MR imaging assessment of myocardial edema with T2 mapping

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Abstract Cardiac magnetic resonance (CMR) provides a high signal-to-noise ratio, high spatial and temporal resolutions, as well as a delayed-enhancement sequence and is therefore considered a reference technique in the field of cardiac imaging. However, currently available sequences are not adequate to assess some pathologic conditions, such as myocardial edema. T2 mapping sequences generate parametric images that are based on the transverse relaxation time (T2) for each voxel. In case of edema, the T2 relaxation time is longer. This review summarizes current knowledge on CMR T2 mapping for assessing myocardial edema.

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Myocardial edema is an important pathophysiologic component in many acute, ischemic and non-ischemic heart diseases (myocardial infarction, myocarditis, Takotsubo cardiomyopathy, graft rejection, etc.). To date, only CMR can assess non-invasively myocardial edema, by using T2-weighted sequence images. These images are based on the prolongation of the transverse relaxation time caused by edema, because of water accumulation, and an increased proportion of free water [1,2]. Edema appears as a high signal intensity on these images, the most common sequence being STIR (Spin Echo with Triple Inversion Recovery) where the signal from fat and blood pool is suppressed to improve

Abbreviations: AAR, Area at risk; CMR, Cardiac magnetic resonance; EMB, endo-myocardial biopsy; LE, Late enhancement; MRI, Magnetic resonance imaging; MVO, Microvascular obstruction.

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the contrast between edema, normal myocardium and left ventricular cavity. T2-weighted images have, however, many limitations, making them poorly robust for assessing myocardial edema [3]. The limitations include: a low signal-to-noise ratio (and therefore a mediocre contrast between the healthy and edematous areas), a high dependency on magnetic field inhomogeneity, a loss of signal secondary to cardiac motion across the plane in black blood preparation, a subendocardial slow flow hyperintensity, susceptibility to motion artifacts and finally subjective visual interpretation [3,4]. Some authors have tried to overcome these limitations by developing a hybrid bright-blood TSE-SSFP T2-weighted sequence [5,6].

T2 mapping, or T2 transverse relaxation time mapping, is a technique used to construct a parametric image based on the transverse relaxation time of each voxel. This review examines current knowledge on myocardial edema assessment using 1.5 T CMR T2 mapping.

**T2 mapping sequence: principles**

Magnetic resonance imaging measures the energy released by protons during the relaxation phase, energy that has previously been accumulated during the excitation phase. The relaxation phase includes a longitudinal component characterized by the T1 relaxation time (time to recover 63% of initial magnetization) and a transverse component characterized by the T2 relaxation time (time to recover 37% of the initial magnetization). The T1 and T2 values vary with the biochemical features of tissues and thereby enhance CMR diagnosis.

The T2 relaxation time is measured using the T2-prepared SSFP sequence [7]. This sequence is prospectively ECG-triggered and generates three T2-weighted images, based on a balanced SSFP sequence started after preparation for magnetization. Preparation is applied over an increasing period (0, 24 and 55 ms), which allows increasing echo times to be applied. The repetition time is 3 RR intervals to achieve longitudinal relaxation (Fig. 1). A transverse relaxation curve can then be constructed over 7 RR intervals i.e. a recording time of 7 seconds for a patient with a heart rate of 60 beats per minute. The parametric image is created based on the T2 value calculated (in ms) for each voxel. Motion correction (MOCO) may be applied. T2 maps can be analyzed visually on a grey (or color) scale but can also be analyzed quantitatively with rapid measurements in regions of interest drawn by the investigator.

At 1.5 T, the normal myocardium T2 value was measured at 52 ± 3 ms by Girì et al. in 14 healthy volunteers and at 55 ± 5 ms in 73 healthy volunteers by Wassmuth et al. The value is independent of body surface area or heart rate [7,8]. These values have been confirmed in other studies. Verhaert et al., Manrique et al., Usman et al., Thavendiranathan et al. and Gouya et al. reported values of 55 ± 2 ms, 56 ± 5 ms, 52 ± 3 ms, 54 ± 3 ms and 56 ± 4 ms, respectively, in healthy volunteers [9–13]. One study reported a significantly higher normal 4-cavity T2 value (60 ms) than for the short axis T2 value (56 ms), probably due to a partial volume effect and residual myocardial motion [8]. In this study, the T2 value correlated inversely with wall thickness as the region of interest defined by the investigator may have included left ventricular cavity or epicardial fat voxels, an effect which could produce false positive results in clinical practice [8]. The normal myocardial T2 measure was lower at 3 T (39 ± 5 ms) [14].

From the literature, it appears that the feasibility and the reproducibility of the T2 mapping sequence are excellent. One hundred percent of the images in the Verhaert et al. study were analyzable [9]. An older sequence (HASTE), used by Manrique et al. had a similar rate of analyzable images [10]. Intra- and inter-observer reproducibilities have been reported high, 1 ± 1 ms and 1.6 ± 1.5 ms, respectively, with a test-retest coefficient of variation of 7% [8]. Ugander et al. measured the area at risk (AAR) (in gram, the product of myocardial volume with a T2 value of >2 SD the healthy myocardial value and of the myocardial tissue density estimated to be 1.05 g/cm³) and also found excellent intra- and inter-observer reproducibilities of 0.6 ± 2.6 g and 1.4 ± 4.4 g, respectively [15]. Spatial resolution was reported between 2 × 1.5 × 6 to 2.5 × 2 × 8 mm [8,9,15].

**Pathophysiology of myocardial edema**

In a normal state, intramyocardial water is divided between the intracellular compartment (77%) and the intravascular compartment (23%). Although water molecules diffuse across cellular and vascular membranes, the interstitial intramyocardial component is poor, as a result of Na+/K+-ATP-dependent pumps, and because of bindings between water molecules and intracellular proteins [16]. Different types of acute myocardial injury upset this water balance, leading to accumulation of intercellular (cytogenic edema) followed by interstitial water (vasogenic edema). Edema is an important component of many acute heart diseases, including myocardial infarction, myocarditis, Takotsubo cardiomyopathy and graft rejection. Its pathophysiology is multifactorial and depends on the etiology. Some examples include reduced activity of membrane pumps due to ATP deficiency and water protein bonds caused by acidosis in ischemia, vasodilatation and increased capillary permeability in inflammatory processes [16,17]. In addition to being a marker of acute myocardial injury, the edema is associated with left ventricular systolic and diastolic dysfunction and contributes to the pathophysiology of ischemic microvascular obstruction (MVO). Edema also has an effect on myocardial fibrosis development [18–20]. In acute myocardial infarction, the AAR is defined as the potentially infarcted area in the absence of reperfusion (the area perfused by the occluded coronary artery). The AAR can be subdivided into two components, a necrotic core (non-viable infarcted zone) surrounded by « salvageable myocardium » (viable non-infarcted zone). Edema imaging has long been considered a way to analyze the AAR, but this is now being questioned [21,22].

As water increases the T2 transverse relaxation time, the T2 mapping sequence appears to be promising in order to detect and even quantify myocardial edema.
**Main areas of application of T2 mapping in assessing myocardial edema**

**Ischemic myocardial edema**

As reported in the literature and described below, the T2 value is significantly higher in infarcted segments, without overlap with the normal T2 value (remote myocardium or myocardium of healthy volunteers). The sensitivity for detecting ischemic edema is excellent, far greater than that observed with T2-weighted imaging. **Fig. 2** illustrates a short axis view of the left ventricle in a patient with signs of acute myocardial infarction.
By observing the edema around the necrotic core more information is added to the late enhancement sequence. The high sensitivity appears promising to assess patients with acute chest pain without ST-segment elevation or raised troponin, as myocardial edema occurs early in ischemia [23,24]. In addition, detection of myocardial edema may be useful to assess patients with acute chest pain with non-diagnostic electrocardiogram, elevated troponin but normal coronary angiogram. However, the ischemic etiology cannot be diagnosed solely on T2 mapping images, as no specific pattern has been identified.

T2 value in the area at risk and in the healthy area

Ugander et al. [15] showed, in animal studies, an increased T2 value (71 ± 6 ms vs. 49 ± 3 ms) in the infarcted zone compared to remote myocardium. In humans, Verhaert et al. found that the T2 in the infarcted area was 69 ± 6 ms compared to 56 ± 3 ms in the remote areas in 27 patients hospitalized for acute myocardial infarction and imaged at 2.1 ± 1.3 days (P < 0.0001), the latter value being not significantly different from that of control subjects (56 ± 2 ms, P = NS) [9]. There is almost no overlap between T2 values in the infarcted and healthy areas. In case of MVO, the T2 value was similar to that of the healthy muscle (n = 13, 59 ± 6 ms). Manrique et al. reported similar results in a population of 24 patients hospitalized for ST-segment elevation acute myocardial infarction who were reperfused and imaged within 7 days (infarct core 85 ± 24 ms, remote myocardium 63 ± 10 ms, P = 0.0001), but the T2 value in remote myocardium was higher than in healthy volunteers (56 ± 5 ms, P < 0.0001), indicating that edema is not restricted to the AAR [10]. Finally, the subendocardial T2 value was not different from the subepicardial value in the infarcted area, a finding that is discordant with physiology, as edema has been demonstrated 9 times greater in the infarcted area than in the salvaged myocardium [22]. This appears as an argument against T2 mapping in order to assess the AAR.

Detection of infarcted segments

Compared to late enhancement (LE), Verhaert et al. found 96% detection sensitivity on a patient basis (visual analysis, 26/27 patients), compared to 72% by T2-STIR (18/25 patients, 2 failed recordings due to inadequate breathholding) [9]. Sensitivity was not assessed on a segment basis or using a threshold method. In an animal study, Ugander et al. found no significant difference in the AAR assessment between T2 mapping and the microsphere Gold Standard method (26 ± 2 g et 23 ± 1 g respectively) [15].

Non ischemic myocardial edema

In non-ischemic acute heart diseases (such as myocarditis, Takotsubo cardiomyopathy, transplant rejection, acromegalic heart disease), the T2 value has been shown significantly higher in the edema area than in healthy myocardium. Fig. 3 illustrates a short axis view of the left ventricle in a patient with signs suggestive of viral myocarditis. A cutoff of 59 ms detected edema with sensitivity and specificity of 94% and 97%, respectively. These values are far higher than those observed with T2-weighted sequences [12]. Results are particularly promising in monitoring heart transplant patients when investigating for signs of graft rejection. The endo-myocardial biopsy (EMB), current gold standard for the graft rejection’s diagnosis, is an invasive procedure. Moreover, the results are limited to biopsy samples (risk of false negatives for localized processes, impossibility to assess the extension of the disease). T2 mapping could be performed as a first line exam, providing reassurance in case of normal result (T2 < 56 ms) and suggesting EMB in case of abnormal result [25]. This group also describes the history of patients with pathological T2 (> 56 ms) but normal biopsy (grade 0 or 1) and subsequent

Figure 3. Short axis section on the LV in a patient with signs suggestive of viral myocarditis. On the left: the post-gadolinium late-enhancement sequence shows contrast uptake localized in the middle region of the septum associated with myocyte lysis and diffusion of contrast into the interstitial sector (arrow). On the right: T2 mapping showing an increase in the T2 relaxation time, which extends throughout the septum and the anterior LV wall (arrow).
 graft rejection (grade ≥ 2). This finding is probably due to the focal and therefore partial nature of the histological diagnosis, whereas MRI provides a global assessment.

Heart transplant rejection

Marie et al. measured the interventricular septal T2 value in patients undergoing EMB within 7 days, without immunosuppressive therapy [25]. One hundred and twenty three MRIs were performed. Nineteen patients had grade ≥ 2 rejection, according to the Society for Heart Lung Transplant classification. The T2 value was 50 ± 5 ms, 51 ± 5 ms and 51 ± 8 ms (P = NS) in groups 0, 1A and 1B respectively (i.e. no rejection, slight local rejection and slight effusive rejection). Conversely, the value was higher in grade 2 rejection (57 ± 5 ms, P < 0.05, moderate local rejection) and even higher in grade 3 rejection (65 ± 8 ms, P < 0.05, moderate multifocal rejection or moderate diffuse rejection). No patient had severe (grade 4) rejection. Grade ≥ 2 rejection was associated with a T2 value of 60 ± 7 ms, which was higher than for grades 0-1 (51 ± 6 ms, P = 0.0001), enabling a cut-off value of 56 ms (> 2DS of the normal value) to be defined for the detection of graft rejection with a sensitivity of 89%, a specificity of 70%, a negative predictive value of 97%, and a positive predictive value of only 35%. Usman et al. made a similar study in 25 patients and observed that the T2 value, higher in the 3 patients with rejection (62 ± 3 ms vs. 52 ± 2 ms), systematically normalized after immunosuppressive therapy, suggesting that MRI may also be used to monitor the efficacy of immunosuppressive therapy [11].

Other clinical situations associated with edema

Usman et al. carried out a study on 65 patients including 20 controls, 25 heart transplant patients, 12 acute myocardial infarctions, 6 acute myocarditis and 1 Takotsubo cardiomyopathy [26]. The T2 value was similar for the different conditions, in both the healthy area (about 52 ms) and in the pathological area (about 65 ms). Specifically, the T2 was found to be 67 ± 8 ms in acute myocarditis and 68 ± 4 ms in Takotsubo cardiomyopathy (apical and median segments). Thakrar et al. found a higher T2 value in segments with LE (70 ms) than in the other segments (60 ms) in 25 patients with acute myocarditis [27]. Thavendiranathan et al. found a higher T2 value in pathological myocardium than in the remote myocardium in 30 controls and 30 patients with acute myocarditis (n = 20) or Takotsubo cardiomyopathy (n = 10). Values for the remote myocardium were similar to those measured in controls (65 ± 3 ms versus 54 ± 2 ms, P < 0.001 and 66 ± 4 ms versus 54 ± 3 ms, P < 0.001 respectively) [12]. A cut-off of 59 ms is therefore associated with a sensitivity and specificity of 94 and 97%, respectively, for the detection of myocardial edema. The authors point out that the abnormal region, as visually estimated on T2 mapping, was larger than the dysfunctional region or the region with LE, and that T2-weighted images (STIR) could only be analyzed in 47% of the patients (problems with holding breath, arrhythmia or artifacts). Of the remaining 14 patients, 2 T2-weighted STIR appeared normal whereas T2 mapping was abnormal. Finally, Gouya et al. carried out a study on acromegalic heart disease, which is associated with myocardial edema, reversible on treatment (transphenoidal adenectomy or somatostatin analog) [13]. The T2 value before treatment was 71 ± 12 ms (15 patients), significantly higher than for control patients (56 ± 4 ms, P = 0.0003), and then decreased to 58 ± 7 ms after treatment (P = 0.0007), a value comparable to controls’ one.

Limitations

To date, there have been only few trials, single-centered designed, enrolling few patients. The apical region is difficult to assess because of partial volume effect. Thin left ventricular walls may increase the risk of false positive results (risk of including left ventricular cavity or epicardial fat voxels). The visual interpretation is subjective thereby confirming the benefit of threshold values, although we have to keep in mind that such pathological processes cannot be considered a « all or none » phenomenon but rather a continuum between the healthy areas and the pathological core [12,25]. A hybrid approach combining visual assessment and measurement of the T2-value within regions of interest is probably the best approach for T2 maps analysis and is already applicable in clinical practice. The etiology of the disease cannot be ascertained by T2 mapping as no specific patterns have been identified between the different etiologies. Finally, T2 mapping sequence remains optional for most manufacturers and therefore not widely available.

Conclusion

A T2 mapping sequence measures the T2 transverse relaxation time in each voxel and then creates a parametric image in which intensity reflects the measured T2 value. The image obtained may be analyzed visually on a grey (or color) scale and T2 can be rapidly quantified within regions of interest. Based on the literature currently available, T2 mapping is a highly feasible and reproducible technique, which can both detect and even quantify myocardial edema, in the same way as T2 imaging for assessing iron overload (multi-echo turbo spin-echo sequence). This sequence has many advantages compared to T2-weighted sequences, however, numerous limitations remain and multicenter trials are needed to validate T2 mapping’s clinical utility.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


