The identification of myocardial viability in the setting of left ventricular (LV) dysfunction is crucial for the prediction of functional recovery following revascularization. Although echocardiography, positron emission tomography (PET), and nuclear imaging have validated roles, recent advances in cardiac magnetic resonance (CMR) technology and availability have led to increased experience in CMR for identification of myocardial viability. CMR has unique advantages in the ability of magnetic resonance spectroscopy (MRS) to measure subcellular components of myocardium, and in the image resolution of magnetic resonance proton imaging. As a result of excellent image resolution and advances in pulse sequences and coil technology, magnetic resonance imaging (MRI) can be used to identify the transmural extent of myocardial infarction (MI) in vivo for the first time. This review of the role of CMR in myocardial viability imaging describes the acute and chronic settings of ventricular dysfunction and concepts regarding the underlying pathophysiology. Recent advances in MRS and MRI are discussed, including the potential for dobutamine MRI to identify viable myocardium and a detailed review of the technique of delayed gadolinium (Gd) contrast hyperenhancement for visualization of viable and nonviable myocardium.

Key Words: MRI; spectroscopy; viability; gadolinium hyperenhancement; myocardium.


IN THE LAST FIVE years, there have been multiple technological advances in noninvasive cardiac imaging that are now being translated into new clinical options for the diagnosis and management of cardiac disease. Echocardiography, nuclear imaging, computed tomography (CT), and magnetic resonance imaging (MRI) have established and emerging roles in noninvasive cardiac imaging. Of the clinical applications for cardiac imaging, assessment of cardiac viability has experienced significant growth as a reflection of the rising number of patients with coronary artery disease (CAD)-related left ventricular (LV) dysfunction (1). Despite its relatively recent addition to the cardiac imaging armory, cardiac magnetic resonance (CMR) viability imaging has established a clinical role and is serving to provide new insights into the natural history of myocardial damage and myocardial dysfunction in patients with CAD. CMR can provide morphological, functional (MRI) and metabolic (magnetic resonance spectroscopy, MRS) information about the heart, and offers detailed viability information that cannot be obtained from any other modality.

Throughout the Western world there has been a decline in the number of deaths from myocardial infarction MI but a dramatic increase in the incidence of congestive cardiac failure. In the United States between 1970 and 2000, cardiovascular disease death rates decreased overall by 50%, however mortality rates for congestive heart failure more than doubled and hospitalizations for congestive heart failure more than tripled (1). Palliative treatment options for heart failure are numerous (2), however the ideal treatment is the restoration of myocardial systolic function through revascularization of dysfunctional but viable ischemic myocardium.

There is general agreement that viable chronically hypoperfused myocardium should be revascularized and that nonviable myocardium will not recover systolic function with revascularization. Delaying revascularization in patients with viable myocardium is associated with increased mortality (3). There is, additionally, a weight of observational evidence that revascularization in patients with severe myocardial dysfunction in whom there is no significant viability may be associated with increased risk compared to medical therapy (4,5). Hence, there is a need to identify the presence and extent of viable and nonviable myocardium in order to determine appropriate therapy for the individual. Revascularization (when appropriate) must be expedited, as there is a limited time frame in which chronically ischemic myocardium will remain viable before irreversible damage occurs (6).

DEFINING VIVABLE AND NONVIVABLE MYOCARDIUM.

By definition, viability is continued cell life. A myocyte is viable while alive and nonviable once irreversible cellu-
lar damage and cell death occurs. A number of indirect methods have been used to detect presence of living myocytes for the purpose of in vivo assessment of myocardial viability. As a result, in clinical practice and research settings, viability has been defined in accord with the method used to indirectly demonstrate the presence of living myocytes, leading to a number of de facto definitions of viability. For example: 1) recovery of contractile function following revascularization; 2) response to inotropic stimulation (e.g., dobutamine echocardiography); 3) presence of glucose metabolism (e.g., fluoro-2-deoxyglucose [FDG] positron emission tomography [PET]); and 4) presence of active cellular transport mechanisms (e.g., TI-201 SPECT).

While each of these definitions has been shown to relate to patient outcome, on a cellular level, myocytes remain viable until the point at which cellular membrane integrity fails. By this definition, histology is the ultimate method for inspection of individual cells. Myocytes may be viable in the setting of severely reduced or absent contractile function, resulting from either acute or chronic reduction in perfusion. Differences between the acute and chronic settings in terms of the potential for contractile recovery of myocardium are related to the underlying mechanisms of myocyte dysfunction.

**Dysfunctional But Viable Myocardium—Acute Setting**

Abrupt reduction in myocardial perfusion rapidly results in contractile dysfunction. In the setting of acute ischemia, the presence of regional hypokinesis or akinesia was historically used to aid early detection of MI and was shown to be a prognostically important tool. The extent of acute contractile dysfunction was predictive of subsequent morbidity and mortality (7).

In 1975, the phenomenon of mechanical dysfunction persisting after revascularization, despite the restoration of normal or near normal myocardial perfusion, was noted in conscious dogs undergoing brief coronary occlusions (8). Myocardial stunning is the term used to describe this phenomenon, now recognized to occur in a wide variety of settings. Stunning has been observed following single or multiple episodes of regional ischemia. Stunning may also occur after global ischemia (cardiac arrest), exercise induced ischemia, or in the setting of partially reversible regional ischemia (necrosis of some but not all myocytes) (6).

The pathogenesis of stunning is debated, but likely mechanisms include oxidant stress due to the generation of reactive oxygen species (9) and transient disturbances in calcium homeostasis impacting on contractile function (10). Regardless of the etiology of stunning, the potential for subsequent recovery of myocardial contractility is a function of the extent of myocyte necrosis.

**Dysfunctional But Viable Myocardium—Chronic Setting**

The insult to myocardial cells of chronic ischemia promotes an initially “adaptive” response from the cell, aimed at protecting cellular integrity. Failure of cellular integrity results in the formation of scar tissue, nonviable tissue that has no prospect of functional recovery with revascularization. The term hibernation is used to describe the myocardium that is dysfunctional but retains viability and potential for improvement with revascularization. There are two alternative hypotheses for the etiology of “hibernating myocardium.” The first centers on the belief that chronic hypoperfusion leads to hibernation, as summarized by the following statements (6.11.12):

1. A chronic reduction in resting myocardial perfusion. Baseline coronary flow is chronically reduced by a sufficient magnitude to result in the decrease in myocardial function.
2. This chronic hypoperfusion results in a variety of cellular and subcellular changes that have clinical consequences.
3. There is residual contractile reserve and ongoing metabolic activity in hibernating segments.
4. Depressed myocardial function may recover rapidly on revascularization.

An alternative hypothesis for the etiology of hibernation has arisen from PET assessment of normal resting myocardial blood flow in dysfunctional myocardium. In the setting of exercise or stress, these segments show relatively reduced flow, i.e., reduced flow reserve, leading to the theory that repetitive episodes of ischemia (repetitive “stunning”) may lead to chronic myocardial dysfunction (13,14).

Structural changes underlie the loss of contractile function in hibernating myocardium. A progressive loss of contractile proteins and sarcomeres is seen in substantial numbers of myocytes and this occurs without the loss of cell volume, thus distinguishing hibernating myocardium from cellular atrophy and degeneration. In some cells, this process is limited to the perinuclear region and in others it is more extensive, leaving a few sarcomeres at the cell periphery or none at all (11,12).

Other changes include the reduction in mitochondrial number and size, as well as loss of contact sites between inner and outer mitochondrial membranes (possibly indicating reduced oxidative phosphorylation and mitochondrial creatine kinase activity). Mitochondrial function remains intact, but hibernating myocytes preferentially metabolize glucose rather than free fatty acids. Hibernating cells may also have increased tortuosity of nuclei, with uniformly dispersed heterochromatin, virtual absence of the sarcoplasmic reticulum and T tubules (protrusions from the sarcolemma into the cytoplasm that play a vital role in calcium release), replacement of the sarcoplasmic reticulum by a network of disorganized reticular membranes, and expression of immature (fetal) structural proteins (Fig. 1). Thus, the process of hibernation in chronically underperfused myocardium involves a continuum of downregulation of myocyte metabolism that eventually leads to reductions in mitochondrial numbers, reduction in functional myofibrillar elements, and dedifferentiation of cells. At some point on this continuum, the ability of the cell to recover contractile function becomes compromised. Hence the observation that hibernating myocardium
revascularized ‘too late’ does not recover contractile function promptly, if at all (3).

In summary, multiple definitions have been used in the assessment of myocardial viability based on the method used to detect the presence of viable myocytes. Whether in the setting of acute or chronic ischemia, dysfunctional myocardium may be viable and maintain the potential for functional recovery. Ultimately, the loss of cellular integrity is the final step in a cascade of cellular responses to ischemia and marks the point of no return prior to myocyte death.

NON-MRI VIABILITY IMAGING

Traditional tests for detection of myocardial viability are based on the identification of myocardial segments with either preserved contractile reserve (dobutamine stress echocardiography, DSE), preserved mitochondrial function (sestamibi SPECT), reduced perfusion with preserved metabolic activity (FDG-PET or FDG-SPECT) or reduced perfusion with preserved membrane integrity (thallium SPECT). Segments are defined in a binary fashion as either being viable or nonviable. These tests have differing positive and negative predictive values for identification of viable myocardium (15) (Fig. 2). Disagreement between modalities, in terms of the extent of viable tissue demonstrated, may relate in part to the fact that each modality indirectly examines a different aspect of cellular viability.

Loss of contractile elements precedes the loss of metabolic activity and failure of membrane integrity is the last step preceding cell death. Variation in the extent of myocyte damage within a myocardial segment and the testing modality chosen will influence the likelihood of viability being detected. This theory is supported by
recent observations by Zamorano et al (16), who found that 19% of segments defined as viable by thallium scintigraphy were characterized as nonviable by DSE. The study patients all underwent cardiac transplantation and explanted hearts were examined histologically. As predicted, the number of live cells per segment required for DSE to detect viability was greater than the number required for viability to be detected by thallium redistribution SPECT.

Apart from the potential differences between modalities in their assessment of viability, the way in which accuracy of each modality is determined is influenced by multiple factors. Any observed functional recovery following revascularization will be influenced by the degree and duration of preprocedural cellular structural change, new periprocedural ischemic insults or cell death, the success of the revascularization procedure itself, and the timing and method used to assess change in global or segmental systolic function. These complexities of myocardial viability assessment make interpretation of the available literature and comparison of investigation and treatment options difficult.

Echocardiographic imaging suffers from limitations of echocardiographic windows that will impair image quality in up to 37% of patients having stress echocardiographic viability testing (17–19). It may be difficult to visualize all myocardial segments during stress testing, despite the advances in tissue harmonic imaging and echo contrast agents (20). Radionuclide methods for assessing viability require radiation exposure to the patient. 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. Resolution of SPECT and PET is limited, with a 8–10-mm pixel size. Thus viability must be determined in a binary fashion and the transmural extent of scar tissue cannot be determined.

MAGNETIC RESONANCE VIABILITY IMAGING

CMR is rapidly becoming an accepted clinical tool for the assessment of myocardial viability. Developments in pulse sequences, coils and electrocardiogram (ECG)-gating technology have resulted in substantial improvements in temporal and spatial resolution. This, combined with animal and patient supportive evidence, has led to rising clinical use of CMR in the detection of myocardial viability, using both techniques for assessment of myocardial contractile function and myocyte integrity.

MRS, although not as widely available, can also be used for detection of myocardial viability, and has the unique ability among all imaging techniques of being able to measure the presence of subcellular components required for maintained cellular integrity. Recent advances in spectroscopic techniques will be briefly discussed prior to an overview of applications of MRI in the assessment of myocardial viability.

Tissue Relaxation Characteristics/MRS

While most magnetic resonance images are constructed based on the net magnetic moment of water protons, the net magnetic moments of other nuclei can also be directly observed by CMR, including phosphorus, sodium, and potassium. In addition, spectroscopic techniques can be used to examine protons located on molecules other than water, such as creatine. The balance of these constituents of cells is vital to maintained cellular viability and MRS is the only available technique capable of their observation noninvasively in vivo.

Phosphorus 31 (31P)-MRS can examine cardiac energy metabolism by detecting the spectroscopy profiles of adenosine triphosphate (ATP) and phosphocreatine (PCr). Initial clinical studies have demonstrated the diagnostic value of 31P-MRS for detection of myocardial viability. Yabe et al (21) imaged 31P spectra in patients with CAD who had reversible and irreversible anterior thallium defects on exercise-redistribution SPECT using a 1.5 Tesla magnet. The imaging volume of interest was approximately 30 cm$^3$ in a sagittal plane, and quantification of spectra utilized hexamethyolphosphoramide as the reference standard. A reduction of PCr content was seen in patients, but not in controls. Additionally, reduction in ATP spectra peaks identified the subset of patients who had no thallium redistribution (nonviable myocardium). Although this study provided proof-of-concept for viability imaging, the chemical shift imaging technique (CSI) used sampled large myocardial volumes limited to the anterior wall, and resolution was insufficient to differentiate a mixture of viable and nonviable myocardium within the sample.

Conventional chemical shift imaging has been improved by the use of specialized reconstruction such as spectral localization with optimal point (SLOOP) spread function in order to match the shape of the sensitive region to the anatomy of the object. This has resulted in improved localization and spatial resolution, with decreased contamination during quantification of cardiac PCr and ATP levels in phantoms and healthy volunteers in a 1.5 Tesla magnet (22).

More recently, Pohmann and von Kienlin (23) described accurate measurement of 31P in the normal myocardium by use of acquisition-weighted CSI in a 2-Tesla system. This technique applies k-space weighting and k-space position dependent variable excitation angles during data acquisition and avoids the reduction in signal-to-noise ratio (SNR) encountered when a k-space filter is applied following data is acquisition. The authors were able to demonstrate improved resolution (voxel size 16 cm$^3$), high SNR, and low contamination of acquisition-weighted images with visualization of the posterior wall in many cases (23). Beer et al (24) reported 31P spectra from the anterior wall and adjacent unaffected septum in eight patients with anterior wall motion abnormalities and recent MI. Images were repeated six months following revascularization, and the PCr/ATP ratios were examined. Recovery of wall motion was seen in four patients, none of whom had reduced PCr/ATP ratios in either the septum or anterior wall. In patients with no recovery in wall motion, reduced PCr/ATP ratios were present in infarcted and adjacent myocardium (Fig. 3). This study serves to demonstrate the potential utility of this technique in demonstrating myocardial viability. However, the clinical application is limited by image resolution (voxel size 25 cm$^3$ in this
study) and the current inability of the technique to examine all areas of the heart.

Proton spectroscopy ($^1$H-MRS) theoretically offers a 20-fold improvement in sensitivity over $^{31}$P-MRS of phosphorylated creatine due to the inherently higher sensitivity of proton spectroscopy, the higher concentration of total creatine, and the higher content of $^1$H in the creatine N-methyl resonance. Consequently, $^1$H-MRS allows metabolic interrogation of small voxels ($\leq 10$ cm$^3$) and can be performed at magnetic field strengths of many clinical CMR systems. Bottomley and Weiss (25) employed proton spectroscopy in patients with a history of MI using a 1.5-Tesla magnetic resonance imaging system. Total creatine was significantly reduced in regions of infarction compared to noninfarcted myocardium. They validated the clinical findings in a dog model, and established that enzymatic degradation of creatine in heart extracts resulted in the complete disappearance of the $^1$H N-methyl resonance peak at 3.0 ppm. This study shows for the first time that it is possible to measure creatine within myocardial regions small enough to make this technique clinically useful.

Maintenance of an ionic gradient between the intracellular and extracellular space to preserve sodium and potassium homeostasis is essential for cellular viability. Levels of sodium-23 and potassium-39 can be imaged using MRS and provide another indicator of myocardial viability. From a physiologic perspective and in the narrow context of myocardial viability, sodium-23 and potassium-39 MRS appear similar in demonstration of loss of myocyte integrity due to irreversible injury.

Cannon et al (26) studied a canine model of MI and showed that ex vivo myocardial sodium-23 image intensities were elevated following acute infarction and that the elevation correlated with increased sodium content measured by flame photometry. Using an in vivo canine model, Kim et al (27,28) showed that sodium-23 CMR could be used to measure infarct size and distinguish between reversible and irreversible ischemic injuries in a 4.7-Tesla system. This distinction was thought to be due to equilibration of intracellular and extracellular sodium concentration in irreversibly injured myocytes due to their failure to maintain ionic homeostasis. Fieno et al (29) investigated the potential of direct MRI of potassium-39 to examine viability and demonstrated that potassium image intensities were reduced in irreversibly injured regions of rabbit myocardium secondary to loss of intracellular potassium.

The primary limitation of CMR metabolic imaging to date is that the magnetic resonance signals associated with phosphorus-31, creatine, sodium-23, and potassium-39 are $10^4$ to $10^6$ times smaller than the proton signal associated with water. Although judicious selection of imaging parameters based on differences in relaxation times can partially alleviate this deficit (30), small MR signals generally result in poor spatial resolution and long imaging times. Signal is improved with higher field strengths, and the increased availability of

Figure 3. $^{31}$P spectra from the septal myocardium three weeks after acute MI (voxel size 25 cm$^3$ each) demonstrating the different spectral patterns in the unaffected septum in two patients with nonviable anterior wall (a) and viable anterior wall (b). (Reprinted from MAGMA, 13, Beef et al, ($^{31}$P-MR spectroscopy for the evaluation of energy metabolism in intact residual myocardium after acute myocardial infarction in humans. p. 70-75, 2001, with permission of Elsevier.)
3-Tesla MRI systems is likely to lead to increased interest in the clinical utility of this imaging technique.

**Wall Thickness and Thickening**

The spatial and temporal resolution of cine MRI allows accurate assessment of wall thickness and systolic thickening throughout the cardiac cycle. Various disease states are associated with abnormal wall thickness and thickening, such as infiltrative diseases, e.g., amyloidosis, ventricular hypertrophy, constrictive pericarditis, and hypertrophic cardiomyopathies (31). Regional reduction in myocardial systolic function and wall thickness is a hallmark of ischemic heart disease and occurs in a distribution determined by the coronary artery territories, the extent of disease, and the degree of collateral vascular supply.

The observation of regional wall thinning following MI was first made echocardiographically in patients and animal studies (32–34). Early MRI studies also demonstrated presence of thinning in chronic MI (35). The extent of myocardial thinning at rest has been shown to be a marker of nonviability in terms of the likelihood for functional recovery following revascularization (36), and can predict regional wall viability with similar accuracy to thallium redistribution. An end-diastolic wall thickness ≥0.6 cm echocardiographically has been shown to virtually exclude the potential for recovery of function after revascularization (36).

However, viable myocardium can thin and still retain the potential for recovery of function. Regional thinning may occur early after an infarct, even in the absence of transmural necrosis (37). Circumferential enlargement of an infarcted segment is termed infarct expansion, and is particularly seen following anterior MI (38). This expanded and thinned myocardium may be hypokinetic or akinetic due to single or repeated ischemic insults (9,39). In the hibernation setting, thinning results from alterations in structural protein content that are thought to occur late in the time course of chronic ischemia (11,40).

Contrary to these observations regarding thinning, increased end-diastolic wall thickness may also occur acutely following MI. Increased wall thickness occurs as a result of wall edema (41) and the degree of acute thickening has been shown to correlate with the extent of myocardial necrosis in animal models of reperfused myocardial injury.

Reduction in regional wall systolic thickening is observed following MI. However, the extent of regional wall motion abnormality early after experimentally-induced infarction in dogs is a poor indicator of the extent of tissue necrosis defined histologically (34). Myocardial stunning is the term used to describe the postinfarction regional reduction in systolic function that may persist for hours to weeks despite restored perfusion. This process can also occur following ischemic insult without necrosis.

As knowledge of the pathological processes of hibernation and myocardial remodeling increases, the relationships between wall thickness, thickening, and viability become more complex. Although thinning and akinesis are seen following transmural infarction, wall thinning and impaired systolic thickening do not exclude the presence of viable myocardium (37).

**Contractile Reserve**

DSE using either low-dose or full-dose techniques has an established role in the detection of myocardial viability. Early publications demonstrated the overall concordance of DSE with radionuclide methods for viability detection (42). More recent DSE literature has focused on the prognostic value of DSE-defined viability in patients with CAD and LV dysfunction. In the setting of chronic CAD, Meluzin et al (43) demonstrated that improved LV function following revascularization was proportional to the extent of DSE-defined viability. In another large observational dataset, Afridi et al (44) reported a mortality rate of 6% in patients with revascularized viable myocardium compared to 20% in patients with viability that did not undergo revascularization, 17% in patients without viability who were revascularized, and 20% in patients without viability who were not revascularized.

The popularity of dobutamine stress MRI is based in part on the success and experience with DSE. There is, however, growing evidence in support of the accuracy and prognostic value of stress MRI. First reports of the use of MRI assessment of contractile reserve were published more than a decade ago. In 1995, Dendale et al (45) studied 24 patients early after acute MI with low-dose dobutamine MRI and echocardiography using quantitative assessment of wall motion for both imaging modalities. Concordance between echocardiography and MRI in identifying viable and nonviable segments was 81%. More recently, Zamorano et al (16) reported 91% agreement between DSE and MRI in the detection of viable myocardial segments in a group of patients undergoing cardiac transplantation for ischemic cardiomyopathy. Low-dose dobutamine MRI has also been reported to be a reliable indicator of viability as defined by the presence of F18-FDG uptake on PET.

Baer et al (46) reported 89% agreement between the tests for detection of viable myocardium on a per patient basis.

With segmental recovery of wall thickening as the gold standard, several small clinical studies have reported the positive predictive values of dobutamine MRI ranging from 68% to 87%, and negative predictive values from 69% to 87% (47–49). When analysis is performed on a per patient basis, dobutamine MRI has been reported as having 76% sensitivity, 100% specificity, and 100% positive predictive value for the detection of myocardial viability (47).

Baer et al (50) further explored the relationship between end-diastolic wall thickness and systolic wall thickening using rest and low-dose (10 μg/kg/minute) dobutamine MRI in a group of 43 patients with infarction and LV dysfunction; who had revascularization of the infarct related artery territory. They observed recovery of systolic wall thickening in 63% of patients and found that dobutamine-induced wall thickening was a better predictor of LV functional recovery than was preserved diastolic wall thickness ≥5.5 mm. In agreement with other studies, low-dose dobutamine MRI was 89%
sensitive and 94% specific for prediction of overall LV functional recovery.

Most investigators choose a maximal dobutamine dose of 10 \( \mu \text{g/kg/minute} \) for the assessment of contractile reserve. This is based on the experience of multiple groups as well as on two papers that demonstrate using the technique of myocardial tagging that the peak inotropic response to dobutamine in normal volunteers occurs at 10 \( \mu \text{g/kg/minute} \) and plateaus thereafter (51,52). Dobutamine is discontinued in the event of MRI evidence of ischemia or adverse effects of the stress agent. ECG-gated cine images are acquired at baseline and during dobutamine infusion in order to demonstrate changes in regional wall motion in all myocardial segments.

There are potential advantages and disadvantages of MRI compared to DSE. Dobutamine MRI has the advantage of full visualization of the myocardium, when echocardiography may suffer from impaired image quality. The temporal and spatial resolution of MRI is such that qualitative assessment of all segments is usually possible and there is potential for future use of quantitative methods for determination of wall thickening. Currently, baseline and stress images are compared side by side and viability is defined on a segmental basis as being present when there is increased systolic thickening during dobutamine infusion compared to baseline, i.e., the presence of “contractile reserve” (Fig. 4).

A historical limitation of MRI was reduction in image quality in the setting of increased heart rates, as a result of reduced temporal resolution. The advent of new fast gradient-echo MRI sequences such as trueFISP, FIESTA, or balanced FFE, with tremendously improved temporal resolution, permits capture of cine loops displaying the beating heart, therefore allowing quantitative assessment of wall motion. Real-time imaging with segmented k-space turbo gradient-echo echo-planar MRI has been reported to be feasible under dobutamine stress conditions (53) and advances in coil technology with new image-based (SENSE) and k-space based (SMASH) reconstruction algorithms also permit reductions in imaging times and potentially allow more rapid and accurate assessment of cardiac function during dobutamine infusion (54–56).

An important practical disadvantage of dobutamine cine MRI relates to the risk of administering a dobutamine infusion to a patient in the magnet. Positive inotropic stimulation in patients with CAD is associated with a well-recognized risk of eliciting an arrhythmic or ischemic events 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. Published efficacy studies have reported safety of dobutamine MRI both at low and high doses (20,57,58), however, data recently presented at the Society of Cardiovascular Magnetic Resonance Annual Meeting in 2003 from Wahl et al (59) found that limiting side effects occurred in 7.4% of 1000 consecutive patients having (high-dose) dobutamine stress MRI.

Complication rates of dobutamine MRI for viability detection are minimized by the use of low-dose (10 \( \mu \text{g/kg/minute} \)) dobutamine for detection of contractile reserve. Ischemia may occur at low dobutamine doses, as reported by Hamilton et al (60); who observed MRI evidence of ischemia occurring before a maximal infusion dose of dobutamine was reached in 38% of patients with positive scans undergoing dobutamine stress MRI. In summary, the assessment of contractile function, in particular contractile reserve, by MRI can provide accurate information regarding segmental viability.
Wall thinning or the absence of thickening at rest may not be a reliable marker of viability in view of the potential for maintained viability in thinned and akinetic myocardium in some clinical situations. The presence of contractile reserve can be accurately demonstrated by dobutamine MRI and is a marker for myocardial viability. This technique has potential advantages over echocardiography in patients with poor acoustic windows and can be performed safely.

**Delayed Hyperenhancement**

Given the limitations of defining myocardial viability on the basis of contractile reserve, it is important to see the development of an alternative and potentially complimentary means of defining viability by contrast hyperenhancement MRI. The basis of this development was the demonstration of altered tissue relaxation characteristics in infarcted myocardium on spin echo images (61) and the recognition that this differential between normal and abnormal myocardium could be accentuated by the use of gadolinium (Gd) contrast agents. As the primary action of most currently approved MRI contrast agents is to shorten the longitudinal relaxation time, the goal of pulse sequences for the purpose of examining contrast enhancement patterns is to make image intensities a strong function of T1 (T1-weighted images).

**Background and History of Delayed Enhancement Technique**

Early approaches (ca. 1985) to acquiring T1-weighted images of the heart often employed ECG-gated spin echo images in which one k-space line was acquired each cardiac cycle. Because the duration of the cardiac cycle (~800 msec) was comparable to myocardial T1, the resulting images were T1-weighted. Following contrast agent administration, myocardial T1 was shortened and image intensities increased. Using this approach, a number of investigators reported that while image intensities increased throughout the heart, regions associated with acute MI became particularly bright (hyperenhanced) on the time scale of minutes to tens of minutes after contrast administration (62–69). However, one important limitation of early pulse sequences was the need for relatively long acquisition times and subsequent artifacts due to respiratory motion.

Currently used techniques utilize faster imaging sequences with segmentation of k-space (70). Data can be collected within a single breath-hold with a subsequent reduction in motion artifact. Resolution is further optimized by the use of a trigger delay in the sequence with collection of data within the portion of diastole when cardiac motion is minimal. When the inversion time (TI) is set to null normal myocardium, the segmented inversion recovery (IR) pulse sequence (segmented IR turboFLASH) results in a 500% to 1000% increase in the signal intensity of infarcted compared to remote regions whereas earlier spin-echo techniques gave only a 50% to 100% increase in signal intensity of abnormal myocardium (71). Dramatic improvements in image quality are the result of improved spatial resolution and improved contrast-to-noise ratios (CNRs), making it possible to accurately define small and subendocardial myocardial infarcts using this technique.

**Acute Setting—Animals**

A number of groups have shown that regions of acute MI appear hyperenhanced on T1-weighted images acquired more than a few minutes after contrast administration (62–64,72–74). Delayed hyperenhancement correlates with the presence of histologically defined necrotic tissue after either reperfused or nonreperfused acute myocardial injury. The acquisition of high-resolution (500 × 500 × 500 μm) ex vivo cardiac images allows registration of slices for the direct comparison of triphenyl tetrazolium chloride (TTC)-stained myocardium and ex-vivo MR images. Kim et al (75) utilized this technique in a study of 18 dogs, and demonstrated that MRI accurately depicts histologically defined regions of myocardial necrosis both in reperfused and nonreperfused MI. As seen in Fig. 5, the match between TTC and MRI images is extremely close.

Some observers have suggested that hyperenhancement occurs not only in regions of cellular necrosis but also in a border zone of injured but viable myocardium surrounding the acute infarct, particularly within 24 hours of infarction (76,77). However, this observation is not supported by histological evidence in animal studies that have demonstrated agreement between hyperenhancement and cellular necrosis defined by TTC staining (75). The debate was specifically addressed by Fieno et al (78). In a canine model of acute infarction, histologic TTC-staining was used to define infarcted myocardium, and fluorescent microparticles were injected into the left atrium during coronary occlusion to define the ischemic risk region prior to sacrifice. The perinfarction risk region did not exhibit hyperenhancement as defined by high-resolution ex vivo MRI, and myocyte necrosis was seen exclusively in zones of hyperenhancement (Fig. 6).

The spatial extent of hyperenhancement following acute myocardial injury has been shown to decrease at the time of follow-up imaging in animal studies (75). This observation is in keeping with established understanding of the pathological processes of remodeling following MI (79). Tissue edema initially increases following ischemic myocardial injury. Once edema resolves, there is formation of a dense collagenous scar that occupies relatively less spatial extent of myocardium.

Another potential feature of acute infarct imaging not seen in chronic infarction, is hypoenhancement of a "no-reflow" zone (Fig. 7). Large acute infarcts may exhibit a region of hypoenhancement, usually surrounded by a larger region of hyperenhancement (72,80). The dark region towards the endocardial core of the infarct visible in the first image of Fig. 7 corresponds to a no-reflow region that is characterized by substantially reduced perfusion. This is thought to be due to damage or obstruction at the microcirculatory level that impedes penetration of Gd into the core of the infarct.
Figure 5. Comparison of ex vivo MR images with TTC-stained slices in one animal at three days after infarct. Slices are arranged from base to apex starting at the upper left and advancing left to right, then top to bottom. At the right is a magnified view. (Reprinted from Circulation, 100, Kim et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. p 1992–2000; with permission from Lippincott, Williams & Wilkins.)

Figure 6. Comparison of MRI hyper-enhancement (left upper panel) TTC-staining (left middle panel) and the myocardium at risk (region without fluorescent microparticles, left lower panel) in an animal with a one-day-old reperfused infarction. Light microscopy views of region 1 (not at risk, not infarcted), region 2 (at risk, but not infarcted), and region 3 (infarcted) are shown on the right panels. (Reprinted from J Am Coll Cardiol, 36, Fieno et al. Contrast enhanced magnetic resonance imaging of myocardium at risk: disfunction between reversible and irreversible injury throughout infarct healing. p 1985–1991, 2000, with permission from the American College of Cardiology Foundation.)
Contrast eventually accumulates in these regions and they slowly become hyperenhanced.

**Acute Setting—Humans**

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 (65–68,81–86). The transmural extent of acute infarction, defined by contrast-enhanced MRI (ceMRI) has been shown to predict the likelihood of contractile improvement both on a segmental and global basis (87). In a study of 24 patients with revascularized 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 \( \leq 25\% \) of LV wall thickness. Additionally, in studies of acute myocardial injury in the setting of interventional cardiology, ceMRI has been used to identify new sites of myocardial necrosis following procedures such as septal embolization or radiofrequency ablation (88,89).

Potential clinical relevance of transient hypoenhancement or the no-reflow phenomenon (see acute setting—animals) has been suggested in terms of both prediction of functional recovery and prognosis. Rogers et al (90) noted this phenomenon and categorized myocardial segments according to patterns of first pass perfusion and enhancement early after contrast injection in a group of 17 patients with acute MI. They observed little long-term functional recovery in those segments with an initial hypoenhanced pattern early after contrast injection.

In a study of 17 patients followed for 16 ± 5 months after acute MI, Wu et al (91) 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.

**Acute Setting—Mechanisms of Hyperenhancement**

Following intravenous injection, Gd diffuses rapidly from the intravascular to the extracellular space. The presence of Gd decreases both the longitudinal (T1) and transverse (T2) relaxation times of water protons within the same compartment and this effect predominantly influences T1 at the doses used clinically.

The mechanism by which Gd concentrates in regions of acute irreversible injury is debated, but is likely to relate to the altered sarcolemmal membrane integrity (early after injury) and extracellular matrix structure (late after injury) in these regions. Gd-DTPA is a large molecule, thought to be metabolically inert and to passively diffuse throughout the extracellular space (92). Regions of hyperenhancement are associated with sarcomere membrane rupture when examined by electron microscopy (93), and it is hypothesized that observed changes in Gd-DTPA wash-in and wash-out kinetics may relate to sarcolemmal rupture (Fig. 8) (94).

**Chronic Setting—Animals**

Chronic MI is characterized by dense collagenous scar tissue, however, despite this structural difference from acute infarction, hyperenhancement is still observed. Using the same technique of ex vivo imaging and TTC-staining, regions of hyperenhancement in chronic infarction appear identical to regions defined histologically (Fig. 9).

**Chronic Setting—Humans**

In the setting of chronic infarction in humans, there was initial failure to observe hyperenhancement in patients with prior MI, leading to the conclusion that chronic infarcts did not hyperenhance (82,86,95). Subsequently, reports of hyperenhancement in patients with CAD who had a clinical diagnosis of prior infarction, by Ramini et al (96) and Fedele et al (97), suggested that this conclusion was incorrect. It has since been firmly established by longitudinal studies of patients with acute MI, that healed infarcts do hyperenhance and that the zone of hyperenhancement corresponds to the infarct artery related territory (98). In a study of 32 patients with MI and 20 patients with nonischemic cardiomyopathy, Wu et al (98) found that hyperenhancement did not occur in any patient without CAD, or in normal volunteers. The use of ceMRI to differentiate ischemic from nonischemic cardiomyopathy in patients...
presenting with LV dysfunction is one of the many potential clinical applications of this imaging technique. There is an important relationship between the extent of viable myocardium and potential for functional recovery in the setting of chronic ischemia and LV dysfunction. ceMRI is the only imaging tool to allow the relationship between the transmural extent of viability and functional recovery to be defined in vivo. It has been shown that in patients with LV dysfunction undergoing revascularization surgery, the extent and severity of nonviable tissue defined by ceMRI correlates with the likelihood of functional recovery on a segmental and patient basis (99). Furthermore, the likelihood of recovery in regional contractility decreases progressively as the transmural extent of hyperenhancement before revascularization increases.

**Chronic Setting—Mechanisms of Hyperenhancement.**

The mechanism of hyperenhancement in chronic infarction has not been elucidated. Given that there is probably increased interstitial space between collagen fibers in scar tissue, compared to densely packed myocytes in normal tissue, it is possible that hyperenhancement is simply the consequence of an expanded volume of distribution of Gd in scar tissue (Fig. 8) (93).

**Technical Aspects of ceMRI**

There has been debate regarding the accuracy of ceMRI for defining infarct size and the ideal timing of image acquisition following contrast administration. Some observers have noted a change of up to 28% in the spatial extent of the infarct zone depending on the time of...
imaging after contrast injection (100). Others have demonstrated that the technique is reproducible and that recommended imaging can occur anywhere from 10–30 minutes after contrast, as long as there is appropriate adjustment of the IR sequence. Mahrholdt et al (101) addressed this question directly in an imaging study of patients with healed MI. In 15 patients scanned twice by MRI and by SPECT on the same day, the coefficient of repeatability was ±2.6% of LV mass, compared to a coefficient of repeatability for SPECT of ±4.0% LV mass. In order to understand the conflicting observations, it needs to be appreciated that imaging methods used in studies have differed with respect to the TI selected. The size of the hyperenhanced region visualized depends upon differentiating a border between normal and infarcted myocardium but a maximal ratio of signal intensity between these zones is achieved by “nulling” normal myocardium. The null point of normal myocardium changes as Gd-based contrast washes out, thus necessitating adjustment of the TI for ideal image characteristics. When TI is adjusted appropriately, infarct size remains constant and reproducible (Fig. 10).

Image quality can be maximized by attention to detail. Reduction of the field of view in both phase and read directions maximizes the spatial resolution, allowing a voxel size of approximately 1.4 × 1.9 × 6 mm. As already mentioned, blurring from cardiac motion is minimized by acquiring data during mid-diastole, when there is relative ventricular standstill. Using the segmented IR turboFLASH sequence, the number of segments (amount of k-space data) that can be acquired within mid-diastole is a function of the heart rate. Fewer segments and a greater number of cardiac cycles are required in tachycardic patients. For the average case, 12 cardiac cycles will be required to fill the k-space with a repetition time of 8 msec and 23 lines of k-space acquired during each cardiac cycle, thus segmented IR turboFLASH requires breath-hold imaging. For patients unable to hold their breath, alternative strategies include the use of respiratory navigators or “single-shot” techniques.

Delayed enhancement images can be acquired as soon as blood-pool contrast clears adequately to allow differentiation between the LV cavity and the subendocardium. A 0.1–0.15 mmol/kg dose of Gd provides excellent image contrast between normal and injured myocardium and reduces the time required for clearance of blood-pool contrast. Selection of an appropriate TI is crucial for accurate identification of infarcted myocardium. The TI is chosen to null normal myocardium—the time at which the magnetization of normal myocardium reaches the zero crossing and signal intensity difference between normal and infarcted myocardium is maximal (Fig. 11). Selection of a short TI results in increased signal intensity in normal myocardium. As the TI is shortened it becomes possible to produce an image where normal myocardium is bright and infarcted myocardium is nulled. At the opposite extreme,
a very long TI means the magnetization of normal myocardium is above zero, and it will appear gray. Infarcted myocardium signal intensity is still brighter, but the ability to differentiate normal from abnormal tissue is reduced. After practice, the appropriate TI can usually be selected following one or two test images, and thereafter requires adjustment upward if image acquisition has not been completed within five minutes. Because interstitial concentrations of Gd-DTPA in the myocardium depend primarily upon plasma concentrations, the correct TI needed to null normal myocardium can be estimated from basic physical principles (92,101) (Fig. 12). Newer pulse sequences with a phase-sensitive reconstruction of IR data may allow a nominal TI to be used rather than a precise null time for normal myocardium. This potentially simplifies the choice of TI for the novice (102).

In order to maintain a nulled signal from normal myocardium, sufficient time must be allowed between successive inversion pulses for longitudinal relaxation to occur. The time required for recovery of 96% of the magnetization is approximately four times the TI. Incomplete relaxation artificially shortens the TI required to null normal myocardium and may lead to reduced intensity differential between normal and infarcted myocardium. In practice, images can be obtained every other beat in a patient with a heart rate of 75 bpm (RR interval = 800 msec, TI of normal myocardium following Gd = ~400 msec). Imaging should be performed every third beat in a patient with a tachycardia (103).

Image quality can be reduced by the presence of ghosting artifacts from regions within the field of view that have long TI values such as pleural fluid, pericardial effusion, and cerebrospinal fluid. This artifact can be reduced by the application of a single nonselective saturation pulse approximately 600–800 msec prior to the initial 180° inversion pulse.

The IR turboFLASH sequence has been used exclusively in the majority of animal and human research validating delayed hyperenhancement. Image quality of the turboFLASH sequence may suffer, however, in the setting of cardiac arrhythmia or motion due to a patient’s inability to hold their breath for 15–20 seconds. Newer pulse sequences are being developed that further shorten imaging time, albeit with some possible sacrifice in resolution. The single-shot IR true-FISP sequence allows acquisition of two-dimensional viability data within a single heart beat using a SSFP technique. It may provide an effective means of rapidly screening for the presence of nonviable tissue, in addition to an ideal technique for imaging patients who are unable to be scanned with the normal IR segmented sequences. However, the single-shot technique may underestimate infarct size and has been reported to potentially miss small subendocardial infarcts (104). The segmented IR true-FISP sequence provides a compromise between time and resolution. Although requiring a breath hold, this sequence is significantly faster than the turboFLASH sequence but with maintained resolution.

Clinical Applications of ceMRI

Clinical applications of ceMRI in defining viability are evolving. The prognostic value for the prediction of functional recovery has been shown in both acute and chronic revascularized myocardial injury. Potential future applications of ceMRI include differentiation of ischemic from nonischemic cardiomyopathy (98), and the prediction of response to therapies such as beta-blockers in patients with LV dysfunction (105).

Comparison of ceMRI with other modalities has been favorable. ceMRI-defined viability correlates closely with that defined by FDG-PET (106,107). Köhl et al (107) compared Technetium-99m tetrofosmin SPECT, F-18 FDG-PET and ceMRI in 26 patients. 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 (ischemic 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 cut-off value, sensitivity and specificity of ceMRI for detection of viable myocardium defined by PET were 96% and 84%, respectively.

The advantage of the excellent spatial resolution of ceMRI is in its ability to detect subendocardial infarction that might otherwise be missed using myocardial perfusion imaging. Wagner et al (108) demonstrated this in an animal and clinical study comparing viability defined by delayed hyperenhancement with resting thallium SPECT images. In animals, ceMRI and SPECT detected all segments with >75% transmural MI. MRI also identified 92% of segments with subendocardial infarction (<50% transmural extent), whereas SPECT identified only 28%. In patients, ceMRI identified 181 segments with subendocardial infarction and 47% of these were not detected by SPECT. On a per patient basis, 13% of patients (N = 6) with subendocardial...
infarction defined by ceMRI had no abnormality by resting SPECT (Fig. 13).

The potential to identify subendocardial infarction makes ceMRI a very valuable addition to noninvasive cardiac imaging and to cardiovascular research. Asymptomatic CAD and silent MI is known to occur in risk populations such as patients with diabetes and chronic renal failure. ceMRI provides a potential tool for the very early identification of myocardial damage in these patients. However, the prognostic implication of early identification of subendocardial infarction and the potential application of this imaging in screening risk populations requires further investigation.

Hyperenhancement in Other Disease States

Delayed hyperenhancement has been described in non–CAD-related myocardial necrosis. In acute myocarditis, hyperenhancement has been noted acutely and chronically and may reflect the extent of tissue necrosis. The influence this has on subsequent functional recovery is yet to be confirmed however, initial reports suggest that contrast enhancement persisting four weeks after the onset of symptoms is predictive for functional and clinical long-term outcome (109).

Hyperenhancement has been described in Chagas disease in association with biopsy evidence of myocarditis (110). Hyperenhancement is frequently patchy and localized to the midmyocardium or subepicardium. The extent of myocardial fibrosis, as defined by ceMRI, is inversely correlated with overall LV systolic function (111).

Various patterns of delayed hyperenhancement have also been described in sarcoidosis (112), and cardiac involvement appears more common in patients with multiorgan disease involvement. In limited longitudinal evidence, regression of Gd-DTPA uptake has been observed after corticoid therapy, whereas progression was observed in untreated patients (113).

Patchy, delayed hyperenhancement may occur with malignant infiltration of the myocardium or amyloidosis. However, when a disease involves the myocardium

**Figure 13.** Resting thallium-201 SPECT images and corresponding ceMRI images in two patients with subendocardial MI. In this study comparing resting thallium 201 SPECT and ceMRI in 91 patients with known or suspected CAD, 13% (N = 6) of patients with subendocardial infarction visible by ceMRI had no abnormality detected on resting SPECT images. (Reprinted from Lancet, 361 Wagner et al p 374–379, 2003 with permission from Elsevier.)
diffusely, ceMRI abnormalities may be more difficult to detect, given that the imaging technique usually relies upon differentiating normal from abnormal tissue on the basis of T1. In the case of diffuse infiltration there may be evidence for diffusely increased signal intensity following administration of contrast agents.

In hypertrophic cardiomyopathy, necropsy studies have demonstrated that myocardial scarring is common and that the pattern of scarring is distinct from that seen in ischemic heart disease, being frequently limited to the midwall, the subepicardium, or the junction of the interventricular septum and the right-ventricular free wall (114–118). These distinct patterns of scarring have subsequently been observed in vivo using ceMRI (119–122). Additionally, the presence and extent of delayed hyperenhancement by ceMRI appears to be related to clinical risk factors for sudden death in hypertrophic cardiomyopathy (120).

SUMMARY

CMR imaging has added uniquely to the methods for noninvasive assessment of myocardial viability. It is likely that a combination of cine imaging, stress testing, and delayed hyperenhancement will provide the most complete assessment of myocardial viability by MRI.

Magnetic resonance spectroscopy has potential to allow in vivo imaging of subcellular constituents and has seen recent advances in image resolution with new coil technology. Increasing availability of 3-T MRS is likely to result in increased utilization of this technique.

Myocardial viability assessment using proton imaging at 1.5 T can include high resolution imaging of myocardial contractile function at rest and stress using dobutamine. Experience with this technique is substantial, and there is acceptable safety and efficacy data to support a clinical role in diagnosis of CAD and evaluation of viability. MRI has advantages over echocardiography in terms of visualization of the entire myocardium and has a high specificity and positive predictive value for the identification of viable myocardium on a per patient basis.

The value of delayed contrast hyperenhancement imaging is in accurate identification of infarcted myocardium with resolution that allows the transmural extent of myocardial injury to the determined. Animal and human studies have validated this technique in the settings of acute and chronic infarction. Clinical data supports the prognostic value of identifying the extent of myocardial necrosis following acute infarction or of identifying the extent of scar tissue prior to revascularization in chronic CAD. Nonischemic patterns of myocardial injury have been reported in other disease states, and delayed hyperenhancement may have an additional role in guiding management or determining prognosis in diseases such as myocarditis and hypertrophic cardiomyopathy.

There is potential for delayed hyperenhancement imaging to guide management in CAD and LV dysfunction. The technique permits accurate noninvasive quantification of myocardial viability with visualization of very small infarcts and of subendocardial infarction. This information cannot be obtained using any other imaging modality and may permit early identification of infarction in risk populations. Further clinical research is required to investigate the relationships between the extent and distribution of myocardial scarring and arrhythmic disease or response to therapies for ventricular dysfunction.

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