T1, T2 Mapping and Extracellular Volume Fraction (ECV): Application, Value and Further Perspectives in Myocardial Inflammation and Cardiomyopathies

Anwendung, Nutzen und zukünftige Perspektive des T1- und T2-Mapping sowie der extrazellulären Volumenfraktion (ECV) bei myokardialer Inflammation und Kardiomyopathien

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Key words
- Cardiac
- MR imaging
- amyloidosis
- inflammation
- technical aspects

Abstract

Cardiac magnetic resonance imaging (CMRI) is a versatile diagnostic tool. One of its main advantages is the possibility of tissue characterization. T1-weighted images for scar and T2-weighted images for edema visualization are key methods for tissue characterization. Otherwise these sequences are strongly limited for the detection of diffuse myocardial pathologies. Recently, rapid technical innovations have generated new techniques. T1, T2 mapping and evaluation of the extracellular volume fraction (ECV) allow quantification of diffuse myocardial pathologies and showed great potential in the visualization of fibrosis, edema, amyloid, iron overload and lipid. In the future these techniques might enable the detection of early cardiac involvement, even as a prognosticator. Moreover, therapy monitoring and follow-up might be possible due to versatile parameter quantification with these new techniques.

Key points:
- CMR allows for tissue characterization via T1- and T2-weighted sequences.
- In cases of diffuse, global myocardial pathologies, correct image interpretation with traditional CMR sequences might be difficult.
- T1, T2 mapping and ECV can quantify diffuse, global myocardial pathologies.
- Alterations of myocardial T1 and T2 relaxation times occur in various myocardial diseases (e.g. acute myocarditis).
- In the future mapping might act as a prognosticator or therapy monitoring tool.

Citation Format:
Introduction

Cardiovascular magnetic resonance (CMR) is an essential and powerful diagnostic tool for the evaluation of cardiac diseases. It represents the gold standard in the quantification of cardiac function and is clinically established for the characterization of myocardial tissue and perfusion. According to the consensus recommendations of the “German Societies of Radiology and Cardiology”, CMR is the preferred alternative for many clinical issues [1]. One of CMRs key unique advantages is the possibility of tissue characterization. Current sequences weighted to a magnetic property, like T1 relaxation for scar imaging, which is also known as late gadolinium enhancement (LGE), and T2 relaxation for edema visualization, are preferentially used and only allow qualitative image analysis. However, the corresponding sequences are subject to several limitations, and especially, T2-weighted sequences are known to be prone to artifacts from many different sources. For example, the use of phased array coils can cause signal intensity inhomogeneity, which may obscure myocardial edema. Consequently, interpretation is often challenging and subjective. A major drawback is the inability to delineate global myocardial pathologies such as pan-inflammation or diffuse fibrosis.

In the last couple of years, newer techniques, namely T1 and T2 mapping, have been developed and advanced rapidly. Up to now mapping is increasingly available and integrated in clinical routine settings. Both T1 and T2 mapping are robust single breath-hold sequences (mainly performed in diastole short-axis views) and are characterized by creating colored pixel maps (maps on console are not colored) where each pixel value represents the corresponding T1 or T2 (or T2*) values. Particularly some different T1 mapping techniques are applied and influencing factors on T1 mapping and ECV values are described and discussed in the recent literature [2, 3]. In contrast to T2 mapping, T1 mapping can be performed without contrast agent administration (as native T1 mapping) but also after contrast agent administration (as post-contrast T1 mapping).

Compared to healthy volunteers, native T1 values are higher in diseases causing an increase in the extracellular compartment. This has already been demonstrated for fibrosis [4], edema [5] and amyloid [6]. Lower native T1 relaxivity compared to healthy volunteers was shown in Fabry disease [7] and iron overload [8]. Shortened T1 times in post-contrast T1 mapping are consistent with the presence of diffuse myocardial fibrosis, which could be shown for heart failure [9], ischemic heart disease [10] and in patients with diabetes [11].

The post contrast T1 mapping values are influenced by the speed of renal clearance, gadolinium dose, acquisition time post bolus injection, hematocrit level, and body composition. Therefore, measuring the extracellular volume fraction (ECV) by subtracting pre-and post-contrast maps with hematocrit correction at a sufficient equilibrium, which is normally reached after 15 minutes post bolus injection, was identified as a better alternative [12 - 14]. ECV is a specific parameter for extracellular expansion and is also well validated. ECV is calculated according to the formula: ECV = (1 – hematocrit) * (1 / T1 myocardium post-contrast – 1 / T1 myocardium pre-contrast) / (1 / T1 blood post-contrast – 1 / T1 blood pre-contrast). Amyloid and areas of involved myocardium in myocardial inflammation, for example, showed far higher ECV values than other cardiac diseases [12]. Even a connection between elevated ECV and mortality prediction was reported. In a study with 793 patients suffering from ischemic heart disease, ECV showed potential in the prediction of short-term mortality [15].

T2 mapping, however, enables the identification of myocardial edema in acute infarction and inflammatory disease [16]. Despite improved quantitative assessment of edema also global edema or pan-myocardial inflammation seems to be detectable. In cases of transplant reactions, for example, it could also be demonstrated that even early reactions, which were missed by other imaging modalities, could be detected [17].

In summary, global myocardial tissue changes or involvement can be detected already in early stages of different diseases, and also without contrast media administration by native T1 mapping. The results for both techniques are very promising and mapping is the subject of many current studies in the field of cardiac imaging. The aim of this review article is to highlight the additional value of T1 mapping, T2 mapping and ECV in cardiomyopathies and myocardial inflammation.

Methods and technical comments:

Scanning protocol
All imaging was performed with a 1.5 Tesla scanner (Avanto, Siemens Healthcare, Erlangen, Germany) using a dedicated cardiac coil and CMR protocol containing axial, coronal and sagittal thoracic survey images, steady state free precision (SSFP) sequences aligned to 2 chamber view (CV), 3 CV, 4 CV and short axis (SA), black-blood and LGE imaging, T1 and T2 mapping.

Mapping
Different T1 mapping techniques can be implemented and all techniques deal with different limitations regarding accuracy, precision and reproducibility [3]. On the one hand inversion recovery (IR) sequences, such as the modified look locker inversion recovery (MOLLI) method, are widely available and fully developed. Magnetization transfer hampers the accuracy of MOLLI significantly, whereas the precision is excellent and also a great value of reproducibility is achieved. Measured T1 times therefore are underestimated but precise and are reproducible using IR sequences. On the other hand saturation recovery (SR) methods, such as saturation recovery single-shot acquisition (SASHA), offer a greater value of accuracy because they are less sensitive to magnetization transfer and other limiting factors, but these sequences are noisier and more prone to artifacts. The measured T1 times are more accurate but also more imprecise with a smaller level of reproducibility compared to IR sequences. Actually, a combined IR/SR approach can also be performed and is known as saturation pulse prepared heart rate independent inversion recovery (SAPPHIRE). This approach has many of the benefits of IR and SR sequences but still deals with IR problems.

In our patients T1 mapping was performed as MOLLI sequence [18] and T2 mapping was performed with a standardized T2-prepared single shot SSFP sequence as previously reported [16]. T1 mapping: Data were obtained in end-diastole using a cardiac-gated, SSFP-based MOLLI technique. Imaging parameters were: slice thickness: 8 mm; spatial resolution: 2.2 × 1.8 × 8 mm; 6/8
Post-contrast imaging

Gadobenate dimeglumine (BOPTA) with a dose of 0.15 mmol/kg was injected, LGE imaging was performed 12 minutes after contrast media injection, and post-contrast T1 mapping was performed 15 minutes after contrast media injection (a bolus only approach was used for ECV measurements).

Qualitative and quantitative image assessment

All original images were assessed regarding artifacts due to susceptibility and cardiac, diaphragmatic or respiratory motion. Each motion-corrected series was evaluated for correct image alignment and each map was evaluated as to whether the original images were transformed to an acceptable map.

Measurement of T1 and T2:

After image acquisition T1 and T2 maps were generated after inline motion correction from the MR workstation. T1 times were measured for myocardium and blood pool in regions of interest (ROI) pre and post contrast administration. T2 times were measured in myocardial ROIs. It was emphasized that the ROIs were drawn only on the compact myocardium and did not include the myocardial borders because partial volume averaging artifact and registration error with gradual T1 value changes are present when measuring border areas between the myocardium and the LV cavity even after motion correction. Fig. 1 shows the native T1, post-contrast T1 map and T2 map in a 36-year-old healthy subject at basal short-axis level. In all presented case studies standardized global and focal T1, T2 mapping and ECV measurements were performed.

Imaging in myocardial inflammation (myocarditis) and cardiomyopathies

Myocardial inflammation

Myocarditis is a common disease and is the underlying cause in 12% of cases of sudden death in young adults [19]. Myocarditis is often defined as inflammation of myocardial tissue and is responsible for secondary myocardial diseases, such as dilated cardiomyopathy [20]. Clinical examination, electrocardiogram, echocardiography and serology often lead to an unsatisfactory diagnostic accuracy. For example Troponin T is only present in 35 - 45 % biopsy-proven myocarditis cases[21]. Regional and global wall motion abnormalities are common in myocarditis [22]. Otherwise cardiac dysfunction is not specific for myocardial inflammation and its sensitivity is limited [23, 24].

To overcome these diagnostic difficulties, endomyocardial biopsy (EMB) with immunohistochemistry is a further diagnostic option, which is widely accepted in the diagnostic cascade of myocardial inflammation. The overall complication rate of EMB is described as 6% with severe complications appearing in 0.1% to 0.5% [25]. Considering the addressed risks in conjunction with its invasive character, EMB seems not to be justifiable in patients with less severe disease stages. For these patients CMR is used as a standard diagnostic tool and is characterized by a high degree of safety. The diagnosis of myocarditis with CMR is based on the Lake Louise criteria, which are described in the JACC White Paper by Friedrithch et al. [26]. According to the Lake Louise criteria, myocardial inflammation is present if at least 2 of the 3 following criteria are met: regional or global signal intensity increase in T2-weighted images (ER/edema ratio), increased global myocardial early enhancement ratio between myocardium and skeletal muscles on post-contrast T1-weighted images (early gadolinium enhancement ratio/EGER) and at least one focal myocardial lesion on LGE images with a non-ischemic distribution. If typical LGE is
Radunski et al., however, investigated 104 patients with myocarditis and showed an AUC of 0.86 in the ROC analysis for an ECV level ≥ 0.29, which was superior to native T1 mapping in their study population (patients with myocarditis underwent CMR within a median of 2 weeks after onset of symptoms). 3.) Radunski et al., however, investigated 104 patients with myocarditis and showed an AUC of 0.86 in the ROC analysis for an ECV level ≥ 0.29, which was superior to native T1 mapping in their study population (patients with myocarditis underwent CMR within a median of 2 weeks after onset of symptoms). In summary, it can be stated that both native T1 mapping and ECV are superior to the Lake Louise criteria for the diagnosis of myocarditis, and that native T1 mapping might be influenced by the time between the onset of symptoms and CMR. Therefore, native T1 mapping might be preferentially used in patients with acute myocarditis, whereas the combination of native T1 mapping and LGE might be preferentially used in convalescent disease stages to achieve a high level of diagnostic accuracy.

Fig. 2 shows typical subepicardial streaky myocardial LGE at the basal short-axis level in a 46-year-old male patient and the corresponding T1 maps pre and post contrast media injection in myocardial inflammation. Fig. 3 also demonstrates typical streaky subepicardial and myocardial LGE in a 21-year-old male patient with acute myocardial inflammation at the basal and midventricular short-axis level and the corresponding T2 maps.
Cardiomyopathies

Hypertrophic cardiomyopathy (HCM)

HCM is caused by gene mutations in sarcomere proteins [32, 33] and has a prevalence of 0.2% in the general population [34]. HCM is the most common monogenic cardiac disorder and is a common cause of sudden death in the young population [35]. Varying degrees of myocardial fibrosis are present in HCM [36] and the occurrence of myocardial fibrosis correlates with wall thickness, wall motion abnormalities [37] and ventricular tachycardia [38]. Focal fibrotic infiltrations can be detected via LGE imaging and LGE might also be useful as a biomarker for risk stratification and therapeutic monitoring [39–42]. Otherwise, LGE imaging is limited, or is unable to detect diffuse fibrotic infiltrations [43, 44] and it relies on a comparison between unaffected normal myocardium and regions of focal myocardial damage. Furthermore, qualitative assessment of LGE is operator-dependent and reliable comparison between scans or individuals can be difficult. The additional benefits of T1 mapping in HCM might overcome these problems due to quantification of T1 on a voxel-wise basis. Also detection of early disease stages and diffuse fibrotic infiltrations in HCM might be possible. In the latest published data different T1 mapping techniques showed a good correlation to histologically quantified fibrosis [45–47]. In a study by Dass et al., for example, native T1 values in patients with HCM were significantly higher even in LGE unaffected myocardial tissue areas compared to healthy volunteers [4]. In addition, myocardial post-contrast T1 times are significantly lower in HCM compared to healthy volunteers [48] and are inversely correlated to the degree of fibrosis [46]. Finally, ECV values are significantly elevated in HCM and also in HCM sarcomere mutation carriers, even in the absence of left ventricular hypertrophy [49]. In the future early detection of global myocardial changes due to quantification of ECV might also assist disease-modifying therapies targeting interstitial myocardial fibrosis [49]. A Fig. 3 shows the native T1 map and post-contrast T1 map at the basal short-axis level in a 27-year-old male patient with HCM.

Dilated cardiomyopathy (DCM)

After coronary artery disease DCM is the second most common cause of heart failure [50–52]. Some DCM patients remain stable or even recover with normal ventricular function, while others are symptomatic and may develop arrhythmia or progressive heart failure [49]. DCM is characterized by a complex pathophysiology. Impaired myocardial energetics, myocardial edema, myocardial fibrosis and structural remodeling processes are present in DCM [49]. As in HCM, CMR plays a major role in the diagnosis of DCM due to the previously addressed possibility of tissue characterization. LGE imaging can assess focal myocardial fibrosis and its presence has also recently been identified as a predictor of cardiac death in DCM [52]. On the other hand the quantification of fibrosis achieved by LGE has several limitations as mentioned in the HCM section, and mapping seems to be also approach in DCM. In a 3-Tesla CMR study by Dass et al. native T1 values in DCM were elevated compared to healthy volunteers and the authors concluded that native T1 mapping detects underlying disease processes beyond those assessed by LGE imaging in relatively low-risk individuals [4]. A study by Puntman et al. showed similar results [53]. Also abnormally elevated ECV values were shown in patients with presence of non-ischemic DCM [54]. In a recent study by Nishi et al. T2 mapping showed that the myocardial water content was greater in patients with DCM compared to
normal controls and increased in progressive disease stages [55]. Based on their results, the authors concluded that T2 mapping is a useful technique for the diagnosis and quantification of diffuse myocardial edema in DCM [55].

**Amyloidosis**

In amyloidosis insoluble fibrils accumulate in the extracellular space caused by protein misfolding. As a consequence, the structure and function of many tissues and solid organs including the heart can be damaged [56]. Cardiac involvement is common in primary amyloid light chain (AL) amyloidosis and contributes substantially to morbidity and mortality [57, 58]. Endomyocardial biopsy (EMB) is the gold standard for diagnosis in amyloidosis but is not routinely performed, because of its invasive character and the known associated risks. As further shown, CMR with LGE has great potential for tissue characterization in patients with amyloidosis [59–62]. CMR provides noninvasive diagnosis of patients with cardiac amyloidosis due to the identification of characteristic global or subendocardial LGE patterns. This characteristic LGE pattern is a hallmark for cardiac involvement, and when present, it also correlates with the prognosis of amyloidosis [59, 61]. On the other hand, LGE imaging in patients with suspected cardiac amyloidosis also deals with several problems: gadolinium administration in patients with renal impairment is problematic or even impossible, and the presence of atypical disease patterns with patchy LGE infiltrations and appearances in different locations, which can be present in patients with life-threatening disease, renders diagnosis more difficult [56, 59, 62]. In this context native T1 mapping offers great potential for accurate identification of amyloidosis [6]. Compared to other diseases, the native T1 values are much higher in amyloidosis and the ECV values are also clearly elevated as further studies showed [6, 63]. Therefore, T1 mapping might be applicable as an early disease marker due to the detection of global myocardial changes.
A recent study by Fontana et al. showed that native T1 mapping even offers potential for the differentiation of AL amyloidosis and transthyretin amyloidosis [63]. Due to the absence of edema in amyloidosis, no T2 alterations are detected. Fig. 6 shows the T1 maps pre and post contrast media administration in a 66-year-old female patient with amyloidosis.

**Anderson Fabry Disease (AFD)**

AFD is an X-linked disorder of lysosomal metabolism with an inability to catabolize glycosphingolipid (more precisely globotriaosylceramide) due to a deficiency of the enzyme alpha-galactosidase [64]. Glycosphingolipid accumulates in many organs including the skin, myocardium and kidneys. The classic form of the disease affects male homozygotes and presents in adolescence with burning extremity pain (acroparesthesia) and progressive multi-organ failure [65]. AFD can cause left ventricular hypertrophy (LVH) due to storage of glycosphingolipid in myocytes, valves and vascular endothelium [66]. The cardiac decompensation in AFD is secondary to progressive myocardial fibrosis and is usually more extensive in men than in affected women [64]. Heterozygous female carriers may therefore present with milder disease forms [67]. Like described for other cardiomyopathies, CMR is the imaging technique of choice in suspected cardiac AFD involvement. LGE within the basal infero-lateral wall without affecting the endocardium is characteristic for a cardiac manifestation in AFD [68]. In genetically confirmed AFD, Moon et al. demonstrated that LGE of the infero-lateral wall was present in 50% of the patients [68]. It also seems that the presence of LGE may have a prognostic value. Ries et al. showed that the presence of LGE in patients with AFD was associated with a lack of response to enzyme replacement therapy, which is maybe caused by irreversibly damaged myocardial tissue (scar) [69]. Otherwise enzyme replacement is a promising therapy option, which showed potential for the reduction of left ventricular hypertrophy in a recent long-term study [70].

As already mentioned, lipid in the form of glycosphingolipid is stored in myocytes, and lipid is known to shorten the magnetic resonance imaging parameter T1. In this context T1 mapping appears very promising. Sado et al. showed that septal native T1 mapping values were significantly lower compared to other diseases and discriminated patients with AFD from other diseases with left ventricular hypertrophy without any overlap [7]. T1 values in patients with AFD also correlated inversely with left ventricular wall thickness, whereas T1 values of the infero-lateral wall were elevated when LGE was present [7]. Furthermore, Thompson et al. showed that reduced non-contrast myocardial T1 values are the most sensitive and specific cardiovascular MRI parameter in patients with AFD irrespective of sex and LV morphology and function [71]. ECV in AFD is normal compared to healthy volunteers whereas ECV is higher in other diseases [72]. As in amyloidosis T2 alterations are also not present. Fig. 7 shows the T1 maps pre and post contrast medium administration and the corresponding LGE image at the basal short-axis in a 51-year-old male patient with AFD.

**Takotsubo cardiomyopathy (TTC)**

Acute stress-related takotsubo cardiomyopathy (TTC) has recently emerged as a distinct entity and represents an important acute stress-related clinical disease. TTC mainly affects women and the spectrum of myocardial tissue injury is not well defined yet. Irreversible injury in TTC with LGE is not present [73]. TTC is characterized by its acute and sudden appearance with reduction of left ventricular myocardial function. Due to the acute character of TTC, edema was discussed as a potential tissue marker in TTC and Abdel-Aty et al. showed that edema was encountered in 7 TTC patients in the acute phase [74]. In their study edema was present in the mid-anterior and apical myocardium and also matched with the distribution of hypokinesis [74]. Accordingly the authors concluded that edema is a general feature of TTC and that edema imaging serves as an incremental tool for noninvasive characterization [74]. Also new insights into the pathophysiology of TTC might be provided. Recently on that basis, it could be demonstrated by Thavendiranathan et al. that T2 mapping reliably identified myocardial involvement in patients with TTC and myocardial inflammation [16]. Additionally, T2 mapping delineated greater extents of myocardial edema to all other per-
formed sequences [16]. Fig. 8 shows a TIRM image and a T2 map at the apical short-axis level of a 58-year-old male patient with acute onset TTC.

**Discussion**

Cardiac MRI is a standard diagnostic tool for a growing number of clinical issues. At present, 27 highest grade recommendations for CMR application exists in the German consensus statement [1] and a growing number can be assumed in the next couple of years. T1, T2 mapping and ECV are newer developed sequences in CMR, which are increasingly available and used in clinical routine settings. Their value in cardiac imaging is promising but challenges still remain. Mapping is a powerful tool in the identification and quantification of global or diffuse myocardial processes without further need for EMB like many studies in the recent literature showed. Also there are first signs suggesting that these new techniques detect early stages of different diseases, which were missed by other performed imaging methods or traditionally performed sequences. Mapping and ECV might also have great potential for determining the prognosis of several diseases or their values might even be used for creating endpoints in clinical trials or for therapy monitoring in the future. Due to the rapid progress and technical development with several different sequences up to now, delivery across sites and standardization are desirable objectives in the near future in order to achieve comparability between clinical excellence centers, study groups, and published values.
As the case studies in this review article show, mapping is a robust technique with great potential in the imaging of different diseases. In myocardial inflammation T1, T2 mapping and ECV showed advantages compared to other imaging methods and sequences in the visualization of focal or global myocardial processes due to the quantification of T1 and T2 on a voxel-wise basis. In this context first cut-off values for T1 and T2 were published and led to improved detection of myocardial inflammation in smaller studies. The influence of mapping compared to the Lake Louise criteria in the diagnostic performance of CMR in myocardial inflammation was highly anticipated. In this context especially native T1 and ECV were detected as further improvements, as presented by Ferreira et al. and Radunski et al. [28, 31]. However, in our opinion it still remains to be seen, whether mapping will assume a decisive role in the diagnosis of myocardial inflammation with improved diagnostic accuracy and might not serve as only an increment in CMR settings. Mapping might also replace previous sequences due to radical improvement in reliability. In different cardiomyopathies mapping also showed great potential for the detection of early disease stages even without contrast agent administration (native T1 mapping). Also degrees of fibrotic involvement are assessable without EMB. Based on these results, therapy monitoring of cardiomyopathies via follow-up examinations might be possible and clinical trial endpoints might also be reviewable. Additionally T1 mapping might be used as a prognosticator or may offer additional diagnostic benefits, and also a better understanding of the pathophysiology might be provided. Currently mapping is not only implemented in frequently occurring diseases in CMR. Mapping also showed potential in less frequently occurring cardiac diseases in smaller studies, for example, in sarcoidosis, muscular dystrophy or chemotherapy-induced myocardial changes. The method is becoming increasingly popular and the growing number of publications dealing with cardiac mapping also supports this. Mapping has the potential to increase our understanding of pathophysiology, if interpretation is performed in context with the underlying mechanisms. Table 1 presents published reference values for T1, T2 and ECV in health and disease at different field strengths.

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