Intramyocardial Hemorrhage in Acute Myocardial Infarction: Prognostic Biomarker and Treatment Target?

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Timely primary percutaneous coronary intervention to restore myocardial perfusion is pivotal in acute ST elevation myocardial infarction. The major determinants to reduce myocardial injury before intervention are reducing ischemia duration and severity, and the major determinants after intervention are restoring microvascular flow and minimizing reperfusion injury. When necrosis within the myocardium at risk reaches substantial extent, however, restoration of flow may risk to aggravate the injury by causing intramyocardial hemorrhage (IMH). If microvascular perfusion is restored within ≈30 minutes, myocardial injury is usually detected by troponins, whereas late gadolinium enhancement magnetic resonance imaging (MRI) may demonstrate little or no enhancement as a sign of necrosis.2,3 Myocardial function is often restored completely. With increasing duration of ischemia, however, myocardial cells will progressively lose control of intracellular homeostasis. This leads to progressive myocyte necrosis as a function of time within the myocardium at risk from endocardium to epicardium called the “wavefront phenomenon” by Reimer et al and Reimer and Jennings.3,4 The rate at which the amount of infarcted myocardium increases as a result of this process is slower in man compared with most animal experiments.2,5 Also, with increasing ischemia duration the swelling of ischemic tissue on reperfusion impedes microvascular flow. This no-reflow phenomenon, as described in experimental studies by Kloner and Jennings,6 is likely the mechanism behind the phenomenon that can be seen clinically after reperfusion as a progressive increase of hypointense regions on late gadolinium enhancement MRI7 called microvascular obstruction (MVO). Later during this ischemic process, also the microvasculature, which is more resistant to ischemia than myocardial cells,8 eventually becomes irreversibly injured by disruption of the endothelial wall, and this has been postulated as one of the causes of IMH. By using MRI to depict the inflow of GdDTPA-albumin into reperfused experimental infarction the decrease of microvascular flow has been shown to be a function of duration of reperfusion within the first hour.9 Downstream displacement of thrombus material, either spontaneously or as a result of mechanical reperfusion, may also lead to impaired microvascular flow. Intramyocardial hemorrhage, however, does not occur without reperfusion. Standard care in acute myocardial infarction includes both reperfusion and antithrombotic therapy to keep macro- and microvasculature open. This means that the therapy in itself may promote IMH. Few therapies except for timely reperfusion are aimed at reducing postreperfusion edema or hemorrhage. Both MVO and IMH have been shown to be of prognostic importance for long-term outcome.3,7,10 These phenomena are still debated with regard to the pathophysiologic mechanisms, time course of evolution, how to best image them, their prognostic power, and what might be the best treatment. This is well illustrated by the recent comprehensive review by Betgem et al11 where they suggest T2* MRI to be the best way forward to image IMH. This was questioned in a response by Kidambi and Plein12 who pointed out that an independent prognostic association has not been shown for IMH detected by T2* MRI.

See Article by Carrick et al

In this issue of Circulation: Cardiovascular Imaging, Carrick et al13 provide data with relevance for this discussion. They performed a prospective comparison of MVO from late gadolinium enhancement MRI and IMH from T2 mapping in 245 patients treated for acute myocardial infarction of which 228 were followed up at 6 months post intervention to assess the prognostic values of MVO and IMH. They concluded that the occurrence of IMH was prognostically more significant than MVO. They also performed a substudy with serial imaging of late gadolinium enhancement, T2, and T2* MRI in 30 patients with results showing that myocardial hemorrhage as assessed by T2* mapping followed a progressive time course within the first 2 days after myocardial infarction and was different from MVO, which decreased over time post reperfusion. T2 mapping showed a time course in between. These results add directly to the discussion outlined above and support that MVO and IMH have at least partly different pathophysiological mechanisms and are decoupled over time. It would be interesting to further elucidate differences between T2 and T2* mapping as to their ability to provide similar or different prognostic information. The early progression of IMH in T2* mapping is a potential confounding factor of iron particles from red blood cells taken up by macrophages but not removed from the region as rapid as the resolution of MVO. The inflammatory response, as also investigated by Carrick et al,13 which may be different for IMH and MVO, could also be central in the understanding of prognosis for outcome.

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The early experimental ex vivo dissection findings of Reimer et al.⁴ and Klomer and Jennings,⁶ and the later in vivo vivisection findings by MRI in patients, again demonstrate the importance of translational research for understanding how pathophysiological mechanisms constitute the explanatory basis for modern imaging and in particular the many facets of MRI. As to date MRI has not been established as a routine method to guide acute myocardial infarction therapy. However, as MRI keeps on contributing distinct pathophysiological information, it may have a role in the future to guide therapy in acute myocardial infarction. The depiction and quantification of IMH, which prognosticate worse outcome after reperfusion, may be a step in that direction. Measurement of IMH could, for example, in addition to being a prognosticator, also be a treatment target in itself where different treatment regimens could be designed with the aim to reduce IMH and, hence, hopefully improve short- and long-term outcome. Thus, measurement of IMH could be an integral part in assessing the results of cardioprotective regimens at the time of reperfusion. It could also be an end in itself—to diagnose the presence of IMH to reduce it, possibly by adjusting or modifying antithrombotic therapy or even consider conservative treatment when reperfusion no longer can be expected to salvage myocardium at risk. Even if we still lack information on the independent prognostic power of T2* imaging for assessment of IMH, the results of the study by Carrick et al in this issue of Circulation: Cardiovascular Imaging⁸ contribute additional and important information on the clinical nature, prognostic power, and interrelationship of MVO and IMH.

Disclosures
Dr Arheden is a stockholder of Imacor AB, Lund, Sweden.

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