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EDITORIAL COMMENT

# Gadolinium Can Depict Area at Risk and Myocardial Infarction

## A Double-Edged Sword?*

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Gadolinium-based extracellular contrast agents have enabled cardiac magnetic resonance (CMR) to assess viability and fibrosis at a higher resolution than alternative technologies (1). In this issue of *iJACC*, Matsumoto et al. (2), present convincing data that early contrast enhancement approximately 2 min after administration of gadolinium depicts the area at risk associated with acute myocardial infarction. The convenience of imaging both the area at risk and the infarct size from the same bolus of gadolinium appears to be a huge convenience factor in expediting the assessment of myocardial salvage, but this "2-for-1" benefit is accompanied by the need to understand the kinetics of gadolinium in the infarct and the peri-infarct zone.

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Rather than concluding that gadolinium overestimates acute infarct size, the more appropriate and challenging conclusion is that understanding the kinetics of gadolinium contrast enhancement and washout will help determine why gadolinium can show both the penumbra of the area at risk and the core of late gadolinium enhancement that represents the infarct. It will also be important to understand a concept called the extracellular volume fraction or the closely related term volume of distribution.

The pharmacological characteristics of the gadolinium contrast agents derive many of their medical properties based on the chelates used to make the gadolinium biocompatible and excretable. Immediately after intravascular injection, gadolinium contrast agents are located in the plasma of blood but excluded from the intracellular space of blood cells. This point is important for calibrating estimates of the intracellular volume fraction with measurement of the hematocrit. On arrival in the coronary capillaries, gadolinium rapidly enters the extracellular space, but viable cardiomyocytes exclude gadolinium from the intracellular space. The intracellular space represents approximately 75% of the normal myocardium, whereas the extracellular space accounts for the remaining 25% of the tissue volume, partly in the form of intramyocardial blood volume and partly as interstitial space. Acutely infarcted myocardium accumulates more gadolinium than remote myocardium because ruptured cell membranes permit gadolinium to access what had been the intracellular space. Thus, acutely infarcted myocardium generally looks brighter than viable myocardium on most CMR images unless microvascular obstruction prevents entry of gadolinium into the tissue.

Understanding why gadolinium enhances the area at risk requires some interpretation and extrapolation from previous kinetic studies and observations from T2-weighted imaging of the area at risk. In a careful study of 15 rats with reperfused 2-day-old infarcts imaged continuously for 40 min after contrast administration, Oshinski et al. (3) reported that gadolinium overestimated triphenyltetrazolium chloride metrics of the infarct size for the first 16 ±

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2 min in rats that had 2-h occlusions and for 26 ± 4 min in the 30-min occlusion group. They concluded that accurate determination of infarct size by delayed enhancement CMR requires imaging at specific times after gadolinium diethylenetriamine pentaacetic acid injection, and this time varies with the duration of occlusion. Those were contentious days in the CMR scientific community because some experts had concluded that gadolinium overestimated infarct size (4,5). However, the remarkable improvement in image quality of the new inversion recovery CMR methods (6) and the extensive validations that came out in rapid succession (1,7–14) became an overwhelming tidal force that persuaded the CMR field and cardiology more generally that gadolinium was a new reference standard for viability imaging. However, based on the Oshinski et al. (3) data, our laboratory rigorously tried to perform all acute infarct imaging approximately 20 min after gadolinium injection, which may explain why we believed that gadolinium reasonably correlated with acute infarct size (15).

So what has changed that the study by Matsumoto et al. (2) should change our understanding of gadolinium enhancement of the heart? Most importantly, Matsumoto et al. (2) noticed that early gadolinium enhancement (a.k.a. early contrast enhancement) overestimated infarct size but also took the time to provide an independent metric of the area at risk—T2-weighted images. T2-weighted images have been validated to depict the area at risk in animals (16,17) and in humans (18–21).

More importantly, the early gadolinium enhancement makes pharmacological sense based on the T2 abnormalities in the area at risk and the associated tissue swelling that must represent an expansion of the extracellular space (16–21). Interestingly, Kim et al. (22) published kinetic data that support the existence of an expanded peri-infarct extracellular volume in addition to differing rates of wash-in and washout of gadolinium from normal myocardium, peri-infarct rim, and the infarct. Figure 3 in Kim et al. (22) shows distinct hyperenhancement of the peri-infarct rim early during a continuous infusion of gadolinium, and it is only late during the washout phase that gadolinium-related signal intensity of the infarct exceeded normal myocardium or the peri-infarct rim (22). Thus, there is substantial evidence from the literature to support the early gadolinium enhancement findings of Matsumoto et al. (2), but they are to be congratulated for noticing and proving with independent methods that gadolinium enhances the area at risk early after injection.

The take-home message from this lesson is that gadolinium will overestimate the size of acute myocardial infarctions in the first few minutes after injection and appears to depict the area at risk during that time period. More rapid clearance of gadolinium from viable myocardium and more severe abnormalities in the extracellular volume fraction in the infarct will lead to a situation in which the acutely infarcted myocardium is brighter than either normal myocardium or salvaged myocardium late after contrast injection. The optimal timing of those 2 time periods will need to be defined more precisely. For the short term, the best available data (23) indicate that we should wait at least 10 min after injection for accurate infarct sizing, but a 20-min wait would be safer still. More work is needed to define the kinetics separating these 2 critical measurements such as renal function and microvascular obstruction. That presents the double-edged sword in the story: although it is convenient to be able to measure 2 distinctly different physiologically relevant processes with a single gadolinium injection, we will need to be careful with our timing to avoid hybrid data between the area at risk and infarct size.

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