**Cardiac T1 and T2 Mapping at 1.5T: Nomograms and Evaluation of Deep Learning Reconstruction**

**Statistical Analysis**

🡪 Relevant measurements: T1 and T2 values in 16 AHA segments (“AHA 1” – “AHA 16”) and Septum ROI 1-3 mean: “sept-1-mean”; “sept-2-mean”; “sept-3-mean”

**Aim 1: Acquire age and gender specific reference ranges.**

Following SCMR recommendations (1), upper and lower range of normal will be defined by the mean plus and minus 2 standard deviations of the normal data, respectively. Gender dependent differences in the myocardial T1 and T2 values will be assessed by unpaired t-test. To study the effect of age on T1 and T2 values, we will use multivariable linear regression analysis.

🡪 use DL reconstructions for T1 MOLLI, T1 SMART1, T2, T2 fast

🡪 give gender and age specific reference values for each age group

🡪 Check variability within 1 slice and between slices: slice #1=AHA 1-6, sept-1-mean; #2=AHA 7-12, sept-2-mean; #3=AHA 13-16, sept-3-mean. (our practical clinical question: can we apply the reference values from the septal contour sept-?-mean to all segments in the respective slice?).

Please give average contour size for the septal contours (descriptive): sept-1-area, sept-2-area, sept-3-area

**Aim 2: Evaluate the performance of different relaxometry methods.**

To assess and quantify the test-retest repeatability within sequence, and between-system, between-sequence, and between-reconstruction reproducibility for T1 and T2 mapping as described in Aim 2 subgoals, three metrics will be estimated for each pairwise comparison.

🡪 use “intra-system” subjects for repeatability of sequence at same MR system for DL reconstructions for T1 Molli, T1 Smart1, T2, T2 fast (each n=15)

🡪 use “inter-system” subjects for between-system reproducibility for DL reconstructions for T1 Molli, Smart1, T2, T2 fast (each n=15)

🡪 use all subjects (use scan A for each subject except for the inter-system subjects. For the inter-system subjects please use the scan B) for between-sequence reproducibility 1) MOLLI DL vs SMART1 DL, 2) T2 DL vs T2fast DL. (If data from scan A is not available for intra-system subjects, feel free to use scan B data.)

🡪 use all subjects (use scan A for each subject except for the inter-system subjects. For the inter-system subjects please use the scan B) for between-recon reproducibility 1) MOLLI Std vs MOLLI DL, 2) T2 Std vs T2 DL, 3) T2 DL vs T2 GE.

🡪 for between-reader reproducibility, use subjects from the two “interreader” tables and compare them to the ones in the main tables. Use MOLLI DL and T2 DL data only. Readers were “RVS” and “AF”.

First, intra-class correlation coefficients (ICCs) and associated 95% confidence intervals will be estimated from linear mixed models fit to the corresponding data using the "lme4" package in R (V 4.0.1 or later). A higher ICC indicates that the between-patient variability is greater than the between-protocol/field-strength/test variability, which would suggest that the variability comes from patient heterogeneity, not MR mapping error.

Second, a repeatability coefficient (RC) will be estimated for each direct comparison involving the same units of measurement. In this context, the RC represents the value (in the observed units) under which we would expect an absolute difference (between any two measurements) not to exceed, with 95% confidence. A lower RC value indicates better repeatability/reproducibility.

Finally, to assess any potential bias (or systemic error) across the acquisition protocols/sequences/tests, paired t-tests (two-sided) will be calculated. In this context, a rejected null hypothesis provides evidence of a bias between the systems or the test-retest repeatability. If the data are found not be sufficiently Gaussian in nature, paired Wilcoxon rank sum tests, a non-parametric alternative, will be used instead. Under this testing construct, our primary goal is limiting type II statistical errors, so multiple-testing corrections will be applied to resulting p-values.

All relevant comparisons will be visualized using Bland-Altman plots.

Power Considerations:

For the Aim 2 subgoals for which we have an overall sample size of N=50 patients, we anticipate being able to estimate the 95% confidence interval about our estimated ICC with a half-width of 0.06, under the assumption that we will have strong reproducibility (ICC = 0.90). Moreover, if our mean difference between modalities exceeds 40% of the observed standard deviation of the data for any given pairwise comparison, we anticipate having 80% power to detect that bias using a paired t-test, while limiting our type I error rate to 5%.

For the N=13 comparisons, we anticipate being able to estimate the 95% confidence interval about our estimated ICC with a half-width of 0.13, again under the assumption of strong reproducibility/repeatability (ICC=0.90). Regarding pairwise t-tests, we expect approximately 80% power to detect any pairwise bias if the difference in modalities exceeds 85% of the observed standard deviation of the data, while limiting our type I error rate to 5%.

**Study Synopsis**

Background

Cardiac mapping sequences allow for advanced tissue characterization including the detection and quantification of a broad range of pathologies by measuring the tissue-specific T1 and T2 times (1). Because there is a low reproducibility between different mapping sequences, MRI systems, and sites (2-4), the SCMR recommends acquiring site-specific reference values of at least 15-50 healthy subjects (1). Quantitative mapping results should only be reported when a site-specific reference range has been established. Moreover, local results should be benchmarked against published reference ranges (1). However, only few reference ranges have been published for GE systems.

Mapping sequences are very sensitive to motion and artifacts. GE developed a deep learning (DL) reconstruction that promises an improvement in image quality. This method needs to be tested with respect of repeatability and reproducibility of results.

Purpose & Objectives

This study aims to acquire age- and gender-specific reference ranges of cardiac T1 and T2 values for a variety of mapping methods at 1.5T GE MRI systems. Moreover, we will evaluate DL reconstruction for MOLLI and MEFSE compared to standard reconstruction.

Aim 1. Acquire age- and gender-specific reference ranges of cardiac T1 and T2 values for MOLLI and MEFSE at 1.5T.

Aim 2. Evaluate the performance of different relaxometry methods and reconstruction algorithms at 1.5T in healthy volunteers and patients.

To achieve aim 2, we defined several subgoals:

* Determine the test-retest repeatability for T1 and T2 mapping sequences and reconstructions.
* Determine the between-system, and between-reconstruction reproducibility for T1 and T2 mapping sequences and reconstructions.

**Methods**

The study itself consists of two phases and we are planning to complete them by mid-December 2023:

Phase I: We will generate age- and gender-specific reference ranges based on measurements of 50 healthy volunteers at 1.5T.

Phase II: To test the applicability of the new reference values and to evaluate between-sequence and between-reconstruction reproducibility in clinical routine, we will add mapping sequences to patient exams.

Subject Population

Phase I: 50 healthy volunteers (20-70 years in 10 years intervals with 50% male and 50% female volunteers) will be recruited from UW’s healthy volunteer database, using existing IRB-approved protocols (MR healthy volunteer database – Dr. Reeder, PI; hardware / software evaluation – Dr. Grist, PI).

Phase II: 25 patients referred for cardiac MRI regardless of diagnosis and comorbidities will be recruited in accordance with our IRB-approved protocol (hardware / software evaluation – Dr. Grist, PI).

Study-specific exclusion criteria for healthy volunteers are known heart disease, diabetes mellitus, impaired renal function, amyloidosis, sarcoidosis, and iron overload. Treated hypertension is not an exclusion criterion.

Data Acquisition Methods (Describe how data will be acquired)

It is known that mapping sequences are very sensitive to multiple confounders, such as sequence type (2), acquisition parameters (5), field strength (5), scanner hardware (1, 6), scanner software version (6), and reconstruction method (7). All volunteers will be examined at 1.5T. To determine the test-retest repeatability, n=15 will do a repeat scan at the same system where they have already been examined; To determine the impact of a different MR system of the same model and to confirm transferability of the reference values to MR systems that we routinely use clinically, n=15volunteers will undergo a 2nd exam at a clinically used MR system in the UW University Hospital system. This will be necessary since the SCMR recommends that “native parameter values should only be compared to other parameter values if they are obtained under similar conditions”.

MRI systems

1.5T Signa Artist: UWMR3, EMH

Sequences

Sequence parameters will be chosen according to SCMR recommendations (8) and aligned with routinely used clinical sequences at UW. To cover 16 AHA-segments, we will acquire all sequences in 3 short axis planes of the left ventricle (basal, midventricular, apical). Acquisition order of sequences and MR systems will be chosen randomly for each exam to mitigate changes in the quality of breath holds of the subject. Technologists will be instructed to wait at least 10s in between T1 map acquisitions as well as after prescan (shimming, TG calibration, etc) to avoid errors due to incomplete magnetization recovery (9). We will acquire the following sequences during each exam:

T1: -MOLLI pre-contrast: 5(3s)3; recon with advanced MoCo, with and without DL recon  
T2: -MEFSE (Multi-Echo Fast Spin-Echo), with and without DL recon

To guarantee normal cardiac function in the healthy volunteers, we will acquire a one-breath hold DL cine covering the complete left ventricle in short-axis orientation.

Phase I: Healthy Volunteers

- 1st exam: all 50 subjects will be examined at 1.5T (UWMR3)   
- 2nd exam: 15 subjects at the same 1.5T system (UWMR3)  
 15 subjects at a different 1.5T system of the same model (EMH)  
Total exam time: 40 hrs

Phase II: Patients

- In clinical routine, MOLLI and MEFSE will be acquired in n=25 patients.

Postprocessing

All T1 and T2 maps will be reconstructed offline with cvi42 following clinical standard at UW. All acquired mapping sequences will be reconstructed with and without DL reconstruction.

Data Analysis Methods (Describe how data will be analyzed in order to draw conclusions)

Image Analysis

T1 and T2 maps will be analyzed according to SCMR recommendations (10). We will acquire AHA-segment specific T1 and T2 values for all subjects using cvi42. The maps will be evaluated by an undergraduate student who will be thoroughly trained by an experienced radiologist. After the initial training period, a radiologist will check accurate ROI placement regularly and help with evaluation, if necessary. A subset of studies will be evaluated by a second reader to assess inter-reader variability.