Coronary Artery Disease: Comprehensive Evaluation by Cardiovascular Magnetic Resonance Imaging
RS Tan, MBBS, MRCP, KKW Chen, MBChB, MRCP, FRCR

Abstract
Cardiac magnetic resonance (CMR) imaging has emerged as an important non-invasive cardiac imaging modality. A versatile technique, it has the potential for comprehensive evaluation of coronary artery disease (CAD): cardiac morphology and function, myocardial perfusion, myocardial viability, coronary artery visualisation and atherosclerotic plaque characterisation. Some of these techniques – ventricular function and myocardial viability assessment – have already made mainstream clinical impact. Other techniques have yielded promising initial results, and will become increasingly accepted with technical refinement in scanner hardware and software. This article reviews the current status of clinical CMR imaging for diagnosis of CAD.

Key words: Coronary artery, Perfusion, Ventricular function, Viability

Introduction
Coronary artery disease (CAD) is a major health problem worldwide. With advances in CAD intervention and improvements in treatment and management of CAD, there has been a dramatic increase in the survival rate of patients. This, combined with the effects of an ageing population, has resulted in a growing number of patients with chronic ischaemic heart disease. Detection of disease and evaluation of its severity and complications are important to clinicians. Cardiovascular magnetic resonance (CMR) imaging has the potential for comprehensive non-invasive evaluation of CAD: cardiac morphology and function, myocardial perfusion, myocardial viability, coronary artery visualisation and atherosclerotic plaque characterisation. Comparison with other imaging modalities is contentious and frequently reflects individual institutional expertise. The comparison is inevitably ever in a state of flux as technical improvements and experience evolve in each modality (Table 1).

Modern CMR scanners, enhanced by fast magnetic gradient performance, innovative pulse sequence design and parallel imaging techniques, routinely produce high quality images within reasonable examination times. Unlike invasive cardiac catheterisation, computed tomography (CT) and radionuclide imaging, there is no exposure to ionising radiation or nephrotoxic contrast media. Patient-friendly scanner design, use of silent CMR pulse sequences and the availability of non-ferromagnetic physiologic monitors and resuscitation equipment enhance patient comfort and safety. Due to the potential for device malfunction and induction of ectopy or heat injury, CMR should not be performed in patients with implanted cardioverter-defibrillators, active permanent pacemakers or ventricular assist devices. The presence of well-deployed (and well-epithelised) coronary artery stents and mechanical prosthetic heart valves are not contraindications to CMR.

Ventricular Morphology and Function
Most clinical CMR imaging protocols include ECG-gated cine images acquired in planes parallel and orthogonal to the left ventricular major axis, similar to standard echocardiographic views (Fig. 1). Abnormalities of left ventricular wall motion and thickening can be identified by studying endocardial and epicardial contour excursion. The presence of myocardial thinning suggests prior infarction. Complications of myocardial infarct such as mural thrombus, aneurysmal dilatation, ventricular septal and papillary muscle rupture are readily recognised (Fig. 2). Grid tagging (using spatial modulation of magnetisation pulse sequences) improves assessment of wall motion abnormality.

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CMR can image the heart with large fields of view, free of acoustic window limitations. It provides precise and highly reproducible quantitative measurements of chamber volumes and function. Typically, a stack of short axis cine images encompassing both ventricles from base to apex is acquired in about 10 breath-holds, each lasting about 10 seconds. Ventricular volumes are measured using Simpson’s method of discs (Fig. 3). This method makes no geometric assumption, and is the gold standard for assessment of the right ventricle, the complex shape of which defies assumption, and is the gold standard for assessment of the right ventricle, the complex shape of which defies geometric analyses.10 It is anticipated that in the near future, automated analysis software programmes will become commercially available for routine clinical quantitative myocardial perfusion analysis.

Myocardial Ischaemia

The ischaemic cascade describes the temporal sequence of events that occur during myocardial ischaemia: coronary flow heterogeneity (subendocardial hypoperfusion followed by transmural hypoperfusion), diastolic dysfunction (abnormal myocardial relaxation), systolic dysfunction (diminished contraction), ECG changes and angina. CMR detection of differential myocardial perfusion and contractile abnormalities with pharmacological stress (it is impractical to exercise within the CMR scanner) are 2 strategies for diagnosing myocardial ischaemia.

Vasodilator Stress Myocardial Perfusion Imaging

In myocardial perfusion imaging, temporally resolved multi-slice images of the heart are acquired during first pass following intravenous administration of paramagnetic contrast agent gadolinium-diethylenetriaminepentaacetic (Gd-DTPA). The latter increases T1-weighted tissue signal intensity (SI) as it transits the heart (Fig. 4). With qualitative assessment, reversible perfusion defects (areas of decreased SI) visualised during maximal vasodilatory pharmacological stress (induced with intravenous adenosine) but not during rest indicate ischaemia. The superior spatial resolution afforded by CMR allows delineation of perfusion differences between subendocardial and subepicardial myocardium. Hypoperfused myocardium characteristically appears as a persistent dark subendocardial rim. Experience is, however, needed to discriminate dark subendocardial ring image artifacts, which are typically transient, from true regions of ischaemia.

CMR perfusion studies may be analysed using a semi-quantitative approach. Regions of interest can be drawn within any area of myocardium, and SI versus time curves generated. Semi-quantitative indices of myocardial perfusion include peak SI, first derivative of upslope (derived from curve fit of first-pass SI data), time to peak, mean transit time and area under SI curve. Of these, the regional myocardial upslope parameter, normalised to the upslope parameter of left ventricular blood pool, has been most widely investigated. Decreased regional myocardial perfusion reserve index, i.e. the ratio of stress upslope parameter to its rest value, has been demonstrated to correlate with epicardial artery stenosis. 7,9

Gd-DTPA is an extravascular contrast agent. Besides myocardial blood flow, vascular permeability and contrast medium distribution also influence SI. Due to the non-linear relationship between SI and myocardial blood flow, quantitation of absolute myocardial blood flow requires complex mathematical analyses.10 It is anticipated that in the near future, automated analysis software programmes will become commercially available for routine clinical quantitative myocardial perfusion analysis.

High-dose Dobutamine Stress CMR

Dobutamine has been used for stress wall motion imaging in conjunction with cine CMR. Nagel et al11 compared high-dose dobutamine stress echocardiography (with harmonic imaging) and CMR in 208 consecutive patients with suspected CAD who all underwent subsequent coronary angiography. CMR yielded better image quality with improved sensitivity (86% vs 74%) and specificity (86% vs

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Table 1. Imaging Modalities in the Assessment of Coronary Artery Disease

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- Not applicable; * Limited role; † Fair; ++ Good; +++ Excellent

*Cath: cardiac catheterisation; CMR: cardiac magnetic resonance; CT: multi-slice computed tomography; Echo/MCE: echocardiography and microbubble contrast echocardiography; Nucl/PET: radionuclide perfusion imaging, radionuclide ventriculography and positron emission tomography.
Fig. 1. Typical CMR cardiac imaging planes. Long-axis views: 2-chamber, 3-chamber (left ventricular outflow tract view) and 4-chamber views (top row, left to right). Short-axis views: basal, mid and apical views (bottom row, left to right). Ao: Aorta; LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle.

Fig. 2. Chronic inferior myocardial infarct with pseudoaneurysm formation. Two-chamber (left) and short-axis (right) views. The pseudoaneurysm neck (arrows) is narrow relative to the body. Within its cavity, note mural thrombus (asterisk).

Fig. 3. Simpson’s method of discs. Four-chamber cine image of the heart, from which a stack of short-axis slices, each with equal slice thickness and interslice gap, is positioned to cover the left and right ventricles from the atrioventricular junction to the apex. At each slice, endocardial contours are traced at end-diastole and end-systole. The ventricular volume contained within each slice is the product of the planimetered area and the interslice distance between contiguous images. End-diastolic and end-systolic ventricular volumes are derived from summation of the slice volumes at the appropriate cardiac phases; and ejection fraction calculated accordingly.
Fig. 4. Stress myocardial perfusion imaging demonstrating septal wall ischaemia. Mid-ventricular short-axis images acquired sequentially during first pass infusion of Gd-DTPA, at the 1st, 7th, 10th (top row, left to right), 25th, 30th and 45th (bottom row, left to right) heart beats after start of scan. Note passage of contrast from the right ventricle to the left ventricle. Normal myocardium is brighter than hypoperfused myocardium, and attains the peak intensity faster. The persistent dark rim at the septal subendocardium (arrowheads) represents ischaemia. Typically, CMR perfusion imaging is performed during maximal vasodilatory stress (intravenous adenosine 140 µg/kg/min for 6 minutes; image acquisition at 3 minutes) and rest. Two separate boluses of Gd-DTPA are given at a sufficient time interval apart to allow for washout of the initial dose. Subsecond rapid CMR images of Gd-DTPA first pass through the myocardium are acquired in multiple slices (usually 3 to 4 short axis slices) at a temporal frequency of once every 1 to 2 heart beats, for about a minute.

Fig. 5. Recent anterior myocardial infarct. Two-chamber cine CMR image (left), and delayed hyperenhancement image acquired using a special pulse sequence to null myocardial signal intensity (right). Note transmural hyperenhancement of anterior and apical walls (arrow) indicating infarct. The dark area within the infarct core (arrowheads) indicates microvascular obstruction.

Fig. 6. Respiratory-gated free-breathing CMR imaging of the right coronary artery (arrow) in a healthy subject. The dark vertical band at the right hemidiaphragm represents the navigator echo used for respiratory gating.
patients with uninterpretable echocardiographic images, Hundley et al.\textsuperscript{12} established that inducible ischaemia on dobutamine stress CMR was predictive of major adverse cardiac events.

Improved endocardial visualisation is the main CMR advantage in these studies. The validity of this conclusion needs to be re-examined given the widespread use of recently Food Drug Administration (FDA)-approved microbubble echocardiographic contrast agents, which opacify the left ventricular cavity and greatly enhance echocardiographic endocardial border definition.

**Myocardial Viability**

With advances in medical management, there has been a gradual decline in deaths from myocardial infarction, and a striking increase in the incidence of heart failure among survivors. Detection of dysfunctional but viable myocardium is important because of the potential for restoration of contractile function following revascularisation. Identification of non-viable myocardium is equally important: patients are prevented from undergoing high-risk revascularisation procedures that are unlikely to confer survival benefit.

Thinned myocardium represents chronic healed transmural infarction. On cine CMR imaging, a wall segment with end-diastolic wall thickness \( \leq 6 \) mm connotes low likelihood of functional improvement with revascularisation.\textsuperscript{13,14} This criterion is, however, neither sensitive (recent transmural infarct with incomplete remodelling may not appear thinned) nor specific (viability may be maintained in thinned and akinetic segments in some cases) for myocardial viability. Additionally, low-dose dobutamine stress (up to 10 \( \mu \)g/kg/min) CMR may be used to assess contractile reserve, a marker of myocardial viability.

**Delayed Hyperenhancement**

The best way to detect non-viable myocardium with CMR is with a technique called delayed hyperenhancement (DE), whereby heart imaging is carried out 10 to 30 minutes after intravenous Gd-DTPA administration. DE exploits the altered magnetisation properties induced by increased tissue concentrations of Gd-DTPA in acute and chronic infarct tissues. In acute myocardial infarct, there is a relatively large volume of distribution and avid uptake of Gd-DTPA into the oedematous tissue. In chronic myocardial infarct with fibrous scarring, there is increased extracellular water surrounding the collagenous fibres, which augments Gd-DTPA retention within the scar tissue. By either means, great signal contrast between normal myocardium and infarct tissue is created as more Gd-DTPA washes out of normal myocardium and accumulates in infarcted areas (Fig. 5). In animal studies, the extent of DE correlates very well with myocardial necrosis on histological examination.\textsuperscript{15,16} In humans, the transmural extent of DE, in the setting of either chronic or acute myocardial infarction, is inversely related to regional and global contractile improvement after revascularisation.\textsuperscript{17,18} Transmural extent of DE less than 25% best predicts post-revascularisation contractile recovery. DE compares favourably with positron emission tomography (PET), the acknowledged gold standard for the assessment of viability.\textsuperscript{19}

In acute or recent myocardial infarct, imaging may in some cases reveal areas of markedly reduced SI within the bright infarcted areas. These represent regions of microvascular obstruction (“no reflow”) within the core of the infarct (Fig. 5). These areas are not perfused by the contrast medium, and will enhance extremely slowly. With time, these areas necrose and are resorbed as the myocardium undergoes remodelling. The presence of microvascular obstruction is an independent predictor of adverse prognosis.\textsuperscript{20}

**Coronary Artery Anatomy**

Many CMR techniques are used to image the coronary arteries. The plethora of methods underscores the daunting challenges facing the imager: small coronary vessel size, vessel tortuosity, cardiac and respiratory motion. Ultrafast pulse sequences are obligatory. Images are ECG-gated and acquired during diastole, where there is least cardiac motion. Breath-holding is used to eliminate the effects of respiratory motion. The breath-hold, typically about 30 seconds, imposes a constraint on vessel image resolution and the volume of coverage. Contrast medium may be utilised: image acquisition during first pass of Gd-DTPA increases vessel signal-to-noise ratio, and may plausibly improve coronary artery delineation. Alternatively, respiratory gating using a “navigator” pulse sequence which tracks diaphragmatic motion to ensure image acquisition only during end-expiratory apnoea, allows imaging with free-breathing. This enhances spatial resolution and vessel coverage, but at the expense of increased scan time (Fig. 6).

**Clinical Results**

Multiple single-centre studies of CMR coronary artery imaging using various techniques have produced promising results, with sensitivities approaching 90% for diagnosis of significant proximal coronary artery stenosis.\textsuperscript{21-25} Coronary artery stenosis appears as a discrete area of signal attenuation or dropout distal to the obstruction. Grading of stenosis severity is, however, less satisfactory as flow artifacts secondary to vessel tortuosity also produce signal dropout, resulting in overestimation of severity. In the only multi-centre trial of CMR coronary artery imaging, Kim et al.\textsuperscript{25} demonstrated the reproducibility of a standardised respiratory-gated clinical imaging protocol in multiple
centres in different countries. In this study, proximal, but not distal, segments of the coronary arteries were reliably visualised. Up to 16% of vessel segments were uninterpretable due to poor image quality. Although sensitivity of 93% was seen for identifying significant CAD, specificity was disappointingly low at 42%.

More technical refinements are required before CMR coronary artery assessment can become routine. Current niche indications for CMR include evaluation of anomalous coronary arteries (for which the 3-dimensional nature of CMR is a clear advantage over conventional angiography) and possibly coronary bypass graft patency.

Coronary Blood Flow

CMR measurement of coronary blood flow provides important physiological information, especially in coronary stenoses of intermediate severity. Good correlation between coronary flow reserve (ratio of coronary blood flow at maximal vasodilatory stress to that at rest) measured by magnetic resonance phase shift velocity mapping and invasive Doppler flow wire has been established in normal volunteers and patients with CAD. Among patients who have previously undergone percutaneous coronary intervention, CMR-assessed coronary flow reserve <2 has been reported to be sensitive and fairly specific for detecting flow-limiting restenotic lesions.

Atherosclerotic Plaque

High resolution, multi-contrast CMR imaging can non-invasively image vulnerable atherosclerotic plaques and characterise plaques in terms of their various components (lipids, fibrous cap, thrombus, calcium). Animal and ex vivo studies have shown remarkable correlation between CMR plaque appearance and histology. Most clinical studies have been validated on non-coronary vessels such as the iliac, abdominal aortic and carotid vessels. To date, there have been few studies on coronary vessel wall imaging in normal human volunteers and anecdotal reports on diseased clinical patients.

Imaging of extracoronary vessel wall, e.g. the carotid artery, provides excellent surrogate evidence of coronary atherosclerotic burden. Plaque extent and volume can be accurately measured, and its stability assessed. This valuable information offers a unique opportunity for studying disease pathophysiology, and may be used to follow natural disease progression and therapeutic intervention.

Conclusion

CMR offers comprehensive evaluation of ischaemic heart disease. Quantitative CMR assessment of ventricular function is the gold standard. DE has developed, in a few short years, into a highly accurate and impressive technique for myocardial viability assessment. CMR myocardial perfusion imaging is very promising and is at an advanced stage of development. It will become more widely accepted as quantitative analysis software becomes available. At present, non-invasive coronary artery and atherosclerotic plaque imaging have limited niche applications. To translate the encouraging initial results of specialised laboratories into the wider clinical arena will require more technical refinement.

CMR is a hybrid subspecialty that benefits from the collaboration between cardiologists and radiologists, whose expertise and experience are brought together. CMR’s unique capabilities complement, rather than compete, with other imaging modalities. The biggest clinical challenge facing CMR today is to integrate itself into clinical diagnostic and management pathways. With continual advances in the CMR machine performance, use of higher magnetic field strengths and novel image processing techniques, this will become a clinical reality in the near future.

REFERENCES


