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Title Page

Title: On the accuracy and precision of cardiac magnetic resonance T_2 mapping: a high-resolution radial study using adiabatic T_2 preparation at 3 T

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Abstract

Purpose: The goal of this study was to characterize the accuracy and precision of cardiac T_2 mapping as a function of different factors including low signal-to-noise ratio (SNR), imaging in systole, and off-resonance frequencies.

Methods: Bloch equation and Monte-Carlo simulations were used to determine the influence of SNR and the choice of T_2 preparation echo time (TE_{T2prep}) increments on the accuracy and precision of high-resolution radial cardiac T_2 mapping at 3.0T. Healthy volunteers were scanned to establish the difference in precision and inter- and intra-observer variability between T_2 mapping in diastole and systole, as well as the effect of SNR and off-resonance frequencies on the accuracy of T_2 maps.

Results: The simulations demonstrated that a TE_{T2prep} increment of ~0.75 times the T_2 value of interest optimally increases the precision of the T_2 fit. Systolic T_2 maps were found to have a higher precision(P=0.002), but similar inter- and intra-observer variability compared to diastolic T_2 maps, while off-resonance frequencies beyond ±100Hz cause a significant decrease in both accuracy and precision(P<0.05).

Conclusions: This evaluation of the accuracy and precision of cardiac T_2 mapping characterizes the major vulnerabilities of the technique and will help guide protocol definition of studies that include T_2 mapping.

Introduction

T_2-weighted (T_2w) magnetic resonance imaging (MRI) of the myocardium is a well-established technique for the detection of myocardial edema, which is associated with both acute and chronic cardiac pathologies (1,2). When combined with late gadolinium-enhanced (LGE) imaging after ischemic injuries, it may also allow delineation of the area at risk (AAR), which is of significant benefit for guiding therapy in patients (3). However, conventional T_2w imaging has several limitations, such as the qualitative nature of the resulting images and signal variations due to proximity to the radiofrequency (RF) coils (4). Direct quantification of the T_2 values of the myocardium with T_2 mapping addresses several of these limitations. Due to its quantitative nature, the user-dependent interpretation is eliminated and results can be directly compared between patients or sessions (5-7). The T_2 mapping techniques that have been established in recent years involve acquiring several images with different T_2 preparation module echo times (TE_{T2prep}), combined with a robust cardiac imaging pulse sequence. Imaging pulse sequences including spiral (8), balanced steady-state free precession (bSSFP) (9,10) and gradient-recalled echo (GRE) (7) have been used. Due to the different TE_{T2prep}, the signal in each image has a different T_2 dependence. After the acquisition, T_2 values are computed by fitting an exponential decay curve across the images at each pixel using a two-parameter equation (9). High-resolution radial cardiac T_2 mapping has recently been introduced (7), and may be of specific use in patients with thin myocardium, when available tissue volumes are small, or when small focal increases in T_2 need to be detected (11).

Various studies have been conducted with the above-mentioned approaches to establish reference T_2 values in healthy volunteers and patients (5,7,9,12-17). Unfortunately, the imaging parameters used in these studies varied widely. First, although optimal echo times have been studied for conventional spin-echo T_2 mapping(18), there is no agreed-upon standard for the use of an optimum TE_{T2prep} series in conjunction with a gradient echo signal readout that results in the most accurate T_2 maps. Simultaneously, the already reported TE_{T2prep} have not been tested for their accuracy and precision in different SNR regimes. Accuracy in this case relates to how close the measured and "true" T_2 values are, while precision relates to the extent of the standard deviation. Second, to our knowledge, no quantitative comparison has been made to ascertain the accuracy or precision of T_2 maps obtained in diastolic and systolic acquisition windows. Finally, while the influence of off-resonance frequencies on myocardial T_1 mapping has been studied (19), the accuracy of T_2 mapping as a function of off-resonance has yet to be determined.

The purpose of the study was therefore to evaluate the accuracy and precision of radial high-resolution T_2 mapping as a function of the above-mentioned influences in order to optimize the T_2 mapping protocol. More specifically, the study was conducted with four sub-aims: 1) To evaluate the T_2 mapping precision with different series of TE_{T2prep} at different SNR levels using numerical simulations; 2) To compare the precision and inter- and intra-observer variability of cardiac T_2 mapping in diastole to that in systole in healthy volunteers; 3) To determine the correlation between SNR and the accuracy of the obtained T_2 maps; and 4) To ascertain the influence of off-resonance frequencies on T_2 mapping in healthy volunteers.

Methods

Numerical simulations

Bloch equation (20) simulations were used to model the behavior of the magnetization of a lung-liver-navigated T_2-prepared radial GRE T_2 mapping sequence (repetition time TR=4.9 ms, echo time TE=2.2 ms, 21 lines per heartbeat, RF excitations for imaging with 1 ms windowed-sinc pulses and angle=15°, waiting period 3 heartbeats, simulated heart rate 60 bpm, simulated myocardial T_1=1450 ms) at 3.0 T (Magnetom Trio, Siemens Healthcare, Erlangen, Germany) with a 32-channel chest coil (Invivo, Gainesville, Florida) in Matlab (The Mathworks, Inc, Natick, MA, USA). The adiabatic T_2prep module (21) consisted of two 10ms HS10 adiabatic pulses(22) with a full inversion plateau of 2.2 kHz, flanked by a 2.2 ms 90° and a 1.9 ms -90° rectangular pulse. Root-sum-of-square coil combination of 32 complex channels was used in the simulation to include the noise floor bias that occurs with array coils (23). The myocardial T_2 value was evaluated from 30 to 70 ms in steps of 5 ms. As previously described (7), there is a small but significant degree of T_1 recovery between the end of a T_2prep and the center of the radial readout train (Supporting Figure S1). Although T_2 relaxation would normally cause the magnetization to exponentially decay to zero as a function of increasing TE_{T2prep}, in the case of T_2-prepared radial imaging the signal decays to a non-zero equilibrium due to T_1 recovery. Using Bloch equation simulations, this non-zero equilibrium magnetization can be approximated by a fixed offset δ for a given set of pulse sequence parameters, and is independent of TE_{T2prep} itself, such that:

$$M = M_0 * \left[e^{\frac{-TE_{T2prep}}{T_2}} + \delta \right]. \quad (1)$$

Here M_0 refers to the longitudinal magnetization at TE_{T2prep} = 0 ms, and δ=0.08 is the empirical offset that accounts for T_1 relaxation between the T_2prep and signal acquisition for the set of pulse sequence parameters mentioned above (7).

Using Equation (1), the relative signal of a hypothetical image pixel in the myocardium was calculated for series of three different TE_{T2prep}, and the increment between the TE_{T2prep} was varied from 15 to 60 ms in steps of 5 ms. Equally spaced TE_{T2prep} series were chosen for their expected balance between high signal after short T_2 relaxation durations and high contrast after long T_2 relaxation durations. Monte Carlo simulations (24) were then used to compare the accuracy and precision of T_2 mapping for different TE_{T2prep} series as a function of SNR. Randomly generated noise with a Rician distribution (25) was added to the simulated signal to obtain SNR levels of 20 to 1000 at TE_{T2prep}=0ms. This signal with added noise was then fitted with the two-parameter Equation (1) to obtain the T_2 values. This was then repeated 10,000 times with different randomly generated noise per TE_{T2prep} series and SNR level. The upper limit of the T_2 fit was empirically set to be 100 ms, since the myocardial T_2 value at 3.0T cannot physiologically be that long. The standard deviation of the fitted T_2 values at each SNR level was plotted against the TE_{T2prep} series to determine the effect of the TE_{T2prep} choice on the precision of T_2 mapping at different SNR levels. Similarly, the effect of the SNR on the T_2 fitting precision and accuracy was studied at T_2=45 ms and TE_{T2prep}=[0-30-60] ms. Finally, a plot of the T_2 standard deviation against the TE_{T2prep} series at different input T_2 values was made to study the effect of the T_2 value on the optimum TE_{T2prep} increment. The behavior of the T_2 mapping at off-resonance frequencies from -250 to 250 Hz with steps of 5 Hz was determined using the Bloch equation simulations above, albeit with an extra parameter that incorporated the off-resonance excitation profiles of all RF pulses in the sequence (26).

Comparison of T_2 mapping in diastole and systole

In order to compare the precision and inter- and intra-observer variability of T_2 mapping in systole and diastole, 11 healthy volunteers (age 30±3 years, weight 66±8 kg, heart rate 59±4 bpm, 6 males and 5 females) were scanned. Permission from the Institutional Review Board of the University Hospital of Lausanne (CHUV) was obtained for all the in-vivo imaging studies, and written informed consent for the study and its publication was obtained from all participants prior to the procedure. All volunteers were scanned using a routine T_2 mapping protocol, which includes end-expiration bSSFP cine imaging to characterize the cardiac motion, 3D localized cardiac B_0 shimming of the heart based on a gradient-echo field map (27), followed by navigator-gated (gating window 4 mm, slice tracking factor 0.6 (28)) high-resolution radial T_2-prepared GRE T_2 mapping. T_2 maps were acquired every three heartbeats with a segmented k-space radial acquisition, as described for the numerical simulations, with the following additional parameters: field of view FOV = 320mm^2, 315 radial lines regridded into a 256×256 matrix for an acquired in-plane resolution of 1.25×1.25 mm^2, acquisition window duration = 21×4.9 ms=102.9 ms, and slice thickness = 5 mm. The adiabatic T_2prep module was used with 3 incremental TE_{T2prep} (0, 30, and 60 ms). For respiratory motion correction, a respiratory navigator module with duration 40 ms was applied between the T_2prep and the acquisition. T_2 maps were acquired at a basal, mid-ventricular, and apical level of the left ventricle in both systole and diastole. The systolic acquisition window was timed such that its center overlapped with the center of the cine frames at maximal contraction, while the diastolic acquisition window was timed to start at the first cine frame of relative cardiac quiescence.

T_2 map reconstruction and analysis was performed in Matlab using a custom-written program. Here, the three source images were co-registered using an affine co-registration algorithm (29), and the T_2 relaxation times were calculated for each pixel using Equation (1). The myocardium was then manually traced by conservatively drawing the endocardial and epicardial contours within the homogeneous myocardium (avoiding all regions with possible partial-volume effects from the blood pool), and divided into 16 segments according to the American Heart Association (AHA) segmentation guidelines (30). In each segment, the average T_2 value and its standard deviation as well as the segmented myocardial wall thickness were calculated in both systole and diastole. The systolic and diastolic measurements were then grouped per slice as well as all grouped together. Paired two-tailed Student's t-tests were used to test for significant difference in T_2 values and wall thickness between diastole and systole, while the same t-test was used between the absolute diastolic and systolic segmental standard deviation of all volunteers to calculate the difference in precision. A repeated-measures ANOVA with a Tukey multiple comparison test was used to compare the systolic or diastolic T_2 values of the 3 slices to one another. The segmental analysis was performed by two independent and mutually blinded observers, as well as twice by the same blinded observer with a two week waiting period between analyses. Bland-Altman plots including the mean difference and 95% confidence intervals (CI, defined as 1.96 times the standard deviation of mean difference) (31) were generated from these observations, and inter- and intra-observer variability were established. In order to ascertain the difference in variability between Bland-Altman plots, a paired two-tailed Student's t-test was used between the absolute differences of measurements used for intra- and inter-observer variability. For these t-tests $P \leq 0.05$ was considered statistically significant.

After performing this procedure for all segments in the three slices, the same inter- and intra-observer analyses were also performed for apical and lateral segments only, because these segments are often affected by increased partial volume effects and motion.

SNR analysis

The results of the Bloch equation and Monte Carlo simulations for the TE_{T2prep} series = [0-30-60] ms were verified with a phantom study. A cylindrical phantom with a 10 cm diameter and three concentric compartments that approximate the relaxation times of muscle, fat, and blood was placed between two 6 cm stacks of blankets to approximate the distance of the RF coils to the heart. Spin-echo T_2 mapping (TR=7 s, TE=6.3-400 ms in 8 increments) was used as a gold standard for the T_2 value, while inversion-recovery spin echo T_1 mapping (TR=7 s, inversion time TI=23-4000ms in 9 increments) was used to determine the T_1 value for the Bloch equation simulations and Equation 1. Next, the high-resolution radial cardiac T_2 map was acquired N=64 consecutive times in order to study the SNR. A T_2 map was reconstructed from the first repetition only, and was compared to the SE T_2 map. The mean and standard deviation of each pixel were calculated over the N=64 images with TE_{T2prep}=0ms, and the per-pixel SNR was mapped as the ratio of this mean and standard deviation. The similarity of the pixel-wise standard deviation and SNR in various 'empty' regions of the image were assessed in regions of interest of 20×20 pixels.

To determine the effect of SNR on the accuracy of the T_2 maps, an analysis of the SNR of the images used to calculate the diastolic T_2 maps described above was performed in Matlab. The rationale here was that if lower SNR increases the apparent T_2 value of the myocardium (i.e. lowers the accuracy) in the SNR regimes encountered in vivo, a significant correlation should be found between the SNR and T_2 values of the myocardial segments. To this end, diastolic images

at mid-ventricle level were selected, and the SNR was approximated in the source images at TE_{T2prep}= 0 ms. The myocardium was again segmented according to AHA guidelines and the mean signal intensity of each segment was calculated. For the background noise, an ROI with a minimum area of 250 pixels was drawn in a part of a lung close to the heart where no anatomical structures were identified. The SNR was then approximated as the average signal in the myocardial segment divided by the standard deviation of the noise region (32). For every segment of the myocardium, a sample Pearson correlation coefficient r was calculated between the T_2 values and the SNR of all patients. This was repeated for all segments of all volunteers grouped together.

Effect of the off-resonance frequency on the accuracy of T_2 mapping

To evaluate the effect of off-resonance frequencies on the accuracy of T_2 mapping, eight healthy volunteers were scanned (age 29±4 years, weight 65±15 kg, 4 male, 4 female) using the above-described protocol for a slice at a mid-ventricular level. One T_2 map was acquired on-resonance and was used as a reference image in the study. T_2 maps were subsequently obtained with transmitter frequency offsets of -200 Hz, -100 Hz, -50 Hz, +50 Hz, +100 Hz, and +200 Hz. Image analysis was performed in Matlab using the same program as described above. Mean T_2 values along with their standard deviations were determined for all segments, at all frequency offsets. To determine the regional variation in accordance with off-resonance frequency, septal (segments 8 and 9) and lateral (segments 11 and 12) regions of the left ventricle were analyzed separately. The mean and standard error of the segmental T_2 values of all volunteers for each offset was calculated to determine the influence of off-resonance frequencies on T_2 mapping. Standard error was calculated instead of standard deviation, as the number of acquired maps per frequency offset varied, which is taken into account with the standard error (33). Paired two-

tailed Student's t-tests with Bonferroni correction were performed between the T_2 values of 0 Hz and each of the off-resonance T_2 maps in order to establish the statistically significant differences. For this t-test, $P \leq 0.05$ was considered significant. The observed T_2 values were furthermore compared to the Bloch equation simulations of off-resonance performance that were describe above.

Results

The choice of TE_{T2prep} values and the fitting precision

At a given T_2 value, all TE_{T2prep} series demonstrated the same trend for the tested SNR levels (Figure 1a). In addition to the standard deviation, SNR also affected the accuracy: the measured T_2 value tended to increase as SNR decreased (Figure 1b).The optimum TE_{T2prep} increment (i.e. the series with the lowest standard deviation) increased with the simulated T_2 value (Figure 1c). All simulated series of 3 TE_{T2prep} showed a higher standard deviation at very short and long increments, and an optimum between TE_{T2prep}=[0-25-50] ms for $T_{2=}$30ms and TE_{T2prep}=[0-45-90] ms for $T_{2=}$70ms (Figure 1c).

Comparison of the precision of T_2 maps in systole and diastole

Out of the 11 volunteers scanned, the implemented protocol was not completed in 2 subjects (i.e. apical slice not acquired) due to time constraints. The average heart rate was 58.8±10.2 bpm (range 40-75 bpm), while the acquisition duration per T_2 map was 4.5±0.6 min. All T_2 maps together yielded 162 segments in both diastole and systole, out of which 160 (98%) were eligible for analysis (Figure 2): in two volunteers, the apical inferior segments were excluded in both systole and diastole due to inadequate map quality. The similarly sharp endo- and epicardial

borders in both systole and diastole demonstrate that little motion blurring and partial volume effects occurred.

The mean myocardial T_2 value was 41.7±5.1 ms for diastole and 41.6±4.5 ms for systole (P=0.8). Similarly no difference between the individual slices in systole and diastole (Figure 3) were found, suggesting that there is no physiological difference between the T_2 values measured in systole and diastole, and that the pulse sequence and analysis chain is not likely affected by the choice of the quiescent cardiac phase. However, the precision of the T_2 maps was lower in diastole than in systole (i.e. the abovementioned segmental standard deviations of 5.1 ms and 4.5 ms, respectively; P=0.002). The average segmented wall thickness in the basal, mid-ventricular and apical myocardium in diastole was 3.6±1.3, 3.4±1.2 and 2.4±0.8 pixels, respectively, while it was 6.8±1.5, 5.9±1.5 and 6.0±1.2 pixels in systole ($P \leq 0.004$ between diastole and systole for all three slices).

Bland-Altman plots for intra-observer variability demonstrated that T_2 values measured in diastole had slightly larger differences (Figure 4a, b). The mean intra-observer difference for diastolic T_2 maps was -0.01 ms and the CI for diastole ranged from -1.89 to 1.87 ms, and the mean difference for systolic T_2 maps was 0.1 ms with the CI ranging from -1.5 ms to 1.6 ms. Albeit very small, there was a statistically significant difference between the spread of T_2 values in diastole and systole (P=0.05).

The Bland-Altman plots for inter-observer variability demonstrated nearly the same variation in diastole as in systole (Figure 4c,d). The mean inter-observer difference for diastole was 0.38 ms and the CI ranged from -2.05 ms to 2.8 ms, whereas for systole the mean difference was 0.35 ms and the CI was -2.1 ms to 2.8 ms. The difference in observation precision in diastole and systole

was not statistically significant (*P*=0.86). Observer differences were similarly not significantly different when analyzing only the apical or only the lateral segments (Supporting Figures S2 and S3).

Correlation of SNR and accuracy of T_2 maps

The phantom experiments (Figure 5) confirmed that the T_2 value obtained with the cardiac T_2 mapping sequence matched the spin-echo T_2 reference (T_2=34.4±1.0 ms and 34.2±0.3 ms, respectively). The noise bias (i.e. the apparent SNR outside the phantom over N=64 repeated acquisitions) caused by the coil combination was homogenous at 10.4±1.0 in all regions empty of signal. Similarly, the standard deviation of the signal varied with a maximum of 1.3% between the tested regions of interest, indicating that SNR measurements would only very mildly depend on the chosen region of interest for the noise measurement. The SNR in the muscle compartment of the phantom ranged from 71 to 162, which agrees with the standard deviation and T_2 value as simulated at these SNR levels in Figure 1b.

Segmental analysis of the volunteer source images of the above-mentioned diastolic mid-ventricular T_2 maps indicated that the SNR in the source images with TE_{T2prep}=0 ms ranged from 47 to 205 for all the six segments. The segmental analysis (30) demonstrated that in several volunteers, higher individual T_2 values were observed in the inferior segments (AHA segments 9, 10, and 11). However, the higher T_2 values in these segments were observed both at lower and higher SNR, and there were no significant correlations between segmental SNR and T_2 (all *P*>0.1). The correlation between the SNR and T_2 values for all combined segments was furthermore also not significant (r = 0.14, *P*=0.2).

Effect of frequency offsets on the accuracy of T_2 maps

T_2-prepared GRE T_2 maps were obtained successfully in all eight volunteers. However, due to time constraints, maps could not be acquired at all frequency offsets in all subjects. One volunteer was excluded from statistical analysis due to persistent shimming problems in the on-resonance images.

Qualitative image analysis of the T_2 maps of the volunteers directly revealed that the frequency of the RF pulses has a significant effect on the accuracy of the T_2 maps (Figure 6). There was a clearly visible link between segmental T_2 values and off-resonance, with higher T_2 values for increasing off-resonance frequency. In addition, the individual segments of the myocardium behaved differently within a given volunteer for the various frequency offsets.

Cumulative analysis of all the volunteers for the on-resonance and off-resonance images indicated that the septal and lateral regions of myocardium behave differently as a function of the effect of frequency offsets, although there was a considerable amount of inter-subject variation. The on-resonance mean T_2 value for the septal segments was 40±1.44 ms, whereas for the lateral segments, the mean T_2 value was 39±1.47 ms (Figure 7). At the frequency offset of +50 Hz and -50 Hz, the septal segments showed minimal change in the T_2 values, while in the lateral segments the T_2 values and standard error were considerably higher, in part due to an outlier. For both regions, the T_2 values with the offset of +100Hz were higher than those acquired on-resonance. Significant T_2 increases were observed in both regions for the offsets of -200 Hz and +200 Hz (P<0.001). The observed T_2 values at off-resonance frequencies were furthermore consistent with the Bloch equation simulations (Figure 7, dotted line).

Discussion

Cardiac T_2 mapping has recently gained increasing popularity for the quantitative evaluation of myocardial edema. Investigating the accuracy and precision of radial high-resolution T_2 mapping is thus essential for the establishment of the robustness of this technique, as well as for its further acceptance in clinical practice for the characterization of edema in diseases such as myocardial infarction (34), graft rejection (35), and myocarditis (36).

Numerical simulations suggest there exists an optimal T_2prep series

For the simulated parameter set and relaxation times, the standard deviation of the three-value TE_{T2prep} series was the highest when the TE_{T2prep} values are small or large relative to the T_2 relaxation time of interest. A likely cause for this phenomenon is that there is an optimal balance between observing sufficient T_2 decay between the different TE_{T2prep} on the one hand , and the TE_{T2prep} being too dominated by noise on the other hand. Both the higher and lower simulated SNR regimes demonstrated this dependence on the TE_{T2prep} increment. The optimal TE_{T2prep} furthermore depended on the T_2 value itself: for the range of T_2=35-65 ms that is encountered in human volunteer and patient myocardium at 3T, the optimal TE_{T2prep} increment was roughly 0.75 times the T_2 value of interest. Note that physical limitations such as artifacts due to increased susceptibility at longer TE_{T2prep} are not taken into account in these simulations.

Akçakaya et al. (37) recently demonstrated that Cartesian cardiac T_2 mapping at 1.5T in combination with a +90°/-90° pulse combination as TE_{T2prep}=0 ms, a saturation pulse as TE_{T2prep} =∞ ms and a three-parameter fit (i.e. also fitting δ in Eq. 1) allows for a more accurate T_2 estimation, if all three of these changes are applied simultaneously. However, at 3T the +90°/-90° pulse combination with standard rectangular or sinc pulses (as used in the T_2prep) may lead

to significant artifacts due to magnetic field inhomogeneities, and a straightforward translation to higher field strength is therefore not easily obtained.

Radial systolic T_2 mapping is at least as precise as diastolic T_2 mapping

The comparison of T_2 mapping in diastole and systole suggests that the precision is higher in systole, while their inter-observer variability is similar and the intra-observer variability is lower in systole. The most likely explanation includes that despite the shorter time window without cardiac motion, systolic images offer a larger myocardial area due to myocardial contraction, which results in a larger myocardial pixel sample size, which in turn facilitates the manual selection of contours that exclude regions with partial volume effects near the endo- and epicardial borders. Especially in the apical region, where the myocardium is no longer perpendicular to the image plane and where there is a larger degree of motion, a smaller amount of myocardium without partial-volume effects is available. The papillary muscles are furthermore compacted to the degree that their in- or exclusion is no longer a problem. The end-systolic window position and duration are also less susceptible to heart rate variations than the mid-diastolic window. Moreover, the wall of the right ventricle is more appreciable in systole as compared to diastole, and thus systolic radial T_2 mapping could be more readily applied to study the right ventricular myocardium as well.

These findings remain to be confirmed in patients, who might have shorter or less reproducible systolic rest periods and more heterogeneity in terms of the T_2 values of the myocardium.

In a recent study by Tessa et al. (38), breath-held T_2 mapping with a Cartesian bSSFP readout and voxel size of 2.0×2.2x6 mm^3 was applied at 1.5 T in diastole in systole, and it was concluded that systolic T_2 mapping does not cause an increase in artifacts, and increases the number of

evaluable segments in the heart. An elevation of the apical T_2 values was observed in volunteers and patients when using diastolic T_2 mapping, but this elevation was not found when using systolic T_2 mapping. This elevation in the apical T_2 values was not found in our study, which might be explained by the use of T_2 mapping with a high-resolution (over 3 times smaller voxels) and a motion-robust radial readout (at the cost of a significant increase in scan time), and thus more available voxels without partial volume effects.

The SNR of the in vivo images is sufficiently high to avoid T_2 overestimation

The numerical simulations demonstrated that as SNR gets lower, T_2 is overestimated, most likely due to the Rician nature of the noise and the root-sum-of-squares combination of the coil elements (23). Feng et al. (39) recently demonstrated that a fixed offset fitting model causes significant T_2* overestimation at low SNR in the liver with Cartesian multi-gradient-echo T_2* mapping, although only significantly for very short T_2* values (T_2*<5 ms).

However, as long as SNR is 50 or greater, this overestimation is 2ms or smaller. In the in vivo SNR measurements in the images of the healthy volunteers, the SNR was found to be higher than 50 in all but one analyzed segment. Given that there is no further correlation between the segmental T_2 values and their SNR, and that the standard deviations in the segments are on the order of 3-5 ms, it appears likely that the in vivo T_2 value is not overestimated due to insufficient SNR for the used parameter set. It should be noted that even though the phantom experiments demonstrated that there is no regional dependence of the noise level or bias in the image, single-image SNR measurements obtained from images acquired with multi-element coils should be considered as an approximation only.

Off-resonance regions cause significant T_2 mapping artifacts

Off-resonance frequencies are among the challenges at higher field strengths due to B_0 inhomogeneities in the region of the heart. Since this effect appears as an artifactual myocardial T_2 increase that can be interpreted as edema, it is important to explore this effect and to propose a solution to minimize it. A study on Modified Look-Locker Inversion Recovery (MOLLI) T_1 mapping demonstrated that after cardiac shimming, the mean off-resonance frequency at 3.0 T is 15.4±29.3 Hz (19). In the same study, off-resonance greater than 80 Hz was observed in 4 of 18 subjects at 1.5T, which resulted in more significant T_1 estimation errors that could erroneously be interpreted as subtle regional variation of T_1.

In our study, it was noted that the septal and lateral regions of the myocardium that were studied for off-resonance effects demonstrated different behavior in each subject, although averaged over all volunteers, the effects were similar for both regions and were consistent with the Bloch equation simulations. The anatomical location of the myocardium that was imaged thus also plays a role in off-resonance frequency effects due to the local magnetic field inhomogeneities, which in turn occur due to magnetic susceptibility differences at tissue-air interfaces such as the heart-lung interface (40). Since AHA segment 11 and 12 are adjacent to the lungs, this most likely explains why there was more variation in the T_2 values for all the investigated frequency offsets in these segments (Figure 7b).

An interesting observation was made in the T_2 maps of the volunteer who was excluded from the statistical analysis: the positive changes in the frequency offset locally improved the T_2 values. The mean T_2 value in the mid-septal region (segments 8, 9) was 56.6±3.4 ms on the on-resonance T_2 map, whereas in the images with an offset of +50 Hz and +100 Hz, the mean T_2 value decreased to 52±0.7 ms and 49±5.6 ms, respectively (Figure 8). A possible explanation for

this improvement is that the images acquired on-resonance were already experiencing local off-resonance effects due to inferior shimming, and changing the frequency decreased this off-resonance effect.

Limitations

The main concern in high-resolution T_2 mapping is the prolonged acquisition time, which governs the choice of only three data points for T_2 mapping. Naturally, this may affect the accuracy and precision of the T_2 maps. To take full advantage of the benefits that come with a higher number of well-selected TE_{T2prep} while maintaining the spatial resolution, scan time shortening is mandatory. Therefore, novel image acceleration techniques such as compressed sensing (41) or k-space-weighted image contrast (KWIC) filtering (42) remain to be explored in this context. These experiments were furthermore performed with a conventional adiabatic T_2-Prep sequence (21). Recently, T_2prep modules have been developed that improve fat signal suppression (26) and permit outer volume suppression (43), both of which might improve radial image quality. Additionally, the general findings in the healthy volunteers should also be confirmed in cohorts of patients with a specific pathology to more specifically validate our findings. It should also be noted that, besides the pulse sequence parameters, there also is a minor dependence of the T_2 fitting on the T_1 relaxation time through the δ parameter of Equation 1 (7,10).

Conclusions

We investigated the accuracy and precision of radial high-resolution cardiac T_2 mapping as a function of several potential confounding factors using numerical simulations and imaging in healthy volunteers at 3T. Monte Carlo simulations demonstrated that the linear increment between the individual TE_{T2prep} has an influence on the precision, and that aTE_{T2prep} increment of 0.75 times the T_2 value of interest is recommended when 3 TE_{T2prep} are used.

The volunteer studies demonstrated that systolic T_2 mapping is at least as precise as diastolic T_2 mapping, and that there is no statistically significant difference between the T_2 values measured in either quiescent cardiac phase. There was no correlation between the segmental SNR levels and the T_2 values in healthy volunteers, which indicates that the SNR was always sufficient to avoid T_2 overestimation. Furthermore, frequency offsets larger than ±100 Hz have a large and detrimental effect on the accuracy of T_2 maps, and adequate shimming is mandatory for optimal performance.

It is of significant interest that all the above-mentioned confounders only cause apparent increases in T_2, and never apparent decreases. This means that these confounders can only lead to false positive errors, which decrease specificity, but not sensitivity.

In summary, the above findings will help better guide protocol definition and help justify sample sizes of studies that include T_2 mapping.

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References

1. Friedrich MG. Myocardial edema--a new clinical entity? Nat Rev Cardiol 2010;7(5):292-296.
2. Abdel-Aty H, Simonetti O, Friedrich MG. T2-weighted cardiovascular magnetic resonance imaging. J Magn Reson Imaging 2007;26(3):452-459.
3. Friedrich MG, Abdel-Aty H, Taylor A, Schulz-Menger J, Messroghli D, Dietz R. The salvaged area at risk in reperfused acute myocardial infarction as visualized by cardiovascular magnetic resonance. J Am Coll Cardiol 2008;51(16):1581-1587.
4. Abdel-Aty H, Schulz-Menger J. Cardiovascular magnetic resonance T2-weighted imaging of myocardial edema in acute myocardial infarction. Recent patents on cardiovascular drug discovery 2007;2(1):63-68.
5. Blume U, Lockie T, Stehning C, Sinclair S, Uribe S, Razavi R, Schaeffter T. Interleaved T(1) and T(2) relaxation time mapping for cardiac applications. J Magn Reson Imaging 2009;29(2):480-487.
6. Finn JP, Nael K, Deshpande V, Ratib O, Laub G. Cardiac MR imaging: state of the technology. Radiology 2006;241(2):338-354.
7. van Heeswijk RB, Feliciano H, Bongard C, Bonanno G, Coppo S, Lauriers N, Locca D, Schwitter J, Stuber M. Free-breathing 3 T magnetic resonance T(2)-mapping of the heart. JACC Cardiovasc Imaging 2012;5(12):1231-1239.
8. Foltz WD, Al-Kwifi O, Sussman MS, Stainsby JA, Wright GA. Optimized spiral imaging for measurement of myocardial T2 relaxation. Magn Reson Med 2003;49(6):1089-1097.

9. Giri S, Chung YC, Merchant A, Mihai G, Rajagopalan S, Raman SV, Simonetti OP. T2 quantification for improved detection of myocardial edema. J Cardiovasc Magn Reson 2009;11:56.

10. van Heeswijk RB, Piccini D, Feliciano H, Hullin R, Schwitter J, Stuber M. Self-navigated isotropic three-dimensional cardiac T2 mapping. Magn Reson Med 2015;73(4):1549-1554.

11. van Heeswijk RB, Vincenti G, Monney P, Kourda J, Rotman S, Stuber M, Schwitter J, Hullin R. Free-breathing T2 mapping at 3T for the monitoring of cardiac allograft rejection: initial results. J Cardiovasc Magn Reson 2014;16(Suppl 1):M11.

12. Huang TY, Liu YJ, Stemmer A, Poncelet BP. T2 measurement of the human myocardium using a T2-prepared transient-state TrueFISP sequence. Magn Reson Med 2007;57(5):960-966.

13. Verhaert D, Thavendiranathan P, Giri S, Mihai G, Rajagopalan S, Simonetti OP, Raman SV. Direct T2 quantification of myocardial edema in acute ischemic injury. JACC Cardiovasc Imaging 2011;4(3):269-278.

14. Wassmuth R, Prothmann M, Utz W, Dieringer M, von Knobelsdorff-Brenkenhoff F, Greiser A, Schulz-Menger J. Variability and homogeneity of cardiovascular magnetic resonance myocardial T2-mapping in volunteers compared to patients with edema. J Cardiovasc Magn Reson 2013;15:27.

15. Zia MI, Ghugre NR, Connelly KA, Strauss BH, Sparkes JD, Dick AJ, Wright GA. Characterizing myocardial edema and hemorrhage using quantitative T2 and T2* mapping at multiple time intervals post ST-segment elevation myocardial infarction. Circ Cardiovasc Imaging 2012;5(5):566-572.

16. von Knobelsdorff-Brenkenhoff F, Prothmann M, Dieringer MA, Wassmuth R, Greiser A, Schwenke C, Niendorf T, Schulz-Menger J. Myocardial T1 and T2 mapping at 3 T: reference values, influencing factors and implications. J Cardiovasc Magn Reson 2013;15(1):53.
17. Bönner F, Janzarik N, Jacoby C, Spieker M, Schnackenburg B, Range F, Butzbach B, Haberkorn S, Westenfeld R, Neizel-Wittke M, Flogel U, Kelm M. Myocardial T2 mapping reveals age- and sex-related differences in volunteers. J Cardiovasc Magn Reson 2015;17(1):9.
18. MacFall JR, Riederer SJ, Wang HZ. An analysis of noise propagation in computed T2, pseudodensity, and synthetic spin-echo images. Med Phys 1986;13(3):285-292.
19. Kellman P, Herzka DA, Arai AE, Hansen MS. Influence of Off-resonance in myocardial T1-mapping using SSFP based MOLLI method. J Cardiovasc Magn Reson 2013;15:63.
20. Bloch F. Nuclear Induction. Phys Rev 1946;70(7-8):460-474.
21. Nezafat R, Stuber M, Ouwerkerk R, Gharib AM, Desai MY, Pettigrew RI. B1-insensitive T2 preparation for improved coronary magnetic resonance angiography at 3 T. Magn Reson Med 2006;55(4):858-864.
22. Hwang TL, van Zijl PC, Garwood M. Fast broadband inversion by adiabatic pulses. J Magn Reson 1998;133(1):200-203.
23. Sandino CM, Kellman P, Arai AE, Hansen MS, Xue H. Myocardial T2* mapping: influence of noise on accuracy and precision. J Cardiovasc Magn Reson 2015;17(1):7.
24. Landau DP, Binder K. A guide to Monte-Carlo simulations in statistical physics. Cambridge: Cambridge University Press; 2009.
25. Rice SO. Mathematical Analysis of Random Noise. Bell Sys Tech J 1945;24(1):46-156.

26. Coristine AJ, van Heeswijk RB, Stuber M. Fat signal suppression for coronary MRA at 3T using a water-selective adiabatic T2 -preparation technique. Magn Reson Med 2014;72(3):763-769.

27. Schar M, Vonken EJ, Stuber M. Simultaneous B(0)- and B(1)+-map acquisition for fast localized shim, frequency, and RF power determination in the heart at 3 T. Magn Reson Med 2010;63(2):419-426.

28. Wang Y, Vidan E, Bergman GW. Cardiac motion of coronary arteries: variability in the rest period and implications for coronary MR angiography. Radiology 1999;213(3):751-758.

29. Giri S, Shah S, Xue H, Chung Y-C, Pennell ML, Guehring J, Zuehlsdorff S, Raman SV, Simonetti OP. Myocardial T2 mapping with respiratory navigator and automatic nonrigid motion correction. Magn Reson Med 2012.

30. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. Circulation 2002;105(4):539-542.

31. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1(8476):307-310.

32. Dietrich O, Raya JG, Reeder SB, Reiser MF, Schoenberg SO. Measurement of signal-to-noise ratios in MR images: influence of multichannel coils, parallel imaging, and reconstruction filters. J Magn Reson Imaging 2007;26(2):375-385.

33. Altman DG, Bland JM. Standard deviations and standard errors. Bmj 2005;331(7521):903.

34. Hammer-Hansen S, Ugander M, Hsu LY, Taylor J, Thune JJ, Kober L, Kellman P, Arai AE. Distinction of salvaged and infarcted myocardium within the ischaemic area-at-risk with T2 mapping. European heart journal cardiovascular Imaging 2014;15(9):1048-1053.

35. Usman AA, Taimen K, Wasielewski M, McDonald J, Shah S, Giri S, Cotts W, McGee E, Gordon R, Collins JD, Markl M, Carr JC. Cardiac magnetic resonance T2 mapping in the monitoring and follow-up of acute cardiac transplant rejection: a pilot study. Circ Cardiovasc Imaging 2012;5(6):782-790.

36. Thavendiranathan P, Walls M, Giri S, Verhaert D, Rajagopalan S, Moore S, Simonetti OP, Raman SV. Improved detection of myocardial involvement in acute inflammatory cardiomyopathies using t2 mapping. Circ Cardiovasc Imaging 2012;5(1):102-110.

37. Akcakaya M, Basha TA, Weingartner S, Roujol S, Berg S, Nezafat R. Improved quantitative myocardial T2 mapping: Impact of the fitting model. Magn Reson Med 2014.

38. Tessa C, Diciotti S, Landini N, Lilli A, Del Meglio J, Salvatori L, Giannelli M, Greiser A, Vignali C, Casolo G. Myocardial T1 and T2 mapping in diastolic and systolic phase. Int J Cardiovasc Imaging 2015;31(5):1001-1010.

39. Feng Y, He T, Gatehouse PD, Li X, Harith Alam M, Pennell DJ, Chen W, Firmin DN. Improved MRI R2 * relaxometry of iron-loaded liver with noise correction. Magn Reson Med 2013;70(6):1765-1774.

40. Atalay MK, Poncelet BP, Kantor HL, Brady TJ, Weisskoff RM. Cardiac susceptibility artifacts arising from the heart-lung interface. Magn Reson Med 2001;45(2):341-345.

41. Huang C, Graff CG, Clarkson EW, Bilgin A, Altbach MI. T2 mapping from highly undersampled data by reconstruction of principal component coefficient maps using compressed sensing. Magn Reson Med 2012;67(5):1355-1366.

42. Song HK, Dougherty L. k-space weighted image contrast (KWIC) for contrast manipulation in projection reconstruction MRI. Magn Reson Med 2000;44(6):825-832.

43. Coristine AJ, van Heeswijk RB, Stuber M. Combined T2 -preparation and two-dimensional pencil-beam inner volume selection. Magn Reson Med 2015;74(2):529-536.

Figure legends

Figure 1: Results of the Bloch equation simulations for various SNR levels and T_2 values. (a) Scatter plot of the T_2 standard deviation of the simulated TE_{T2prep} series for an average SNR of 30, 50, 100, and 200 at T_2 = 45 ms. Besides the SNR level itself, the choice of TE_{T2prep} series also has an effect on the fitting precision, with the middle TE_{T2prep} series exhibiting the lowest standard deviation. (b) The effect of SNR on the fitted T_2 values themselves for the TE_{T2prep} series [0-30-60] ms. The error bar representing the standard deviations, while the red dashed line represents the simulation input T_2 value of 45ms. As the SNR decreases, the fitted T_2 values increase concommitantly with their standard deviation, resulting in both less accurate and less precise T_2 maps. (c) The influence of the input T_2 value on the resulting T_2 standard deviation as a function of the choice of TE_{T2prep} series. As the input T_2 value becomes higher, the optimal TE_{T2prep} series also becomes longer.

Figure 2: T_2 maps of an example volunteer at the left-ventricular base, equatorial level, and apex in diastole (upper row) and systole (lower row). (a,b) The T_2 maps demonstrate a homogeneous myocardium, which appears thicker in systolic than in diastolic images. The wall of the right ventricle is also more distinct in systole (white arrows) due to an increased thickness in this phase. (c,d) Contours are added that indicate the segmented myocardium. A larger margin between the contour and the start of the epicardial wall can be observed in systole. (e,f) In the apical diastolic image, there is a region with elevated T_2 on the lateral side, which is not present in the systolic image (black arrow). The line in the map indicates where the T_2 profiles are generated. (g,h) T_2 profiles through the apical T_2 map. Vertical lines indicate the border of the

segmented myocardium, which is significantly wider in the systolic profile. The color bar indicates T_2 values in ms.

Figure 3. T_2 relaxation time measured at different anatomical levels of the heart in diastole and systole. There were no significant differences in average T_2 value between diastole and systole in any slice, although a small trend to lower apical T_2 values can be observed in systole. Similarly, there was no significant difference between any two slices, although there was a trend (P=0.06 and P=0.07 with a repeated measures ANOVA with Tukey's multiple comparison test) for differences between the base and mid-ventricle.

Figure 4: Bland-Altman plots of the intra- and inter-observer variability in diastole (a) and (c) and systole (b) and (d). The central red line represents the mean difference of the observations, whereas the black dashed lines represent the CI. (a) and (b): the difference between two observations is more spread around the mean difference, with diastole demonstrating a higher CI as compared to systole. (c) and (d): It can be observed that the diastolic segments have a larger overall spread, whereas the systolic segments have more outliers. However, the CI for diastole and systole are very similar.

Figure 5. T_2 mapping and SNR measurements in a phantom. The phantom has an outer diameter of ~10 cm and consists of three concentric compartments that approximate the relaxation times of muscle, fat, and blood. a) Spin-echo T_2 map that serves as a gold-standard control. b) High-resolution radial T_2-prepared GRE T_2 map with TE_{T2prep}=[0-30-60] ms from a single average. The T_2 value in the muscle compartment exactly matches that of the SE experiment, but the T_2 in the fat compartment is inaccurate, most likely due to the much shorter relaxation time. c) The

mean signal per pixel in the TE_{T2prep}=0 ms image over N=64 repeated acquisitions. Minor radial streaking artifacts can be observed outside the phantom. d) The per-pixel standard deviation of the signal over the N=64 repeated acquisitions. There is a consistent elevation of the standard deviation on the edges of the compartments in the superior-inferior direction, which is most likely caused by the small gradient vibrations during the acquisitions. e) The per-pixel SNR of the N=64 acquisitions, calculated as the per-pixel mean signal divided by the per-pixel standard deviation of the signal. There is a significant offset due to the root-sum-of-square combination of 32 elements of the array coil. f) The same SNR as in e), but scaled to show the SNR in the phantom itself.

Figure 6: Mid-ventricular T_2 maps acquired on-resonance and off-resonance in two different volunteers. The offset frequencies affect the myocardium differently in the various segments, and this effect is increased at higher offsets. The color bar (in ms) applies to all maps.

Figure 7: Scatter plots of the frequency offsets and mean T_2 values in the healthy volunteers for segment 8 & 9(a) and segment 11 & 12 (b). The error bars represent the standard error, while the dashed lines indicate the results of the Bloch equation simulations. The T_2 values with the offset frequency of 0 Hz for both the regions are not statistically different (P=0.5) and the general behavior with an increased frequency offset is similar. However, the spread of T_2 values between the volunteers was significantly larger in the lateral segments, as evidenced by the larger standard error. (a) For septal regions, there was no statistically significant difference between the on resonance T_2 values and frequency offsets of ±50 Hz (P=0.7 & 0.6) and for the offset of +100

Hz(P=0.1). For the offset of ±200 Hz, there was an elevation in the T_2 values which reached statistical significance (P<0.001 and 0.007 for -200 Hz and +200 Hz, respectively). (b) For the lateral region, there was no statistically significant difference between on- and off-resonance T_2 values for both ±50 Hz (P=0.5) and ±100 Hz (P=0.1). There was a considerable increase in T_2 values for the offset ±200 Hz (P=0.007 and 0.02 for -200 Hz and +200 Hz, respectively).

Figure 8: T_2 maps of the healthy volunteer in which the on-resonance T_2 mapping failed. (a) The on-resonance T_2 map exhibits a noisy area with high T_2 values (arrow) in the septal region of the left ventricle. (b) A +50 Hz off-resonance T_2 map of the same volunteer demonstrates that the same area (arrow) has lower T_2 values, while at +100 Hz off-resonance (c) the map shows a further T_2 decrease in the same region (arrow).

Supporting Figure S1. Bloch equation simulations of the dependence of the T_2 fit on the local T_1 relaxation time. It can be observed that as T_1 increases (as it does in for example edematous tissue), the fitted T_2 slightly decreases, thus causing a slight underestimation of the concomitant T_2 increase. Given that in the case of a ~30% T_1 increase as can occur in myocardial infarction, T_2 increases by ~55% (Bulluck et al., JCMR 2015), this concomitant 4% underestimation appears to be small.

Supporting Figure S2. Observer variability in the apical segments only. a-b) The intra-observer variability for diastole and systole demonstrated no significant difference (P=0.56). c-d) The inter-observer variability had a larger CI in the diastolic than in the systolic T_2 maps: -2.5 to 3.08 ms and -2.1 to 2.2 ms, respectively. However, this difference was also not statistically significant at P=0.21.

Supporting Figure S3. Observer variability in the lateral segments only. a-b) The intra-observer variability for diastolic T_2 mapping appears to be slightly higher than that in systole with the CI from -1.7 ms to 1.8 ms and -1.1 ms to 1.6 ms, respectively. However, these differences were not significant (P=0.31). c-d) The same trend could be observed for inter-observer variability, where the diastolic T_2 mapping had a slightly larger CI than the systolic T_2 mapping: -2.2 ms to 2.8 ms and 1.7 ms to 2.8 ms, respectively. However, this difference was again not statistically significant at P=0.53.