Expert Perspective

Magnetic Resonance Imaging in the Detection of Myocardial Viability: The Role of Delayed Contrast Hyperenhancement

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Magnetic resonance imaging (MRI) has emerged as a new noninvasive modality in the investigation of cardiovascular disease during the last decade.[1,2] Cardiovascular magnetic resonance (CMR) has well-established imaging capabilities for the assessment of global and regional left ventricular (LV) function and mass. Its potential for the assessment of ischaemic heart disease is currently being explored in many centres. The main focus is currently myocardial tissue characterisation, aiming to detect the ischaemic myocardium and myocardial scar. Capabilities for myocardial characterisation have been greatly improved with the introduction of the delayed-enhancement technique, following injection of gadolinium-based contrast agents. CMR versatility also includes coronary magnetic resonance angiography,[3,4] plaque imaging and blood flow measurements. In this article, we will review the rapidly expanding role of delayed contrast-enhanced CMR in myocardial scar imaging and in guiding management of ischaemic cardiomyopathy.

Absolute contraindications to CMR at present include permanent pacemakers, defibrillators, and cerebral aneurysm clips,[5] although recent studies suggest that newer devices may be safe.[6,7] Prosthetic heart valves and coronary artery stents are safe, although they may produce some artefacts. The safety of new stents and high field strengths needs to be ascertained individually.[1]

Basic MRI physics - techniques

MRI is based on the principle of nuclear magnetic resonance.[8] According to this principle, a signal can be detected when a sample is placed in a magnetic field and is irradiated with radiofrequency energy of a certain frequency, the resonant frequency. The signal is produced by the interaction of the sample nuclei with the magnetic field. Because hydrogen atoms are a major constituent of the human body, their nuclei (single positively charged protons) are the ones which are usually imaged by MRI. According to quantum mechanics, protons spin on their own axes and therefore the hydrogen nucleus as a moving charge generates its own tiny magnetic field, known as its magnetic moment. If the hydrogen nucleus is placed in a strong external magnetic field, it experiences a turning force, known as a torque. This is similar to a compass needle which experiences a force in the earth's magnetic field and turns so that it is aligned with the direction of the field. Thus, hydrogen nuclei align themselves almost parallel and antiparallel with the external field, rotating around the axis of the field like a spinning top with a precessional (resonant)

frequency proportional to the field strength. There is a small excess of protons spinning parallel (this is the lowest energy state available) giving rise to a net magnetisation vector.

MRI is based on the magnetisation that is induced in the human body when it is placed in the scanner. The scanner consists of a large superconducting magnet which produces a strong magnetic field, typically 1.5 Tesla, which is about 30000 times the strength of the earth's magnetic field. When a scanning sequence starts, electromagnetic energy is transmitted as a radiofrequency pulse from a transmitting coil to the body nuclei, at the resonant frequency, exciting them to a higher energy state. The net magnetisation vector in this higher energy state moves out of the direction of the external field. As soon as this pulse is switched off, the magnetisation vector starts to revert to its former position, via two relaxation processes, called longitudinal (T1) and transverse (T2) relaxations, releasing a signal, in the form of radio waves, which is detected by a receiver coil. Different tissues return to their lower energy states at different relaxation times and so tissues can be differentiated. The localisation of the signals in the body is achieved by short-term spatial variations in magnetic field strength, generated by the gradient coils. The received signals can be reconstructed using a mathematical technique called a Fourier transformation and powerful computing to give an MRI image.

All MRI images are produced using pulse sequences, which are stored in the scanner computer. A pulse sequence contains radiofrequency pulses and gradient pulses which have carefully controlled durations and timings. Basic pulse sequences used in CMR are spin-echo sequences (black blood imaging), which produce detailed anatomical images, and gradient-echo sequences (bright blood imaging), including the new steady-state free precession sequences, which produce information on flow and function. Gadolinium is a paramagnetic MRI contrast agent that influences the magnetic relaxation times of local tissues, therefore altering their returning signal. Gadolinium-based contrast agents are safer than iodinated ones used in radiography because they are not nephrotoxic and have a much lower incidence of allergic reactions than radiography contrast agents.[1]

Non-invasive imaging of myocardial viability by standard imaging techniques

Since the introduction of myocardial revascularisation methods such as coronary artery bypass grafting (CABG) and percutaneous coronary intervention, the issue of identifying dysfunctional yet viable myocardium has arisen. The term "hibernating myocardium" was historically used to characterise a chronic condition of "resting LV dysfunction due to reduced coronary blood flow that can be partially or completely reversed following myocardial revascularisation and/or by reducing myocardial oxygen demand."[9] On the other hand, the phenomenon of reversible global LV dysfunction after brief coronary occlusion and reflow was called "myocardial stunning."[10,11] It has also been postulated that repetitive, intermittent ischaemic episodes leading to a chronic myocardial stunned state could underlie the baseline contractile dysfunction of hibernating myocardial segments.[12] Detecting viable myocardium, whether hibernating or stunned, is of paramount clinical importance. Both definitions, however, pose a dilemma to any imaging test, since they include contractile recovery after treatment (revascularisation) as criteria for the definition of a pre-treatment pathological state. Without violating these definitions, "hibernating" or "stunned" myocardium cannot be diagnosed with any imaging test without successful revascularisation. And other terms may have to be used to express the likelihood of functional recovery after revascularisation. The living, or viable, myocyte is an attractive alternative goal for imaging, since it does not involve functional recovery for the assessment of the diagnosis.

A number of indirect methods have been used to detect the presence of living myocytes for the purpose of in vivo assessment of myocardial viability. As a result, in clinical practice, as well as research settings, viability has been defined in relation to the method used, aiming to demonstrate the presence of living myocytes indirectly. Such definitions include: i) recovery of contractile function following revascularisation (echocardiography and CMR); ii) response to inotropic stimulation, namely myocardial contractile reserve (e.g. dobutamine stress echocardiography or dobutamine stress CMR); iii) presence of glucose metabolism (e.g. fluoro-2-deoxygluclose [FDG] positron emission tomography [PET]); iv) presence of active cellular transport mechanisms, namely membrane integrity (e.g. ^{201}Tl single photon emission computed tomography [SPECT]); and v) more recently, intact capillary circulation using myocardial contrast echocardiography.

These methods have variable sensitivity and specificity values for the identification of viable myocardium. An average sensitivity of 84% and specificity of 81% have been reported for dobutamine stress echo-

cardiography, whereas pooled analysis of ^{201}Tl viability studies assessing post revascularisation functional recovery reveals high sensitivity (88%) but low specificity (49%). The respective values for PET were 88% and 73%.[13] There is no ideal method to identify viable myocardium, although PET is widely regarded as the gold standard. All imaging modalities however have their advantages and limitations and all depend on the local expertise.

Optimal acoustic windows are sometimes difficult to obtain using echocardiography, and this may impair image quality in patients having stress echocardiographic viability testing.[14] It may be difficult to visualise all myocardial segments during stress testing, despite the advances in tissue harmonic imaging and echo contrast agents.[15,16] Radionuclide methods for assessing viability require the patient to undergo significant radiation exposure. Attenuation from breast or diaphragm can hinder image interpretation in the case of SPECT, and metabolic imaging requires expert attention to insulin and glucose levels prior to FDG injection. Furthermore, the resolution of SPECT and PET is limited, with a 10-14 and 4-6 mm pixel size, respectively, at best. Thus, viability must be determined in a binary fashion and the transmural extent of scar tissue cannot be determined.

Assessment of viable and nonviable myocardium by CMR

Unlike echocardiography, PET and SPECT, CMR has the potential to show both viable and non-viable myocardium, the latter by delayed hyperenhancement of standard magnetic resonance contrast agents. Similar to echocardiography, cine CMR allows dynamic imaging of cardiac wall motion, but is characterised by superior endocardial border definition, facilitating more accurate wall motion assessment. Wall motion is typically assessed by standard views which include a series of approximately 10 short-axis views, a 4-chamber and a left-ventricular outflow-tract view. The imaging involves so called bright-blood techniques, allowing for a high contrast between bright blood pool and dark heart muscle. Depending on the particular pulse sequence and scanner used, 10 to 30 images are typically acquired during a breath hold of approximately 10 seconds. The image acquisition is synchronised with the ECG, which allows the generation of images of different contractile stages representing an average of several heart beats during the breath-hold period. Several single centre studies have shown that contractile reserve can be assessed with cine CMR using low-dose dobutamine. In one study, dobutamine CMR was 89% sensitive and 94% specific in predicting functional recovery on an individual patient basis.[17]

CMR tissue tagging is a particularly useful technique that can quantify local myocardial segmental shortening.[18] In tagging, a grid is superimposed over the image plane, nulling the tissue along the lines and leaving small cubicles of tissue that change their shape during contraction, except in non-contractile muscle. This technique also appears to be advantageous as it can be quantified, using sophisticated image analysis tools, to measure myocardial segmental shortening and strain. The presence of contractile reserve by dobutamine tagged CMR was 89% sensitive and 93% specific for functional recovery at 4 to 8 weeks after revascularisation.[19] An important practical disadvantage of dobutamine cine CMR relates to the risk of administering a dobutamine infusion to a patient enclosed in the magnet bore. Positive inotropic stimulation in patients with coronary artery disease is associated with a well-recognised risk of eliciting an arrhythmic or ischaemic event and the position of the patient within the magnet impairs physician-patient interaction. In addition, the diagnostic utility of ECG monitoring is diminished within the magnetic field.[20]

Magnetic resonance spectroscopy (MRS), although not as widely available, can also be used for the detection of myocardial viability. MRS assesses viability by quantifying regional myocardial metabolism and chemistry. Instead of using the ^{1}H nucleus as the signal source (as in MRI), MRS can detect and quantify the concentrations of ^{31}P-, ^{23}Na-, and ^{13}C-nuclei, which are components of normal cardiac energetics.[20,21]

Delayed enhancement CMR

Technique and experimental evaluation

Delayed contrast-enhanced CMR is a technique which, by using a gadolinium based contrast agent, is able to differentiate non-viable myocardium (appearing as "white") from viable myocardium (appearing as "black") (Figure 1). The initial observation of contrast uptake in myocardial infarction (MI) with MRI dates back to 1984 and was made in a canine acute MI model.[22] Using the MRI techniques of the mid-eighties, a number of investigators reported that while image intensities increased throughout the heart, regions associated with acute MI became particularly bright (hyperenhanced) more than a few minutes after contrast administration.[20]

However, it took another ten years until the appropriate MRI technique was developed to increase

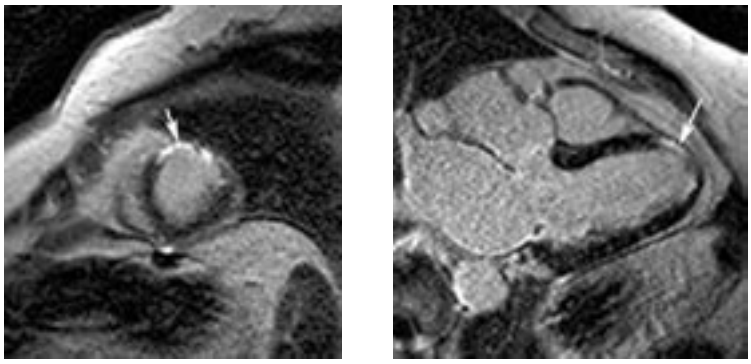

Figure 1. Representative example of delayed contrast-enhanced cardiovascular magnetic resonance. Short-axis (left) and long-axis (right) views of a chronic, transmural apical anterior myocardial infarction. Infarct territory appears hyperenhanced ("white") compared with normal ("dark") myocardium.

the signal intensity of infarcted compared to normal myocardium. This methodology, which can be applied on most CMR scanners, involves a technique to suppress (null) the signal of normal myocardium and increase the signal intensity of infarcted myocardium where the contrast agent accumulates. The suppression technique is based on a so-called inversion recovery fast gradient-echo pulse sequence and relies on operator input and careful dosing and timing. The MRI technique used for showing delayed enhancement typically requires breath-hold imaging. Typically, the images are obtained as for contractility, with approximately 10 short axis and additional long axis views. The contrast agent dose is standardised and should be given strictly according to body weight. Both 0.1 and 0.2 mmol/kg body-weight protocols have been established for gadolinium-DTPA. In our department, we use the higher (0.2 mmol/kg) gadolinium dose, which has a slightly higher contrast and requires a waiting period of 15 minutes to obtain the optimal contrast.

Before the late enhancement imaging, the selection of an appropriate inversion time is crucial for the accurate identification of infarcted myocardium. The inversion time is the time between the inversion pulse and the centre of the data acquisition window (mid-diastole). In order to select the optimal inversion time, a series of approximately 10 test images have to be obtained with varying inversion times (e.g. 200, 220, 240 ... 300 ms). From these images the operator has to determine the appropriate inversion time by choosing the image where the myocardium is most effectively nulled (black). Newer pulse sequences with a phase-sensitive reconstruction of inversion recovery data may allow a nominal inversion time to be used, rather than a precise null time for normal myocardium. These techniques can provide consistent contrast between infarcted and normal myocardium and potentially simplify the choice of inversion time.[20] Unlike X-ray contrast agents, which directly attenuate the X-rays, MRI contrast agents act indirectly by manipulating surrounding water. In the MRI terminology, the gadolinium molecule shortens the T1-relaxation time of surrounding water molecules and water with gadolinium becomes brighter than water alone. This effect will only be visible if the scanner has been adjusted to pick-up signal from substrates with short T1-relaxation times (T1-weighted sequence).

Delayed hyperenhancement in both acute and chronic infarction has been investigated in both animals and humans. Delayed hyperenhancement correlates with the presence of histologically defined necrotic tissue after either reperfused or non-reperfused acute myocardial injury. In a study with dogs, Kim et al[23] demonstrated that MRI accurately depicts histologically defined regions of myocardial necrosis both in reperfused and non-reperfused MI. The acquisition of high-resolution (500 χ 500 χ 500 μm) ex vivo cardiac images allowed registration of slices for the direct comparison of triphenyl tetrazolium chloride (TTC)-stained myocardium and ex-vivo MRI images. The match between TTC and MRI images was extremely close.

The mechanisms of the delayed hyperenhancement have been investigated. In acute MI, myocyte necrosis results in membrane rupture and interstitial oedema. Regions of hyperenhancement are associated with sarcomere membrane rupture when examined by electron microscopy, and it has been hypothe-

sised that the changes observed in gadolinium-DTPA wash-in and wash-out kinetics may relate to sarcolemmal rupture.[24] Following intravenous injection, gadolinium diffuses rapidly from the intravascular to the extracellular space. Because gadolinium-DTPA is primarily an extracellular, interstitial agent, the volume of distribution for the contrast molecules increases within the infarcted imaging voxel.[25-28] The increased gadolinium concentration within infarcted tissue shortens the T1 relaxation time (at the doses used clinically). Thus, infarcts appear hyperenhanced. Another contributory mechanism is abnormal contrast molecule kinetics within infarcts. By electron microscopy, in a study in rabbits,[24] the hyperenhanced regions not only had extensive myocardial cell membrane rupture but also a 37-fold increase in the number of capillaries with erythrocyte stasis. Therefore, the reduced functional capillary density could prolong contrast washout by two mechanisms: the smaller effective capillary surface area decreases the rate of solute transport and increases the distance that solute has to travel to diffuse out of the affected region. Because diffusion time is directly proportional to the square of the distance travelled, modest decreases in capillary density significantly lengthen washout times.

In terms of chronic infarction Kim et al,[23] using the technique of ex vivo imaging and TTC staining, demonstrated that regions of hyperenhancement in chronic myocardial infarction in dogs appear identical to regions defined histologically. The mechanism of hyperenhancement in chronic infarction has not been fully elucidated. Similar to acute infarcts, chronic infarcts have increased gadolinium concentrations and tissue-blood partition coefficients.[26] This suggests that the extracellular space is increased in collagenous scars and explains the increased volume of distribution for gadolinium in chronic infarction. Reduced capillary density in chronic scars also reduces contrast washout, leading to the hyperenhancement.[29]

Clinical studies of delayed enhancement CMR

The extensive evidence from animal models of acute infarction has provided a foundation for numerous patient studies that have confirmed the presence of hyperenhancement following acute MI.[25,30-33] Lima et al[25] described the contrast-enhanced CMR patterns in 22 individuals 8 days after MI. Virtually all patients had increased signal intensity at 10 minutes after contrast bolus in the region perfused by the infarct-related artery. This MRI region correlated well with fixed thallium defect size, potentially indexing infarct size. In another study[34] of 24 patients with revascularised first MI, the best predictor of global improvement in systolic function was the extent of dysfunctional myocardium that was not infarcted or had infarction comprising <25% of LV wall thickness.

In addition to hyperenhancement, acutely infarcted territories often demonstrate marked heterogeneity by contrast-enhanced CMR, which reflects the status of the microvasculature. In the first few minutes after contrast bolus, some patients develop a hypoenhanced region with decreased signal intensity, in the subendocardial layer of the myocardium, which later enhances.[25] Hypoenhancement correlates with an increased incidence of total coronary occlusion at initial angiography after MI, electrocardiographic Q-waves, and greater regional dysfunction by echocardiography. However, up to half of the patients with hypoenhancement ultimately have a widely patent infarct-related artery after revascularisation. Hence, it has been postulated that these regions represent the no-reflow phenomenon or regions of microvascular obstruction described in experimental studies and in humans by nuclear and echocardiographic techniques.

Potential clinical relevance of transient hypoenhancement or the no-reflow phenomenon has been suggested in terms of both prediction of functional recovery and prognosis. In a study of 17 patients followed for 16 ± 5 months after acute MI, Wu et al[35] reported that the risk of adverse events increased with increasing infarct size, as defined by the hyperenhanced zone. However, after controlling for infarct size, events were independently related to the presence or absence of microvascular obstruction in the infarct territory. In a chronic setting in humans it has been firmly estab-

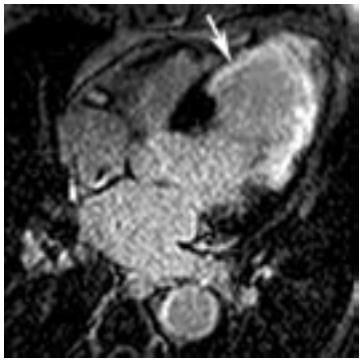

Figure 2. Delayed enhancement cardiovascular magnetic resonance image in a patient with known 3-vessel disease and ischaemic cardiomyopathy. On this image (4-chamber view), an extensive area of nearly transmural hyperenhancement is seen, including the inferoseptal, apical and mid-lateral myocardium. This area corresponds to non-contracting, non-viable myocardium.

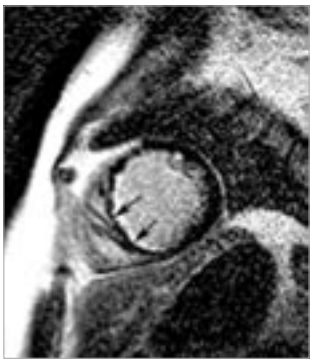

Figure 3. Cardiovascular magnetic resonance image (short-axis view) showing delayed hyperenhancement at the septum. Note the extent of the hyperenhancement involving 50% of the thickness, whereas the rest of the septal wall is nonenhanced, suggesting viable myocardium.

lished that healed infarcts do hyperenhance and that the zone of hyperenhancement corresponds to the infarct artery related territory.[36]

Clinical applications of contrast-enhanced CMR in defining viability are in the process of evolving (Figure 2). Contrast-enhanced CMR is unique in its ability to assess transmurality because of its greater spatial resolution (Figure 3). Contrast-enhanced CMR is the only imaging tool to allow the relationship between the transmural extent of viability and functional recovery to be defined in vivo. The prognostic value for the prediction of functional recovery has been shown in both acute and chronic revascularised myocardial injury. Transmural extent can identify stunned myocardium after acute reperfused MI.[34] Decreasing extents of transmurality are the best correlates of improved long-term regional contractile function and overall ejection fraction.

Just as with echocardiography, there is an important relationship between the extent of viable myocardium and the potential for functional recovery in the setting of chronic ischaemia and LV dysfunction. Kim et al[37] showed that, in patients with LV dysfunction undergoing revascularisation surgery, the extent and severity of nonviable tissue defined by contrast-enhanced CMR correlates with the likelihood of functional recovery on a segmental and patient basis. Furthermore, the likelihood of recovery in regional contractility decreases progressively as the transmural extent of delayed enhancement before revascularisation increases. In this study, 50 patients with ischaemic LV dysfunction were assessed before and after revascularisation with contrast-enhanced and cine CMR. Segmental wall thickening was analysed semi-quantitatively. The extent of delayed enhancement within each segment (expressed as a percentage of the total segmental area) was graded on a 5-point scale, with 0 indicating no enhancement; 1, 1% to 25% tissue involvement; 2, 26% to 50%; 3, 51% to 75%; and 4, 76% to 100%. Of the segments with no enhancement (i.e. viable by contrast-enhanced CMR), 78% experienced functional recovery. Moreover, functional recovery was seen in 86% of the non-enhanced segments that had at least severe hypokinesia before revascularisation and 100% of the akinetic or dyskinetic segments. Of the segments with >75% transmural late enhancement, only 1.7% experienced improved contractility after revascularisation. The rate of functional recovery was 10% in the 51% to 75% group, 42% in the 26% to 50% group, and 60% in the 1% to 25% group. Another study[38] demonstrated similar findings for a patient cohort with more severe cardiomyopathy (LV ejection fraction 28 ± 10%), with 82% of regions with no scar improving, compared with only 18% with >50% scar.

Comparisons of contrast-enhanced CMR with other modalities have been favourable. In one study, 20 chronic infarct patients underwent two consecutive contrast-enhanced CMR and two resting SPECT examinations.[39] The main findings were that the size of healed infarcts as determined by CMR does not change between 10 and 30 minutes after contrast injection and that the reproducibility of the CMR measurement compares favourably with that of SPECT. The advantage of the excellent spatial resolution of contrast-enhanced CMR is in its ability to detect subendocardial infarction that might otherwise be missed using myocardial perfusion imaging (Figure 4). Wagner et al[40] demonstrated

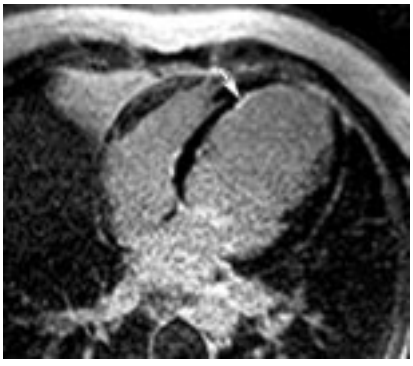

Figure 4. The advantage of the excellent spatial resolution of contrast-enhanced cardiovascular magnetic resonance is in its ability to detect subendocardial infarction that might otherwise be missed using myocardial perfusion imaging. In this example a subtle subendocardial area of hyperenhancement is visualised, localised in the apical septal segment.

this in an animal and clinical study comparing viability defined by delayed enhancement with resting thallium SPECT images. In animals, contrast-enhanced CMR and SPECT detected all segments with >75% transmural MI. CMR also identified 92% of segments with subendocardial infarction (<50% transmural extent), whereas SPECT identified only 28%. In the patients, there was complete agreement between CMR and SPECT for segments with large transmural extents of infarction (>75%). However, in detecting subendocardial infarcts there was a marked discordance. Among the segments with <50% transmural hyperenhancement by MRI, SPECT did not detect a fixed perfusion defect in 47%.

Contrast-enhanced CMR has also been compared with PET in patients with ischaemic cardiomyopathy.[41] In severely dysfunctional segments, the extent of hyperenhancement was 80 ± 23% in segments with matched perfusion metabolism defects (nonviable by PET criteria), but only 33 ± 25% in perfusion metabolism mismatched segments (ischaemic and viable) and 9 ± 14% in normal segments. Segmental glucose uptake by PET inversely correlated with the segmental extent of hyperenhancement and a cut-off value of 37% segmental hyperenhancement optimally differentiated viable from nonviable segments defined by PET. Using this threshold, the sensitivity and specificity of contrast-enhanced MRI for detection of viable myocardium defined by PET were 96% and 84%, respectively. In another study in patients with severe ischaemic heart failure, although hyperenhancement correlated with areas of decreased flow and metabolism, it identified scar tissue more frequently than PET, reflecting the higher spatial resolution.[42]

Regarding the comparison between delayed hyperenhancement and dobutamine stress CMR,[43,44] the existing data so far demonstrate that, for dysfunctional regions with >50% scar by delayed hyperenhancement, the negative predictive value is quite high and is likely to be higher than that found by dobutamine CMR. For regions with <25% scar, it is possible that dobutamine CMR may provide a higher positive predictive value than delayed hyperenhancement. However, in this group there is such a large amount of viability, and the potential for benefit is so great, that it is probably sensible to be concerned about the possibility of a false-negative dobutamine CMR result. Besides, contrast-enhanced CMR does not require infusion of a pharmacological stress agent in the magnet. Thus, contrast-enhanced CMR is safer, requires less intense monitoring, is easier to implement, and is faster to complete. It also appears to be somewhat easier and faster to interpret.

Since widespread clinical attention was drawn to contrast-enhanced CMR more than 4 years ago, numerous centres have reproduced the major findings and demonstrated value in conditions beyond that of ischaemic heart disease. Delayed enhancement has been described in non-coronary artery disease-related myocardial necrosis/fibrosis. In acute myocarditis, gadolinium-enhanced CMR helps non-invasive diagnosis and recognition of areas of involvement. The diagnosis of early stages (nodular enhancement) can be differentiated from that of later stages (diffuse enhancement) qualitatively as well as quantitatively.[45,46] Another potential application of contrast-enhanced CMR is the differentiation of ischaemic from non-ischaemic dilated cardiomyopathy.[36] In hypertrophic cardiomyopathy, distinct patterns of scarring have been observed by using contrast-enhanced CMR. These patterns of scarring are different from that seen in ischaemic heart disease. Moreover, in patients with hypertrophic cardiomyopathy the presence and extent of delayed hyperenhancement appears to be related to clinical risk factors for sudden death.[47]

Delayed enhancement CMR is rapidly progressing in both the clinical and research arenas on a broad range of fronts. Its excellent resolution, high accuracy and safety make it a powerful tool both for today and increasingly in the future. By using delayed enhancement imaging, we are likely to understand new and existing pathologies better, and this will help in planning new management strategies in cardiovascular disease.

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