arthritis, and up to 39% of rheumatoid arthritis patients have been reported to show focal LGE patterns, probably related to earlier myocarditis [83]. However, diffuse fibrosis is also common in rheumatoid arthritis and cannot be detected by LGE. In a pilot study, native T1 values were slightly elevated in rheumatoid arthritis patients compared with controls, and disease activity scores correlated positively with diffuse fibrosis regardless of LGE presence [84]. Furthermore, in ankylosing spondylitis myocardial ECV, quantified by T1 mapping was correlated with the degree of disease activity and may be a potential marker for disease monitoring [85].

Cardiac involvement is also common in systemic sclerosis and remains asymptomatic until the late stages of the disease. Low-grade inflammation, perfusion defects, and diffuse myocardial fibrosis have already been well described as co-existing factors [86]. They can be detected by T2-STIR and LGE imaging. However, LGE is limited in the assessment of diffuse myocardial fibrosis, especially when the entire myocardium is homogeneously affected [87].

The use of native T1 and T2 mapping has also facilitated the early detection of lupus myocarditis and mirrors the response to anti-inflammatory treatment [88]. Recently, Greulich et al. [89] documented that patients with ANCA-associated vasculitis demonstrated increased T1, ECV, and T2 values, and these findings seem to be independent of LGE. Finally, myocardial tissue characterization using T1 and T2 mapping enabled the non-invasive detection of cardiac involvement and activity of myocardial inflammation in patients with systemic sarcoidosis [90].

Iron Overload Disease

The quantification of cardiac iron deposition in various iron overload diseases such as thalassemia, sickle cell disease, and myelodysplastic syndrome, is performed by T2*. This technique has been validated against pathology

and represents the currently used gold standard for the non-invasive assessment of iron overload [91]. However, myocardial T1 mapping shows the potential for improved detection of mild iron loading, and its superior reproducibility has potential implications for clinical trial design and therapeutic monitoring [92]. Finally, ECV is significantly increased in thalassemia major and is associated with myocardial iron overload, as assessed by T2* [93].

Evaluation of Cardiotoxicity Post-Chemotherapy

Changes in contrast-enhanced T1-weighted signal intensity, upon which T1 mapping is based, occur with small but significant LVEF declines 3 months after the receipt of cardiotoxic chemotherapy and indicate that changes in T1-weighted signal intensity may serve as an early marker of subclinical injury related to cardiotoxic chemotherapy [94]. Additionally, myocardial T1 and ECV were found to be early tissue markers of ventricular remodelling in children with normal ejection fraction post-anthracycline therapy, and are related to cumulative dose, exercise capacity, and myocardial wall thinning [95].

Neurologic Diseases where T1 and T2 Mapping Is Currently Proven Useful

Duchenne Muscular Dystrophy and Myotonic Dystrophy

Duchenne muscular dystrophy patients have elevated left ventricular myocardial native T1 and ECV, even if LVEF is normal and there is an absence of LGE, and therefore they have the potential to serve as surrogate cardiomyopathy indices to follow up outcome measures for clinical trials [96, 97]. Similarly, myotonic dystrophy is also associated with structural alterations, and post-contrast myocardial T1 time was found to be shorter in these patients compared with controls, reflecting the presence of diffuse myocardial fibrosis [98].

Limitations of T1 and T2 Mapping

T1 and T2 mapping offer quantitative assessment of changes in tissue composition. However, one of the major obstacles for their clinical use is the variation in native T1 and T2 values related to imaging equipment and sequence. Further investigation is needed to establish “nor-

mal” reference ranges for native T1 and T2 relaxation values because there is great variation among manufacturers, magnetic field strengths, and clinical parameters. These reference values are required to distinguish various disease conditions from normal myocardium, especially in cases of diffuse disease. Knowledge of the properties of specific MR scanners is necessary for the clinical application of these techniques.

Furthermore, the full clinical utility of T1 and T2 mapping is yet unknown because many diseases have not been adequately studied. There are still pending questions about (a) the potential replacement of LGE by native T1 mapping in the assessment of fibrosis, (b) whether native T1 mapping is more useful than T2 mapping in the evaluation of myocardial infarction, or whether they are complementary, and (c) how ECV can influence the clinical management of patients with heart disease.

Conclusion

Native and post-contrast T1 mapping, T2 mapping, and ECV provide important knowledge into fundamental disease processes affecting the myocardium that can otherwise be difficult to detect. Although it seems that they can significantly affect the clinical decision making, a multicentre application and a community-wide approach (including MRI vendors, funding agencies, academics, software companies, contrast agent manufacturers, and clinicians) are still missing. Therefore, more research is required before a large-scale application for clinical decision making can be recommended.

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