

Reproducibility of Myocardial T_1 and T_2 Relaxation Time Measurement Using Slice-Interleaved T_1 and T_2 Mapping Sequences

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Purpose: To assess measurement reproducibility and image quality of myocardial T_1 and T_2 maps using free-breathing slice-interleaved T_1 and T_2 mapping sequences at 1.5 Tesla (T).

Materials and Methods: Eleven healthy subjects (33 ± 16 years; 6 males) underwent a slice-interleaved T_1 and T_2 mapping test/retest cardiac MR study at 1.5T on 2 days. For each day, subjects were imaged in two sessions with removal out of the magnet and repositioning before the subsequent session. We studied measurement reproducibility as well as the required sample size for sufficient statistical power to detect a predefined change in T_1 and T_2 . In a separate prospective study, we assessed T_1 and T_2 map image quality in 241 patients (54 ± 15 years; 73 women) with known/suspected cardiovascular disease referred for clinical cardiac MR. A subjective quality score was used to assess a segment-based image quality.

Results: In the healthy cohort, the slice-interleaved T_1 measurements were highly reproducible, with global coefficients of variation (CVs) of 2.4% between subjects, 2.1% between days, and 1.7% between sessions. Slice-interleaved T_2 mapping sequences provided similar reproducibility with global CVs of 7.2% between subjects, 6.3% between days, and 5.0% between sessions. A lower variability resulted in a reduction of the required number of subjects to achieve a certain statistical power when compared with other T_1 mapping sequences. In the subjective image quality assessment, >80% of myocardial segments had interpretable data.

Conclusion: Slice-interleaved T_1 and T_2 mapping sequences yield highly reproducible T_1 and T_2 measurements with >80% of interpretable myocardial segments.

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Myocardial interstitial diffuse fibrosis, inflammation, and edema are present in many diseases such as cardiomyopathy,¹ hypertension,² aortic regurgitation,³ and myocarditis.⁴ Therefore, noninvasive assessment of myocardial tissue composition of fibrosis, edema, and inflammation may have an important clinical impact in diagnosis, prognosis, and monitoring of therapy. Myocardial tissue relaxometry has been emerging as a clinically powerful tool to characterize myocardial tissue composition.⁵ Myocardial T_1 relaxation time changes in the presence of interstitial diffuse

fibrosis and can be assessed using native T_1 and extracellular volume (ECV) mapping.^{6,7} Changes in myocardial T_2 relaxation time in the presence of edema and inflammation can also be quantitatively measured using myocardial T_2 mapping.^{4,8,9}

Over the past decade, there have been numerous advances in cardiac MR sequences for myocardial T_1 and T_2 mapping.^{10–23} T_1 mapping sequences sample the magnetization recovery curve to enable estimation of T_1 recovery by voxel-wise curve fitting. The modified Look-Locker

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inversion recovery (MOLLI)¹³ and shortened MOLLI (ShMOLLI)¹⁴ sequences are widely used for myocardial T_1 mapping. Saturation recovery based sequences, such as modified Look-Locker acquisition using saturation recovery,¹⁵ SATuration recovery single-SHot Acquisition (SASHA),¹⁶ and saturation method using adaptive recovery times for cardiac T_1 mapping (SMART₁Map) sequence,¹⁷ have also been investigated. These sequences allow more accurate T_1 measurements, however, with a penalty in precision and reproducibility.¹⁸

A combination saturation and inversion recovery based sequence, i.e., saturation pulse prepared heart rate independent inversion recovery (SAPPHIRE)¹⁹ sequence has also been investigated. A free-breathing slice-interleaved T_1 mapping sequence (STONE)²⁰ has been recently proposed that enables T_1 measurements of five short-axis slices over the entire left ventricle in a free-breathing 95 second scan. This sequence is based on interleaving data acquisition for different slices during the recovery time of adjacent slices. A longer recovery of spins for each individual slice results in improved accuracy and precision.²⁰

Myocardial T_2 mapping is often performed by acquiring multiple T_2 prepared (T_2 prep) balanced steady-state free-precession images, each followed by rest periods of magnetization recovery, and estimating the voxel-wise T_2 values.²¹ This is often performed with one breathhold for each slice. Three-dimensional (3D) myocardial T_2 mapping is an alternative to 2D T_2 mapping so as to improve spatial resolution and coverage of myocardial T_2 mapping.²² A slice-interleaved T_2 mapping sequence was recently developed by implementing a slice-selective T_2 Prep to interleave the data acquisition for different slices in subsequent heartbeats.²³ This free-breathing slice-interleaved T_2 mapping sequence allows T_2 measurements of five parallel left ventricular (LV) short-axis slices with similar precision as a single-slice T_2 mapping sequence, but with a fourfold reduction in acquisition time.²³

In recent years, there has been interest in applying regional myocardial T_1 and T_2 mapping as imaging markers of disease progression or response to a specific therapy/intervention. Knowledge of measurement reproducibility is important to distinguish between changes that could be attributable to measurement variability and those that are the result of disease progression or therapeutic intervention. Furthermore, to justify the sample size for the achievement of a specific statistical power, the reproducibility of these measurements needs to be known. Finally, image quality assessment should be performed to take into account the percentage of nondiagnostic images acquired with these sequences. To address these challenges, we sought to: (1) investigate reproducibility of recently developed free-breathing slice-interleaved T_1 and T_2 mapping sequences in a cohort of healthy adult subjects by performing a

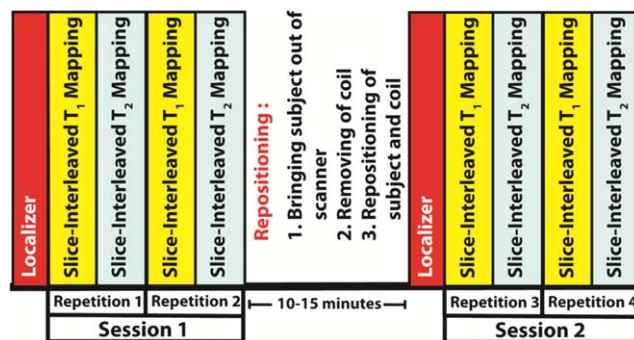


FIGURE 1: Study protocol: Healthy subjects ($n = 11$) underwent MR imaging to assess acquisition reproducibility between days, sessions, and repetitions. The study protocol was identical in both days. Each sequence was repeated twice per session. Between two different sessions, subjects were taken out of the scanner, and the 32-channel phased array coil was repositioned before starting the next session.

comprehensive test/re-test study; (2) investigate the required sample size to achieve certain statistical power for detection of a predefined change in native T_1 or T_2 ; and (3) assess overall T_1 and T_2 map image quality using the slice-interleaved T_1 and T_2 mapping sequences in patients with known or suspected cardiovascular disease referred for clinical cardiac MR.

Materials and Methods

All imaging was performed on a 1.5T Philips Achieva (Philips Healthcare, Best, The Netherlands) MRI system using a 32-channel cardiac coil. The study was Health Insurance Portability and Accountability Act (HIPAA) compliant. The imaging protocol was approved by our institutional review board and written informed consent was obtained from each participant prior to scanning.

Reproducibility Assessment

In a prospective study, we recruited 11 healthy adult subjects (33 ± 16 years; 6 men) without contraindications for cardiac MR to participate in a 2-day test/retest study using an imaging protocol shown in Figure 1. Each subject underwent cardiac MR imaging on two different days (between-day reproducibility) with the identical imaging protocol. After image localization, the subjects were imaged using slice-interleaved T_1 and T_2 mapping sequences in five left ventricular short-axis view slices over the entire ventricle (from apex to base). Each sequence was repeated twice (within-session reproducibility). Following completion of the first imaging session, subjects were taken out of the scanner for a 10- to 15-min break with removal of the coil. Subsequently, subjects were scanned again, after image localization, for a second session (between-session reproducibility) with two repetitions per sequence.

T_1 mapping was performed using slice-interleaved T_1 mapping sequence with the following parameters: five short-axis slices, in-plane resolution = 2.1×2.1 mm², slice thickness = 8 mm, slice gap = 4 mm, field-of-view = 320×320 mm², repetition time/echo time/alpha (TR/TE/ α) = 2.8 ms / 1.38 ms / 70°, SENSE-rate = 2, linear ordering, 10 linear ramp-up pulses and acquisition window = 218.8 ms, bandwidth = 1879.7 Hz/pixel.

T₂ mapping was performed using slice-interleaved T₂ mapping sequence with the following parameters: five short-axis slices, in-plane resolution = 2.1 × 2.1 mm², slice thickness = 8 mm, slice gap = 4 mm, field-of-view = 320 × 320 mm², TR/TE/α = 2.8 ms / 1.38 ms / 55°, SENSE-rate = 2.3, linear ordering, 10 linear ramp-up pulses and acquisition window = 191.1 ms, bandwidth = 1879 Hz/pixel. Images for both T₁ and T₂ mapping were acquired during free-breathing with slice tracking. A two-dimensional pencil beam navigator was positioned at the dome of the right hemidiaphragm to monitor the diaphragmatic motion and to correct the slice position during imaging. Slice tracking was used without any respiratory gating.

Impacts on Sample Size Calculation

Using T₁ and T₂ measurements from our healthy subject cohort, we performed statistical analyses to determine the number of subjects that are needed to achieve a certain power for detection of specific changes in T₁ and T₂. For sample size assessment, we compared the results of slice-interleaved T₁ with T₁ measured using MOLLI and ShMOLLI. As we did not directly acquire data using MOLLI or ShMOLLI, this variability was extracted from a previously published study.¹⁸ Correspondingly, we compared the results of slice-interleaved T₂ with T₂ measured by using single-slice T₂ mapping sequence. The data for the single-slice T₂ sequence were acquired in the same sessions as the slice-interleaved sequences with our 11 healthy subjects using the identical study design. The sequence was performed by using the following parameters: five short-axis slices, in-plane resolution = 2.1 × 2.1 mm², slice thickness = 8 mm, slice gap = 4 mm, field-of-view = 320 × 320 mm², TR/TE/α = 2.9 ms / 1.43 ms / 55°, SENSE-rate = 2.3, linear ordering, 10 linear ramp-up pulses and acquisition window = 197.3 ms, bandwidth = 1879 Hz/pixel. T₁ and T₂ measurements from the mid-LV slice were used for all calculations in the sample size analysis.

Image Quality Assessment

For patient image quality assessment, we prospectively enrolled 246 patients (54 ± 15 years; 73 women) with known or suspected cardiovascular disease referred for a clinical cardiac MR exam over a period of 15 months. The imaging protocol was approved by our institutional review board and written informed consent was obtained from each participant before each examination for the addition of T₁ and T₂ mapping sequences to their standard clinical exam. Slice-interleaved T₁ and T₂ mapping sequences were acquired in addition to their clinically indicated imaging protocol. Imaging parameters were similar to the healthy subject study. The slice-interleaved T₁ mapping sequence had the following imaging parameters: five short-axis slices, in-plane resolution = 2.1 × 2.1 mm², slice thickness = 8 mm, slice gap = 4 mm, field-of-view = 360 × 352 mm², TR/TE/α = 2.8 ms / 1.39 ms / 70°, SENSE-rate = 2, linear ordering, 10 linear ramp-up pulses and acquisition window = 239.8 ms, bandwidth = 1845 Hz/pixel. The slice-interleaved T₂ mapping sequence had the following parameters: five short-axis slices, in-plane resolution = 2 × 2 mm², slice thickness = 8 mm, slice gap = 4 mm, field-of-view = 320 × 320 mm², TR/TE/α = 2.8 ms / 1.41 ms / 55°, SENSE-rate = 2.5, linear ordering, 10 linear ramp-up pulses and acquisition window

= 188.7 ms, bandwidth = 1785.7 Hz/pixel. Because of limited availability of scan time and the heterogeneity of our patient cohorts, no reproducibility assessments were performed in this cohort.

Data Analysis

REPRODUCIBILITY STUDY. All images were transferred to a separate workstation for analysis. T₁ and T₂ mapping of each scan were estimated by voxel-wise curve fitting of the signal after motion correction. In-plane motion between different images of T₁ and T₂ maps were corrected using image registration by a nonrigid image registration algorithm.²⁴ T₁ values were estimated by fitting the recovery curve to a two-parameter and T₂ values to a three-parameter fitting model.²⁵ The endocardial and epicardial contours of the LV myocardium were manually outlined. The anterior right ventricular (RV) insertion point was marked as a point of reference to generate a 26-segment model of five slices over the entire left ventricle from apex to base.

Additionally, a mean T₁/T₂ estimate was generated for each of the five single slices and for the entire ventricle. Artifacts were excluded by manually drawn regions of interest (ROIs) and any segment with visual artifacts after segment analysis was excluded from the analysis. A second experienced reader analyzed T₁ and T₂ measurements for one repetition in all subjects, which was compared with results of the corresponding repetition of the first reader, to assess interobserver agreement by using intraclass correlation coefficient (ICC) analysis. Intraobserver agreement was assessed by using ICC analysis for two corresponding repetitions of each subject analyzed by one reader. Continuous values were presented as mean ± standard deviation (SD). The Shapiro-Wilk test was used to assess for normal distribution. CV analysis was generated to assess variability between subjects, days and sessions and was visualized by box plots. Significance was considered as *P*-value less than 0.05. Data analysis was performed with SPSS software (SPSS, Version 17, Inc., Chicago, IL) and Matlab software (The MathWorks Inc., Natick, MA).

IMPACTS ON SAMPLE SIZE CALCULATION. A linear mixed effects model was used to calculate variance estimations for the effect of volunteers, days, sessions, repetitions, and remaining unspecified factors (i.e., heart rate, etc.). For this model, imaging day is nested within subjects, session is nested within day, and repetition is nested within session. This analysis provides individual variances for each individual factor, a pooled variance and pooled standard deviation for each T₁ (slice-interleaved/MOLLI/ShMOLLI) and T₂ (slice-interleaved/single-slice) mapping sequence. The sample size assessment was performed for 90%, 85%, and 80% power groups for detection of different changes in T₁ and T₂ values at a type 1 error of 0.05.

IMAGE QUALITY ASSESSMENT. Subjective image quality was assessed by two readers (S.B. with 2 years of experience and C.L. with 6 years of experience) using a 26-segment LV model. The LV was divided into five short-axis slices perpendicular to the longitudinal axis of the heart. This leads to five circular sections of the LV-myocardium (basal, three mid-ventricular and apical slices). Only slices with complete circular section of the LV were included.

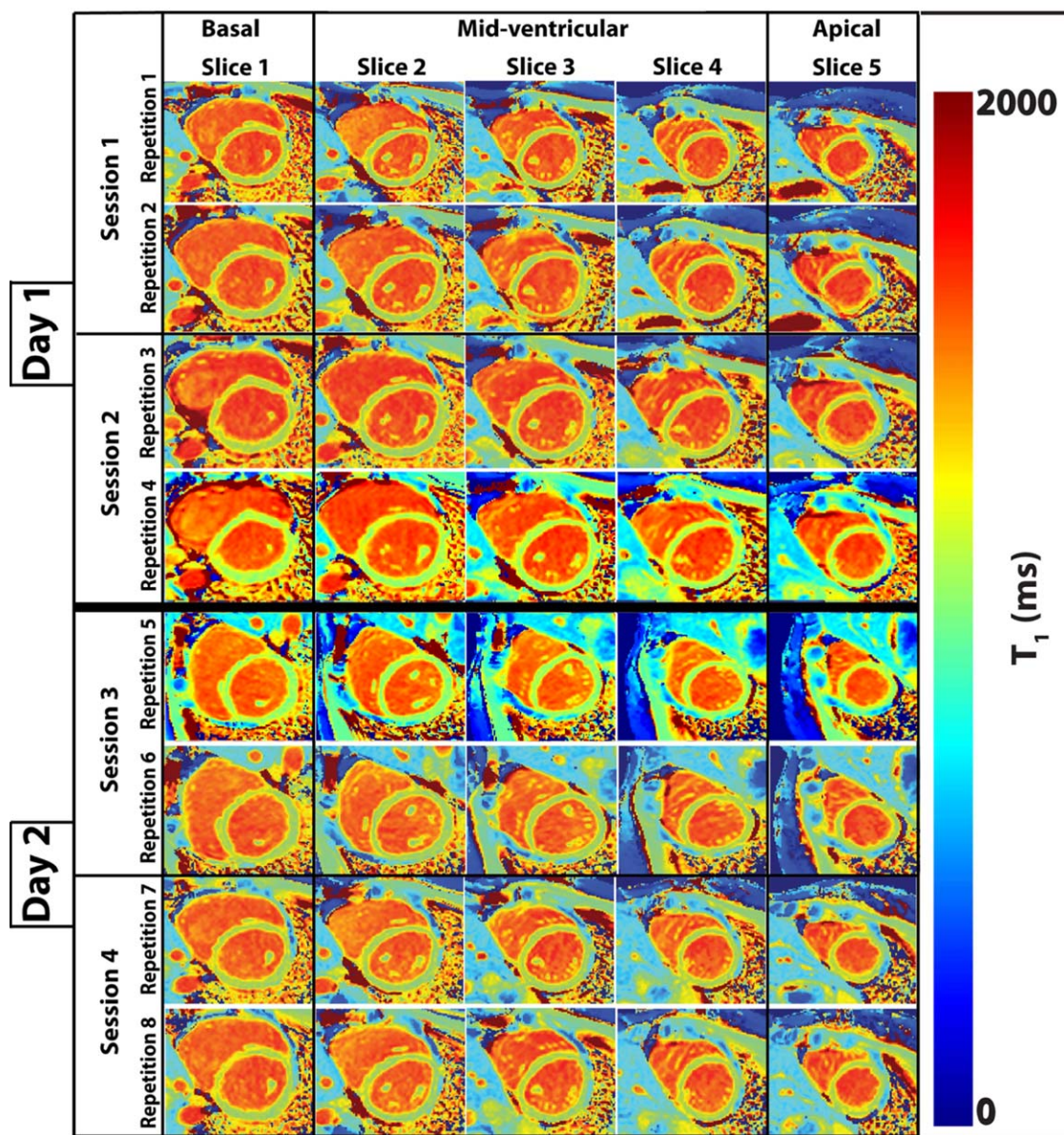


FIGURE 2: Example T_1 maps acquired with the STONE sequence.

Each of the three most basal sections were divided into six segments of 60° each. Each of the two most apical slices were divided into four segments of 90° each. Segments were evaluated independently by two readers. A score of 1 was given if the segment was of acceptable image quality for analysis, defined in this study as having at least a 5×5 pixel ROI not affected by artifact. Otherwise, a score of 0 was given to this segment. Interobserver agreement for both slice-interleaved T_1 and T_2 maps were calculated.

Results

Reproducibility Study

Figure 2 shows example T_1 mapping images of five short-axis LV slices for the slice-interleaved T_1 sequence with eight repetitions (2 days \times two sessions \times two repetitions). All five slices of the eight repetitions appear with homoge-

neous quality and without artifacts. Figure 3 is an example of eight repetitions of T_2 mapping of five LV slices for slice-interleaved T_2 sequence. All slices in all repetitions of this subject show homogeneous quality and are without artifacts. Figure 4 shows individual and group global T_1 and T_2 estimates among all 11 healthy subjects at each repetition. Each sequence was repeated twice per session. There were two sessions on each of the 2 days. The results including SDs for both sequences appeared very similar between different repetitions, sessions and days. The global mean T_1 time for slice-interleaved T_1 was 1063 ± 22 ms and the global mean T_2 time for slice-interleaved T_2 was 48 ± 5 ms. Figure 5 shows global T_1 and T_2 estimates for each of the five slices among all repetitions and subjects. The slices within each sequence showed similar global T_1 and T_2 estimates. Segments compromised by severe artifacts were

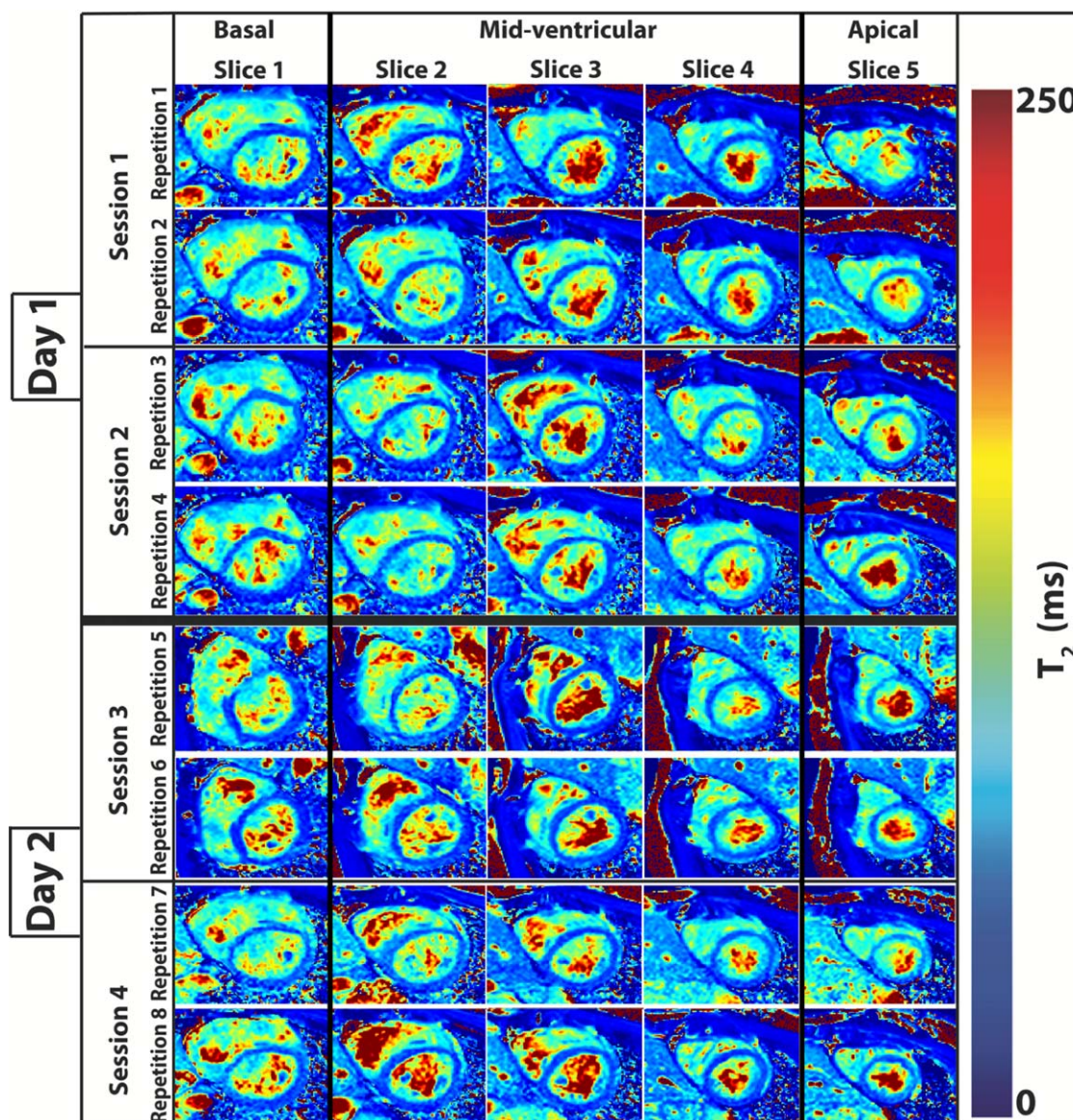


FIGURE 3: Example T_2 maps acquired with the free-breathing slice-interleaved T_2 mapping sequence.

excluded (T_1 : 5.6% and T_2 : 16.3%). Slice-interleaved T_2 showed a higher tendency for motion artifacts than slice-interleaved T_1 .

The CV analysis between different subjects, days, and sessions and for both sequences showed a high reproducibility with global CVs of $< 5\%$ between days, sessions and subjects (Fig. 6). The CV analysis for individual slices showed a low variability for slice-interleaved T_1 (global CV per slices: slice 1 = 2.7%; slice 2 = 2.8%; slice 3 = 3.2%; slice 4 = 3.1%; slice 5 = 3.7%) as well as slice-interleaved T_2 (global CV per slices: slice 1 = 12.5%; slice 2 = 11.5%; slice 3 = 8.8%; slice 4 = 9.4%; slice 5 = 8.3%). The most apical and most basal slices (slice 1 and slice 5) showed similar reproducibility as compared to the three mid-ventricular slices (slices 2–4) in both sequences after exclusion of segments with severe artifacts.

The interobserver agreement for slice-interleaved T_1 sequence showed an excellent agreement with an ICC of 0.86 (95% confidence interval: 0.13 to 0.97). The interobserver agreement for slice-interleaved T_2 sequence was very strong with an ICC of 0.75 (95% confidence interval: 0.17–0.93). The intraobserver agreement for slice-interleaved T_1 sequence showed an excellent agreement with an ICC of 0.87 (95% confidence interval: 0.35–0.97) and the intraobserver agreement for slice-interleaved T_2 sequence was very strong with an ICC of 0.77 (95% confidence interval: 0.12–0.94).

Impacts on Sample Size Calculation

Figure 7 shows the required sample size to detect changes in T_1 measured using STONE, MOLLI, and ShMOLLI at three different statistical power levels ($>90\%$, $>85\%$,

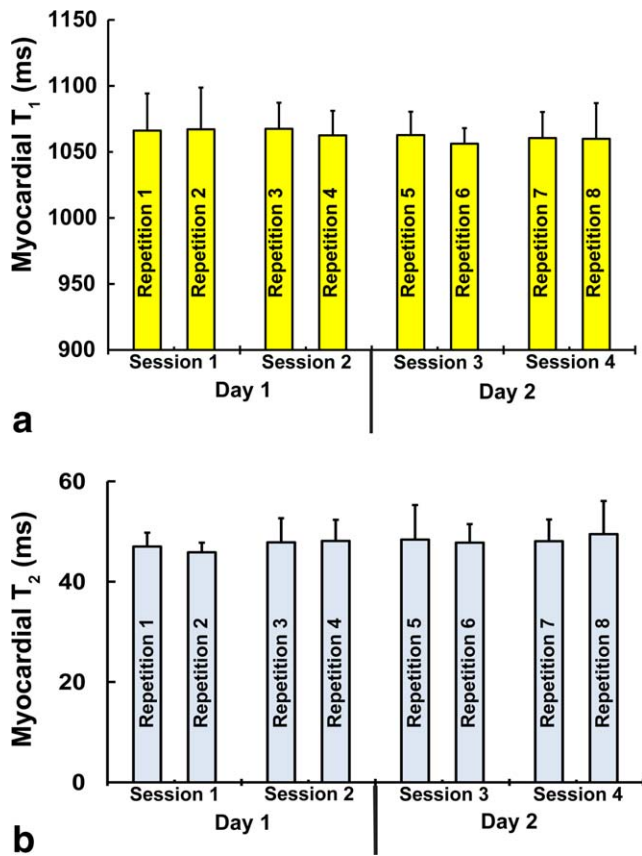


FIGURE 4: Mean \pm standard deviation (among different subjects) of global myocardial T₁ (A) and T₂ (B) measurements for different repetitions.

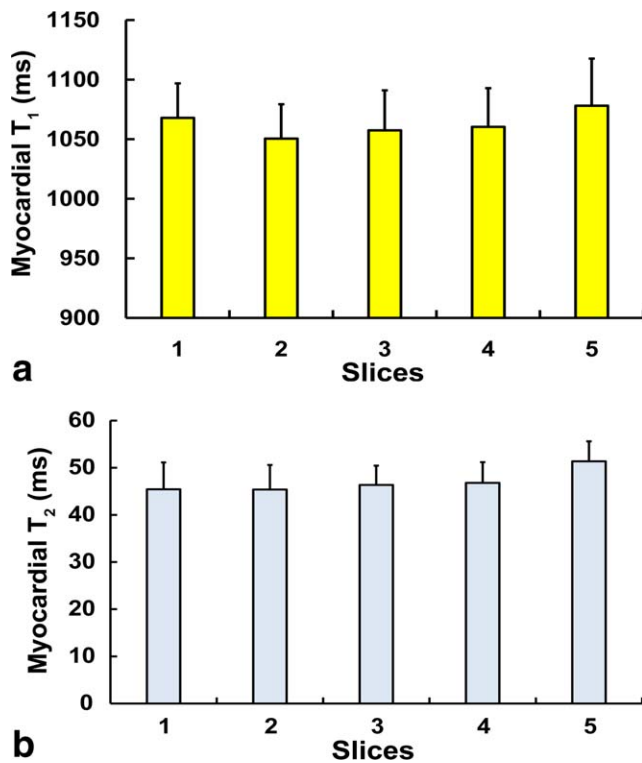


FIGURE 5: Mean \pm standard deviation (among different subjects) of global myocardial T₁ (A) and T₂ (B) estimates for different slices (basal: slice 1, mid-ventricular: slices 2–4, and apical: slice 5).

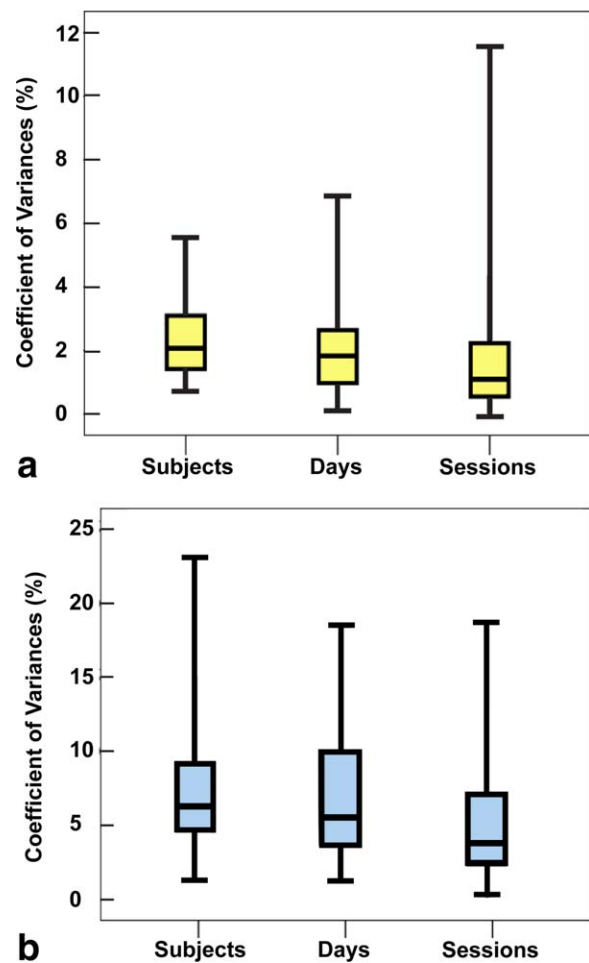


FIGURE 6: Coefficient of variation analysis for T₁ (A) and T₂ (B) mapping sequences to assess the variability between different subjects, days and sessions.

>80%). The required sample size for detection of a specific T₁ difference is smaller for STONE than for MOLLI and ShMOLLI. Figure 8 shows the required sample size to detect changes in T₂ measured by using slice-interleaved T₂ and single-slice T₂ mapping sequences at three different statistical power levels (>90%, >85%, >80%). For both T₂ sequences, the required sample sizes are very similar for detection of T₂ differences. For detection of T₂ differences of ≤ 10 ms, single-slice T₂ requires fewer subjects than slice-interleaved T₂.

Image Quality Assessment

Five patients were excluded from analysis due to incorrect positioning of the slices and/or reconstruction error. Figure 9 shows the subjective image score (averaged between the two readers) for each of the 26 T₁ and T₂ map segment. The lowest scores consistently seen on both T₁ and T₂ maps were at the most basal and most apical slices (slices one and five, respectively) and adjacent to the RV insertion points into the interventricular septum. The mean visual quality scores for the most basal slices were 0.81 ± 0.04 and 0.81 ± 0.04 for T₁ and T₂ maps, respectively. The

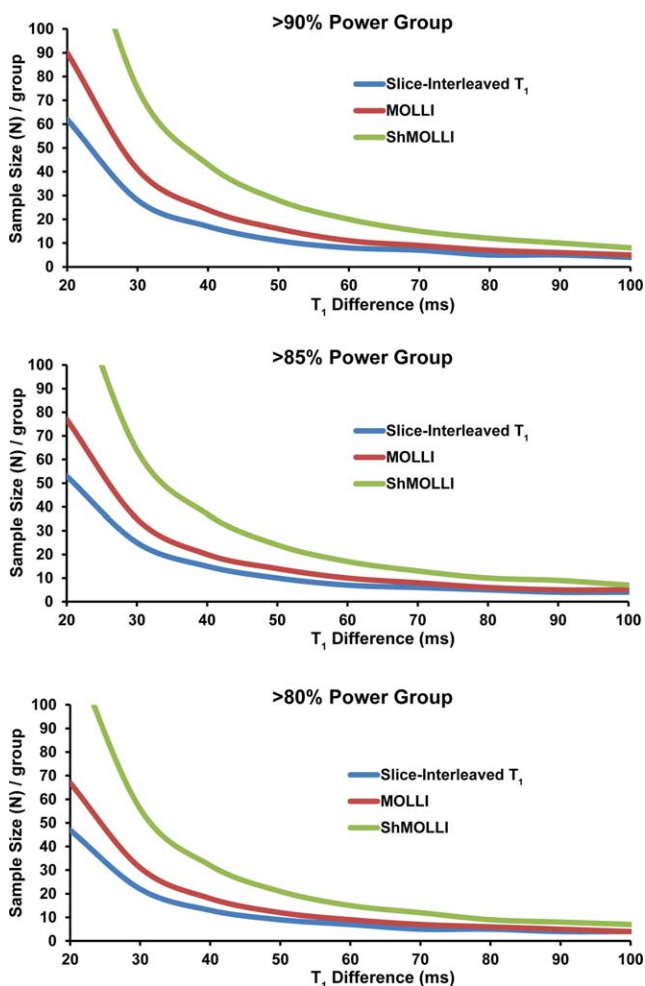


FIGURE 7: Assessment of required sample size for detection of corresponding T₁ differences in STONE, MOLLI, and ShMOLLI mapping sequences for three different power levels (>90%, >85%, >80%; $\alpha = 0.05$).

mean visual quality scores for the most apical slices were 0.61 ± 0.03 and 0.76 ± 0.03 for T₁ and T₂ maps, respectively. The septal wall segments demonstrated the best scores in both T₁ and T₂ maps, with mean visual quality scores of 0.85 ± 0.09 and 0.84 ± 0.04 for T₁ and T₂ maps, respectively. Using the Wilcoxon signed-rank test, the mean score differences between basal and septal as well as apical and septal segments were significantly different ($P < 0.001$) for T₁ and T₂ maps, respectively.

The interobserver agreement for visual quality scores of slice-interleaved T₁ maps showed strong agreement with an ICC of 0.74 (95% confidence interval: 0.64–0.81). The interobserver agreement for quality scores of slice-interleaved T₂ sequence was moderate to good with an ICC of 0.60 (95% confidence interval: 0.35–0.74).

Discussion

In this prospective study examining T₁ and T₂ reproducibility with slice-interleaved T₁ and T₂ mapping sequences in

healthy subjects and subjective image quality in patients with known or suspected cardiovascular disease, we found that these two free-breathing sequences provide excellent reproducibility. The subjective image quality analysis demonstrated >80% of segments are suitable for quantitative measurements, allowing regional measurements, which are

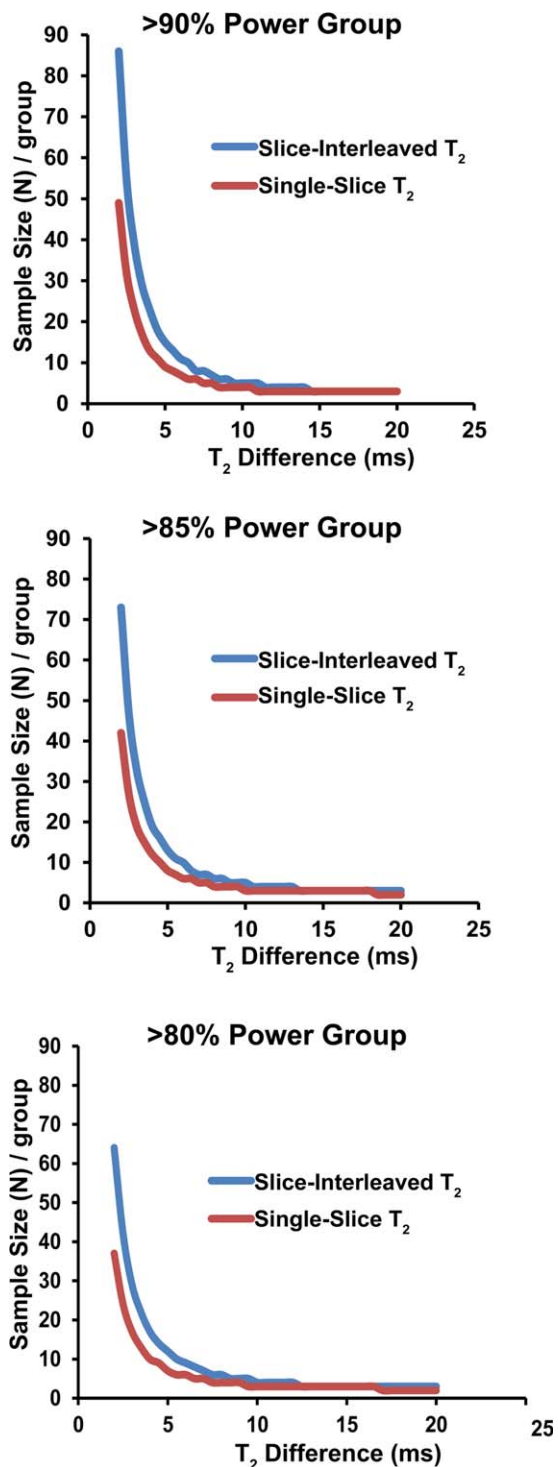


FIGURE 8: Assessment of required sample size for detection of corresponding T₂ differences in slice-interleaved T₂ and single-slice T₂ mapping sequences for three different power levels (>90%/ >85%/ >80%; $\alpha = 0.05$).

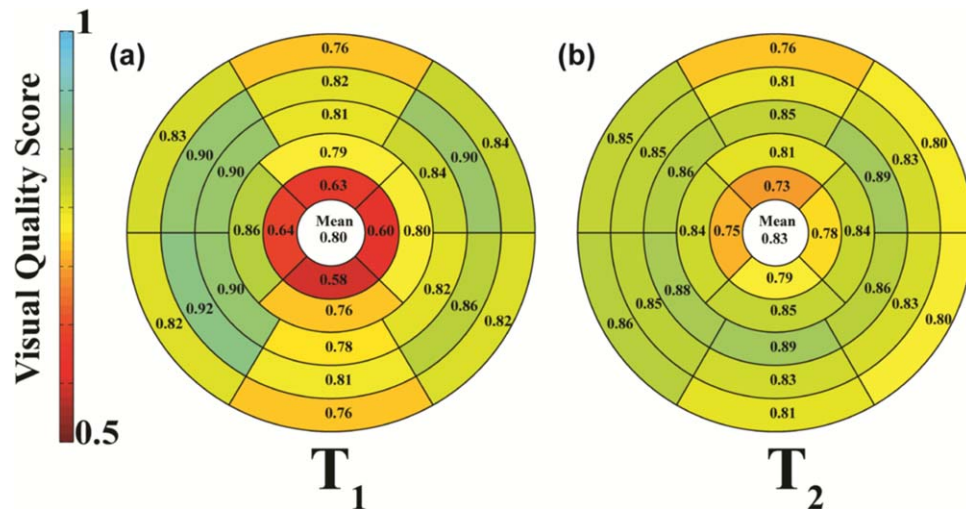


FIGURE 9: A 26-segment polar map of the left ventricle showing the average visual quality scores (0 = poor; 1 = good) for the two readers using the 26 segment LV model for T₁ mapping (a) and T₂ mapping (b), respectively.

important in certain diseases such as myocarditis and hypertrophic cardiomyopathy.

Our results expand on previous observations regarding the reproducibility of T₁ mapping using different T₁ mapping sequences.¹⁸ While SASHA and SAPHIRE have excellent accuracy compared with MOLLI and ShMOLLI, they have lower reproducibility. The STONE sequence has a longer recovery time than MOLLI,^{18,20} which improves accuracy and precision. Our data also support improved reproducibility of the STONE sequence as the coefficient of variation analysis for STONE was lower than similar studies with MOLLI.²⁶ There are very limited data on reproducibility for myocardial T₂ mapping.²⁷ In a test/retest study involving two separate days, Wassmuth et al²⁷ reported a high reproducibility of T₂ mapping with coefficients of variation from 6.6% to 7.6% depending on different imaging orientation.

Over the past several years, there have been significant advances in pulse sequence design for myocardial tissue characterization using T₁ and T₂ mapping. As we embark on the next challenge of using these sequences in larger clinical studies, we should incorporate measurement variability in power calculations for future studies. Our preliminary results demonstrated that the STONE T₁ sequence will lower the sample size needed to achieve a prespecified power to detect changes in T₁. In addition to advantages of reduced scan-time and free-breathing acquisition compared with other available T₁ mapping sequences, a lower sample size may reduce the overall cost of clinical studies and increase the sensitivity to detect smaller changes in T₁ in longitudinal studies. Our T₂ power calculation shows that similar numbers of patients are needed for the two sequences to detect expected T₂ differences; however, slice-interleaved T₂ will still require a shorter scan time. In our calculation, we did not consider nondiagnostic segments that should be accounted for when planning a clinical study

to guarantee sufficient statistical power. Additional studies are warranted to calculate sample sizes in specific population of patients that might contain different degrees of T₁ and T₂ variability.

Our study has several limitations. The reproducibility measurements were only assessed in a small cohort of healthy young adult subjects and the statistical power analysis was mainly based on results in healthy subjects. The reproducibility may be lower in patients with different cardiovascular diseases. For example, in patients with dilated cardiomyopathy, the LV wall is often thin, making it difficult to measure T₁ or T₂ values. In our experience, it is difficult to perform similar test/retest studies on two separate days in patients; therefore, we only performed this study in healthy subjects. T₁ and T₂ may be dynamic. In our healthy cohort, we attributed the measurement variability to performance of the imaging sequence rather than to the changes in underlying T₁ or T₂. Nonetheless, this may not be the case in patients. We did not assess reproducibility of postcontrast T₁ or ECV in our healthy cohort as this would require contrast administration and hematocrit measurement. Additionally, we did not measure hematocrit in our patients, thus we only performed native T₁ sequence.

In conclusion, slice-interleaved T₁ and T₂ mapping yield highly reproducible myocardial T₁ and T₂ values, which may have implications for the determination of required sample sizes in larger clinical studies. Full LV coverage allows for assessment of various myocardial segments, with >80% for T₁ and >83% for T₂ maps of interpretable segments.

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