

Assessment of stable coronary artery disease by cardiovascular magnetic resonance imaging: Current and emerging techniques

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Abstract

Coronary artery disease (CAD) is a leading cause of death and disability worldwide. Cardiovascular magnetic

resonance (CMR) is established in clinical practice guidelines with a growing evidence base supporting its use to aid the diagnosis and management of patients with suspected or established CAD. CMR is a multi-parametric imaging modality that yields high spatial resolution images that can be acquired in any plane for the assessment of global and regional cardiac function, myocardial perfusion and viability, tissue characterisation and coronary artery anatomy, all within a single study protocol and without exposure to ionising radiation. Advances in technology and acquisition techniques continue to progress the utility of CMR across a wide spectrum of cardiovascular disease, and the publication of large scale clinical trials continues to strengthen the role of CMR in daily cardiology practice. This article aims to review current practice and explore the future directions of multi-parametric CMR imaging in the investigation of stable CAD.

Key words: Cardiovascular magnetic resonance; Coronary heart disease; Myocardial perfusion; Viability; Prognosis

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Core tip: Coronary artery disease (CAD) is a leading cause of death worldwide. Cardiovascular magnetic resonance (CMR) is established in clinical practice guidelines with a growing evidence base supporting its use to aid diagnosis and management of patients with suspected or established CAD. CMR is a multi-parametric imaging modality that yields high spatial resolution images that can be acquired in any plane for assessment of global and regional cardiac function, myocardial perfusion and viability, tissue characterisation and coronary artery anatomy, all within a single study protocol and without exposure to ionising radiation.

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INTRODUCTION

Coronary artery disease (CAD) is a leading cause of death and disability worldwide^[1]. Despite major advances in the treatment of CAD resulting in significantly decreased mortality rates, CAD remains the single most common cause of death in the European Union, leading to 19% of deaths in men and 20% of deaths in women^[2]; in the United States, CAD causes 1 in every 7 deaths, accounting for 370213 deaths in 2013^[3]. The economic health burden of CAD is substantial with an estimated cost of CAD management at €60 billion in the European Union^[4], and \$182 billion in the United States^[3]. Cardiovascular medicine benefits from a myriad of diagnostic methods that can guide intervention and clinical decision-making. Invasive coronary X-ray angiography delineates coronary anatomy in patients presenting with stable chest pain, however there is a low yield of obstructive CAD in those referred, and there are associated risks, albeit low, from major complications and ionising radiation^[5]. Furthermore unless measurement of fractional flow reserve (FFR) is performed, routine coronary angiography does not give information on ischaemia burden, which according to current guidelines, is required to guide revascularisation decisions. Non-invasive functional imaging modalities such as single-photon emission computed tomography (SPECT), dobutamine stress echocardiography (DSE), cardiovascular magnetic resonance (CMR) or positron emission tomography (PET) are used to diagnose CAD, guide clinical decision making and confer prognostic information and consequently are well established for these roles in clinical practice guidelines^[6,7].

CMR is a unique multi-parametric imaging modality producing high spatial resolution images that can be acquired in any plane for the assessment of global and regional cardiac function, myocardial perfusion and viability, tissue characterisation and proximal coronary artery anatomy, all within a single study and without exposure to ionising radiation (Figure 1). Historically, long scanning times, limited scanner availability and narrow bore sizes restricted the use of CMR, but these issues have been largely resolved, such that CMR has become a first line investigation for suspected stable angina in many centres in the United Kingdom and Europe. Consequently CMR is part of international clinical practice guidelines for the assessment of known and unknown stable CAD and for the identification of those who may benefit from revascularisation^[6-9]. This review aims to focus on the current utility of CMR for the diagnosis of suspected stable CAD and potential future developments and applications of CMR in this role.

CMR IN STABLE CAD

A CMR protocol for the investigation of stable CAD will typically take between 30-60 min and involves the acquisition of cine images in multiple planes for the assessment of left ventricular function and volumes, stress and rest myocardial perfusion imaging and late gadolinium enhancement (LGE) imaging for the assessment of myocardial viability and scar quantification (Figure 2).

CMR is the reference standard non-invasive technique for the measurement of left ventricular (LV) and right ventricular (RV) volumes, and ejection fraction, with high intra- and inter-observer reproducibility^[10,11]. Steady state free precession cine imaging is typically performed for the assessment of LV function to enable visual assessment of global and regional myocardial function in a similar manner to echocardiography; however there are no limitations due to poor acoustic windows or large body habitus degrading image quality. CMR volumetric analysis is performed by acquiring a stack of contiguous breath held cine images from the base of the heart to the apex; the endocardial and epicardial borders are subsequently contoured giving mass, volumes and function. Thus CMR provides a true 3D analysis of LV and RV function unlike 2D echocardiography that relies on geometric assumptions for volumetric calculations. Furthermore specific myocardial tagging pulse sequences can be performed that enable more detailed assessment of intra-myocardial mechanics beyond ejection fraction, including torsion, twist, strain and strain rates^[12]. Additionally, feature tracking is a novel post-processing method of quantitatively assessing strain and strain rate using standard cine images without having to acquire further imaging sequences as is the case with standard CMR tissue tagging^[12,13].

DIAGNOSIS OF CAD

Ischaemia detection by CMR is performed using either vasodilator or inotropic stress. Ischaemia detection by CMR is recommended as a first line strategy for investigating suspected angina in patients with an intermediate pre-test likelihood of CAD in both the current European Society of Cardiology (ESC) and National Institute for Health and Care Excellence (NICE) guidelines (Table 1)^[6,14], whilst the United States guidelines are more conservative and give a grade IIa recommendation for stress perfusion CMR in patients with uninterpretable ECGs or unable to exercise^[7].

STRESS PERFUSION CMR

Stress perfusion CMR requires the induction of hyperaemia by a vasodilating agent, and then observation of the passage of a gadolinium based contrast agent (GBCA) through the myocardium to identify perfusion defects. Typically the vasodilating agent used is adenosine though regadenoson and less commonly dipyridamole and nicorandil are also

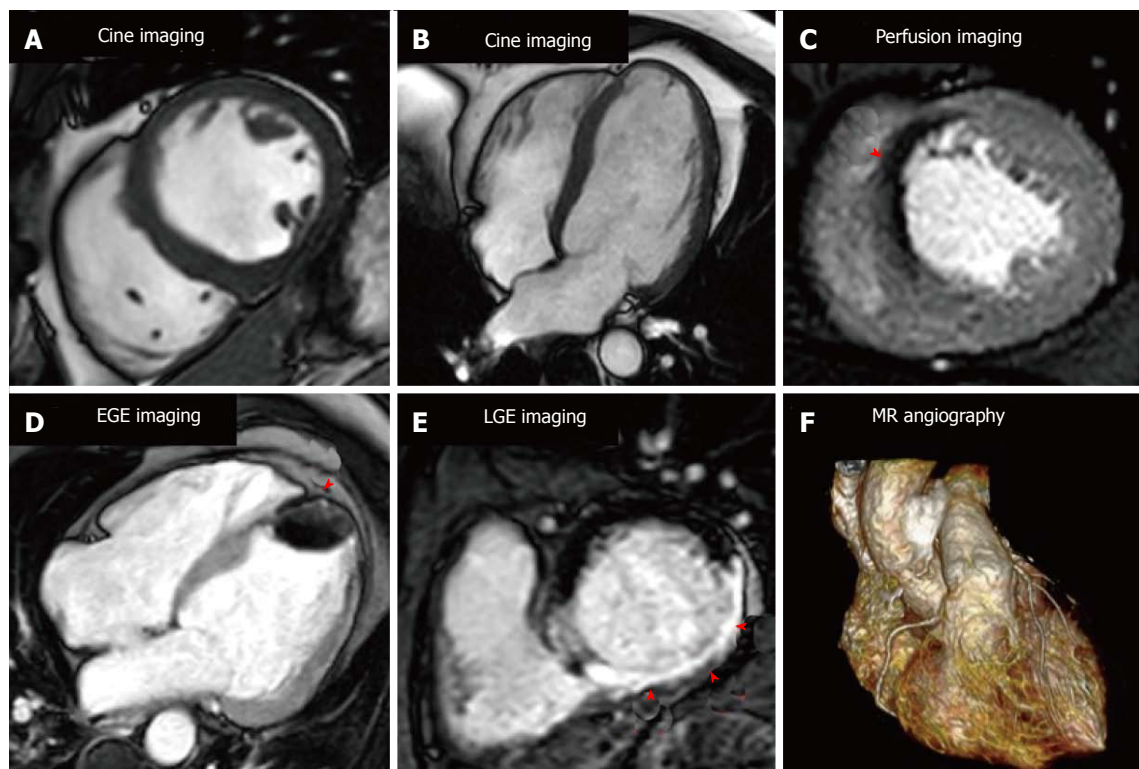


Figure 1 Cardiovascular magnetic resonance imaging techniques. A and B show short axis and 4 chamber cine images respectively for anatomical and functional assessment; C shows stress perfusion with a septal perfusion defect (arrow); D shows early gadolinium enhancement imaging with a large apical thrombus (arrow); E is late gadolinium enhanced imaging with a transmural inferior infarction (arrows); F is 3D whole heart magnetic resonance angiography. LGE: Late gadolinium enhancement; EGE: Early gadolinium enhancement.

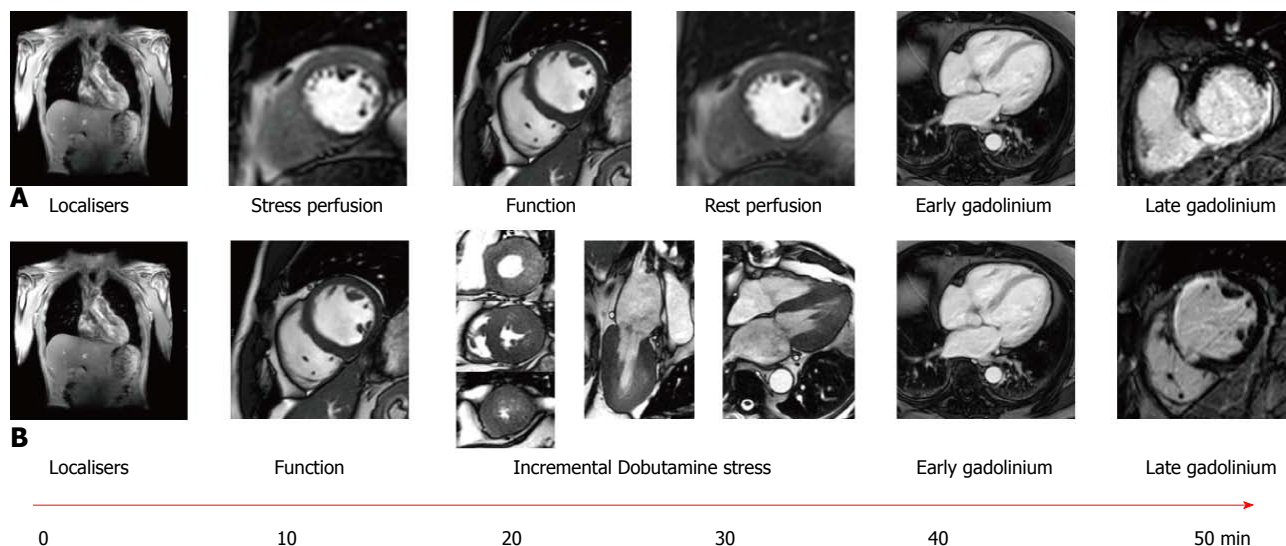


Figure 2 Cardiovascular magnetic resonance multi-parametric protocols for the investigation of suspected coronary artery disease. A shows a typical multi-parametric cardiovascular magnetic resonance protocol for the investigation of stable coronary artery disease with adenosine stress perfusion; and B with incremental dose dobutamine stress.

used. Adenosine produces vasodilatation in most vascular beds, including the coronary circulation, *via* A2A and A2B receptors^[15]. Adenosine is given as an intravenous infusion typically at a rate of 140 mcg/kg per minute, though this can be increased if there is no haemodynamic response; the main side effects of adenosine are transient heart block, and bronchospasm can be caused in those with reversible

airways disease^[15]. Regadenoson is a new selective A2A adenosine receptor agonist that is given *via* an intravenous bolus, has less respiratory side effects than adenosine, and has recently been approved by both the FDA and in Europe for this indication^[16,17]. The coronary micro-vasculature can dilate up to 4 or 5 times from the resting state to ensure adequate tissue perfusion for example during exercise.

Table 1 European Society of Cardiology and American College of Cardiology Foundation/American Heart Association Recommendations for cardiovascular magnetic resonance in stable coronary artery disease

ESC guidelines	
Suspected/stable coronary artery disease ^[6]	
In patients with suspected stable coronary artery disease and pretest probability of 15%-85% stress imaging is preferred as the initial test option if local expertise and availability permit	Class I
An imaging stress test is recommended in patients with resting ECG abnormalities, which prevent accurate interpretation of ECG changes during stress	Class I
CMR should be considered in symptomatic patients with prior revascularisation (PCI or CABG)	Class II a
Risk stratification is recommended based on clinical assessment and the results of the stress test initially employed for making a diagnosis of stable coronary artery disease	Class I
CMR is recommended in the presence of recurrent or new symptoms once instability has been ruled out	Class I
In symptomatic patients with revascularised stable coronary artery disease, CMR is indicated rather than stress ECG	Class I
CMR is recommended for risk stratification in patients with known stable coronary artery disease and a deterioration in symptoms if the site and extent of ischemia would influence clinical decision making	Class I
Recommendations for imaging to determine ischemia to plan revascularisation ^[6,144]	
An imaging stress test should be considered to assess the functional severity of intermediate lesions on coronary arteriography	Class II a
To achieve a prognostic benefit by revascularisation in patients with coronary artery disease, ischemia has to be documented by non-invasive imaging	Class I
Following MI with multivessel disease, or in whom revascularisation of other vessels is considered, CMR for ischaemia and viability is indicated before or after discharge	Class I
Heart failure ^[8]	
CMR should be considered in patients with HF thought to have CAD, and who are considered suitable for coronary revascularization, to determine whether there is reversible myocardial ischaemia and viable myocardium	Class II a
AHA guidelines	
Diagnosis and management of stable coronary artery disease ^[7]	
CMR can be used for patients with an intermediate (10%-90%) to high (> 90%) pretest probability of obstructive IHD who have an uninterpretable ECG and at least moderate physical functioning or no disabling comorbidity	Class II a
CMR is reasonable for patients with an intermediate to high pretest probability of IHD who are incapable of at least moderate physical functioning or have disabling comorbidity	Class II a
Pharmacological stress CMR is reasonable for risk assessment in patients with SIHD who are unable to exercise to an adequate workload regardless of interpretability of ECG	Class II a
CMR is reasonable in patients with known SIHD who have new or worsening symptoms (not unstable) and who are incapable of at least moderate physical functioning or have disabling comorbidity	Class II a

ESC: European Society of Cardiology; CMR: Cardiovascular magnetic resonance; ECG: Electrocardiogram; CABG: Coronary artery bypass graft; PCI: Percutaneous coronary intervention; AHA: American Heart Association; IHD: Ischemic heart disease; SIHD: Stable ischemic heart disease.

However the microvasculature distal to a stenosed coronary artery is already near-maximally vasodilated at rest and consequently when hyperaemia is provoked a coronary steal effect is caused. GBCAs increase the signal intensity in T1 weighted images and the passage of GBCAs through the myocardium causes healthy myocardium to become brighter while regions of hypoperfusion ("ischaemia") remain dark (Figure 3).

The diagnostic accuracy of stress perfusion CMR for the detection of CAD is well validated. A meta-analysis of 37 studies demonstrated a combined sensitivity of 89% (95%CI: 88%-91%) and specificity of 76% (95%CI: 73%-78%) for perfusion CMR for the diagnosis of CAD^[18]. The CE-MARC study ($n = 752$), the largest prospective randomised single-centre trial of CMR in this context showed superiority of perfusion CMR over SPECT, with a higher sensitivity (87% vs 67%, $P < 0.0001$) and negative predictive value (91% vs 79%, $P < 0.0001$) but similar specificity (83% vs 83% $P = 0.916$) and positive predictive values (77% vs 71%, $P = 0.061$)^[19,20]. Furthermore in a pre-specified gender sub analysis of CE-MARC, CMR showed similar sensitivity for CAD detection in both males and females, whilst SPECT had significantly lower sensitivity in females compared to males^[21].

The multi-centre, multi-vendor MR-IMPACT II trial

($n = 515$) also confirmed CMR's superior sensitivity compared to SPECT (67% vs 59%, $P = 0.024$) but with a lower specificity (61% vs 72%, $P = 0.038$)^[22]; however unlike CE-MARC only the stress/rest perfusion component of the CMR protocol was analysed. CE-MARC included analysis of LGE for scar detection, cine imaging for regional ventricular function and magnetic resonance angiography (MRA) for coronary artery anatomy, and a subsequent sub-analysis of CE-MARC demonstrated the additive diagnostic accuracy of the summation of these components of the multi-parametric protocol^[23].

Stress perfusion CMR has also been validated against FFR in a recent meta-analysis with a pooled sensitivity and specificity of 0.90 (95%CI: 0.86-0.93) and 0.87 (95%CI: 0.82-0.90) at the patient level and 0.89 (95%CI: 0.83-0.92) and 0.86 (95%CI: 0.77-0.92) at the coronary artery and territory levels^[24]. Furthermore CMR stress perfusion had comparable sensitivity and specificity to cardiac CT and PET in a recent meta-analysis of non-invasive imaging modalities, and was superior to both SPECT and DSE when using FFR as the reference standard^[25]. Most trials thus far have excluded patients with arrhythmia amid concerns regarding ECG gating, however the diagnostic accuracy of stress perfusion CMR remains high in suspected CAD patients with AF or

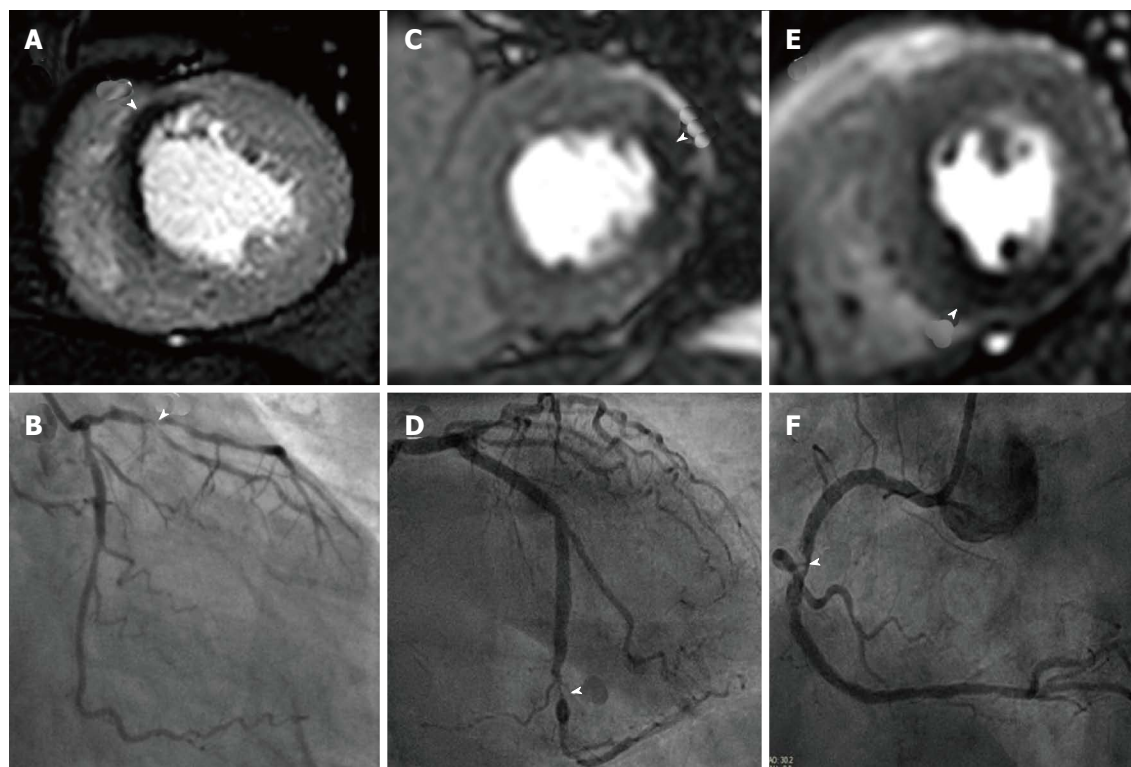


Figure 3 Cardiovascular magnetic resonance perfusion techniques. A is a high spatial resolution *k-t* BLAST stress perfusion CMR study at 3.0T showing an antero-septal perfusion defect with corresponding left anterior descending lesion in B; C shows a transmural lateral perfusion defect at standard resolution at 1.5T with corresponding circumflex lesion in D; E shows a transmural inferior perfusion defect at standard resolution at 1.5T with corresponding right coronary artery lesion in F. BLAST: Broad-use linear acquisition speed-up technique; CMR: Cardiovascular magnetic resonance.

frequent ectopy (sensitivity 80%, specificity 74%)^[26].

1.5T VS 3.0T FIELD STRENGTH

Although 1.5T remains the standard field strength used in clinical CMR, imaging at a higher field strength of 3.0T offers increased signal to noise and contrast to noise ratios thereby giving improved spatial and temporal enhancement^[27]. Consequently the diagnostic accuracy of perfusion imaging at 3.0T may be improved, and in a small direct comparison of CMR perfusion at 1.5T, 3.0T ($n = 61$) showed greater diagnostic accuracy in both single vessel (AUC: 0.89 vs 0.70; $P < 0.05$) and multi-vessel disease (AUC: 0.95 vs 0.82, $P < 0.05$)^[28]. Furthermore, 3.0T has been compared to 1.5T using FFR as reference standard, corroborating its superior diagnostic accuracy^[29,30]. The higher 3.0T field strength does however pose challenges with greater field inhomogeneity, susceptibility artefacts and higher local energy deposition. Also, many implants deemed "MR compatible" at 1.5T cannot be scanned at 3.0T^[31]. These issues are however being overcome with improved technology and the use of multi-transmit radiofrequency CMR techniques improving field homogeneity^[32].

IMPROVING PERFUSION IMAGING

Currently typical CMR perfusion imaging acquires 3 short axis slices of the left ventricle with an in-plane spatial

resolution of 2-3 mm. Developments in CMR technology however now allow faster scan speeds; these novel acquisition techniques allow accelerated data acquisition based on spatio-temporal undersampling (*k-t* SENSE or *k-t* BLAST and highly constrained back projection HYPR, compressed sensing and others)^[33]. These faster data acquisition techniques have been applied to achieve in-plane spatial resolution < 2 mm or full-coverage of the LV using 3D whole-heart perfusion imaging. High spatial-resolution imaging offers benefits by significantly reducing dark rim artefacts, as these are directly proportional to voxel size^[34]. Moreover there is improved ability to detect sub-endocardial ischaemia which is critical in multi-vessel disease where there is a lack of reference healthy myocardium for comparison^[35,36]. High spatial-resolution perfusion CMR has been validated at both 1.5T and 3.0T against quantitative coronary angiography (QCA) with improved diagnostic accuracy at both field strengths compared to standard resolution perfusion imaging^[27,36,37]. Furthermore validation against FFR gave sensitivity and specificity to detect stenoses at a threshold of FFR < 0.75 of 0.82 and 0.94 ($P < 0.0001$) respectively, and an area under the curve of 0.92 ($P < 0.0001$)^[38].

Conventional stress perfusion CMR is typically acquired in 3 short-axis slices, and thus unlike SPECT does not truly calculate global ischaemia burden. Accelerated acquisition techniques can also be employed to achieve full LV coverage using a 3D whole-heart single shot acquisition.

Such 3D acquisitions can overcome the assumptions made about “missing” myocardium between the slices from conventional 2D multi-slice perfusion imaging. Two studies have validated the feasibility and diagnostic accuracy of 3D stress perfusion CMR against FFR; at 1.5T 3D perfusion demonstrated a sensitivity, specificity and diagnostic accuracy of 90%, 82% and 87% respectively and 91%, 90% and 91% respectively at 3.0T^[39,40]. Furthermore in a recent multicentre trial of 3D stress perfusion at 3.0T, sensitivity and specificity were 84.7% and 90.8% relative to the FFR reference^[41]. The main motivation for 3D perfusion is to give a more accurate quantification of total myocardial ischaemia burden; evidence from SPECT suggests a prognostic benefit for revascularisation in those with an ischaemia burden > 10%, with an ischaemia burden of 10% conferring a risk of approximately 5% for death or MI per year^[42,43]. Ischaemia burden as measured by 3D stress perfusion CMR has been compared to SPECT and showed good correlation ($r_s = 0.70$, $P < 0.001$)^[44]. Intriguingly a recent pilot study compared ischaemia burden by high-resolution perfusion (using 3 short axis slices) and 3D perfusion imaging (providing whole heart coverage) suggesting that there was also a good correlation between the techniques ($r = 0.72$; $P = 0.001$), and that therefore the two methods are potentially interchangeable^[45].

QUANTITATIVE PERFUSION

CMR stress perfusion studies are normally reported in a qualitative manner; however this can prove challenging in diffuse or multi-vessel disease where there is no healthy reference myocardium to use as a visual comparator. These situations can introduce subjectivity into the analysis and consequently quantitative measurement techniques have been developed to provide an objective assessment of myocardial blood flow. A number of different methods of quantitative analysis have been assessed with the Fermi deconvolution method showing most accuracy when compared to microspheres in an explanted porcine model at 1.5T and mice at 3.0T^[46,47], and when compared to SPECT and with QCA^[48]. When compared to angiography with FFR, an MPR threshold of 1.58 detected a stenosis with an FFR < 0.75 with a sensitivity of 0.80, specificity of 0.89 ($P < 0.0001$), and area under the curve of 0.89 ($P < 0.0001$)^[38]. Myocardial perfusion reserve derived from quantitative CMR perfusion has also shown good correlation to PET imaging, the imaging modality that is widely regarded as the reference standard non-invasive measure of myocardial blood flow^[49,50]. Currently, time consuming post-processing has limited quantitative perfusion methods to a research tool, but automated methods are being developed that may potentially overcome this^[51].

DOBUTAMINE STRESS CMR

GBCAs have an excellent safety profile^[52], but in patients with poor renal clearance (*e.g.*, on dialysis) there is

a risk of nephrogenic systemic fibrosis^[53]. In those patients unable to have GBCAs inotropic stress CMR is an alternative. Inotropic stress CMR is typically performed with dobutamine in a similar manner to DSE with inducible regional wall motion abnormalities identified in territories supplied by a stenosed coronary artery at peak stress. Unlike DSE however, DSMR's accuracy is not limited by body habitus or in those with poor acoustic windows and in a single centre study DSMR was shown to have significantly greater diagnostic performance to DSE in this context^[54]. However echocardiography in this study was performed without harmonic imaging and contrast agents, so that the performance of DSE is likely to be underreported compared with contemporaneous methods. DSMR has a comparable safety profile to DSE with an event rate of 0.1% for sustained VT and 0.4% for non-sustained VT, and 1.6% for atrial fibrillation; patients thus require close monitoring during scanning and resuscitation equipment needs to be available^[55]. DSMR has been shown to have high diagnostic accuracy for the detection of CAD with one meta-analysis of 14 trials showing a pooled sensitivity of 0.83 (95%CI: 0.79-0.88) and specificity of 0.86 (95%CI: 0.81-0.91)^[56]; furthermore a single centre trial of DSMR vs perfusion CMR showed similar diagnostic accuracy^[57]. First-pass perfusion can be performed additionally at peak dobutamine stress to provide incremental diagnostic accuracy^[58], and can be a useful adjunct in challenging patient groups such as those with pre-existing wall motion abnormalities or dyssynchrony from left bundle branch block^[59].

Exercise is commonly used rather than pharmacological agents as the stressor in echocardiography, and gives useful prognostic information such as workload in metabolic equivalent (METs) in addition to ischaemia testing^[60,61]. CMR is limited in this respect due to the need for supine scanning and consistent positioning within the scanner. Recent studies however have assessed the feasibility of exercise stress CMR and showed comparable accuracy to echocardiography, though it has yet to reach mainstream clinical use^[62,63]. Promising developments are “steppers” and cycle ergometers that can attach directly to the MRI scanner, and thereby eliminate the need to transfer the patient from the exercise equipment into the scanner^[64,65].

Prognosis from stress CMR

Both perfusion CMR and DSMR provide excellent prognostic information, and this has recently been shown in two large meta-analyses. One meta-analysis of 14 studies including 12178 patients showed that a negative stress CMR was associated with a 1.03% annualised event rate, comparable to the normal population^[66]. A further meta-analysis of 19 studies including 11636 patients showed a similar annualised event rate of 0.8% for a negative stress CMR over a mean follow up of 32 mo^[67]. In a large prospective study of 1229 patients undergoing adenosine stress with a mean follow-up period of 4.2 ± 2.1 years, patients with reversible perfusion deficits had a 3-fold

increased risk of major adverse cardiovascular events, with significantly more cardiac deaths ($P < 0.0001$) and nonfatal myocardial infarctions ($P < 0.001$)^[68]. Similarly the data from DSMR mirrors the results of first-pass perfusion CMR with a negative study conferring an equally low annual event rate of 1.3%^[66,69]. Recently the five-year outcome data from CE-MARC were published with prognostic data for both CMR and SPECT in the same patient population. The analysis showed that although an abnormal result from both tests was a strong indicator of future major adverse cardiovascular events (MACE), CMR was superior at predicting time to MACE in this population^[70]. Furthermore CMR remained the only independent predictor of outcome after adjustment for major cardiovascular risk factors, stratification for initial patient treatment and coronary angiographic findings^[70]. These findings likely reflect CMR's overall greater diagnostic accuracy, combined with CMR's higher spatial resolution enabling greater identification of subendocardial scar compared to SPECT^[71]; a feature known to confer prognostic significance beyond ejection fraction, and clinical or angiographic features^[72].

EARLY AND LATE GADOLINIUM ENHANCEMENT IMAGING

GBCAs have a large molecular weight and cannot penetrate an intact cell membrane; consequently GBCAs are constrained to the extracellular space. In healthy myocardium the extracellular space is limited and contrast enters and clears rapidly. The extracellular space in infarcted myocardium however is substantially increased compared to normal myocardium and is less vascular. Thus in chronic myocardial infarction scar tissue composed of a matrix of collagen fibres has significantly increased extracellular space, leading to GBCA accumulation (slow washout), whilst in acute infarction GBCAs passively diffuse across disrupted myocardial cell membranes and into the intracellular space (greater volume of distribution)^[73]. Thus both acute and chronic myocardial infarction retain more GBCAs. Imaged with T1 sensitive acquisition methods, this results in a higher signal.

Early gadolinium enhancement imaging is performed immediately following contrast administration; this allows mainly the visualisation of ventricular thrombi that appear "dark/black" due to a lack of contrast uptake as they are non-vascular (Figure 4). CMR has been shown to be superior to both trans-thoracic echocardiography and trans-oesophageal echocardiography for the identification of ventricular thrombi^[74,75]. LGE imaging is performed between 10-20 min after contrast administration, an appropriate inversion time is set to null the normal myocardium and the areas where gadolinium is retained enhances (Figure 4). Typically a stack of short axis slices, a 4-chamber view and VLA are acquired. Alternatively, 3D LGE CMR imaging enables whole heart quantification of scar burden to be acquired in a shorter time period (although with a reduction in image quality), which may

provide an alternative for patients that struggle to breath-hold^[76,77].

VIABILITY ASSESSMENT

CMR viability assessment using LGE enables the accurate detection, and extent and trans-murality of previous myocardial infarction to be determined, and identifies regions with potential to recover function following revascularisation. Hibernating myocardium is dysfunctional myocardium that has been down-regulated through a process of chronic/repetitive ischaemia and which has the potential for functional recovery when blood flow is restored. LGE imaging detects replacement of normal viable myocytes by focal necrosis or fibrosis with high spatial resolution, and has excellent correlation to histopathology^[73]. Furthermore the degree of transmural extent of hyper-enhancement on LGE imaging has a direct association to the potential for functional recovery following revascularisation; Kim *et al*^[78] demonstrated that segments with less than 25% hyper-enhancement were most likely to attain functional recovery whilst segments with over 75% hyper-enhancement were unlikely to improve, notably this was irrespective of whether the region was initially hypokinetic, dyskinetic or akinetic. A meta-analysis of 331 patients using 50% trans-murality of hyper-enhancement reported a sensitivity of 95% (95%CI: 93%-97%) and specificity of 51% (40%-62%) for predicting functional recovery^[79].

CMR viability assessment is not however limited to just LGE imaging; whilst LGE identifies the transmural extent of scarring, the use of low-dose dobutamine (LDD) identifies the contractile reserve. Myocardium is considered viable if there is a 2 mm or more increase in systolic wall thickening within a segment following administration of LDD (5-10 mcg/kg per minute)^[80]. While scar burden on LGE has been shown to be most sensitive method for assessment for functional recovery compared to LDD and diastolic wall thickness^[81], LDD CMR offers higher specificity and PPV for prediction of functional recovery (91% and 93%, respectively)^[79]. Consequently a stepwise approach utilising LGE first followed by LDD if the trans-mural extent of LGE in the territory of the diseased coronary is between 1%-50% has been proposed^[82]. Recently both tissue tagging and feature tracking have been used to give quantitative viability assessment with LDD and have been suggested as possible methods to reduce reliance on operator experience in what is currently a qualitative method of assessment^[83-85].

LGE imaging has a grade A recommendation to determine myocardial viability prior to revascularisation in the ACCF/AHA/SCMR appropriate use guidelines^[86], though viability assessment by LGE is currently not recommended for this indication in ESC or US practice guidelines for management of stable CAD or coronary revascularisation^[6,7,9,87]. The utility of viability assessment has been questioned recently following the results of the STICH trial and the subsequently published viability sub-study that showed no mortality benefit from re-

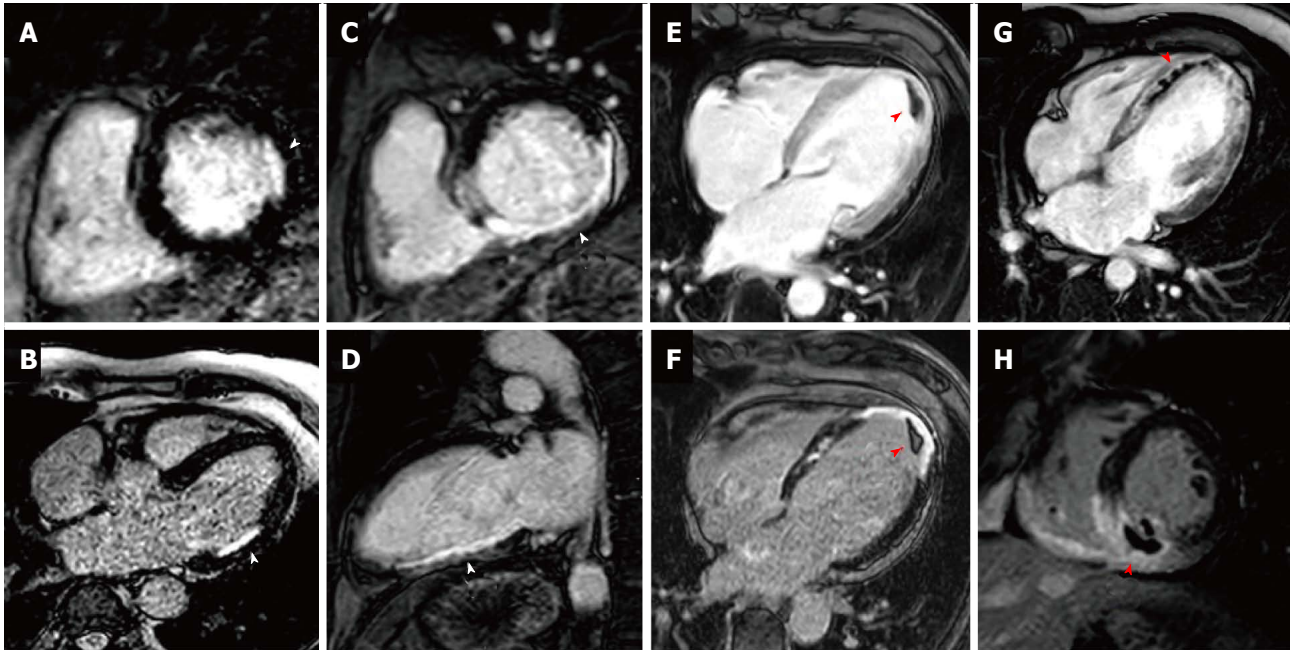


Figure 4 Early and late gadolinium enhancement. A and B show a lateral sub-endocardial infarction on short axis and 4 chamber LGE respectively; C and D show a full thickness inferior infarction on LGE imaging on short axis and VLA respectively; E and F show EGE and LGE imaging respectively of a full thickness apical infarction with an apical thrombus appearing black (highlighted by red arrow); G shows an extensive acute antero-apical infarction with a core of microvascular obstruction visible within the hyperenhancement on EGE (red arrow); H shows an acute inferior wall infarction with MVO and extension into the right ventricle on LGE (red arrow) imaging. LGE: Late gadolinium enhancement; EGE: Early gadolinium enhancement; MVO: Mitral orifice.

vascularisation following viability assessment^[88,89]. This is contrary to prior observational data in large meta-analyses including over 3000 patients with viability; revascularisation was associated with 79.6% reduction in annual mortality ($P < 0.0001$) compared with medical treatment^[90,91] and presence of dysfunctional viable myocardium by LGE-CMR without revascularisation is an independent predictor of mortality in patients with ischemic LV dysfunction^[92]. Questions have been asked however whether the STICH sub-study results would have been different if CMR had been used rather than SPECT, and consequently in Europe the third highest indication for CMR remains the assessment of viability^[93].

SCAR BEYOND VIABILITY ASSESSMENT

In addition to identifying viable myocardium, the presence and extent of LGE provides valuable prognostic information, and the extent of scar burden by LGE is readily quantified and reproducible on CMR^[94]. Impairment of left ventricular ejection fraction is well recognized as an independent risk factor in those with coronary artery disease^[8,95]; LGE can provide additive prognostication in these patients and a recent study of 1560 patients established that the presence of scar by LGE irrespective of LVEF identified those at risk of increased mortality^[96]. Furthermore a meta-analysis showed that the presence of LGE increases the risk of death by 4.77% and MACE by 3.9% and that each gram of scar measured by LGE increased the hazards of death and MACE by 4% and 5%, respectively^[97]. Additionally the identification of previously unrecognized MI by LGE confers a significantly increased

risk of both mortality and MACE^[72,98].

The extent of scar burden by LGE in patients with ischaemic heart disease has also been identified in a number of studies to be an independent predictor of ventricular arrhythmias in patients with internal cardiac defibrillators (ICD)^[99-101], and a recent meta-analysis of 1105 patients with ICDs determined that the extent of LGE was predictive of ventricular arrhythmia whilst LVEF was not^[102]. Additionally in a high risk cohort of patients with a mean LVEF of 35% being considered for ICD implantation, LGE demonstrated that significant scarring ($> 5\%$ LV) in patients with LVEF $> 30\%$, conferred a risk similar to those with LVEF $\leq 30\%$ ^[103]. Equally, in patients with LVEF $\leq 30\%$, minimal or no scar burden established a lower risk cohort similar to those with LVEF $> 30\%$ ^[103]. Other studies have identified the presence of a "grey zone" on LGE imaging, a heterogeneous region of viable and non-viable myocardium at the infarct periphery, as predictive of VT^[104,105].

LGE and quantification of scar burden has also been used to predict responsiveness to cardiac resynchronization therapy (CRT)^[106], and identification of scarring in the pacing region of the LV lead has been associated with non-response to device therapy^[107,108]. In a similar method to imaging the coronary artery anatomy, coronary venous anatomy can be reliably demonstrated using GBCAs, which can potentially aid planning of device implantation^[109]. The combination of coronary venous imaging, assessment of ventricular function and LGE may be a useful adjunct in the management of patients with ischaemic cardiomyopathy being considered for CRT, as well as risk stratifying those being considered for

defibrillator therapy.

COST EFFECTIVENESS

The economic burden of CAD is enormous with £6.8 billion spent in 2012 in the United Kingdom; in the United States over 15 million people have CAD costing the US economy \$108.9 billion/year^[110,111]. Cost effectiveness analyses help to inform optimal management pathways in order to maximise health care benefit within the constraints of limited resources. In the United States a low yield has been reported at diagnostic angiography with just over 40% of patients referred having obstructive CAD^[5]. CMR can act as a potential gatekeeper to invasive coronary angiography in order to reduce downstream costs as well as reduce risk from unnecessary invasive assessments.

Health economic analyses based on the CE-MARC dataset identified that despite the higher initial cost of CMR to SPECT, the superior diagnostic accuracy of CMR lead to an overall greater cost effectiveness in models of the United Kingdom, German and Swiss healthcare systems^[112-114]. A study of 1158 German patients being investigated for suspected CAD were randomised to either DSMR prior to angiography or direct to angiography; DSMR prior to invasive angiography led to a saving of 12466€ of hospital costs per life year, furthermore this cost saving was maintained through a median period of 7.9 years follow-up^[115].

In a cost analysis comparing CMR and X-ray angiography vs angiography and FFR to determine the need for revascularisation, CMR and angiography was more cost-effective below a CAD prevalence of 62%, 65%, 83% and 82% for the Swiss, German, United Kingdom, and the United States health care systems, respectively^[116]. These studies confirm that as well as the established high diagnostic accuracy, CMR is also a financially advantageous investigative strategy in patients with CAD.

RECENTLY PUBLISHED AND FUTURE STUDIES

Studies thus far have predominantly focused on the diagnostic accuracy of CMR; forthcoming multi-centre clinical effectiveness trials are however focused on evaluating clinical pathways to improve patient outcomes. The recently published CE-MARC 2 trial is a prospective, multi-centre, 3-arm parallel group, randomised controlled trial comparing multi-parametric CMR vs UK NICE CG95 guidance^[14] vs AHA/ACCF SPECT appropriate-use criteria^[117] to investigate patients with suspected CAD (pre-test likelihood 10%-90%) requiring further investigation^[118,119]. The primary outcome measure was FFR defined unnecessary angiography (FFR > 0.8) with the important safety secondary outcome measure of MACE at 1 and 3 years. CE-MARC 2 showed overall that CMR guided care resulted in significantly reduced rates of

unnecessary angiography at 12 mo compared to routine guideline directed care^[119].

Contemporary registry data from the United States suggests roughly 12%-26% of elective PCI are deemed inappropriate with considerable variation in practice between sites^[120,121]. Both FAME and DEFER showed improved outcomes using FFR guided revascularisation based on ischaemia detection, compared to reliance on visual assessment at angiography^[122,123]. These trials would suggest that a better way of selecting patients prior to invasive revascularisation procedures is required. CMR offers a non-invasive ischaemia assessment and the MR-INFORM trial aims to establish if perfusion CMR could act as a non-invasive surrogate to FFR to determine the need for revascularisation in patients with stable CAD^[124]. MR-INFORM is a multi-centre, non-inferiority study comparing adenosine perfusion CMR vs angiography with FFR measurement to guide revascularisation decisions in patients with stable angina and moderate to high probability of CAD; the primary endpoint is the occurrence of MACE at one year. The trial has completed recruitment and is expected to report in 2017.

The prognostic benefit of revascularisation in stable coronary artery disease is a topic of debate; both the COURAGE trial and BARI-2D failed to show any prognostic benefit of revascularisation over optimal medical therapy (OMT) in patients with stable CAD^[125,126]. Determination of extent of ischaemia in both these 2 trials was however limited; in COURAGE only 33% of patients had moderate/severe ischaemia and moreover around 40% had < 5% ischaemia^[127]. In both trials however those with a higher residual ischaemia burden had a worse prognosis^[127-129]. The ISCHEMIA trial aims to test the hypothesis that a routine invasive strategy with early cardiac catheterisation and revascularisation plus OMT is superior to a conservative management strategy of OMT for patients with moderate or severe ischemia^[42]. The trial aims to recruit over 8000 patients worldwide with ischaemia determined by non-invasive imaging (CMR, stress echocardiography, SPECT) with a primary endpoint of time to cardiovascular death or non-fatal myocardial infarction.

Coronary artery evaluation

Coronary MRA (CMRA) allows the non-invasive anatomical assessment of coronary arteries; currently clinical indications are limited to the detection of aberrant origin of coronary arteries, coronary ectasia and/or aneurysms (class I indication) and evaluation of bypass grafts (class II indication)^[130,131]. CMRA for diagnosis of CAD is not presently part of routine clinical practice. The initial multi-centre experience using CMRA in this context showed interpretable image quality in 84% of proximal and middle coronary artery segments, though with a specificity of 42%; CMRA did however exclude triple-vessel disease and left main coronary artery stenosis with a negative predictive value of 100%^[132]. Progress in CMRA techniques have improved significantly however, and a recent multi-centre study showed that CMRA at 1.5T detects significant

CAD with a sensitivity of 88% and specificity of 72% and a negative predictive value of 88%^[133]. Furthermore one study showed in a direct comparison between CMRA and CT coronary angiography (CTCA) there was no significant difference between coronary imaging at 3.0T and 64-slice CTCA for the detection of CAD with a sensitivity of 87% vs 90% ($P = 0.16$) and specificity of 77% vs 83% ($P = 0.06$) respectively^[134].

Currently CMRA techniques are time consuming and there are questions over the incremental diagnostic merit they provide in addition to established perfusion protocols; the CE-MARC study found no additional diagnostic benefit by including CMRA into a full multi-parametric protocol vs the perfusion/LV function/LGE combination (overall accuracy 84.6% vs 84.2% ($P = 0.5316$))^[23]. Moreover there was no significant improvement in diagnostic accuracy when CMRA was added to perfusion imaging at 1.5T and compared to FFR as the reference standard^[135].

FUTURE DIRECTIONS

T1 mapping

Native T1, T1 mapping, and extra cellular volume fraction quantification are novel methods for CMR tissue characterisation. These techniques are currently research tools that have shown promise for diagnosis and prognostication in acute coronary syndromes and other rare disease processes (*e.g.*, Amyloid and Fabry's disease), presently however they do not have an established role in the diagnosis or management of stable ischaemic heart disease^[136,137]. Post myocardial infarction however a role for these imaging "biomarkers" is being established in predicting both prognosis and adverse LV remodelling^[138,139].

Blood oxygen level dependent

CMR uses the paramagnetic properties of deoxyhaemoglobin as an endogenous contrast agent; increasing deoxyhaemoglobin content leads to a reduction of signal intensity on T2 or T2* weighted images^[140]. The magnitude of the BOLD effect depends on the static magnetic field strength, with an exponential increase at 3.0T from 1.5T; consequently most studies have used 3.0T. Thus far BOLD has shown good correlation with QCA and conventional CMR perfusion imaging, but studies are generally small and single centre, limiting its clinical validation^[141,142].

Finally hyperpolarised CMR is making the transition from animal studies to human applications. Hyperpolarisation methods artificially increase the number of molecules in one orientation resulting in a significant increase in MR signal; combined with ¹³C enriched metabolic tracers enable real time imaging of *in vivo* substrate metabolism, coronary angiography and quantitative perfusion imaging^[143]. The results of human hyperpolarisation studies are eagerly awaited.

CONCLUSION

Over the last decade the evidence base for the diag-

nostic accuracy of CMR for the investigation of stable coronary artery disease has been confirmed through the publication of large-scale clinical trials and meta-analyses, and CMR is now firmly established in clinical practice guidelines. CMR enables assessment of cardiac dimensions, function, ischaemia, scar burden and tissue viability in a single study without exposure to ionising radiation. CMR also offers prognostic information with a normal stress CMR associated with a < 1% risk of death or MI at 2 years, whilst the presence of LGE confers added prognostication above and beyond simple LV ejection fraction. New technical developments continue apace and ongoing large clinical trials will further clarify the role of CMR in routine clinical practice and guide the future development of international guidelines.

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