Influence of Myocardial Hemorrhage on Staging of Reperfused Myocardial Infarctions With T2 Cardiac Magnetic Resonance Imaging

Insights Into the Dependence on Infarction Type With Ex Vivo Validation

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ABSTRACT

OBJECTIVES This study sought to determine whether T2 cardiac magnetic resonance (CMR) can stage both hemorrhagic and nonhemorrhagic myocardial infarctions (MIs).

BACKGROUND CMR-based staging of MI with or without contrast agents relies on the resolution of T2 elevations in the chronic phase, but whether this approach can be used to stage both hemorrhagic and nonhemorrhagic MIs is unclear.

METHODS Hemorrhagic (n = 15) and nonhemorrhagic (n = 9) MIs were created in dogs. Multiparametric noncontrast mapping (T1, T2, and T2*) and late gadolinium enhancement (LGE) were performed at 1.5- and 3.0-T at 5 days (acute) and 8 weeks (chronic) post-MI. CMR relaxation values and LGE intensities of hemorrhagic, peri-hemorrhagic, nonhemorrhagic, and remote territories were measured. Histopathology was performed to elucidate CMR findings.

RESULTS T2 of nonhemorrhagic MIs was significantly elevated in the acute phase relative to remote territories (1.5-T: 39.8 ± 12.8%; 3.0-T: 27.9 ± 16.5%; p < 0.0001 for both) but resolved to remote values by week 8 (1.5-T: −0.0 ± 3.2%; p = 0.678; 3.0-T: −0.5 ± 5.9%; p = 0.601). In hemorrhagic MI, T2 of hemorrhage core was significantly elevated in the acute phase (1.5-T: 17.7 ± 10.0%; 3.0-T: 8.6 ± 8.2%; p < 0.0001 for both) but decreased below remote values by week 8 (1.5-T: −8.2 ± 3.9%; 3.0-T: −5.6 ± 6.0%; p < 0.0001 for both). In contrast, T2 of the periphery of hemorrhage within the MI zone was significantly elevated in the acute phase relative to remote territories (1.5-T: 35.0 ± 16.1%; 3.0-T: 24.2 ± 10.4%; p < 0.0001 for both) and remained elevated at 8 weeks post-MI (1.5-T: 8.6 ± 5.1%; 3.0-T: 6.0 ± 3.3%; p < 0.0001 for both).

The observed elevation of T2 in the peri-hemorrhagic zone of MIs and the absence of T2 elevation in nonhemorrhagic MIs were consistent with ongoing or absence of histological evidence of inflammation, respectively.

CONCLUSIONS Hemorrhagic MIs are associated with persisting myocardial inflammation and edema, which can confound staging of hemorrhagic MIs when T2 elevations alone are used to discriminate between acute and chronic MI. Moreover, given the poor prognosis in patients with hemorrhagic MI, CMR evidence for myocardial hemorrhage with persistent edema may evolve as a risk marker in patients after acute MI. (J Am Coll Cardiol Img 2019;12:693–703) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
Staging myocardial infarctions (MIs), particularly differentiating the acute from the chronic phase of MI, is a common requirement for making clinical decisions. Over the past decade, cardiac magnetic resonance (CMR) has evolved to fill this need. Specifically, key studies have demonstrated that an approach combining both late gadolinium enhancement (LGE) and T₂-weighted CMR can be used to stage MI (1). Although LGE CMR (2) is the gold standard for accurately detecting irreversible myocardial injury (3,4), recent concerns about gadolinium-based contrast agents present challenges to their use in patients with severe renal dysfunction (5). Several studies have shown that native (contrast-free) T₁ mapping can be used to characterize MIs as well. Notably, the capability of native T₁ mapping for detecting acute MI based on a significant amount of edema within acute MI territories has been demonstrated (4-11). Recent studies by Kali et al. (12,13) have provided evidence that native T₁ mapping at 3.0-T, when combined with T₂-based imaging, can also enable characterization of chronic MIs without contrast agents. Thus, the collective evidence in the literature suggests that T₂ CMR is critical for imaging-guided staging of MIs when used in conjunction with contrast-enhanced infarct imaging (e.g., LGE) or contrast-free CMR (e.g., native T₁ mapping at 3.0-T).

A growing body of evidence supports the notion that hemorrhagic MIs are associated with prolonged inflammation, well after the formation of scar tissue (11,14,15). Because inflammation is typically associated with T₂ elevations, it is unclear whether the resolution of T₂ signals to baseline levels is sufficient to stage all (hemorrhagic and nonhemorrhagic) MI types. Moreover, given that the outcomes in post-MI patients are increasingly recognized to be dependent on MI type (16-19), there is strong motivation to reassess the capabilities of T₂ CMR in the staging of both hemorrhagic and nonhemorrhagic MIs.

We hypothesized that staging of MIs as acute (within 1 week of MI) or chronic (8 or more weeks after MI) based on resolution of T₂ CMR must take into account whether reperfused MIs are hemorrhagic or nonhemorrhagic. We tested our hypothesis in clinically relevant animal models of acute (<1 week after MI) and chronic MIs (8 weeks after MI) at 1.5- and 3.0-T, along with histopathologic analysis.

MATERIALS AND METHODS

ANIMAL PREPARATION AND HANDLING. Dogs (n = 27; weight 20 to 25 kg) were studied according to protocols approved by the institutional animal care and use committee. A time line of the canine studies is shown in Figure 1. Reperfused MI at the left anterior descending coronary artery territory was created with a no-flow ischemia in the left anterior descending coronary artery below the first diagonal for 3 h, followed by reperfusion. Animals were imaged with CMR under general anesthesia and mechanical ventilation on day 5 and week 8 post-MI, hereinafter referred to as the acute and chronic phases of MI, respectively. Animals that survived the MI were randomized for imaging at 1.5-T (1.5-T group) or 3.0-T (3.0-T group). After the week 8 CMR, animals were sacrificed, and their hearts were harvested for histology and immunohistochemistry.

CMR ACQUISITIONS AND ANALYSIS. CMR studies were performed in 1.5- and 3.0-T (Espree and Verio, respectively, Siemens Healthcare, Erlangen, Germany) clinical systems. After whole-heart shimming and scouting, electrocardiograph-gated, breath-held, contiguous, slice-matched short-axis T₁, T₂, and T₂* maps and LGE covering the whole left ventricle were acquired. LGE signal intensities and native T₂, T₂*, and T₁ values of hemorrhagic territories (core [Hemo+] and periphery of hemorrhage [Peri-Hemo+]) within MI, nonhemorrhagic territories (Hemo−), and remote (Remote) myocardium were measured using commercial software. Details of the imaging sequences and image analyses, including blinding, and interobserver and intraobserver, are provided in the Supplemental Appendix.

HISTOLOGY AND IMMUNOHISTOCHEMISTRY. Infarcted territories identified on CMR were visually matched to the infarcted sections delineated by triphenyltetrazolium chloride (TTC) staining using anterior papillary muscle as a landmark. Representative samples of infarcted and remote myocardium from these sections were selected for histopathologic analysis (hematoxylin and eosin [H&E] for tissue damage, Masson trichome for fibrosis, and Perl stain for iron) and immunohistochemistry (MAC387 for newly recruited macrophages). Within the infarcted regions, the presence of yellow-brown stain and iron in Perl stain was used to identify hemorrhagic regions. If infarcted territories showed evidence of MAC387-positive cells, the MI territories were confirmed for the presence of active inflammation in the chronic phase of MI.
STATISTICAL ANALYSIS. On the basis of CMR analysis, results were pooled into 8 groups (Supplemental Tables 1 and 2) based on field strength (1.5-T vs. 3.0-T), age of infarction (acute vs. chronic), and MI territory (Hemo−, Peri-Hemo, Hemo−). The data from each group were labeled on the basis of field strength, MI type, and age of MI. Statistical analysis was performed using IBM SPSS Statistics 23 (IBM Corp., Armonk, New York). The interobserver reliability in measuring LGE, T1, T2, and T2* values was assessed using an intraclass correlation coefficient (ICC). Bonferroni corrections were used to adjust the significance level for multiple comparisons. Additional details on statistical analysis are provided in the Supplemental Appendix.

RESULTS

Twenty-four animals were available for imaging (12 animals at 1.5-T and 12 at 3.0-T; 3 died during reperfusion). On T2* CMR, hemorrhage was evident in 15 animals (7 from the 1.5-T group and 8 from the 3.0-T group) and appeared hypointense both in the acute and chronic phases. The corresponding sections from these animals were positive for iron on histopathology. No hemorrhage was evident in the other animals (n = 9; absence of T2* loss and iron deposits within MI territories from corresponding histological sections). Some aspects of the T1 and T2 data from 11 animals have been previously reported (13). On the basis of LGE, a total of 958 imaging slices (LGE, T2*, T2, T1) were identified as positive for MI, but 62 of these images (T2*, T2, T1) were excluded from analysis because of uninterpretable image quality; thus, the final analysis was performed on 896 imaging slices.

Representative LGE images and corresponding noncontrast-enhanced T2*, T2, and T1 maps from animals with and without hemorrhage in the acute and chronic phases of MI, acquired at 1.5- and 3.0-T, are shown in Figures 2 and 3, respectively. Similar to previous studies (14,20), nonhemorrhagic MIs were identified as those MIs without T2* loses in the acute phase (Figures 2C and 3C) or chronic phase (Figures 2D and 3D), independent of field strength. These regions were visualized with marked hyperintensities on T2 maps at 1.5- and 3.0-T in the acute phase (Figures 2C and 3C, respectively). The same animals followed to the chronic phase did not show any hyperintensities within the MI zone on T2 maps at 1.5- or 3.0-T (Figures 2D and 3D, respectively). On T1 maps in the acute phase, these regions were visualized with marked hyperintensities at 1.5- and 3.0-T (Figures 2C and 3C, respectively). The infarcted regions of same animals followed to chronic phase of MI were visualized with mild T1 hyperintensities at 1.5-T (Figure 2D) and moderate to high T1 hyperintensities at 3.0-T (Figure 3D).

Similarly, hemorrhagic MIs were visualized as hypointense regions on T2* maps in acute and chronic phases at 1.5-T (Figures 2A and 2B) and 3.0-T (Figures 3A and 3B, respectively) within the MI territories identified on LGE CMR. On T2 maps acquired in the acute phase of MI, hemorrhagic territories identified on T2* maps were visualized as hypointense core surrounded by hyperintense rim on T2 map at 1.5-T (Figure 2A) and 3.0-T (Figure 3A). Notably, the core of the hemorrhage on T2 maps was
(A, B) Representative LGE images and native T2*, T2, and T1 maps acquired 5 days (acute) and 8 weeks (chronic) after reperfusion in a dog with hemorrhagic MI. (C, D) Representative LGE images and native T2*, T2, and T1 maps acquired 5 days (acute) and 8 weeks (chronic) after reperfusion in a dog without hemorrhagic MI. LGE = late gadolinium enhancement; MI = myocardial infarction.
(A, B) Representative LGE images and native T2*, T2, and T1 maps acquired 5 days (acute) and 8 weeks (chronic) after reperfusion in a dog with hemorrhagic MI. (C, D) Representative LGE images and native T2*, T2, and T1 maps acquired 5 days (acute) and 8 weeks (chronic) after reperfusion in a dog without hemorrhagic MI. LGE = late gadolinium enhancement; MI = myocardial infarction.
moderately hyperintense relative to the remote myocardium at both field strengths. In the chronic phase of MI, T1 maps showed moderately hyperintense regions surrounding the zone of T2* loss at 1.5-T (Figure 2B) and 3.0-T (Figure 3B). However, the core territories of MI (i.e., regions showing T2* loss) appeared to be mildly hypointense relative to the remote territories at both field strengths. In T2 maps, hemorrhage appeared hypointense relative to peri-hemorrhagic or nonhemorrhagic zones in the acute phase and hypointense relative to the remote myocardium in the chronic phase at 1.5- and 3.0-T.

The interobserver variability measures (ICCs) for all subset of measurements were >0.8. Mean and 95% confidence interval of ICC scores are provided in Supplemental Table S2. Mean LGE, T2*, T2, and T1 values of hemorrhagic, peri-hemorrhagic, non-hemorrhagic, and remote regions; respective relative differences with respect to the remote myocardium (ΔLGE [%], ΔT1 [%], ΔT2 [%], ΔT2* [%]); and absolute differences for T1, T2, and T2* (ΔT1, ΔT2, ΔT2*), along with comparisons, are given in Supplemental Tables 1 (1.5-T) and 2 (3.0-T).

**LGE AND NATIVE MULTIPARAMETRIC MAPPING OF HEMORRHAGIC AND NONHEMORRHAGIC MI AT 1.5- AND 3.0-T**

**LGE.** The effect of the age and composition of the MI as well as field strength on LGE, and the relative change in LGE (%) are shown in Supplemental Figure 1. Details are summarized here.

**Core hemorrhagic territories.** The relative changes of LGE signal intensities of hemorrhagic territories in the acute phase was significantly lower than those in the chronic phase at 1.5- and 3.0-T (p < 0.005). Consistent with previous reports (14), the acute MI territories with hemorrhage also showed evidence of microvascular obstruction on LGE, which was absent in the chronic MI territories with a history of reperfusion hemorrhage.

**Peri-hemorrhagic territories.** There were no significant differences in the relative changes of LGE signal intensities between the acute and chronic phases in the peri-hemorrhagic territories at 1.5- and 3.0-T (p = 0.105 at 1.5-T; p = 0.061 at 3.0-T), although there was a trend toward higher relative signal intensities in the chronic phase than in the acute phase at both field strengths.

**Nonhemorrhagic territories.** There were no significant differences in the relative changes in LGE signal intensities between the acute and chronic phases in the nonhemorrhagic territories (p = 0.414 at 1.5-T; p = 0.775 at 3.0-T).

**NATIVE T2**

The effect of age and composition of the MI, as well as field strength, on T2 and relative ΔT2 (%) are shown in Figure 4. T2 of all MI and remote territories were significantly higher at 1.5-T compared to 3.0-T (p < 0.005). At 1.5- and 3.0-T, T2 of all MI territories were higher in the acute phase than in the chronic phase. Other findings are summarized here.

**Core hemorrhagic territories.** Mean T2 of acute hemorrhagic MI territories was higher than mean T2 of remote myocardium at both field strengths (p < 0.005). However, in the chronic phase, mean T2 of hemorrhagic MI territories were lower than mean T2 of remote myocardium at both field strengths (p < 0.005). Mean ΔT2 of hemorrhagic zone in the acute phase was significantly higher than that in the chronic phase at both field strengths (p < 0.005 for both).

**Peri-hemorrhagic territories.** In the acute and chronic phases of MI, mean T2 of peri-hemorrhagic territories was significantly higher than mean T2 of remote territories at both field strengths (p < 0.05). Mean T2 of peri-hemorrhagic territories in the acute phase was significantly higher than that in the chronic phase (p < 0.005 at 1.5- and 3.0-T). Mean T2 of hemorrhagic territories in the acute and chronic phases of MI were significantly lower than mean T2 of peri-hemorrhagic territories at both field strengths (p < 0.005).

**Nonhemorrhagic territories.** In the acute phase, mean T2 of nonhemorrhagic acute MI territories was significantly higher than mean T2 of remote territories at both field strengths (p < 0.005). However, in the chronic phase, there was no difference in mean T2 between infarcted and remote myocardium (p = 0.720 at 1.5-T; p = 0.636 at 3.0-T). Notably, mean ΔT2 of nonhemorrhagic territories in the acute phase was significantly greater than that in the chronic phase (p < 0.005 at 1.5- and 3.0-T). Moreover, in the acute phase, mean ΔT2 of peri-hemorrhagic regions was not significantly different from mean ΔT2 of nonhemorrhagic regions (p = 0.32 at 1.5-T; p = 0.10 at 3.0-T). However, in the chronic phase, mean ΔT2 of peri-hemorrhagic regions was significantly higher than mean ΔT2 of nonhemorrhagic regions (p < 0.005 at 1.5- and 3.0-T).

**NATIVE T2* AND T1.** The effect of age and composition of MI on relative ΔT2* (%) and ΔT1 (%) are shown in Supplemental Figures 2 and 3, respectively, at 1.5- and 3.0-T. T2* of all MI and remote territories were significantly higher at 1.5-T compared to 3.0-T (p < 0.005), whereas T1* of all MI and remote territories were significantly lower at 1.5-T compared to 3.0-T.
(p < 0.005). Other findings are summarized in the following.

**Core hemorrhagic territories.** Mean $T_2^*$ of hemorrhagic territories was significantly lower relative to remote myocardium in the acute and chronic phases of MI at 1.5- and 3.0-T (p < 0.005). At 1.5-T, mean $T_2^*$ of hemorrhagic territories in the acute phase was larger than in the chronic phase of MI (p < 0.005), but this difference was not observed at 3.0-T (p = 0.239). In the acute phase of MI, mean $T_1$ was significantly higher in the hemorrhagic territories compared to the remote myocardium (p < 0.005 at 1.5- and 3.0-T). However, in the chronic phase, mean $T_1$ of hemorrhagic MI territories was lower than mean $T_1$ of the remote myocardium at 1.5-T (p < 0.005) but not different from one another at 3.0-T (p = 0.443). At 1.5- and 3.0-T, $T_1$ of hemorrhagic MI territories was significantly larger in the acute phase than in the chronic phase (p < 0.0001).

**Peri-hemorrhagic territories.** Mean $T_2^*$ in the acute phase of MI was significantly higher in the peri-hemorrhagic regions relative to remote territories (p < 0.005 at 1.5- and 3.0-T); however, there was no difference in the chronic phase (p = 0.426 at 1.5-T; p = 0.287 at 3.0-T). $T_2^*$ of hemorrhagic territories was significantly lower than $T_2^*$ of peri-hemorrhagic territories.
territories at both phases of MI ($p < 0.005$ at 1.5- and 3.0-T). $T_2^*$ of peri-hemorrhagic MI territories was significantly larger in the acute phase than in the chronic phase ($p < 0.05$ at 1.5- and 3.0-T). $T_1$ of the peri-hemorrhagic territories in the acute and chronic phases was significantly higher than in the remote myocardium ($p < 0.005$ at 1.5- and 3.0-T). At 1.5-T, mean $T_1$ of peri-hemorrhagic territories was not different between acute and chronic phases of MI ($p = 0.111$) but was lower in the chronic phase compared to the acute phase at 3.0-T ($p = 0.042$).

**Nonhemorrhagic territories.** Mean $T_2^*$ of non-hemorrhagic territories was significantly higher relative to remote myocardium in the acute phase of MI at 1.5- and 3.0-T ($p < 0.005$ for both) but was not different from remote myocardium in the chronic phases of MI ($p = 0.081$ at 1.5-T; $p = 0.536$ at 3.0-T). There was also no significant difference between $\Delta T_2^*$ of peri-hemorrhagic and nonhemorrhagic territories when compared for infarct age or field strength ($p > 0.20$ for all comparisons). At 1.5-T, mean $T_2^*$ of non-hemorrhagic territories in the acute phase was larger than in the chronic phase of MI ($p < 0.0001$), but this difference was not observed at 3.0-T ($p = 0.316$). Mean $T_1$ of the nonhemorrhagic territories in the acute and chronic phases of MI was significantly higher than mean $T_1$ of remote myocardium at 1.5- and 3.0-T ($p < 0.005$ for all). Notably, mean $\Delta T_1$ of nonhemorrhagic territories in the acute phase was greater than that in the chronic phase at both field

**FIGURE 5** Histopathologic Findings From Myocardial Tissue Section of Hemorrhagic and Nonhemorrhagic Chronic MIs

Representative ex vivo images ($T_2^*$-weighted and corresponding TTC stained sections) from dogs with hemorrhagic and nonhemorrhagic MIs. Remote myocardial sections from a dog with a history of hemorrhagic MI are shown for reference. TTC images were used to localize the infarct zone, and ex vivo $T_2^*$-weighted images were used to identify whether the infarcted zones were of hemorrhagic origin (based on hypointensities within infarcted myocardium). Histopathology (H&E for tissue damage, EMT for fibrosis, and Perl for iron, at 4× and 40×) and immunohistochemistry (MAC387) analyses were performed from corresponding segments collected from the infarct core and remote sections. H&E = hematoxylin and eosin; EMT = elastin masson trichrome; MI = myocardial infarction; TTC = triphenyltetrazolium chloride.
strengths (p < 0.005). There was no significant difference between ΔT₁ of peri-hemorrhagic and non-hemorrhagic regions at both phases of MI (p > 0.30 at 1.5-T and 3.0-T). T₁ of nonhemorrhagic MI territories was significantly larger in the acute phase than in the chronic phase (p < 0.006 at 1.5-T and 3.0-T).

**HISTOPATHOLOGY OF HEMORRHAGIC AND NONHEMORRHAGIC INFARCTIONS.** Representative histopathologic images from animals with hemorrhagic and nonhemorrhagic infarctions sacrificed at week 8 of MI are shown in Figure 5. TTC staining confirmed the presence or absence of infarcted myocardium. Specifically, TTC staining of hemorrhagic territories (identified as described in the following text) showed brownish stain within the infarct core, whereas this was not evident in non-hemorrhagic territories. H&E stains showed evidence of myocardial injury, and elastin masson trichrome stains showed extensive fibrosis within infarcted regions. Perl stains showed substantial localized iron within hemorrhagic territories (identified as MI regions with T²⁺* loses on ex vivo images). However, this was not evident in nonhemorrhagic territories (identified as MI regions without evidence of T²⁺* loses on ex vivo images) or remote myocardium from hemorrhagic or nonhemorrhagic MIs. Microstructural histopathologic features of remote myocardium obtained in animals with hemorrhagic and nonhemorrhagic MIs did not show evidence of tissue damage on H&E stains and little or no evidence of fibrosis. MAC387 stains showed active infiltration of newly recruited macrophages (~1 week) in regions of iron deposits (from hemorrhagic MIs), but this was not evident in MI regions without iron (nonhemorrhagic MIs).

**DISCUSSION**

More than a decade ago, Abdel-Aty et al. (1) demonstrated that T₂⁺ CMR can be used to discriminate between acute and chronic MIs. Their approach relied on the resolution of T₂ elevations, associated with edema in the acute phase of MI, to discriminate between acute and chronic MIs. Recent clinical studies reported in the literature, however, have suggested that T₂ elevations could continue to persist well into the chronic phase of MIs, when edema is expected to be fully resolved. In this study, we examined the capabilities and limitations of T₂⁺ CMR for discriminating between acute and chronic MIs in 2 important types of reperfused type MIs, namely, those with and those without hemorrhage. Specifically, we tested the hypothesis that the resolution of T₂ elevations (initially observed in the acute phase) in the chronic phase depends on the infarction type (hemorrhagic vs. nonhemorrhagic MIs) and that staging MIs based on T₂ CMR requires knowledge of MI type.

Consistent with previous reports on T₂ between acute and chronic phases of MI, nonhemorrhagic infarct zones showed significantly elevated T₂ in the acute phase that resolved to remote values by the chronic phase, independent of strength. However, in line with the recent observations by Bulluck et al. (11), this was not observed in the peri-hemorrhagic territories, as these regions showed modest elevation in T₂ relative to the remote myocardium. This finding was independent of field strength and was suggestive of persistent edema in peri-hemorrhagic territories at week 8 post-MI. Histopathologic analysis confirmed the presence of T₂ elevations surrounding iron deposits within fibrotic myocardium to be related to ongoing inflammation (recruitment of new macrophages) within the infarct core, providing a rationale as to why T₂ remains elevated well after the initial hemorrhagic injury. Hemorrhagic territories also showed interesting T₂ behavior between the acute and chronic phases. In the acute phase, these territories were hypointense relative to the peri-hemorrhagic regions but hyperintense relative to the remote territories. However, in the chronic phase, they were hypointense relative to the peri-hemorrhagic regions and remote myocardium, suggesting that at least a partial resolution of edema in the presence of iron deposits enables T₂ maps to generate negative contrast in chronic hemorrhagic MI territories at 1.5-T and 3.0-T. Hence, the findings here support the notion that hypointense chronic MI territories in T₂ maps at 1.5-T and 3.0-T could be interpreted as regions with a history of hemorrhagic damage, especially if they are localized within a rim of T₂ elevation.

This study also provided additional insight into changes in T₂⁺ and T₁ in hemorrhagic and non-hemorrhagic infarctions. First, mean T₂⁺ of all territories at 3.0-T was lower than at 1.5-T, which is expected because T₂⁺ relaxation has a strong dependence on field strength (21). We also found that the relative change in T₂⁺ of all MI territories with respect to remote myocardium was significantly higher in the acute phase than in the chronic phase. This suggests that edema significantly influences T₂⁺ values, although the hemorrhage imparts an even greater influence than edema on T₂⁺. These findings support the possibility that T₂⁺ relaxation of the infarcted myocardium may be multiexponential, but additional
studies are needed to investigate this possibility. Our assessment of the $T_1$ of MI territories relative to the remote myocardium also revealed important features. $T_1$ of hemorrhagic and peri-hemorrhagic territories was significantly higher at 3.0-T than at 1.5-T. This is consistent with previous reports of field-dependent $T_1$ elevations in both acute and chronic phases (9,13). Notably, the $T_1$ values in both territories decreased but remained substantially elevated compared to the remote myocardium in the chronic phase of MI, which supports the rationale for using native $T_1$ mapping at 3.0-T for identifying chronic MI territories. Previous studies have also demonstrated that, although the $T_1$ elevations in the acute phase are likely the result of edema, in the chronic phase they are likely driven by fibrosis (13). However, our findings of $T_1$ changes in the hemorrhagic territories provide further insight. Although the pattern of $T_1$ decreasing from the acute to the chronic phase was consistent with other territories at 1.5- and 3.0-T, the magnitude of the decrease was significantly different. Specifically, we found that in the chronic phase of hemorrhagic territories, $T_1$ values were lower than in the remote myocardium at 1.5-T but not different at 3.0-T. This is likely due to the competing field-dependent effects of iron, which drives $T_1$ lower, and replacement fibrosis, which increases $T_1$ contrast. This suggests that compared to 1.5-T, at 3.0-T the $T_1$ contribution of fibrosis dominates the $T_1$ contribution of iron. We also found that in the acute phase of MI, $T_1$ within the hemorrhagic territories at both field strengths was significantly reduced, which is likely related to the competing effects between hemorrhagic remnants (decrease $T_2$) and interstitial edema (increase $T_1$). Our findings of LGE, $T_2^*$, $T_2$, and $T_1$ on the types of MI with respect to MI age and how they contribute to image contrast (hyper-, hypo-, or iso-intense) relative to remote tissue at 1.5- and 3.0-T are summarized in Supplemental Figure 4.

**STUDY LIMITATIONS.** A potential limitation of our study is that our findings are limited to dogs. Thus, the physiological differences between humans and dogs need to be recognized in interpreting the findings. Nonetheless, canine models of reperfused MI have been successfully used to investigate parallel physiological aspects of MI in humans (2,12,13,16,17,22). Moreover, the findings from our study provide insight into how $T_2$-based CMR can be used to assess infarct age; however, in practice, clinical history and other imaging metrics may also be used in conjunction with $T_2$ CMR to determine the time course of MI.

**CONCLUSIONS**

Hemorrhagic MIs are associated with persisting myocardial inflammation and edema, which can confound staging of hemorrhagic MIs when $T_2$ elevations alone are used to discriminate between acute and chronic MI. Moreover, given the poor prognosis in patients with hemorrhagic MI, CMR evidence for myocardial hemorrhage with persistent edema may evolve as a risk marker in patients after acute MI.

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**PERSPECTIVES**

**COMPETENCY IN MEDICAL KNOWLEDGE:** Acute versus chronic stage of nonhemorrhagic MI can be determined on the basis of resolution of edema in CMR. However, edema resolution is not a specific discriminator for staging hemorrhagic MI in CMR because chronic hemorrhagic MI territories are associated with prolonged inflammation, which facilitates edema within the myocardial scar. Hence, accurate staging of infarct age based on CMR requires knowledge of whether the index MI was hemorrhagic, which may be gleaned by incorporating $T_2^*$-based imaging into CMR examinations.

**TRANSLATIONAL OUTLOOK:** The time course of edema and inflammation in the chronic phase of reperfused MIs, specifically contrasting the potential differences between hemorrhagic and nonhemorrhagic MIs, remains to be investigated in patients. In addition, longitudinal CMR studies extending months to years after reperfusion are needed to determine whether a combined evaluation of $T_2$ and $T_2^*$ CMR may be more valuable than $T_2$ CMR alone to accurately stage MI. Moreover, given the poor prognosis in patients with hemorrhagic MI, CMR evidence for myocardial hemorrhage with persistent edema may evolve as a risk marker in patients after acute MI.
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APPENDIX For an expanded methods section as well as supplemental tables and figures, please see the online version of this paper.