Myocardial Salvage
Retrospection, Resolution, and Radio Waves

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CARDIOVASCULAR MAGNETIC RESONANCE (CMR) IS ESTABLISHED AS A MAJOR TECHNIQUE IN CLINICAL CARDIOLOGY.1 AN ONGOING PIPELINE OF NEW CLINICAL INDICATIONS IS BEING FED FROM CLINICAL AND BASIC RESEARCH THAT IS THROWING NEW LIGHT ON PATHOPHYSIOLOGY OF CARDIOVASCULAR DISEASE AND SOLVING CLINICAL PROBLEMS. ONE SUCH ADVANCE IN THE LAST 5 YEARS HAS BEEN THE CLINICAL UPTAKE OF LATE-GADOLINIUM-ENHANCEMENT CMR, WHICH YIELDS EXQUISITE HIGH-RESOLUTION IMAGING OF INFARCTION IN THE NECROTIC (ACUTE) OR SCARRED (CHRONIC) PHASE,2 MAKING CMR THE CLINICAL GOLD STANDARD TECHNIQUE FOR ASSESSING INFARCT SIZE3 AND VALUABLE FOR ASSESSING POTENTIAL REGIONAL FUNCTIONAL RECOVERY (VIABILITY).4 IN THIS ISSUE, ALETAS ET AL5 INDICATE THAT CMR ALSO MAY BE USED TO MEASURE MYOCARDIAL SALVAGE DURING ACUTE INFARCTION.

Myocardial salvage is defined as the difference between the actual and potential infarct size, the latter defined as the initial area at risk during acute coronary occlusion. It is an important concept because its measurement can be used to determine strategies to optimize management of acute myocardial infarction (MI) based on the idea that eventual clinical outcome is related to the size of infarction and that minimization is therefore beneficial. Clinical trials of minimization of infarction have a long and distinguished pedigree.6 Myocardial salvage can be measured in several ways, but some are applicable to individuals and others only to groups of patients. Thus, an intervention in acute MI can be tested for benefit by randomization of a cohort of patients to intervention or not, with follow-up of final infarct size surrogates such as ejection fraction or enzyme release. Alternatively, the same intervention can be tested for its direct effect on salvage, which allows assessment of the individual response in relation to the outcome variables and group outcomes. This strategy allows a much clearer assessment of confounding factors; thus, direct measures of salvage are attractive both scientifically and for clinical practice in individuals.

The most widely practiced technique for directly measuring myocardial salvage currently is single photon emission tomography imaging with a technetium perfusion tracer that can be injected during coronary occlusion.7 Prolonged myocardial tracer residence with minimal redistribution allows imaging of the area at risk several hours after the acute presentation and even after clinical interventions, because the image will represent tracer uptake at the time of injection, with the defect representing area at risk. A subsequent predischarge rest perfusion scan identifies the final infarction size, which is smaller than the area at risk if myocardial salvage has occurred. This approach has been applied very successfully in trials, particularly those from the Mayo Clinic8 and Munich,9 and has confirmed that the degree of myocardial salvage is an independent predictor of outcome.10 However, the logistics of such investigations, particularly the initial single photon emission tomography study representing the area at risk, are formidable for multicenter trials. In particular, the tracer (6-hour half-life) must be available at all times for immediate injection during coronary occlusion before any intervention, injection should be performed in line with radiation safety guidelines, and good-quality imaging of the area at risk needs to be completed at each participating center within 8 hours, which poses problems at night. Aletas et al5 suggest that T2 CMR might serve as an alternative means of assessing the area at risk, with the notable feature of decoupling the imaging for some days after the acute presentation (retrospection). Late-gadolinium-enhancement CMR can be used to depict the final infarct size and thence myocardial salvage by subtraction.

There are a number of questions to address in relation to the interpretation of T2 CMR in the setting of acute infarction: What is T2; how is it measured; how well described is the occurrence, distribution, and severity of edema in infarction; what does the T2 signal increase in infarction mean; how well validated is the T2 disturbance in relation to the area at risk; how long does the increased T2 signal last; and what is the relation of the T2 high signal area and that of late gadolinium enhancement? Despite gaps in our knowledge, the overall understanding of the answers to these questions is quite reasonable.

Tissue T2 is a measurable property describing 1 aspect of magnetic relaxation that is directly affected by changes in tissue biochemistry, especially tissue water.11 This suggests that increasing T2 should be useful in identifying edema. Other influences on myocardial T2 are changes in proteins during ischemia (such as cross-linking) and reperfusion, which may affect the time to appearance and the intensity of T2 change. T2 can be imaged by CMR in standard magnets using standard T2-weighted acquisitions, and image analysis is simply based on identifying increased regional signal intensity. Recent literature on edema in acute MI is not abundant, and quantification is difficult because of fixation artifact and other factors in histological studies. Peri-infarction edema is well recognized, however, and older reports of infarction indicate a 25% increase in myocardial water content, regional swelling, and transmural...
distribution of edema. T2 CMR studies also show transmural T2 signal increases in acute infarction, even in those infarctions that ultimately show subendocardial scar. This lends credence to the concept that the distribution of T2 signal abnormality exceeds that of scar and represents the nonlethal injury zone (the area at risk) during acute coronary occlusion in humans, which is in accordance with animal experiments. Also consistent with these interpretations is the reduction in T2 seen with successful treatment of myocardial edema with mannitol. The increase in T2 observed with edema takes a minimum of 1 hour to be manifest in humans, can be identified in dogs within 4 hours, and only completely resolves some months later. One question that has been raised regarding MI imaging by late-gadolinium-enhancement CMR is whether in the acute setting the gadolinium enhancement is confined to the necrotic area or whether extension occurs into the border zone of myocardial edema without necrosis, which might have increased intersitial space that could harbor gadolinium. The study by Aletras et al firmly answers this question and demonstrates that late gadolinium enhancement is limited to the area of necrosis only. The lack of increased gadolinium signal in the border zone indicates that its partition coefficient must be similar to normal myocardium and less than within the area of necrosis, which is in accordance with experimental evidence. This can be reconciled if there is balanced intracellular and extracellular edema occurring in the border zone.

CMR is not the only technique that can identify ischemia in retrospect. In nuclear cardiology, the fatty acid tracer 123I-β-methyl-p-iodophenyl-pentadecanoic acid (BMIPP) also has similar properties, and the mechanism appears to be due mainly to a metabolic imprint related to a persistent decrease in β-oxidation with increased shunt retention of BMIPP in the triglyceride pool. This tracer has been evaluated extensively in Japan and more recently in the United States and has attracted the label of an ischemic memory tracer. This property can be exploited during exercise testing with favorable comparison to thallium or in the acute infarction setting to determine the area at risk well after the coronary occlusion. A single study comparing BMIPP and T2 CMR in humans with acute infarction showed T2 CMR to have improved accuracy for identifying culprit lesions. The positron emission tracer 18F-fluorodeoxyglucose also shows persistent glucose metabolism derangement after ischemia. Studies comparing the area at risk between T2 CMR and these tracers would be of interest.

One issue that has arisen is the confidence with which the area at risk can be demarcated with T2 CMR, which depends on the contrast that exists between normal and at-risk myocardium and the robustness of the technique. T2 CMR can be performed using breathholds typically <15 seconds with high resolution, which is greatly superior to nuclear techniques. However, the contrast-to-noise ratio between the area at risk and normal myocardium is quite low (2.9 in the article by Aletras et al). Higher values would be expected in human studies because high-resolution imaging was used in the animals, but it is worth dwelling on this point. Changes in T1 in areas of acute infarction were first reported in the early 1980s; subsequent reports showed that injection of gadolinium could enhance the contrast between infarcted and normal myocardium. However, the technique was not used clinically, not the least reason being the severe lack of access to CMR at that time. The use of CMR in infarction did not take off until the introduction of the late-gadolinium-enhancement technique, when a simple inversion pulse sequence introduced a quantum leap in contrast between normal and infarcted tissue, with a typical contrast-to-noise ratio of 19, which is substantially greater than that reported for T2. A question therefore is whether the contrast-to-noise ratio of the T2 scans can be boosted to make clinical use in humans robust. There are many means by which this might be achieved, and the article by Aletras et al may well hasten their clinical development.

How might strategies to measure myocardial salvage affect clinical management of patients presenting with acute MI? Although thrombolysis and primary angioplasty have become the first-line treatments for acute MI in many countries, this does not obviate the value of further myocardial salvage studies or their application in individual patients. One obvious group in whom this technology can be applied is those who present late after infarction, typically >12 hours after onset of symptoms, for whom primary angioplasty is not an automatic choice. The issue in such patients is to individualize the decision to proceed. It is possible to imagine patients at this stage whose coronary artery has been continuously occluded and whose infarction wave front has virtually reached the border of the area at risk. Another patient, however, may have intermittent coronary occlusion; for this patient, periodic perfusion, ischemia, and infarction could result in stuttering infarction that might leave substantial salvageable myocardium. It is reasonable to consider that the latter patient has something to gain from late immediate angioplasty.

In addition, adjunctive treatments to reperfusion therapies remain of considerable interest. These typically will require considerable resources to study and a multicenter approach in clinical trials. CMR assessment of myocardial salvage is attractive for a number of reasons in this setting. First, the requirement for 24-hour immediate availability in the emergency room of technetium myocardial perfusion tracer is obviated. Second, image resolution is substantially improved, leading to higher-fidelity measurements and thus smaller sample sizes. Third, it would be entirely possible to operate a hub-and-spoke model for the CMR scans, with a number of participating hospitals that might not have sufficient CMR expertise or availability contributing patients to a nearby hub expert center for predischarge assessment of salvage. Fourth, an important ethical consideration for such research is that the radiation burden of nuclear studies can be avoided.

In conclusion, the experimental understanding from animal studies for the use of CMR to assess myocardial salvage is sound, and translation into human studies is likely with improved methodology. This includes improving T2 image contrast through sequence optimization and defining the optimal timing for T2 imaging in humans. Also of value would be evaluating the T2 response to infarction in the presence and absence of reperfusion, evaluating the myocardial T2 response to exercise-induced ischemia, and clinical experience. Using
CMR for clinical myocardial salvage studies appears eminently feasible and is logistically attractive.

Disclosures

None.

References


