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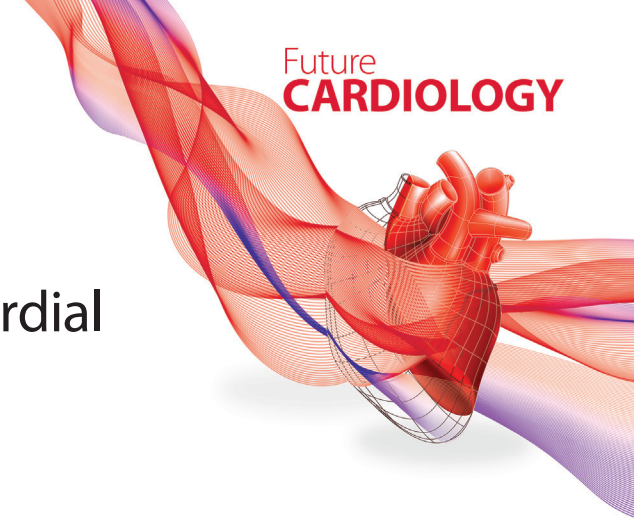

Cardiac MRI assessment of myocardial perfusion

Yasmin S Hamirani[1] & Christopher M Kramer*[,1,2]

ABSTRACT: Coronary artery disease is the most common cause of mortality and morbidity around the globe. Assessment of myocardial perfusion to diagnose ischemia is commonly performed in symptomatic patients prior to referral for cardiac catheterization. Among other noninvasive imaging modalities, cardiac MRI (CMR) is emerging as a highly sensitive and specific test for myocardial ischemia and infarction. Resting perfusion on CMR is used to evaluate for microvascular obstruction, which is shown to predict adverse left ventricular remodeling and cardiac events after acute myocardial infarction. This article summarizes the current understanding of CMR perfusion.

KEYWORDS

• 3D perfusion • cardiac MRI • fractional flow reserve • microvascular obstruction • myocardial perfusion • quantitative perfusion • rest • stress

Background

Despite significant improvement in the diagnostic and treatment strategies for coronary artery disease (CAD), it remains the leading cause of morbidity and mortality around the world across both genders. Significant stenosis of the coronary artery can lead to myocardial ischemia, which can be addressed medically or via invasive coronary intervention or surgery. Management is dependent upon the patient's symptoms and extent of myocardial ischemia, with the goal of alleviating symptoms and preventing myocardial infarction (MI), left ventricular (LV) dysfunction, malignant arrhythmias and cardiac death.

Noninvasive assessment is often used in symptomatic patients, prior to referral for an invasive coronary angiogram (with or without fractional flow reserve [FFR] measurement) to assess for CAD. Single-photon emission computed tomography (SPECT), contrast perfusion echocardiography, positron emission computed tomography (PET) and cardiac computed tomography perfusion imaging are all methods of assessing myocardial perfusion. However, each method has its limitations: for example, SPECT, PET and cardiac computed tomography involve radiation exposure, while contrast echocardiography is limited by difficult acoustic windows in certain patients and limited availability of the technique.

Cardiac MRI (CMR) is a rapidly growing, noninvasive, imaging modality for assessing for the presence of CAD. CMR is now considered the gold standard for cardiac function assessment. Currently available CMR scanners have the potential to acquire cardiac images with significantly improved signal to noise ratio, and spatial and temporal resolution. CMR is increasingly used to evaluate rest and stress perfusion, and to identify myocardial ischemia and infarct with a high degree of accuracy. Similarly, utility of CMR is studied in the setting of acute MI to assess for microvascular obstruction (MVO), which is shown to be associated with adverse cardiovascular events despite timely intervention.

Myocardial perfusion imaging via CMR: technique

CMR myocardial perfusion imaging is performed via first pass perfusion of the myocardium using chelated-gadolinium contrast, which is an extravascular and extracellular agent. Due to its paramagnetic effect, gadolinium alters the local magnetic field and enhances the relaxation rate of nearby

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water protons. Tissues that are well perfused show enhanced signal on T1-weighted images. With low dose gadolinium administered for perfusion imaging, the T2 and T2* effects do not dominate and, thus, do not interfere with the bright signal in the perfused tissues [1,2]. Intravascular gadolinium-based contrast agents were studied more than a decade ago and while some of them are on the market (Vasovist) in Europe, others never made it to market [3]. First pass perfusion imaging is performed as part of a vasodilator stress test (with stress and rest images) to identify ischemia and infarct **(Figure 1)**. The strength of CMR is its ability to provide comprehensive information in regards to myocardial chamber volumes, overall LV ejection fraction and wall motion, myocardial perfusion and late gadolinium enhancement (LGE) to assess for evidence of fibrosis.

Detection of severity of epicardial CAD is the most common reason for performing CMR perfusion studies. They can also be performed at rest to assess the microvascular circulation in the setting of acute MI.

• Rest perfusion

Typically, ECG-gated T1-weighted images are obtained using gradient echo, hybrid gradient echo-planar or steady state free precession imaging. Three LV short axis slices (base, mid and apex) are obtained corresponding to the American Heart Association 16-segment model [4]. Images are acquired during the first pass of gadolinium. Rest perfusion is considered abnormal if upon gadolinium administration, a low signal on T1-weighted images is detected in a myocardial segment, which persists for a period of at least five heartbeats [5].

• Stress perfusion

The most commonly used vasodilator stress agent in clinical practice is adenosine (140 µg/kg/min intravenously [IV] for 3 min), however, dipyridamole (0.56–0.84 mg/kg body weight IV over 4–6 min) and regadenoson (0.4 mg IV bolus) have been used in clinical studies. The concept behind vasodilator stress imaging is that hyperemic flow is decreased in myocardial segments that are supplied by a significantly stenosed epicardial coronary artery (>50%) **(Figure 2)** [6]. Some studies have used perfusion imaging during dobutamine stress CMR. In one such study performed on 455 patients scheduled for invasive coronary angiography (ICA), the addition of perfusion imaging to wall motion analysis with dobutamine improved the sensitivity from 85 to 91% at the cost of decreased specificity from 82 to 70% without changing the overall diagnostic accuracy [7]. Image quality is often degraded at the high heart rates with higher doses of dobutamine and, thus, this approach has not been widely adopted.

Resting myocardial perfusion imaging in acute MI to assess the microvasculature

MVO on CMR can be identified by two techniques: resting perfusion imaging and by LGE images. On resting first pass perfusion imaging, MVO is characterized as areas of reduced signal intensity (hypoenhancement) [8] that persist for >2 min, in comparison to homogenously increased signal intensity in the normal myocardium after contrast administration. This is labeled as 'early MVO' in comparison to 'late MVO', which is seen in LGE images as an area of central hypoenhancement within the hyper enhanced region **(Figure 3)** [9]. The severity of hypoenhancement on perfusion images is seen to be consistent with severe microvascular damage. Both early and late MVO is shown in studies to be associated with incomplete ST segment resolution [10]. 'Early MVO' has a limitation in regards to less coverage of the LV myocardium, low signal to noise ratio and lower spatial resolution. Despite the limitations, presence of 'early MVO' in acute MI, regardless of timely intervention with angioplasty, has been associated with lack of recovery of myocardial function. Late MVO carries with it a worse prognosis as it depicts a region of such severe microvascular damage that contrast has not yet arrived there as long as 10–20 min after infusion.

More than a decade ago, Wu *et al.* performed CMR in 44 patients 10 ± 6 days postacute MI and performed follow-up for 16 ± 5 months [11]. This study showed that even after controlling for infarct size, MVO remained a prognostic marker for cardiovascular events ($\chi^2 = 5.17$; $p < 0.05$) and was significantly associated with fibrous scar formation and LV remodeling. Similarly, Ørn *et al.* performed CMR on day 2 and 7, 2 months and at 1 year in 42 patients post single vessel angioplasty for acute MI [9]. After adjusting for infarct size at day 2, detectable MVO at 1 week was noted to be an independent predictor of infarct size at 1 year along with increased LV volumes and lower LV ejection fraction ($p = 0.003$). Another study showed that presence of MVO and LGE at 1-week postacute MI was an indicator of no

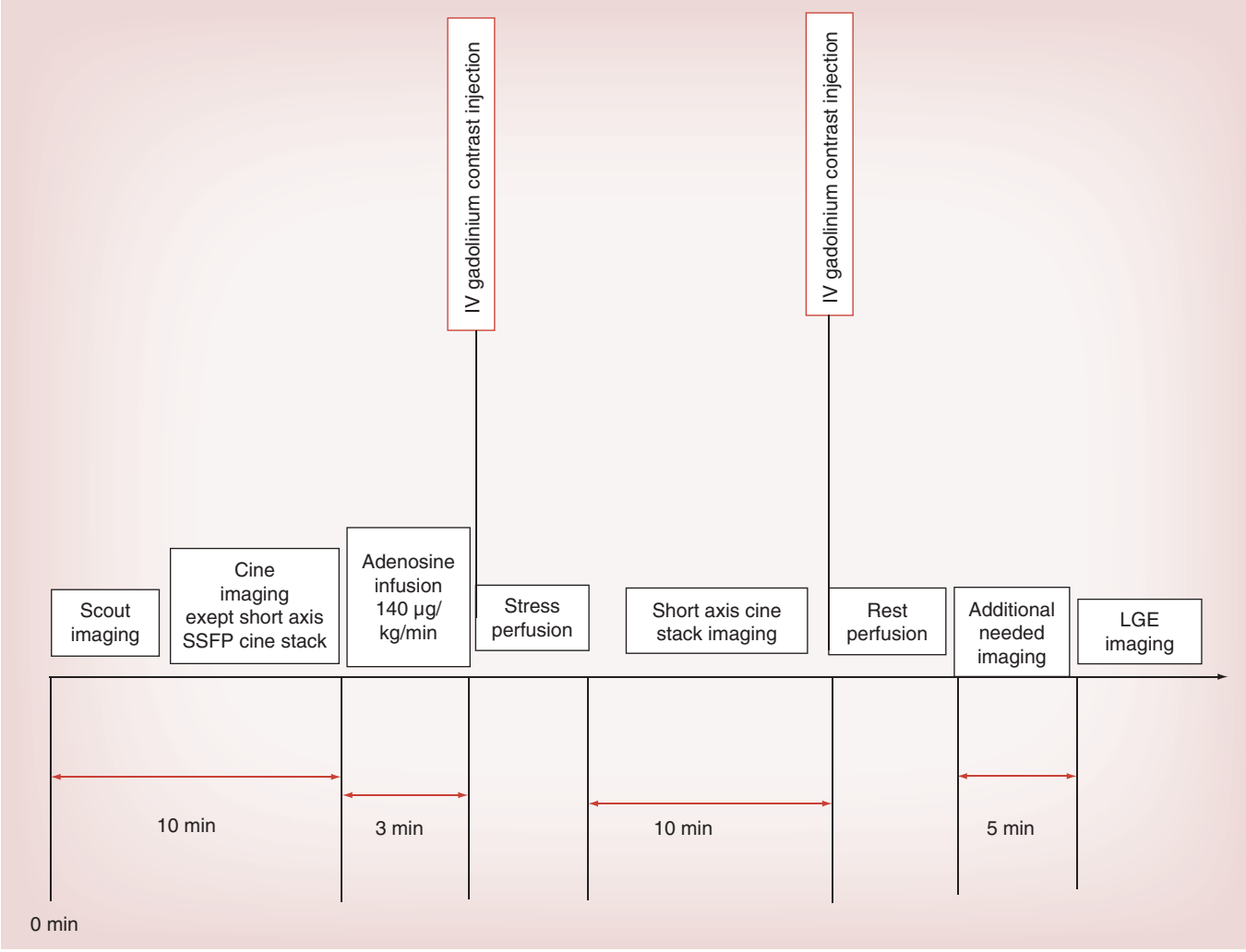

Figure 1. Vasodilator stress cardiac MRI protocol at our center.
IV: Intravenous; LGE: Late gadolinium enhancement; SSFP: Steady state free precession.

improvement in follow-up LV ejection fraction versus patients with only LGE where a partial improvement in LV function was noted at 8 weeks [12]. Lund *et al.* on CMR rest perfusion images, acquired 6 ± 3 days post MI (60 patients) revealed MVO to be an indicator of larger infarct size (>20% of the LV area), reduced thrombolysis in myocardial infarction grade flow of the infarct related artery before revascularization and significantly increased peak releases of creatinine kinase and creatinine kinase-MB ($p < 0.001$) [13].

Rest-stress myocardial perfusion using CMR to assess for CAD

Vasodilator stress CMR is used to assess for CAD in symptomatic patients. After publication of multiple prospective, single center trials, Nandalur *et al.* published a meta-analysis in 2007 [14]. They examined stress CMR perfusion studies where ICA was used as the gold standard to detect CAD. This study showed that both a negative CMR in the presence of symptoms, and a positive CMR in intermediate and low risk patients, have high prognostic value. Recently de Jong *et al.* performed a comparative meta-analysis of perfusion contrast echocardiography, SPECT, PET and CMR with invasive CA as the gold standard [15]. To diagnose >70% stenosis on coronary angiography, the comparative sensitivity and specificity of CMR, perfusion echocardiography and SPECT was: sensitivity (91% vs 87% vs 83%) and specificity (80% vs 72% vs 77%).

Data is now available from three randomized controlled trials. **(Table 1)** [14,16–18]. These studies have confirmed the noninferior (and superior in some studies) performance of stress

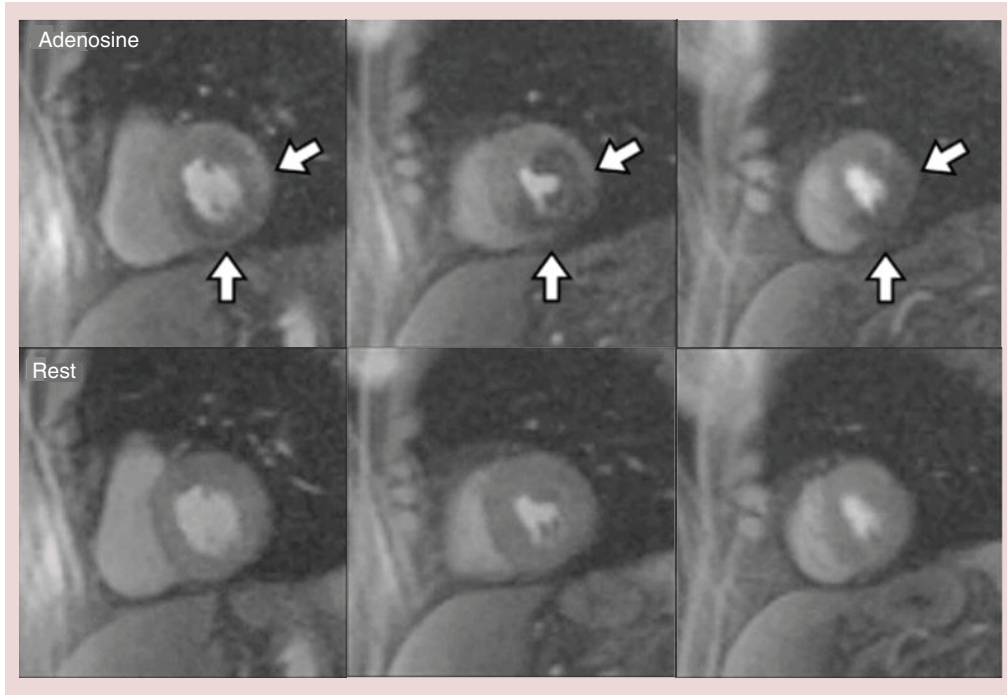

Figure 2. Qualitative interpretation of cardiac MRI perfusion imaging. Top row shows adenosine stress images, while the bottom row shows rest images. Left column: basal left ventricle; middle column: mid left ventricle; right column: apical left ventricle. The white arrows point to a large perfusion defect in the anterolateral, infero-lateral, inferior and infero-septal wall, extending from the basal to the apical slice. Adapted with permission from [6].

CMR compared to SPECT in a realistic clinical environment.

The 'MR-INFORM study' [19], is another prospective randomized controlled trial that is under progress. It aims at comparing medical treatment with coronary intervention in patients with stable CAD. Adenosine stress CMR-based coronary intervention will be compared with FFR-based coronary intervention and major adverse cardiac events over 1 year will be analyzed as the primary end point. Bettencourt *et al.* compared noninvasive CMR perfusion with invasive assessment of physiologic significance of a coronary lesion via FFR [20]. Their study population included symptomatic intermediate-to-high risk patients. They compared CMR perfusion with ICA and FFR with FFR cut-off of <0.80. In this study, in a per patient analysis the sensitivity, specificity, PPV, NPV and accuracy of stress CMR was 89, 88, 85, 91 and 88%, respectively, while on a per vessel analysis they were 80, 93, 79, 94 and 90%, respectively.

3 T & whole-heart 3D CMR perfusion

Adenosine stress CMR perfusion imaging at 1.5 T is well established. However, the potential superiority of imaging at 3 T has recently been tested in a handful of studies and it is speculated that 3 T might become the preferred CMR field strength for adenosine stress CMR in clinical practice. However, more data is needed in this regard.

Manka *et al.* [21], found the sensitivity, specificity and accuracy of 3 T CMR perfusion to be 92, 74 and 83% as compared to ICA. Walcher *et al.* performed adenosine stress CMR on both 1.5 T and 3 T scanners, and found that the sensitivity at 3 versus 1.5 T was 84 versus 75% with a specificity of 90 versus 75% for ≥50% stenosis on ICA [22]. Similarly, when using >70% stenosis as the reference standard, 3 T perfusion was found to be more sensitive (96 vs 89%) and more specific (88 vs 80%). 3 T whole-heart 3D CMR perfusion is another recent technical advance [23], but this was not found to be superior to traditional three-slice CMR perfusion.

Quantitative perfusion analysis on CMR

Quantification of myocardial perfusion has been an area of active research in CMR over the past few years. Myocardial blood flow increases during stress. Myocardial perfusion reserve (MPR) can

be calculated as the ratio of stress versus resting flow. Quantitative CMR is performed to calculate absolute myocardial blood flow (ml/min/gm) on dynamic first pass perfusion imaging, by various techniques including: two-compartment modeling, Fermi function modeling, model-independent analysis and Patlak plot analysis [24]. In the Fermi model, time intensity curves are constructed in the myocardium and the arterial input function is measured from the LV cavity or ascending aorta using constrained deconvolution of myocardial signal intensity curves. The constrained deconvolution analysis uses the delay time between LV blood pool and myocardial enhancement and controls for the time duration of the plateau portion of the curve. As a final step mathematical deconvolution is performed [25]. Pack *et al.* compared the four models and found that global myocardial perfusion estimates at rest were similar with the four models [24]. At stress the Fermi function models was noted to give 25% higher estimate of blood flow. Overall, MPR values with the models were not significantly different, indicating that any of them can be used for MRP measurements. A good correlation was found between PET-MPR and CMR-MPR in a study on 41 patients with known or suspected CAD ($r = 0.75$; $p < 0.0001$) [26].

CMR quantitative perfusion data is now available in various populations (syndrome X) [27], various myocardial regions (subepicardium vs subendocardium) [28], using different techniques (manual vs automatic) [29], and with different vasodilator agents (adenosine and regadenoson [30]).

A comparison of qualitative CMR perfusion (Q-CMR-P) and quantitative CMR perfusion analysis was performed by Patel *et al.* on 30 patients [6]. The sensitivity, specificity and accuracy for the assessment of >50% stenosis on ICA of Q-CMR-P versus MPR was 79, 83 and 80% versus 88, 67 and 83%, respectively. A stepwise reduction in MPR was noted with increasing coronary artery stenosis, that is, MPR was 2.42 ± 0.94 with <50% coronary stenosis versus 2.14 ± 0.87 for 50–70% stenosis versus 1.85 ± 0.77 for >70% coronary stenosis. For the evaluation of myocardial ischemic burden, no difference in the Q-CMR-P was noted between triple vessel and single vessel CAD (31 ± 20% vs 21 ± 26%, $p = 0.26$), whereas when MPR analysis was used, patients with triple vessel CAD had significantly increased ischemic burden compared with single vessel CAD (60 ± 38% vs 25 ± 41%). Thus, in this study quantitative MPR analysis was found to differentiate patients with multivessel from those with single vessel CAD **(Figure 4)**.

The inter-study reproducibility of quantitative CMR perfusion at 3 T was studied by

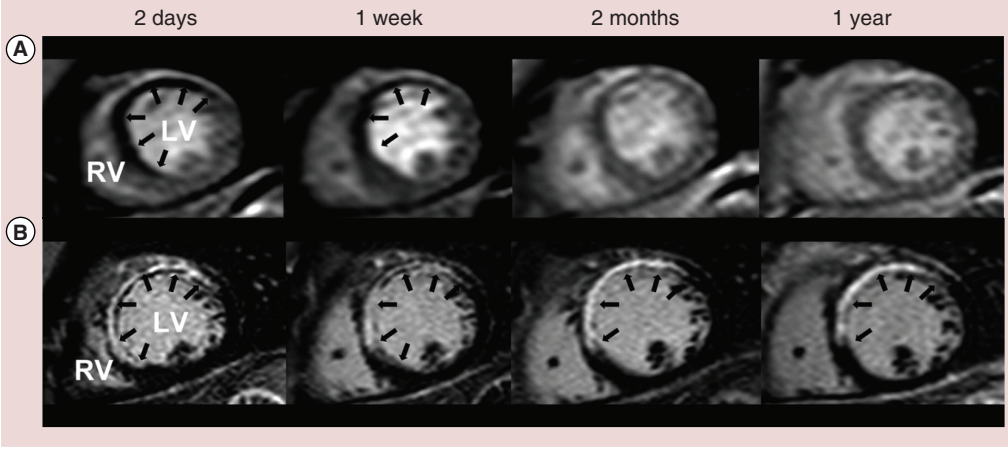

Figure 3. Typical pattern of microvascular obstruction in a patient with ST-elevation myocardial infarction due to an occluded left anterior descending artery, treated with primary percutanous coronary intervention. (A) Demonstrates first pass perfusion images with hypoperfusion of the anteroseptum, especially at day 2 and week 1 postmyocardial infarction. **(B)** Demonstrates late gadolinium-enhanced images with the dark signal at the subendocardium at each time point representing regions of microvascular obstruction.
LV: Left ventricle; RV: Right ventricle.
Adapted with permission from [9].

Table 1. Meta-analysis and randomized controlled trials on vasodilator cardiac MRI stress/rest perfusion.

Study	Publication year	Number of patients	MRI scanner	Perfusion model	Population characteristics	Comparison modality	Gold standard	Results	Critiques of the study	Ref.
Nandalur *et al.*	2007	11,183 (14 studies) included (From 1516 patients [24 studies])	1.5 T	Variable	Prevalence of significant CAD: 57.4%		ICA	S: 91% (95% CI: 88–94%) Sp: 81% (95% CI: 77–85%) PLR: 5.10 (95% CI: 3.92–6.28) NLR: 0.11 (95% CI: 0.07–0.15)	Meta-analysis	[14]
Schwitter *et al.* (MR-IMPACT trial)	2008	241 (18 centers)	1.5 T	AHA-16 segment	Exclusion criteria: decompensated HF; CABG, significant arrhythmias	SPECT (G & NG)	ICA (≥50% stenosis)	AUC: CMR vs SPECT (G + NG): 0.86 ± 0.06 vs 0.67 ± 0.5; p = 0.013 AUC: CMR vs G-SPECT: 0.86 ± 0.06 vs 0.75 ± 0.08; p = 0.18 AUC: CMR vs SPECT in MVCAD: 0.89 ± 0.06 vs 0.70 ± 0.5; p = 0.006	G-SPECT not available in half of the patients	[16]
Greenwood *et al.* (CE-MARC trial)	2012	752 (single center)	1.5 T	AHA-17 segment	Inclusion criteria: suspected angina + ≥1 CVRF Exclusion criteria: Prior CABG Prevalence of significant CAD: 39%	G-SPECT	ICA ≥70% stenosis or LM disease)	CMR vs SPECT S: 86.5 vs 66.5% Sp: 83 vs 83% PPV: 77 vs 71% NPV: 90.5 vs 79%	Single-center study Lower accuracy of SPECT noted as compared to prior publications	[17]
Schwitter *et al.* (MR-IMPACT II study)	2013	533 (33 centers in Europe and USA)	1.5 T	AHA-16 segment	Prevalence of significant CAD: 49%	G-SPECT preferred, NG-SPECT allowed	ICA	CMR vs SPECT S: 67 vs 59% Sp: 61 vs 72%		[18]

AHA: American Heart Association; AUC: Area under the curve; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; CMR: Cardiovascular MRI; CVRF: Cardiovascular risk factor; G: ECG-gated; HF: Heart failure; ICA: Invasive coronary angiography; LM: Left main; MVCAD: Multivessel coronary artery disease; NG: Non-ECG-gated; NLR: Negative likelihood ratio; NPV: Negative predictive value; PLR: Positive likelihood ratio; PPV: Positive predictive value; S: Sensitivity; Sp: Specificity; SPECT: Single-photon emission computed tomography.

Morton *et al.* [31]. CMR perfusion was performed three times during a single day on 16 healthy volunteers. The global rest and stress perfusion along with MPR were comparable with a coefficient of variation (CV) of 16.0, 26.8 and 23.9%, respectively. The corresponding territorial CVs were 27.5, 35.2 and 33.5%, respectively. The authors concluded that the inter-study reproducibility of quantitative myocardial perfusion is reasonable and best for global rest perfusion. However, the results appear to be dependent on the voxel size, acquisition and postprocessing methods. Misregistration and partial volume artifacts also impact the results. Fast and nearly automatic techniques are in development to quantify myocardial perfusion at both rest and stress.

Latest techniques in acquiring perfusion images on CMR

Perfusion CMR interpretation is sometimes limited by the presence of dark-rim artifacts that can lead to false-positive results. These artifacts are related to limited spatial resolution and cardiac motion. Additionally, ECG gating difficulties, especially in patients with atrial fibrillation or multiple extra atrial or ventricular beats can result in image degradation and nondiagnostic scans.

Recent technical innovations in imaging are aimed at addressing these artifacts. These alter coil encoding and spatiotemporal correlations and include: ungated, radial dynamic perfusion [32], free breathing myocardial perfusion [33], high resolution CMR perfusion [34,35] including k–t BLAST (Broad-use Linear Acquisition Speed-up Technique) [36] and k–t SENSE (k-space and time sensitivity encoding) [37] and sliding window conjugate gradient highly constrained back projection reconstruction (SW-CG-HYPR) [35]. Some of these techniques have resulted in significantly improved image quality with improved contrast to noise and signal to noise ratio, and have reduced the extent and transmurality of dark rim artifacts. However more work is underway to compare these to more previously used techniques.

CMR myocardial perfusion & prognosis

In low-to-intermediate risk patients suspected of CAD, stress CMR provides prognostic information in regards to major adverse cardiac events. Nandalur's meta-analysis demonstrated that a negative stress CMR in a low to intermediate risk patient (<60% probability of CAD) decreases the probability of CAD to ≤20% [14]. Similarly, in an intermediate to high risk patient (>40% probability of CAD), when the stress CMR is positive, it increases the probability of CAD to approximately 80%. The prognostic information of stress CMR was compiled in a meta-analysis from our center by Lipinski *et al.* [38]. Data was analyzed from 19 studies inclusive of 11,636 patients with known or suspected CAD. The

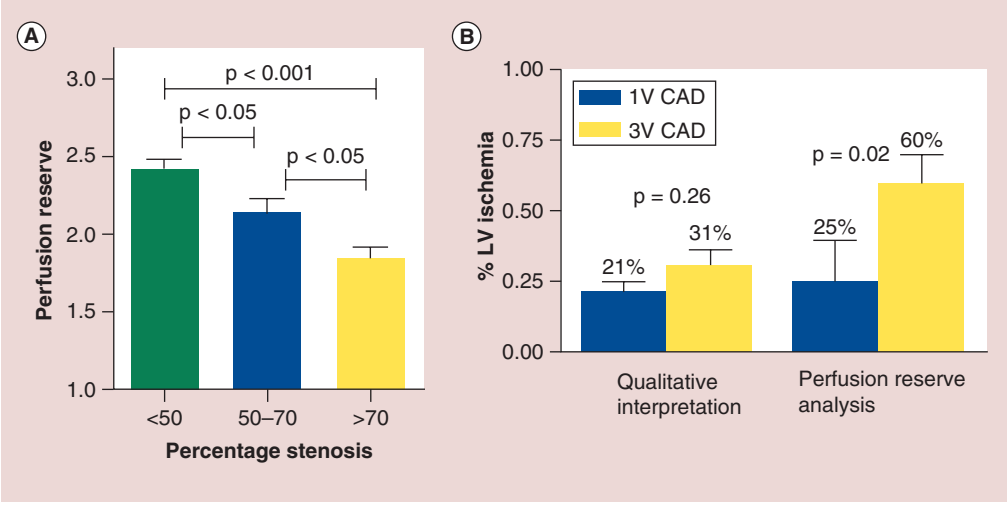

Figure 4. Quantitative perfusion analysis on stress cardiac MRI. (A) Relationship between perfusion reserve and percentage stenosis on cardiac catheterization. **(B)** Comparison of qualitative perfusion analysis with perfusion reserve to assess degree of ischemia in single and multivessel CAD.
CAD: Coronary artery disease; LV: Left ventricle.
Adapted with permission from [6].

mean follow-up was 32 months. In patients with a positive test on follow-up, the annualized event rate, CV death and MI were 4.9, 2.8 and 2.6%, respectively. Patients with a negative stress CMR on the other hand, had <1% annualized event rate, CV death or nonfatal MI on follow-up. This clearly indicates that stress CMR provides excellent prognostic information in regards to risk stratification of patients with known or suspected CAD.

Limitations in myocardial perfusion analysis by CMR

Despite an expansion in the utilization of CMR perfusion in clinical settings, its practice is limited due to the lack of availability of CMR imaging expertise in many centers. This is changing as more data are being published with CMR and more imaging specialists are being trained in the techniques. The additional limiting factors with CMR perfusion are patient-related such as obesity, claustrophobia, poor gating, motion artifacts, contraindications to use of vasodilator agents and obtaining appropriate heart rate response with stress testing. The latter can usually be addressed by increasing stress agent dose, for example for adenosine.

Future perspective

Multicenter randomized controlled trials have established stress CMR to be noninferior, and even superior as compared to SPECT for CAD assessment. Recent studies have demonstrated its prognostic capacity for predicting risk of future major adverse cardiovascular events in intermediate to high-risk patients. Rest perfusion in the setting of acute MI can demonstrate MVO, which is indicative of poor functional recovery of the myocardium and poor prognosis for the patient. Ongoing studies are assessing the superiority of 3 T CMR scanners in perfusion assessment as well as the effectiveness of MPR measurements. With additional studies establishing the predictive utility of MVO on CMR, resting perfusion analysis may become an important prognostic tool after acute MI. The future appears very promising, in regards to technological innovation in CMR, resulting in reduced image acquisition time, automated analysis and decreased artifacts.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

EXECUTIVE SUMMARY

- Despite significant improvement in the diagnostic and treatment strategies for coronary artery disease, it remains the leading cause of morbidity and mortality in the USA.
- Noninvasive assessment is often used in symptomatic patients, prior to referral for an invasive coronary angiogram (with and without fractional flow reserve measurement) to assess for coronary artery disease.
- Cardiac MRI (CMR) is increasingly used to evaluate rest and stress perfusion, to identify myocardial ischemia and infarct with high degree of accuracy.
- CMR myocardial perfusion imaging is performed via first pass perfusion of the myocardium by using chelated-gadolinium, which is an extravascular and extracellular contrast agent.
- The strength of CMR is its ability to provide information in regards to myocardial chamber volumes, overall left ventricular ejection fraction and wall motion, myocardial perfusion abnormalities and late gadolinium-enhanced images to assess for evidence of fibrosis.
- Data from three randomized controlled trials using stress CMR is now available. These studies have confirmed the noninferior (and superior in some studies) performance of stress CMR relative to single-photon emission computed tomography in a realistic clinical environment.
- Adenosine stress CMR perfusion imaging at 1.5 T is well established. However, the potential superiority of imaging at 3 T has recently been tested in a handful of studies and it is speculated that 3 T might become the preferred CMR field strength for adenosine stress CMR in clinical practice.

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