Microvascular Integrity in Myocardial Injury

The Irony of Iron Deposition

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Infarct size and extent of transmural involvement are major determinants of left ventricular (LV) remodeling after myocardial infarction (MI), and restoration of the patency of the coronary artery alone remains the most important intervention to limit the extent of myocardial injury.¹ Noninvasive imaging modalities, such as contrast echocardiography² and cardiac magnetic resonance imaging,³ have shown that the integrity of microvasculature early on determines the viability of the myocardium in the area at risk.⁴ On the other hand, the extent of microvascular damage, persistent microvascular occlusion (PMO), and myocardial hemorrhage resulting from ischemia and reperfusion have been shown to adversely influence LV remodeling after MI regardless of the size of the infarct.⁵ It has also been observed that the deposition of iron in myocardium after infarction is associated with adverse LV remodeling and electrical abnormalities.⁶ The mechanisms by which PMO and interstitial hemorrhage lead to adverse LV remodeling and cardiovascular outcomes are not well understood.

In this issue of Circulation: Cardiovascular Imaging, Kali et al⁷ investigated the possible relationship between PMO, the extent of crystalline iron deposition in the myocardium, and adverse LV remodeling. Their study included 33 canines, wherein the left anterior descending was occluded for 3 hours followed either by reperfusion (n=17) or permanent occlusion (n=16). Serial cardiac magnetic resonance imaging was performed in all animals on day 7 (acute phase) and day 56 (chronic phase) post MI. On the basis of cardiac magnetic resonance–verified evidence of PMO and iron deposition, the animals in the reperfused group were classified into PMO+/T2*+(n=9), PMO+/T2*−(n=4), and PMO−/T2*−(n=4). The nonreperfused MI were classified into PMO+/T2*+(n=15) and PMO−/T2*−(n=1). LV structural and functional remodeling was assessed, and volume of infarct was defined; PMO and iron were quantified for the acute and chronic phases. The histopathologic analysis was performed at the end of experiments to define the extent of fibrosis and iron deposition, and immunohistochemical characterization of inflammatory cells (neutrophils and macrophages), cytokines (interleukin-1β and tumor necrosis factor-α), and proteinases (matrix metalloproteinase-9). In addition, transmission electron microscopy and energy dispersive X-ray spectroscopy were performed. PMO with iron deposition (PMO+/T2*+) was present in the majority of animals during the acute phase of MI in both the reperfused and nonreperfused groups, albeit significantly higher in the nonreperfused (15/16) compared with the reperfused (9/17) animals. In the chronic phase, although there was no evidence of PMO in either group, presence of iron deposition was directly proportional to the PMO volume during the acute phase. Of note, there was no animal in either group in which iron deposition was observed without PMO. In the reperfused group, PMO could still result in iron deposition within the infarcted territories in the chronic phase even if it was not associated with reperfusion hemorrhage as seen acutely on T2*-weighted images. On the other hand, in the nonreperfused group, there was no difference in the amount of iron deposition in the acute and chronic phases because 15 of 16 nonreperfused animals already had iron deposition in the acute phase. The consistent relationship between PMO size and iron deposition even in the nonreperfused group goes against the classical notion that there is no infarct-related hemorrhage in nonreperfused MI and emphasizes the importance of PMO as a predictor/precursor of LV remodeling and outcomes independent of reperfusion strategy. Transmission electron microscopy and chemical elemental analysis showed that iron accumulation occurred in the form of aggregates of crystalline nanoparticles in the ferric state within lysosomes of the macrophages. The quantity of iron deposition correlated with the macrophages and interleukin-1β, tumor necrosis factor-α, and matrix metalloproteinase-9 activity. The resorption of the infarct had a linear relationship to iron content in the healing phase and adverse LV remodeling.

The presence of iron affects the function of different immune cells.³ Iron is thought to activate the nuclear factor-κB pathway that plays an important role in innate immunity and inflammation. Neutrophils and macrophages play a major role during the healing of an infarct. Iron has been shown to inhibit the phagocytic activity of neutrophils. Interestingly, in vitro studies have shown that heme-induced interleukin-1β production by macrophages can be inhibited by iron chelating agents.¹⁰ Previous studies have also demonstrated that administering deferoxamine before and during ischemia and reperfusion resulted in a significant improvement in the LV function.¹¹ The animals receiving deferoxamine before reperfusion showed a remarkable LV functional recovery compared with those who...
received it after initiation of reperfusion. This study by Kali et al.\(^1\) showed iron deposition even in the nonreperfused animals several weeks after MI in the presence of PMO alone. The authors proposed that degradation of the stagnant blood in the PMO could lead to iron deposition in the chronic healing phase.

Traditionally, it is thought that the extent of myocardial remodeling post MI depends on area at risk (ie, the extent of perfusion abnormality as a result of epicardial vessel occlusion and the time to reperfusion). Therefore, logically, most acute and chronic therapeutic strategies revolve around timely revascularization and anti-ischemic/heart failure therapies. This article confirms that PMO and iron crystalline deposition could play an important role in determining adverse remodeling. It has previously been shown in prospective randomized trials that iron chelation therapy in patients with MI results in modest reduction in adverse cardiovascular outcomes.\(^2\) Similarly, anti-inflammatory therapies, such as colchicine, have been shown to reduce infarct size and myocardial scar formation postinfarct.\(^3\) However, even though small size studies have investigated the role of therapeutic strategies directed at preserving microvascular integrity, there have been no randomized clinical trials that examine the possible therapeutic intervention that preserves microvascular integrity (acutely) in the setting of MI.

This study is important as it proposes that, independent of revascularization status, PMO is an important determinant of intramyocardial iron deposition, which through series of inflammatory mediators, contributes to post-MI LV adverse remodeling and cardiovascular outcomes. The emphasis of the results in this study should not revolve around the difference between reperfused and nonreperfused arteries because the value of early revascularization post-MI has been proven in a multitude of studies in various clinical settings. Rather, the focus must remain on potential therapeutic targets that could incrementally help preserve microvascular integrity acutely and potential role of anti-inflammatory and iron chelation therapy in MI. It would be attractive should iron chelation evolve to be organ-specific without affecting systemic iron content or iron stores.\(^4\)

It is well known that microvascular damage in the setting of acute MI can be because of direct ischemic and oxidative damage to the vessels, microvascular stasis and compression of the vasculature by necrotic or swollen myocytes, and platelet microemboli resulting from either plaque rupture or coronary intervention. Ischemia-induced release of cytokines may also contribute to microvascular dysfunction in remote areas of the myocardium.\(^5\) Should microvascular integrity be upgraded as an investigational target to complement the enormous benefits accrued from reperfusion? Studies such as the one in discussion would lead the way.

**Disclosures**

None.

**References**


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