Published in final edited form as:

JACC Cardiovasc Imaging. 2011 June ; 4(6): 619–621. doi:10.1016/j.jcmg.2011.04.006.

Gadolinium Can Depict Area at Risk and Myocardial Infarction: A Double Edged Sword?

Andrew E. Arai, MD

Cardiovascular and Pulmonary Branch National Heart, Lung and Blood Institute National Institutes of Health Department of Health and Human Services

Gadolinium-based extracellular contrast agents have enabled cardiac magnetic resonance (CMR) to assess viability and fibrosis at higher resolution than alternative technologies. (Kim, Fieno et al. 1999) In this issue of *JACC Cardiovascular Imaging*, Hidenari Matsumoto et al from Rakuwakai Otowa Hospital, in Kyoto, Japan present convincing data that early contrast enhancement approximately 2 minutes after administration of gadolinium depicts the area at risk associated with acute myocardial infarction. The convenience of imaging both area at risk and infarct size from the same bolus of gadolinium proffers to be a huge convenience factor in expediting the assessment of myocardial salvage but this “two-for-one” benefit is accompanied by the need to understand the kinetics of gadolinium in the infarct and the peri-infarct zone.

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 (LGE) 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. Upon arrival in the coronary capillaries, gadolinium rapidly enters the extracellular space but viable cardiomyocytes exclude gadolinium from the intracellular space. The intracellular space represents about 75% of the normal myocardium while 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 since 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 MR images unless microvascular obstruction prevents entry of gadolinium into the tissue.

© 2011 American College of Cardiology Foundation. Published by Elsevier Inc. All rights reserved.

Andrew E. Arai, MD Cardiovascular and Pulmonary Branch National Heart, Lung and Blood Institute National Institutes of Health Building 10, Rm B1D416, MSC 1061 10 Center Drive Bethesda, MD 20892-1061 arai@nih.gov Phone: 301-496-3658 Fax : 301-402-2389.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Understanding why gadolinium enhances the area at risk requires some interpretation and extrapolation from prior 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 minutes after contrast administration, Oshinski et al reported that gadolinium overestimated triphenyltetrazolium chloride metrics of infarct size for the first 16 ± 2 minutes in rats that suffered 2 hour occlusions and for 26 ± 4 minutes in the 30 minute occlusion group.(Oshinski, Yang et al. 2001) They concluded that accurate determination of infarct size by delayed enhancement MRI requires imaging at specific times after Gd-DTPA injection, and this time varies with the duration of occlusion. Those were contentious days in the cardiac MRI scientific community since some experts had concluded that gadolinium overestimated infarct size.(Kramer, Rogers et al. 2000; Saeed, Lund et al. 2001) However, the remarkable improvement in image quality of the new inversion recovery MRI methods(Simonetti, Kim et al. 2001) and the extensive validations that came out in rapid succession(Kim, Fieno et al. 1999; Kim, Judd et al. 1999; Fieno, Kim et al. 2000; Hillenbrand, Kim et al. 2000; Kim, Wu et al. 2000; Rochitte, Kim et al. 2000; Choi, Kim et al. 2001; Ricciardi, Wu et al. 2001; Wu, Judd et al. 2001) became an overwhelming tidal force that persuaded the cardiac MRI field and cardiology more generally that gadolinium was a new reference standard for viability imaging. However, based on the Oshinski data, our laboratory rigorously tried to perform all acute infarct imaging about 20 minutes after gadolinium injection which may explain why we believed gadolinium reasonably correlated with acute infarct size.(Ingkanisorn, Rhoads et al. 2004)

So what has changed that the study by Matsumoto et al should change a field that has been the stalwart technique of cardiac MRI? Most importantly, Matsumoto et al noticed that early gadolinium enhancement images (EGE or ECE) 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(Aletras, Tilak et al. 2006; Tilak, Hsu et al. 2008) and in humans.(Friedrich, Abdel-Aty et al. 2008; Carlsson, Ubachs et al. 2009; Wright, Adriaenssens et al. 2009; Berry, Kellman et al. 2010)

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.(Aletras, Tilak et al. 2006; Friedrich, Abdel-Aty et al. 2008; Tilak, Hsu et al. 2008; Carlsson, Ubachs et al. 2009; Wright, Adriaenssens et al. 2009; Berry, Kellman et al. 2010) Interestingly, Kim et al published kinetic data supports the existence of an expanded peri-infarct extracellular volume in addition to differing rates of wash-in and wash-out of gadolinium from normal myocardium, peri-infarct rim, and the infarct.(Kim, Chen et al. 1996) Their figure 3 shows distinct hyperenhancement of the peri-infarct rim early during a continuous infusion of gadolinium and it is only late during the wash-out phase that gadolinium-related signal intensity of the infarct exceeded normal myocardium or the peri-infarct rim.(Kim, Chen et al. 1996) Thus, there is substantial evidence from the literature to support the early gadolinium enhancement findings of Matsumoto et al 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 extracellular volume fraction in the infarct will lead to a situation where the acutely infarcted myocardium is brighter than either normal myocardium or salvaged myocardium late after contrast injection. The optimal timing of those two time periods will need to be defined more precisely. For the short term, the best available data(Huber, Muthupillai et al. 2008) indicates we should wait at least 10

minutes after injection for accurate infarct sizing but a 20 minute wait would be safer still. More work is needed to define the kinetics separating these two critical measurements such as renal function and microvascular obstruction. That presents “the double edged sword in the story”: while it is convenient to be able to measure two 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.

References

- Aletras AH, Tilak GS, et al. Retrospective determination of the area at risk for reperfused acute myocardial infarction with T2-weighted cardiac magnetic resonance imaging: histopathological and displacement encoding with stimulated echoes (DENSE) functional validations. *Circulation*. 2006; 113(15):1865–1870. [PubMed: 16606793]
- Berry C, Kellman P, et al. Magnetic resonance imaging delineates the ischemic area at risk and myocardial salvage in patients with acute myocardial infarction. *Circ Cardiovasc Imaging*. 2010; 3(5):527–535. [PubMed: 20631034]
- Carlsson M, Ubachs JF, et al. Myocardium at risk after acute infarction in humans on cardiac magnetic resonance: quantitative assessment during follow-up and validation with single-photon emission computed tomography. *JACC Cardiovasc Imaging*. 2009; 2(5):569–576. [PubMed: 19442942]
- Choi KM, Kim RJ, et al. Transmural extent of acute myocardial infarction predicts long-term improvement in contractile function. *Circulation*. 2001; 104(10):1101–1107. [PubMed: 11535563]
- Fieno DS, Kim RJ, et al. Contrast-enhanced magnetic resonance imaging of myocardium at risk: distinction between reversible and irreversible injury throughout infarct healing. *J Am Coll Cardiol*. 2000; 36(6):1985–1991. [PubMed: 11092675]
- Friedrich MG, Abdel-Aty H, et al. The salvaged area at risk in reperfused acute myocardial infarction as visualized by cardiovascular magnetic resonance. *J Am Coll Cardiol*. 2008; 51(16):1581–1587. [PubMed: 18420102]
- Hillenbrand HB, Kim RJ, et al. Early assessment of myocardial salvage by contrast-enhanced magnetic resonance imaging. *Circulation*. 2000; 102(14):1678–1683. [PubMed: 11015347]
- Huber S, Muthupillai R, et al. Safety of gadoversetamide in patients with acute and chronic myocardial infarction. *J Magn Reson Imaging*. 2008; 28(6):1368–1378. [PubMed: 19025944]
- Ingkanisorn WP, Rhoads KL, et al. Gadolinium delayed enhancement cardiovascular magnetic resonance correlates with clinical measures of myocardial infarction. *J Am Coll Cardiol*. 2004; 43(12):2253–2259. [PubMed: 15193689]
- Kim RJ, Chen EL, et al. Myocardial Gd-DTPA kinetics determine MRI contrast enhancement and reflect the extent and severity of myocardial injury after acute reperfused infarction. *Circulation*. 1996; 94(12):3318–3326. [PubMed: 8989146]
- Kim RJ, Fieno DS, et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. *Circulation*. 1999; 100(19):1992–2002. [PubMed: 10556226]
- Kim RJ, Judd RM, et al. Relationship of elevated ²³Na magnetic resonance image intensity to infarct size after acute reperfused myocardial infarction. *Circulation*. 1999; 100(2):185–192. [PubMed: 10402449]
- Kim RJ, Wu E, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med*. 2000; 343(20):1445–1453. [PubMed: 11078769]
- Kramer CM, Rogers WJ Jr. et al. Contractile reserve and contrast uptake pattern by magnetic resonance imaging and functional recovery after reperfused myocardial infarction. *J Am Coll Cardiol*. 2000; 36(6):1835–1840. [PubMed: 11092653]
- Oshinski JN, Yang Z, et al. Imaging time after Gd-DTPA injection is critical in using delayed enhancement to determine infarct size accurately with magnetic resonance imaging. *Circulation*. 2001; 104(23):2838–2842. [PubMed: 11733404]
- Ricciardi MJ, Wu E, et al. Visualization of discrete microinfarction after percutaneous coronary intervention associated with mild creatine kinase-MB elevation. *Circulation*. 2001; 103(23):2780–2783. [PubMed: 11401931]

- Rochitte CE, Kim RJ, et al. Microvascular integrity and the time course of myocardial sodium accumulation after acute infarction. *Circ Res*. 2000; 87(8):648–655. [PubMed: 11029399]
- Saeed M, Lund G, et al. Magnetic resonance characterization of the periinfarction zone of reperfused myocardial infarction with necrosis-specific and extracellular nonspecific contrast media. *Circulation*. 2001; 103(6):871–876. [PubMed: 11171797]
- Simonetti OP, Kim RJ, et al. An improved MR imaging technique for the visualization of myocardial infarction. *Radiology*. 2001; 218(1):215–223. [PubMed: 11152805]
- Tilak GS, Hsu LY, et al. In vivo T2-weighted magnetic resonance imaging can accurately determine the ischemic area at risk for 2-day-old nonreperfused myocardial infarction. *Invest Radiol*. 2008; 43(1):7–15. [PubMed: 18097272]
- Wright J, Adriaenssens T, et al. Quantification of myocardial area at risk with T2-weighted CMR: comparison with contrast-enhanced CMR and coronary angiography. *JACC Cardiovasc Imaging*. 2009; 2(7):825–831. [PubMed: 19608131]
- Wu E, Judd RM, et al. Visualisation of presence, location, and transmural extent of healed Q-wave and non-Q-wave myocardial infarction. *Lancet*. 2001; 357(9249):21–28. [PubMed: 11197356]