Magnetic resonance imaging of the microcirculation in acute coronary syndromes

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Abstract

Microvascular damage is frequently observed in the setting of acute coronary syndromes (ACS). Imaging of the microcirculation is playing an increasingly important role in the risk stratification of patients presenting with acute coronary syndromes, furthering our understanding about coronary microcirculatory patho-physiology in this setting. Of the available imaging methods, cardiac magnetic resonance (CMR) holds particular promise for in vivo detection and assessment of microvascular dysfunction. The CMR methods currently available are described in this review with an overview of how CMR may be used to improve our understanding of microvascular damage in ACS and allow the development of potential cardio-protective measures.

Keywords: microvascular dysfunction; magnetic resonance imaging (MRI); acute coronary syndrome; myocardial infarction

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Metabolic Imaging

Introduction

Myocardial perfusion is controlled by various factors acting to regulate the coronary circulation. The epicardial arteries contribute only 7% to overall coronary resistance, while the microcirculation (arterioles <150 um in diameter) exerts most control on coronary blood flow and subsequent myocardial perfusion [1]. The microvasculature is hence responsible for the maintenance of coronary vasomotor tone, allowing a dilator stimulus such as ischemia to cause a three- to five-fold increase in coronary flow [2]. This vasodilatory reserve is progressively weakened in the presence of coronary atherosclerosis, as the coronary resistance is redistributed from the microvasculature to the less elastic epicardial circulation. Ultimately, vasodilator reserve is lost, and myocardial hypoperfusion ensues, prolonged periods of which cause irreversible myocardial necrosis. The severity and degree of irreversibility correlate proportionately with the extent of microvascular injury within the boundaries of the infarcted muscle [3].

In clinical practice microvascular dysfunction is frequently observed in the setting of acute coronary syndromes, especially following reperfusion of acute myocardial infarction. Despite

establishing angiographic patency of the infarct-related epicardial artery, myocardial blood flow can remain inadequate, a phenomenon known as "no-reflow" [4]. No-reflow occurs in up to 30% of patients, and is thought to be a consequence of microemboli and subsequent microvascular obstruction (MVO) [5]. The severity of microvascular dysfunction post infarction has been demonstrated to be an important correlate of left ventricular (LV) functional recovery, cardiovascular morbidity and mortality and is proportionate to infarct size [6,7]. Additionally, MVO has been shown to be a powerful independent predictor of adverse outcome [7,8].

Kloner et al. first described to the presence of MVO in a canine coronary artery occlusion-reperfusion model, demonstrating a link between angiographic no-reflow phenomenon and severely damaged intramural microvessels with specific histological features of endothelial cell swelling, protrusions, and decreased pinocytic vesicles [9]. Additional histological changes that have been suggested to occur during the formation of MVO are the production of reactive oxygen species leading to the disruption of endothelial cells, fibrin and platelet deposition, neutrophil activation, and hemorrhagic red cell extravasation following reperfusion. Epicardial thrombi and microvasculature thrombosis may also result from necrotic plaque particulates being showered distally into the myocardium following plaque rupture or as a result of coronary interventional procedures [10–13].

Imaging of the microcirculation is playing an increasingly important role in the risk stratification of patients presenting with acute coronary syndromes, furthering our understanding about coronary microcirculatory patho-physiology in this setting. This may subsequently allow development of potential cardio-protective measures to aid current therapies [14].

Several techniques and modalities have been described to identify microvascular injury following acute MI [6,7,15–18]. Of these, cardiac magnetic resonance (CMR) imaging has become the reference standard for assessment of myocardial injury as it allows accurate assessment of function, perfusion abnormalities, extent of infarction, edema, and myocardial salvage [19] (a composite marker of adverse outcome), as well as delineation of MVO in a single examination [20]. The most frequently used CMR techniques to delineate and differentiate microvascular damage are described in the remainder of this article.

Late-gadolinium enhancement

Most current gadolinium-based contrast media are extracellular agents, with rapid distribution within the intravascular and interstitial space, but exclusion from the intracellular space of intact myocytes. In the context of acute myocardial injury, the cell membranes can no longer exclude the contrast from the intracellular space and injured myocardium therefore takes up and retains more contrast agent than viable myocardium. In addition, clearance of contrast agent from injured myocardium is reduced. The CMR technique of late-gadolinium enhancement (LGE) makes use of the differences in the distribution volume of the contrast agent, and with appropriate imaging parameters depicts acutely infarcted myocardium as an area of hyper-enhanced myocardium compared to regions of non-infarcted myocardium [21]. Due to its high spatial resolution and tissue contrast LGE imaging can accurately depict the extent and transmurality of myocardial injury after acute myocardial infarction including micro-infarcts as low as 1 gram of tissue [22]. In addition, the pattern of hyperenhancement can be used to differentiate infarction from other types of acute injury such as myocarditis [22,23]. In the presence of MVO, MRI contrast media do not reach the infarct core affected by the reperfusion injury. On LGE images, the MVO zone therefore appears as a dark core residing within a hyper-enhanced infarct zone (Fig. 1). The appearance of the MVO on LGE imaging is a highly dynamic process and due to contrast agent diffusion into the infarcted core, the size of the dark MVO core reduces with increasing imaging time from contrast injection. Therefore, images are often acquired 1–2 minutes after contrast administration, when the MVO appears largest (Fig. 2). However, it is not certain, when the optimal

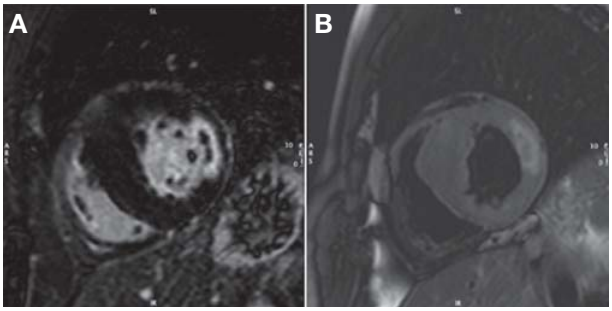

Fig. 1 ***A)*** *Lateral wall LGE with MVO.* ***B)*** *T2-weighted image showing edematous region with dark core in area of MVO, suggesting intramyocardial hemorrhage.*

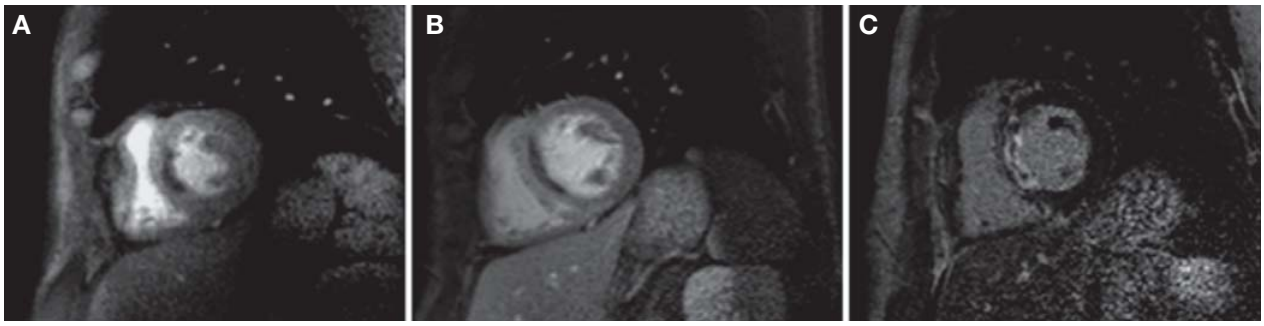

Fig. 2 *CMR of a patient presenting with an AMI 2 days ago and with 'no-relow' observed during angiography.* ***A)*** *First-pass perfusion images acquired at rest show a septal wall defect in the area of MVO.* ***B)*** *Early gadolinium enhancement (EGE) acquired 2 minutes after first pass perfusion shows a similar defect caused by MVO.* ***C)*** *LGE images acquired 10 minutes later delineate the infarct zone in white and a smaller MVO (due to contrast diffusion into the MVO over time).*

time is to image MVO and some studies have suggested that imaging at 10 minutes is most predictive of remodeling [24]. The transmurality of LGE and the amount MVO present are both inversely related to the eventual left ventricular (LV) ejection fraction and predicts the likelihood of recovery of regional wall motion [25,26].

T2 weighted imaging

One of the patho-physiological consequences of acute ischaemia is an increase in unbound water in the ischemic tissue [27]. T2-weighted CMR (T2w CMR) is sensitive to the water content of tissue and therefore allows the delineation of acutely ischemic myocardium. The area of high signal on T2w CMR has been shown to accurately correlate with the area at risk assessed by microspheres [27]. Additionally, increased myocardial T2 signal may be observed within 30 minutes of ischemia onset—detecting myocardial injury prior to both troponin and LGE [28]. Some controversy remains about the precise mechanism of hyperenhacement on T2w CMR in acute ischaemic injury and T2w CMR methods have lower signal to noise ratio than LGE methods and may be more prone to flow and motion related artifacts [29]. Expertise is therefore needed for the acquisition and interpretation of T2w images. In patients who have severe microvascular dysfunction, reperfusion injury can result in a hemorrhagic transformation of the infarct core, often seen following PCI, which has independent adverse effects on LV remodeling [30]. Hemorrhage present within the myocardium lowers T2 signal, allowing these areas to be identified as a hypointense core within the infarct (Fig. 1) [31].

Myocardial salvage index

Mortality following myocardial infarction is related to several factors, one of which is the amount of myocardium subtended by the infarct-related vessel; the hypoperfused area at risk (AAR) as a result of the ischemic insult [32,33]. Combined, LGE and T2 weighted CMR allow the distinction between infarcted and potentially viable myocardium; LGE delineates the former, whilst T2- imaging determines the latter (Figs. 1 and 3). These CMR methods therefore permit the calculation of a myocardial salvage index (MSI), by correcting the amount of necrotic myocardium for the extent of AAR. From a microcirculatory perspective this index combines information regarding irreversibly damaged microvasculature (LGE) and potentially viable microvasculature (T2w CMR), and if timely reperfusion occurs, the degree of myocardium salvaged is the principal mechanism by which patients with recent myocardial infarction benefit from reperfusion therapies [34]. Reaffirmed by Eitel et al.'s recent prospective demonstration that MSI is a strong independent predictor of both major adverse cardiovascular events

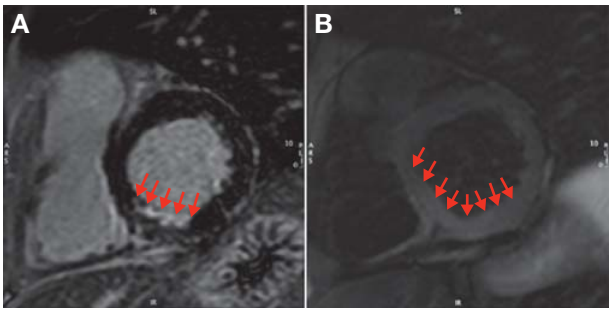

Fig. 3 *A) LGE image - subendocardial inferior myocardial infarction. B) T2-weighted image of "area at risk."*

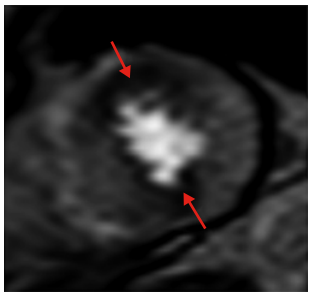

Fig. 4 *Dynamic first-pass perfusion image – anterior and inferior ischemia.*

and mortality at six months and in the longer term (median of 19 months) following reperfused STEMI [19, 35].

Perfusion CMR

Dynamic contrast-enhanced myocardial perfusion-CMR is based on the monitoring of contrast medium wash-in kinetics into the myocardium. Data can be acquired at rest and during a hyperemic state, which is most frequently pharmacologically induced with a concurrent intravenous adenosine infusion. One of the key advantages of perfusion-CMR over other imaging methods is its high spatial resolution of <3mm or even higher with recent methods, allowing the differentiation of perfusion to the subendocardial and subepicardial myocardial layers (Fig. 4) [36]. In myocardial regions supplied by arteries with hemodynamically significant coronary disease, myocardial perfusion CMR during hyperemia shows delayed and reduced wash-in of contrast agent compared to regions with normal myocardial perfusion [37,38]. In the setting of acute MI, myocardial perfusion CMR can demonstrate areas of MVO during first pass assessment. Subsequent late gadolinium enhancement can be used to confirm the presence of the MVO and assess its change in size over time (Fig. 2) [5].

Conclusion

The coronary microcirculation is critical in the perfusion and mechanical functioning of the myocardium. Increased understanding of the importance of this vascular compartment has allowed improvements in therapeutic strategies in the management of various conditions such as acute myocardial infarction. Non-invasive imaging, particularly with the advent and advancement of CMR, has allowed improved risk stratification of patients, with greater understanding about possible prognosis and likely recovery in function following ischemic injury. The numerous facets to cardiac magnetic resonance imaging are both valuable, and synergistic to one another, in assessing and differentiating myocardial necrosis from injured but viable myocardium. Further advancement will allow routine quantification of all of these parameters, further enhancing the reproducibility and applicability of CMR in both clinical and research settings. •

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