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Coronary Artery Disease

Determination of Location, Size, and Transmurality of Chronic Myocardial Infarction Without Exogenous Contrast Media by Using Cardiac Magnetic Resonance Imaging at 3 T

Avinash Kali, MS; Ivan Cokic, MD; Richard L.Q. Tang, MD; Hsin-Jung Yang, MS; Behzad Sharif, PhD; Eduardo Marbán, MD, PhD; Debiao Li, PhD; Daniel S. Berman, MD; Rohan Dharmakumar, PhD

Background—Late-gadolinium–enhanced (LGE) cardiac MRI (CMR) is a powerful method for characterizing myocardial infarction (MI), but the requisite gadolinium infusion is estimated to be contraindicated in ≈20% of patients with MI because of end-stage chronic kidney disease. The purpose of this study is to investigate whether T₁ CMR obtained without contrast agents at 3 T could be an alternative to LGE CMR for characterizing chronic MIs using a canine model of MI.

Methods and Results—Canines (n=29) underwent CMR at 7 days (acute MI [AMI]) and 4 months (chronic MI [CMI]) after MI. Infarct location, size, and transmurality measured by using native T₁ maps and LGE images at 1.5 T and 3 T were compared. Resolution of edema between AMI and CMI was examined with T₂ maps. T₁ maps underestimated infarct size and transmurality relative to LGE images at 1.5 T and 3 T, which was not observed in CMI (P=0.49 and P=0.81, respectively) at 3 T. T₁ maps underestimated infarct size and transmurality relative to LGE images at 1.5 T. Relative to the remote territories, T₁ of the infarcted myocardium was increased in CMI (P<0.05) and T₂ of the infarcted myocardium was increased in AMI (P<0.001) but not in CMI (P>0.20) at both field strengths. Histology showed extensive replacement fibrosis within the CMI territories. CMI detection sensitivity and specificity of T₁ CMR at 3 T were 95% and 97%, respectively.

Conclusions—Native T₁ maps at 3 T can determine the location, size, and transmurality of CMI with high diagnostic accuracy. Patient studies are necessary for clinical translation. (Circ Cardiovasc Imaging. 2014;7:471-481.)

Key Words: fibrosis ▪ myocardial infarction

Prognostic outcome in patients with myocardial infarction (MI) is significantly determined by the location, size, and transmurality of the MI.¹⁻⁵ During the past decade, late-gadolinium–enhanced (LGE) cardiac MRI (CMR) has evolved into a robust noninvasive imaging technique for detecting acute MIs (AMIs) and chronic MIs (CMIs) with excellent diagnostic accuracy and prognostic significance.⁶⁻¹¹ However, accurate infarct sizing using LGE imaging is limited by the gadolinium kinetics.⁹⁻¹¹ Effective nulling of the remote myocardium,¹² and its qualitative nature. Contrast-enhanced T₁ mapping has been proposed as a potential alternative because it is quantitative in nature and does not require nulling of the remote myocardium.¹³,¹⁴ Nevertheless, like LGE imaging, the T₁ value of infarcted myocardium in contrast-enhanced T₁ mapping depends on the gadolinium kinetics.¹⁵ Moreover, once contrast-enhanced imaging is deemed necessary for assessment of myocardial viability, all other imaging sequences are typically required to be prescribed ahead of LGE imaging, which could impose practical limitations on the execution of the imaging examination, especially when rapid assessment of viability is all that may be necessary. Finally, perhaps most importantly, contrast-enhanced imaging requires administration of a gadolinium chelate, which is contraindicated in patients with chronic end-stage kidney disease,¹⁶ which is a rising epidemic.¹⁷ In fact, according to the US Renal Data System, the fraction of patients with cardiovascular disease who have chronic kidney disease is >40%. Recent studies have shown that ≥20% of AMI (ST-segment–elevation MI and non–ST-segment–elevation MI) patients have late-stage chronic kidney disease (glomerular filtration rate <45 mL/min per 1.73 m²), in whom LGE is expected to be contraindicated.¹⁸,¹⁹

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By definition, native T₁ mapping does not require exogenous contrast media. Hence, in addition to the patients
with renal insufficiency, the technique can be safely used in significant fraction of patients for whom LGE imaging or contrast-enhanced T1 mapping is warranted but are contra-indicated for gadolinium. Recent studies have shown that native T1 mapping can reliably detect AMI at both 1.5 T and 3 T.\textsuperscript{13,20–22} In contrast, the diagnostic performance of native T2 mapping to detect CMI has been shown to be poor at 1.5 T.\textsuperscript{13} Preliminary studies in nonischemic cardiac pathologies in animals and humans have noted intrinsic T2 dependence on myocardial collagen content.\textsuperscript{23} Recent studies have demonstrated the tremendous potential of native T1 mapping at 3 T to reliably detect and quantify diffuse myocardial fibrosis in nonischemic settings, such as aortic stenosis,\textsuperscript{24} hypertrophic cardiomyopathy,\textsuperscript{25,26} and dilated cardiomyopathy.\textsuperscript{25,26}

We hypothesized that magnetic field–dependent T2 elongations permit native T1 mapping to reliably detect and quantify replacement myocardial fibrosis associated with CMI at 3 T. To test our hypothesis, we rigorously studied the native T1 characteristics against LGE features of myocardial images acquired at 1.5 T and 3 T using canine models of AMI and CMI.

**Methods**

**Animal Model**

Canines (n=33; 20–25 kg body weight) were studied according to the protocols approved by Institutional Animal Care and Use Committees. MI was created by ligating the left anterior descending artery for 3 hours followed by reperfusion. Animals were allowed to recover for 7 days before the CMR studies.

**CMR Studies**

Four canines died during the first few hours of reperfusion despite resuscitation efforts. The remaining 29 canines underwent CMR studies at 7 days (acute) and 4 months (chronic) after reperfusion. Nineteen of the 29 canines were scanned on a 3-T clinical MRI system (MAGNETOM Verio, Siemens Healthcare), whereas the remaining 10 canines were studied according to the clinical protocol approved by Institutional Animal Care and Use Committees. MI was created by ligating the left anterior descending artery for 3 hours followed by reperfusion. Animals were allowed to recover for 7 days before the CMR studies.

**Image Analyses**

T1 and T2 maps were constructed from the native T1-weighted and T2-weighted images, respectively. All image analyses were performed on cvi42 image analysis software (Circle Cardiovascular Imaging Inc, Calgary, Canada). Remote (viable) myocardium was identified on the LGE image because the region showed no hyperintensity and a reference region of interest was drawn in it. Infarcted myocardium was identified on the LGE image as the region with mean signal intensity (SI) >5 SDs than that of reference region of interest.\textsuperscript{27–29} Hypointense cores of microvascular obstruction that were not detected as infarcted myocardium on LGE images by the thresholding criterion were manually included in the final analysis for infarct size and transmurality.

The reference region of interest drawn on LGE image was copied on to the corresponding T1 map. Infarcted myocardium was then identified on the T1 map using the mean+5SD criterion. To account for the dependence of Modified Look-Locker Inversion Recovery T1 values on heart rate, the T1 values were corrected, and the threshold was further adjusted as previously described.\textsuperscript{13} Hypointense cores of acute hemorrhage or chronic iron deposition\textsuperscript{30,31} that were not detected as infarcted myocardium on T1 maps by the thresholding criterion were manually included in the final analysis for infarct size and transmurality.

Infarct sizes from both LGE images and T1 maps were measured as the percentage of total LV volume, as well as on the basis of standard American Heart Association 17-segment model. Measurements from the 17th segment were excluded from the final analysis to discount the partial volume effects at the apical cap. Infarct transmurality was determined as the percentage extent of the infarct along 100 equally spaced chords on each slice. Mean transmurality was obtained by averaging the infarct transmurality across all the chords that have ≥1% scar extent. T1 and T2 values of the remote and infarcted myocardium (as identified on LGE images using mean+5SD criterion) were measured from T1 and T2 maps, respectively. Hypointense cores within infarcted myocardium were excluded from this analysis to eliminate the confounding effects of acute hemorrhage or chronic iron deposition on acute myocardial edema or chronic replacement fibrosis.

| Table 1. Typical Imaging Parameters Used to Acquire Different Cardiac MR Images at 1.5 T and 3 T |
|-----------------|-----------------|-----------------|-----------------|-----------------|---|
| Imaging Method  | Cine            | Native T1 map   | Native T2 map   | LGE             |   |
| Field strength | 3 T            | 1.5 T           | 3 T            | 3 T            | 1.5 T|
| Sequence       | Balanced SSFP  | Modified look-locker inversion recovery | T2-prepared SSFP | IR: prepared GRE |
| TR/TE, ms      | 3.2/1.6        | 3.5/1.75        | 2.2/1.1        | 2.4/1.2        | 2.8/1.4        | 2.2/1.1        | 3.0/1.5        | 3.5/1.75 |
| Flip angle     | 50°            | 70°             | 35°            | 50°            | 70°             | 25°     | 40° |
| Bandwidth (Hz/pixel) | 1371         | 930             | 1057           | 1002           | 1371           | 1002         | 586     | 1002 |
| In-plane resolution | 1.3×1.3 mm²   | 6 mm            |                |                |                |            |    |
| Slice thickness| 25–30 cardiac phases | 8 TIs; 2 inversion blocks of 3+5 images; minimum TI=110 ms; TI increment=80 ms| T2-preparation times of 0, 24 and 55 ms | Optimal TI to null the remote myocardium |   |

GRE indicates gradient recalled echo; LGE, late-gadolinium enhancement; SSFP, steady-state free precession; TE, echo time; and TR, repetition time.
Statistical Analyses

Statistical analyses were performed using IBM SPSS Statistics (version 21.0, IBM Corporation, Armonk, NY). Normality of the data was tested using the Shapiro–Wilk test and quantile–quantile plots. Depending on the normality of the data, percentage infarct size and mean transmurality were compared between LGE images and T1 maps using either paired t test or Wilcoxon signed-rank test. Additionally, mixed-model ANOVA was used to compare percentage segmental infarct size measured from the 2 techniques. Bland–Altman analysis was performed to estimate the agreement between the 2 techniques. Simple linear regression was performed to estimate the correlation between the 2 techniques with respect to infarct size and transmurality measurements. Measurements from the native T1 maps and LGE images were chosen as the dependent and explanatory variables, respectively. The slope and the intercept of the best fit line were estimated as the dependent and explanatory variables, respectively. Using LGE images as the gold standard, sensitivity and specificity of native T1 maps to detect infarcted myocardium were compared. The slope and the intercept of the best fit line were compared using mixed-model ANOVA. Similarly, percentage change in the LGE-SI of infarcted myocardium relative to remote myocardium at the segmental level were measured. Receiver-operating characteristic (ROC) analysis was performed to measure area under the curve (AUC). The predictor variable used to generate the ROC curves was the infarct size measured on a segmental basis from the T1 maps. T1 and T2 values of the remote and infarcted myocardium were compared using mixed-model ANOVA. Similarly, percentage change in the LGE-SI of infarcted myocardium relative to remote myocardium was compared with the percentage change in T1. Statistical significance was set at P<0.05 for all analyses.

Results

Detection of Acute MI at 3 T

All canines sustained MIs as verified by the presence of gadolinium hyperenhancement on LGE images acquired at 7 days after reperfusion. Representative LGE images and T1 maps acquired at 7 days after MI from a canine scanned at 3 T are shown in Figure 1. Bulls-eye plots depicting the infarct extent on 17-segment model and transmurality are also shown for both LGE images and T1 maps in Figure 1. Infarct location and spatial extent were visually well correlated between LGE images and T1 maps. In AMI at 3 T, T1 maps modestly overestimated infarct size (13.2±8.4% versus 11.6±6.8%; P=0.007) and transmurality (64±19% versus 56±17%; P=0.007) relative to LGE images. Mean segmental infarct size measured using T1 maps was also greater than that measured using LGE images (P=0.016). Bland–Altman analysis showed good agreement between LGE images and T1 maps for measuring infarct size (bias, 2.22±2.34%; Figure 2A) and transmurality (bias, 7.07±10.25%; Figure 2B). Strong correlations were observed between LGE images and T1 maps for measuring infarct size (R², 0.94; slope, 1.20, P=0.011; intercept, 0.01, P=0.98; Figure 2C) and transmurality (R²=0.72; slope, 0.93, P=0.62; intercept, 11.14; P=0.20; Figure 2D). At 3 T, T1 maps detected AMI in 149 of 158 segments that were positive for infarction on LGE images (94% sensitivity; 95% confidence interval [CI], 90–98). T1 maps were negative for AMI in 138 of 146 segments (94% specificity; 95% CI [91–98]). ROC analysis showed that the AUC was 0.96 (Figure 2E).

Detection of CMI at 3 T

Representative LGE images and T1 maps, along with the bulls-eye plots for infarct extent and transmurality, acquired from a canine scanned at 3 T 4 months after MI are shown in Figure 3. Infarct locations and its spatial extent were visually identical on LGE images and T1 maps in CMI. There was no significant difference between the LGE images and

![Figure 1](http://circimaging.ahajournals.org/) Detecting acute myocardial infarction at 3 T. Representative late-gadolinium–enhanced (LGE) images and T1 maps of basal, midventricular, and apical slices acquired at 7 days after myocardial infarction from a canine scanned at 3 T are shown. Infarcted myocardium (highlighted blue pixels in the processed images) was identified on both LGE images and T1 maps using the mean+5SD criterion with respect to the reference region of interest drawn in remote myocardium (blue contour). Bulls-eye plots depicting the extent and transmurality of the infarcted myocardium are also shown for both LGE images and T1 maps. The number within each segment indicates the percentage volume of that segment that was detected as infarcted myocardium by the mean+5SD criterion. For transmurality, each slice was divided into 100 equally spaced chords with the first chord placed at the anterior insertion of the right ventricle into the left ventricle. Each concentric ring on the Bulls-eye plot represents each short-axis slice with the most basal slice represented by the outermost ring.
T₁ maps for measuring infarct size (5.6±3.7% versus 5.5±3.7%; \(P=0.61\)) and transmurality (44±15% versus 46±15%; \(P=0.81\)). Mean segmental infarct size, measured using T₁ maps, was not different compared with that measured using LGE images (\(P=0.49\)). Bland–Altman analysis showed excellent agreement between LGE images and T₁ maps for measuring infarct size (bias, −0.08±0.68%; Figure 4A) and transmurality (bias, 0.45±8.14%; Figure 4B). Excellent correlations were observed between LGE images and T₁ maps for measuring infarct size (\(R^2, 0.97; \text{slope}, 0.98, P=0.68; \text{intercept}, 0.02, P=0.94\); Figure 4C) and transmurality (\(R^2, 0.75; \text{slope}, 0.84, P=0.18; \text{intercept}, 8.11, P=0.18\); Figure 4D). At 3 T, T₁ maps detected CMI in 135 of 142 segments that were positive for infarction on LGE images (95% sensitivity; 95% CI [92–99]). T₁ maps were negative for CMI in 158 of 162 segments (97% specificity; 95% CI [95–100]). ROC analysis showed that the AUC was 0.99 (Figure 4E).

**Detecting AMI at 1.5 T**

Representative LGE images and T₁ maps, along with bulls-eye plots (obtained using the mean+5SD criterion), acquired from a canine scanned at 1.5 T at 7 days after MI are shown in Figure I in the Data Supplement. Infarct location was visually well correlated between LGE images and T₁ maps at 1.5 T. However, using the mean+5SD criterion at 1.5 T, T₁ maps significantly underestimated the infarct size (9.4±5.6% versus 15.5±9.4%, respectively; \(P<0.001\)) and transmurality (59±5% versus 76±6%, respectively; \(P<0.001\)) in AMI relative to LGE images. Segmental comparison of infarct sizes in AMI showed significant underestimation by T₁ maps compared with LGE images (\(P<0.001\)). Bland–Altman analysis showed poor agreement between LGE images and T₁ maps for measuring infarct size (bias, −1.76±3.27%; Figure 5B) measured using the mean+5SD criterion. However, strong correlations were observed between LGE images and T₁ maps for measuring acute infarct size (\(R^2, 0.86; \text{slope}, 0.57, P<0.001; \text{intercept}, −1.40, P=0.36\); Figure 5C) and transmurality (\(R^2, 0.77; \text{slope}, 0.71, P=0.06; \text{ intercept}, 4.63, P=0.66\); Figure 5D). At 1.5 T, T₁ maps were positive for AMI in 92 of 110 segments (84% sensitivity; 95% CI [77–91]) and negative for AMI in 37 of 50 segments (74% specificity; 95% CI [62–86]). ROC analysis showed that the AUC was 0.86 (Figure 5E). Using the previously reported mean+3SD criterion for detecting AMI on T₁ maps at 1.5 T, infarct size (16.4±8.2%) and transmurality (81±9%) measured using T₁ maps were not significantly different from those measured using the mean+5SD criterion on LGE images (\(P=0.28\) for infarct size and \(P=0.18\) for transmurality).

**Detecting CMI at 1.5 T**

Representative LGE images and T₁ maps, along with bulls-eye plots (obtained using the mean+5SD criterion), acquired from a canine scanned at 1.5 T at 4 months after MI are shown in Figure II in the Data Supplement. Mean infarct size (2.1±1.2% versus 4.8±1.8%; \(P<0.001\)) and transmurality (47±7% versus 66±9%; \(P<0.001\)) measured on T₁ maps using the mean+5SD criterion in CMI were significantly lower than those measured on LGE images. Segmental comparison of infarct sizes in CMI showed significant underestimation by T₁ maps compared with LGE images (\(P<0.001\)). Bland–Altman analysis showed poor agreement between LGE images and T₁ maps for measuring infarct size (bias, −2.74±1.31%; Figure 6A) and transmurality (bias, −19.67±6.70%; Figure 6B). Moderate correlations were observed between LGE images and T₁ maps for measuring infarct size (\(R^2, 0.44; \text{slope}, 0.43, P=0.004; \text{intercept}, −0.03, P=0.97\); Figure 6C) and transmurality (\(R^2, 0.51; \text{slope}, 0.61, P=0.18\) for transmurality).
**Figure 3.** Detecting chronic myocardial infarction (MI) at 3 T. Representative late-gadolinium–enhanced (LGE) images and $T_1$ maps of basal, midventricular, and apical slices acquired at 4 months after MI from a canine scanned at 3 T are shown. Infarcted myocardium (highlighted dark blue pixels in the processed images) was identified on both LGE images and $T_1$ maps as in Figure 1. Hypointense core of chronic iron deposition within the hyperintense infarcted myocardium was not detected as infarcted myocardium by the mean+5SD criterion and was manually included in the final analysis (highlighted light blue pixels in the processed images). Bulls-eye plots depicting the extent and transmurality of the infarcted myocardium are also shown for both LGE images and $T_1$ maps. Excellent correlations were observed between LGE images and $T_1$ maps in terms of the location, spatial extent, and transmurality of the infarcted myocardium. Magnified views (right) of the infarcted myocardium detected on the midventricular and apical slices clearly show the concordance between LGE images and $T_1$ maps.

$P=0.10$; intercept, 6.60, $P=0.65$; Figure 6D). At 1.5 T, $T_1$ maps were positive for CMI in 52 of 90 segments (58% sensitivity; 95% CI [48–68]) and negative for CMI in 55 of 70 segments (78% specificity; 95% CI [69–88]). ROC analysis showed that AUC was 0.79 (Figure 6E). Using the less stringent mean+3SD criterion for detecting CMI on $T_1$ maps at 1.5 T, $T_1$ maps still significantly underestimated the infarct size and transmurality relative to those measured by using mean+5SD criterion on LGE images (infarct size from $T_1$ map: 3.4±1.6%, $P<0.001$; transmurality from $T_1$ map: 52±20%, $P<0.001$).

**T1, T2, and LGE Characteristics of Infarcted Myocardium at 3 T and 1.5 T in Acute and Chronic Infarctions**

Table 2 summarizes the $T_1$, $T_2$, and LGE-SI characteristics of infarcted and remote myocardium at 3 T and 1.5 T at 7 days and 4 months after MI. Representative LGE images, $T_1$ maps, and $T_2$ maps acquired from 4 different canines at 3 T and 1.5 T during the acute and chronic phases of MI are shown in Figure 7.

Compared with remote myocardium, mean $T_1$ and $T_2$ of the infarcted myocardium were increased by 329±119 and 18±6 ms, respectively, in AMI at 3 T ($P<0.001$ for both cases). In terms of infarcted to remote myocardium contrast, percentage change in LGE-SI was 28-fold higher than the percentage change in $T_1$ ($P<0.001$). However, the coefficient of variation of the percentage change in LGE-SI was 2-fold higher than the percentage change in $T_1$ (0.66 versus 0.30), indicating a greater variability in LGE versus $T_1$ image contrast.

In CMI, significant $T_1$ increase was still visually evident within infarcted myocardium at 3 T, whereas edema within the infarcted myocardium, typically visualized via $T_2$ images, seemed to have resolved. Mean $T_1$ of infarcted myocardium in CMI at 3 T was increased by 239±104 ms with respect to remote myocardium ($P<0.001$), whereas mean difference in $T_2$ values of infarcted and remote myocardium in CMI at 3 T was not statistically significant (2±3 ms; $P=0.19$). Mean $T_1$ of the infarcted myocardium in CMI was significantly lower than that in AMI ($P<0.001$). However, no significant difference was observed between mean $T_1$ values of remote myocardium measured during the acute and chronic phases ($P=0.21$).

Consistent with the acute studies, percentage change in LGE-SI was 40-fold higher than the percentage change in $T_1$ ($P<0.001$). However, the coefficient of variation of percentage change in LGE-SI was 1.5-fold higher (0.65) compared with the percentage change in $T_1$ (0.42), again indicating a higher degree of variability in LGE versus $T_1$ image contrast.

In AMIs at 1.5 T, significant $T_1$ increase was visually evident within infarcted myocardium, whereas moderate $T_1$ increase was visible in infarcted myocardium. Mean $T_1$ of infarcted myocardium at 1.5 T in AMI was 184±77 ms higher.
than that of remote myocardium \((P<0.001)\), whereas mean 
T1 of infarcted myocardium was 20±7 ms higher than that 
of remote myocardium \((P<0.001)\). Percentage change in the 
LGE-SI was ≈26-fold higher than the percentage change in T1 
at 1.5 T \((P<0.001)\). Compared with 1.5 T, infarcted to remote 
myocardium T1 contrast in AMI was ≈2-fold higher at 3 T.

Four months after MI, neither T1 nor T2 increase was visually 
evident within infarcted myocardium at 1.5 T. Mean T1 value 
of infarcted myocardium at 1.5 T in CMI was mildly higher 
by 89±38 ms than that of remote myocardium \((P=0.037)\). 
Mean difference in T2 values of infarcted and remote myo-
cardium was not statistically different from 0 (2±5 ms; 
\(P=0.55)\). Mean T1 of the infarcted myocardium in CMI was 
significantly lower than that in AMI \((P<0.001)\). No significant 
difference was observed between the mean T1 values of the 
remote myocardium during the acute and chronic periods of 
MI \((P=0.23)\). Percentage change in the LGE-SI was 34-fold 
higher than percentage change in T1 at 1.5 T \((P<0.001)\).

Figure 4. Diagnostic performance of native T1 maps for detecting chronic myocardial infarction at 3 T. Bland–Altman analysis showed 
excellent agreement between late-gadolinium–enhanced (LGE) images and T1 maps for measuring infarct size (A) and transmurality (B) during the chronic phase at 3 T. Excellent correlations were observed between LGE images and T1 maps for measuring infarct size \((R^2, 0.97; C)\) and transmurality \((R^2, 0.75; D)\). Receiver–operating characteristic analysis showed that the area under the curve (AUC) was 0.99 (E). LV indicates left ventricle.

Figure 5. Diagnostic performance of native T1 maps for detecting acute myocardial infarction (AMI) at 1.5 T. Bland–Altman analysis showed 
moderate agreement between late-gadolinium–enhanced (LGE) images and T1 maps for measuring infarct size (A) and transmurality (B) using 
the mean+SD criterion at 1.5 T in AMI. T1 maps significantly underestimated infarct size and transmurality compared with LGE images. 
However, strong correlations were observed between LGE images and T1 maps for measuring acute infarct size \((R^2, 0.86; C)\) and transmurality \((R^2, 0.77; D)\). Receiver–operating characteristic analysis showed that area under the curve (AUC) was 0.86 (E). LV indicates left ventricle.
Compared with 1.5 T, infarcted to remote myocardium T₁ contrast in CMI was ≈50% higher at 3 T.

**Histopathologic Validation of Replacement Fibrosis in CMI**

Figure 8 shows representative LGE images and T₁ maps acquired at 3 T from 3 different canines at 4 months after reperfusion along with slice-matched ex vivo triphenyl tetrazolium chloride and elastin Masson trichrome staining images. Both LGE images and T₁ maps agreed well with ex vivo triphenyl tetrazolium chloride images in terms of the spatial location of the infarction. Elastin Masson trichrome staining showed extensive replacement fibrosis within infarcted myocardium, which validated that T₁ hyperintensity in the CMI predominantly arose from fibrosis. Similar evidence was observed in the other animals.

**Discussion**

Characterizing CMIs using CMR has immense clinical importance for predicting long-term LV function, assessing the efficacy of therapeutic regeneration, and risk stratifying patients for cardiac defibrillator implantation. However, the use of LGE imaging for this purpose is partly limited by the contraindication of gadolinium infusion in ≈20% of the patients with AMI with chronic end-stage kidney disease. Noncontrast approaches for viability imaging can, therefore, be of significant value for the clinical and therapeutic management of patients with MI.

**Table 2. T₁, T₂, and LGE Signal Intensity Characteristics of Acute and Chronic Myocardial Infarction at 1.5 T and 3 T**

<table>
<thead>
<tr>
<th>Field Strength</th>
<th>3 T</th>
<th>1.5 T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time after MI</td>
<td>Day 7</td>
<td>Month 4</td>
</tr>
<tr>
<td>Tissue type</td>
<td>Remote</td>
<td>Infarcted</td>
</tr>
<tr>
<td>Native T₁, ms</td>
<td>1230±63</td>
<td>1563±154</td>
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<tr>
<td>Native ΔT₁ between remote and infarcted myocardium, ms</td>
<td>329±119</td>
<td>239±104</td>
</tr>
<tr>
<td>T₂, ms</td>
<td>46±4</td>
<td>64±9</td>
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<tr>
<td>ΔT₂ between remote and infarcted myocardium, ms</td>
<td>18±6</td>
<td>2±3</td>
</tr>
<tr>
<td>%Change in native T₁ with respect to remote</td>
<td>26±8</td>
<td>19±7</td>
</tr>
<tr>
<td>%Change in LGE signal intensity with respect to remote</td>
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<td>790±513</td>
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<tr>
<td>Sensitivity of native T₁ maps</td>
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<tr>
<td>Specificity of native T₁ maps</td>
<td>94%</td>
<td>97%</td>
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LGE indicates late-gadolinium enhanced; and MI, myocardial infarction.
Our study confirms the hypothesis that native T1 mapping at 3 T can reliably characterize CMIs with high specificity and sensitivity. Using a canine model of MIs and threshold-based detection of infarcted myocardium, we have demonstrated that native T1 maps at 3 T can accurately determine location, size, and transmurality of CMI just as well as LGE CMR. We also found that using the same threshold-based criterion on native T1 maps at 1.5 T tended to significantly underestimate infarct size and transmurality obtained from LGE images in both AMI and CMI. We also tested whether using the previously tested, less stringent, mean+3SD criterion significantly improves the diagnostic performance of T1 mapping at 1.5 T. Consistent with the previously reported observations, our results indicated that T1 maps at 1.5 T can reliably determine infarct size using the mean+3SD criterion in AMI but significantly underestimate infarct size at 1.5 T in the CMI despite the less stringent criteria. The ability to reliably detect infarcted myocardium at 3 T compared with 1.5 T is further explained by our findings that infarcted to remote myocardium T1 contrast is 2-fold higher at 3 T relative to 1.5 T in AMI, and 1.5-fold higher in CMI. Our results suggested that native T1 mapping at 3 T can be a reliable alternative to LGE for characterizing CMI with the potential for clinical translation. In addition, our results are consistent with previously reported observations that myocardial edema, as detected using T2-based imaging, resolves in the chronic phase of infarction, and T2-based imaging in conjunction

Figure 7. T1 and T2 characteristics of infarcted myocardium at 1.5 T and 3 T during acute and chronic phases of infarction. Representative late-gadolinium–enhanced (LGE) images, T1 maps, and T2 maps acquired at 1.5 T and 3 T from 4 different canines at 7 days and 4 months after myocardial infarction (MI) are shown. Arrows point to the hyperintense sites of LGE, T1, and T2. Significant T1 and T2 increases were visually evident within the infarcted territories in acute MI (AMI) at 3 T. Whereas T1 elevations persisted at 4 months after MI at 3 T, T2 of the infarcted myocardium returned to baseline levels. At 1.5 T, T1 and T2 of infarcted myocardium were significantly increased in AMI. However, both T1 and T2 values of the infarcted myocardium were not visually different from those of remote myocardium in chronic MI at 1.5 T.

Figure 8. Histopathologic validation of replacement fibrosis detected on late-gadolinium–enhanced (LGE) images and native T1 maps during the chronic phase of myocardial infarction (MI) at 3 T. Representative LGE images and T1 maps acquired from 3 different canines scanned at 3 T at 4 months after MI are shown along with the corresponding ex vivo slice-matched triphenyl tetrazolium chloride (TTC)-stained and elastin Masson trichrome (EMT)-stained images. Highlighted blue pixels on the processed images show the site of infarction on LGE images and T1 maps, whereas arrows point to the site of infarction in TTC and EMT images. Both LGE images and T1 maps agreed well with ex vivo TTC images in terms of spatial location of the infarcted myocardium. T1 maps could reliably detect infarctions ranging in size from 1.2% of the total LV (Dog 1) to 12.9% of the total LV (Dog 3). Highlighted light blue pixels on the processed T1 map from dog 3 point to the presence of chronic iron deposition. Corresponding to the chronic iron deposition seen on T1 map, TTC image shows a yellow-brown discoloration in the necrotic core indicating the presence of iron. Additional histological validation using EMT staining confirmed extensive replacement fibrosis within the infarcted regions indicating that T1 hyperintensity in the chronic phase of infarction at 3 T predominantly arose from fibrosis. Scale bars on the magnified views of EMT images measure 2 mm.
with LGE imaging can be used to differentiate between AMIs and CMIs. Together, these techniques may allow for reliable T1 mapping of native myocardium at 3 T, which may be necessary for detecting AMI predominantly because of fibrosis. This is consistent with previous reports showing significant T1 elevations with diffuse myocardial fibrosis in nonischemic cardiomyopathies, such as aortic stenosis, hypertrophic cardiomyopathy, and idiopathic dilated cardiomyopathy.

Our study showed that one of the primary reasons that CMIs are more reliably characterized at 3 T is because of the biophysical differences in T1 relaxation of remote myocardium and infarcted myocardium at 3 T and 1.5 T. We found that because the field strength is increased from 1.5 T to 3 T, the T1 values of the noninfarcted (remote) myocardium and the infarcted (fibrotic) myocardium are increased by ≥29% and ≥40% (Table 2), respectively. This is consistent with previous studies, which have rigorously shown that T1 of a given tissue can increase between ≥10% and ≥70% at 3 T compared with 1.5 T, and that the extent of the increase is dependent on the type of tissue. Although the mechanistic underpinnings of native T1 elongation in CMIs are not entirely clear, there are a few possible explanations. One potential mechanism is that the apparent diffusion coefficient in CMIs is higher than that of remote myocardium, which implies greater diffusivity of water molecules, lower viscosity, lower correlation times of molecular motion, and hence longer T1 values. In addition, another possibility is the potential bias in T1 values measured using Modified Look-Locker Inversion Recovery sequences with steady-state free precession readouts, which may be subject to magnetization transfer effects. Robson et al have shown that magnetization transfer effects can lead to T1 underestimation by Modified Look-Locker Inversion Recovery. Scholz et al and Weber et al have shown that the magnetization transfer effects are reduced in AMIs and CMIs, which could potentially lead to longer apparent T1 values within infarcted myocardium. Nevertheless, further studies are necessary to fully elucidate the mechanisms and their relative contributions to the underlying T1 elongations observed in CMIs.

Our study showed that LGE images have ~30-fold higher contrast relative to the proposed native T1 maps at 3 T. Although the high image contrast of infarcted myocardium in LGE images is attributable to the use of gadolinium-based contrast agents, the imposed nulling of remote myocardium by inversion-recovery preparation is another significant contributor to the observed contrast. In this context, it should be noted that as in LGE imaging, inversion-recovery preparation may also be introduced to significantly improve image contrast between infarcted and remote myocardium in native T1-weighted techniques as well. Based on the T1 values of remote myocardium (1250 ms) and CMIs (1490 ms) at 3 T, an inversion-recovery preparation that nulls remote myocardium gives a 12% equilibrium magnetization available for readout from infarcted myocardium. Similarly, assuming that the contrast-enhanced T1 values (10 minutes after gadolinium injection) of remote and infarcted myocardium at 3 T are 400 and 230 ms, respectively, an inversion-recovery sequence that nulls remote myocardium (such as conventional LGE imaging) gives a 40% equilibrium magnetization available for readout from infarcted myocardium. This suggests that, if used, inversion-recovery preparation can potentially increase the image contrast between infarcted and remote myocardium by 900% compared with the current levels. Experimental studies are necessary to confirm these theoretical estimations. Nevertheless, although this is expected to improve the
visualization of CMI, the current T1 mapping approach evaluated here still provides excellent diagnostic accuracy.

Together with previous studies, our study has shown that native T1 mapping has great potential for widespread clinical applicability in the setting CMI. Although a few studies have assessed the prognostic significance of T1 hyperenhancement in AMI, future studies that elucidate the relationship of T1 hyperenhancement in the CMI to long-term LV function, collagen metabolism, and extracellular matrix remodeling are necessary.

Study Limitations
First, the sample size used in this study is relatively small but comparable with those used in previous studies in patients with MIs. Second, this study relied on identifying the remote territory on the basis of LGE. Additional studies are necessary to examine whether remote territories can be reliably identified solely on the basis of native T1 maps. Third, we did not evaluate the proposed approach in the clinical setting. Hence, additional studies are required to determine the diagnostic performance of native T1 maps in patients with CMI. Fourth, we limited our analysis to the mean+5SD threshold because this criterion has been shown to be robust for delineating infarcted myocardium in LGE imaging. Nevertheless, a comprehensive study comparing the different thresholding criteria with ex vivo histology-based infarct sizing may be necessary for further validation. However, such a study needs to take into account potential changes in T1 after animals are euthanized and registration between CMR images and ex vivo standard. Finally, our analysis was limited to left anterior descending infarctions. Additional studies are needed to extend our findings to infarctions in other coronary territories.

Conclusions
Native T1 mapping at 3 T can reliably determine infarct location, size, and transmurality of CMI with high diagnostic accuracy that is comparable with conventional LGE imaging. Given its nonreliance on exogenous contrast media, potential efficiency improvements associated with workflow during imaging sessions, and quantitative nature, native T1 mapping provides an appealing alternative for viability imaging when LGE imaging is contraindicated. Patient studies are necessary for clinical translation.

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Disclosures
None.

References
from infarct characterization. 
late-gadolinium–enhanced CMR, especially in patients who are contraindicated for gadolinium but would otherwise benefit from chronic MIs using a canine model of infarction. We show that the proposed CMR approach has excellent diagnostic accuracy in the quantitative assessment of infarct size and myocardial edema with high diagnostic accuracy:


CLINICAL PERSPECTIVE

Prognostic outcome in patients with myocardial infarction (MI) is significantly determined by the location, size, and transmurality of the MI. During the past decade, late-gadolinium–enhanced cardiac MRI (CMR) has evolved into a robust non-invasive imaging technique for detecting acute and chronic MI with excellent diagnostic accuracy. However, it is estimated that in ≈20% of the acute MI population with comorbidity of late-stage chronic kidney disease, late-gadolinium–enhanced CMR may be contraindicated. In this work, we propose and test a contrast-agent–free CMR approach for characterizing chronic MIs through a canine model of infarction. We show that the proposed CMR approach has excellent diagnostic accuracy relative to late-gadolinium–enhanced CMR. We anticipate that the proposed approach may be a compelling alternative to late-gadolinium–enhanced CMR, especially in patients who are contraindicated for gadolinium but would otherwise benefit from infarct characterization.
Supplementary Figure 1: Detecting acute myocardial infarction at 1.5T. Representative LGE images and T₁ maps of basal, mid-ventricular and apical slices acquired at 7 days post reperfusion from a canine scanned at 1.5T are shown. Infarcted myocardium was identified as in Figure 1. Good correlation was observed between LGE images and the T₁ maps in terms of location of the infarcted myocardium.
Supplementary Figure 2: Detecting chronic myocardial infarction at 1.5T. Representative LGE images and T₁ maps of basal, mid-ventricular and apical slices acquired at 4 months post reperfusion from a canine scanned at 1.5T are shown. The LGE image and T₁ map were poorly correlated with respect to the spatial extent and location of the infarcted myocardium. Note that in the apical slice, there is a complete mismatch in the infarcted myocardium detected by the LGE image and the T₁ map. T₁ hyperintensity
observed in the apical slice was possibly due to partial volume effects. Bulls-eye plots showed significant underestimation of infarct size and transmurality on T₁ maps relative to LGE images (p<0.001 for both cases).