

Imaging the Area at Risk in Myocardial Infarction With Cardiovascular Magnetic Resonance

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Myocardial infarction (MI) remains an enormous problem confronting society, representing a leading cause of cardiovascular mortality and a prevalent cause of heart failure. Cardiovascular magnetic resonance (CMR) is emerging as a versatile tool to catalyze our understanding of this entity. At the population level, CMR epidemiology data from the Imaging Cardiac Evaluation to Locate Areas of Necrosis and Detect MI study¹ of older community-dwelling people reveal an enormous burden of MI, demonstrating that that most MIs are not detected clinically (Figure), perhaps related to variation in the symptoms that patients may experience.² These striking data that used the late gadolinium enhancement (LGE) CMR technique initially described by Kim and colleagues³ underscore the need for continued vigilance and further investigation into the prevention of MI, the detection of MI, and the specific mechanisms of injury. While the current emphasis on “door to balloon times” with prompt percutaneous intervention to restore myocardial blood flow has decreased short-term mortality to the 2% to 5% range,⁴ other relevant outcomes such as in-hospital heart failure⁵ and 30-day rehospitalization⁶ remain prevalent. Collectively, these observations suggest further opportunities to maximize myocardial salvage, and a need to improve our understanding of how therapies can prevent and/or minimize myocardial damage. Such knowledge may translate into even better outcomes. Investigators require robust tools for these endeavors.

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At the preclinical and basic science levels, application of CMR to animal models of disease permit detailed investigations into the pathophysiology of MI. Cine imaging with CMR permits accurate measures of left ventricular mass, volumes, and ejection fraction. With the addition of intravenous gadolinium-based contrast agents that are inherently extracellular for viable cells, LGE identifies *irreversibly injured* tissue by visualizing the contrast that passively diffuses into (1) necrotic myocytes that cannot maintain their membrane integrity or (2) the replacement fibrosis into which the MI invariably transitions during the chronic phase. Notably, the LGE technique is perhaps the most rigorously validated technique to detect and quantify acute and chronic MI.^{3,7,8} In fact, CMR with LGE is the only imaging technique for MI that is validated in an international, multicenter, double-blinded, randomized trial.⁷ These CMR techniques render straightforward the quantitation of MI mass relative to global left ventricular mass.

But this parameter of “percent of left ventricular mass that is infarcted” is not the desired metric to measure *myocardial salvage* needed to test the efficacy of a proposed experimental intervention. For this purpose, the preferred metric is the MI size divided by the denominator of *jeopardized myocardium* supplied by the culprit coronary artery, which reflects the “area at risk (AAR).” One can therefore define the proportion of myocardial salvage mathematically as $1 - \text{MI}/\text{AAR}$. Assessing myocardial salvage instead of “percent of left ventricular mass that is infarcted” promises greater statistical power and fewer animal experiments to demonstrate efficacy of a proposed intervention. Yet, the AAR is more challenging to measure than myocardial mass because it requires distinguishing unaffected myocardium from injured myocardium that remains viable.

In this issue of *JAHA: Journal of the American Heart Association*, Grieve et al publish a novel and elegant “whole heart” 3-dimensional method to measure MI size and AAR *ex vivo* in rodents.⁹ Analogous to microspheres, they use iron oxide microparticles to mark perfused myocardium that excludes the AAR. The signal loss from T2* decay introduced by the iron oxide microparticles causes black dots in perfused myocardium evident on CMR gradient echo images. These dots effectively depict the delivery of iron microparticles by

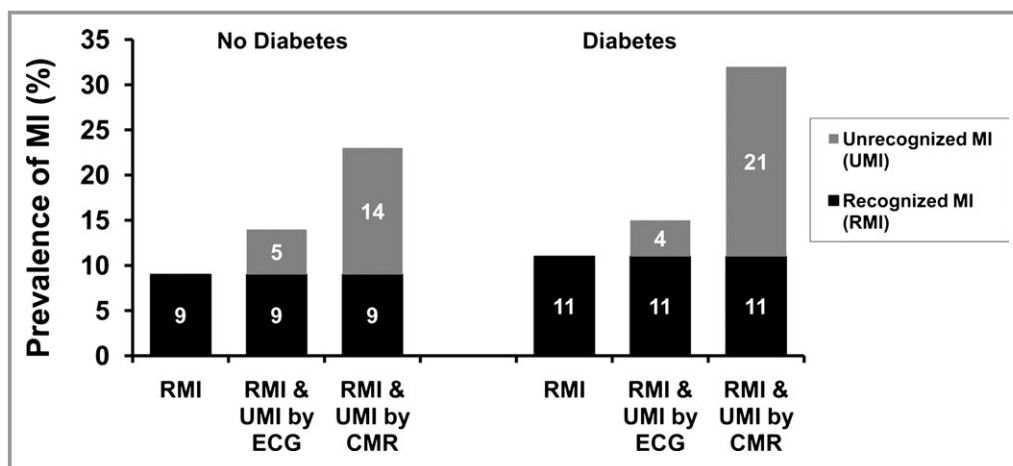


Figure. Fewer than half of all MIs in randomly selected community-dwelling older persons defined by CMR are clinically recognized.¹ The prevalence is displayed according to diabetes status. CMR indicates cardiovascular magnetic resonance; MI, myocardial infarction.

perfusion in vivo, whereas the AAR specifically lacks these particles. Within the AAR, gadolinium contrast causes brightening of the infarct itself because gadolinium contrast enters the necrotic myocytes, increasing the local volume of distribution for this contrast agent that is visible on LGE images. Viable cells exclude gadolinium contrast, showing the viable myocardium with the AAR. The video provided by Grieve et al showing progressive cut-away images through the heart in 3 dimensions is impressive and nicely displays their technique.

Their technique provides unambiguous delineation of the AAR that is primarily based on the *absence of perfusion*, which has advantages over other techniques. While T2 or T1 parametric mapping for myocardial edema¹⁰—that is, the tissue *response* to the impaired perfusion—is useful to delineate the AAR for large animals and humans, such parametric mapping is more difficult to translate in rodents with exceedingly high heart rates where fundamentally different pulse sequences are required. Moreover, the AAR that may be apparent initially with in vivo T2 or T1 parametric mapping might be transient and ultimately disappear ex vivo.

Imaging the AAR provides a tool for investigators studying the impact of therapy to alter the course of an evolving MI. For example, the concept of myocardial regeneration with the use of stem cell therapy for the treatment of MI has drawn much attention. However, promising initial studies in animal models of MI¹¹ have failed to demonstrate convincing efficacy in recent human clinical trials.^{12,13} We note that many of these studies in both animals and humans used myocardial function (regional wall motion or global left ventricular ejection fraction) or infarction size as the primary outcome. As investigators continue to refine stem cell therapy protocols, perhaps the ability to measure infarct size relative to AAR may provide an improved understanding of the effects of

these novel therapies. One would expect that the principles outlined in the methodology reported by Grieve et al would extend to large animal models as well.

The iron oxide microparticle AAR technique also introduces several avenues of investigation beyond myocardial salvage therapeutics. For example, one can explore how diffuse myocardial fibrosis¹⁴ influences myocardial salvage strategies. Or, one could further validate the usefulness of changes in myocardial T1 or T2 that has not been universally accepted as a bona fide measure of myocardial edema.^{15,16} Finally, one could also explore the time course of evolving myocardial T1 or T2 changes occurring with variable degrees of ischemia and reperfusion.

The work by Grieve et al builds on the prior advances in imaging MI. By specifically imaging the AAR, which is the preferred denominator for quantifying myocardial salvage, the iron oxide microparticle AAR technique can catalyze investigations into acute MI therapeutics and develop a deeper understanding of its mechanisms of disease.

Disclosures

None.

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