



Role of cardiovascular magnetic resonance in acute coronary syndrome

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INTRODUCTION

Acute coronary syndrome (ACS) represents a life-threatening manifestation of atherosclerosis, which usually occurs in the setting of sudden plaque erosion or rupture with intracoronary thrombosis and partial to complete cessation of the downstream myocardial perfusion.¹ The diagnosis, management, and treatment of the various forms of ACS, which include persistent ST-segment elevation myocardial infarction (MI), non-ST-segment elevation MI, and unstable angina (UA), have rapidly been evolving in recent years with subsequently a significant decrease in early and late mortality.^{2–4} Nevertheless, large multicenter studies have shown despite early and successful reperfusion and optimized medication, the actual hospital mortality remains approximately 7%, not mentioning the evolution towards ischemic heart failure in a considerable number of surviving patients.⁵

The current diagnostic tools - i.e., blood biomarkers (e.g. troponin), electrocardiography, and ultrasonography - are key tools in the diagnosis of ACS and fast patient triage, but these markers provide only a partial insight in the complex, evolving processes occurring in the jeopardized myocardium.⁶ Moreover, patients with ACS encompasses a broad and heterogeneous population and many patients with acute chest pain turn out not to have ACS. The accurate diagnosis and differentiation of ACS from other acute cardiac diseases (e.g. aortic dissection, pulmonary embolism, myocarditis, Takotsubo cardiomyopathy) which is essential for therapeutic decision making and specific therapies (e.g. timely reperfusion) may be challenging or even impossible with the above diagnostic tools.

Cardiovascular magnetic resonance (CMR) imaging offers the cardiologist a comprehensive view on ACS at the tissue level (e.g. edema, necrosis, microvascular injury, hemorrhage) and may add important information for the diagnosis and differential diagnosis of ACS. As recent studies have demonstrated CMR-derived parameters yield independent prognostic value in addition to traditional risk factors, CMR may be also important for patient risk stratification. Despite the diagnostic and prognostic utility of CMR in ACS many cardiologists are not yet familiar with this fascinating and clinically helpful imaging modality. The aim of this review is therefore to elucidate the role of CMR in this group of cardiac high-risk patients.

CARDIOVASCULAR MAGNETIC RESONANCE: TECHNICAL FEATURES

Magnetic resonance images are created using the relaxation behavior of hydrogen protons in a high magnetic field – typically 1.5T or 3.0T – following excitation by selective radiofrequency pulses.⁷ The magnetic resonance technique, which was first applied for medical purposes more than three decades ago, has been characterized by a tremendous technical evolution over the years. Generally speaking it has evolved from a static imaging technique requiring long acquisition times towards a highly versatile, fast and organ-dedicated imaging modality. Also for cardiovascular applications,

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this technique has a lot to offer but on the other hand faces many specific difficulties, likely explaining why it took much longer than for most other organs to get truly integrated in clinical practice.

Intrinsic strengths are the high spatial and contrast image resolution, the free choice of image plane and size of field of view allowing an excellent view on the heart and great vessels. However, specific sequence modifications are needed to get rid of image blurring due to motion incurred by the heart, respiration and flowing blood.⁷

Cardiac motion and blood flow are frozen by synchronizing data acquisition to the electrical activity of the heart (*electrocardiographic gating*). Respiratory motion is halted by performing the acquisition during (repeated) breath-holds or by using a respiratory navigator monitoring the diaphragmatic excursion.

Similar to MR imaging in other parts of the body, cardiovascular magnetic resonance (CMR) sequences are either *spin-echo* or *gradient-(recalled)-echo based*. Spin-echo images offer a morphologic view on the heart and pericardium. These sequences are designed that blood has a *dark* or *black-blood* appearance, thus providing a natural contrast with the myocardium and vessel walls.⁸ Using a different *weighting* (e.g., T1- and T2-weighting) information can be achieved about tissue characteristics.

The gradient-(recalled)-echo sequence should be regarded as a versatile, multi-purpose sequence which can be used for functional, perfusion, and angiographic imaging, and similar to spin-echo imaging is often used for cardiac tissue characterization. For functional cardiac imaging, balanced steady-state free-precession (SSFP) imaging has become the gradient-echo sequence of choice.⁹ The high signal of blood at SSFP provides an excellent contrast with the myocardium. Images can be obtained with a high temporal resolution (e.g. every 30 ms) over the cardiac cycle and played in a cine loop, allowing to assess cardiac motion and deformation. Paramagnetic gadolinium-based contrast agents alter tissue magnetization and relaxation, and are often used in CMR for a variety of purposes. Firstly, ultrafast gradient-echo imaging during the passage of intravenously administered gadolinium-chelates through blood vessels and myocardium can be used for three-dimensional MR angiography, and evaluation of myocardial perfusion, respectively. Secondly, differences in wash-in and wash-out kinetics, and distribution volume of the administered contrast agents can be exploited for cardiac tissue characterization.

CMR is rapidly evolving from a pure imaging modality toward a modality offering quantitative data with regard to tissue markers (using T1, T2, T2* mapping techniques), myocardial perfusion, blood flow and myocardial function.¹⁰ It should be noted that administration of gadolinium compounds is contra-indicated in patients with severe renal insufficiency.¹¹ Moreover, permanent pacemakers and ICD's are considered a contra-indication for CMR, and although MR-conditional devices have become available, the benefits versus potential risks of performing a CMR should be carefully weighted in each individual patient.¹²

HOW TO APPLY CMR IN PRACTICE

In patients with a typical presentation of ACS, there is currently no role for CMR in the diagnostic work-up and patient triage. These patients need urgent (STEMI) or a timely (NSTEMI) reperfusion of the infarcted vessel. However, it may be of great value in patients with a doubtful clinical presentation, and/or equivocal routine diagnostic tests. After the treatment/reperfusion of acute MI CMR is able to visualize the exact tissue damage and provides important prognostic information.

CMR in patients with acute infarction

In acute MI patients, CMR is typically performed in the first two to five days following the acute event, which in experienced hands is finished in about 30 minutes. Patient monitoring during the exam is important. However, it is of note that the ECG signal is disturbed – and therefore not clinically useful – once the patient is inside the magnet. Visual and verbal patient contact, blood pressure measurements and pulse oximetry allow close patient monitoring. Moreover, in case of adverse events the personal should be trained for rapid evacuation and resuscitation in an MR safe environment. Once patient preparation and positioning in the magnet is completed, imaging is started with a set of preparatory scans including scout views which are used for determining cardiac imaging planes.

Next, a series of different sequences are applied to comprehensively study the heart, and to answer the clinical question (Figure 1) Cardiac function is studied using SSFP cine imaging along the different cardiac axes, allowing to evaluate myocardial wall motion and contraction patterns, and to visualize valve leaflet motion as well as abnormal – regurgitant/stenotic – flow patterns. At least one set of

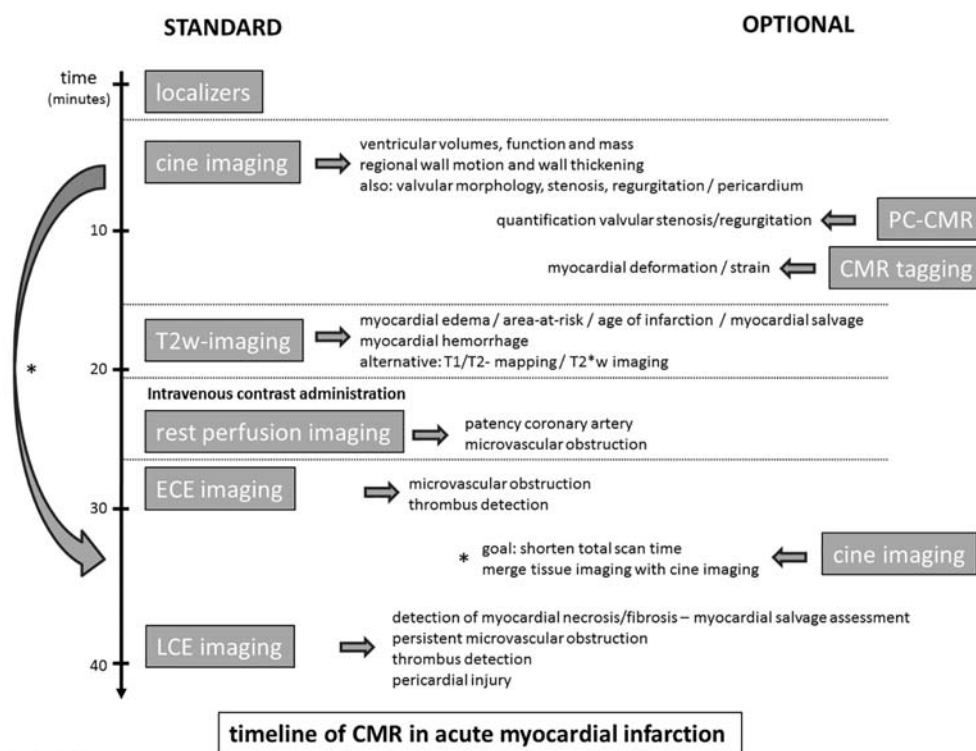


Figure 1. Timeline of comprehensive CMR in a patient with established diagnosis of acute myocardial infarction. The standard sequences are shown on the left, the optional sequences on the right. To shorten total imaging time, cine imaging can be performed following contrast administration. Abbreviations: PC-CMR, phase-contrast CMR. Adapted from Ischemic Heart Disease by Bogaert J and Dymarkowski S, in *Clinical Cardiac MRI Second Edition*, Bogaert J, Dymarkowski S, Taylor AM, Muthurangu V (eds). Springer Heidelberg, Germany (ISBN 978-642-23034-9).

contiguous cine images completely encompassing the ventricles - usually in short-axis direction - is acquired to calculate ventricular volumes, myocardial mass and ejection fraction.

In ACS patients, the ischemically injured - *jeopardized* - myocardium can be reliably depicted by T2-weighted imaging. Alternatively, sequences such as pre-contrast T1 mapping and T2 mapping, have shown appealing initial results for this purpose.¹³⁻¹⁴ Myocardial perfusion patterns - reflecting the adequacy of myocardial reperfusion - are studied using the first-pass of intravenously injected gadolinium contrast agents through the heart.¹⁵ Similar information with regard to the presence of microvascular obstruction can be obtained using the so-called *early contrast enhanced* (ECE) imaging.¹⁶ Areas of incomplete myocardial reperfusion are depicted as dark, non-enhancing areas. *Late contrast enhanced* (LCE) imaging - performed 10-15 minutes post-contrast administration - is used for myocardial infarct imaging. Since the injured myocardium enhances, it may be of interest to perform at least a part of cine imaging (e.g. in cardiac short-axis) after contrast administration, thus providing a kind of merged viability-functional imaging (Figure 2).¹⁷⁻¹⁸

In case of concomitant valve pathology, phase-contrast or velocity-encoded cine imaging can be applied to quantify regurgitant flow volumes and/or measure peak velocities/transvalvular gradients.¹⁹ Moreover, a series of CMR sequences are available for additional measurements, but these are mostly applied in a scientific setting. Amongst them, CMR myocardial tagging has been of great use to unravel the myocardial deformation patterns in infarct patients, providing similar information as can be obtained by tissue Doppler imaging.²⁰

Finally, image analysis and interpretation are performed on off-line dedicated workstation. To quantify ventricular volumes and myocardial mass, endo- and epicardial borders are contoured manually or using (semi)-automated approaches. A similar approach is used to assess the extent of quantify the extent of the jeopardized and/or infarcted myocardium. Studies have shown an excellent reproducibility of CMR post-processing with low inter- and intra-observer variability for LV volumes, ejection fraction, infarct size and myocardial salvage assessment.²¹⁻²²

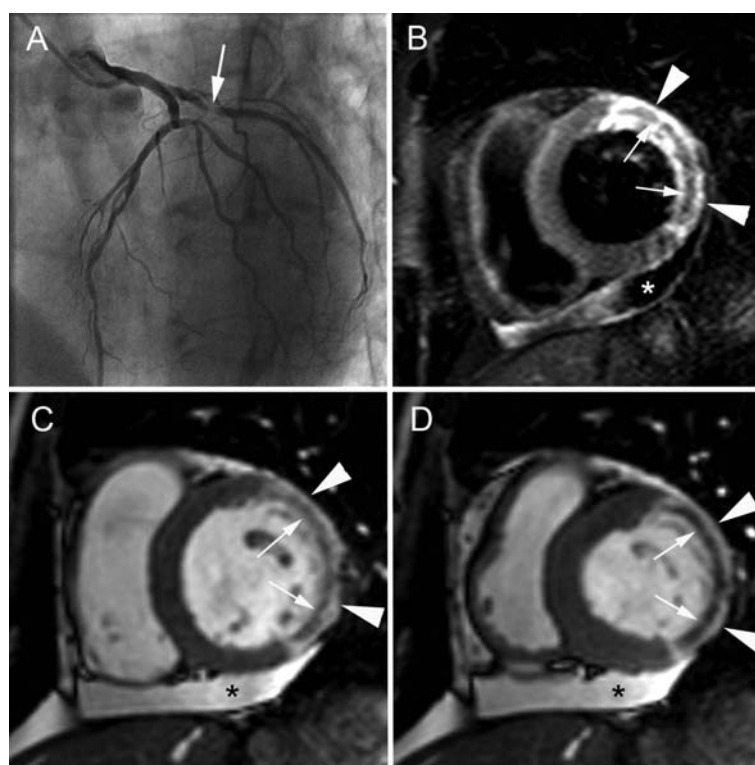


Figure 2. Extensive hemorrhagic myocardial infarction in 60-year-old woman presenting with non-STEMI. Cardiac catheterization shows 95% stenosis in proximal left circumflex coronary artery (arrow, A) and 80% stenosis in mid LAD. Both lesions treated with PCI. CMR, performed 5 days after the acute event, shows extensive myocardial edema in the entire lateral LV wall (arrowheads, B) with presence of a central dark zone (arrows, B) reflecting intramural hemorrhage. Cine CMR imaging in cardiac short-axis at end diastole (C), and end systole (D) shows transmurular enhancement of the lateral LV wall (arrowheads, C, D) with presence of a microvascular obstruction (arrows, C,D). Note significant impairment of the contractility in the infarcted myocardium while systolic wall thickening is well preserved in the viable – dark-gray – myocardium. LV function at CMR is mildly to moderately reduced (EF 40%). Presence of a mild pericardial effusion(*, B, C, D).

CMR in patients with clinical suspicion of ACS

In patients with clinical suspicion of ACS but equivocal diagnostic testing, a modified CMR protocol is used including morphological and/or functional depiction of significant coronary stenoses, and exclusion of extracardiac causes of acute chest pain such as aortic dissection or pulmonary embolism (Figure 3) Stress perfusion CMR imaging alone, or in combination with rest perfusion CMR imaging is an accurate technique to depicting hemodynamically significant stenosis.^{23–24} Intravenous administration of vasodilator (e.g. adenosine, dipyridamole) causes a preferential flow towards normally perfused myocardium at the expense of blood flow to areas perfused by hemodynamically significant stenoses (Figure 4). Hypo-perfused myocardium appears as dark, non-enhancing myocardium at first-pass myocardial perfusion CMR. Combining rest-stress perfusion allows calculation of myocardial perfusion reserve.²⁵ At present, a variety of three-dimensional (3D) free-breathing and breath-hold CMR techniques are available for coronary artery imaging allowing to visualize large portions of the coronary artery tree.^{26–27} Imaging can be targeted on the course of the coronary arteries or contain the whole-heart. Finally, bright blood (SSFP) imaging and contrast-enhanced 3D mono-phasic or time-resolved CMR angiography can be applied to diagnose aortic dissection or pulmonary embolism, as cause of acute chest pain.

VISUALIZATION AND CHARACTERIZATION OF THE JEOPARDIZED MYOCARDIUM

The *jeopardized* myocardium – i.e., the myocardium devoid of blood supply distally to the coronary artery occlusion – is *at risk* of becoming necrotic if not timely reperfused. Restoring reperfusion aims to halt the irreversible cell necrosis and to salvage the ischemically injured, still viable myocardium.

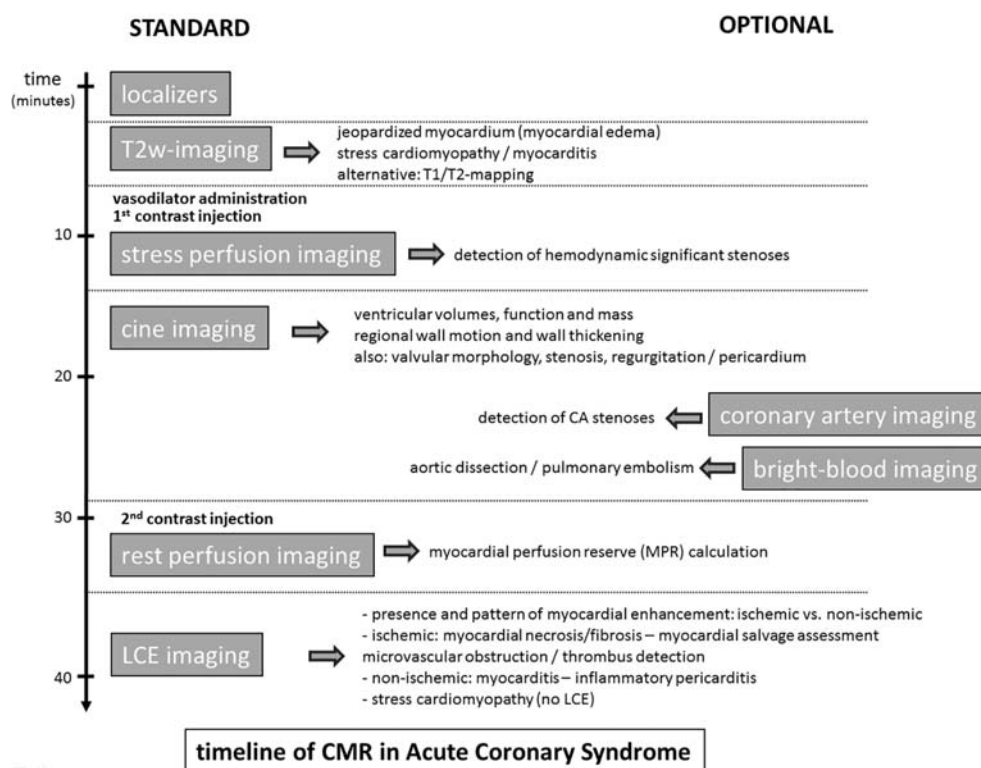


Figure 3. Timeline of comprehensive CMR in a patient with clinical presentation of ACS. The standard sequences are shown on the left, the optional sequences on the right. Adapted from Ischemic Heart Disease by Bogaert J and Dymarkowski S, in *Clinical Cardiac MRI Second Edition*, Bogaert J, Dymarkowski S, Taylor AM, Muthurangu V (eds). Springer Heidelberg, Germany (ISBN 978-642-23034-9).

The extent of jeopardized myocardium is mainly determined by the location of the culprit lesion along the coronary artery. In contrast, myocardial cell death is multifactorial determined including time of symptom onset to reperfusion, imbalance between oxygen need and supply, severity of coronary artery occlusion, presence of prodromal angina as well as presence of collaterals, success of revascularization, and reperfusion injury.^{28–30} Assessment of the extent of the jeopardized myocardium or *area at risk* is important, but remains challenging. It can be estimated using ECG criteria such as the total amount of ST-segment deviation on admission (Aldrich method) and angiographic criteria such as BARI, APPROACH risk score.³¹ Moreover, this area can be visualized by injection of a tracer (SPECT) or contrast material (cardiac computed tomography) prior to PCI but this approach is rarely used in clinical practice because most patients are immediately transferred to cardiac catheterization for PCI.³²

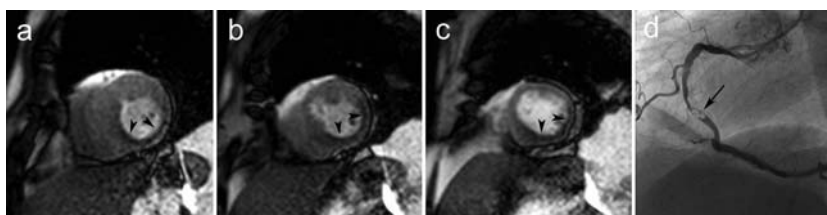


Figure 4. Example of an extensive perfusion defect in the inferolateral LV wall during stress perfusion CMR (a-c) in a patient with a high-grade stenosis of the mid right coronary artery (arrow, d). First-pass perfusion CMR during adenosine stress at 3 short-axis levels (basal, a; mid, b; apical, c) shows presence of an extensive hypoenhancement of the entire inferior and inferolateral LV wall. Note the concomitant lack of systolic wall thickening (most remarkable in the basal slice) caused by myocardial ischemia. Adapted from *Myocardial Perfusion* by Bogaert J and Goetschalckx K, in *Clinical Cardiac MRI Second Edition*, Bogaert J, Dymarkowski S, Taylor AM, Muthurangu V (eds). Springer Heidelberg, Germany (ISBN 978-642-23034-9).

CMR, in contrast, offers an appealing alternative to visualize the area at risk. Moreover, this information can be combined with infarct imaging, thus allowing calculation of a myocardial salvage ratio.^{33–36} Back in the 1980s, it was reported that in ischemically damaged myocardium, T₁ and T₂ relaxation times increase due to an augmentation of free water (caused by disturbances in cellular membrane function and presence of interstitial edema).^{37–38} This phenomenon can be exploited to noninvasively discriminate normal from ischemic myocardium.

Over the years, in particular, T₂-weighted imaging has increasingly been used for this purpose. Jeopardized myocardium appears bright (“hyperintense”) compared to normal myocardium (Figure 5).¹⁴ Abnormalities on T₂-weighted imaging occur in an experimental setting about 30 minutes after onset of ischemia and are closely matched to the area of myocardial dysfunction.³⁹ The abnormalities remain visible at least one week after the acute event, thus providing a method to retrospectively obtain evidence of a recent ischemic myocardial event.³² In patients with a clinical suspicion of ACS, detection of myocardial edema can allow the identification of the infarct-related artery (IRA) whereas lack of increased myocardial signal intensity on T₂-weighted imaging practically excludes an acute ischemic event.⁴⁰ However, since myocardial edema may occur in other ‘acute’ cardiac conditions, such as myocarditis or stress cardiomyopathy, as well, abnormal findings on T₂-weighted imaging should be interpreted correctly, using information obtained by LCE and cine imaging. Although well-validated in animal models, some concerns remain with regard to the accuracy of T₂-weighted imaging in depicting the myocardium at risk.^{41–45} Moreover, several T₂-imaging CMR methods have become available for myocardial edema depiction. The different sequences, however, are not interchangeable and their reproducibility is variable.⁴⁶

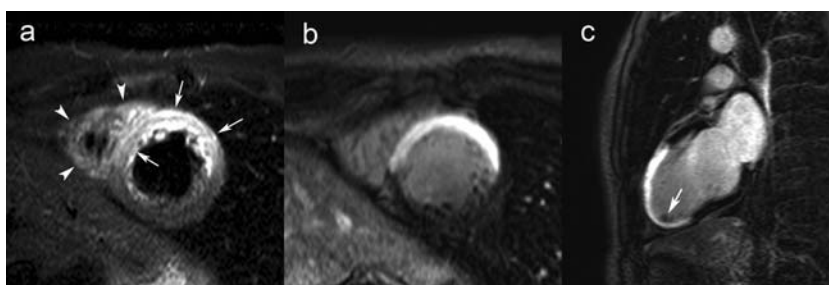


Figure 5. Combined T₂-weighted and LCE imaging in a patient with a reperfused anteroseptal myocardial infarction. Short-axis T₂-weighted imaging (a), and LCE imaging in short-axis (b) and vertical long-axis plane (c). While the extent of edema can be well appreciated on T₂-weighted imaging (arrows, a), there is a strong enhancement transmurular enhancement on LCE imaging (b) of the anteroseptal LV wall, corresponding to the area the edema. The involvement of the LV apex can be appreciated on the vertical long-axis view (c). Note the presence of a small thrombus in the LV apex (arrow, c). Extension of myocardial edema to the RV free wall (arrowheads, a). Adapted from *Ischemic Heart Disease* by Bogaert J and Dymarkowski S, in *Clinical Cardiac MRI Second Edition*, Bogaert J, Dymarkowski S, Taylor AM, Muthurangu V (eds). Springer Heidelberg, Germany (ISBN 978-642-23034-9).

While T₂-imaging provides information with regard to the area at risk, contrast-enhanced imaging is essential to visualize the infarcted myocardium.^{47–48} The contrast kinetics as well as the distribution volume of an extracellular gadolinium-based contrast agent are altered in the infarcted myocardium which results in an increased accumulation of gadolinium molecules and subsequently a greater shortening of T₁-relaxation time in the irreversibly damaged myocardium compared to normal myocardium. Use of an inversion-recovery pre-pulse has a major impact on improving infarct visualization.⁴⁹ In brief, longitudinal relaxation is tissue specific and this phenomenon can be exploited to enhance contrast between normal and pathological myocardium. This pre-pulse in combination with an appropriate inversion time enables to nullify signal of normal myocardium which results in an excellent depiction of infarcted myocardium – with infarct volumes as small as or even less than 1g of myocardial tissue. Infarct images are typically acquired relative late – i.e. 10 to 15 minutes – post-contrast administration, yielding the most accurate appraisal of the extent of myocardial necrosis (Figure 5). As mentioned above, this sequence is called LCE imaging in contrast to ECE imaging acquired immediately following contrast administration which is used for other purposes (e.g. microvascular obstruction). Using a multi-slice two-dimensional or three-dimensional approach

encompassing the ventricles, the presence and extent of infarcted myocardium can be visualized and quantified – expressed as a volume or as percentage of LV mass. A myocardial infarct is typically located in one of the coronary perfusion territories, is always subendocardial located and has a variable transmural extent.

A myocardial salvage ratio can be calculated relating infarct size measured by LCE imaging to area at risk measured by T2-weighted imaging (Figure 6).^{33,35,36} This ratio provides valuable information with regard to the extent of irreversible myocardial damage in the jeopardized myocardium.⁵⁰ On one end of the spectrum is the *aborted MI* with presence of myocardial edema but with no evidence of infarction on LCE,⁵¹ while infarcts involving the entire area at risk have a ratio of 0. The myocardial salvage ratio is directly related to post-reperfusion ST-segment resolution, and inversely to adverse LV remodeling and it bears independent prognostic value.^{35,52–53}

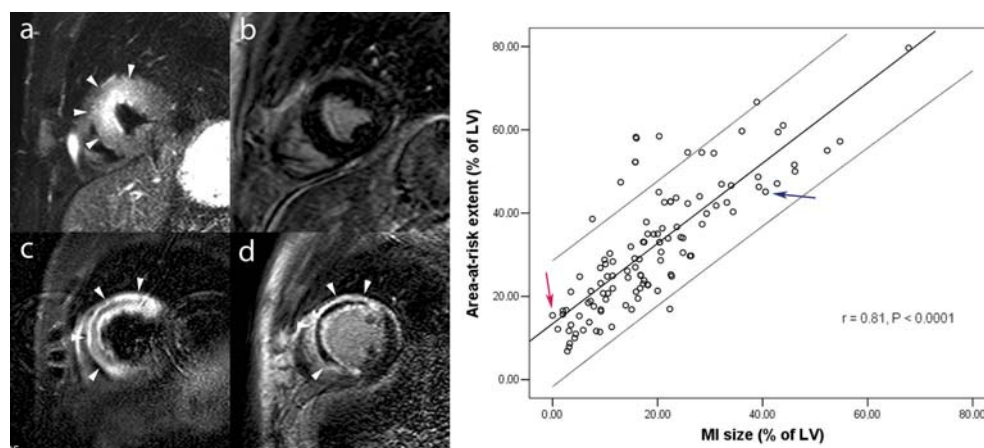


Figure 6. Complementary value of T2-weighted and LCE imaging in acute myocardial infarction. Short-axis T2-weighted imaging (a, c) and LCE imaging (b, d). Patient one shows a large area of myocardial edema in the anteroseptal LV wall (arrowheads, a) but not late enhancement (b), corresponding to an aborted MI. Patient two shows an extensive area of myocardial in the anteroseptal LV wall (arrowheads, c). Following contrast administration strong enhancement occurs in the anteroseptal LV wall (arrowheads, D). The extent of enhancement nearly equals the extent of myocardial edema, leaving no or minimal amount myocardial salvage. In addition, this patient shows a large central dark zone within the edematous myocardium corresponding to myocardial hemorrhage (c), and an extensive area of MVO (d). The relationship between extent of myocardial edema – reflecting the area-at-risk – and extent of late enhancement – reflecting infarct size – obtained in 137 patients is shown in the graph (adapted from Masci et al. 2010). On the graph, patient one is shown by the red arrow, patient two by the blue arrow.

TISSUE MARKERS OF MYOCARDIAL INFARCTION SEVERITY

Infarct size and transmuralty

A key characteristic of myocardial tissue is its low regenerative capacity since myocytes are terminally differentiated having lost the capacity to renew damaged myocardium. As a consequence, irreversibly damaged myocardium is replaced by an afunctional fibrotic scar. Thus, the amount of contractile tissue lost – or the infarct size – reflects infarct severity, is a crucial determinant of adverse LV remodeling and patient outcome, and therefore often used as surrogate end point to assess the efficacy of novel treatments.^{54–56} LCE imaging is a well-validated, accurate and reproducible tool for infarct sizing independent of the time post-infarction.^{57–59} Moreover, it is key to depict small-sized infarcts, as little as 1g of tissue, that drop below the radar of ECG other imaging modalities such as SPECT.^{60–61} Since the presence of unrecognized MI's portends unfavorable outcome, CMR has become a preferred modality for infarct detection and sizing.⁶² Moreover, since timely reperfusion may stop the transmural progress of necrosis and salvage the jeopardized myocardium in the viable subepicardial layers, assessment of infarct transmuralty is another tissue marker of infarct severity which because its high spatial and contrast resolution can be well assessed by CMR.⁶³ Several studies have shown that increased infarct transmuralty is related with lack of inotropic reserve and impaired recovery of contractile function, and is associated with more pronounced post-infarct wall thinning, aneurysm formation and adverse ventricular remodeling.^{64–67}

Microvascular obstruction

Although endothelial cells are more resistant to prolonged ischemia than myocytes, successful coronary reperfusion is often associated with failure to achieve uniform myocardial reperfusion, i.e., the so-called “no-reflow” or “microvascular obstruction” (MVO) phenomenon.⁶⁸ It is believed that other mechanisms such as reperfusion injury, distal embolization, and likely also an individual susceptibility contribute to the occurrence of MVO.⁶⁹ For example, Rochitte and colleagues showed a significant increase in the extent of MVO and infarct size as well as the ratio of MVO to infarct size during the first 48 hours after MI, supporting the concept that microvascular and myocardial injury continue beyond reperfusion.⁶⁸ MVO occurs in both ST-segment and non-ST-segment elevation MI with a prevalence ranging from 5% to more than 50%.^{69–72} Presence and extent of MVO is related to the duration of ischemia time, coronary collaterals, more severe myocardial damage, and importantly is independently associated with lack of functional recovery, adverse remodeling, and worse patient outcome.^{72–78} Information with regard to the presence of MVO comes at CMR as a free bonus when intravenous contrast material is injected.^{78–82} In case of MVO, this part of the myocardium does not enhance (i.e. remains dark) after contrast administration. The presence and maximal extent of MVO can be best evaluated with first-pass myocardial perfusion imaging, or at ECE imaging.^{16,82} Use a long inversion time is advantageous to visualize MVO at ECE.⁸³ As gadolinium-molecules diffuse in the MVO, the extent as well as the prevalence of MVO decrease following contrast administration (Figure 7).^{16,72} Several studies have shown that persistent MVO at LCE imaging is prognostically more relevant than MVO at ECE, and it may be the best prognosticator of hard clinical events.^{78,84–85} Limiting microvascular damage and improving microvascular circulation in acute MI patients has become an area of intensive research, often using CMR-based endpoints.^{86–90}

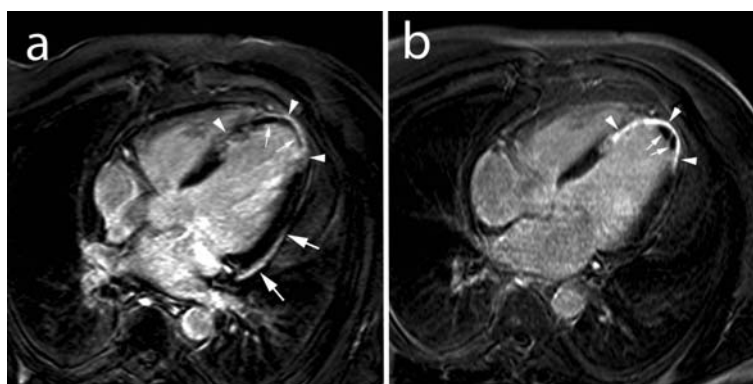


Figure 7. Post myocardial infarction LV remodeling in a 52-year-old male with anteroapical myocardial infarction. LCE imaging in the horizontal long-axis image plane at 1 week (a) and 4 months (b) post-infarction. At 1 week, presence of diffuse enhancement of the apical part of the ventricular septum and LV apex (arrowheads, a), with a large area of microvascular obstruction (small arrows, a). Note the presence of pericardial enhancement over the laterobasal part of the LV (arrows, a). At 4 month follow-up, the infarct has thinned and strongly enhances (arrowheads, b). Note the presence of a small mural thrombus in LV apex (arrows, b). Adapted from *Ischemic Heart Disease* by Bogaert J and Dymarkowski S, in *Clinical Cardiac MRI Second Edition*, Bogaert J, Dymarkowski S, Taylor AM, Muthurangu V (eds). Springer Heidelberg, Germany (ISBN 978-642-23034-9).

Intramycardial hemorrhage

Despite successful recanalization of the culprit lesion, studies in animal models and patients have frequently shown the presence of myocardial hemorrhage in the infarct core.^{91–93} It is believed that reperfusion of ischemic myocardium with irreversible microvascular damage may cause intramycardial hemorrhage (IMH) with massive red blood extravasation into the extracellular space. This phenomenon is associated with longer ischemia times, severity of flow depression before reperfusion and extent of necrosis, and has been observed after pharmacological and mechanical reperfusion. Exploiting the paramagnetic properties of the hemoglobin breakdown product - deoxyhemoglobin - causing shortening of T₂-relaxation times, T₂-weighted and T₂*-weighted CMR can be used to noninvasively demonstrate IMH.^{94–98} Whereas the jeopardized myocardium in non-hemorrhagic infarcts is homogeneously bright, hemorrhagic infarct presents with a central dark

appearance (Figure 2). CMR studies have invariably shown that IMH is related to more extensive infarcts with higher infarct transmuralty and lower baseline EF. IMH is independently related to adverse regional and global LV remodeling, lack of functional recovery, markers of late arrhythmic risk, and worse patient outcome.^{99–102} Since IMH is consistently associated with (large) MVO, most likely the presence of IMH reflects greater cellular damage resulting in greater adverse remodeling and poorer outcomes.⁷⁰ Thus, future strategies aimed at preserving microvascular integrity may improve patient outcome by reducing IMH.⁹⁶

Myocardial infarct heterogeneity

Patients with a recent history of MI are at increased risk for arrhythmias. Whereas the center of the infarcted myocardium evolves towards a dense fibrous scar incapable of depolarization, the infarct border zone in contrast - containing a mixture of non-viable and viable myocardium - may be an arrhythmogenic substrate potentially causing ventricular arrhythmias and sudden cardiac death. CMR has potential to depict infarct tissue heterogeneity, and thus to estimate increased risk for sudden cardiac death.^{103–104} Dense fibrotic myocardium at LCE imaging has typically a high signal intensity (SI) - defined as ≥ 5 SD above the SI of normal myocardium. Lower SI - i.e. between 2SD and 5SD - the so-called 'gray' myocardium corresponds to infarct areas with variable amounts of fibrosis and myocytes. Of note, the gray myocardium is not necessarily confined to the infarct border, but can also be found in more central locations, and also in the papillary muscles.¹⁰⁵ High spatial resolution imaging may improve visualization of infarct heterogeneity and may be an important predictor of arrhythmogenic clinical events.¹⁰⁵

Right ventricular infarction

Isolated right ventricular (RV) infarction is rare (<3% of all infarcts), and therefore, infarction of the RV is usually an expression of a biventricular MI.¹⁰⁵ In most cases, the LV is predominantly involved with a variable degree of infarct extension towards the anterior or inferior RV wall, causing RV dysfunction. Lack of functional recovery, however, is associated with high mortality rate. Current techniques, such as ECG with right precordial leads and echocardiography, underestimate the true incidence of RV ischemic injury. Imaging of the thin, trabeculated RV wall is challenging, even with high spatial and contrast resolution techniques such as CMR. Nevertheless, this technique has been of great value to better appreciate reversible and irreversible RV damage using a comprehensive approach including T2-weighted, LCE and cine imaging.^{106–108} Grothoff and colleagues showed that RV injury evidenced by CMR yields strong, independent predictive value of clinical outcome after acute reperfused STEMI.¹⁰⁹

ROLE OF CMR IN PATIENTS WITH ACUTE CHEST PAIN SUSPECTED OF ACS

Growing evidence has been nurturing the role of CMR in evaluating patients with acute pain. Although evolving ECG abnormalities and increased cardiac biomarkers remain key diagnostic tools in decision making in ACS patients, many "ACS" patients do not have ACS. Moreover, cardiac troponin is a highly sensitive but poorly specific biomarker of ischemic myocardial damage, since any condition provoking myocyte necrosis will result in a rise in cardiac troponin. Also, the increase in cardiac troponin is limited to a narrow time window reducing the sensitivity to depict subacute MI. Furthermore, ECG abnormalities may overlap between ischemic and non-ischemic cardiac etiology, and small infarcts may not necessarily cause typical ECG abnormalities. Comprehensive CMR provides valuable information in the majority of the above patients (Figure 3). Several studies have shown that CMR can be applied in the emergency department to confirm or to exclude ACS in patients with chest pain but absent ST-segment elevation.^{110–113} Stress perfusion CMR is accurate to depict hemodynamic significant stenoses,^{23–24} can be easily integrated in a CMR protocol but patients are not allowed to have caffeine-containing beverages consumed 24 hours prior to a CMR perfusion study. Moreover, although much progress has been achieved in the field of CMR coronary imaging, results are not always consistent,^{114–115} and multidetector computed tomography (MDCT) is a faster and more appealing alternative for non-invasive coronary artery imaging.¹¹⁶ Additionally, coronary artery imaging can be combined with imaging of the thoracic aorta and pulmonary arteries using a so-called triple rule-out MDCT approach.¹¹⁷ The current value of CMR, at present, in ACS patients is primarily in the diagnostic work-up of patients with acute chest pain showing normal or non-obstructed coronaries at cardiac catheterization.¹¹⁸ The diagnostic problem to solve is whether these patients have a

spontaneous recanalization of the culprit lesion, obstruction of one of the smaller side branches, another cardiac disease causing ECG changes and release of cardiac enzymes, or an extracardiac origin of their complaints. In case of spontaneous clot resolution, CMR is often able to depict signs of myocardial ischemic damage, such as myocardial edema, LCE and functional impairment in a coronary artery perfusion territory. CMR findings in occlusion of one of the side branches are similar but the abnormalities are much more limited in extent and do not correspond to the perfusion territory found in typical MI's. Instead these present as focal involvement of the myocardium corresponding to the perfusion territory of the affected side branch. Retrospective analysis of the 'normal' coronary angiograms may reveal a missed proximal occlusion of one of the side branches, although often no abnormalities can be depicted.

A substantial number of patients presenting acute chest pain, troponin raise but unobstructed coronary angiograms turn out to have acute myocarditis.¹¹⁸ Comprehensive CMR has evolved as a valuable clinical tool for the diagnosis of suspected acute myocarditis.^{119–121} Abnormalities include focal to generalized myocardial edema, hyperemia on ECE, area of focal LCE, functional abnormalities and concomitant pericardial pathology.¹²² Similar to infarct patients, myocardial edema in acute myocarditis can be depicted by T2-weighted CMR techniques, while newer T2-mapping techniques are promising to better depict the extent of abnormalities.¹²¹ Myocardial contrast enhancement, using LCE, is a frequent finding in the clinical setting of suspected myocarditis and is associated with active inflammation at histopathology. The pattern of enhancement, however, is different from the enhancement pattern in acute MI, providing a powerful tool to differentiate both entities. Two patterns are typical for myocarditis, a) subepicardial (patchy) distribution in the free LV lateral wall, b) an intramural, rim-like pattern in the septal wall (Figure 8).¹²³ In myocarditis patients, presence of LCE is

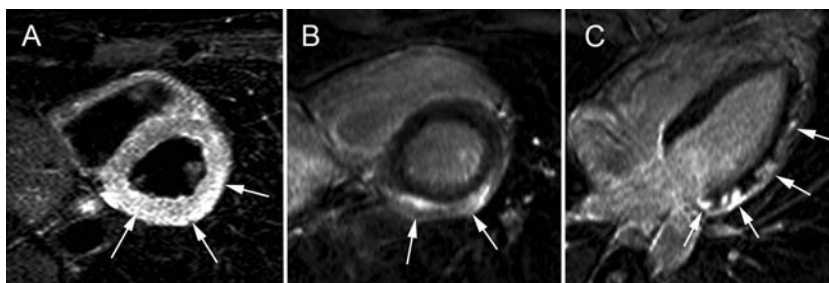


Figure 8. Acute myocarditis in 49-year-old male patient presenting with acute chest pain, cardiac enzymes, ST-elevation (lateral leads) but normal coronary arteries at cardiac catheterization. Short-axis T2-weighted imaging shows diffuse myocardial edema in the lateral LV wall (arrows, A). At LCE imaging (short-axis, B; horizontal long-axis, C) multifocal subepicardial enhancement is present (arrows, B, C). This pattern of CMR abnormalities is strongly suggestive of acute myocarditis.

the strongest, independent predictor of adverse outcome.¹²⁴ In a recent study, Francone et al. showed that the CMR sensitivity is dependent on the clinical pattern of presentation, yielding the highest sensitivity in patients with an infarct-like clinical presentation.¹²⁵ Finally, native and post-contrast T1 mapping with calculation of myocardial extracellular volume (ECV) hold promise in further improving the accuracy of CMR to diagnose acute myocarditis.^{126–127} Stress cardiomyopathy or takotsubo cardiomyopathy represents a reversible LV dysfunction with acute myocardial infarction-like ST-segment elevation without coronary artery lesions and with minimal myocardial enzymatic release. The typical presentation is apical – less frequently midventricular – ballooning with preserved contractility in the other LV segments. Although the diagnosis is usually established at left ventriculography during cardiac catheterization, CMR is of particular interest to differentiate this entity from an acute myocarditis or acute MI.¹²⁸ CMR typically shows a pattern of LV dysfunction, myocardial edema, and absence of necrosis/fibrosis on LCE (Figure 9).¹²⁹

CMR IN INFARCT REMODELING

Myocardial necrosis triggers inflammatory and reparative processes in the affected myocardium. Whereas in an initial phase infarct swelling/expansion occurs due to myocardial edema and inflammatory reaction, the necrotic myocardium is consecutively replaced by granulation tissue ultimately evolving towards scarred tissue, a process deemed to take several weeks. This process of

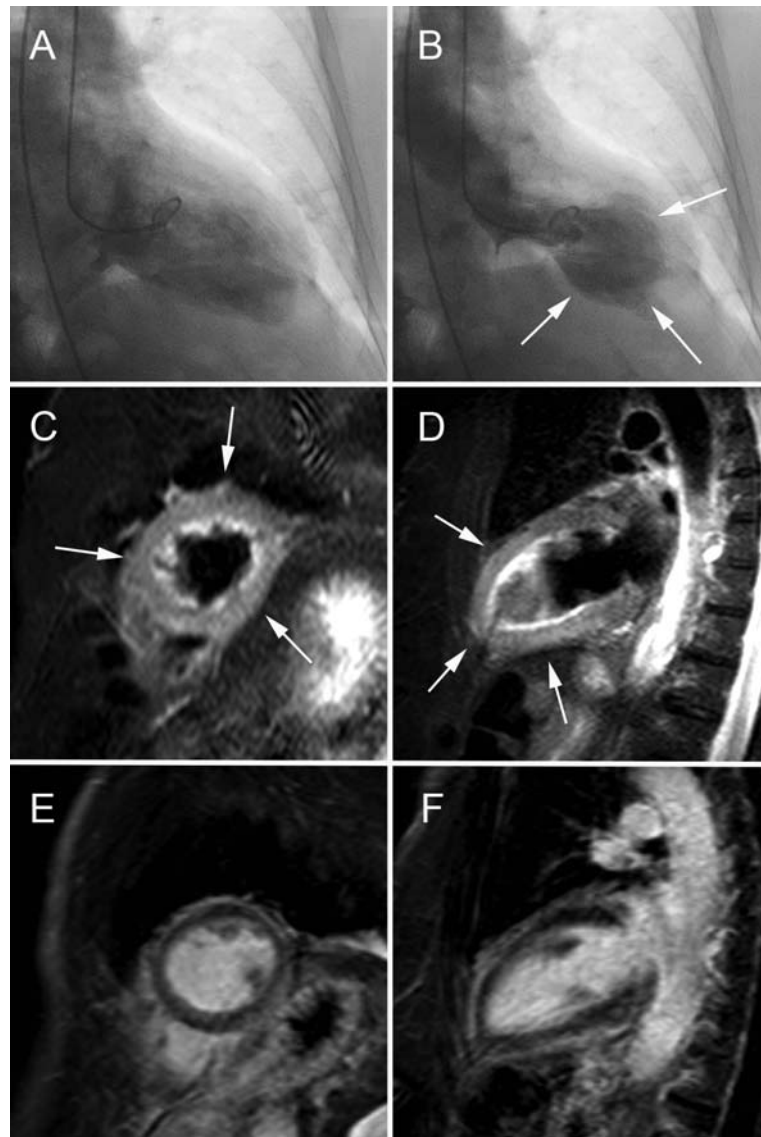


Figure 9. Takotsubo cardiomyopathy in 78-year-old woman presenting with retrosternal chest pain irradiating to shoulders, ST-elevation V6-I and mildly increased cardiac enzymes. Findings of apical ballooning (arrows, B) at cardiac catheterization (end-diastolic A and end-systolic (B) time frame). T2-weighted CMR in short-axis (C) and vertical long-axis (D) and LCE CMR in short-axis (E) and vertical long-axis (F). Presence of diffuse myocardial edema in apical half of LV (arrows, C, D). No evidence of increased myocardial enhancement at LCE CMR (E, F). Cine CMR imaging (not shown) shows moderate to severe hypokinesia in apical part of LV with global LV EF of 40%.

infarct healing is coupled with adaptive ventricular remodeling. Since CMR fuses *in vivo* tissue characterization with function imaging, this technique has extensively been used the last two decades to study infarct and ventricular remodeling (Figure 7).⁶² Moreover, its noninvasive approach allows long-term follow up to better understand the processes contributing to evolution towards ischemic heart failure.^{59,99}

IMAGING OF INFARCT-RELATED COMPLICATIONS

Acute MI may be associated by potentially harmful, even lethal complications such as aneurysm and thrombus formation, valve leakage and post-infarction pericardial injury. Using a comprehensive CMR approach even rare complications, such as a dissecting myocardial hematoma, can reliably be depicted. Although CMR has no primary role in detecting mitral valve leakage post-infarction, it enables to depict papillary muscle infarction as potential cause of valve regurgitation.^{105,130–132} CMR is

definitely the best imaging modality to depict ventricular thrombi (Figure 7). In particular contrast-enhanced imaging allows to depict or to exclude even small thrombi, typically appearing as dark structures surrounded by the contrast-enhanced blood.^{132–133} CMR may help in differentiating true from false aneurysms.¹³⁴ Finally, since the damage inflicted by the coronary artery occlusion is not halted at the myocardial border, but may affect in the pericardium as well, acute MI patients frequently show pericardial effusion and/or inflammation, which can be very well depicted at CMR (Figure 7).^{135–137}

CMR AND PROGNOSIS ASSESSMENT IN ACS

Prognosis assessment and predicting of future major adverse cardiac events (MACE) in patients with ACS are crucial. CMR, because of its versatility, may be of great value. Firstly, in patients with suspected CAD but no evidence of prior myocardial infarction, stress imaging (either perfusion or dobutamine) help in patient risk stratification by adding important complementary information to recognized risk factors such as impairment in LV ejection fraction.^{138–141} Other CMR findings adding incremental value for prediction of future events are presence of LV hypertrophy (defined as LV wall thickness ≥ 12 mm or LV mass > 96 g/m² in men and > 77 g/m² in women), and evidence of ischemia-related myocardial scarring – reflecting prior MI – at LCE imaging.^{142–144} In ACS patients in whom MI is excluded by cardiac biomarkers and non-diagnostic electrocardiograms, stress perfusion CMR is a more accurate predictor of future events than traditional risk factors. In acute MI, the multi-parametric approach by CMR has shed new light on risk stratification. This technique allows accurate assessment of ventricular volumes and function, infarct sizing, visualization of infarct transmural extension and tissue characterization of the jeopardized and infarcted myocardium. Many of the CMR parameters bear independent predictive value.^{52,53,73,78,101,109,131} However, since some of the parameters are interrelated (e.g. MVO and IMH) further studies are necessary to determine whether there are the expression of one phenomenon (e.g. microvascular injury) or are independent parameters.⁷²

CONCLUSIONS

CMR has revolutionized our look on ACS and myocardial infarction imaging, offering an in-vivo tool for characterization of the reversible and irreversible myocardial damage, assessment of the functional consequences, depicting infarct-related complications, and evaluating of ventricular remodeling. CMR is key in differentiating ACS from non-ACS related causes of chest pain. Several CMR biomarkers provide independent predictive value of patient outcome. Finally, CMR is increasingly used to evaluate efficacy of novel treatment strategies in ACS patients.

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