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iFORUM

NEWS AND VIEWS

T2-Weighted Imaging to Assess Post-Infarct Myocardium at Risk

Matthias G. Friedrich, MD, Han W. Kim, MD, Raymond J. Kim, MD
Montreal, Quebec and Calgary, Alberta, Canada; and Durham, North Carolina

Section Editor: Christopher M. Kramer, MD

TO UNDERSTAND THE AMOUNT OF SALVAGED MYOCARDIUM AFTER reperfusion of acute myocardial infarction (MI), it is essential to know the area of myocardium at risk (AAR) before reperfusion to assess salvaged myocardium as AAR minus final infarct size. Measuring myocardial salvage offers tremendous potential for development of novel pharmacologic agents that can reduce reperfusion injury and thereby increase myocardial salvage in reperfused MI. In animal studies, dyes such as phthalocyanine blue injected directly into the coronary circulation have been used to assess AAR. In humans, contrast echocardiography has been used in the catheterization lab before reperfusion to make this measurement (1). Although accurate and useful, this technology is available in very few laboratories around the world on a moment's notice when a patient presents with an MI. A technique to measure AAR in MI that could be applied after reperfusion would be ideal. T2-weighted (T2-W) imaging by cardiac magnetic resonance (CMR) seems to be just such a technique, as demonstrated in the studies presented here in the iForum piece by Matthias Friedrich, MD. T2-weighted imaging is sensitive to myocardial edema, and it is thought that the area of edema can mark the original AAR. T2-weighted imaging was first applied in the mid-1990s, but it is only in the last few years that it has begun to hit its clinical stride.

But hold on . . . Han Kim, MD, and Raymond Kim, MD, point out that T2-W imaging might not be ready for prime time. They present data that raise questions about the presence of edema within the area of salvaged, reversibly injured myocardium. In addition, there are several technical issues with some of the CMR pulse sequences used for this technique and how the data is acquired. There is no consensus yet within the CMR community with regard to how this data is optimally acquired and quantitatively analyzed. A newer quantitative technique called T2-mapping might be 1 answer in this regard (2). Nevertheless, the further development and application of T2-W imaging in the measure of myocardial salvage is a fascinating advance in the field of cardiovascular imaging that our readers should watch as the story unfolds in the next few years.

PRO

Matthias G. Friedrich, MD
CMR Centre, Montreal Heart Institute, Department of Cardiology, Université de Montreal, Montreal Quebec, Canada; and Stephenson Cardiovascular MR Centre at the Libin Cardiovascular Institute of Alberta, Departments of Cardiology and Radiology, University of Calgary, Calgary, Alberta, Canada

Relevance of the AAR in patients after acute MI. The AAR represents the myocardial perfusion bed that is directly affected by ischemia due to the acute occlusion of a coronary artery. The tissue is subject to a cascade of reversible and irreversible injury, after a centrifugal expansion in an endo-toward-epicardial "wavefront." Importantly, the wave of irreversible injury (oncosis, followed by necrosis) is preceded by reversible injury of the entire AAR (3). Accordingly, if blood flow is restored before, persistent ischemic damage can be prevented. Depending on the total ischemia time of reperfused MI, more or less of the AAR is salvaged. Because the injury in the salvaged region is reversible, there is functional recovery, which is deemed beneficial for the patient with respect to quality of life and longevity. Therefore the presence and extent of myocardial salvage indicates the success and relevance of acute revascularization.

The clinical impact of this information depends on the clinical scenario. In symptomatic patients with late presentation after acute MI or with apparently unsuccessful thrombolysis, for example, the absence or presence of salvageable myocardium would be helpful to guide therapy with respect to the indication for a late or "rescue" coronary intervention. Furthermore, the timeliness of revascularization could be retrospectively assessed.

Currently, however, the main value of assessing the AAR and myocardial salvage might be its utility as an endpoint in clinical trials. Although acute revascularization is routinely performed, markers indicating its success are scarce and not well-defined. Because of a lack of strong surrogate markers, clinical trials need large samples, resources, and time. Given the highly dynamic nature of acute coronary syndrome before, during, and after revascularization, it remains challenging to relate clinical and periprocedural factors to outcome. There is especially a need for a better understanding of the impact of late or repeated reperfusion on myocardial salvage. Although infarct size certainly is an excellent prognostic marker, clinical studies on the impact of any therapeutic intervention suffer from scatter introduced by the varying size of the perfusion bed. Therefore the proportional size of myocardial salvage within the initial myocardium at risk would be a much stronger marker for the efficacy of novel perfusion strategies.

Important pathophysiological aspects of the AAR in acute myocardial ischemia. Acute ischemia leads to a multitude of metabolic changes with immediate reversible and subsequent irreversible consequences. Within minutes after its onset, there is a conformational change of intracellular macromolecules, transforming water from its "bound" (gel-like) form into a "free," fluid state. Furthermore, the breakdown of the adenosine triphosphatase-dependent potassium ion/sodium ion exchange leads to inflow of free water into cells, followed by a loss of endothelial membrane integrity with subsequent net water inflow into the AAR. All these processes add to an increased free water fraction.

Any acute myocardial injury is associated with multiple metabolic and structural changes. Within minutes of no-flow ischemia, the lack of oxygen leads to edema in the affected perfusion bed, before the onset of irreversible injury and significant vascular damage (3). Edema is not only an inherent and essential component of the early pathophysiological response to no-flow ischemia but might also have significant implications for reperfused myocardium, leading to left ventricular dysfunction and expansion of tissue injury (4).

Of note, edema is more pronounced after reperfusion (5). Furthermore, due to conformational changes, proteins and other macromolecules release water from its gel-like, bound state, to a fluid, free state. Importantly, this is associated with up to 100× higher T2 relaxation times (6), a contrast-generating effect that can be used by CMR.

AAR imaging with CMR. The rapid change of T2 relaxation times in the AAR during acute ischemia was studied in several animal models (7), but only after the introduction of a clinically more robust triple-inversion recovery black blood turbo spin echo sequence in 1996 did T2-W imaging become useful for clinical research. Subsequent reports showed that T2-W CMR differentiates acute from chronic MI (8) and is useful in patients with acute myocardial disease of unclear etiology or with suspected acute coronary syndrome (9).

Importantly, high signal intensity in T2-W CMR, in the absence of abnormal late gadolinium (Gd) enhancement in the same area, reflects reversible ischemic injury (10), making it useful in diseases without overt necrosis. As such, a reversibly injured myocardium, the salvaged AAR after acute revascularization was identified as an important diagnostic target for T2-W CMR (11). The accuracy of this approach has been validated in canine (12) and murine (13) models. The extent of the AAR is more accurately defined by T2-W imaging than by using the endocardial extent of bright signal intensity areas in late Gd enhancement images (14). Figure 1 shows a clinical example of myocardial salvage as visualized by CMR.

Myocardial salvage as defined by high signal intensity in T2-W images with absent late Gd enhancement abnormalities has been used as an endpoint in several clinical trials on revascularization (15) and has shown prognostic value (16).

Other clinical studies included acute myocarditis (17) and hypertrophic cardiomyopathy (18). Recently, a multicenter trial identified myocardial edema to be 1 of 4 essential criteria, in combination with a lack of a significantly brighter signal intensity in late Gd enhancement images (reflecting irre-

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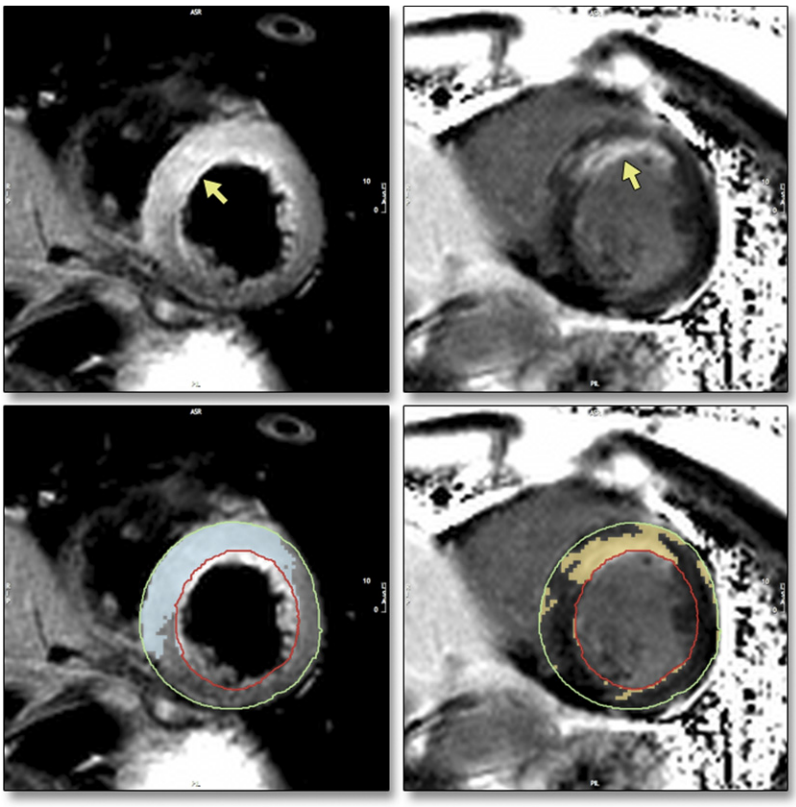

Figure 1. Myocardial Salvage as Visualized by Cardiac Magnetic Resonance With the Body Coil

Left upper panel: T2-weighted cardiac magnetic resonance image showing bright signal intensity in the anterior, anteroseptal, and inferoseptal segments, combined with thickened myocardium. **Right upper panel:** late gadolinium enhancement image of the same slice: bright signal intensity, mostly endocardial, in the anteroseptal segment. **Lower panels:** quantitative evaluation of signal intensity of both images with the same thresholding algorithm on the basis of automated identification of 2 signal intensity classes (normal/abnormal), without user interaction.

versible injury) (19). Moreover, the assessment of myocardial edema as an in vivo marker for acute myocardial injury also improves risk stratification in patients with acute chest pain and allows triage to appropriate treatment (9). These examples underscore the incremental value of T2-W CMR in addition to contrast-enhanced CMR.

Specific advantages of T2-W CMR include its safety profile (lack of radioactivity or radiation, no contrast agent needed) and high spatial resolution. Most importantly, however, the comprehensive assessment of ventricular mass, volumes, and function as well as acute tissue injury and—combined with contrast-enhanced CMR—infarct size and pericardiac and valvular pathology during 1 single scan is unparalleled in its diagnostic, workflow, and cost-related efficiency. The accuracy and reproducibility of CMR not only recommend it for clinical research but also for various clinical scenarios and follow-up studies.

The method offers several advantages over single-photon emission computed tomography (20)—which is limited by poor spatial resolution and the need for 2 separate scans—and echocardiography, because functional abnormalities often are not sharply defined and it is difficult to distinguish active motion from tethering.

Current limitations of T2-W CMR. Spin echo sequences used for T2-W imaging are often limited by a low signal-to-noise ratio, motion artifacts, and incomplete blood suppression. The signal intensity in T2-W images is also subject to the coil sensitivity profile of surface coils. Therefore, accurate and diagnostic T2-W CMR requires the use of the body coil or a coil sensitivity correction algorithm as well as careful and consistent selection of sequence parameters. Arrhythmia treatment during the scan may be considered.

Newer sequences such as T2-prepared gradient echo protocols (21), hybrid sequences (22), bright blood approaches (23), or additional adiabatic pre-pulses (24) further improve image quality.

A mere visual assessment of the signal intensity in T2-W images is subjective and might give inaccurate results, and a quantitative analysis is preferable.

Direct measurement of T2 relaxation times ("T2 mapping") might be less dependent on confounders affecting signal intensity (2). T1 mapping might also be useful for assessing myocardial edema, yet published data are lacking.

Finally, myocardial edema is not specific for the underlying etiology. Although patient history and the regional distribution of edema most often are conclusive, the pathology itself might be multifactorial. The CMR of edema, its regional distribution, and relation with necrosis and dysfunction, however, allow for an integrated analysis of the findings.

Conclusions. T2-weighted imaging is emerging as the diagnostic tool of choice to assess and quantify the myocardial AAR after acute MI. The technique allows not only for a better understanding of post-revascularization pathophysiology but also for quantifying the success of acute reperfusion in individual clinical settings. Despite existing yet addressable limitations, the diagnostic information provided by T2-W CMR is comprehensive, unique, incremental, and relevant.

CON

Han W. Kim, MD*†
Raymond J. Kim, MD*†‡
**Duke Cardiovascular Magnetic Resonance Center, Duke University Medical Center, Durham, North Carolina; †Department of Medicine, Duke University Medical Center, Durham, North Carolina; and the ‡Department of Radiology, Duke University Medical Center, Durham, North Carolina*

T2-CARDIAC MAGNETIC RESONANCE FOR DELINEATING MYOCARDIUM AT RISK (MAR) is thought to be ready for prime time (25). At some centers, it is being used to inform patient management decisions, and a search of major registries (Clinicaltrials.gov and Current Controlled Trials) shows T2-CMR is being used to provide the primary or secondary endpoint in 15 trials including 3,000 patients worldwide (26). However, there are several troubling aspects of the available evidence. We critically review the published data, given the serious ramifications, and examine the physiological and technical assumptions underlying this application.

Validation studies? Three studies are widely quoted as proof that T2 hyperintense regions delineate the MAR after acute MI. García-Dorado et al. (7) demonstrated in 15 ex vivo pig hearts that the area of T2 hyperintensity was comparable to the MAR defined by fluorescein staining. However, the infarcted region was never delineated, and it is unclear whether there might have been an equally good correlation between T2 and infarct size. Additionally, it is notable that the 3 largest MAR measurements (which primarily drive the correlation) were all from hearts with nonreperfused infarcts, the group in which T2 signal was only minimally elevated in the ischemic zone. Aletras et al. (12) showed in 9 canines with acute reperfused MI that the area of T2 hyperintensity was similar to the MAR measured by fluorescent microspheres, and both were larger than infarct size defined by pathology. However, the MAR map had poor spatial resolution, because large transmural tissue blocks were used for microsphere counting. Tilak et al. (27) reported in 14 canines with nonreperfused MI that the area of T2 on post-MI day 2 correlated well with the area of hypoperfusion delineated by first-pass CMR on day 0, and both were larger than infarct size measured by pathology. Fluorescent microspheres were administered in 12 animals but not used to measure the MAR. Thus, all 3 studies were small, and the conclusions were based primarily on size comparisons between CMR images or CMR and pathology. None showed any images or data directly comparing the shape and contour of the T2 abnormality with the shape and contour of the MAR as delineated by pathology.

There are numerous other studies that conclude that T2-CMR can identify the MAR, but these do not provide an appropriate pathology reference of the MAR. Rather, they infer T2-CMR depicts the MAR because the T2 hyperintense region is measured to be larger than infarct size as determined by delayed-enhancement CMR (DE-CMR) or pathology (11,13,15,16,23). This type of evidence is indirect (28) and beset with concerns, as discussed in the following text.

Usually not discussed are studies that suggest T2-CMR delineates the area of acute infarction rather than the MAR. Johnston et al. (29) studied 19 canines undergoing coronary occlusion with or without reperfusion. Despite a clear transmural reduction in blood flow in the ischemic zone as verified by microspheres (i.e., MAR is transmural), T2 measured by spectroscopy was elevated only in tissue from the endocardial half of the ischemic zone and not from the epicardial half. Miller et al. (30) reported, on 16 canines with reperfused MI, that hyperintense regions on T2-CMR were usually subendocardial and matched regions of infarction delineated by pathology rather than viable ischemic regions defined by microspheres. Likewise, T2 as measured by spectroscopy was elevated only in infarcted tissue and not in viable at-risk myocardium. Ryan et al. (31) demonstrated in 16 canines with variable coronary occlusion times that only animals with infarction demonstrated hyperintense regions on T2-CMR, whereas none of the animals without infarction had T2 abnormalities, despite regional systolic dysfunction (stunning) at the time of imaging. Moreover, T2 hyperintense regions correlated with infarct size but not the MAR as delineated by contrast echocardiography.

Edema in irreversible versus reversible ischemic injury. T2 signal is linearly related to myocardial water content (7,32). However, from a mechanistic viewpoint, the assumption that T2-CMR depicts the MAR because of myocardial edema is questionable. The bulk of experimental evidence points to substantial edema occurring in the infarcted region, with minimal edema occurring in the MAR portion with reversible injury. For instance, Whalen et al. (33) observed a 44% increase in water content in myocardium exposed to ischemia sufficient to result in infarction of approximately one-half the tissue. Shorter ischemic periods leading to reversible injury did not lead to changes in water content. From this data, one can calculate that a pure sample of irreversibly injured myocardium would have an 88% increase in water content. Jennings et al. (34) reported a 9.6% increase in water content in myocardium reversibly damaged by 15 min of ischemia followed by 20 min of reperfusion. However, up to 40% of the increase in tissue water was secondary to reactive hyperemia, which would be expected to resolve 1 to 2 days later. Thus, after ischemic injury, the difference in edema between infarcted and salvaged (reversibly injured) myocar-

dium should be approximately 9-fold (88%/9.6% = 9.2) or higher.

Therefore, if T2-CMR truly tracked edema, signal differences between infarcted and reversibly injured myocardium should be far greater than between reversibly injured and normal myocardium. Assuming that first-order increases in T2 signal are linearly related to increases in edema (7,32), one might expect for a 50% increase in signal within the infarct zone that there should be a 0% to 5% increase in signal for salvaged myocardium within the MAR. Thus, even if salvaged myocardium could be distinguished from normal tissue, T2-CMR images should not depict the MAR as a region of homogeneous hyperintensity.

What about published statements that point to prior physiology studies as evidence that substantial edema occurs in salvaged, reversibly injured myocardium? In general, the studies quoted describe edema in the setting of ischemia but do not distinguish between irreversible and reversible injury (7,35). Because they involve severe ischemic injury in which substantial infarction is expected or shown, the data are equally consistent with much or all of the edema arising from irreversible injury.

Perhaps due to this conundrum concerning the lack of edema in salvaged myocardium, it has been proposed that changes in fractions of water (protein-bound vs. "free") rather than total water might explain the findings (25). Certainly, T2 can change with alterations in protein structure (smaller or larger assemblies) without changes in overall protein mass or water volume (36); however, the proposed mechanism is suspect for several reasons. First, there are no data that show fractions of water are changed in salvaged myocardium. Second, if salvaged myocardium without increased total water could have significantly elevated T2, this would then have been inconsistent with the totality of data published so far showing a tight, nearly linear relationship between T2 and total water (7,32). Third, if ischemia sufficient to result in reversible injury without edema can greatly elevate T2, why then does ischemia that results in irreversible injury

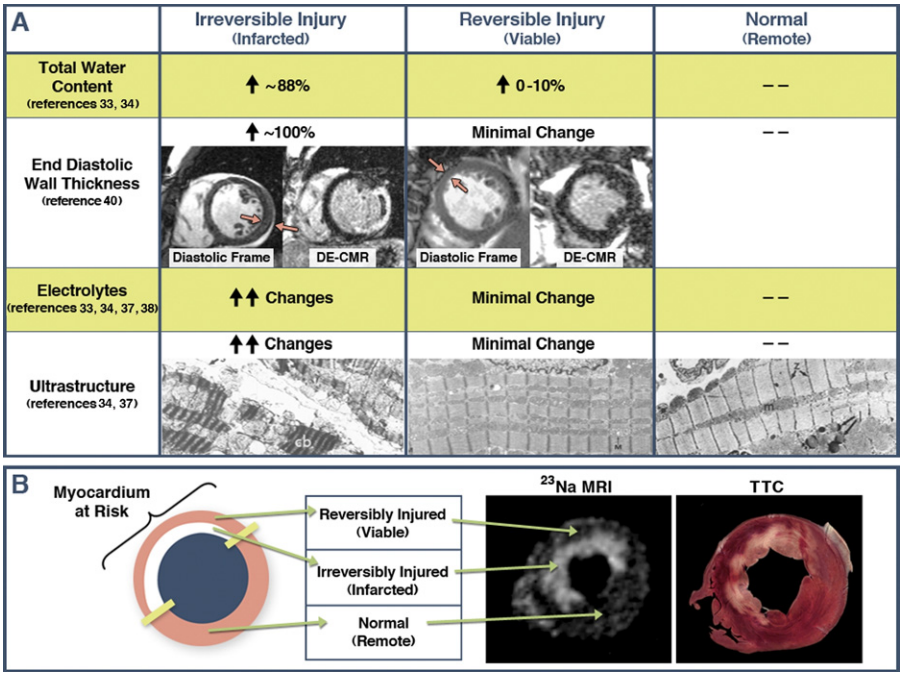

Figure 2. Dramatic Changes In Irreversible Injury Versus Minimal Changes in Reversible Injury

(A) Summarization of expected changes in several biological characteristics in myocardium after ischemic injury and reperfusion, with comparisons between irreversibly injured, reversibly injured, and normal tissue. **Orange arrows** point to regions that are akinetic on cine-cardiac magnetic resonance (CMR) from temporary occlusion to the left circumflex and left anterior descending coronaries, respectively. Note the near doubling of end-diastolic wall thickness in the patient with transmural infarction but no increase in wall thickness in the patient with reversible injury. This is consistent with substantial edema occurring in irreversible but not reversible injury and consistent with published studies showing that acute increases in end-diastolic wall thickness after myocardial infarction correlates directly with the transmural extent of infarction (40). Electron microscopy images were reproduced, with permission, from Jennings et al. (34) and Kloner et al. (37). Irreversibly injured tissue shows greatly distorted ultrastructure with formation of vacuoles, large subsarcolemmal blebs, contraction bands and swollen mitochondria containing dense bodies. In reversibly injured tissue, ultrastructure is virtually indistinguishable from control (normal) tissue. **(B)** Demonstrates that total myocardial sodium content as reflected by ^{23}sodium magnetic resonance imaging (^{23}Na MRI) is substantially elevated in infarcted regions but not in salvaged myocardium at-risk, which is consistent with changes in total water content measured in pathology studies. Reproduced, with permission, from Kim et al. (39). Given these findings, it is perplexing that T2-CMR apparently can delineate between normal and reversibly injured tissue but not between reversibly injured and infarcted tissue. DE = delayed-enhancement; TTC = triphenyltetrazolium chloride.

with a large amount of edema not have further increases in T2? It would seem that this would require yet a second unproved mechanism to explain why all the edema in infarcted tissue has no additional effect on T2. Finally, T2 (and T1) relaxation values of biological tissues should reflect the composition and microenvironment of that tissue. Yet, after ischemia and reperfusion, the large differences in edema between myocardium suffering irreversible compared with reversible injury are mirrored by similar large differences in electrolytes, high-energy phosphates, and fine structure by light and electron microscopy (33,34,37–40). In brief, there are dramatic changes in all these characteristics in irreversibly injured tissue compared with minimal-to-no changes in reversibly injured tissue (Fig. 2). Given these findings, it is perplexing that T2-CMR apparently can delineate between normal and reversibly injured tissue but not between reversibly injured and infarcted tissue.

T2-CMR technical issues. There are a myriad of reasons why conventional, dark-blood T2-CMR might overestimate infarct size without the need to surmise that T2 hyperintensity delineates the MAR (28). Surface coils can lead to hyperintense regions simply on the basis of proximity to the coil (Fig. 3A). Bright signal from static cavity blood might mimic edema, and motion-related signal loss in 1 region might cause other regions to appear hyperintense despite no actual changes in T2 (Figs. 3B and 3C). The latter 2 artifacts are particularly pernicious in that these might be associated with physiological changes occurring after MI rather than occurring randomly. Specifically, injured myocardium is likely hypokinetic, which is often associated with adjacent stagnant cavity blood. Likewise, hypokinetic myocardium, even without edema, might appear hyperintense in comparison with normal regions that have suffered signal loss because of vigorous motion. Newer bright-blood techniques with or without T2 mapping might substantially reduce these artifacts (2,21–23); however, there are no data validating these techniques in comparison with an appropriate pathology reference of the MAR. Moreover, all T2 techniques are limited by the relatively small changes in T2 expected for edematous myocardium. Aletras et al. (12) reported a contrast-to-noise ratio between hyperintense and normal regions of only 2.9 for T2-CMR, which is substantially less than the 19 that is typical for DE-CMR (41).

Another technical issue concerns the method of quantifying the size of hyperintense regions. Many studies have arbitrarily defined "bright" myocardium as regions with signal >2 SDs above remote on T2-CMR but >5 SDs above remote on DE-CMR (11,16,28). By using a lower threshold for T2-CMR, one increases the likelihood that edema size will often be substantially greater than infarct size simply from partial volume (28). Results using full-width at half maximum methods might be more reproducible but not necessarily more accurate (42). The addition of 1 or 2 very bright pixels within the hyperenhancement zone might substantially reduce measured infarct size by raising the full-width at half maximum threshold and rendering a majority of the "grey zone" (admixture of infarcted and viable myocardium) as part of normal tissue.

So how can we know whether the consistent overestimation of infarct size by T2-CMR is artifactual or real? Some clues are found by returning to bedrock physiological principles. After coronary occlusion, cell death is not simultaneous throughout the MAR but progresses as a "wavefront" from endocardium to epicardium over several hours (43). Without timely reperfusion, infarction becomes transmural, reflecting an absence of salvageable myocardium within the MAR. Thus, if MAR size measured by T2-CMR were larger than infarct size in the setting of transmural infarction, this would be nonphysiological. Therefore it is puz-

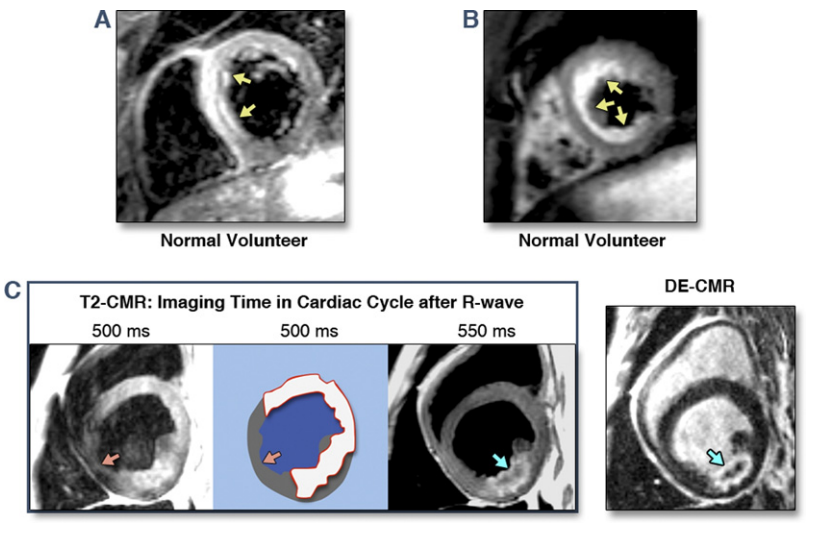

Figure 3. T2-CMR Technical Limitations: Artifacts Mimicking Edema

(A, B) On conventional T2-cardiac magnetic resonance (CMR), hyperintense regions might be visualized in normal volunteers because of inhomogeneities in myocardial signal and slow cavity blood flow. **(C)** Simply changing the timing of T2 imaging during the cardiac cycle can lead to different regions of hyperintensity. If a region of signal loss **(orange arrows)** is considered normal myocardium, the extent of hyperintensity might be large **(red contour)**. Also note that the region of apparent T2 hyperintensity extends far beyond the lateral borders of the infarcted region as delineated by delayed-enhancement (DE)-CMR. In the T2 image taken 550 ms after the R-wave, the hyperintense region **(blue arrow)** is not fully transmural, and the shape and contour seems to exactly match that of the infarcted region on DE-CMR.

zling that Berry et al. (44), with bright-blood T2 techniques, report similar amounts of substantial salvage for both transmural and nontransmural infarction. We are unaware of any of the other investigations reporting that edema size is greater than infarct size that describe this data as a function of infarct transmurality.

In their landmark study of the wavefront phenomenon, Reimer and Jennings (43) describe a corollary principle (i.e., there is no wavefront circumferentially because there is no perfusion gradient in that direction). Reperfusion after only 40 min of ischemia resulted in a confluent subendocardial infarct (approximately 28% transmural) that extended to within 1 to 2 mm of the lateral edge of the MAR. Although some investigators initially suggested the existence of a wide lateral "border zone" of intermediate-level perfusion, later studies showed this was a partial volume artifact due to the limited resolution of the techniques used, and with progressively higher levels of sampling resolution, investigators have concluded that there is no zone of intermediate perfusion (or injury) at the lateral border (43,45). This is consistent with anatomical studies showing "end-capillary loops" without microvascular connections between adjacent vascular beds in both canines and man (46,47). The implications of this is that there should be no meaningful salvage at the lateral borders of the infarct, yet the published reports are replete with examples of T2 hyperintensity extending laterally, usually in both directions, far beyond the lateral border of the infarct delineated by DE-CMR (Fig. 1) (11,12,14,25). One caveat should be mentioned. In patients with multivessel disease, it is possible that the infarct-related artery before occlusion provided substantial collateral flow to a second coronary artery perfusion territory. Thus, during infarction, a second vascular bed becomes ischemic. Theoretically, this could result in an MAR that extends laterally beyond the infarct. However, in this situation: 1) the entire circumference of the second vascular bed should be equally ischemic; 2) the level of ischemia needs to be within a narrow range that does not result in subendocardial infarction within the second bed; 3) the MAR should, realistically, extend laterally only on 1 side of the infarct; and 4) this is known to be very rare even in the setting of chronic, diffuse multivessel disease (48).

Address correspondence: Dr. Christopher M. Kramer, University of Virginia Health System, Departments of Medicine and Radiology, P.O. Box 800170, Lee Street, Charlottesville, Virginia 22908-0001. *E-mail: ckramer@virginia.edu.*

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Key Words: myocardial infarction ■ myocardial salvage ■ myocardium at risk ■ T2-weighted imaging.