The region of myocardium hypoperfused during ischemia, also known as the area at risk (AAR), has sought our attention since the earliest understandings of the wavefront of progressive myocardial infarction (MI) due to acute coronary syndromes (ACS).1 Edema took center stage as evidence accrued that cardiomyocytes take on water in the setting of ischemia and reperfusion;2 this, in turn, led to the notion that the myocyte’s survival was determined by whether sarcolemmal membrane resistance was exceeded.3 The development of nuclear scintigraphic techniques afforded demonstration of the perfusion deficit in vivo at the time of presentation. Comparison with histology in a number of autopsy hearts confirmed that in many patients, a large scintigraphic defect often was present despite a small area of irreversibly injured or infarcted myocardium; that is, there appeared to be myocardium at risk of irreversible injury but potentially salvageable.4 The authors presciently concluded that this group of patients had the “greatest promise for intervention.”

Articles see p 210 and 228

Fast forward to the present era of rapid mechanical revascularization coupled with a host of pharmacological maneuvers to restore blood flow, and what do we find: reduced but still significant morbidity (≥3.4% patients per year develop heart failure after MI),5 mortality (~20% of men and women aged >40 years die in the first year after initial MI),6 and cost of subsequent care (~$32,000 per patient is spent in the first year after MI).7 Although increased infarct size consistently portends worse outcomes,8,9 it would make sense to develop interventions that reduce ultimate infarct size while myocardium is still salvageable; this, in turn, requires reliable techniques to delineate the AAR. Short tau inversion recovery (STIR) has long been the workhorse cardiac magnetic resonance (CMR) technique for in vivo myocardial edema imaging,10 with a landmark study by Aletras et al11 in 2006 proving that the edematous myocardium delineated by T2-weighted STIR exactly matched the AAR by fluorescent microspheres in a dog model of MI. Interestingly, AAR by T2-weighted STIR acquired after percutaneous coronary intervention (PCI) in patients with ST-segment elevation MI has been shown to match AAR by single-photon emission computed tomography with the radioisotope injected before PCI,12 suggesting validity for its use in computing area of salvaged myocardium. However, several well-known limitations have hampered widespread clinical use of this technique, particularly in patients with irregular rhythms or difficulty with breathholding—both of which are not uncommon in patients with ACS.

Two articles in this issue of Circulation: Cardiovascular Imaging take important steps toward improving the utility of myocardial edema imaging with T2-weighted CMR. Payne et al13 studied 54 patients with troponin-positive MI post-PCI, using a single CMR examination with both the traditional STIR and the more recently developed acquisition for cardiac-unified T2 edema (ACUT2E) technique for myocardial edema imaging.14 ACUT2E afforded greater interreader consensus and better agreement with angiographic and electrocardiographic risk scores. Although the authors’ claim of superior accuracy must be tempered by lack of data from patients who were edema negative, this “bright blood” technique did appear to define AAR more extensively and reliably than STIR. Furthermore, STIR delineated a smaller region than late gadolinium enhancement (LGE) in one third of patients with acute MI, which is not consistent with the notion of AAR.

Dall’Armellina et al15 provide some insights into the time course of edema resolution with 4 T2-weighted CMR studies after MI using a T2-prepared steady-state free precession sequence that also overcomes many of the limitations of STIR. Although the extent of increased myocardial signal intensity on T2-weighted images remained stable during the first week after MI, edema was significantly reduced at 2 weeks. As previously shown,16 the LGE signal diminished between the first and fourth CMR visit. We do not know from this work, unfortunately, how the LGE signal parallels (or diverges from) T2 signal changes during the crucial 1- and 2-week visits. Such studies would involve additional gadolinium-based contrast agent exposures; however, the results of such a trial in appropriately selected subjects would have provided valuable information to guide timing of viability assessment in decision making regarding both revascularization and perhaps device therapy.

Some controversy has emerged recently as to the uniqueness of information provided by T2-CMR, particularly in comparison with myocardial characterization by LGE. It has been proposed that if one were to use a lower threshold to assign LGE positivity, such as signal intensity exceeding 2 SD above the mean of remote myocardium instead of the more stringent mean +5 SD threshold, one could delineate
the same AAR with LGE that T2 imaging provides. The experience of other groups, including our own, suggests that these 2 techniques yield distinct information (Figure). Given the many challenges in obtaining consistent T2-weighted images, we have abandoned STIR imaging in favor of quantitative T2 mapping, which offers precise cutoffs for identifying abnormal myocardium in ACS.

With improvements in both qualitative T2-weighted and quantitative T2 techniques, the potential impact of myocardial edema imaging in the care of patients with ACS should be reassessed. Most studies to date (recently reviewed by Friedrich et al20) have focused on the patient whose acute ACS management already has been completed—typically in postrevascularized ST-segment elevation MI, where T2-CMR has shown utility in trials of interventions to reduce AAR. Comparative effectiveness studies are needed to prove that acquiring this additional information at discharge or a few weeks thereafter improves outcomes. For instance, if AAR predicts adverse remodeling and heterogeneous depolarization, it is intriguing to consider T2-CMR-guided trials that target AAR with existing or novel therapies to reduce post-MI heart failure and arrhythmias. Our investigative team has shown potential diagnostic and prognostic utility of T2-CMR in patients with non-ST-elevation ACS.21 Patients with non-ST-elevation ACS comprise the majority of patients with ACS, and experience significant morbidity and mortality at follow-up due in part to uncertainty in initial evaluation and management. Although prospective, randomized trials of T2-CMR-guided management in appropriately selected patients with non-ST-elevation ACS are needed to test the upfront value of identifying myocardium at risk, it is appealing to consider its clinical utility before there has been extensive irreversible injury and when management decision making is still under way. It may be that T2-CMR could direct our attention to the myocardium in non-ST-elevation ACS patients who are most likely to benefit from urgent invasive assessment and intensive adjuvant antithrombotic and antiplatelet therapy versus those who might be just as well served with a more conservative approach.

Even if STIR has left the building, the salvageable myocyte has not. Previously established findings prompt new questions about what edema imaging is trying to tell us. More robust recognition of myocardium at risk of irreversible injury afforded by improved steady-state free precession-based T2-weighted imaging or T2 mapping can now be incorporated into: (1) ACS trials of novel therapeutics to salvage myocardium at risk; (2) clinical assessment of the symptomatic patient requiring refinement in diagnosis and targeted management; (3) improved diagnosis of other conditions marked by myocardial edema, such as myocarditis and tako-tsubo cardiomyopathy; and (4) evaluation of chemotherapy-induced and other subacute myocardial injury syndromes to advance mechanistic insights and guide better cardioprotection. We have learned much from remarkably precise identification of irreversibly injured myocardium; the door is now wide open to better identify and rescue salvageable myocardium, improving patient outcomes with techniques that make T2 myocardial imaging a less risky business.

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References
1. Reimer KA, Jennings RB. The “wavefront phenomenon” of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. Lab Invest. 1979;40:633–644.


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