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TOPIC HIGHLIGHT

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Diagnosis and management of ischemic cardiomyopathy: Role of cardiovascular magnetic resonance imaging

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Abstract

Coronary artery disease (CAD) represents an important cause of mortality. Cardiovascular magnetic resonance (CMR) imaging evolved as an imaging modality that allows the assessment of myocardial function, perfusion, contractile reserve and extent of fibrosis in a single comprehensive exam. This review highlights the role of CMR in the differential diagnosis of acute chest pain by detecting the location of obstructive CAD or necrosis and identifying other conditions like stress cardiomyopathy or myocarditis that can present with acute chest pain. Besides, it underlines the prognostic implication of perfusion abnormalities in the setting of acute chest pain. Furthermore, the review addresses the role of CMR to detect significant CAD in patients with stable CAD. It elucidates the accuracy and clinical utility of CMR with respect to other imaging modalities like single-photon emission computed tomography and positron emission tomography. Besides, the prognostic value of CMR stress testing is discussed. Additionally, it summarizes the available CMR techniques to assess myocardial viability and describes algorithm to identify those patient who might profit from revascularization those who should be treated medically. Finally, future promising imaging techniques that will provide further insights into the fundamental disease processes in ischemic cardiomyopathy are discussed.

Key words: Coronary artery disease; Cardiovascular magnetic resonance imaging; Prognostic value; Stress testing; Viability

Core tip: Coronary artery disease (CAD) represents an important cause of mortality. This review highlights the role of cardiovascular magnetic resonance (CMR) in the differential diagnosis of acute chest pain. It underlines the prognostic implication of perfusion abnormalities in the setting of acute chest pain and addresses the role of CMR to detect significant CAD in patients with stable CAD. Besides, the prognostic value of CMR stress testing is discussed. Additionally, it summarizes the available CMR techniques to assess myocardial viability. This review describes a treatment algorithm and presents new imaging techniques that might give further insights into the fundamental disease processes in ischemic cardiomyopathy.

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INTRODUCTION

Coronary artery disease (CAD) has a high prevalence in industrialized countries[1] and is therefore an important cause of mortality in the Western world[2]. Cardiac magnetic resonance (CMR) imaging offers the unique opportunity to non-invasively detect coronary artery stenoses and has become the gold standard for the assessment of viability. The detection of coronary artery stenoses can be performed using either vasodilator stressors like adenosine to detect myocardial ischemia or inotropic agents such as dobutamine to identify regional wall motion abnormalities. Due to its excellent temporal and spatial resolution, the possibility to assess myocardial perfusion without exposure to ionizing radiation and the independence of an acoustic window, CMR offers plenty advantages over other imaging modalities like stress echocardiography or single-photon emission computed tomography (SPECT).

CMR TESTING IN PATIENTS WITH ACUTE CHEST PAIN

The exclusion of coronary artery stenoses in patients presenting with acute chest pain in the absence of diagnostic electrocardiographic changes or negative cardiac enzymes still remains a challenge. In these low risk patients CMR has proved to be a reliable risk-stratification tool. Kwong *et al*[3] was the first to demonstrate the utility of CMR for triage of patients with acute chest pain in the emergency department. He showed that the combination of CMR rest perfusion and late gadolinium enhancement (LGE) in patients presenting at an emergency department with angina and non-diagnostic electrocardiogram (ECG) had a sensitivity of 100% for non-ST-segment elevation infarction and a sensitivity of 84% sensitivity for acute coronary syndrome (ACS) as well as a specificity of 85% (Figure 1). Besides, CMR proved to be the strongest predictor of ACS and had an independent diagnostic value over clinical parameters including ECG, initial troponin-I , and the thrombolysis in myocardial infarction risk score. In a further study by Ingkanisorn *et al*[4], adenosine stress CMR was performed in 135 patients with chest pain and excluded myocardial infarction who presented at the emergency department. In this setting, adenosine perfusion abnormalities had 100% sensitivity and 93% to predict CAD. Furthermore, none of the patients with a normal adenosine stress examination was diagnosed with significant CAD or suffered from an adverse outcome during a follow-up period of one year. In a retrospective study by Hartlage *et al*[5] using either adenosine or dobutamine stress CMR in 255 patients presenting at the emergency department with acute low-risk chest pain and no prior history of CAD the negative predictive value for the primary endpoint of cardiac death, nonfatal acute myocardial infarction, obstructive CAD on invasive coronary angiography or recurrent chest pain, was 100% and 99%, respectively. Therefore, adenosine and dobutamine stress CMR proved to be reliable modalities to exclude obstructive CAD and a negative stress study provides an excellent intermediate-term prognosis. Besides, in patients with intermediate risk presenting at the emergency department, stress CMR reduced cardiac-related costs of the index visit and over the first year without increasing major cardiac events[6].

In addition, CMR can identify the underlying cause of conditions that present like ACS. In stress cardiomyopathy [Takotsubo cardiomyopathy (CMP), Figure 2], patients present with acute chest pain and/or dyspnea, modest elevation in cardiac troponin level and new ECG abnormalities despite the absence of significant (> 50%) obstructive coronary artery disease or angiographic evidence of acute plaque rupture. In these patients with marked apical or midventricular ballooning the absence of myocarditis or typical ischemic transmural LGE on CMR confirms the diagnosis[7-11]. Myocarditis (Figure 3) is another differential diagnosis in patients with acute chest pain that can be addressed with CMR allowing to visualize the key features of myocarditis: inflammation, hyperemia, edema, necrosis, myocardial dysfunction as well as accompanying pericardial perfusion in a single study[12-16].

CMR STRESS TESTING IN PATIENTS WITH STABLE CAD

The feasibility of stress CMR to detect coronary artery stenosis in patients with known or suspected CAD is well established[17-21]. In a meta-analysis[22] comparing 114 SPECT, 15 positron emission tomography (PET) and 37 CMR myocardial perfusion imaging studies for the detection of angiographically detected coronary artery stenoses ⩾ 50%, all three imaging modalities proved to accurately detect obstructive CAD. Metaregression showed that CMR and PET have a significantly higher diagnostic accuracy than SPECT. In contrast to nuclear techniques, CMR perfusion is not affected by attenuation artifacts, has the highest spatial resolution and is therefore able to even subendocardial perfusion deficits[23]. The sensitivity and specificity to detect CAD ranged between 79%-88% and 81%-91% for dobutamine stress CMR or 67%-94% and 61%-85% for adenosine stress CMR, in meta-analysis[24-26] and a multicenter study[27]. The use of 3.0 T has shown to provide even higher diagnostic accuracy[28,29], however this technique is not widely available, yet and no data from multicenter studies exist so far.

However, CMR stress testing is not only able to detect CAD but also offers prognostic information. A study performing adenosine stress CMR using 1.5 and 3.0 T in 815 consecutive patients with stable CAD could show that the addition of inducible ischemia reclassified patient risk beyond standard clinical variables and improved discrimination of major adverse cardiac events[30]. These results were confirmed by another single center study[31] enrolling 1229 patients with stable angina. Recent meta-analysis[32,33] also proved that a negative adenosine or dobutamine stress CMR had a high negative predictive

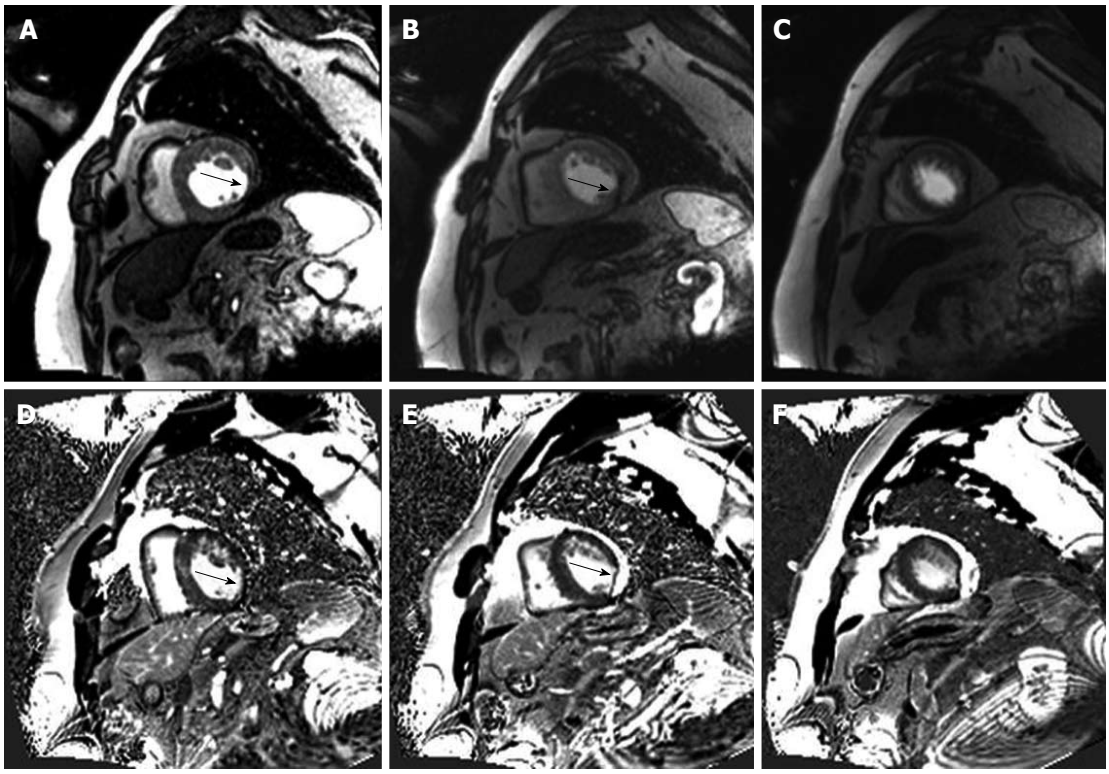

Figure 1 Patient presenting with an subacute non-ST-segment elevation infarction. Cardiovascular magnetic resonance (CMR) images of a 54-year-old man who presented with typical chest pain. Troponin was elevated to 1.9 μg/L. CMR rest perfusion (A-C) shows a subendocardial perfusion deficit inferolateral and lateral on the basal (A) and midventricular (B) short axis slice. The black arrow highlights the subendocardial perfusion deficit. Late gadolinium enhancement (D-F) of the representative short axis also revealed a hyperenhancement inferolateral and lateral (black arrow) indicative of a subacute myocardial infarction.

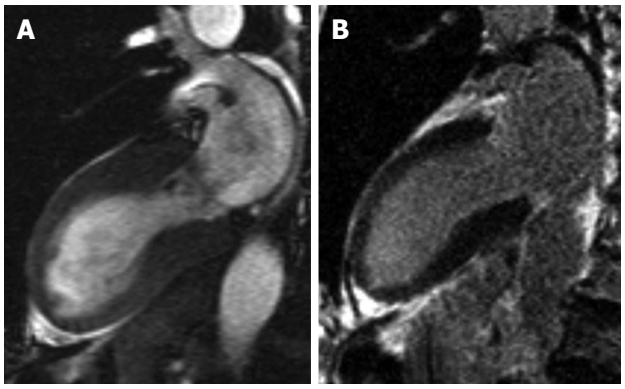

Figure 2 Patient with takotsubo cardiomyopathy. Example of a 45-year-old woman presenting with acute chest pain, anterior ST-segment elevation on electrocardiogram. Cardiovascular magnetic resonance cine images of showed a typical apical ballonning of the left ventricle (A). Late gadolinium enhancement images (B) could rule out myocardial infarction and did not show any fibrosis.

value for adverse cardiac events. Besides they showed that inducible perfusion defects as well as wall motion abnormalities had a comparable ability to identify low-risk patients.

Therefore, in the actual guidelines for the management of patients with stable CAD, stress imaging using either echocardiography, CMR or SPECT has become an integral part in the work-up of patients with a pretest probability (PTP) of CAD between 15%-65% and a left ventricular function (LVEF) ⩾ 50% as well as in patients with a PTP of 66%-85% or a LVEF < 50%[34]. An imaging study should also be considered in symptomatic patients with prior revascularization [percutaneous coronary intervention (PCI) or coronary artery bypass graft][34]. In patients with coronary artery stenoses of angiographic intermediate severity causing a perfusion defect on CMR it could be shown that these patients are at higher risk for major adverse cardiac events (MACE) within the following 18 mo after the procedure, whereas deferring PCI in patients with intermediate coronary artery stenoses and no evidence of ischemia seemed to be save[18]. Thus, current guidelines suggest to consider an imaging stress test to assess the functional severity of intermediate lesions on coronary arteriography[34]. The decision to proceed to invasive angiography is not only based on symptoms and risk factors but also on the extent and severity of ischemia[34] (Figure 4).

GENDER-BASED PROGNOSTIC VALUE OF CMR STRESS TESTING

In women, CAD develops 7 to 10 years later than in men. However, it is still the major cause of death in women[35]. Moreover, the risk of heart disease in women is often underestimated. Due to the underrecognition of heart disease and differences in clinical presentation in women, treatment strategies are less straightforward in women. In a study by Coelho-Filho *et al*[36] performing adenosine

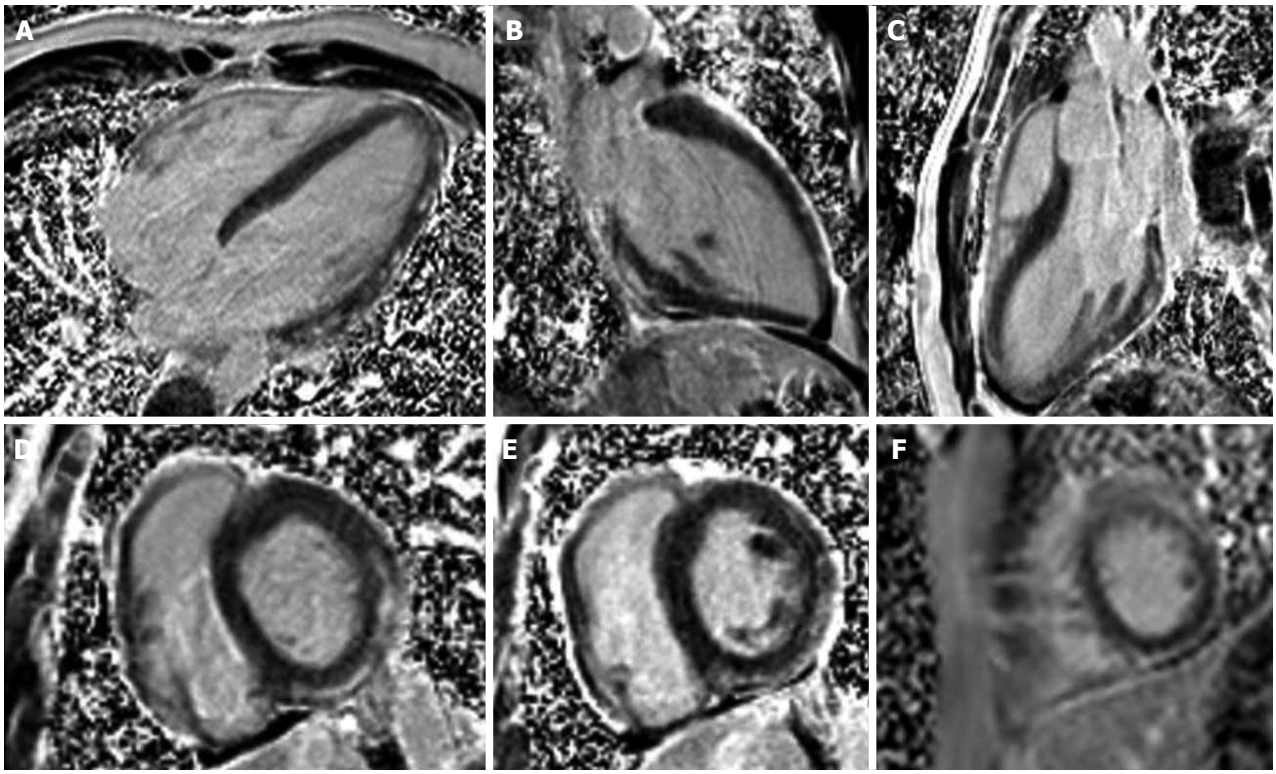

Figure 3 Patient with acute chest pain due to myocarditis. A 16-year-old boy who presented with acute chest pain and palpitations 1 wk after a gastrointestinal infection. Troponin was 2.4 μg/L. Late gadolinium enhancement cardiovascular magnetic resonance showed a patchy midmyocardial and epicardial hyperenhancement of the lateral, anterior and inferior wall. These findings are typical of acute myocarditis.

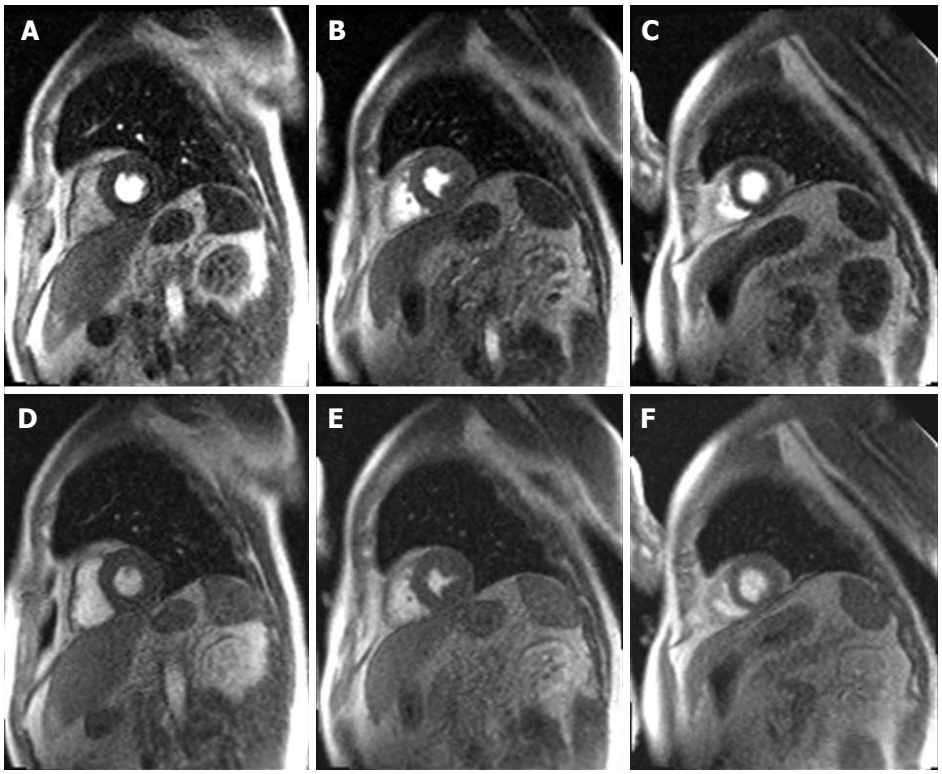

Figure 4 Adenosine stress perfusion imaging. A 63-year-old patient who presented with stable angina for more than 6 mo. Adenosine stress (A-C) *vs* rest perfusion (D-F) revealed myocardial ischemia only during stress perfusion of the basal inferior and lateral as well as midventriucular inferoseptal wall. The patient did not show a late gadolinium enhancement. Coronary angiography showed a 60% stenosis of the medial right coronary artery that was treated with percutaneous coronary intervention and stent implantation due to the detected ischemia.

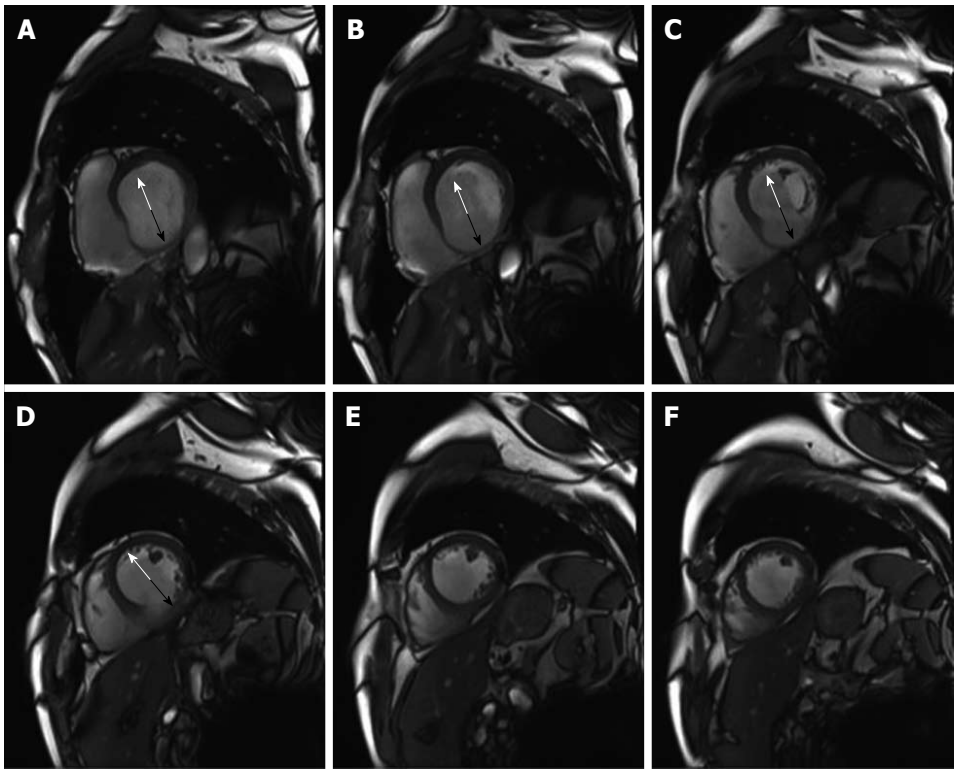

Figure 5 End diastolic wall thickness. Representative end diastolic short axis images from basal (A) to apical (F) of a patient with previous inferior myocardial infarction. The anterior, septal and lateral region (white arrow, A-D) show a preserved end diastolic wall thickness (EDWT) > 6 mm suggesting viable myocardium, whereas EDWT of the inferior wall (black arrow, A-D) is ≤ 6 mm indicating myocardial scarring.

stress imaging in 237 men and 168 women referred for ischemia assessment, myocardial ischemia was the strongest predictor of MACE in both sexes. In a large study[37] using a combined adenosine and dobutamine stress CMR protocol in 471 men and 208 women, Jahnke *et al*[37] could show that CMR perfusion and wall motion abnormalities are equally suited for cardiac risk stratification in both sexes. In women, a negative stress CMR resulted in very low event rates during the following 4 years whereas, the event rates in men increased after the second year. These results might suggest that it is feasible to prolong the generally proposed 2-year warranty period of a negative CMR stress test to 4 years in women.

ROLE OF CMR IN THE DETECTION OF MYOCARDIAL VIABILITY IN ISCHEMIC HEART DISEASE

In clinical practice myocardial viability is characterized by functional recovery 6 wk to 6 mo after successful revascularization. CMR offers 3 methods to assess myocardial viability: end-diastolic wall thickness, low dose dobutamin stress CMR and LGE.

The easiest technique is to evaluate the maximal end-diastolic wall thickness (EDWT) because it only requires to determine the maximal EDWT on the cine images at rest. In the course of acute myocardial infarction structural changes are associated with myocardial thinning in the core zone of the infarction. In a study comparing EDWT on resting CMR and[18] fluorodeoxyglocose positron emission tomography (FDG PET) in 35 patients with myocardial infarction, Baer *et al*[38] could prove that myocardial segments with an EDWT ≥ 5.5 mm showed a normal FDG uptake, whereas myocardial segments with an EDWT < 5.5 mm revealed a significantly FDG uptake. Several studies using either a cut-off of 5.5 mm[39,40] or 6 mm[41,42] in patients with chronic ischemic myocardial dysfunction could show that myocardial segments with wall thinning below the cut-off have a low likelihood of functional recovery after revascularization.

Overall these studies[39-42] proved that EDWT has a good sensitivity and negative predictive value but only reasonable positive predictive value and poor specificity to predict functional recovery.

Figure 5 shows an example of a patient with a previous inferior myocardial infarction with severe thinning of the inferior myocardial wall segments.

Low dose dobutamine (≤ 10 μg/kg per minute) stress CMR is another technique used to evaluate myocardial viability. At low doses, dobutamine supports coronary vasodilatation and increases myocardial contractility[43]. Viable myocardium is distinguished by the identification of improved contractility under low dose dobutamine infusion. Several studies[39-41,44-46] proved that a CMR-derived systolic wall thickening > 2 mm during low dose dobutamine stress is able to identify myocardial segments with functional recovery after revascularization. Accord-

Transmural extent of hyper-enhancement (%)	0	1-25	26-50	51-75	> 75
Improved contractility after revascularization (%)	78	60	42	10	< 2

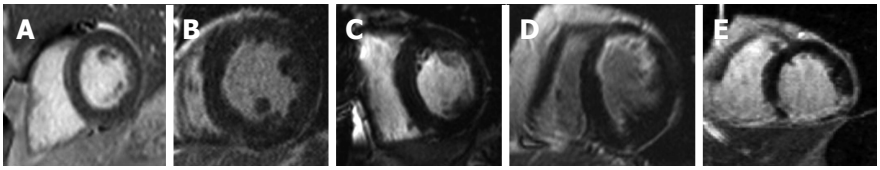

Figure 6 Late gadolinium enhancement imaging. Representative late gadolinium enhancement images of patients without scar (A), with a transmural extent of hyperenhancement of 1%-15% (B), 26%-50% (C), 51%-75% (D) and more than 75% (E) and the respective percentage of improved contractility according the study by Kim *et al*[51].

ing to these studies[39-41,44-46], the major strength of low dose dobutamine stress CMR is its high overall accuracy, specificity and positive predictive value.

LGE that was first applied by Kim *et al*[47] has now become the gold standard for the evaluation of myocardial viability in ischemic heart disease. In nonviable tissue, the extracellular contrast agent spreads in a larger volume of distribution which results in delayed washout kinetics[48]. Moreover, late enhancement imaging sequences suppress the signal derived from remote myocardium resulting in high image contrast. Hence, this technique allows the detection of even very small myocardial infarctions ($\geqslant$ 0.7 g of myocardial mass)[49]. In a meta-analysis by Romero *et al*[50] LGE with a cut-off of < 50% transmurality of scar tissue had a high sensitivity and a high negative predictive value to predict functional recovery. In patients with chronic ischemic heart disease the identification of viable myocardium is important to predict improvement of LVEF and survival after revascularization. In these patients the functional recovery was also linked to the transmural extent of scar[51]. Kim *et al*[51] could show that in segments without scar the functional recovery was 78% whereas in segments with a scar transmurality of more than 75%, the likelihood of contractility improvement after revascularization was less than 2% (Figure 6). As illustrated in Figure 6, the ability to predict functional recovery in segments with an intermediate scar transmurality between 1% and 75% ranged between 60% and 10%. In these patients with an intermediate scar transmurality an additional low-dose dobutamine stress examination helps to identify segments that show a contractile reserve. A combined approach of LGE enhancement imaging and low-dose dobutamin stress imaging proved to be the optimal approach to predict recovery after revascularization[44]. Therefore, in patients with wall motion abnormalities at rest the following algorithm as described by Nagel *et al*[52] should be applied. LGE imaging should be used as first line imaging modality to identify patients without a scar who should undergo revascularization. Patients with more than 50% LGE transmurality should be treated medically. In patients with less than 50% LGE transmurality an additional low dose dobutamine stress CMR should be performed to detect patients with an improved contractility who are likely to benefit from revascularization. Whereas patients with less than 50% LGE transmurality but without assessment of contractile reserve should be treated medically. This algorithm indicates that in patients without evidence of LGE or with a LGE > 50% transmurality, LGE imaging alone is sufficient. In case that an additional low dose dobutamin stress exam is required CMR allows to assess myocardial contractile reserve and LGE in a single comprehensive exam.

In patients with acute myocardial infarction and wall motion abnormalities CMR, Beek *et al*[53] could also proof that LGE CMR is able to detect hibernating myocardium that is able to functionally recover. Further studies[54,55] demonstrated that the transmural extent of delayed gadolinium enhancement correlates with the ability of functional improvement after acute myocardial infarction. Therefore, the distinction between reversible and irreversible dysfunctional myocardium in the acute setting after infarction also has a prognostic implication.

PROGNOSTIC ROLE OF LGE IN ISCHEMIC HEART DISEASE

Moreover, myocardial scar has been demonstrated to be the cause of malignant reentrant ventricular arrhythmias causing sudden cardiac death in patients after myocardial infarction[56]. In patients with ischemic cardiamyopathy, Kwon *et al*[57] revealed that a greater extent of myocardial scar was associated with a significantly increased mortality or the need for cardiac transplantation, improving further risk stratification. In patients undergoing ICD implantation with CAD, the extent of myocardial scarring visualized by LGE CMR was significantly associated with appropriate device therapy and identified a subgroup of CAD patients with an increased risk of life-threatening ventricular arrhythmias[58].

FUTURE INDICATIONS FOR CMR IN PATIENTS WITH CAD

Novel methods like precontrast T_1 maps enable the detection of acute and chronic myocardial infarction[59] and might represent a further field to establish the use of CMR as a key to tissue characterization. In a combined clinical protocol native T1 mapping was suggested to reveal area at risk in ACS[60,61].

Extracellular volume (ECV) maps as a CMR marker for myocardial fibrosis can be generated if pre and post contrast T_1 images are registered[62]. In contrast to LGE

CMR, ECV is also able to visualize very early fibrotic changes[63].

In the future, T1 mapping and ECV may provide more profound insights into fundamental disease processes of the myocardium. Both techniques might affect clinical decision making, but to date are not yet part of the routine work-up. Besides, the reproducibility of the results still needs to be shown in multi-centre studies[64].

CONCLUSION

CMR is a non invasive imaging for the workup of patients with known or suspected CAD. It allows the detection of significant coronary stenoses in patients with acute and chronic chest pain. Moreover, it offers the unique opportunity to detect myocardial ischemia and viability or wall motion abnormalities and fibrosis in one examination. Novel techniques like T1 mapping and ECV will further expand the scope of application in the future.

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