

# Accuracy, Precision, and Reproducibility of Four T1 Mapping Sequences: A Head-to-Head Comparison of MOLLI, ShMOLLI, SASHA, and SAPPHIRE<sup>1</sup>

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## Purpose:

To compare accuracy, precision, and reproducibility of four commonly used myocardial T1 mapping sequences: modified Look-Locker inversion recovery (MOLLI), shortened MOLLI (ShMOLLI), saturation recovery single-shot acquisition (SASHA), and saturation pulse prepared heart rate independent inversion recovery (SAPPHIRE).

## Materials and Methods:

This HIPAA-compliant study was approved by the institutional review board. All subjects provided written informed consent. Accuracy, precision, and reproducibility of the four T1 mapping sequences were first compared in phantom experiments. In vivo analysis was performed in seven healthy subjects (mean age  $\pm$  standard deviation, 38 years  $\pm$  19; four men, three women) who were imaged twice on two separate days. In vivo reproducibility of native T1 mapping and extracellular volume (ECV) were measured. Differences between the sequences were assessed by using Kruskal-Wallis and Wilcoxon rank sum tests (phantom data) and mixed-effect models (in vivo data).

## Results:

T1 mapping accuracy in phantoms was lower with ShMOLLI (62 msec) and MOLLI (44 msec) than with SASHA (13 msec;  $P < .05$ ) and SAPPHIRE (12 msec;  $P < .05$ ). MOLLI had similar precision to ShMOLLI (4.0 msec vs 5.6 msec;  $P = .07$ ) but higher precision than SAPPHIRE (6.8 msec;  $P = .002$ ) and SASHA (8.7 msec;  $P < .001$ ). All sequences had similar reproducibility in phantoms ( $P = .1$ ). The four sequences had similar in vivo reproducibility for native T1 mapping ( $\sim 25$ – $50$  msec;  $P > .05$ ) and ECV quantification ( $\sim 0.01$ – $0.02$ ;  $P > .05$ ).

## Conclusion:

SASHA and SAPPHIRE yield higher accuracy, lower precision, and similar reproducibility compared with MOLLI and ShMOLLI for T1 measurement. Different sequences yield different ECV values; however, all sequences have similar reproducibility for ECV quantification.

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**Q**uantitative myocardial T1 mapping is a cardiovascular magnetic resonance (MR) technique that provides in vivo tissue characterization (1,2). Alterations of native myocardial T1 times have been observed in the presence of a variety of pathologic conditions (3). Furthermore, native and postcontrast administration T1 mapping can be performed to measure the extracellular volume fraction (ECV) (4), which has important prognostic value (5,6) and shows promise for the detection of diffuse myocardial fibrosis (7,8).

Several T1 mapping techniques have been proposed by using different acquisition schemes to sample the T1 recovery signal (1,9–20). Multiple images with different T1-weighting are generally acquired and used to provide quantitative T1 estimates by using a model of the T1 recovery signal (1,9–20). Despite the promise of these T1 mapping techniques to improve diagnosis, prognosis, and monitoring response to therapy in a variety of

cardiomyopathies, there is no current standard approach or recommendation for clinical cardiac MR protocols. T1 measurements can be altered by several factors, such as the acquisition scheme, magnetization transfer, flow, T2 effect, and motion (3,10,21–24). Therefore, the characterization of each approach in term of accuracy, precision, and reproducibility is crucial to reach a consensus (3).

Although these techniques have been individually evaluated, no comparison has yet been performed across inversion recovery, saturation recovery, and combined saturation and inversion recovery sequences. The purpose of this study was to compare accuracy, precision, and reproducibility of four commonly used myocardial T1 mapping sequences: modified Look-Locker inversion recovery (MOLLI), shortened MOLLI (ShMOLLI), saturation recovery single-shot acquisition (SASHA), and saturation pulse prepared heart rate independent inversion recovery (SAPPHIRE).

### Advances in Knowledge

- Saturation recovery single-shot acquisition (SASHA) and saturation pulse prepared heart rate independent inversion recovery (SAPPHIRE) sequences yield consistent high accuracy of T1, but modified Look-Locker inversion recovery (MOLLI) and shortened modified Look-Locker inversion recovery (ShMOLLI) are biased by several confounding factors ( $P < .05$ ).
- MOLLI and ShMOLLI have higher precision for T1 mapping than SASHA and SAPPHIRE ( $P < .05$ ).
- All four T1 mapping sequences have similar reproducibility for T1 mapping (~25–50 msec;  $P > .05$ ).
- The four T1 mapping sequences yielded different in vivo ECV values ( $P < .001$ ); however, they all have similar reproducibility (~0.01–0.02;  $P = .11$ ).

### Materials and Methods

S.W., W.J.M., and R.N. are inventors of a pending U.S. patent entitled “Methods for scar imaging in patients with arrhythmia,” which described the SAPPHIRE imaging sequence for imaging of scar and fibrosis. All subjects were imaged by using a 1.5-T MR imager (Achieva; Philips Healthcare, Best, the Netherlands) and a 32-channel cardiac phased array receiver coil. In this Health Insurance Portability and Accountability Act-compliant study, the imaging protocol was approved by our institutional review board, and informed consent was obtained from all participants. Detailed methods are provided in Appendix E1 (online).

### Implications for Patient Care

- SAPPHIRE and SASHA can be used for accurate myocardial T1 assessment.
- MOLLI and ShMOLLI provide higher precision for myocardial T1 assessment.

### Phantom Study

A phantom that contained 14 vials (nickel chloride doped agarose) with different T1 and T2 values was used for the comparison of the four T1 mapping sequences. Reference T1 and T2 measurements were first obtained by using spin-echo acquisitions. Each of the four T1 mapping sequences was then acquired 10 times by using an electrocardiogram-triggered single shot acquisition with a balanced steady-state free precession readout (repetition time msec/echo time msec, 3.1/1.5; field of view,  $360 \times 337$  mm<sup>2</sup>; voxel size,  $1.9$  mm<sup>2</sup>  $\pm$  2.5; section thickness, 8 mm; number of phase-encoding lines, 70; linear ordering, 10 linear ramp-up pulses; sensitivity encoding factor, 2; MOLLI and ShMOLLI flip angle, 35°; SASHA and SAPPHIRE flip angle, 70°).

### In Vivo Study

Seven healthy adults (mean age, 38 years  $\pm$  19 [standard deviation]; four men, three women) were recruited for in vivo comparison of the four

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#### Abbreviations:

ECV = extracellular volume fraction  
 MOLLI = modified Look-Locker inversion recovery  
 SAPPHIRE = saturation pulse prepared heart rate independent inversion recovery  
 SASHA = saturation recovery single-shot acquisition  
 ShMOLLI = shortened modified Look-Locker inversion recovery

#### Author contributions:

Guarantor of integrity of entire study, R.N.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, S.R., R.N.; clinical studies, S.R., M.F., R.N.; experimental studies, S.R., S.W., M.F., K.C., K.K., W.J.M., R.B.T., R.N.; statistical analysis, S.R., L.H.N., P.K.; and manuscript editing, S.R., S.W., M.F., K.C., P.K., W.J.M., R.B.T., R.N.

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Conflicts of interest are listed at the end of this article.

sequences. Figure E1 (online) shows the study design of the in vivo study. Each subject participated in two cardiac MR examinations on two separate days (mean interval, 53 days  $\pm$  24). On the first day, precontrast imaging was performed twice (examinations 1 and 2) and was followed by two postcontrast MR examinations approximately 15–20 minutes and approximately 30–35 minutes after injection of 0.1 mmol/kg of gadobenate dimeglumine (MultiHance; Bracco Diagnostic, Princeton, NJ). A blood sample was drawn from each subject before the first cardiac MR examination to measure hematocrit. Each subject was removed from the imager after the first precontrast imaging session to simulate a new examination. Each sequence was acquired within an end-expiration breath-hold by using an electrocardiogram-triggered single-shot acquisition with a balanced steady-state free precession readout (3.1/1.5; field of view, 360  $\times$  337 mm<sup>2</sup>; acquisition matrix, 188  $\times$  135; voxel size, 1.9  $\times$  2.5 mm<sup>2</sup>; section thickness, 8 mm; number of phase-encoding lines, 70; linear ordering, 10 linear ramp-up pulses; sensitivity encoding factor, 2; flip angle, 70°; bandwidth, 1085 Hz/pixel). Three sections were acquired in the left ventricular short axis orientation with each T1 mapping sequence. On the second day, a single native T1 mapping session (examination 3) was set up to acquire three sections in a similar short-axis orientation with the same four T1 mapping sequences.

### Data Analysis

Accuracy, precision, and reproducibility of the four T1 mapping sequences were analyzed in the phantom study. Reproducibility of native T1 mapping and ECV measurement was evaluated in vivo in healthy subjects. Native T1 mapping reproducibility was measured from the two precontrast examinations that were acquired within the same MR examination (ie, two precontrast examinations on day 1) and across two separate MR examinations (ie, second precontrast examination on day 1 vs examination on day 2) ECV reproducibility was assessed

between two ECVs derived from the second precontrast examination and the first postcontrast examination, and the second precontrast examination and the second postcontrast examination.

### Statistical Analysis

The accuracy of the four sequences measured in the phantom study was compared by using a Kruskal-Wallis test, and a *P* value less than .05 indicated statistical significance. When the Kruskal-Wallis test found statistical significance, Wilcoxon rank sum tests were performed for each pair of sequences. The Wilcoxon rank sum test was considered to be statistically significant if it had a *P* value less than .05. The same methodologic parameter was used to analyze the signed accuracy bias, the precision, and the reproducibility of the four sequences in the phantom study.

The in vivo reproducibility of native T1 measurement obtained with the four sequences was compared by using a mixed-effect model. A similar test was used to compare the in vivo reproducibility of ECV measurements. *P* values less than .05 indicated statistical significance for each effect. Bonferroni correction was used for pair-wise comparison of sequences, which resulted in a statistical significance threshold of *P* < .008.

### Results

Table E1 (online) summarizes the T1 and T2 measurements of the four sequences obtained in the phantom study. Results are reported for each of the 14 vials. Substantial variations were observed in T1 estimates measured from the four sequences, especially in the presence of elevated T1 times or low T2 times. Accuracy and signed accuracy bias of each sequence are reported in Table E2 (online). Excellent accuracy was achieved by using SASHA and SAPHIRE for all T1 and T2 ranges. MOLLI and ShMOLLI showed less accuracy than SASHA (*P* = .02 and *P* = .04, respectively) and SAPHIRE (*P* = .025 and *P* = .045, respectively), with substantial T1 underestimation for large T1 times (>1000 msec) or lower

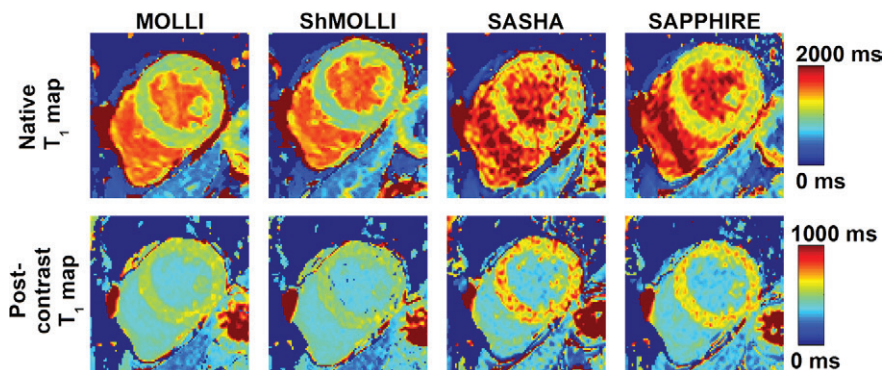
T2 times (<100 msec). Statistical differences were found among the four sequences in term of precision (*P* = .001) (Table E3 [online]). MOLLI had higher precision than both SASHA (*P* < .001) and SAPHIRE (*P* = .002). In addition, there was a trend for MOLLI to be more precise than ShMOLLI (*P* = .07) and for ShMOLLI to be more precise than SASHA (*P* = .07). There were no statistical differences in term of precision between ShMOLLI and SAPHIRE (*P* = .11) or between SAPHIRE and SASHA (*P* = .22). The reproducibility analysis over all vials revealed no statistical difference among the four sequences (*P* = .1).

Figure 1 shows examples of in vivo T1 maps obtained in a 53-year-old patient with all four T1 mapping sequences. Myocardium T1 obtained from MOLLI and ShMOLLI appears much lower than with SASHA and SAPHIRE. However, greater variability is observed in SASHA and SAPHIRE T1 maps.

Summary measurements of native myocardial T1 data obtained in healthy subjects during the same MR examination are reported in Figure 2. There was a statistically significant difference among the four sequences in native T1 time (*P* < .001). SASHA and SAPHIRE provided similar native T1 times of approximately 1200 msec (*P* = .83). Lower native T1 times were obtained with ShMOLLI and MOLLI compared with SASHA (*P* < .001) and SAPHIRE (*P* < .001). Reproducibility of native T1 mapping within the same MR examination is reported in Figure 2B. There was a statistically significant difference among the four sequences (*P* = .03). MOLLI and ShMOLLI had similar reproducibility (*P* = .91). SAPHIRE and SASHA had similar reproducibility (*P* = .39). There was a trend for MOLLI and ShMOLLI to be more reproducible than SAPHIRE (*P* = .06 and *P* = .07, respectively) and SASHA (*P* = .01 and *P* = .02, respectively).

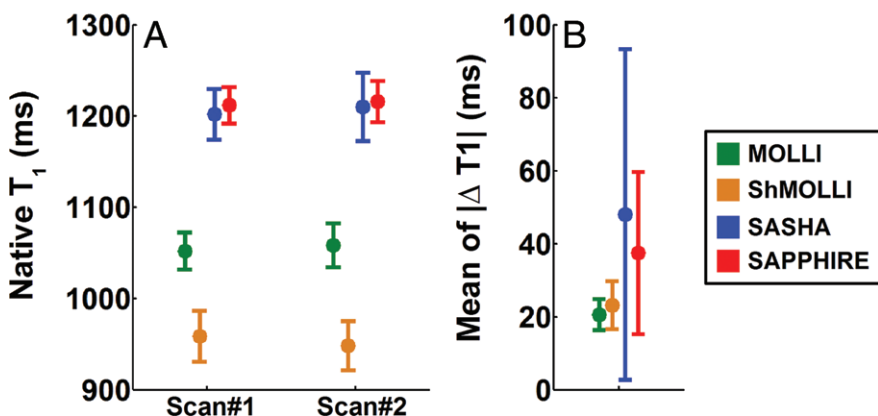
Figure 3 shows the variation of myocardial T1 measurements across sections. There was no section effect on native T1 time measurements, which was revealed by the mixed-effect model (*P* = .16).

**Figure 1**



**Figure 1:** Images show example T1 maps acquired with all four T1 mapping sequences (top row) before and (bottom row) after administration of contrast material in a 53-year-old man. Myocardial T1 values over the left ventricle obtained with MOLLI (native, 1012 msec  $\pm$  60; postcontrast administration, 527 msec  $\pm$  30) and ShMOLLI (native, 924 msec  $\pm$  70; postcontrast administration, 501 msec  $\pm$  33) were lower than those obtained with SASHA (native, 1254 msec  $\pm$  191; postcontrast administration, 659 msec  $\pm$  81) and SAPHIRE (native, 1160 msec  $\pm$  95; postcontrast administration, 625 msec  $\pm$  55). MOLLI and ShMOLLI provided improved precontrast and postcontrast map quality with less variability.

**Figure 2**



**Figure 2:** Box and whisker plots show, *A*, native myocardial T1 measurements and, *B*, reproducibility within the same MR examination in healthy subjects by using MOLLI, ShMOLLI, SASHA, and SAPHIRE. There were no statistically significant differences in native T1 times obtained with SASHA (examination 1, 1202 msec  $\pm$  56; examination 2, 1210 msec  $\pm$  76) and SAPHIRE (examination 1, 1212 msec  $\pm$  40; examination 2, 1216 msec  $\pm$  46) ( $P = .83$ ). Remaining paired sequence comparisons were statistically significant ( $P < .001$ ). Lower native T1 times were obtained with ShMOLLI (examination 1,  $\sim$ 959 msec  $\pm$  56; examination 2, 948 msec  $\pm$  54) and MOLLI (examination 1,  $\sim$ 1052 msec  $\pm$  41; examination 2, 1058 msec  $\pm$  48) compared with SASHA ( $P < .001$ ) and SAPHIRE ( $P < .001$ ). There were statistically significant differences among the four sequences in term of reproducibility ( $P = .03$ ). MOLLI and ShMOLLI had similar reproducibility (21 msec  $\pm$  9 vs 23 msec  $\pm$  13, respectively;  $P = .91$ ). SAPHIRE and SASHA had similar reproducibility (37 msec  $\pm$  44 vs 48 msec  $\pm$  91;  $P = .39$ ). MOLLI and ShMOLLI trended toward being more reproducible than SAPHIRE ( $P = .06$  and  $P = .07$ , respectively) or SASHA ( $P = .01$  and  $P = .02$ , respectively).  $\Delta T1 =$  change in T1.

Figure 4 shows the reproducibility of native T1 mapping from two separate MR examinations. Heart rate in the healthy subjects was 68 beats/min  $\pm$  9 on day 1

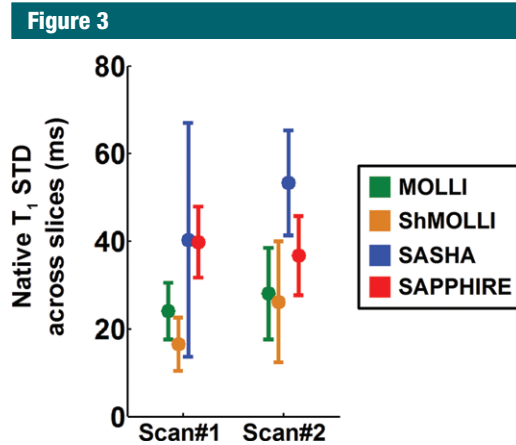
and 65 beats/min  $\pm$  9 on day 2, with an intrasubject variation of 8 beats/min  $\pm$  3 between the 2 days. The four sequences provided similar reproducibility ( $P = .11$ ).

ECV measurements and reproducibility are shown in Figure 5. ECV values measured with MOLLI (ECV,  $\sim$ 0.27) and ShMOLLI (ECV,  $\sim$ 0.26) were higher than with SASHA (ECV,  $\sim$ 0.18;  $P < .001$ ) and SAPHIRE (ECV,  $\sim$ 0.20;  $P < .001$ ). There was no statistically significant difference in term of ECV reproducibility among the four sequences ( $P = .11$ ).

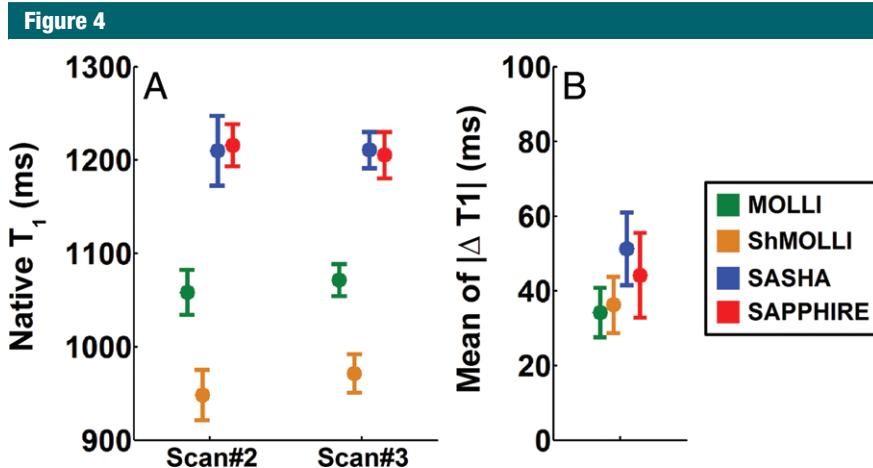
**Discussion**

In this study, we compared four T1 mapping sequences and assessed their accuracy, precision, and reproducibility. The phantom study revealed that SASHA and SAPHIRE have superior accuracy, inferior precision, and similar reproducibility to MOLLI and ShMOLLI. Reproducibility results were confirmed in vivo in healthy subjects where all sequences had similar reproducibility for native myocardial T1 mapping. Different sequences yield different in vivo ECV values but reproducibility of ECV measurements is similar with all sequences.

We found that MOLLI and ShMOLLI led to an underestimation of myocardial T1 values for both the phantom and the healthy subject study. These underestimations were found to be more prominent with higher T1 values. These data are consistent with previous studies (21–23,25,26), which identified several factors affecting MOLLI measurements, such as T2-dependence, magnetization transfer effect, and dependence on the inversion efficiency. SASHA and SAPHIRE yielded excellent accuracy for all range of studied T1 values. These results are also in good agreement with previous work (12,24), which showed that SASHA is not T2-dependent, is insensitive to inversion efficiency (21), and has low sensitivity to magnetization transfer (23). Since phantom and in vivo T1 estimates are in good agreement between SASHA and SAPHIRE, this validates that the T2-dependence and the magnetization transfer have little effect on SAPHIRE. This is a major finding which demonstrates that SAPHIRE estimate true T1 times and not apparent T1 times. Myocardial ECV measurements



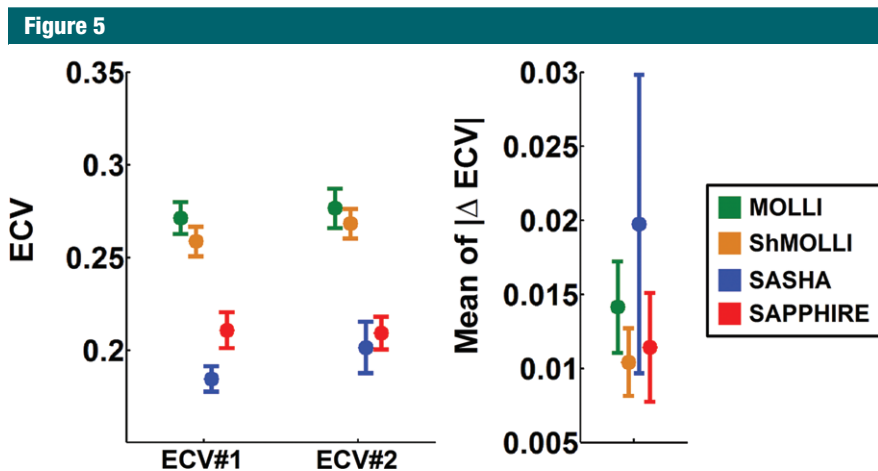
**Figure 3:** Box and whisker plot shows native myocardial T1 variation across sections (*slices*) calculated from four T1 mapping sequences in healthy subjects. Shown are standard deviations over sections of the T1 mean of a region of interest over the septum. Over the two precontrast examinations of day 1, the T1 variation across sections was lower with MOLLI (examination [*scan*] 1, 24 msec ± 13; examination 2, 28 msec ± 21) and ShMOLLI (examination 1, 17 msec ± 12; examination 2, 26 msec ± 28) than SAPHIRE (examination 1, 40 msec ± 16; examination 2, 37 msec ± 18) and SASHA (examination 1, 40 msec ± 53; examination 2, 53 msec ± 24). Mixed-effect model did not reveal any statistically significant section effect ( $P = .16$ ).



**Figure 4:** Box and whisker plots show, *A*, native myocardial T1 measurements and, *B*, reproducibility between two separate MR examinations in healthy subjects by using the four sequences of MOLLI, ShMOLLI, SASHA, and SAPHIRE. Shown are the second native T1-weighted examination on day 1 (examination [*scan*] 2) versus native T1-weighted examination on day 2 (examination 3). Reproducibility is reported as the absolute difference between the two precontrast myocardial T1-weighted examinations. MOLLI and ShMOLLI provided similar reproducibility with an average absolute T1 variation of 34 msec ± 13 and 36 msec ± 15, respectively. Although SASHA and SAPHIRE provided slightly lower reproducibility (51 msec ± 19 and 44 msec ± 23, respectively), there were no statistical differences among the sequences ( $P = .11$ ).  $\Delta T1$  = change in T1.

obtained in normal subjects were in good agreement with previous studies that reported values of  $0.25 \pm 0.03$  for MOLLI (27) and  $0.27 \pm 0.03$  for ShMOLLI (28). ShMOLLI and MOLLI had a statistically significant difference in ECV measurements compared with SASHA and SAPHIRE. This implies that standardized ECV and thresholds need to be defined independently for each sequence. The ECV reproducibility of the four sequences was similar in healthy subjects. The ECV accuracy was not studied in this study because it is difficult to obtain in vivo reference ECV measurements. However, bias in T1 estimates obtained with the ShMOLLI and MOLLI approach are nonlinear (ie, they affect more T1 values that are higher) and are thus expected to cause ECV measurements bias.

There are several limitations in this study. The sample size of the in vivo study was small, which may have limited ability to detect subtle differences between the sequences. A parametric procedure was used for in vivo analysis based on an assumed normal distribution of our data. However, this assumption had limitations that could have affected our in vivo findings. A flip angle of  $70^\circ$  was used for in vivo imaging with MOLLI and ShMOLLI, and could have slightly degraded the reproducibility of these two sequences. Different regions of interest were drawn for each T1 map, which could have introduced different partial volume contributions. Fatigue effects could have affected the in vivo study since the sequence order was not randomized. In vivo T1 times were only measured in the septum. Therefore, comparison of reproducibility in the septum may not be reflective of other regions. Our in vivo data were not motion corrected because no commercial image registration technique was available for our imager. Despite specific care taken to ensure that the delineated myocardial area was contained within the myocardium in all T1-weighted images, motion-induced artifacts could have led to some bias in T1 estimates. The effect of contrast agent and contrast dose was not evaluated in this study. Finally, this



**Figure 5:** Box and whisker plots show, *A*, ECV measurements and, *B*, ECV reproducibility in healthy subjects by using the four T1 mapping sequences. ECV reproducibility was measured as the absolute difference between two ECVs, which were calculated from the second precontrast examination and the first postcontrast examination (*ECV #1*) and the second precontrast examination and the second postcontrast examination (*ECV #2*). Variations were observed in ECV measurements among the four T1 mapping sequences ( $P < .001$ ). Similar ECV measurements were obtained with MOLLI and ShMOLLI ( $\sim 0.27$  vs  $\sim 0.26$ ;  $P = .13$ ). Lower ECV values were obtained with SAPHIRE ( $\sim 0.20$ ) and SASHA ( $\sim 0.18$ ) compared with MOLLI or ShMOLLI ( $P < .001$ ). The difference between SAPHIRE and SASHA was statistically significant ( $P = .002$ ). Reproducibility of ECV measurements ranged from 0.01 to 0.02 for all sequences. There was no statistically significant difference for ECV reproducibility among the four sequences ( $P = .11$ ).

study was performed in healthy adults. Patients will demonstrate a wide range of pathologic myocardial T1 and ECV values, and greater variability in contrast agent excretion rates, heart rates, and motion artifact compared with healthy volunteers, which may affect the results.

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