
Cardiac MRI: A preferred method for assessing myocardial ischemia and infarct burden

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During the past 20 years, cardiac MRI (CMR) has earned growing acceptance as a modality for assessing myocardial ischemia, viability, and function. Accurately assessing ischemic risk and identifying hemodynamically significant coronary artery disease amenable to revascularization can be challenging tasks with non-invasive imaging modalities. Here, we aim to discuss how cardiac MRI achieves both with a single study without exposure to ionizing radiation.

Indications for CMR for ischemic heart disease (IHD)

Table 1 lists the appropriate indications for the use of CMR as reported in

the 2006 ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging.

According to the 2012 American Heart Association guidelines,¹ stress CMR can be useful for patients for initial diagnosis with an intermediate-to-high pretest probability of obstructive IHD who have an uninterpretable ECG and at least moderate physical functioning or no disabling comorbidity (class II Level of Evidence: B). Stress CMR is at the same level of recommendations as pharmacologic stress echocardiography or SPECT. In particular, CMR is recommended as the initial test for IHD diagnosis in patients with resting ECG abnormalities which prevent accurate interpretation of ECG changes during stress (IB), in patients with a non-conclusive exercise ECG (IB), in patients with known IHD and deterioration in symptoms if the site and extent of ischemia would influence clinical decision making (IB), and for re-assessment in patients with stable IHD in the presence of recur-

rent or new symptoms once instability has been ruled out (IC).¹

Stress imaging

Principle of stress imaging

Epicardial arteries and resistance arterioles comprise the coronary blood supply. In the absence of epicardial coronary stenosis, an increased oxygen myocardial demand can be achieved by an increase in coronary flow due to arterial vasodilatation, commonly referred to as “coronary reserve,” which can increase up to four times the basal blood flow. This is shown in Figure 1. In the presence of an epicardial stenosis, as the coronaries are already dilated to maintain constant coronary flow, it is unable to augment further in the event of increased myocardial demand.² The resulting oxygen demand and supply mismatch leads to myocardial ischemia at rest if blood flow is insufficient at basal conditions and ischemia on stress if an increased oxygen demand exceeds oxygen supply.

Myocardial ischemia involves a typical sequence of events termed the

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Table 1. Appropriate indications for CMR

Type of CMR Test	Appropriate Indication
Stress (dobutamine or adenosine)	Indeterminate pre-test probability of CAD Uninterpretable ECG or unable to exercise Exercise is preferred if the patient is able Prior coronary angiography (catheterization or CT) Stenosis of unclear significance
CMR for Structure/morphology	Evaluation of LV function post-MI or in heart failure patients Positive cardiac enzymes without obstructive atherosclerosis on angiography
Evaluation of myocardial scar	To determine the location and extent of myocardial necrosis including no-reflow regions Post-MI To determine viability prior to revascularization Establish likelihood of recovery of function with revascularization (PCI or CABG) or medical therapy Indeterminate viability assessment by SPECT or dobutamine echo

“ischemic cascade,” shown in Figure 2. The cascade begins with metabolic alterations, followed first by diastolic then by systolic dysfunction. This leads to electrocardiographic changes and subsequent precordial pain.³

Myocardial ischemia can be identified by metabolic alterations detected with PET imaging, perfusion defect reversibility detected by CMR with adenosine/Lexisan, dipyridamole or dobutamine, regional wall motion abnormalities seen by echocardiography and CMR, or ECG changes detected by standard stress test treadmill.

Stress CMR agents

The most commonly used pharmacological agents for stress testing include: adenosine infusion (or regadenoson, which is administered as a bolus), dipyridamole, and dobutamine.

Coronary vasodilators—Adenosine, regadenosine, and dipyrimadole are coronary vasodilators used for assessment of myocardial perfusion with CMR. They act via different mechanisms in the adenosine pathway, with adenosine directly binding to multiple types of adenosine receptors, regadenoson selectively binding to A₂ receptors, and dipyrimidole blocking the cellular re-uptake of adenosine, to result in coronary vasodilatation and subsequent increase in coronary flow. In the presence of a significant coronary stenosis, these agents induce a relative hypoperfusion in the territory of the stenosis by a steal phenomenon, typically without inducing true ischemia. Contraindications to adenosine include second- or third-degree AV block, severe bronchospasm, or use of dipyridamole (which blocks the cellular uptake of adenosine, increasing the concentration of adenosine at its receptors).

Dobutamine—Dobutamine is a sympathomimetic drug with a short half-life (2 min) that mainly acts on β_1 cardiac receptors resulting in positive inotropic and chronotropic effects. It has a lesser mechanism of action on the β_2 receptors with slight vasodilatory effect.⁴ Beta blockers are held 24 to 48 hours

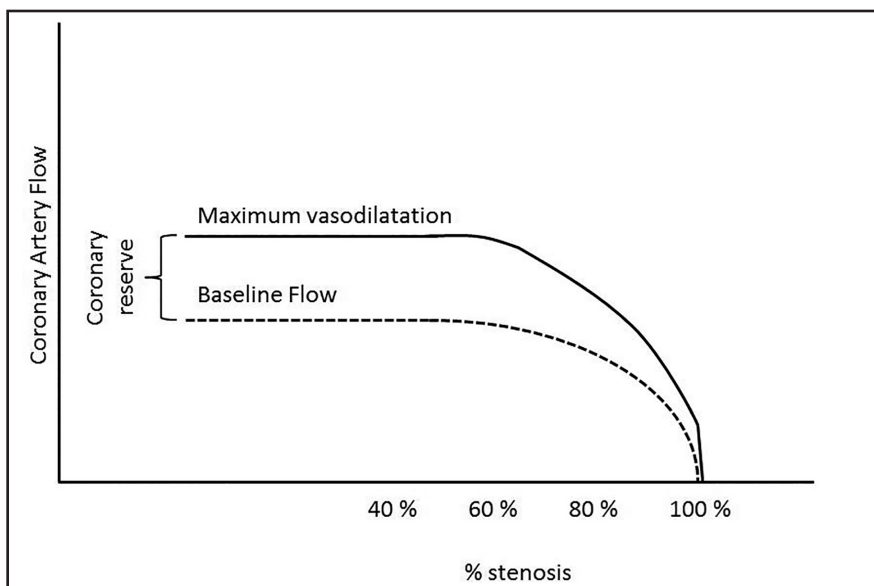


FIGURE 1. Coronary blood flow as determined by % stenosis. There is a progressive reduction in coronary reserve with increasing coronary artery stenosis.

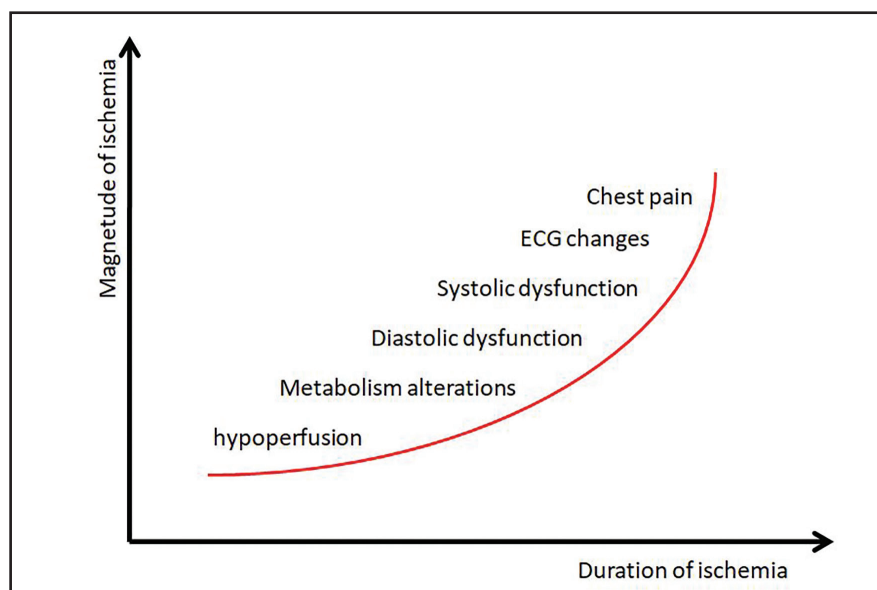


FIGURE 2. The ischemic cascade. Myocardial ischemia triggers a cascade of events.

before the test as they counteract the effects of dobutamine.

Stress CMR technique

Continuous medical surveillance (blood pressure, ECG and SaO₂ monitoring) is required during the performance of the examination.

Coronary vasodilators—adenosine, dipyridamole—The following is a commonly used protocol for stress-perfusion CMR, previously described by Klem et al. Standard balanced steady state free precession (bSSFP) breath-hold cine sequences at rest in the standard views (apical, mid, and basal short-axis views; 4, 2, and 3 chamber views) are first acquired. Stress is induced with an adenosine infusion (140 µg/kg/min; total duration: 6 mins) or after dipyridamole slow injection (0.56-0.84 mg/kg). Immediately after the intravenous injection of a contrast agent (Gadolinium: 0.1 mmol/kg), MR first-pass perfusion scanning on stress is performed using identical views and a T1 weighted sequence such as magnetization-prepared fast gradient-recalled echo (GRE) with non-selective saturation recovery preparation pulse or a balanced steady state free precession (bSSFP) sequence. Generally 3 views (apical, mid and basal short axis) can be acquired every heartbeat, with 6 views

every 2 heart beats, allowing a dynamic study of the perfusion.

Standard CMR cine sequences are then performed to evaluate for wall motion abnormality. LGE sequences are then performed 10-15 mins following the initial gadolinium administration.

Stress-perfusion images may be obtained prior to rest, given their relative importance to the study and fact that rest imaging is typically unnecessary following a normal stress evaluation. If stress CMR is performed initially, adenosine is advantageous given its short half-life, as no reversal agent is necessary. With both regadenoson and dipyridamole, reversal with aminophylline may be performed.

Dobutamine—The standard protocol begins with the acquisition of standard CINE SSFP sequences (apical, mid and basal short axis and 2, 3, 4 chamber long axis view) at rest. Dobutamine is then infused intravenously and the dosage is increased every 3 mins (10, 20, 30, 40, and 50 mg/kg per minute). A low level stress (5-10 µg/kg/minute of dobutamine) is used to assess viability whereas higher dose (up to 50 µg/kg/min) allows one to reach the theoretical maximal frequency to detect ischemia at stress. The infusion is stopped when 85% of the maximal heart rate is achieved, new or worsening wall motion

abnormality develops in 1 or greater LV segments, BP increases to greater than 240/20mmHg or SBP drops >40mmHg, or if the patient develops adverse symptoms or persistent arrhythmias. At every 3 min stage, cine sequences with conventional views are repeated. Atropine (up to 2 mg) can be utilized to augment the heart rate response, although this is contraindicated in patients with narrow angle glaucoma, myasthenia gravis, obstructive uropathy, and obstructive gastrointestinal disorders. Contraindications to dobutamine include severe hypertension (>=220/120mmHg), unstable angina, severe aortic stenosis (gradient >50mmHg or AVA <1cm²), uncontrolled atrial fibrillation, HCM, and CHF.

Perfusion imaging may be performed with dobutamine; however, it is complicated by the resultant heart rate increase not seen with adenosine and dipyridamole.

Perfusion CMR

In clinical practice, myocardial perfusion is assessed with CMR by evaluation of contrast enhancement during the first pass of a contrast agent bolus through the cardiac chambers and the myocardium using gadolinium and the stress agent (adenosine/Regadenoson, dipyridamole, or dobutamine).

Perfusion CMR images are analyzed using the AHA 17 segment model (shown in Figure 3). The presence of segmental myocardial hypoenhancement reflects a relative hypoperfusion in comparison to other territories. Examples of first pass CMR perfusion images are shown in Figure 4. Short axis cine sequences at rest and stress are shown in Figure 5.

Interpretation of perfusion sequences can be limited by the presence of Gibbs ringing artifact at the blood-myocardial interface (mimicking a subendocardial hypoenhancement by creating a dark rim artifact due to sub-pixel shifting). However, the artifact is transient and typically occurs at the arrival of contrast in the left ventricular cavity, before its arrival into the myocardium, and disappears after 8 to 10 frames.⁵

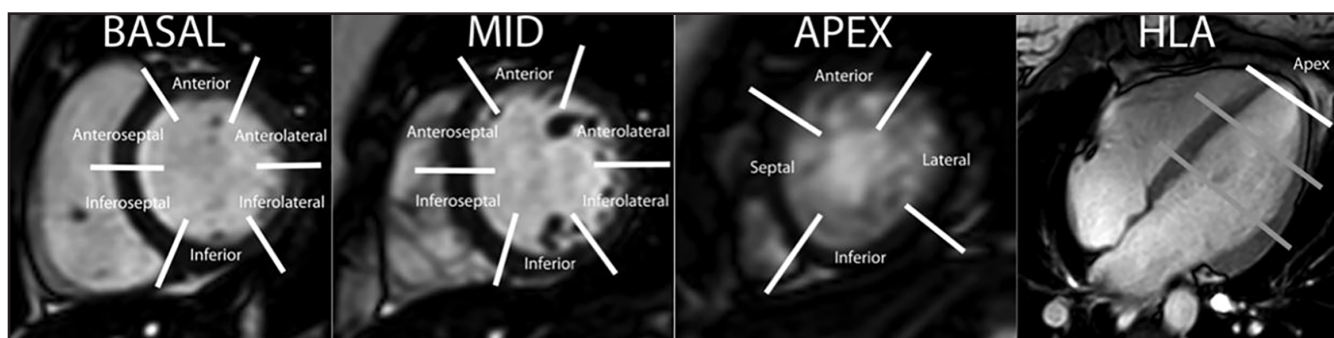


FIGURE 3. The myocardial 17 segment AHA model described using cardiac MR CINE images. Short axis cine images are shown at the cardiac base, mid-ventricular level and at the apex, followed by a horizontal long axis cine image.

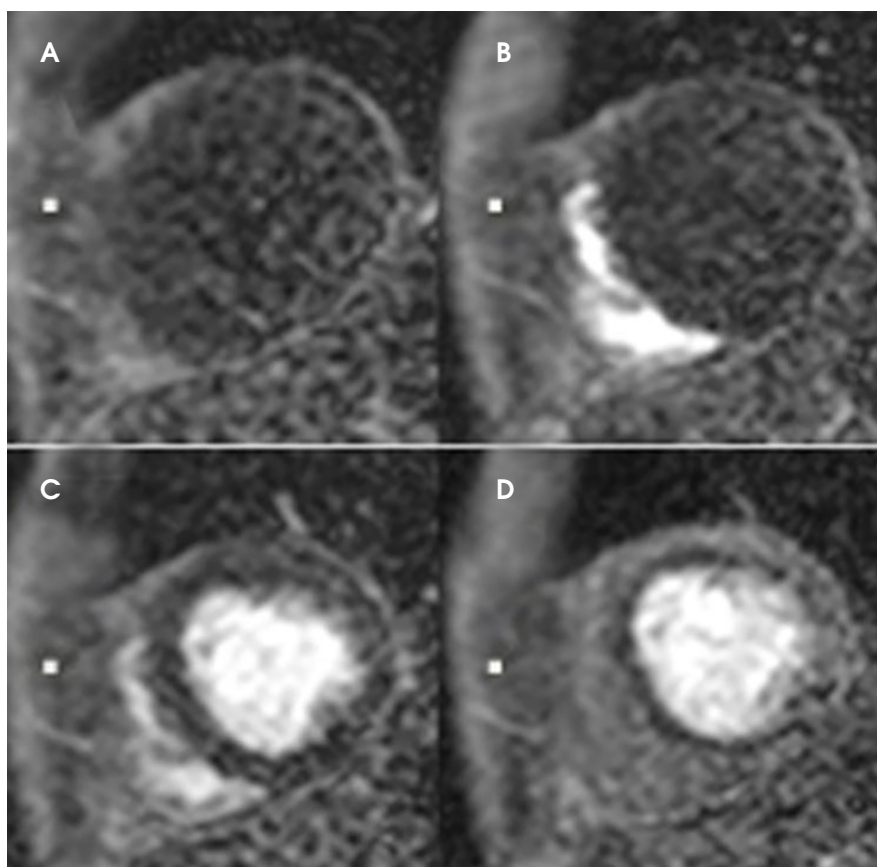


FIGURE 4. First pass stress CMR perfusion images (short axis) with dipyridamole. (A) Pre-contrast image. (B) Gadolinium opacification of the right ventricle. (C) Gadolinium opacification of the left ventricle. (D) First pass perfusion image of the left ventricle demonstrating diffuse subendocardial hypoperfusion in a patient with triple vessel coronary disease.

Abnormalities in wall motion may be seen using either pharmacologic method; however, dobutamine has demonstrated greater sensitivity than adenosine.⁶ Myocardial contraction is analyzed using the AHA 17 segment model as in perfusion CMR.⁷

On dobutamine stress CMR, viability is defined by improvement of wall motion contractility in at least 2 contiguous

segments at low dose (5 or 10 µg/kg per min). Ischemia is defined by an induction of wall motion abnormality in at least 2 contiguous segments during stress or if a biphasic response (improvement at low dose followed by decreasing contractility at higher dose) was demonstrated in areas with resting wall motion abnormalities. The test is negative if >85% of the theoretical maximal heart rate is reached

with no induced wall motion abnormality. The test is non diagnostic if >85% of the theoretical maximal heart rate is not reached and no induced wall motion abnormalities are seen. The test is positive if the presence of ischemia is detected. Wall motion abnormalities detected by adenosine/dipyridamole typically indicate severe stenoses and have been seen to be predictive of subsequent clinical events.⁸

Late gadolinium enhancement (LGE)

LGE is a well-documented technique that allows detection of myocardial scar with gadolinium, which shortens the T1 relaxation time. The addition of this sequence to CINE SSFP and perfusion CMR provides valuable information regarding myocardial viability as well as expected recovery following revascularization.

After the administration of the extracellular contrast agent (gadolinium chelates are typically used), infarcted or fibrotic tissue demonstrates increased signal on T1-weighted sequences due to reduced clearance and increased volume of distribution of the contrast agent in these regions.⁹ Ten to 30 minutes after intravenous injection of gadolinium (0.10-0.20 mmol/kg), gradient-echo inversion recovery (FLASH/PSIR) sequences are performed. The inversion time is set with a Look-Locker sequence at the point of optimal myocardial nulling, allowing a better quantification of the infarcted bright zone.

The infarct size defined by LGE hyperenhancement is a well-established strong predictor of outcomes after myocardial

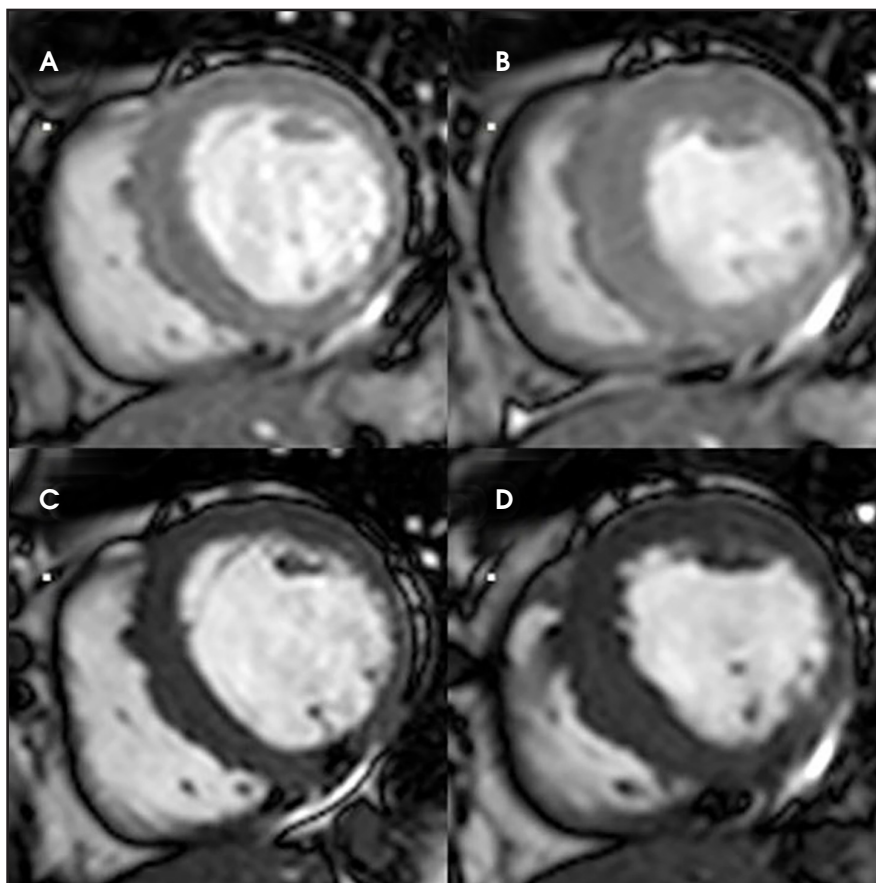


FIGURE 5. Stress CMR. Short axis cine sequences are acquired with the same view at rest (top) and at stress (bottom). Images demonstrate a fixed lack of motion and myocardial thickening in the lateral wall as evidenced in end-systole (at rest (B) and at stress (D)) and at end-diastole [at rest (A) and at stress (C)].

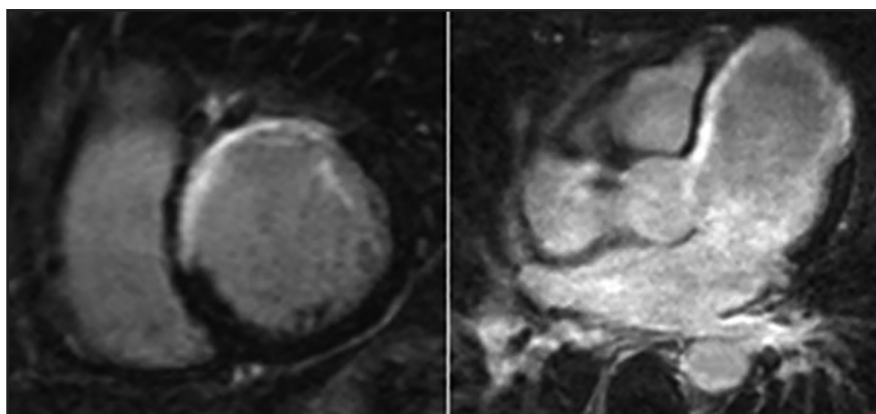


FIGURE 6. Patterns of late gadolinium enhancement (LGE) with high-risk features showing enhancement of greater than 50% of the myocardial thickness. The short axis (left) and horizontal long axis (right) images demonstrate enhancement of greater than 50% of the myocardial thickness in the anterior through septal mid and basal walls in an LAD distribution. The transmural extent of enhancement is a prognostic factor of myocardial functional recovery after revascularization.

infarction (MI).¹⁰ Examples are shown in Figure 6. The transmural extent of hyperenhancement (<25%, 25-50%, 50-75%, >75%) predicts the functional

improvement of the myocardium.¹¹ In clinical practice, 50% transmural extent of LGE is considered as a reasonable and practical cut-off to predict functional

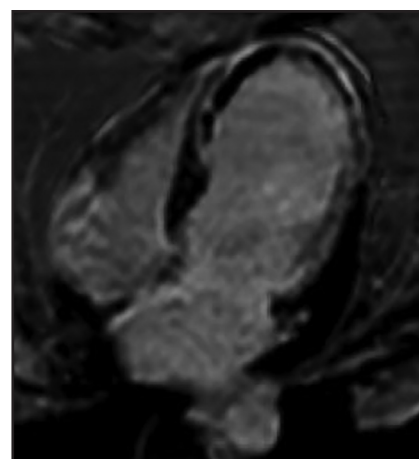


FIGURE 7. Patterns of late gadolinium enhancement (LGE) with microvascular obstruction. There is a large area of microvascular obstruction as evidenced by sub-endocardial low signal with overlying myocardial enhancement in an LAD distribution.

recovery after revascularization.¹² LGE also detects microvascular obstruction (MVO) after acute MI, which is associated with poor clinical outcomes.¹³ MVO appears as an area of low signal intensity surrounded by enhancement and is described in Figure 7. After an acute MI, LGE is useful to assess size, extension, transmural extent of the infarcted zone, and the presence of MVO. In case of a chronic MI, the sequence can assess viability for possible revascularization. This sequence is also useful for distinguishing between ischemic cardiomyopathy with the presence of segmental, subendocardial LGE or transmural LGE from a non-ischemic process, such as with myocarditis or Takotsubo cardiomyopathy in patients presenting with acute chest pain and elevated cardiac enzymes.¹⁴ Figure 8 describes the zones of delayed enhancement seen in an area at risk.

CMR vs PET and SPECT

Invasive coronary angiography is considered the gold standard for determining presence of coronary artery stenosis. When compared to coronary angiography, the diagnostic sensitivity and specificity of dobutamine cine-CMR are 83% and 86%, respectively.¹⁵ Adenosine stress perfusion CMR has

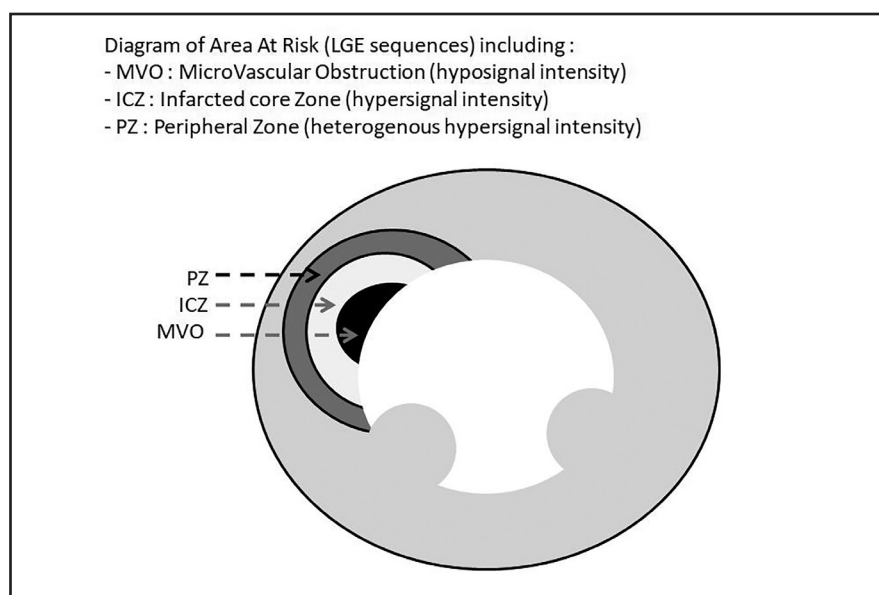


FIGURE 8. Area At Risk. Delayed enhancement zones are shown. Infarct core zone (ICZ), peripheral zone (PZ), area at risk (AAR), and transmural myocardial infarction with microvascular obstruction (MVO) are shown. Reproduced with permission from the Radiological Society of North America (RSNA).

Table 2. Contraindications for various components of a cardiac MRI

Dipyridamole	Dobutamine	Gadolinium	MRI
<ul style="list-style-type: none"> • Asthma • High degree atrio-ventricular blocks • Recent stroke (< 1 month) • Bilateral carotid stenosis, arterial hypotension 	<ul style="list-style-type: none"> • Unstable angina or recent MI (<1 week) • Severe aortic stenosis • Hypertrophic obstructive cardiomyopathy • Recent history of life threatening arrhythmia • Uncontrolled hypertension 	<ul style="list-style-type: none"> • Severe renal dysfunction 	<ul style="list-style-type: none"> • Claustrophobia • Pregnancy • Non-MRI-compatible metallic objects (nerve stimulators or cochlear implants)

a better sensitivity and specificity than with dipyridamole (90% and 81% versus 86% and 77%).¹⁶ Perfusion CMR has superior sensitivity and inferior specificity in comparison to SPECT.¹⁷ The diagnostic performance of CMR is similar to that of PET.¹⁸

Functional significance of coronary artery stenosis is best approximated by invasive pressure wire-derived fractional flow reserve (FFR). With FFR as reference, the sensitivity and specificity of adenosine stress CMR were 91% and 94%.¹⁹

Cardiac stress perfusion MRI has higher spatial resolution (2 mm) compared with SPECT (10 mm) and PET (5 mm), allowing greater sensitivity for detecting ischemic defects. In addition,

there are no attenuation artifacts with CMR, conferring it a higher sensitivity in detecting diffuse balanced ischemia when compared to SPECT.²⁰

CMR vs dobutamine echocardiography

Using invasive coronary angiography as a reference, dobutamine stress CMR has been reported to have higher sensitivity and specificity compared to dobutamine echocardiography (86.2% and 85.7% vs 74.3% and 69.8%).²¹ A more recent meta-analysis further supported this relationship with a sensitivity of 89% with CMR compared to 84% with stress echocardiography for excluding hemodynamically significant CAD determined by FFR.²²

Feasibility and safety

The safety of dobutamine CMR is comparable to dobutamine echocardiography with about 1 severe adverse event over 1000 scans.²³ Perfusion stress MRI also has a good safety profile and greater feasibility than dobutamine stress MR, at approximately 100%. Excluding patients with contraindications to cardiac MRI, the main limitations to stress CMR include difficulty obtaining an acceptable ECG signal and patient claustrophobia.

Contraindications.

Contraindications are shown in Table 2.

Future development

Characterization of infarcted myocardial tissue—Area at risk

After an acute MI, infarcted myocardium can be better characterized by distinguishing between the microvascular obstruction zone, the infarction core necrosis, the peripheral infarction zone, and the ischemic zone with delineation of the myocyte area at risk.²⁴

T2 relaxation time reflects the myocardial water content and has been shown to regions of edema in infarcted tissue.²⁵ The area at risk, corresponding to myocyte edema, shows high signal intensity on T2-weighted black blood with fat saturation sequences but no LGE on delayed-enhancement images. The infarcted core necrosis also shows increased signal on T2 weighted images, although there is LGE on delayed-enhancement images. The LGE zone can be divided into a homogeneously hyper-enhancing core reflecting non-viable myocardium surrounded by a rim of heterogeneous hyper-enhancement called the peripheral zone.²⁴ T2 mapping can reduce the artifacts and loss of contrast seen with T2 weighted images through a quantitative method; however, it may underestimate the true area at risk.²⁶ Precontrast (native) and postcontrast T1 mapping can be helpful in detecting interstitial edema in the setting of acute myocardial infarction as well as extracellular volume expansion with chronic myocardial infarction.^{27, 28}

CMR angiography

Although coronary MR angiography has made considerable improvements during the last two decades, it is still not widely applied per current guidelines.^{14,29} With the development of newer techniques (high-field strength, 32-channel cardiac coils, higher parallel imaging factors, and free breathing respiratory-gated sequences), coronary MR angiography approaches the diagnostic performance of 64-section CT.³⁰ Moreover, unlike CT, MRA allows the assessment of the coronary lumen in a segment with heavily calcified plaque. There are a number of applications under investigation, including use of T1-weighted 3D black blood MR sequences to characterize coronary atherosclerotic plaque.³¹

Conclusion

CMR is a safe and proven modality for detecting ischemic heart disease. Within a single study, CMR is able to assess rest and stress regional contraction, and localize and evaluate regions of myocardial ischemia and viability, of importance given the prognostic impact for the patient. With performance that is comparable to PET/SPECT and at times favorable compared to stress echocardiography, it is now an essential tool for diagnosing ischemia and for determining the likelihood of success following myocardial revascularization.

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