

CMR Delayed Enhancement Imaging in Coronary Artery Disease

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Delayed Enhancement MRI – from bench to bedside

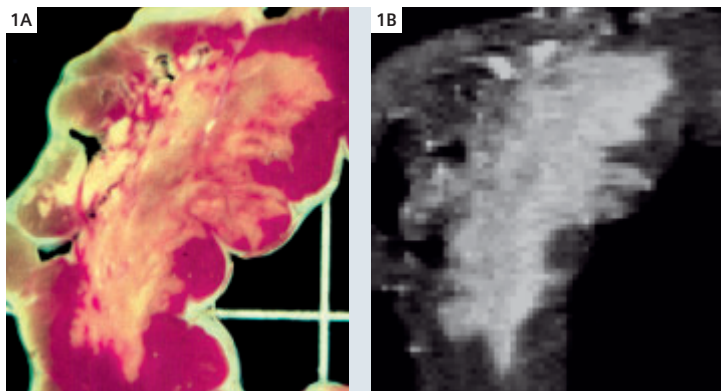
Imaging myocardial injury using T1-weighted pulse sequences after the administration of intravenous gadolinium contrast media has been performed since the mid 1980's. A major advance of this technique was achieved with the development of a pulse sequence (segmented inversion-recovery turbo-FLASH) which allowed an increase in signal difference between "normal" and "hyper-enhanced" tissue 10-fold compared to older pulse sequences. This technique, named **delayed contrast-enhanced MRI** (DE-MRI) was introduced in the late 1990's and may be considered already the gold-standard for the detection of irreversibly damaged myocardium. This development of DE-MRI and its subsequently emerging clinical applications parallels the steadily increasing importance of cardiovascular magnetic resonance in routine clinical patient care.

What is hyperenhanced or "bright" myocardium?

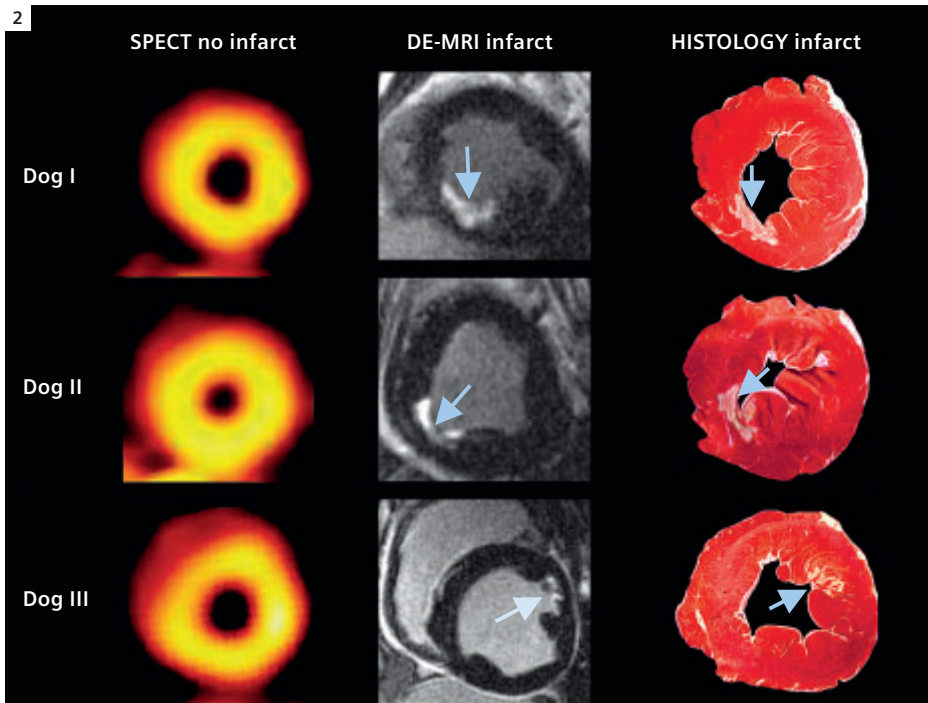
The underlying concept is that infarcted tissue accumulates gadolinium and can be visualized as hyperenhanced or "bright" regions on T1-weighted

images acquired at least 10 minutes after gadolinium injection. How can we understand that a "non-specific" contrast agent can distinguish between viable and nonviable myocardium, especially across the wide range of tissue environments that occur during infarct healing? One should conceptually not think of DE-MRI as a tissue- or necrosis-specific staining technique or a ligand binding to specific receptors. Gadolinium is an inert extracellular contrast agent and the amount of contrast agent in a given tissue distribution volume determines the image signal intensity – the more contrast per distribution volume the higher the signal. An important physiological fact to remember is that the tissue volume in normal myocardium is predominately intracellular (~ 75% of the water space). Because extracellular contrast media is excluded from this space by the intact sarcolemmal membrane, the volume of distribution of a contrast medium in normal myocardium is quite small (~ 25% of water space), and one can consider viable myocytes as actively excluding contrast media. The unifying mechanism for the hyperenhancement effect of nonviable myocardium may then be the absence of viable myocytes rather than any inherent properties that are specific for acutely

Infarcted myocardium accumulates gadolinium and can be visualized as hyperenhanced or "bright" regions on T1-weighted images.



1 Comparison of high-resolution ex-vivo DE-MRI images (right) with acute myocyte necrosis defined by histopathology (left). Note that the size and shape of the infarcted region (yellowish-white region) defined histologically by staining is nearly exactly matched by the size and shape of the hyper-enhanced (bright) region on DE-MRI. (Adapted from Kim RJ, Fieno DS, Parrish TB, et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. *Circulation* 1999; 100: 1996; with permission).



2 Short axis views from three animals with subendocardial infarcts. DE-MRI detected even small infarcts (arrowheads) which were missed by SPECT. (Adapted from Wagner A, Mahrholdt H, Holly TA, et al. Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of sub-endocardial myocardial infarcts: an imaging study. *Lancet* 2003; 361: 376; with permission.)

necrotic tissue, collagenous scar, or other forms of nonviable tissue.

In animal models of ischemic injury directly comparing DE-MRI to histopathology a nearly exact agreement between the size and shape of infarcted myocardium by DE-MRI to that by histopathology was demonstrated (Figure 1). It has been shown that DE-MRI can delineate between reversible and irreversible myocardial injury independent of wall motion, infarct age, or reperfusion status. Human studies demonstrate that DE-MRI is effective in identifying the presence, location, and extent of MI in both the acute and chronic settings. Additionally, DE-MRI provides scar size measurements that are closely correlated with positron emission tomography (PET) in patients with ischemic cardiomyopathy, and provides results superior to single-photon emission computed tomography (SPECT) in patients with subendocardial infarctions.

Advantages of DE-MRI over other viability techniques

A DE-MRI scan for assessment of viability is quite simple (see section on protocol), can be performed in a single exam of less than 30 minutes duration and does not require pharmacological or physical stress. Additionally, DE-MRI is rarely performed in isolation, rather it is one component in a more comprehensive study that is tailored to the specific

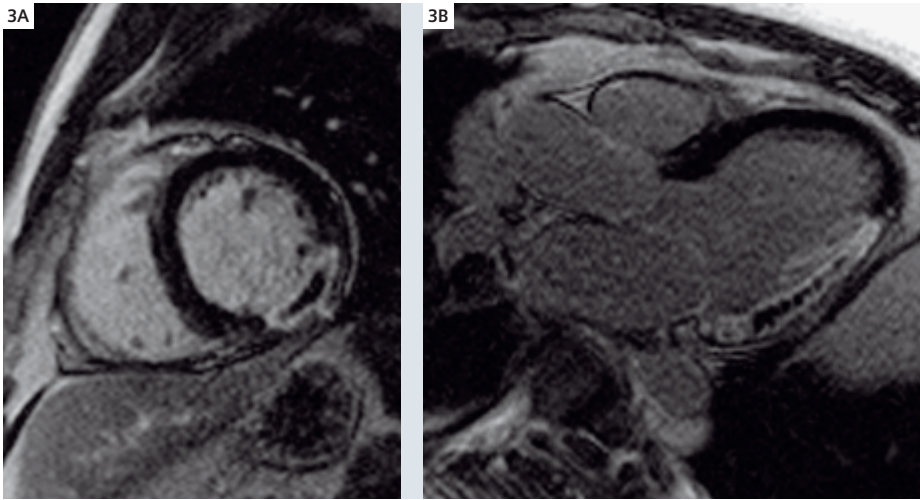
patient. It may be combined with a stress component for ischemia assessment, cine images for functional assessment, flow velocity mapping for evaluation of valvular disease, or a vascular study to assess aortic pathology to mention just a few of the possible combinations.

A major advantage of DE-MRI is the high spatial resolution. With a standard implementation, a group of 10 hyperenhanced pixels (voxel, 1.9 x 1.4 x 6 mm) in a typical image would represent an infarction of 0.16 grams, or a region one thousandth of the LV myocardial mass. This level of resolution, more than 40-fold greater than SPECT, allows visualization of even microinfarcts that cannot be detected by other imaging techniques (Figure 2).

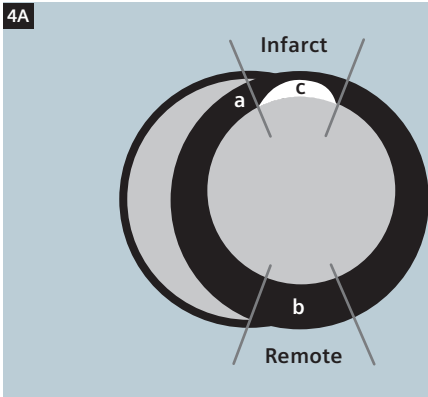
Further, DE-MRI is different from radionuclide imaging in that it provides direct visualization of both non-viable and viable myocardium. For instance, rather than simply identifying a region of acute infarction as non-viable due to reduced tracer activity, DE-MRI can distinguish between acute infarcts with necrotic myocytes and acute infarcts with necrotic myocytes and damaged microvasculature. The latter, termed the "no-reflow phenomenon", indicates compromised tissue perfusion despite restoration of epicardial artery patency. DE-MRI performed 5–10 minutes after contrast provides high image quality and delineates regions with more

DE-MRI can delineate between reversible and irreversible myocardial injury independent of wall motion, infarct age, or reperfusion status.

The voxel resolution of CMR is 40-fold greater than SPECT, allowing visualization of microinfarcts that cannot be detected by other imaging techniques.



3 Short axis and long axis images from a patient with acute myocardial infarction. Note that the transmural infarct is composed of a bright area with a central black core corresponding to an area of no-reflow.



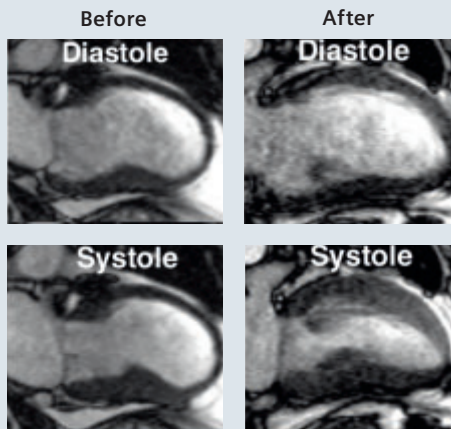
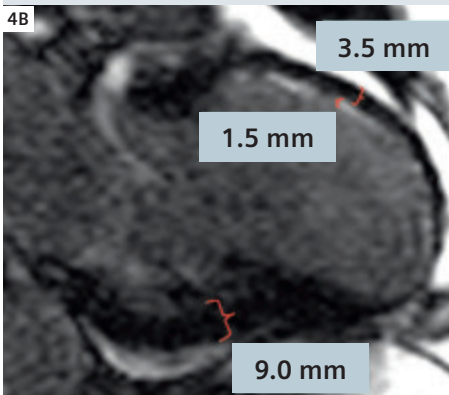
Quantification of regional viability (% viability)

Direct: $\frac{a}{a+c}$

Indirect: $\frac{a}{b}$

4 (4A) Illustration of the differences between a direct and indirect method of quantifying regional viability. Viable myocardium is displayed in black and infarcted myocardium displayed in white.

(4B) Long axis MR images of a patient before and two months after revascularization. Although the akinetic anterior wall is "thinned" (diastolic wall thickness = 5 mm; remote zone = 9 mm), DE-MRI demonstrates that there is only a subendocardial infarction (1.5 mm thick). A direct assessment of viability would show that the anterior wall is predominantly viable (3.5 mm / 5 mm = 70% viable), whereas the indirect method would show that the anterior wall is predominantly nonviable (3.5 mm / 9 mm = 39% viable).



DE-MRI (magnified)

Before
Cine

After
Cine

Cine MR images obtained following coronary revascularization demonstrate full recovery of wall motion and diastolic wall thickness. Full motion movies can be viewed at <http://dcmrc.duhs.duke.edu/NF10>. (Modified from Heart 2004; 90: 137–140 with permission.)

profound microvascular damage (Figure 3). The ability to simultaneously visualize non-viable and viable myocardium provides additional advantages. For example, DE-MRI can accurately assess ventricular remodeling following acute MI at an early time point before measurements of ventricular volumes, internal dimensions, and ventricular

mass have changed. This is possible since DE-MRI can assess serially, concurrent directionally opposite changes such as resorption of infarcted tissue and hypertrophy of viable myocardium. When only viable myocardium can be visualized, the "percentage of viability" in a given segment is assessed indirectly and generally refers to the

amount of viability in the segment normalized to the segment with the maximum amount of viability. Conversely, when both viable and infarcted myocardium can be visualized, the “percentage of viability” can be assessed directly and expressed as the amount of viability in the segment normalized to the amount of viability plus infarction in the same segment (Figure 4A). These differences in the way in which viability is measured can alter clinical interpretation. Figure 4B demonstrates MR images in a patient with chronic coronary disease and an akinetic anterior wall. Although the anterior wall is thinned, only a small subendocardial portion of the anterior wall is infarcted. In this case, the indirect method would show that the anterior wall is only 39% viable (compared to the remote region), whereas the direct method would show that the anterior wall is 70% viable. The indirect method would predict no recovery of wall motion after revascularization whereas the direct method would predict recovery. The post-revascularization images (bottom-right panel) demonstrate in this patient the direct method was correct.

Clinical applications of DE-MRI

Prediction of functional recovery in ischemic disease

As the patient example in Figure 4 shows, one clinical application of DE-MRI is to identify patients with potentially reversible ventricular dysfunction from those with irreversible dysfunction. With the ability of DE-MRI to directly visualize the transmural extent of infarction (and viability) functional improvement after revascularization can be predicted in both acute and ischemic disease.

In the context of acute myocardial infarction, prompt revascularization therapy has been shown to result in salvage of ischemic but viable myocardium, improvement in ejection fraction (EF), and long-term improvement in survival. In the immediate post-infarction setting, even after successful reperfusion, myocardial dysfunction may persist, and it is difficult to distinguish whether it is due to myocardial necrosis or to myocardial stunning. Differentiation between these two conditions is important because patients with a large area with dysfunction but only little necrosis (i.e. predominantly stunned) would be expected to have marked functional and clinical improvement. In contrast, patients with a dysfunctional region that is predominantly necrotic would not be expected to

have much functional improvement. Studies in patients with acute myocardial infarction and successful revascularization showed that transmural extent of infarction was highly predictive of improvement in wall motion and global function (see recommended reading for details). The transmural extent of infarction determined by DE-MRI has also been shown to predict response to myocardial revascularization in patients with chronic ischemic heart disease. Similar to findings in the acute setting, likelihood of functional improvement was inversely related in a progressive stepwise fashion to transmural extent of infarction. Several studies have demonstrated that there is a progressive relationship between the likelihood of contractile response to revascularization and the transmural extent of infarction as evidenced by DE-MRI.

DE-MRI for heart-failure assessment

We have discussed thus far the ability of DE-MRI to predict the likelihood and magnitude of functional improvement after revascularization in both acute and chronic ischemic disease. There is however a significant proportion of patients, in whom myocardial dysfunction and heart failure (ischemic cardiomyopathy) persists even after revascularization, or in whom revascularization is not possible due to a variety of reasons (e.g. associated comorbidities, poor distal targets, or diffuse atherosclerotic disease). In addition, a significant proportion of patients have dysfunction in the absence of CAD (nonischemic cardiomyopathy). The utility of DE-MRI for diagnostic assessment of heart failure patients is manyfold. We will discuss here some established and emerging applications:

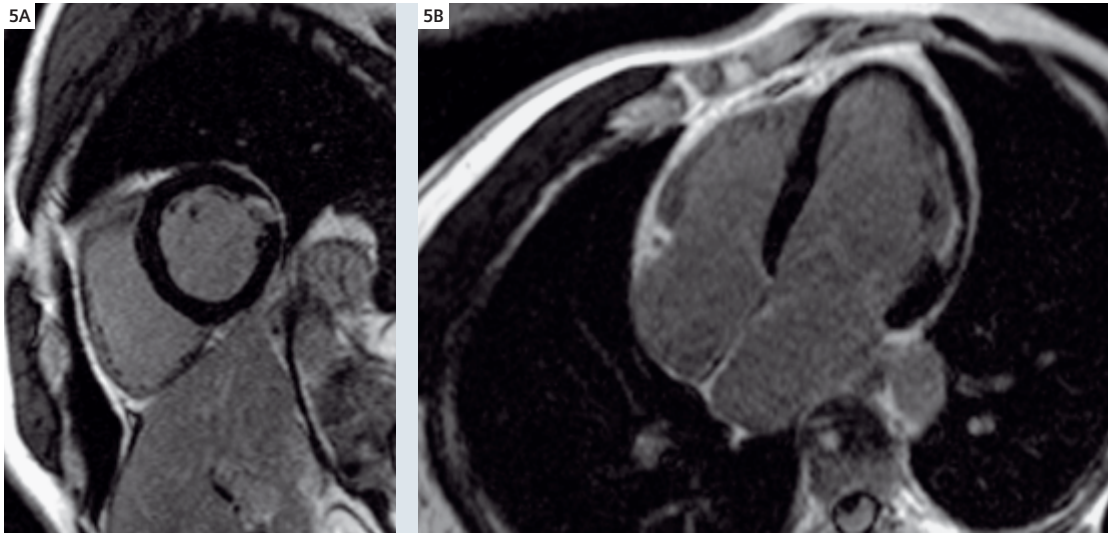
1. The ability of DE-MRI to provide in-vivo images corresponding to ex-vivo pathological sections allows the determination of underlying pathology of cardiomyopathies. This application is based on the concept that both presence and pattern of scar can be used to discriminate between myopathic processes. The typical pattern of hyperenhancement that occurs in patients with myocardial infarction and thus with ischemic cardiomyopathy can be explained by the pathophysiology of myocardial ischemia. Following approximately fifteen minutes of coronary occlusion, a wavefront of myocardial necrosis begins in the subendocardium and progresses transmurally with increasing duration of occlusion. Therefore, hyperenhancement can

DE-MRI allows visualization of the transmural extent of myocardial infarction.

The transmural extent of infarction determined by DE-MRI predicts the response to myocardial revascularization in patients with chronic ischemic heart disease.

The distribution pattern of DE allows the determination of underlying pathology of cardiomyopathies.

2D/3D & PSIR TurboFLASH/TrueFISP IR sequences are provided for delayed enhancement imaging in the Advanced Cardiac Package.



5 Typical DE-MRI images (5A: short-axis and 5B: 4-chamber view) of a patient with coronary artery disease and previous myocardial infarct in the lateral wall. The hyperenhancement of CAD pattern typically involves the subendocardium extending towards the subepicardium. The transmural extent of infarction is well visualized.

Different delayed enhancement patterns can be seen in non-ischemic cardiomyopathies such as HCM, cardiac amyloidosis, cardiac sarcoid or myocarditis.

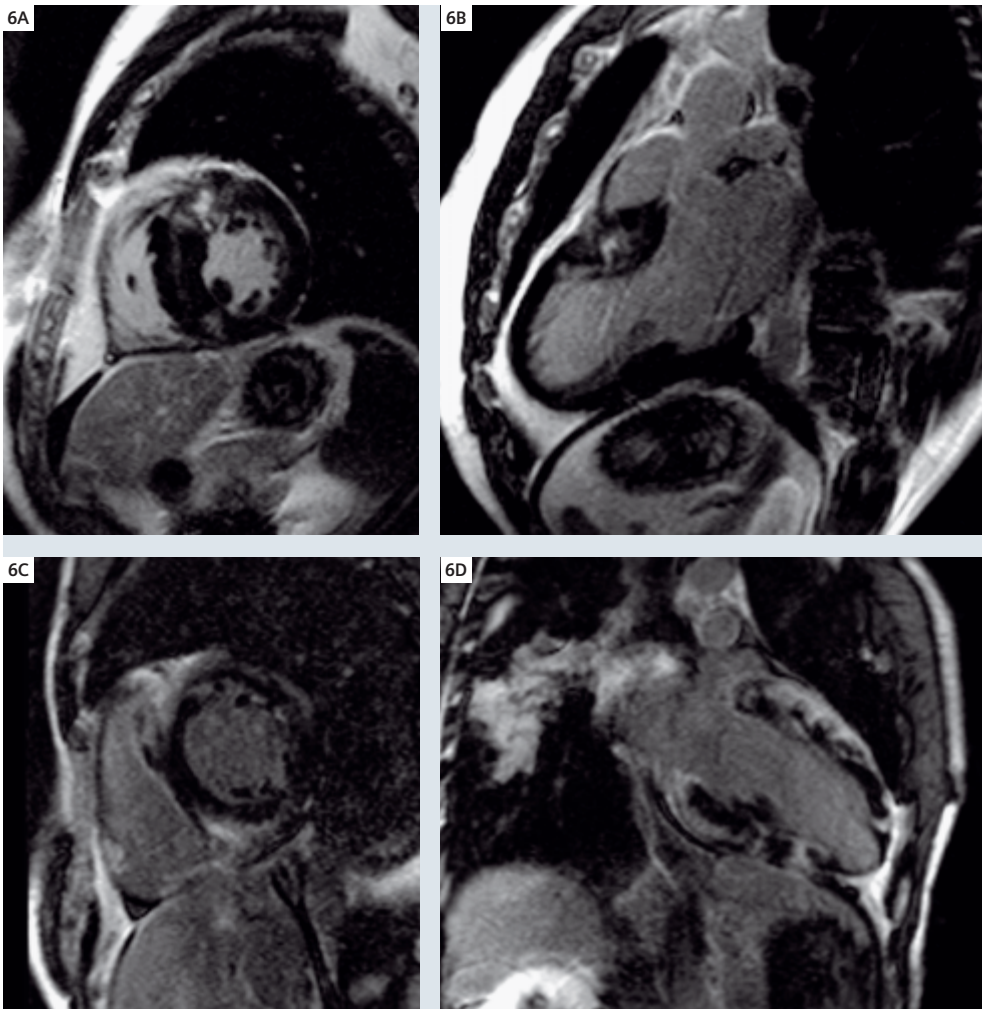
For CMR stress studies, cine and perfusion studies at rest and stress are combined with DE to identify scar tissue.

be classified as “ischemic” type or “non-ischemic” type, the former involving the subendocardium (i.e. subendocardial or transmural) and be located in a region that is consistent with the perfusion territory of an epicardial coronary artery (Figure 5). Hyperenhancement pattern has been shown to provide diagnostic utility for distinguishing between ischemic and non-ischemic cardiomyopathies. While classification of cardiomyopathies as ischemic or non-ischemic is an important means of dichotomizing patients with systolic dysfunction, prior studies have found that disease-specific differences in etiology of myocardial dysfunction alter prognosis and therapy. Among patients with non-ischemic cardiomyopathies, therapeutic options include corticosteroids for treatment of cardiac sarcoid or myocarditis, alkyloids in the setting of cardiac amyloid, α -galactosidase enzyme replacement therapy in the setting of Anderson-Fabry’s disease, and septal ablation or myomectomy in the setting of hypertrophic cardiomyopathy. DE-MRI evidenced hyperenhancement can occur in all of these conditions, having been reported in inflammatory conditions such as myocarditis, infiltrative cardiomyopathies such as sarcoid, systemic processes such as amyloid or Chagas disease, and genetic abnormalities such as hypertrophic cardiomyopathy or Anderson-Fabry’s disease. Each of these conditions results in myocardial dysfunction as a result of diverse pathological processes and is associated with differences in hyperenhancement patterns (Figure 6).

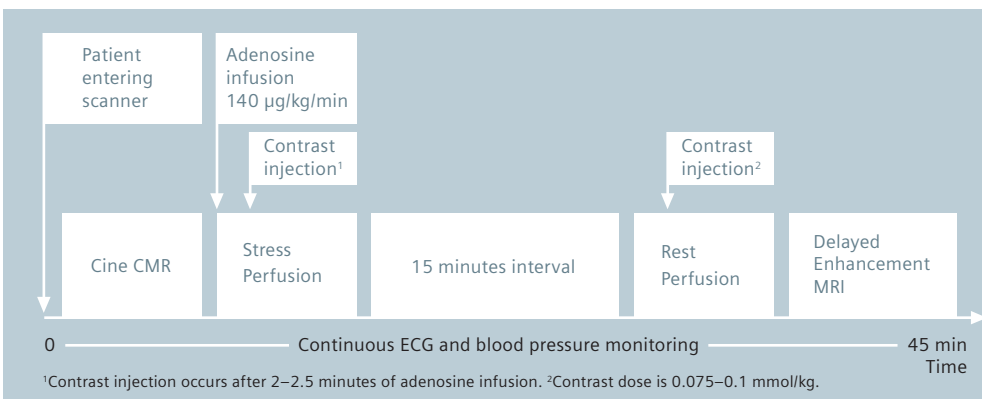
2. In patients with congestive heart failure, several studies have shown that medical therapy using

beta-blockers can result in improvement in LV function, heart failure symptoms, and long-term survival. A significant heterogeneity exists, however, in the response to beta-blockers among individual patients. It has been shown that patients with the most advanced disease have less capacity to respond to beta-blockers, because less viable myocardium exists. Similar to the situation in patients undergoing coronary revascularization, an inverse relationship was found between the transmural extent of infarction and the likelihood of improvement in regional contractility and LVEF after beta-blocker therapy. Furthermore, this parameter from DE-MRI was directly related to the magnitude of reverse remodeling (i.e. a decrease in LV enddiastolic volume index and LV end-systolic volume index).

DE-MRI as part of a multi-component stress test
MRI stress testing is being increasingly performed in clinical practice for evaluation of patients with ischemic heart disease. There are two techniques available, dobutamine cine CMR, analogous to dobutamine stress echocardiography, and vasodilator (adenosine) stress perfusion. The latter appears to be more practical and faster in the clinical scenario. In addition to providing information on stress perfusion, which could be obtained in approx. 5 minutes scan time, CMR can provide a very comprehensive evaluation if stress perfusion is combined with other CMR components. In our experience, the optimum combination is stress/rest perfusion CMR with delayed enhancement CMR (Figure 7). While the former detects perfusion



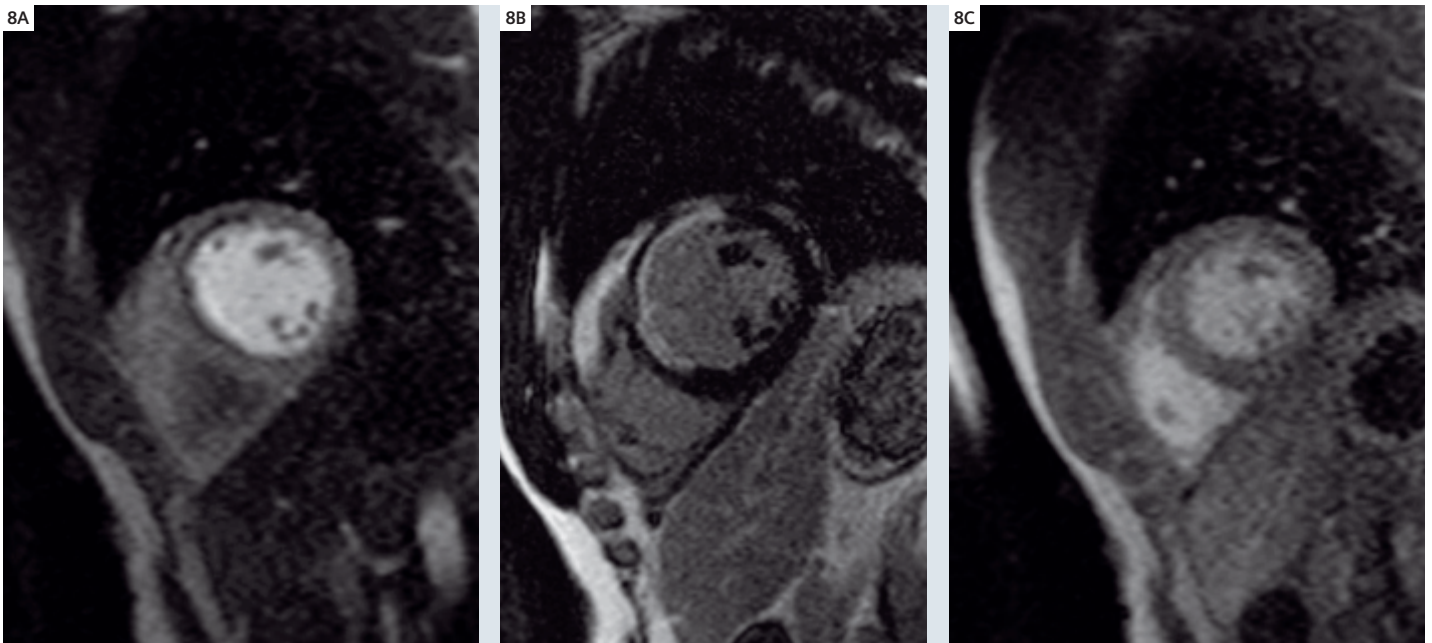
6 Examples of patient images with non-CAD type of hyperenhancement. Patient 1 is a 32-year-old male with hypertrophic cardiomyopathy. DE-MRI revealed extensive scarring at the right ventricular insertion sites into the septum (**A, B**). Patient 2 is a 28-year-old male with pulmonary sarcoidosis, an MRI scan performed for further evaluation of ventricular tachycardia revealed extensive cardiac involvement (**C, D**).



7 Flow-diagram of a multi-component CMR stress perfusion study. Note that DE-MRI is performed after two injections of gadolinium contrast ($2 \times 0.07\text{--}0.1$ mmol/kg) for stress and rest perfusion, which provides sufficient contrast for delayed enhancement imaging without additional contrast injections.

defects, DE-CMR provides further information regarding the cause of those defects. For example, perfusion defects that are matching in spatial extent to bright areas (scar) on DE-CMR are caused by infarcted myocardium (Figure 8). In contrast, a perfusion defect detected in dark (viable) myocardium by DE-CMR is consistent with inducible

ischemia. Occasionally, artifactual defects are observed on perfusion CMR which may impose difficulties in image interpretation. We found DE-CMR to be also useful to differentiate artifactual perfusion defects from true perfusion defects due to coronary artery disease. Artifactual defects occur in identical location, intensity and extent on serial



8 Patient example of a stress CMR study demonstrating complementary information of stress/rest perfusion and DE-MRI. Note that the subendocardial perfusion defect seen during stress (**A**) matches in spatial extent the scarred area on DE-MRI (**B**) indicating that there is infarct but no ischemic viable myocardium. Rest perfusion images (**C**) can be useful for differentiation of true perfusion defects from artifacts.

DE-MRI provides an important non-invasive tool for studying associations between scar characteristics and arrhythmic risk.

image acquisitions if imaging parameters are kept unchanged. Therefore we acquire for every patient both stress and rest perfusion images and compare these to DE-CMR findings. The only physiological scenarios where myocardial perfusion is thus severely reduced to cause rest defects are a) resting ischemia and b) infarcts. In the former scenario, the patient would likely be symptomatic at rest, thus not a good candidate for stress testing. In the latter scenario, which is more common in clinical practice, we have an independent technique for infarct detection to confirm our perfusion findings: DE-CMR. Consequently, if matched defects are not confirmed to be infarcts on DE-CMR they can be identified as artifactual. We found that considering these physiologic principles when interpreting the multi-component CMR stress test can increase the accuracy significantly (see recommended reading for details).

DE-MRI can be performed as a stand-alone procedure and takes less than 30 minutes.

DE-CMR for assessment of patients with arrhythmias

Myocardial scar forms a substrate for ventricular tachyarrhythmias, with a relationship between scar morphology and arrhythmic risk demonstrated in both experimental and epidemiologic studies. Data from animal studies indicates that both scar

size and scar morphology influence arrhythmic risk. DE-MRI evidenced hyperenhancement provides highly accurate assessment of both scar size and morphology, with improved scar detection in comparison to other modalities such as myocardial scintigraphy (SPECT). Thus, DE-MRI provides an important non-invasive tool for studying associations between scar characteristics and arrhythmic risk. Interesting insights into the relationship between hyperenhancement and arrhythmogenic potential has been provided in several investigations and has started to transition into clinical trials to investigate the potential of this technique for prediction of clinical SCD risk.

DE-MRI imaging protocol – as simple as it is

A DE-MRI scan can be performed in a single brief examination which requires only a peripheral intravenous catheter which is placed before the patient enters the MRI scanner, and does not require pharmacologic or physiologic stress. After obtaining scout images to delineate the short and long axis views of the heart, cine images are acquired to provide a matched assessment of left ventricular (LV) morphology and contractile function with the viability characterization from DE-MRI. Short-axis views (e.g. 6 mm slice thickness with 4 mm gap to

match contrast-enhancement images) are taken every 10 mm from mitral valve insertion to LV apex along with two to three long-axis views in order to encompass the entire LV. The patient is then given a bolus of 0.10–0.20 mmol/kg intravenous gadolinium by hand or power injection. After a 10–15 minute delay to allow the contrast media to distribute, high spatial resolution delayed enhancement images of the heart are obtained at the same slice locations as the cine images, using a 2D segmented inversion recovery fast gradient-echo (seg IR-GRE, e.g. 2D IR TurboFLASH) pulse sequence. For patients who are acutely ill and unable to perform breath-holds an alternative is offered by using a subsecond “snapshot” imaging technique. This single-shot, inversion-recovery, steady state free-precession sequence can be used in analogy to the segmented gradient echo sequence. Parallel Acquisition Techniques (iPAT) are used to speed up imaging. This technique has been shown to be highly accurate with only mildly reduced sensitivity and possible underestimation of the transmural extent of infarction. Another option is a 3D sequence during free breathing using the navigator technique to account for breathing motion.

The pulse sequence parameters are set up similar to any other cardiac MRI sequence, the only specific parameter to DE-MRI is the inversion time (TI). This is the time required from the inversion prepulse (which provides T1-weighting) to the center of the read-out portion of the sequence and should be set to “null” signal from normal myocardium. What that means is that the signal from myocardium is minimized i.e. black, thereby the infarct which has different T1-characteristics than normal myocardium has the largest difference in signal and appears bright on the image. The correct TI has to be determined for each scan and depends on factors such as the contrast dose and timing of imaging after administration of contrast. Obtaining the correct TI can be accomplished with little training. For those starting with DE-MRI the cardiac pulse-sequence package includes tools to allow the beginner to identify the right TI time: the TI-Scout displays the identical scan location with an array of different TI-times, which allows the scanner operator to determine the correct TI (where myocardium appears black) for subsequent acquisitions using the IR-GRE sequence. Alternatively a phase-sensitive IR-GRE (e.g. PSIR) sequence can be used

which can be used over a broad range of TI-time, thus making it unnecessary to optimize the TI. In general, most delayed enhancement images are acquired during an 8–10 s breath-hold, single shot phase-sensitive IR-GRE (PSIR) images in even less than 4 seconds. The imaging time for the entire examination is under 30 minutes. Figures 3, 5 and 6 demonstrate DE-MRI images from typical patient scans.

Summary

Delayed enhancement MRI provides clinically important information in a wide range of cardiac pathologies, in those frequently encountered in cardiology practice such as coronary artery disease and heart failure as well as less common problems such as in patients with cardiomyopathies or ventricular arrhythmias. It provides in-vivo information to the clinician that used to be only available to the pathologist on macroscopic exploration. In our institution DE-MRI is part of every cardiac exam. DE-MRI is a very robust technique and can be performed easily on a standard MRI scanner equipped with a cardiac package.

Single-shot PSIR sequences can be used for accurate DE-MRI especially in patients with breath-holding difficulties or arrhythmia.

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DE-MRI provides in-vivo information to the clinician that used to be only available to the pathologist on macroscopic exploration.

Recommended Reading

- 1 Kim RJ, Shah DJ, Judd RM. How we perform delayed enhancement imaging. *JCMR* 2003;5:505–514.
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