Imaging

MRI in acute myocardial infarction

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Although acute myocardial infarction (AMI) is still one of the main causes of high morbidity in Western countries, the rate of mortality has decreased significantly. The main cause of this drop appears to be the decline of the incidence of ST-segment elevation myocardial infarction (STEMI) along with an absolute reduction in case fatality rate once STEMI has occurred. Myocardial ischaemia progresses with the duration of coronary occlusion and the delay in time to reperfusion determines the extent of irreversible necrosis from subendocardial layers towards the epicardium in accordance with the so-called ‘wave-front phenomenon’. Coronary artery recanalization, either by thrombolytic therapy or primary percutaneous intervention, may prevent myocardial cell necrosis increasing salvage of damaged, but still viable, myocardium within the area at risk. Magnetic resonance imaging (MRI) can provide a wide range of clinically useful information in AMI by detecting not only location of transmural necrosis, infarct size and myocardial oedema, but also showing in vivo important microvascular pathophysiological processes associated with AMI in the reperfusion era, such as intramyocardial haemorrhage and no-reflow. The focus of this review will be on the impact of cardiac MRI in the characterization of AMI pathophysiology in vivo in the current reperfusion era, concentrating also on clinical applications and future perspectives for specific therapeutic strategies.

Keywords
Acute myocardial infarction • Pathophysiology • Magnetic resonance imaging

Introduction

Although acute myocardial infarction (AMI) is one of the major causes of morbidity in Western countries,1 mortality has decreased significantly and this drop appears to be the result of the decline in the incidence of ST-segment elevation myocardial infarction (STEMI) along with the absolute reduction of overall mortality of AMI.2 The reduction of mortality for AMI is due to the efficacy of current therapeutic strategies focused on an early reopening of the infarct-related artery, either by thrombolytic therapy or primary percutaneous coronary intervention (PCI), which represents the most effective way to limit infarct size (IS) and reduce transmural extent of necrosis. Reperfusion therapy modifies traditional pathological features of AMI, because coronary artery recanalization can prevent the transmural progression of myocardial necrosis.3,4 Indeed, reperfusion after prolonged coronary occlusion may develop into reperfusion injury associated with impairment of microcirculatory flow and possible further deterioration due to intramyocardial haemorrhage. The pathological consequences of reperfusion strategies can be currently detected in vivo by cardiac magnetic resonance imaging (MRI), a non-invasive tool that allows the translation of features previously studied only by experimental models from bench to bedside. Cardiac MRI can provide a wide range of information such as myocardial oedema (myocardium at risk), location of transmural necrosis, quantification of IS and microvascular obstruction leading also to intramyocardial haemorrhage.5 Moreover, cardiac MRI provides an accurate and reproducible modality for the assessment of global ventricular volumes and function,6 representing the most powerful phenotyping tool for a global evaluation of post-infarction remodelling. This review will demonstrate the impact of cardiac MRI in the in vivo assessment of the pathophysiology of AMI in the current reperfusion era, focusing also on clinical applications and future perspectives for therapeutic strategies.

Technical advantages of cardiac magnetic resonance

Cardiac MRI represents a non-invasive technique with increasing applications in AMI providing the assessment of function, perfusion and tissue characterization in a highly reproducible manner during a single examination even in patients with acoustic window

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Cine MRI for evaluation of cardiac volumes, mass, and systolic function is considered a gold standard compared with other imaging modalities, since it does not apply geometric assumptions. The high values of reproducibility and accuracy (standard error for left ventricular, LV, mass and volume is about 5%) are particularly useful to reduce sample size in clinical trials. The steady-state free precession sequences for cine images have replaced the older turbo gradient echo due to increased natural contrast between blood and endocardial border. Consecutive breath-hold short axis of the heart (temporal resolution of 50 ms or less) are used to obtain functional assessment: after delineation of endocardial and epicardial borders the summation of discs method is applied. New three-dimensional MRI acquisition offers the advantage to cover the entire myocardium with a single breath hold of 20–30 s, but with lower temporal resolution (100 ms). Regional myocardial function including wall thickening, evaluation and measures of myocardial strain may be performed.

In patients with suspected coronary disease, myocardial perfusion reserve measured by cardiac MRI yields high diagnostic accuracy for the detection of flow-limiting lesions. Perfusion MRI is performed at rest and again during a vasodilator stress administration (i.e. adenosine, dipyridamole) using a ‘first-pass’ technique with fast intravenous injection of a gadolinium-based contrast agent. The myocardial signal increases in normal well-perfused myocardium, but not in the regions of myocardial ischaemia.

Tissue characterization by cardiac MRI is due to the evaluation of proton relaxation times T1 and T2. Currently T2 images are used in non-contrast approaches, whereas T1 sequences are used for contrast-enhanced studies (i.e. previous cited first pass). Increased myocardial water content increases signal on T2-weighted images, such as inflammation. Myocardial oedema in the acute phase of myocardial infarction can be visualized as a bright signal on T2-weighted images, defining ‘myocardium at risk’. The major advantages of this technique are to distinguish chronic from acute infarction, and to quantify the proportion of myocardial salvaged assessed retrospectively by comparing T2-weighted oedematous size and late enhancement images. Late gadolinium enhancement (LGE) images are T1-weighted inversion recovery sequences acquired about 10 min after intravenous administration of gadolinium and the inversion time is chosen to null myocardial signal using ‘inversion time scout’ or ‘look locker’ sequences. Gadolinium is an extracellular agent, which enhances its distribution volume in certain conditions such as necrotic or fibrotic myocardium, assuming a bright signal (hyperenhancement), opposed to dark viable myocardium. Cardiac MRI highlights the region of scar or fibrosis as small as 0.16 g and the reproducibility is high with a coefficient of reproducibility reported equal to ±2.4% of LV mass in chronic setting. The pattern of LGE is useful to differentiate post-infarction necrosis (subendocardial or transmural LGE) from fibrosis in non-ischaemic dilated cardiomyopathies (mid-wall LGE, subepicardial LGE), or myocarditis (subepicardial or focal LGE). Delayed post-contrast sequences are currently used also to evaluate persistent microvascular dysfunction/damage: in the context of white LGE regions (infarcted myocardium) may coexist dark hypoenhanced areas, traditionally referred to as microvascular obstruction. Microvascular obstruction has been initially defined as hypoenhancement at 1–2 min after gadolinium injection.
however, persistent microvascular damage is currently evaluated on delayed post-contrast sequences.\textsuperscript{31}

Myocardial ischaemia: area at risk

During the early phase of a coronary occlusion, the subsequent discrepancy between myocardial oxygen supply and demand lead to myocardial ischaemia, characterized by a specific pattern of metabolic and ultrastructural alterations.\textsuperscript{32} If ischaemia persists, myocardial injury becomes irreversibile and the necrosis extends from the subendocardium towards the subepicardium in accordance with the ‘wavefront phenomenon’ described initially by Reimer and Jennings.\textsuperscript{3,4} The final IS depends mainly on the extent of the so-called ‘risk area’, defined as the myocardial area related to an occluded coronary artery with complete absence of blood flow, either antegrade or collateral.\textsuperscript{13} Up to now, myocardium at risk has been measured by single photon emission computer tomography (SPECT)\textsuperscript{34} using the injection of a
technetium-based tracer before opening of the occluded vessel, and by contrast echocardiography.\textsuperscript{35} Recently, cardiac MRI is used to visualize and to quantify the area at risk since increased myocardial signal intensity depicted by T2-weighted sequences are very sensitive to water-bound protons indicating an increased water content with an active myocardial inflammation and tissue oedema. The concept of infarct-related oedema was initially evaluated on animal models of AMI, in which a linear correlation between myocardial-free water content of the infarcted region and prolongation of its T2 relaxation time is demonstrated.\textsuperscript{19} Subsequent experimental studies have shown that the area of high T2 signal abnormality closely matched the area at risk determined on histology.\textsuperscript{36,20} In particular, Aletras et al.\textsuperscript{20} have demonstrated in an animal model, with 90 min of coronary occlusion followed by reperfusion, that the area at risk measured by microspheres was comparable with the area of increased signal on T2-weighted images 2 days later. At first, the application of T2-weighted imaging in the clinical setting is used to differentiate acute from chronic myocardial infarction.\textsuperscript{22} However, the most important application of MRI ischaemia-related oedema regards the evaluation of ‘salvaged myocardium’ (Figure 4). Cury et al.\textsuperscript{37} have recently applied T2-weighted imaging to improve the accuracy in the diagnosis of myocardial ischaemia in patients arriving to the emergency room with acute chest pain, negative biomarkers and inconclusive ECG. However, the most intriguing application is the possibility to assess quantitatively the reversible and irreversible injury in reperfused AMI. Experimental data have shown that in AMI the area with high T2 signal exceeds that of irreversible injury. In fact, Choi et al.\textsuperscript{38} have demonstrated in a pig model the high signal on T2-weighted images reflects both irreversible and reversibly injured, but essentially the viable, peri-infarct zone. On this basis, Friedrich et al.\textsuperscript{23} have compared T2-weighted images with LGE to visualize reversible and irreversible myocardial injury, respectively. Thereafter, many clinical studies have evaluated the potential of MRI to assess myocardial oedema\textsuperscript{39–41} in comparison with well-established techniques.\textsuperscript{42} However, the recent interventional study performed by Francone et al.\textsuperscript{43} represents a cornerstone for future investigation for the application of the counterwise area of myocardium at risk in the clinical setting. In this study,\textsuperscript{44} the concept of reduction of total viable myocardium

**Figure 4** Myocardium at risk represents the myocardial area related to an occluded coronary artery with complete absence of blood flow. An example of ‘risk area’ on septal wall (hyperenhancement) is described on panel A on T2-weighted images, the so-called ‘remote myocardium’ with normal blood flow appears dark, without signs of oedema, on the lateral wall. In the example B myocardial at risk (oedema) on anterior, septal and inferior wall is shown: note inside the hyperenhancement on T2-weighted images the presence of a hypoenhancement core suggesting intramyocardial haemorrhage. Panels C and D represent a case of acute septal myocardial infarction. Panel C shows T2-weighted images with transmural oedema extending toward all septal wall even partially in the inferior and anterior wall (black asterisk). Panel D shows the same slice after delayed contrast injection: note that the bright signal intensity shows a late gadolinium enhancement extent of 75% of the entire segment only in the anterior septal wall. Note the absence of late gadolinium enhancement in the previous areas involved by oedema (white arrows), representing area of myocardium at risk.
amount in proportion to the delay on time-to-reperfusion is demonstrated in vivo: in particular, the salvaged myocardium (quantified as the difference between area of increase in T2 signal and area of LGE) is markedly reduced (2.1%) when reperfusion occurs > 90 min after coronary occlusion in contrast with 8.5% in patients with ≤90 min of delay.

Progression of necrosis: viability

According to the concept of ‘wavefront phenomenon of myocardial death’, IS increases, extending from the endo to the epicardium with an increasing duration of coronary occlusion. If ischaemia persists, myocardial injury becomes irreversible, usually between 20 and 45 min after coronary occlusion: a prompt coronary lumen recanalization is able to prevent the progression of necrosis leading in some cases to an ‘aborted AMI’. The major determinant of final transmural necrosis and microvascular damage is the duration of ischaemia, as recently demonstrated in vivo by MRI. Beyond the potentially reversible events (ischaemia and oedema), cardiac MRI can be used for assessment of the extent of the irreversible necrosis using delayed contrast-hypoenhanced images. Non-viable infarcted tissue is usually seen on MRI as a ‘hypoenhanced’ area after contrast injection, so-called LGE (Figure 2). In the setting of AMI, the extracellular space is expanded, also by oedema and inflammation, and the contrast agent enters the intracellular space through damaged cell membranes. The LGE assessment has been validate against animal models and represents a permanent memory of myocardial injury even after the acute phase of infarction. However, in the first days after AMI, LGE is more extensive compared with the chronic phase, when the healing process is complete. Oshinski et al. using a rat model of AMI, showed that, immediately after contrast injection, the enhanced region overestimates the true IS, on histology, by 20–40%. Saeed et al. have suggested that LGE does not occur exclusively in regions with myocardial necrosis but also involves the border zones of injured but viable myocardium surrounding AMI. Other clinical studies have observed an initial overestimation of IS that gradually decreases over time. Recently, Ingkanisorn et al. have found that IS on MRI appeared to diminish in size on follow-up from 16 ± 12 to 11 ± 9% (P < 0.003). The same reduction on IS was noted by Hombach et al. in a large population study. Baks et al. evaluating the effects of primary PCI on early and late IS described a 31% decrease in LGE between 5 days and 5 months. More recently, LGE extent has been evaluated during the hyperacute phase of STEMI: Larose et al. have performed in STEMI patients a cardiac MRI within 12 h of primary PCI and at 6 months discovering a reduction in LGE volume from 22 to 16% (P = 0.01).

These observations are notable from a clinical point of view, even if the measurement of IS by MRI is highly reproducible, the chosen time of imaging along the healing process can yield different results. The reduction of IS associated with the healing process is 25% of initial size over 4–6 weeks. However, the improved reproducibility of LGE with detection of smaller changes in IS allows for substantial reduction in sample size for clinical trials, even when one takes into consideration variability between patients.

Another technical issue to take into account when comparing ISs in different AMI populations is the dose of gadolinium used. In a recent international multicentre trial, the sensitivity of LGE rose with increased gadolinium dose, reaching 99 and 94% in acute and chronic myocardial infarction, respectively, with the 0.3 mmol/kg dose.

The measurement of LGE seems to provide additive value as a predictor of adverse outcomes after AMI above ejection fraction. Before recent studies on AMI, IS within 1 week from AMI was directly related to LV remodelling and was a stronger predictor of future events than measures of LV systolic performance. More recently, Larose et al. demonstrated that the occurrence of LV dysfunction at 6 months invariably increased with greater LGE: a cut-off of ≥23% LGE measured on hyperacute MRI showed the best accuracy for late LV dysfunction (sensitivity 89%, specificity 74%).

After the healing process is completed and necrotic tissue has been replaced by a scar, MRI provides clinically relevant information concerning viability. Cardiac MRI offers a unique tool to assess multiple interrelated clinical markers of viability in a single test with a limited time consumption, moreover considering that LGE technique together with cine MRI takes no more than 30 min to perform. Scintigraphic techniques and stress echocardiography have been so far considered the mainstay of viability diagnosis. However, the role of MRI in the assessment of myocardial viability is rapidly increasing as it has the advantage of being performed under resting conditions, without exposing the patient to radiation. Stress echocardiography with low dose of dobutamine represents an inexpensive imaging tool for viability evaluation. However, the high inter-observer variability and inter-individual differences in image quality for echo-stress imaging explain the lower sensitivity compared with LGE technique. Moreover, in the setting of AMI a pharmacological stress is not usually indicated. Initially in an experimental model, Hillenbrand et al. have demonstrated that LGE is not detected in regions with severe but reversible ischaemic injury and that there is an inverse relationship between the transmural extent of necrosis and recovery of function. The first clinical application of MRI to identify reversible myocardial dysfunction has been made by Kim et al. who have determined the accuracy of MRI in predicting recovery in a series of patients with chronic coronary artery disease and LV dysfunction undergoing myocardial revascularization. In the assessment of myocardial viability in AMI patients, when the extent of LGE is <50% the likelihood for functional recovery is efficient. Direct comparison with PET, as a gold standard, has shown excellent results. In particular, Klein et al. performing MRI and PET within 1 week in patients with ischaemic disease and LV systolic dysfunction, have found a good correlation between the two tests. Notably, more than half of subendocardial infarcts, which have been detected by MRI, have been classified as normal by PET. Kuhl et al. have found similar results with 36% of segments normal by PET, but showing subendocardial LGE on MRI. When comparing SPECT imaging, the main advantage of MRI LGE is its spatial resolution of 1–2 mm (in plane), contrary to about 10 mm with SPECT scans. Therefore, MRI can identify subendocardial necrosis when perfusion by SPECT appears unaltered. Wagner et al. discovered the improvement in infarct...
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Reperfusion injury: no-reflow phenomenon, microvascular obstruction and haemorrhage

Even if coronary artery flow recanalization represents the most effective way to reduce IS, the process of reperfusion may itself produce a series of consequences described in experimental setting, including myocyte death, microvascular damage with ‘no reflow’ phenomenon, stunned myocardium and reperfusion arrhythmias. The clinical relevance and also the most accurate tool to visualize and quantify microvascular damage secondary or not to reperfusion injury remains to be identified and so far, there is no definitive consensus regarding the best imaging modality. In this clinical scenario, it is reasonable to assume that cardiac MRI may represent a cornerstone imaging tool yet validated against established traditional techniques (i.e. contrast-echocardiography). In one of the first experimental studies Judd et al. correlated the MRI findings with pathology, by thiflavin-S staining, using a reperfused canine infarct model. The authors demonstrated that hypoenhancement within bright regions of LGE on delayed post-contrast sequences, so-called ‘dark zones’, were areas of no-reflow. In humans, Lima et al. described a well-defined time–intensity curve of different areas of enhancement occurring in human myocardial infarcts, on the basis of the wash-in and wash-out kinetics of contrast agent. In agreement with these observations, the assessment of microvascular damage had been performed using MRI first-pass perfusion and the delayed post-contrast sequences. However, Lund et al. found differences in sensitivity between first-pass and delayed hypoenhancement, which was confirmed by recent studies. Currently, it is generally accepted that delayed hypoenhancement is less sensitive than first pass because small no-reflow zones become rapidly enhanced owing to diffusion of the extracellular contrast medium from surrounding regions without impaired microvasculature. Moreover, the persistence of a hypoenhancement on delayed contrast sequences (10–20 min after injection) seems to characterize a persistent microvascular damage (Figure 5). In conclusion, a complete protocol, including both techniques, should be performed in the current evaluation of AMI by cardiac MRI.

More recently, microvascular damage detected by MRI has been evaluated in comparison with coronary Doppler flow reserve. Hirsch et al. found that the typical presence of early systolic retrograde flow associated with no-reflow on intracoronary flow measurements was associated with the presence of microvascular obstruction assessed on LGE images. Furthermore, multivariate regression analysis revealed that the extent of microvascular obstruction on MRI was the only independent factor related to early systolic retrograde flow and diastolic deceleration rate. Cardiac MRI features of reperfusion injury have been compared also with well-known angiographic perfusion parameters like TIMI (thrombolysis in myocardial infarction) flow and myocardial blush grade (MBG). In a recent study by Appelbaum et al., in 21 patients who underwent successful primary PCI and MRI, evidence of impaired perfusion at first pass was present in 90% of cases with post-PCI myocardial perfusion grade (0/1/2), but only in 18.2% with normal one. Porto et al. by analysing 27 patients with AMI, found a linear correlation between decreasing MBG and MRI signs of vascular obstruction, thus confirming the relationship between post-PCI reperfusion index and MRI measures of microvascular impairment. However, recently Nijveldt et al. did not find any statistically significant relationship between early or late microvascular obstruction and TIMI flow or MBG in 60 patients with AMI treated with primary PCI. Larger multi-centre population studies are needed to verify the relationship between angiographic perfusion indexes and MRI for the detection of microvascular damage.

Cardiac MRI features of no-reflow also have prognostic significance in terms of clinical outcome and changes in LV volumes. Even if the ‘dark zones’ on MRI indicate poor prognostic significance, the real mechanism underlying these features is not yet well understood in human AMI, since no-reflow represents a complex time-sensitive phenomenon, which remains to be fully understood. In fact, the ‘no-reflow phenomenon’ refers to absent distal myocardial reperfusion after a prolonged period of ischaemia, despite the culprit coronary artery’s successful recanalization, and likely secondary to both luminal obstruction (i.e. neutrophil plugging, platelets, atherothrombotic emboli) and external compression by oedema and haemorrhage. The haemorrhagic AMI reflects the metamorphosis of ischaemic infarcts in the ‘reperfusion era’, and are commonly observed after prolonged ischaemia once myocardial cell necrosis is well established. Garcia-Dorado et al. have discovered in an experimental model that microvascular damage is an early event, and that intramyocardial haemorrhage plays a role later in reperfusion injury. Microvascular cell damage causes leakage of blood out of the injured vessel and the subsequent healing process is characterized by haemoglobin degradation. As for intracranial haemorrhage, MRI can enhance tissue characterization through changes in relaxation times T1 and T2, reflecting changes in image signal intensity. By assessing the paramagnetic susceptibility effects of deoxyhaemoglobin, we have recently confirmed previous experimental observations in which dark areas on post-contrast inversion recovery sequences indicate not only the presence of microvascular obstruction, but also of intramyocardial haemorrhage. As shown in experimental models, the extent of the hemorrhagic area correlates with the size of ‘dark zones’ on LGE sequences;
these preliminary results are confirmed by clinical studies\textsuperscript{81,82} and elucidate the clinical significance of intramyocardial haemorrhage. In a large population study, patients with haemorrhagic AMI have shown a lower pre-PCI TIMI flow; moreover the area at risk, IS and ratio of IS to area at risk were significantly larger.\textsuperscript{5} Furthermore, the size of ‘dark zones’ on post-contrast images is larger, and interestingly present in all patients with haemorrhagic AMI. Recently, Beek \textit{et al.}\textsuperscript{83} have confirmed that the hypoenhancement on T2-weighted images, suggesting intramyocardial haemorrhage, is present in the majority of patients with dark zones on LGE and also closely related to markers of IS and function. However, it has no prognostic significance beyond delayed hypoenhancement.

Of note, in both studies, no differences in time from onset of symptoms to revascularization between haemorrhagic and non-haemorrhagic AMI patients have been found, suggesting that factors such as the magnitude of collateral flow, preconditioning, and others may influence the final outcome of myocardial revascularization. In this regard, cardiac MRI is currently the only non-invasive, reliable and reproducible imaging technique that may detect the presence of haemorrhage. Despite emerging studies about the presence of intramyocardial haemorrhage on T2-hypoenhancement, experimental validation by histology is lacking. Further studies with comparable protocols and reperfusion strategies are necessary to clarify the clinical role of haemorrhage beyond microvascular obstruction, since it still remains unclear whether haemorrhagic AMI are at increased risk of rupture or whether they are just a marker of myocardial reperfusion.\textsuperscript{75}

\textbf{Significance of MRI findings to ventricular remodelling}

Delayed reperfusion therapy may increase IS and lead to adverse LV remodelling due to infarct expansion, thinning of the necrotic segment associated with dilatation, as well as compensatory hypertrophy of remote myocardium. Cardiac MRI measures of ventricular volumes and mass are more accurate and reproducible than other imaging techniques (Figure 6). In this regard, MRI is particularly suitable for the study of large infarcts with aneurysmatic ventricular chamber dilatation since LV volume and mass evaluations are independent from geometric assumptions. Since the first clinical studies by Wu \textit{et al.}\textsuperscript{30} and Hombach \textit{et al.},\textsuperscript{31} it has become clear that IS, transmural infarction and persistent microvascular damage on delayed post-contrast images are strong predictors of adverse post-infarct remodelling over and above other clinical parameters. Further clinical studies confirmed that IS was the main determinant

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{After a prolonged ischaemia the necrosis becomes transmural and as final consequences a microvascular damage may appear inside infarction. On T1 inversion recovery post-contrast sequences, the persistent microvascular damage appears dark (so-called ‘dark zones’) (white asterisks) in the middle of late gadolinium enhancement, representing the myocardial necrosis on the inferior wall on panel A (note the involvement of right ventricular inferior wall seen as an intense late gadolinium enhancement), and antero-septal wall on panel B. Panels C and D show the same patient: on C a transmural late gadolinium enhancement on the antero-septal wall with a dark zone is shown, smaller than example B. Panel D represents the T2-weighted sequences of the same patient: inside the oedema (bright signal on anterior and septal wall) can be detected a hypoenhancement core suggesting intramyocardial haemorrhage and corresponding to the dark zone on delayed post-contrast sequence.}
\end{figure}
of LV volumes. In a 76 patient population, we have also demonstrated that the (per patient) number of LV segments with transmural necrosis have additional predictive value for early LV remodelling independently of microvascular damage; by receiver operating characteristic analysis, the presence of four LV segments with transmural necrosis represents a powerful predictor of adverse remodelling after primary PCI. Recently, Lund et al. have confirmed that IS on MRI is a stronger predictor of remodelling than microvascular damage; on the contrary Nijveldt et al. have found that the presence of microvascular obstruction, and not its extent, is the most powerful predictor of changes in global function and LV end-systolic volume at follow-up. The more severe microvascular damage indexed by intramyocardial haemorrhage on T2-weighted images also has a prognostic role relative to adverse remodelling. Indeed, Ganame et al. have demonstrated on multivariate analysis that myocardial haemorrhage is an independent predictor of adverse LV remodelling, independently of the initial IS.

Novel cardiac MRI parameters have emerged as possible potential indices of adverse remodelling, and the most attractive, from a physiopathological point of view, is myocardial salvaged. So far, the most widely practiced technique for measurement of myocardial salvaged is SPECT. However, using SPECT there are some limitations, such as poor spatial resolution. Furthermore, this technique requires the injection of the tracer immediately and the SPECT imaging within a few hours after revascularization. Another technique may be contrast echocardiography with intravenous or intracoronary injection of microbubbles before revascularization of the infarct-related artery. Cardiac MRI is a simple ‘one-stop-shop’ tool to evaluate myocardium at risk and myocardial necrosis during the same examination early after AMI, evaluating oedema on T2-weighted images. Franco et al. recently showed that the presence and the extent of salvaged myocardium markedly decreases when reperfusion occurs after > 90 min of coronary occlusion. Therefore, only the patients reperfused early (within 90 min) have shown a significant increase in LV ejection fraction. Based on this concept, Masci et al. have recently found in a prospective cohort of 137 patients that ‘myocardial salvage index’ is independently associated with adverse LV remodelling. These findings remain unchanged after multivariate analysis and correction for the occurrence of microvascular obstruction, infarct transmurality and baseline ejection fraction. More recently, Eitel et al. have confirmed that myocardial salvaged index is the strongest predictor of major cardiac events and mortality at 6-months follow-up.

The capability of cardiac MRI to be a comprehensive phenotyping tool to demonstrate in vivo the complex pathophysiology of AMI opens new perspectives in the evaluation of the efficacy of novel reperfusion strategies and therapies.

Role of MRI on mechanical and arrhythmic complications after AMI

Cardiac MRI allows the possibility to detect the majority of mechanical complications following AMI. Isolated case reports have defined the role of MRI in myocardial wall rupture detection, moreover, in clinical studies other complications such as pericardial enhancement suggesting inflammation, as well as pericardial effusion have been described. Interestingly, LGE on MRI has detected right ventricular involvement in association with inferior AMI more frequently than current standard techniques; this is important because in these patients, the right ventricular ejection fraction represents a significant predictor of prognosis.

In addition, the detection of ventricular thrombi by MRI, in particular with early gadolinium enhancement is superior to that of echocardiography, defining morphological delineation and spatial extent (Figure 1). Application of LGE sequences for LV thrombosis detection has been reported to be superior than cine MRI and echocardiography. In patients undergoing surgical LV reconstruction, a complete cardiac MRI protocol has shown higher sensitivity (88%) and specificity (99%) compared with transthoracic (23%, 96%) and transoesophageal (40%, 96%) echocardiography. Long-inversion-time imaging has been suggested to increase accuracy for thrombi detection. Moreover, the total amount of LGE by MRI has been demonstrated to be a risk factor for thrombus deposition.

A novel potential application of MRI regards the identification of possible arrhythmic risk areas. In preliminary clinical studies, through MRI, the peri-infarct zone is portrayed by the visualization of a grey border zone near the central infarcted core. This ‘grey zone’ has been related to post-infarction mortality as well as inducibility, during electrophysiological studies. Further studies in the acute setting of AMI, possibly using novel molecular imaging techniques, may clarify the role of the peri-infarct zone as an early predictor of ventricular arrhythmias as well as giving a more complete understanding of the substrate for arrhythmias in the heterogeneous ‘grey zone’ including the potential roles of oedema and inflammation.

Cardiac MRI value for differential diagnosis assessment

Cardiac MRI may be very useful in the emergency room for the rapid assessment of extra-cardiac causes of chest pain and
mostly because it offers the opportunity to identify areas of in vivo inflammation and replacement fibrosis. Combining cine-images and tissue characterization sequences (T1, T2 weighted), Assomull et al. have evaluated the role of cardiac MRI in patients with chest pain, elevated troponins and unobstructed coronary arteries. The most common diagnosis has been myocarditis (50%), followed by myocardial infarction despite coronary angiography (11.6%), thus providing a new diagnosis in 65% of patients, and excluding significant pathologies in the others. Recently, Baccouche et al. have elucidated the diagnostic performance of MRI and endomyocardial biopsy in patients with troponin-I positive acute chest pain in the absence of significant coronary artery disease. In these 82 subjects a MRI diagnosis of myocarditis has been made in 58%; typical LGE for infarction in 5%, 1% hypertrophic cardiomyopathy, 1% dilated cardiomyopathy, and non-conclusive MRI in 20%. Typical apical ballooning findings without LGE deposition have been found in 15% and have been considered diagnostic for tako-tsubo cardiomyopathy. Moreover, comparison of diagnostic MRI procedures with the corresponding diagnostic endomyocardial biopsies have demonstrated a substantial match of diagnoses (kappa = 0.70).

Further studies to evaluate the accuracy of cardiac MRI vs. histology and the prognostic significance of LGE patterns in patients with normal coronary arteries are needed to improve the clinical impact of MRI.

Cardiac MRI safety implications

Cardiac MRI has been traditionally considered a non-invasive imaging tool; however the presence of a magnetic field and contrast administration involves even safety issues that need to be explained. Also the MRI scanner room, with the presence of static and gradient fields may interact with ferromagnetic objects and this may cause electric currents. Finally, the body scanner may transmit radiofrequency waves into the patients. Because of these factors patients are screened for implanted cardiovascular devices prior to undergoing MRI. Potential complications of MRI examinations in patients with pacemaker or implantable cardioverter defibrillator (ICD) include damage or movement of the device, inhibition of the pacing output, induction of life-threatening arrhythmias, cardiac stimulation, heating of the electrode tips. Currently, an MRI terminology has been intended to elucidate matters related to biomedical implants and devices to ensure the safe use of MRI technology. This classification includes the following definitions: (i) ‘MRI safe’, no hazards in all magnetic resonance environments, (ii) ‘MRI conditional’, no known hazards in a specific MRI environment with constraints on the specific conditions of use, and (iii) ‘MR unsafe’, hazards in all magnetic resonance environments. Recently, a new commercially available Advisa DR MRI (Medtronic, Inc., Minneapolis, MN) has been implanted, and it is the second generation SureScan pacemaker designed to minimize the potential interactions with the electromagnetic fields used for MRI systems. Moreover, the patient positioning restriction for the Advisa MRI SureScan Pacing System has been removed, allowing for the first time scans of the chest area. However, cardiac MRI examination of patients with pacemakers is discouraged and the European position paper specified a group at very high risk (pacemaker-dependent) in which indication has to be re-considered, and low-risk patients (pacemaker- non-dependent). Cardiac MRI examination in patients with ICD should not be performed unless the centre is highly experienced and only when the benefits expected outweigh the risks taking into account even the possibility of artefacts due to device. However, for both devices a full interrogation prior and immediately after MRI scan has to be done and repeated 1 week and 3 months later.

Finally, regarding coronary artery stents, data currently available indicate that many of these could be considered as ‘safe’, including drug-eluting stents.

The second important issue on safety regards contrast administration related to nephrogenic systemic fibrosis (NSF) that may occur after exposure to the extracellular non-ionic low osmolar gadolinium-based contrast agent gadodiamide. Nephrogenic systemic fibrosis is a systemic fibrosing disorder that principally affects the skin, but can involve virtually any tissue in the human body. In subjects with normal renal function, free gadolinium is removed through the kidney with a half-life of approximately 3 h; in patients with impaired renal function, this half-time is significantly longer. So far, NSF has not been described in patients with preserved renal function. Current risk factors for NSF include principally acute or severe renal failure due to advanced chronic kidney disease (glomerular filtration rate < 30 mL/min/1.73 m²). Moreover, other clinical characteristics possibly implied are severe liver failure, peri-operative liver transplant, kidney transplant, hepatorenal-syndrome, thrombophilia. Taking into account all these risk factors and gadolinium exposure, the 1-year incidence of NSF has been estimated to be between 1 and 4.6%. Since a therapy for NSF is not yet established, it is fundamental to evaluate renal function in the context of AMI since patients treated with primary PCI may have kidney failure for nephrotoxicity of iodine contrast media.

Future perspectives: developments and clinical applications

Cardiac MRI represents a promising modality for a tissue characterization of AMI, beyond traditional morpho-functional indexes. Moreover, cardiac MRI parameters may in the future be used with greater frequency as surrogate imaging end points of morbidity and mortality for testing novel therapeutic strategies as in the case of pharmacologic interventions and cellular-based therapies. Another important question to address in the future is the further determination of the true prognostic significance of the many parameters evaluated by MRI in patients with AMI. Prognostic stratification is important for STEMI to better stratify patients at risk of negative ventricular remodelling. However, even for non-ST segment elevation acute coronary syndromes cardiac MRI represents a promising tool to identify new prognostic parameters to select patients for an early invasive management.

The most well-recognized MRI features used to evaluate novel therapies are IS and microvascular obstruction. For example, the effect of cyclosporine, administrated at the time of reperfusion,
has been tested using IS and LV remodelling as end points of therapeu tic intervention.\textsuperscript{111} In addition, contrast-enhanced MRI has also been used to define the effect of intracoronary stem cell therapy.\textsuperscript{112} Similarly, MRI is applied to assess the next generation of techniques utilized to manage no-reflow, including the application of devices to prevent distal microembolization. In this regard, IS measured by MRI has been recently used to evaluate the impact of a manual thrombectomy device.\textsuperscript{113}

Ongoing research will be directed to standardizing the cardiac MRI protocol and to evaluating in large multi-centre population studies the significance of different imaging features for clinical outcome, arrhythmogenic risk stratification and remodelling. Finally, future technical improvements, such as molecular imaging, will likely enable a better understanding of reperfusion injury and the natural repair mechanisms following AMI as well as the biologic determinants of LV remodelling including neovascularization through angiogenesis.\textsuperscript{114}

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References


85. Öm S, Manheken C, Anand IS, Squire I, Nalge E, Edvardsson T, Dickstein K. Effect of left ventricular scar size, location, and transmurality on left ventricular remodeling with healed myocardial infarction. Am J Cardiol 2007;99:1109–1114.


