Additional file 1: Repeatability of ECV measurement using MOLLI T1 mapping

Pre and post contrast MOLLI T1 mapping images were acquired with standard techniques in the basal, mid and apical short axis orientations. Each MOLLI slice was acquired within an end-expiration breath-hold by using an ECG-triggered acquisition with a balanced steady-state free precession (SSFP) readout (TR=2.8 ms, TE=1.0 ms, flip angle=35º, slice thickness=8 mm, spatial resolution=1.8 x 1.8 mm). Post-contrast MOLLI T1 images were obtained approximately 10-15 min after the last injection of gadoteridol.

Pre- and post-contrast T1 of myocardium and blood were measured on a Syngo multimodality workplace (Siemens, Erlangen, Germany) by placing a region of interest (ROI) in the left ventricular midwall to avoid contamination with signal from blood pool. Approximate ROI sizes were 5.2 cm^2, 4.8 cm^2 and 2.4 cm^2 for base, mid and apical short axis segments. When late gadolinium enhancement (LGE) was present in the slice, a region in the remote myocardium was chosen. The volume of distribution in the

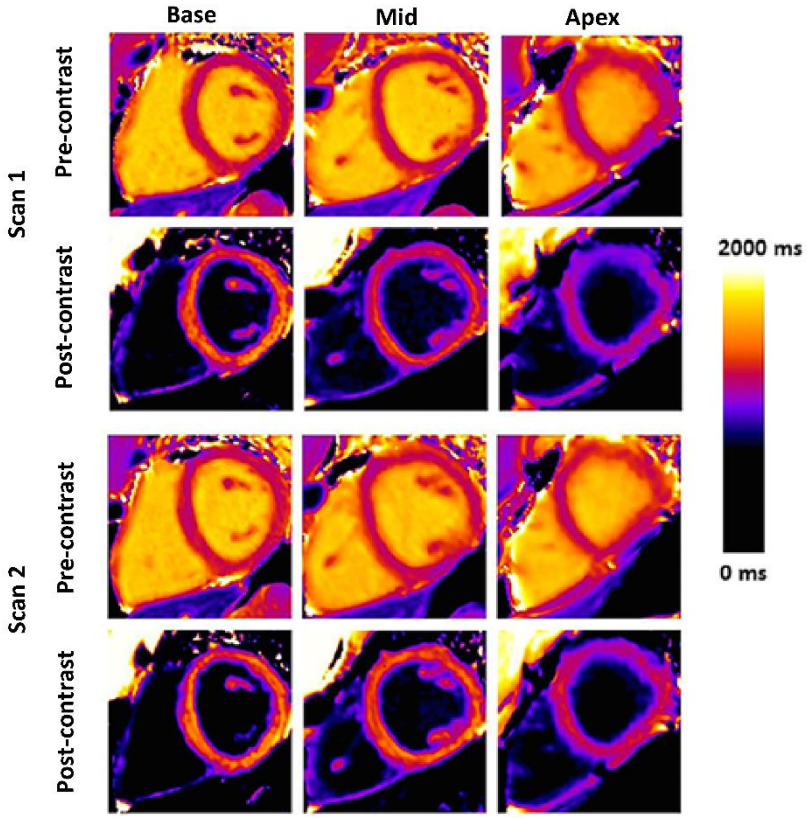

Figure A1.1: Representative images of MOLLI T1 mapping. The figure shows the similarity of T1 maps between scan 1 and scan 2.

myocardium, also known as the extracellular volume (ECV) fraction, was then calculated for each slice from the T1s and measured hematocrit, the volume of distribution.

STATISTICAL ANALYSIS

Comparisons between the two scans were made using Student two-tailed paired t-test. A p value of <0.05 was considered statistically significant. Coefficients of variation were calculated to assess inter-study reproducibility. Bland-Altman analysis was performed to assess the agreement between studies. Statistical analyses were performed using STATA software version 13 (StataCorp, College Station, TX).

RESULTS

There was no statistically significant difference of heart rate between visits during pre and post contrast MOLLI T1 mapping image acquisition (66±12 vs 65±11, p=0.75 for pre-contrast; 74±10 vs 72±10, p=0.64 for post-contrast). All MOLLI T1 mapping images were good quality, however, not all left ventricular (LV) slices were obtained twice. As a result, a total of 26 slices (8 basal, 10 mid and 8 apical) were available for analysis. Representative MOLLI T1 mapping images from both scans are shown in Figure A1.1. The overall mean ECV was 25.9±2.5 for scan 1 and 26.4±2.8 for scan 2. Mean ECV is shown in Table TA1.1. Myocardial ECV was significantly higher in the apical slices compared to the basal and mid slices (p=0.003, p=0.04 respectively). Myocardial ECV measurement based on MOLLI T1 mapping demonstrated an excellent inter-study reproducibility with CoV of 6-8% (Table TA1). Good agreement was also demonstrated by the Bland-Altman plot (Figure A1.2).

Myocardial slice	Mean ECV ± SD Scan 1	Mean ECV ± SD Scan 2	Coefficient of Variation (%)
Base	24.5±1.2	24.9±2.5	6.5
Mid	25.5±2.1	26±2.1	7.7
Apex	27.7±2.9	28.2±3.2	6.8
Overall	25.9±2.5	26.4±2.8	6.8

Table TA1.1: Summary of myocardial ECV estimates for basal, mid and apical slice.

DISCUSSION

MOLLI sequences for T1 mapping have been validated with high levels of inter-study reproducibility of myocardial native T1, post-contrast T1 (1, 2) and ECV measurement (3, 4). In this study, we found an inter-study reproducibility with CoV of ~7% which was similar to the findings reported by Singh et al. (3) and Liu et al. (5) for ECV derived from MOLLI T1 mapping on a 3T scanner. Singh et al. imaged 10 subjects with aortic stenosis with studies ~7 days apart, and Liu et al. examined healthy volunteers with a different contrast dose and the studies a mean of 51 days apart. Both works (3) (5) imaged only a single slice. In the current study, we observed high inter-study reproducibility of ECV measurement for each LV slice (base, mid and apex). Average ECV from either all LV slices or from mid LV slices were comparable to the previous reports of ECV derived from MOLLI T1 mapping in the myocardium of healthy participants (6, 7) and in remote myocardium of participants with a history of chronic myocardial infarction (8). However, we observed that the ECV of apical LV slices was significantly higher than basal and mid LV slices. This was possibly due to a partial volume effect between the myocardium and blood pool in the apical slices. That is, this effect could have been caused by the curvature and the thickness of the LV wall at the prescribed position for the apical slices, since the MOLLI sequence had relatively large slice thickness and relatively low spatial resolution. Higher ECV of apical LV slices was previously shown by Tessa et al. (9) in which the relevant artifact and/or partial volume effect were present mainly in the apical LV slice. Correspondingly, von Knobelsdorff-Brenkenhoff et al. (10) explained an increase in pre-

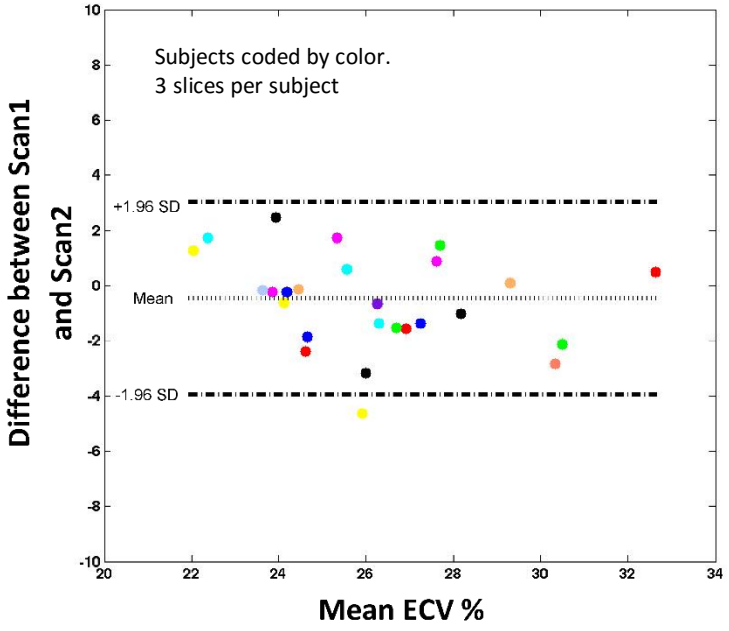

Figure A1.2: Inter-study agreement of myocardial extracellular volume (ECV) fraction as determined by MOLLI T1 mapping.

contrast T1 and a decrease in post-contrast T1 from base to apex by partial volume effects of blood signal being included in the voxel.

Based on this result, special attention should be paid to the prescription of apical LV slice position and orientation. It is desirable to reduce slice thickness and increase spatial resolution for apical slices. Furthermore, regions of interest (ROI) in apical slices should be selected in such a way that partial volume pixels are excluded from the ROI. The partial volume effect represents one of the key limitations of MOLLI T1 mapping of thin walled cardiac structures such as the right and left atria.

The contrast injection protocol in this study was primarily designed for ungated/self-gated myocardial perfusion and did not use the contrast injection timing protocol for MOLLI T1 mapping described by Messroghli et al. (46). However, the post-contrast MOLLI T1 images were obtained at 10-15 min after the last contrast bolus injection as per standard MOLLI methods. The similarity with other findings indirectly indicates that T1 post-contrast maps acquired at a slightly higher heart rate, that is, as part of a rest/stress protocol using regadenoson, is feasible. Myocardial ECV from T1 mapping techniques including MOLLI depend on the amount of blood in the myocardial tissue voxels, and this is not typically considered with T1 mapping methods. This may be slightly altered in this study since the heart rate did not completely return to baseline after regadenoson in this study. The high fraction of blood in the myocardial tissue may result in higher ECV. Although MOLLI T1 mapping technique provides high precision and reproducibility, it tends to underestimate the actual T1 value (15). Other T1 mapping techniques (saturation recovery single-shot acquisition [SASHA], and saturation pulse prepared heart rate independent inversion recovery [SAPPHIRE]) have shown higher accuracy for T1 assessment but with less precision (15). Head to head comparison of the accuracy and repeatability of ECV assessment for different T1 mapping techniques is still limited and requires further elucidation.

In conclusion, inter-study repeatability with a CoV of 6.8% was obtained for ECV measurements using MOLLI T1 mapping.

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