Building a Unified Mechanistic Insight Into the Bimodal Pattern of Edema in Reperfused Acute Myocardial Infarctions: Observations, Interpretations, and Outlook*

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Over the past 50 years, the understanding of the pathophysiology of myocardial edema in the setting of acute myocardial infarction (MI) has evolved significantly. Controlled animal studies have demonstrated that ischemia or transient ischemia followed by reperfusion lead to myocardial edema. In particular, ischemia promotes intracellular edema and the extent of edema is directly related to ischemia duration. Several studies have also shown that reperfusion after transient ischemia can lead to extensive interstitial edema.

The evidence supporting these findings has been based on invasive standards: histologic observations of changes in tissue ultrastructure; and desiccation studies, which report on tissue water content based on relative differences between wet and dry weight of myocardial samples of interest. Although these invasive measurements can provide direct evidence, assessment of edema on the basis of these standards is limited to a single time point. Thus, to determine temporal changes of edema in the same subject pertaining to given pathology (e.g., ischemia or ischemia followed by reperfusion), serial assessments on the basis of noninvasive methods are necessary.

Over the past 2 decades, cardiac magnetic resonance (CMR) imaging has evolved into an invaluable noninvasive tool to assess myocardial edema. Among the various CMR methods, T2-based approaches have been extensively used to study ischemia and ischemia/reperfusion (I/R) injury in animals and patients. Although T2-based CMR is routinely used to investigate pathophysiology of acute MI in the preclinical setting, there is evidence suggesting the clinical importance for imaging myocardial edema in patients with MI. Notably, such assessment is now central to discriminating between acute and chronic MI (1). Additionally, edema is an early marker of ischemia for noninvasively identifying an ongoing MI's territory, even before tissue necrosis is observed (2).

Perhaps the most passionately explored aspect of myocardial edema in CMR is the retrospective definition of the area at risk (3,4). Once the area at risk can be quantified, identifying the salvageable myocardium becomes possible (5), because the necrotic myocardium can be determined with late-gadolinium-enhanced CMR. Determination of salvageable myocardium, on the basis of noninvasive imaging, is believed to be important in assessing the efficacy of new therapeutic strategies to minimize myocardial injury in acute MI. Hence, accurate assessment of myocardial edema is important to avoid errors in estimates of the area at risk and salvageable myocardium.

Recently, Fernández-Jiménez et al. (6) reported that myocardial edema post-I/R follows a bimodal pattern: a rapid evolution of edema that subsides in 24 h followed by a second wave of edema that progressively increases, peaking on day 7. They demonstrated this phenomenon using a swine model of I/R.
with 40 min of ischemia before reperfusion. Their serial assessment of myocardial edema at 2 h, 24 h, 4 days, and 7 days post-reperfusion used previously validated T2-based CMR approaches. Nonetheless, they also provided compelling histologic evidence for this bimodal pattern of edema from tissue desiccation studies performed in subsets of animals at the respective time points.

In this issue of the Journal, Fernández-Jiménez et al. (7) extend their previous studies and report on the pathophysiology of the bimodal pattern of edema. The first wave of edema flows from reperfusion and the second wave is related to an active inflammatory response associated with infarct healing. Importantly, they show that the first wave of edema is absent in nonreperfused infarctions to support their hypothesis that early edema is solely from reperfusion. Furthermore, the second wave of edema coincided with the inflammatory response in the infarcted myocardium. The authors are to be commended for undertaking a mechanistic investigation into the pathophysiology of the bimodal pattern of edema in reperfused acute MIs. Their findings are original in that they studied the temporal patterns of edema intensely at multiple time points within a week of reperfused and nonreperfused acute MIs. Their frequent profiling to map temporal changes in inflammation on the basis of immunohistochemistry is also new, as is the subsequent relating of these changes to T2 in reperfused MI at multiple time points.

These intriguing findings raise several questions related to acute MIs. In particular, both studies (6,7) used a swine model of I/R with 40 min of ischemia, just crossing the ischemic threshold for 50% transmural MI (8). It is unclear whether these findings would extend to shorter and, more importantly, longer periods of ischemia, which can lead to greater frequency of transmural infarctions, microvascular obstructions (MVO), and intramyocardial hemorrhage. Moreover, the current data rely on animal sacrifice at different points in time to assess myocardial edema and immunohistochemistry, which assume identical MI characteristics of all animals. Although it is likely that swine models provide consistent MI size over a fixed ischemic period, variations in experimental conditions could produce differences in other MI characteristics. In this study, significant differences in histological scores of hemorrhage between animals sacrificed on days 1, 4, and 7 provide potential evidence supporting this possibility. Future studies that aim to systematically follow inflammation and edema noninvasively using advanced imaging strategies (e.g., novel positron emission tomography tracers in multimodal positron emission tomography/magnetic resonance scanners [9] or combining 19F with 3H CMR [10]) in the same animal may provide additional insights.

As the authors carefully note, resorption of water from the initial wave of edema remains incomplete by 24 h post-reperfusion, evidenced by the positive elevation in water content (from desiccation studies) at 24 h relative to baseline. Nonetheless, in the same tissue, T2 values at 24 h returned to baseline values. As the authors indicate, this discrepancy may be attributable to changes in magnetic properties of red blood cells after I/R, which can drive T2-based signals lower and counteract T2 elevation from edema. Per the brain data, the breakdown of hemoglobin can be visualized as a hypointense region by day 1 after hemorrhagic strokes (11); these effects are scaled with the scanner’s field strength. Moreover, even nonreperfused MIs (i.e., nonhemorrhagic MIs) can lead to signal losses in T2*-based CMR from hemoglobin breakdown, even in the absence of hemorrhage (12). In the current study, an important feature evident in the serially measured T2 values in nonreperfused MIs is the elevation in T2 values after 120 min of ischemia, which seems to decrease significantly by 24 h. The initial edema wave in these infarcts likely springs from ongoing ischemia, nicely confirming previous reports (2). Subsequent decrease in T2 values in the same MIs by 24 h is plausible, perhaps because of the breakdown of “trapped” blood within the vasculature, which can impart a significant signal loss in T2*-based CMR, particularly at 3-T. Thus, although edema can be assessed using T2-based CMR, one must consider the contemporaneous evolution of other substrates that can modulate T2-based CMR signal characteristics in acute MIs.

The authors’ finding that edema is unstable during the first week of acute MI also needs careful interpretation. First, both studies show changes in T2 values but not relative volume of edematous myocardium, which is of substantial interest to those retrospectively evaluating area at risk or salvaged myocardium. Second, area at risk on the basis of T2-based CMR has only been validated with an invasive standard on day 2 after reperfusion (3). Thus, the acute assessment of edema using T2 for estimation of area at risk outside this time point, particularly on day 1 post-reperfusion, would not be substantiated. Third, assessing changes in diastolic wall thickness throughout the acute MI period would be valuable to determine whether changes in edema correlate with changes in diastolic wall thickness. Finally, the
authors’ finding that the edema is bimodal directly contrasts previous reports in humans (13) and canines (14) with reperfused acute MI, which have shown that edema volume is relatively flat between days 1 and 7. These differences may be in part caused by the species studied, experimental conditions (difference in ischemic periods preceding reperfusion), reported indexes of edema (intensity vs. volume), and/or subjective elements used in image analysis to identify territories of edema.

The understanding of myocardial inflammation secondary to acute and chronic MI continues to evolve. It is known that the healing process in non-reperfused MI is slow primarily because of physical obstructions limiting macrophage infiltration into the infarct site. In reperfused infarctions, either similar, worse, or better scenarios of macrophage infiltrations are possible. This is because not all reperfused infarctions are the same: some MIs have no MVO, others have some MVO, yet others have extensive MVO and hemorrhage. Several studies have shown that presence of MVO impairs macrophage infiltration and healing. As confirmed more recently, presence of hemorrhage can further extend inflammatory burden and prolong infarct healing (11,15). Hence the low density of macrophage activity within the MI territory may not be synonymous with edema evolution within the early phase of an acute MI. Notably, in the current study, substantial hemorrhagic burden was present, at least in some animals, as evidenced by the histology scores on day 4. Additional studies are needed to examine whether the same temporal course of inflammatory response can be observed in the absence of MVO or hemorrhage.

The authors are to be congratulated for their novel findings relating bimodal edema patterns to an early wave of edema from reperfusion and a deferred wave of edema, coinciding with the inflammatory response, in a swine model of acute MI. Their intriguing findings add to the understanding of tissue characteristics of acute MI, but are limited to the specific animal model investigated. Further investigations will help generalize the observations of bimodal patterns of edema, and establish additional mechanistic insight across the spectrum of acute MI in humans.

**REFERENCES**


**KEY WORDS** acute inflammation, acute myocardial infarction, cardiac magnetic resonance imaging, ischemia/reperfusion injury, myocardial edema