

Detecting acute coronary syndromes by magnetic resonance imaging

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Abstract

Only a small subset of the many patients presenting with chest pain are eventually diagnosed with acute coronary syndromes (ACS). Early identification of this high-risk group can be challenging, particularly since many will initially have non-diagnostic electrocardiograms and normal cardiac enzymes. There is, therefore, great clinical interest in new methods for better detection of ACS. A number of important recent studies using cardiac magnetic resonance (CMR) as well as new developments in CMR techniques have led to growing excitement over the possibility of using CMR to improve detection of ACS. This review will provide an overview of these developments and suggest possible uses of CMR for this indication.

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Introduction

Acute coronary syndromes (ACS) span a broad range of clinical presentations, including ST-elevation myocardial infarction, non-ST-elevation myocardial infarction (NSTEMI), and unstable angina. In the United States, more than 5 million patients per year are evaluated in the emergency department (ED) setting for chest pain or other symptoms suggestive of ACS [1]. A minority of these patients will present with significant electrocardiogram (ECG) changes and/or positive troponins requiring immediate admission and usually also cardiac catheterization. At the other end of the spectrum, a small proportion of patients will be assessed as having a very low probability of ACS based on clinical evaluation alone and be discharged early from the ED. The majority of patients, however, will be determined to have an intermediate risk for having underlying ACS. In this group, initial serologic markers are negative for cardiac injury and resting ECG changes are non-diagnostic for ACS. Although

serum troponins are extremely sensitive for detecting myocardial infarction (MI), by definition, these assays do not detect unstable angina. Furthermore, the time course of troponin elevation is from a few hours to a few days after myocardial necrosis. Thus, measurements outside this time window may be negative and falsely reassuring. Finally, it is well recognized that the ECG can be completely normal in ACS. The fear of discharging someone with possible underlying ACS results in the admission of the great majority of these patients who ultimately prove to have no evidence for ACS [2]. Only about 30% of patients admitted for suspected MI are eventually diagnosed with ischemic heart disease [2]. On the other hand, up to 4% of chest pain patients discharged from the ED experience an MI within 30 days with potential fatal consequences and serious medico-legal implications [3].

Physicians thus routinely face the question of how to manage patients who present with possible ACS at initial clinical evaluation. There is, therefore, great clinical interest in new methods for better detection of

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ACS. A number of important recent studies using cardiac magnetic resonance (CMR) as well as new developments in CMR techniques have led to growing excitement over the possibility of using CMR to improve detection of ACS. In this review, we will provide an overview of these developments and suggest possible uses of CMR for this indication.

Detection of myocardial infarction

The most accurate and best validated CMR technique for diagnosis of MI is late gadolinium enhancement (LGE) imaging. This method requires intravenous administration of gadolinium contrast followed by inversion recovery imaging after a delay of about 10 minutes [4]. Normal myocardium appears black or nulled, whereas nonviable regions appear bright or enhanced. The mechanism of the enhancement is likely based on the principle that gadolinium chelates are extracellular agents that cannot cross intact cell membranes; and in normal myocardium myocytes are densely packed thus excluding gadolinium [5]. The overall concentration of gadolinium is therefore small in normal myocardium. With acute myocyte necrosis (as in acute MI or myocarditis), there is membrane rupture, which allows gadolinium to diffuse into myocytes. This results in increased gadolinium concentration, shortened T1 relaxation, and thus leads to signal enhancement. Interestingly, in the chronic setting, the mechanism is similar with scar replacing necrotic tissue and expanding the interstitial space, leading to increased gadolinium concentration and enhancement. Extensive validation of this CMR LGE imaging technique has been done in animal models of infarction, showing a nearly exact relationship between the size and shape of infarcted myocardium by CMR LGE imaging to that of histopathology [6]. Moreover, these studies have shown that CMR LGE can distinguish between reversible and irreversible injury independent of wall motion, infarct age, and reperfusion status. Human studies have shown that infarct size measured by CMR LGE is closely associated with peak cardiac enzyme release [7] and measurements by positron emission tomography [8]. CMR LGE has been shown to be more sensitive than singlephoton emission computed tomography (SPECT) in detecting subendocardial infarcts and infarcts in nonanterior locations [9]. Furthermore, the high spatial resolution of CMR LGE has been shown to allow detection of even microinfarctions, involving as little as 1 g of tissue such as those occurring in the context of percutaneous coronary stenting [10].

Importantly, CMR LGE is the only imaging technique to have been tested in a prospective randomized multicenter trial for detection of MI [11]. A total of 566 patients with first-time MI were scanned after cardiac

catheterization in 26 centers. The study showed that the sensitivity of CMR LGE reached 99% and 94% in acute and chronic MI, respectively. Furthermore, the correct location (based on the infarct-related artery) was identified in more than 97% of patients. This shows that this imaging technique is clinically robust and can be used reliably across different centers and vendors.

Differentiating acute from chronic MI and demarcation of the area-at-risk

Acute and chronic MI can be difficult to differentiate with conventional imaging. Both will typically exhibit wall-motion abnormalities on echocardiography, and both cause defects on SPECT scans. Likewise, as described above, both acute and chronic MI will look identical with CMR LGE. Chronic MI is more likely to be associated with a thin wall on CMR imaging or echo, but this finding is not specific. Thus, these imaging methods cannot reliably differentiate acute from chronic MI. This distinction can be critical when evaluating a patient with possible ACS who has a history of prior MI.

Recently there has been significant interest in the detection of myocardial edema, which may be a feature of many types of acute myocardial injury. The subtle increase in water content of the myocardium may be detectable with CMR using T2-weighted imaging (*Figure 1*). Abdel-Aty et al suggested that T2-weighted CMR was able to differentiate acute from chronic MI with 96% specificity in a study of 73 patients with acute or chronic MI [12]. It has also been suggested that the combination of T2-weight imaging of myocardial edema and LGE can measure the myocardium at-risk and the extent of salvageable myocardium (area-at-risk minus the infarcted myocardium) [13]. T2-weighted edema may also persist for some time after ACS, in theory allowing detection after the acute event. However, black-blood T2-weighted techniques are challenged by relatively low contrast-to-noise ratio as well as intra-cavitary flow artifacts in regions of slow flow adjacent to wall motion abnormalities [14,15]. Inhomogeneities of myocardial signal intensity caused by through-plane motion or associated with the use of surface coils can exceed the subtle differences caused by acute ischemia or infarction [14,15]. There is therefore great interest in developing newer T2-weighted pulse sequences that may be more clinically robust [16].

Detection of unstable angina in the absence of myocardial necrosis

By definition unstable angina is not associated with myocardial necrosis and therefore is not detected by

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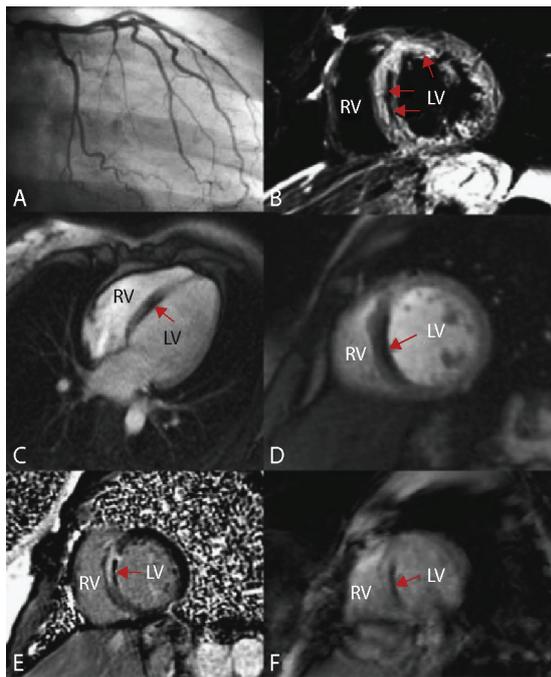


Figure 1. A middle-age woman was admitted with acute chest pain and elevated serum troponins. While urgent coronary angiography did not reveal any significant coronary stenosis (A), multi-modality cardiac MRI provided evidence of an acute coronary syndrome. T2-weighted fast spin-echo imaging demonstrated an area of high signal-intensity consistent with transmural myocardial edema (area-at-risk) in the anteroseptal wall (B, arrows). Although there was no significant epicardial coronary stenosis, evidence of tissue no-reflow was seen in the subendocardium of the anteroseptal wall within the area-at-risk (B, black arrow), on first-pass myocardial perfusion imaging as a dense perfusion defect (C and D, arrows), and on LGE imaging within the gadolinium-enhanced area of infarction (E, arrow). In addition, very low signal intensity was seen in this region by T2* imaging raising the suspicion of co-existing intramyocardial hemorrhage (F, arrow).

CMR LGE. However, regional wall-motion abnormalities may suggest this diagnosis in the absence of baseline abnormalities. Unfortunately, in the ED setting, it is often not known if baseline wall-motion abnormalities existed. In addition, wall motion abnormalities are not specific to ACS and can be seen in nonischemic conditions such as cardiomyopathies as well as inflammatory or infiltrative diseases.

Combined use of different CMR techniques can provide complimentary information that can be obtained in a single examination. Both wall-motion abnormalities and resting perfusion defects may be seen with MI and unstable angina. However, the absence of LGE in that region would effectively rule out MI.

Unfortunately significant underlying coronary artery disease (CAD) can still be present in the absence of resting perfusion defects, wall-motion abnormalities, and CMR LGE. The identification of significant CAD in

this setting would require additional performance of stress imaging, which can also be done with CMR. Whether this necessarily represents unstable angina as opposed to the incidental finding of CAD, however, is debatable. Thus there is interest in the possible use of T2-weighted imaging to detect the presence of myocardial edema from recent ischemia that has subsequently resolved. Given the previously mentioned technical challenges, it appears that further technical improvement is needed for T2-weighted imaging sequences to be used in reliably detecting recent resolved ischemia in the absence of LGE.

Clinical studies using CMR to detect ACS

Kwong et al. performed CMR within 12 hours of presentation in 161 consecutive ED patients presenting with chest pain but no ECG evidence for MI [17]. The CMR protocol comprised myocardial perfusion at rest, cine wall motion, and LGE imaging. The authors found a sensitivity and specificity of 84% and 85%, respectively, of a resting CMR for detecting subsequent ACS defined as 70% coronary stenosis or positive stress test within 8 weeks of the index hospitalization. In addition, all 10 cases (100%) of acute myocardial infarction in that cohort defined by elevation of serum troponins, not detected by history and physical examination and resting admission ECG, were detected by CMR imaging. Detection of regional wall-motion abnormalities was the most powerful part of the CMR study in this setting where perfusion abnormalities may be normal in between episodes of pain, and infarction may not yet be established. CMR was more sensitive than ECG, troponins, and Thrombolysis In Myocardial Infarction (TIMI) risk score and was the strongest predictor of ACS on multivariate logistic regression analysis (Figure 2). A subsequent clinical study by the same group of investigators, showed that in ED patients with chest pain, non-diagnostic ECGs and negative troponins, an abnormal adenosine CMR examination predicted with high sensitivity (100%) and specificity (93%) which patients had significant CAD during one-year follow-up [18]. Furthermore, no patients with a normal adenosine CMR study had a subsequent diagnosis of CAD or adverse outcome. Plein et al studied 68 patients presenting with non-ST-segmentelevation acute coronary syndrome (NSTEMI-ACS) with CMR imaging of myocardial function, perfusion (rest and adenosine-stress), viability (by LGE), and coronary artery anatomy [19]. Visual analysis of CMR was carried out. CMR imaging data from all pulse sequences were first reviewed in combination, and then in a subsequent interpreting session, analyzed individually. Comprehensive CMR analysis yielded a sensitivity of 96% and a specificity of 83% to predict the presence of

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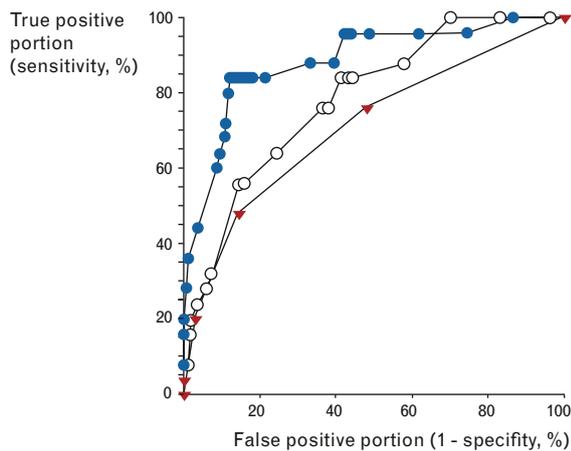


Figure 2. On the basis of multivariate logistic regression analysis, MRI has additional predictive value over clinical parameters, including ECG and troponin-I, for diagnosis of acute coronary syndrome (ACS). To predict ACS, the receiver-operator characteristic curves for the TIMI risk score (dark triangles) and the current logistic regression models without MRI (open circles) and with MRI (dark circles) were determined. First published in Kwong R et al [17] ©2003 American Heart Association.

significant coronary stenosis (>70% on cardiac catheterization) and was more accurate than analysis of any individual CMR method; CMR was also found to be significantly more sensitive and accurate than the TIMI risk score. More recently, Cury et al reported the incremental value of T2-weighted imaging in 64 consecutive patients presenting with chest pain to the ED with negative cardiac enzymes and no ECG changes suggestive of coronary ischemia [20]. They reported that adding T2-weighted imaging to a core CMR protocol of cine and CMR LGE imaging increased diagnostic accuracy in detecting ACS, primarily on the basis of improving diagnostic specificity by discriminating patients with prior MI who did not have ACS from those who did. Nevertheless, T2-weighted imaging alone failed to detect 4 of the 9 patients with unstable angina presumably related to the previously mentioned difficulties with current T2-weighted imaging sequences. Overall, CMR provided incremental value in the detection of ACS over and above traditional risk stratification with the changes detected by CMR occurring before the rise in cardiac enzymes.

Important mimickers of ACS

Myocarditis may present with symptoms similar to ACS as well as positive troponins and ischemic ECG changes. The pattern of enhancement on CMR LGE can be very useful in distinguishing this from MI [21,22]. Enhancement from MI proceeds in a wave-form from endocardium to epicardium and thus always involves the endocardium. This is in contrast

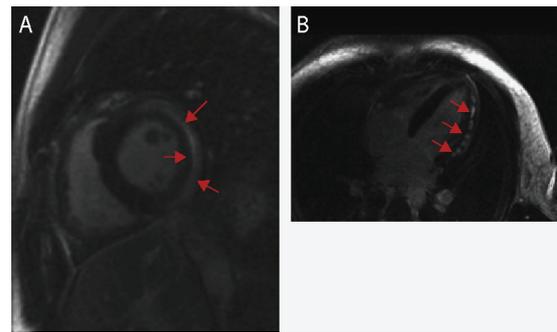


Figure 3. CMR LGE imaging of a patient with acute myocarditis. A, Short-axis view and B, Four-chamber view showing diffuse patchy midmyocardial and epicardial late gadolinium enhancement with sparing of the subendocardium. This epicardial pattern of LGE is not consistent with acute coronary syndrome. First published in Basic et al [23] ©2010 American Heart Association.

to the pattern in myocarditis, which often spares the endocardium and involves the mid-myocardium or epicardium (Figure 3) [23]. Takotsubo cardiomyopathy (apical ballooning syndrome) often presents in an identical fashion to ACS. Cardiac catheterization shows nonobstructive CAD and apical motion abnormalities. The absence of enhancement on CMR LGE can differentiate this entity from apical MI [24,25].

Conclusions

There is growing evidence that CMR may provide incremental improvement in assessment of ACS in some patients. In particular, LGE CMR is regarded as the gold-standard imaging technique for detection of MI and is highly accurate, reproducible, and well validated. LGE also provides unique ability to differentiate ACS from non-coronary syndromes that mimic ACS such as myocarditis. Using multiple CMR techniques (wall-motion analysis, resting perfusion, stress perfusion) in addition to LGE has been shown to increase diagnostic utility for detection of ACS in the ED setting. Preliminary studies have reported using T2-weighted edema imaging for the detection of ischemia in the absence of MI or for the differentiation of acute from chronic MI. However, further technical improvement appears to be necessary in order for T2-weighted edema CMR imaging to perform with sufficient robustness to be used in daily clinical practice.

Clearly the initial diagnostic assessment of possible ACS will continue to be firmly based on clinical evaluation, serial ECGs, and cardiac enzymes. CMR shows promise as an additional tool in this setting. However, additional studies are required to establish the optimum patient groups who may benefit from this approach. The lack of widespread availability of CMR

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equipment and trained operators in the emergency room setting are currently limiting factors to the utility of this technique. Like other imaging modalities such as CT in this setting, CMR will need to demonstrate improved patient outcomes from its use, in terms of reducing costs or enhancing management efficiency, in large randomized studies. However, given its unique capability of characterizing multiple aspects of myocardial physiology and its non-invasiveness, further clinical investigations and technical developments are in progress. ■

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