Rapidly restoring blood flow in the epicardial coronary artery after an acute obstruction is critical for limiting myocardial tissue damage and salvaging the area at risk. Minimizing the acute injury to the myocardium after an ischemic event (ie, infarct size) has been strongly correlated with improved outcome. In fact, large myocardial infarctions (MIs) have been associated with pronounced adverse outcomes. (MIs) have been associated with pronounced adverse outcomes. Understandably, this has lead to the affirmation that time is muscle, and efforts are routinely made to quickly restore blood flow to ischemic myocardium.

See Article by Bulluck et al

However, for >40 years, we have known that not all MIs are the same. Pioneering work by Kloner et al in large animal models demonstrated that microvascular obstruction (MO), also assessed as no-reflow phenomenon, could complicate some acute MIs. A more severe case of MO has been observed to lead to intramyocardial hemorrhage, a case where the microvasculature ruptures, likely during reperfusion, and red blood cells are extravasated. Notably, MO leads to compromised blood flow to the microvasculature even after the blood flow is re-established to the culprit epicardial coronary artery. These studies and numerous others that followed showed that reperfusion can impart additional acute damage to the myocardium, often referred to as ischemia–reperfusion injury, and is a strong predictor of adverse outcome in patients. Thus, the importance of reducing ischemia–reperfusion injury is well recognized and has been the subject of intense investigation for the past few decades.

Advances in imaging, particularly cardiac magnetic resonance imaging (CMR), have been central to shedding light on the tissue characteristics of acute MI and enabling the assessment of time-dependent changes in the heart. In particular, late-gadolinium enhancement has been important in sizing of MI and for identifying the presence of no-reflow territories in the acute setting. Nearly 2 decades ago, a key study by Wu et al showed that the cardiovascular event–free survival in patients without late or persistent MO (ie, those hypointense territories surrounded by hyperintense zones in late-gadolinium enhancement) was 30% better than those with late MO during a 2-year follow-up period. Importantly, this study showed that late MO was more frequently observed in large acute MIs and that the appearance of MO was not limited to large acute MIs and that when controlled for infarct size, late MO was an independent predictor of event-free survival. Since then, several studies have reported similar findings. More recently, a multinational consortium reported that the presence of late MO carries a 4-fold greater risk for MACE in the chronic period than acute MI size. This suggests that reducing late MO or their effects in the convalescent phase of MI holds even a greater promise in reducing MACE than just limiting infarct size.

Over the past decade, driven by advances in CMR, particularly T2* and T2 mapping, there has been a growing interest on the role of intramyocardial hemorrhage (IMH), specifically with regard to its prognostic value in post-MI patients. Consistent with earlier studies by Kloner et al, CMR studies in dogs by Kumar et al demonstrated that IMH is always accompanied by late MO, and T2* imaging can be instrumental in identifying the presence of IMH within acute MI territories. Since then, the use of T2* CMR for imaging reperfusion hemorrhage in patients has also been demonstrated. Several studies to date have shown that >50% of infarcts with late MO have IMH, whereas the most recent evidence by Robbers et al and Carrick et al suggest that >75% of late MO are accompanied by IMH. Ganame et al first reported that patients with a history of IMH had significantly worse LV remodeling than those without IMH at 4 months post MI. In a subsequent larger study of 346 patients, Eitel et al showed that the presence of hemorrhage carries an excess of 2-fold greater risk for MACE compared with infarcts that are not hemorrhagic (16% versus 7%) at 6 months post MI. More recent studies by Carrick et al in 228 patients showed similar results including that the patients with IMH had a markedly diminished ejection fraction than those without IMH in the acute period, at 7 months post MI. Mather et al have demonstrated a close association between IMH and late arrhythmogenic risk. Despite the growing number of studies, which show significant association between IMH, chronic iron, and MACE, the causal connection between those findings and MACE has not been established, but mechanistic insights are emerging.
Recent studies by Kali et al. demonstrated that IMH in the acute phase could lead to chronic/residual iron deposition within the MI territories well past the acute phase of MI both in a canine model and in a small cohort of patients with reperused ST-elevation MI. On the basis of histological evidence from canine hearts, the same study also showed that the site of iron deposition to be highly inflammatory with macrophages preferentially being recruited to the site of iron even during the chronic phase of MI. In subsequent studies, Cokic et al. reported that residual iron deposits are associated with late action potentials in animals and are a powerful predictor of malignant ventricular arrhythmias and sudden cardiac death in post-MI patients. Recent studies by Kali et al. revealed that iron is deposited within chronic MI as ferric oxide crystals and impart an unrestrained proinflammatory insult on the heart. Importantly, proinflammatory burden has long been known to accentuate tissue injury and increase adverse LV remodeling.

In this issue of Circulation: Cardiovascular Imaging, Bulluck et al. have examined the effects of IMH in 48 reperfused ST-segment–elevation myocardial infarction patients followed ≤6 months post MI. Based on T2* CMR, they found that ~80% of the patients with acute MI had residual iron 5±2 months post MI. In addition, they found that the T2 of the infarct zone (T2 infarct) surrounding the residual iron territory to be significantly elevated compared with those without residual iron. In addition, they found that in patients with poor LV remodeling, T2 infarct was higher than those without a history of IMH. This study is the largest study to date to report on the residual iron in ST-elevation MI patients with a history of IMH. As such, it lends important tissue-specific evidence into the long-term consequences of IMH, particularly during the convalescent period of MI in humans.

The findings of Bulluck et al are compelling and are consistent with that of Kali et al. First, both studies showed residual iron within the MI territories of ST-elevation MI patients, albeit the current study followed a larger number of ST-segment–elevation myocardial infarction patients. Although Kali et al did not demonstrate elevated T2 within chronic MI in patients with IMH, which is suggestive of edema in the surrounding territories of residual iron, their demonstration of significant localized inflammation in canine hearts is consistent with observation of Bulluck et al. Although it remains to be directly confirmed, it is likely that the increased inflammation may be the prominent source of edema similar to cases where myocardial inflammation and edema have been previously demonstrated to go hand in hand.

There is another important implication associated with the findings of Bulluck et al for CMR. Although late-gadolinium enhancement can identify acute and chronic MI, T2 imaging is used to discriminate between the two. Important studies by Abdel-Aty et al. showed that acute and chronic MI could be discriminated on the basis of edema because it is thought that edema is typically resolved after 1 to 2 weeks post MI; hence, edema is absent in chronic MI. The current findings by Bulluck et al forces us to now carefully examine whether T2 mapping alone is sufficient to accurately discriminate between acute and chronic MI.

Most importantly, the findings by Bulluck et al provide mounting evidence that the effects of IMH are not limited to the acute setting in which it takes place—rather, it imparts a long-lasting effect on the myocardium. Hence, methods to minimize IMH and iron could be invaluable in curbing the incidence of MACE in MI patients. However, currently available post-MI medications are not specific to patients with IMH and have not been shown to be specifically beneficial to those who develop IMH compared with other MI types. If the inflammatory response to residual iron proves to drive adverse LV remodeling, then preventing IMH at the early phases of acute MI or minimizing residual iron in the longer term may prove to be an important therapeutic strategy in minimizing adverse LV remodeling and MACE. In this regard, iron chelation therapy would appear to be a natural choice.

The recent TACT (Trial to Assess Chelation Therapy) in post-MI patients showed that 6 months of EDTA therapy did not significantly decrease adverse cardiovascular events (cardiovascular death, MI, or stroke). Notably, however, EDTA is (1) not specific (or dosed) for ferric iron; (2) cannot cross cell membranes; and (3) known to mainly chelate divalent ions. Notably, recent study by Kali et al showed that iron is intracellular and is trivalent. Other studies have also explored iron-specific chelation therapies but have been limited to acute MI (ie, 1–2 days post MI). Common to both TACT and acute MI studies to date are that neither stratified the patients for a viable chelation therapy based on evidence of IMH or iron within MI.

On the balance, the growing evidence of adverse outcomes associated IMH and the associated iron deposition is incontestable. Thus, a therapeutic strategy that can be translated rapidly to reduce such outcomes would have a profound impact on post-MI care and answer the outstanding and growingly important question, whether hemorrhage is causally connected to the observed outcomes. Should hemorrhage and its long-term effects pass the “litmus test” of causality, CMR stands to play a central role in the management of acute and chronic MI patients. Among the multiple therapeutic avenues that can be explored and given that iron chelation therapies in post-MI setting have not been adequately tested, are we ready to re-evaluate it in acute and chronic MI patients who are confirmed for IMH or iron?

Disclosures

None.

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"Rusty Hearts": Is It Time to Rethink Iron Chelation Therapies in Post–Myocardial-Infarction Setting?
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