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Cardiovascular Magnetic Resonance Imaging - What the General Cardiologist Should Know.

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ABBREVIATIONS

AAR	Area-At-Risk
AMI	Acute Myocardial Infarction
ASL	Arterial Spin Labelling
BOLD	Blood Oxygen Level Dependent Imaging
CAD	Coronary Artery Disease
CMR	Cardiovascular Magnetic Resonance
FFR	Fractional Flow Reserve
GBCA	Gadolinium Based Contrast Agent
GRE	Gradient Recalled Echo
IMH	Intra-Myocardial Haemorrhage
LGE	Late Gadolinium Enhancement
LV	Left Ventricle
MO	Microvascular Obstruction
MSI	Myocardial Salvage Index
RF	Radiofrequency
RV	Right Ventricle
SE	Spin Echo
SNR	Signal-to-Noise Ratio
SPECT	Single-Photon Emission Computed Tomography
T1	Longitudinal Relaxation Time
T1w	T1-weighted image
T2	Transverse Relaxation Time
T2w	T2-weighted image
TE	Echo Time

TR   Repetition Time

Learning Objectives

1. To understand basic CMR physics and to appreciate CMR safety issues, especially in relation to implanted medical devices and contrast agents.

2. To describe the common indications for performing a clinical CMR study.

3. To become familiar with the diagnostic ability of CMR and its influence on patient management.

Introduction

The recent developments in cardiovascular imaging have led to a number of options for the in non-invasive investigation of heart disease. Echocardiography, due to its widespread availability and relative cost, will remain the initial investigation of choice. Computed tomography coronary angiography (CTCA) and single-photon emission computed tomography (SPECT) are widely adopted internationally for the investigation of stable coronary disease, and positron emission tomography (PET) and hybrid technologies appear to have future potential.

Cardiovascular magnetic resonance (CMR) is an established advanced cross-sectional imaging modality for the functional and anatomical assessment of a wide range of cardiovascular disease. CMR is safe, does not use ionising radiation, provides diagnostic and prognostic information, and guides patient management.[1,2] The relative duration of the scan time, expense and lack of portability, however, puts the onus on CMR to demonstrate superiority over other imaging modalities. The extensive and growing evidence base for CMR has established it as the reference standard imaging test for many cardiovascular conditions. As such CMR is firmly

established in both national and international clinical guidelines[3-6] with recognised international training syllabi and accreditation/certification processes.[7-9]

CMR demand continues to expand, particularly in the UK, where there was a reported 253% increase in scans performed between 2008 and 2013.[10] There is also high demand in some European countries[1], which is being driven predominantly by increased referral rates for imaging of known/suspected coronary artery disease (CAD), cardiomyopathy and adult congenital heart disease (ACHD). A British Cardiovascular Society working group predicted that by 2015 there would be a need for ~2275 scans per million of population, which for the current UK population of over 60 million would equate to a trebling of demand in the 5 years from 2010-2015.

One of the key advantages of CMR is its multi-parametric approach, due to the availability of numerous different pulse sequences which can be applied to interrogate different aspects of the cardiovascular system and diagnose its pathological processes. Not all techniques can/are performed in all patients, therefore to select/request a comprehensive imaging protocol, the user should understand the full range of MR pulse sequences and their clinical applications. In this review we will outline the basic CMR physics and the pulse sequences, describe the established clinical indications and the application of CMR for these, and finally describe the emerging techniques and future developments.

A) Basic CMR Physics, Methodology & Safety

1. Basic CMR Physics

CMR imaging uses a strong superconducting magnet (cooled in liquid helium) to produce images with high spatial resolution, excellent soft tissue contrast and ability to define any tomographic plane.[11] The magnet operates at a field strength measured in units of Tesla (T), with 1T ≈ 20,000 times the earth's magnetic field. Three types of magnetic fields are used to produce images: a strong, static magnetic field (B0), magnetic field gradients (which can be rapidly switched on and off and are used to encode spatial information) and a radiofrequency (RF) field.

CMR uses the signal generated from magnetising hydrogen nuclei (protons) which are naturally abundant in biological tissues. When a patient is placed into the scanner the protons within free water and lipid molecules align their magnetic 'moment' (direction) either parallel or anti-parallel to the static B0 field. Slightly more nuclei align in the parallel direction, so together they produce a net magnetisation in the longitudinal direction. For imaging purposes an RF pulse is applied, delivering energy to the protons, which tilt the magnetisation away from alignment with B0 and into the transverse plane. When this extrinsic RF pulse is removed, magnetisation returns gradually to its equilibrium state, releasing this energy in the form of a radiofrequency signal. This process is repeated several times with different magnetic gradients applied to generate the image data.

The relaxation of protons back to their equilibrium state after withdrawal of the RF pulse is defined by two important parameters known as T1 and T2.[12] The T1 relaxation time is defined as the duration taken for approximately 63% of the recovery of longitudinal magnetisation to occur. This increases with increasing magnetic field strength. T2 relaxation is the time when 63% of the transverse magnetisation of

excited tissues has decayed and exhibits substantially less dependence on magnetic field strength. In biological tissues, T2 values are substantially shorter than T1. Fat has short T1 and T2 relaxation; fluids have long T1 and T2 relaxation; and non-fatty soft tissues (e.g. myocardium) have long T1 and short T2 relaxation.

Both the delay between successive RF pulses (Repetition Time, TR) and between each RF application and subsequent signal readout (Echo Time, TE) can be specified by the operator.[12] This is exploited for purposes of tissue characterisation by permitting imaging sequences preferentially weighted to T1 (T1w:short TE and TR,) or T2 (T2w:long TE and TR). Image contrast can also be adjusted by the introduction of additional magnetisation preparation steps, such as saturation or inversion RF pulses. The two most commonly used pulse sequence types in CMR are Spin Echo (SE) and Gradient Recalled Echo (GRE). SE sequences are generally used for static anatomical definition. SE produces high quality T1w and T2w images and is termed black-blood imaging (as blood appears black).[13] On T1w SE images, fluid typically appears dark and fat bright, whereas both are bright on T2w images.

GRE sequences permit fast cine acquisition (motion) with high temporal resolution and typically generate bright-blood images (both blood and fat are bright).[14] In addition to standard cine imaging, it is also possible to assess intra-myocardial motion by "tagging" the myocardium with a grid pattern and then tracking its deformation through the cardiac cycle.[15] Analysis of the displacement of tagging features permits measurement of myocardial strain, strain rate and torsion.[16] Furthermore the measurement of strain with feature tracking software using standard cine images is widely available.[17]

Flowing blood can be given a different phase value compared to stationary tissue when certain magnetic fields are applied. These are used in phase-contrast GRE

sequences, also called velocity encoded sequences, which are used to quantify blood flow velocity. A velocity image is by generated, known as a phase-map, in which pixel intensity depends upon the phase of the transverse magnetisation, rather than its magnitude.[18] Pixels are displayed as either dark (moving away from the phase-encoding direction), bright (towards) or mid-grey (stationary). Phase-contrast velocity mapping is typically used to measure blood flow e.g. aortic or pulmonary valvular regurgitation[19] and total flow volumes per cardiac cycle with both forward and reverse flow components measurable(Fig6e). CMR allows precise alignment of the imaging plane (in-plane or through-plane) with the direction of flow but is limited by temporal resolution (typically 25-45ms, 10-fold lower than Doppler echocardiography) and thus may underestimate peak values in high velocity jets (e.g. severe aortic stenosis).[20]

The duration of a CMR scan typically ranges from 30 minutes to an hour depending on the complexity of the referral question(s). Patients are breath-held for the acquisition of most images, which with modern fast scanners can be just a few seconds in duration, and this can be adjusted according to patient ability. Vector-cardiogram (equivalent to ECG) triggering and gating are used to prevent image distortion due to cardiac motion;[21] with cine images acquired during the entire cardiac cycle (prospective triggering or retrospective gating[22]) and static images preferentially acquired during diastole (prospective triggering). Most images are acquired over a number of cardiac cycles (segmented imaging) such that arrhythmias and poor breath holding can degrade image quality,[23] although in most cases diagnostic quality information can still be obtained by using arrhythmia rejection algorithms, non-breath holding (free breathing) or single-shot acquisition.

2. Image Quality and Artefacts

CMR image acquisition can be associated with a number of classical artefacts,[24] although in the vast majority of cases an experienced technologist can minimise these to produce diagnostic quality images. The most common include:

- Image aliasing: indicative of too small a field a view with signal from peripheral parts of the body wrapping centrally into the main image.

- Ghosting artefact from respiratory motion: caused by movement of tissue between each TR with subsequent misplacement of signal in the image.

- Arrhythmia artefact: Cardiac arrhythmia, or poor quality ECG triggering, generates cardiac motion artefacts during cine acquisition due variation in R-R intervals.

- Chemical shift artefact: typically a signal void at the interface between fat layers and surrounding water-based tissue. It is important to recognise in order to avoid misinterpretation e.g. the false impression of aortic wall dissection "flap".

- Metallic artefact: can significantly degrade images, appearing as a large signal void and surrounding geometric distortion; particularly affecting GRE based pulse sequences.

- Dark–rim artefact: refers to a band of transient low signal in the endocardium during first-pass perfusion imaging when contrast agent first enters the LV cavity. Unlike genuine regions of hypoperfusion the low signal resolves within a few heartbeats as myocardial enhancement occurs.

- Complex flow signal loss: Turbulent blood flow commonly associated with valvular pathology can cause phase shift dispersion and appear as signal loss artefact. Caution is required as the area of signal void may not be directly related to the severity of the valve lesion.

Further reading on this subject can be found in this 2-part review.[12,18]

3. CMR Safety and the Safety of Implanted Medical Devices

The magnetic field of the MR scanner is ALWAYS on and although the magnetic field is strongest within the bore of the magnet, the surrounding fringe field can also adversely affect pacemakers and other implants. Importantly, any ferromagnetic objects will accelerate towards the magnet bore, posing a projectile hazard with potentially fatal consequences (e.g. oxygen cylinder, wheelchairs etc). For these reasons, health and safety regulations dictate a controlled area must be defined enclosing the 0.5mT fringe field.[25] Access to this area is restricted to trained staff, and patients who have been screened in particular for pacemakers, cerebral aneurysm clips and ocular foreign bodies. Items of hospital equipment and medical devices should all be classified using the American Society for Testing Materials (ASTM) guidance as MR Safe, MR conditional or MR unsafe with procedures in place to ensure safe working practice.[26]

Both mechanical and bioprosthetic heart valves, including transcatheter aortic valve implants, and intracoronary and aortic stents are all generally considered safe to scan shortly after implantation. The online resource www.MRISafety.com provides an extensive list of tested medical devices/implants. MR conditional pacemakers and defibrillators are now increasingly being implanted. However, MR imaging remains conditional on meeting stringent manufacturer safety criteria and requires prior reprogramming and also immediate post-imaging parameter checks to ensure safe device operation before the patient leaves the department. Extra-cardiac implants and foreign bodies also need assessed for safety. Further reading from Dill et al. [27]

4. CMR Contrast Agents: Indications and Safety

Intravenously administered gadolinium chelate-based contrast agents (GBCA)(0.1-0.2mmol/Kg), are typically extracellular (distributing in both the intravascular and interstitial compartments) and highly paramagnetic,[28] shortening T1 relaxation times and increasing signal intensity on T1w images.

The reported incidence of allergic reactions to gadolinium is very low (~1:10,000); at least one order of magnitude lower than that of iodinated contrast agents.[29] The use of several GBCA in patients with advanced renal insufficiency has been associated with Nephrogenic Systemic Fibrosis,[30] although newer 'cyclic' contrast agents appear not to cause this condition. The FDA advises avoiding GBCA in patients with acute or chronic severe renal insufficiency (eGFR<30ml/min/1.73m^2), renal dysfunction of any severity due to the hepato-renal syndrome or in the perioperative liver transplant period (unless diagnostic information is essential and otherwise unattainable). Those patients with severe renal insufficiency receiving GBCA should be considered for haemodialysis to enhance the contrast agent's elimination. Although no harm has been reported during pregnancy, GBCA's cross the placental barrier and are not recommended in pregnant patients unless the benefits outweigh the risks.[25] Breastfeeding can continue uninterrupted after the use of GBCA.[31]

B. Established Clinical Indications for CMR

The most common referral indications for CMR are for the assessment of myocardial ischaemia & viability, heart failure, cardiomyopathy and ACHD. CMR offers a unique multi-parametric assessment, detailing anatomy, function and flow, delineating scar from healthy myocardium, providing accurate tissue characterisation and with the addition of stress techniques, can identify inducible myocardial ischaemia.[32] CMR is

the reference standard for assessment of left and right ventricular (RV) volumes and function.

1. Stable Coronary Artery Disease

CMR is established for the investigation of patients presenting with stable chest pain. The 2013 European Society of Cardiology (ESC) guidelines on the management of stable CAD[4] give a Class I recommendation (Level of evidence B) for non-invasive stress testing for those patients with a pre-test probability of 15-85%, with stress perfusion CMR being one of the recommended imaging options.

A CMR study for this purpose typically includes cine imaging in multiple planes for assessment of left ventricular (LV) volumes and global and regional function, stress and rest perfusion for myocardial ischemia and late gadolinium enhancement (LGE) for delineation of scar and assessment of viability (Fig1). The combination of the above techniques in a single multi-parametric exam allows the quantification of LV ejection fraction, ischemic burden and determines myocardial viability, which can be used to risk-stratify patients and guide revascularisation. Its use as a first line diagnostic tool in patients presenting with chest pain has been subject to recent large scale clinical trials showing high diagnostic accuracy for the detection of CAD.[33 34] One recent large meta-analysis of CMR for the detection of CAD demonstrated a pooled sensitivity of 89% (95%CI: 88%-91%) and specificity of 76% (95%CI:73%-78%).[35] Furthermore a normal stress perfusion CMR study is associated with a good prognosis.[36]

- Global and Regional LV Volumetric Assessment

CMR is the reference standard in terms of accuracy and reproducibility of quantitation of LV volumes, mass and for the assessment of regional and global systolic

function;[37] the latter remains the most powerful predictor of mortality in cardiovascular disease. LV volumes are performed with a contiguous stack of cine images parallel to the mitral valve annulus providing full coverage of the left ventricle (Video1). Full acquisition typically takes only a couple of minutes using breath hold techniques, and free breathing approaches are also possible.

- Myocardial Stress Techniques

Demonstration of myocardial ischaemia can be performed with either vasodilatory stress agents (adenosine, regadenoson and less commonly dipyridamole or nicorandil) or with an inotropic stress agent (dobutamine). Vasodilatory stress is the preferred method with a bolus of GBCA delivered at peak stress (Video2). On first pass perfusion CMR, relative hypoperfusion indicating ischaemia is detected by reduced/delayed peak signal intensity during the myocardial contrast passage. Conventional stress perfusion CMR images are typically acquired in 3 short axis slices every cardiac cycle to assess all segments of the AHA/ACC model (excluding the apical cap), although if imaging time allows additional views (for example a long axis view) may be acquired. Inotropic stress is mostly used to detect wall motion abnormalities in the presence of functionally significant coronary stenoses without the need for a GBCA (Video 3) although first pass perfusion imaging at peak inotropic stress may also be performed for additional value.[38] Performing pharmacological stress requires additional departmental safety procedures, including access to emergency drugs and resuscitation equipment. Despite the inability to monitor ECG ST-segment changes during stress, the rates of major complications are similar to other non-invasive stress imaging modalities.[1,39]

- Late Gadolinium Enhancement for Scar Detection and Viability Assessment

This technique typically involves GRE inversion recovery imaging around 10-15 minutes after the administration of a bolus of GBCA (0.1-0.2mmol/kg). The contrast agent in healthy tissue has a rapid wash-out and images are acquired such that signal from normal myocardium appears dark (black). In acute MI the volume of distribution of the contrast agent is increased due to the destruction of sarcolemmal membranes and wash-out is delayed, thus more contrast is retained at the time of imaging, shortening the T1 of the tissue. Imaging is performed so that infarcted myocardium appears bright (white). Similarly, in chronic MI, the presence of replacement fibrotic tissue increases the contrast volume of distribution, such that chronic MI's also appear bright (white). This process of tissue characterisation is unique to CMR and is now one of the most fundamental techniques in CMR practice (see later in this review).

- Coronary Artery Imaging

Unlike cardiac CT coronary angiography which produces exquisite anatomical images of the coronary arteries, the clinical utility of detection coronary artery stenosis by magnetic resonance angiography (MRA) remains to be established. This is due to the required long imaging times, more limited spatial resolution, and the impact of cardiac and respiratory motion on MRA image quality. The CE-MARC study demonstrated that the inclusion of MRA had no additional overall diagnostic benefit within the multi-parametric protocol of myocardial perfusion, left ventricular function and viability assessment [33,40], which has been supported by other CMR data[41]. Coronary MRA, however, is useful for detecting the location of coronary aneurysms (such as those seen in Kawasaki disease), and the presence of anomalous coronary arteries

with accurate delineation of their anatomical course[42]; the principal advantage of MRA being the lack of ionising radiation in children and younger adults.

- Cost Effectiveness of CMR

The use of CMR as the initial strategy for the detection of coronary artery disease has been shown to be cost effective using both the United Kingdom's National Institute for Health and Care Excellence guidance for lower and upper limit thresholds (£20-30,000) per quality adjusted life year (QALY)[43] and in other international healthcare models.[44,45]

- Future Clinical Direction

Technological advances in acquisition techniques (software) and hardware (scanners with higher field strengths and improved cardiac phased-array coils) have allowed the development of advanced perfusion techniques. These use highly accelerated pulse sequences based on spatio-temporal undersampling which allow the acquisition of high resolution images (in-plane<$1.5mm^2$)[46] permitting the detection of sub-endocardial myocardial ischaemia and 3D whole heart myocardial perfusion imaging with full left ventricular coverage.[47,48] Other techniques such as blood oxygen level dependent (BOLD) imaging[49] and arterial spin labelling (ASL)[50] are able to detect myocardial ischaemia without the use of contrast agents. BOLD uses the inherent magnetic differences between oxygenated and deoxygenated blood to detect differences in signal intensity in ischaemic vs. non-ischaemic myocardium, and is able to detect 'ischaemic' myocardium through the use of vasodilator stress techniques'.[49]. In terms of future CMR provision and clinical service planning, the National Horizon Scanning Centre suggested that CMR may become the gold

standard for assessing myocardial viability[51] and the preferred option for myocardial perfusion imaging.[52]

2) Acute Myocardial Infarction

Multi-parametric imaging with CMR has high diagnostic accuracy for the detection of CAD in the assessment of both ST-segment and non-ST-segment elevation acute coronary syndromes[53,54], and also has the ability to give insight into the pathological consequences of acute myocardial infarction (AMI).

- Myocardial Oedema.

Myocardial oedema occurs when prolonged ischaemia triggers an inflammatory response in reversibly injured myocytes and is a very early marker of acute myocardial injury, developing before both ischaemic myocardial necrosis or even troponin release.[55] T2w imaging is a non-contrast scan which exploits the different paramagnetic properties of water-bound protons with long T2 relaxation times to provide intrinsic (water-specific) image contrast(Fig2a). These images however typically have low signal-to-noise ratio (SNR) and require experience to interpret. This technique is able to differentiate acute from chronic infarction [56,57]. T2w imaging also allows accurate delineation of the area-at-risk (AAR) in acute infarction[56] and can be used to estimate myocardial salvage index (MSI), which is calculated by subtracting the infarcted area (determined by LGE imaging) from the oedematous area (AAR) as a measure of efficacy of revascularisation.[58] Since oedema can persist, even when ischaemic ECG changes and myocardial dysfunction have resolved, T2w imaging has become an useful research tool for the evaluation of novel antithrombotic and adjuvant revascularization techniques.

- Microvascular Obstruction & Intra-myocardial Haemorrhage

CMR is able to detect both microvascular obstruction (MO) and intra-myocardial haemorrhage (IMH). MO occurs after acute myocardial injury and correlates with the angiographic appearance of 'no-reflow' phenomena. By CMR it can be imaged during first-pass perfusion, early gadolinium enhancement (EGE) imaging (1-2min after contrast injection)(Fig2b) and LGE imaging (10-15min after contrast injection)(Fig2c).[59] MO appears as a dark core within the high-intensity infarcted areas and is a strong predictor of adverse ventricular remodelling and clinical outcome, independent of infarct size or LV ejection fraction (LVEF).[60-64]

Patients may be further stratified if IMH is detected within the area of MO. Severe structural and functional damage of the microcirculation allows extravasation of red blood cells through endothelial walls into the reperfused myocardium. IMH can be visualised as a hypointense core on T2 (Fig2a) or T2* imaging due to the paramagnetic effects of haemoglobin degradation products. IMH is a predictor of adverse remodelling[65], related to infarct size[66] and indicates worse prognosis over and above MO alone.[67] These individual markers may be more powerful predictors of outcome than the traditionally used LV ejection fraction.

- Thrombus & Other Post Myocardial Infarction Complications

The formation of ventricular thrombi on the endocardial surface of infarcted myocardium is a recognised complication of AMI. Thrombus is best observed with EGE imaging when signal in both myocardium and blood pool is bright, enhanced by the contrast agent (Fig2d&e). Thrombus is avascular and therefore appears as a dark filling defect within the bright blood pool. CMR has been reported to significantly

outperform trans-thoracic echocardiography for the identification of ventricular thrombi.[68,69]

Furthermore CMR is able to detect (Fig2f), accurately size and assess the haemodynamic significance of a post-infarct ventricular septal defect (VSD), potentially guiding the suitability and sizing for a percutaneous VSD closure device.[70] Accurate volumetric quantification of both the right and left ventricles, or comparison of flow measurements of the pulmonary and systemic circulations, can also be used to calculate the shunt ratio.

CMR is also useful in the detection of ventricular aneurysm (Fig2g&h), pseudoaneurysms (Fig2i and Video4) and assessment and quantification of mitral regurgitation post AMI. Furthermore the high spatial resolution of CMR allows the detection and quantitation of RV infarction with LGE (Fig2c) and cine imaging, which has additional prognostic importance.[71] Other settings where CMR plays a decisive role in clinical management is in those patients with Troponin-positive chest pain and unobstructed coronary arteries, where the main differential diagnoses include occult infarction, acute myopericarditis, atherosclerotic plaque rupture and thrombosis with spontaneous recanalisation, coronary artery spasm and Takotsubo cardiomyopathy (TTC).[72] Depending on the time delay between the CMR scan and the index event, CMR is able to identify the cause for troponin elevation in those with an apparently normal X-ray angiogram in 65-77% of patients.[72,73] Rates of myopericarditis reportedly range from 26-50% with occult myocardial infarction present in up to a third of cases and TTC in around a fifth of cases if scanned during the acute presentation.[73]

3) Assessment of Myocardial Viability to Guide Revascularisation

CMR assessment of myocardial viability in chronic stable CAD is achieved through either i) demonstration of the inotropic reserve of wall motion abnormalities with dobutamine; ii) more commonly, through the assessment of the transmurality of the infarcted myocardium with LGE imaging or iii) a combination of both.

Low-dose dobutamine stress CMR (5-10 mcg/kg/min) relies on the demonstration of inotropic reserve in post-ischaemic viable myocardium. Cine imaging is performed at each stage of inotropic stress to assess all segments of the left ventricular myocardium in order to determine wall thickness and contractility. A 2mm, or more, increase in systolic wall thickness during inotropic stress infers myocardial viability.[74] LGE imaging, is widely accepted as the imaging technique of choice for the accurate delineation of myocardial scar and hence assessment of viability. The transmural extent of hyper-enhancement predicts functional improvement after revascularisation.[75,76] Segments with <25% of transmural hyper-enhancement are likely to exhibit functional recovery, whilst those segments with >75% transmurality are unlikely to benefit from revascularisation, irrespective of the extent of the resting wall motion abnormality.[75] Furthermore transmurality of LGE is a stronger predictor of regional and global functional recovery following revascularization than resting end diastolic wall thickness.[77] The assessment of myocardial viability using a 50% transmural cut off on LGE imaging has been reported to have a sensitivity of 95% (95%CI: 93-97%) and specificity of 51% (40-62%) to predict segmental functional recovery following revascularisation.[76] Inotropic reserve assessed by low dose dobutamine has significantly higher specificity (91%)[76] suggesting a combination of the two techniques might improve diagnostic performance for those segments with 25-75% of transmural LGE.[78]

Shortly after acute MI the determination of the transmural extent of infarction may be over-estimated, as some of the hyper-enhancement on LGE imaging may be due to reversible myocardial oedema, rather than non-viable scar. Despite this, the transmural extent of hyper-enhancement has been shown to predict functional recovery when performed within the first week of an acute event.[79]

4) Non-Ischaemic Cardiomyopathies

CMR allows comprehensive evaluation of the patient with known or suspected cardiomyopathy and is recommended by the ESC guidelines for this purpose.[6] CMR is able to rule out underlying ischaemia/infarction, allows accurate estimation of biventricular volumes and function [37] and can quantify concomitant valvular heart disease. Characterisation of the extent and location of myocardial fibrosis with LGE imaging and quantification of extracellular fibrosis with T1 mapping can help diagnose and risk stratify a number of pathologies.[32] T2w pulse sequences can be used to identify myocardial oedema, and T2* pulse sequences to detect and quantify cardiac and liver iron overload in a variety of multiple transfusion syndromes (e.g. Thalassaemia[80]) and predict outcomes.[81]

The presence of LGE has been linked to adverse outcomes in a number of the cardiomyopathies. In dilated cardiomyopathy, the finding of mid-myocardial fibrosis (Fig3c) is associated with sudden cardiac death (SCD), malignant ventricular arrhythmias and heart failure events.[82-85] These finding have been replicated in the hypertrophic cardiomyopathy population, where the presence of LGE (Fig3a&b) has been associated with ventricular tachyarrhythmia[86] and a 2.5 times increased risk of SCD.[87,88] Similarly, there is evidence that presence of LGE pertains to an adverse outcome in cardiac sarcoid.[89-91]

Amyloidosis is a systemic disease caused by the deposition of misfolded proteins and cardiac involvement confers poor prognosis (Fig3f). CMR has led to increased detection of cardiac amyloidosis with the location and extent of LGE having been shown to differentiate amyloid subtypes.[92] Both the presence and transmurality of LGE[93] and T1 mapping[94] in amyloidosis determine prognosis. A low intra-myocardial T1 gradient (subepicardial T1 minus subendocardial T1) is indicative of increased amyloid deposition (spread of the disease from the endocardium to epicardium) and has been associated with reduced survival.[95] This is one of the clinical scenarios where quantitative reporting of T1 mapping can prove useful. Another is that of the x-linked lysosomal storage disorder, Anderson-Fabry disease, a treatable condition leading to concentric, non-obstructive ventricular hypertrophy due to the intracellular accumulation of cellular glycosphingolipid. Classically there is mid-myocardial LGE enhancement of the infero-lateral wall, and native T1 values are low.[96] Arrhythmogenic RV cardiomyopathy/dysplasia (ARVC/D) is an important cause of ventricular arrhythmias and SCD. The 2010 AVRC/D modified task force criteria recognise CMR as a key imaging modality to assist with this diagnosis. Regional RV akinesia/dyskinesia or dyssynchronous RV contraction and an indexed RV end-diastolic volume of $\geq110mL/m^2$ (male) or $\geq100mL/m^2$ (female) or RV ejection fraction $\leq40\%$ is considered a 'major criteria' for the diagnosis of ARVC/D (Video 5). Minor diagnostic criteria by CMR are RV wall motion abnormalities as above with indexed RV end-diastolic volumes ≥100 to <110 mL/m^2 (male) or ≥90 to <100 mL/m^2 (female) or RV ejection fraction $>40\%$ to $\leq45\%$.[97] Finally, with regard to acute myocarditis, the presence of LGE is the best predictor of mortality (Fig3d).[98] CMR also has a clinical role in the diagnosis of left ventricular non-compaction, transplant

cardiomyopathy, Chagas disease and chemotherapy induced-cardiomyopathy. Further reading from Parsai et al.[99]

5) Pericardial disease

Pericardial effusions are a common finding on routine cardiac imaging.[100] The physiological significance of which can be evaluated with cine imaging to assess for RV diastolic collapse, right atrial collapse and paradoxical motion of the interventricular septum. Inferior vena cava size can also be easily quantified and can be a marker of insipient cardiac tamponade.[101] Cross-sectional imaging occasionally identifies a primary (e.g. lung, breast) malignancy in the case of malignant effusions. T1 characteristics of the effusion can be helpful in determining its composition; a low signal usually represents transudate with a high signal suggesting an exudative effusion.[102] The intermediate T1 signal of blood and exudate renders them less easy to distinguish. Pericardial fluid is seen as high signal (bright) on cine imaging(Fig4c), and loculation and pericardial stranding can often be seen.[103] T1w axial black blood imaging is the best modality for the assessment of pericardial thickening (in the absence of pericardial effusion). Normal pericardial thickness on CMR imaging is 1.2 to 1.7mm,[104] and is best measured at the level of the RV free wall, as it can be difficult to identify along the lateral and posterior LV wall. Pericardial thickening of >4mm(Fig4b) is generally considered pathological and is often the result of pericarditis or malignancy.[104]

Pericardial constriction often presents a diagnostic challenge for the cardiologist. CMR can be used alongside cardiac CT (useful for quantification of pericardial calcification), echocardiography and invasive cardiac catheterisation to facilitate the diagnosis. In constriction the pericardium is usually, but not always, thickened; thickening may be

patchy or involve the entire pericardium. Bi-atrial dilatation is ubiquitous and there may also be distortion of RV morphology. Fast cine imaging during free breathing allows real-time evaluation of ventricular interdependence (Video6).[105] Myocardial tagging techniques allow the relationship between the pericardium and the myocardium to be assessed. In a normal heart, the pericardium can be seen to slide over the myocardium during systole. In constrictive pericarditis, the pericardium is adherent to the myocardium due to the presence of fibrous adhesions and the independent relationship during systole is lost.[106] Other pericardial diseases such as tumours, cysts and congenital pericardial conditions can be characterised using CMR (Fig4). Further reading from Bogaert and Francone.[102,103]

6) Vascular Imaging

CMR is well placed to perform serial vascular assessment due to its lack of ionising radiation and the relative safety of GBCA. Although CMR can be used to assess for acute aortic pathology, ease of access and fast acquisition protocols mean that CT is usually the modality of choice in this setting.[107] However, CMR is preferred for long-term serial monitoring of type-B dissection(Fig5d) or surgically repaired aortas(Fig5c). Alongside the important morphological information obtained by T1w black blood imaging, measurements can be taken from the sagittal oblique and left ventricular outflow tract (LVOT) cine images with a high degree of accuracy and reproducibility.[108,109] Three-dimensional data with contrast enhanced MRA may be acquired. MRA is a volume rendered technique which uses a fast contrast bolus during imaging of the region of interest as contrast passes through during the arterial or venous phase (Fig5b & Video7).[110] Whilst this is considered less accurate for taking specific measurements it can be helpful with surgical planning to demonstrate the

proximal and distal extent of aneurysms and for demonstrating branch vessels or collaterals.[111] CMR is increasingly used by the electrophysiologist to assist with planning for catheter ablation and pulmonary vein isolation for atrial fibrillation, using MRA of the pulmonary veins (Fig5b,e&f) which can be imported into the electro-anatomical mapping software in the catheter lab.[112]

7) Valvular heart disease

CMR is well placed to evaluate the adverse ventricular remodelling seen in chronic valvular heart disease. The high degree of contrast between valvular structures and blood pool on cine images allows valvular planimetry in most cases.[113,114] Phase-contrast imaging may be also used to calculate the aortic valve area (AVA) by the continuity equation. As with echocardiography, CMR may overestimate AVA by planimetry compared with the continuity equation .[115]

The presence and direction of regurgitant jets can also be visualised during cine imaging to act as guide for optimisation of velocity sampling (Fig6a-d). Phase-contrast CMR can be used for the assessment of stenotic lesions (Fig6e), although it shows a systematic underestimation of valvular gradients when compared with echocardiography. The technique is most useful for the quantification of valvular regurgitation, where CMR out-performs echocardiography.[116,117] In the case of aortic and pulmonary valve regurgitation, the regurgitant fraction can be reproduced with a high degree of accuracy (Fig6e), and regurgitant fraction derived from CMR imaging has been linked with outcome in this setting.[19,117] CMR has been demonstrated to have superiority over echocardiography for the assessment of mitral regurgitation[118] and is particularly useful post-transcatheter aortic valve implantation (TAVI)(for assessment of valvular and paravalvular aortic regurgitation).[119]

Mitral regurgitation fraction can also be calculated by subtracting the aortic forward flow (derived from phase-contrast velocity mapping) from the LV stroke volume. This can be helpful in patients with suboptimal echocardiographic imaging windows or when there is a degree of uncertainty of in the severity of the mitral regurgitation, usually in the case of eccentric jets which can be underestimated by echocardiography(Figure 6).[120,121] Furthermore CMR may concurrently assess the great vessels during the same examination, an important factor in cases such as bicuspid aortic valve disease (whereby coarctation and aortopathy commonly co-exist) and Tetralogy of Fallot (whereby pulmonary arterial tree malformations are common).

8) Cardiac Mass/Tumours

Although rare, the consequences of cardiac tumours, even those of benign aetiology, can be catastrophic. CMR is excellent for differentiating cardiac thrombi from tumours[122] and plays an important role in accurately identifying some cardiac tumours due to its ability to characterise tissue composition and to image in multiple planes. CMR is now recommended as a first line investigation in the diagnostic work up of those with a suspected tumour.[123] The CMR protocol in patients with suspected tumours includes multiple different image types. T1w axial black blood imaging allows the assessment of the entire thorax and can identify primary tumours or mediastinal lymphadenopathy, as well as the identification of pleural and pericardial involvement. T1w imaging with and without fat suppression allows the identification of benign lipomas. T2w imaging should be performed as the signal intensity of this compared with T1w imaging can help differentiate between various tumour types (cystic lesions for example appear very bright on T2w imaging)(Fig4a).[124] Cine imaging in at least 2 orthogonal planes is used to identify the size, mobility and extent

of the tumour in addition to its relationship with adjacent structures. Myocardial tagging can be used to assess for infiltration into adjacent myocardial tissue, which can be detected as subtle areas of contractile dysfunction. First pass perfusion imaging allows assessment of tumour vascularity, usually a prominent feature of malignant lesions. EGE and LGE imaging completes the CMR assessment of tumours to detect thrombus, scar and fibrosis; the latter is especially useful in the case of fibroma, where hyper-enhancement is very striking (Fig4de&f).

- Benign vs malignant lesions

The majority (~75%) of cardiac tumours are benign, the most common being myoxmas, lipomas, fibromas, papillary fibroelastomas and haemangiomas.[125] Benign cardiac lesions are usually well circumscribed with no evidence of local invasion. Malignant lesions tend to appear 'craggy' with heterogenous composition and are often associated with local invasion, pleural and pericardial effusions. The majority of malignant cardiac lesions are secondary metastases, however, primary cardiac tumours such as angiosarcoma and rhabdomyosarcoma are occasionally seen. 'Pseudotumours' seen as masses on echocardiography are often easily reclassified as extra-cardiac structures, normal anatomic variants or left ventricular thrombus by CMR. Further reading from Motwani et al.[124]

9) Congenital Heart Disease

A comprehensive review of the use of CMR in the assessment of paediatric and ACHD is beyond the scope of this article; CMR remains a ubiquitous imaging tool for the serial (life-long) assessment of many of these complex patients. The 2010 ESC guidelines on ACHD management provide a comprehensive review of the literature.[126] CMR is an essential part of the evaluation and management of many

patients with paediatric and ACHD due to the lack of ionising radiation and its ability to accurately assess all facets of the heart and great vessels, from accurate volume and mass quantification, great vessel characterisation, flow assessment and shunt calculation.[127] A common indication for CMR in this population is for the serial assessment of RV size and function in patients with repaired of Tetralogy of Fallot, where severe/free pulmonary regurgitation is commonly seen. In this setting, CMR assessment of RV volume and function can guide timing of pulmonary valve intervention.[126,128] Another common indication in the ACHD population is that of aortic coarctation assessment (Fig5a), especially for the assessment of aneurysm formation or re-coarctation at the site of previous surgical repair.

C. Future Direction

Currently, there are several large prospective, multicentre trials involving CMR,which are likely to shape future international guidelines, diagnostic pathways and utility of CMR in clinical practice. CE-MARC-2[129] is a multicentre randomised controlled trial designed to compare the management strategy of CMR vs. NICE guidance[5] vs. AHA/ACC SPECT appropriateness criteria,[52] for the investigation of patients with stable chest pain of suspected cardiac origin. Patients presenting with chest pain and a pre-test likelihood (PTL) of CAD of between 10-90% are randomised to have either CMR, SPECT or follow NICE guidance (where patients with low PTL of underlying CAD (10-29%) undergo CTCA; intermediate PTL (30-60%) non-invasive investigation with SPECT and high PTL (61-90%) direct to coronary angiography). This trial is designed to assess the impact of each strategy in reducing the rates of unnecessary invasive angiography, which is important from a clinical, economic and patient preference perspective. The MR-INFORM study [26] is a non-inferiority trial designed

to compare the role of CMR vs. that of coronary angiography with invasive FFR to guide revascularization decisions in patients with stable angina and an intermediate to high likelihood of CAD. The multi-centre Hypertrophic Cardiomyopathy Registry is a natural history study of 2750 patients undergoing both CMR, genetic & biomarkers with the aim to identify novel markers of increased cardiovascular risk.[130] Finally tissue characterisation with myocardial mapping techniques (particularly T1 mapping) are an exciting development. Myocardial tissue mapping are quantitative techniques, removing objective interpretation, and offer the promise of standardising CMR measurements. These have been demonstrated to be sufficiently accurate and reproducible to translate into the clinical pathway to guide diagnosis,[96] inform prognosis[131] and have the future potential to guide and monitor treatment strategies.[132]

D. Limitations of CMR

Whilst CMR is established and recommended in international clinical guidelines, limitations and omissions in the literature must be recognised. The relative duration of the scan time, expense and lack of portability puts the onus on CMR to demonstrate superiority over other imaging modalities. In this review we present some of the prognostic information which may be obtained by CMR, and in some circumstance superiority over other imaging techniques, although it should be recognised some of these data are quite limited. The aforementioned ongoing multi-centre clinical studies will go some way to address this knowledge gap.

E. Summary

CMR is an established advanced imaging modality with a number of unique advantages, recognised clinical indications and a growing evidence base in aiding diagnosis, predicting outcomes and influencing patient management. The test for any new imaging modality is how it can translate into the clinical pathway by changing patient management and affecting clinical outcomes and ongoing studies will address this. With the increasing availability and proven safety, CMR has now become an essential imaging tool for all cardiologists (both generalists and sub-specialists) and it will have a pivotal role in a new era of multi-modality cardiovascular imaging.

F. Key Points

1. CMR is a versatile cross-sectional imaging modality for the functional and anatomical assessment of a wide range of cardiovascular diseases

2. CMR stress techniques are well established for the diagnosis of myocardial 'ischaemia'.

3. CMR is able to differentiate acute vs chronic myocardial infarction and image the complications of acute MI.

4. CMR is well established for the assessment of heart failure and cardiomyopathies.

5. CMR is useful for tissue differentiation in cardiac masses/tumours

6. CMR is an essential part of the evaluation and management of many patients with paediatric and adult congenital heart disease.

H. Figures & Legends

Figure 1. CMR in a patient with Stable Coronary Artery Disease

Top Panel) Short axis cine stack used for demonstration of global and regional ventricular function (Video 1). Middle Panel) Adenosine stress (top row) and rest (bottom row) first pass perfusion demonstrating inducible inferior and infero-lateral hypoperfusion (ischaemia) (arrows) consistent with severe stenosis of the right coronary artery (Video 2). Bottom Panel) Late gadolinium enhancement image demonstrating no evidence of myocardial infarction.

Figure 2. CMR in Acute Myocardial Infarction

A) T2w image with high signal (oedema) of the inferior LV and RV wall (arrow) with an area of hypointense core representing intra-myocardial haemorrhage (star). B) Early gadolinium enhancement (EGE) image with dark central core of the inferior wall representing an area of microvascular obstruction (MO). C) Late gadolinium enhancement (LGE) image with full thickness myocardial infarction demonstrated by hyperintense (white) areas of the inferior wall and inferior septum extending into the RV. The central dark area (arrow) is MO. D&E) LV apical thrombus on EGE image (arrows). F) Short axis LGE image with ventricular septal defect (star). G&H) Inferior aneurysm (arrows) with thrombus. I) Contained apical LV rupture with thrombus (arrow) (Video 4).

Figure 3. CMR in Cardiomyopathy

A) Hypertrophic cardiomyopathy with severe asymmetrical septal hypertrophy and fibrosis on 4-chamber late gadolinium enhancement (LGE) image. B) Short axis view of the same HCM patient demonstrating the marked diffuse septal LGE. C) Dilated non-ischaemic cardiomyopathy with extensive mid-wall fibrosis. D) Patient presenting with chest pain with extensive septal mid-wall and epicardial lateral wall fibrosis: CMR findings typical of myocarditis. E) 4-chamber LGE image showing dilated right ventricle with RV late enhancement (arrows). Cine imaging also demonstrated impaired function and dyskinetic regional wall motion (Video 5) consistent with a diagnosis of arrhythmogenic right ventricular cardiomyopathy). F) Inability to null the LV myocardium during LGE imaging which is a classical CMR feature of cardiac amyloid. G) Panel of 4 LGE images demonstrating an ischaemic cardiomyopathy with severely dilated LV and full thickness myocardial infarction (white) and an aneurysmal lateral wall. There is also a basal lateral thrombus (see arrow).

Figure 4. CMR in Pericardial Disease & Tumours

A) Large pericardial cyst with high signal on T2 weighted imaging (arrow). B) Pericardial thickening on cine imaging with ventricular interdependence on free breathing imaging (see Video 6). C) Large global pericardial effusion seen on cine imaging (arrows). Images D,E&F show a myocardial fibroma of the anterior wall: D) T1 weighted black blood short axis view with the fibroma isointense compared to normal myocardium and skeletal muscle (star). E) T2-weighted short axis view showing the fibroma characteristically hypointense (star) (unlike other tumours). F) LGE image confirming hyper-enhancement confined to the fibrous lesion (star).

Figure 5. CMR in Vascular Disease

A) 3D volume rendered contrast enhanced magnetic resonance angiogram (MRA) demonstrating aortic coarctation (arrow). B) 3D volume rendered contrast enhanced MRA for pulmonary vein anatomy (Video 7). C) Repaired Type A aortic dissection with an eccentrically directed jet of aortic regurgitation (arrow). D) Chronic Type B aortic dissection. E&F) Contrast enhanced MRA showing severe right lower pulmonary vein stenosis (arrows) post-AF ablation.

Figure 6. CMR in Valvular Heart Disease

A) 4-chamber cine image showing bi-leaflet mitral valve prolapse and a central jet of mitral regurgitation (arrow). B) Central jet of mitral regurgitation (arrow). C) Short axis view of the aortic valve demonstrating severe stenosis. Subsequent valve planimetry revealed a valve area of 0.8cm^2. D) Right ventricular outflow tract view with pulmonary stenosis (arrow). Panel E) Short axis phase-contrast velocity mapping of the aortic valve and a flow /time curve demonstrating severe aortic regurgitation. Quantitative analysis showed net forward flow volume through the aortic valve of 130ml, reverse flow 50ml and hence regurgitant fraction of 38%.

G. Online Supplemental Videos & Legends

Video 1. Short axis cine stack which enables the calculation of absolute left ventricular cavity size, wall thickness and global & regional function.

Video 2. First pass perfusion imaging with adenosine stress (top row) and at rest (bottom). There is inducible hypoperfusion (ischaemia) of the inferior and infero-lateral wall.

Video 3. Cine imaging with peak inotropic (dobutamine) stress (top row) and at rest (bottom row).

Video 4. 4 Chamber cine imaging demonstrating contained apical left ventricular rupture with thrombus.

Video 5. . Axial cine imaging showing a dilated right ventricle with impaired right function and regional dyskinesia abnormalities. This demonstrates a major criteria for the diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia.

Video 6. Real time free breathing cine imaging demonstrating ventricular interdependence as flattening of the inter-ventricular septum on inspiration seen with pericardial constriction.

Video 7. Three-dimensional contrast enhanced magnetic resonance angiography of the thoracic aorta, showing a repaired coarctation.

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