Role of Cardiac Magnetic Resonance Imaging in the Assessment of Myocardial Viability

Kesavan Shan, MD; Godwin Constantine, MD; Mohan Sivananthan, MD; Scott D. Flamm, MD

Dysfunctional myocardium that remains viable has the potential for contractile recovery after reperfusion. Dysfunctional but viable myocardium has been broadly divided into 2 closely linked pathophysiological states, myocardial hibernation and stunning. Hibernating myocardium is the result of an ischemic insult leading to contractile dysfunction despite adequate reperfusion. Hibernating myocardium describes downregulation of myocyte metabolism as a result of prolonged reduction in perfusion, or, in some cases, repetitive episodes of myocardial stunning. The exact nature of structural changes in hibernating myocardium remains controversial. However, a spectrum of histological alterations has been noted, ranging from cellular dedifferentiation (fetal phenotype) to cellular degeneration (with more extensive fibrosis) with loss of contractile and cytoskeletal proteins. Worsening histological perturbations correlate with increasing duration of chronically low perfusion. Thus, accurate and early detection of viable myocardium has become an increasingly important guide to prognosis and therapy. Until recently, scintigraphic techniques and stress echocardiography were the mainstay of diagnosis. The focus of the present article is on the rapidly emerging clinical role of cardiovascular MRI (CMR) in the detection of viable myocardium.

Clinical Importance of Determining Myocardial Viability

In patients with chronic ischemic left ventricular dysfunction, improvements in ejection fraction and exercise capacity after revascularization have been well documented. The prognostic importance of detecting myocardial viability hinges on 2 major considerations. First, medically treated viable myocardium is a harbinger of further nonfatal ischemic events and higher overall mortality. In patients with significant viable myocardium, the annual mortality rate is more than 4-fold greater in those treated medically compared with those patients who have had successful revascularization. Second, discrimination between viable and nonviable dysfunctional myocardium allows patients to avoid the risks associated with revascularization when they are unlikely to benefit. Although limited by the lack of large randomized studies, a recent meta-analysis indicated that the annual mortality rate in patients with dysfunctional myocardium undergoing revascularization is more than twice as great in those without significant viability (7.7%) when compared with those with viable myocardium (3.2%). Moreover, the perioperative mortality rate is substantially increased (to approximately 10%) in the absence of viability.

Detection of Myocardial Viability by CMR

CMR has the unique ability to evaluate several markers of myocardial viability that are of proven value. Reliable and accurate assessment of myocardial scar burden, coronary perfusion, and contractile reserve by CMR are all becoming well established. With the rapid evolution of CMR techniques, advances in the assessment of coronary flow reserve, coronary anatomy, and myocardial metabolism continue to be made.

Delayed-Enhancement MRI

Direct imaging of myocardial fibrosis is now possible with the use of an inversion-recovery prepared T1-weighted gradient-echo sequence after the intravenous administration of a gadolinium-chelate (Gd). This CMR technique has been named delayed-enhancement (DE-MRI) and demonstrates nonviable tissue as “hyperenhanced” or bright. Both interstitial and replacement fibrosis hyperenhance similarly with DE-MRI for reasons described below. The hyperenhancement of interstitial fibrosis is more commonly seen (and recently described) in infiltrative entities such as hypertrophic cardiomyopathy, where the issue of viability is less prominent. The present article will focus on identification of replacement fibrosis secondary to ischemic injury and its relationship to myocardial viability.

The DE-MRI technique is rapidly assuming a prominent role in the assessment of viability, as it has the advantages of being performed under resting conditions and without patient exposure to radiation. The clinical utility of DE-MRI in the delineation of nonviable myocardium has been confirmed by...
direct comparison with several clinically established markers of myocardial viability, including contractile reserve, perfusion, metabolism, and most recently, electromechanical mapping.17

DE-MRI performed in conjunction with segmental wall motion assessment by resting cine images has helped define several broad pathophysiological categories. Lack of hyperenhancement or mild degrees of hyperenhancement (<25% of the segment) in the presence of normal wall motion or segmental dysfunction generally indicates that the segment will recover contractile function. In contrast, a segmental wall motion abnormality in combination with >75% hyperenhancement strongly suggests that the segment will not recover contractile function. The prognostic value of DE-MRI seems clear in these cases. However, the outcome after revascularization is less clear in dysfunctional segments that show intermediate degrees of hyperenhancement (>25% and <75%). The available data suggest heterogeneity of response to revascularization; as such, the potential for contractile recovery of these segments is uncertain. It is likely that there is a continuum with regard to the ability of dysfunctional segments to recover function based on the transmural extent of infarction. Adjunctive information from other markers of viability, such as inotropic reserve with low-dose dobutamine, imaged with either echocardiography or MRI, may help refine the classification of these segments as clinically viable or nonviable.

The exact cause of hyperenhancement (increased T1 shortening) of myocardial scar, consisting of replacement fibrosis, with Gd remains incompletely understood. However, evidence suggests that the likely mechanism is a combination of delayed wash-in and wash-out kinetics of nonviable tissue and different volumes of distribution of Gd in viable and nonviable regions.18–21 An increased volume of distribution occurs in both chronic and acutely infarcted myocardium, as there is an increase in the interstitial space. In the former, the presence of fibrotic tissue increases the interstitial space per unit volume, whereas in the latter, the loss of sarcomere membrane integrity increases the potential interstitial volume. Gadolinium diffuses rapidly into the interstitial, but not intracellular, space; thus, both chronically and acutely infarcted myocardium have increased concentrations of Gd per unit volume of tissue resulting in hyperenhancement relative to viable myocardium.20,21

The majority of recent published data support the notion that the hyperenhanced regions have sustained irreversible ischemic injury.22–26 Although many investigators have evaluated the use of contrast enhancement in myocardial infarction throughout the 1980s and 1990s, Kim et al22 published the initial article describing what is now known as the DE-MRI technique. In this seminal study in a canine model, the left anterior descending artery was instrumented and occluded either transiently or permanently. DE-MRI of the explanted hearts was compared with 2,3,5-triphenyltetrazolium chloride-stained pathology specimens at 1 day, 3 days, or 8 weeks after instrumentation, with near-perfect correlation demonstrated between hyperenhancement on MRI and irreversible damage at pathology22 (Figure 1).

These findings laid the foundation for subsequent investigations in both animals and humans demonstrating that the extent of hyperenhancement on a segmental or regional basis is a critical determinant of contractile recovery.23–25 Hillenbrand et al,25 in an animal model, evaluated the relationship between the transmural extent of hyperenhancement at 3 days and the contractile recovery at 28 days after myocardial infarction and found that when the segmental transmural extent of hyperenhancement was <25%, the majority (87%) of segments improved function, whereas when the extent of hyperenhancement was >75%, functional recovery was unlikely, with intermediate degrees of hyperenhancement resulting in intermediate likelihood of recovery. Similar findings were observed in 41 patients with chronic ischemic disease undergoing revascularization. On follow-up studies 2½ months after revascularization, dysfunctional segments with <25% hyperenhancement had an increased likelihood of functional recovery, whereas dysfunctional segments with >50% hyperenhancement had little chance of functional improvement.24 This spectrum in potential for contractile recovery is consistent with observations from stress echocardiographic studies, which have demonstrated that the hibernating myocardium has a continuum of histological and biochemical perturbations that define its ability to recover.2,29

Subsequent human studies in acute myocardial infarction have similarly demonstrated the utility of DE-MRI techniques in predicting functional recovery.21 In a group of 24 patients who presented with first myocardial infarction and had DE-MRI performed within a week of the acute event, the best predictor of global improvement at 2 to 3 months was the extent of dysfunctional myocardium without or with <25% hyperenhancement. Similarly, Gerber et al,30 in a series of 20 patients, found that the absence of hyperenhancement in dysfunctional segments had a sensitivity of 82% for predicting contractile recovery (Figure 2).

Further evidence for the importance of defining the transmural extent of hyperenhancement comes from another study by Gerber et al.31 In that study on canines within 48 hours of...
infarction, segments with transmural hyperenhancement showed no significant inotropic reserve when assessed with low-dose dobutamine-tagged MRI, and nontransmural hyperenhancement was associated with contractile reserve, consistent with residual viability. These findings underline the relationship between the degree of recovery of contractile reserve and the extent of transmural scarring. These findings are also congruent with studies using dobutamine stress echocardiography (DSE) for inotropic response and quantitative $^{20}$T$_1$ scintigraphy for examining the percentage of myocardial fibrosis and correlating the subsequent contractile recovery in the hibernating myocardium.

However, a few studies have debated the exact physiological significance of hyperenhancement. These discrepancies may be explained by differences in the MRI techniques employed and variances in defining the transmural extent of infarction. Registration errors between techniques may also represent a potential cause of discrepant results.

In one such study, Kramer et al reported that regions of hyperenhancement demonstrated contractile reserve and functional recovery. They studied 23 patients within 4 days of first myocardial infarction after reperfusion. Low-dose dobutamine MRI (Dob-MRI) was performed, followed by contrast-enhanced MRI (first pass and delayed imaging), with functional recovery assessed at 3 months. In this study protocol, hyperenhancement appeared to be present even in viable segments. These investigators also found that the absence of first-pass hyperenhancement conferred a good prognosis for contractile recovery. This work is in contradistinction to the results reported by Gerber et al, who performed contrast and tagged MRI on 20 patients at 4 days and at 7 months after acute myocardial infarction. Using receiver operating characteristic analysis, these authors found that the absence of hyperenhancement had a sensitivity and accuracy of 82% and 74%, respectively, in predicting functional recovery, whereas the absence of early first-pass hyperenhancement had little value in predicting functional recovery. The possibility exists that a significant proportion of the hyperenhanced viable segments that showed inotropic reserve in Kramer’s series were nontransmural.

An earlier study by Rogers et al also had findings at odds with the majority of work on hyperenhancement. This study reported that hyperenhancement was associated with viable tissue, determined by subsequent functional recovery. However, the MRI sequences employed were those typically used for perfusion protocols and dissimilar to the described DE-MRI protocol. Saeed et al also have suggested that although hyperenhanced regions consist of predominately scar tissue, they may also encompass a small area of viable peri-infarction myocardium. This finding is based on the study of rat infarcts employing a necrosis-specific MR contrast medium (mesoporphyrin). Variations in contrast uptake between species may well exist, and, along with the differences in imaging protocols used, could explain the overestimation of infarcted tissue in this animal study.

Rehwald et al recently provided further convincing evidence that DE-MRI is highly specific for irreversibly injured myocardium. These authors used electron probe x-ray microanalysis (EPXMA) to simultaneously examine concentrations of Gd, Na, P, S, Cl, K, and Ca in myocardium and used histological staining to define areas of scar. Acute and chronic infarction and at-risk peri-infarction zones were analyzed. Compared with remote regions, Gd levels measured by EPXMA were more than doubled in acutely infarcted nonviable areas and were 4-fold higher in chronically infarcted regions. The concentration of Gd was not elevated after reperfusion in regions that were considered at risk but not infarcted. This work confirms that elevations in myocardial Gd are confined to regions of histologically defined irreversible ischemic injury.

In summary, a preponderance of both clinical and experimental data point to the conclusion that hyperenhancement is specifically localized to acutely infarcted myocardium and chronic scar tissue and has high accuracy for predicting functional recovery. With the presently available sequences, however, acute and chronic infarction cannot necessarily be distinguished, although this may be possible using adjunctive imaging techniques.

Preliminary observations suggest that the high spatial resolution of contrast CMR may also allow further refinement of risk stratification in patients with acute myocardial infarction containing areas of microvascular obstruction. Wu et al, in a series of 44 patients 10±6 days after infarction, found that microvascular obstruction (defined as hyperenhancement seen 1 to 2 minutes after contrast injection) was a significant marker of postinfarction complications (Figure 3). Similar findings have been shown on contrast echocardiographic studies. Recently, the direct visualization of discrete microinfarctions after percutaneous coronary interventions also has provided further insight into periprocedural elevations in creatine kinase–MB enzyme levels. As technology continues to progress, the clinical utility of contrast-enhanced MRI in the detailed analysis of myocardium and scar tissue will have a wider clinical role.

**Contractile Reserve**

The value of assessing inotropic reserve in the detection of viable myocardium by low-dose DSE is well established and has been reviewed extensively. Low-dose Dob-MRI in detecting coronary viability using the same underlying principles has emerged as a technique of comparable accura-
Metabolism and Coronary Flow Reserve

Impaired coronary flow reserve and metabolic downregulation are characteristic findings in myocardial hibernation. Noninvasive assessment of coronary flow reserve and metabolism should further improve the ability to delineate myocardial hibernation.

To date, PET, which is expensive and not widely available, is the only available noninvasive modality that allows direct quantification of both coronary flow and metabolism and has demonstrated clinical importance in assessing metabolic changes of dysfunctional yet viable myocardium.6,50,51 Di Carli et al48 assessed 93 patients (mean ejection fraction of 25%) for 31 months and found that the annual survival rate of nonrevascularized patients with evidence of viability was 50%, compared with 92% in those with no PET mismatch. Eitzman et al50 also using PET, found a cardiac event rate of 50% in patients with depressed left ventricular function and evidence of myocardial hibernation. Similarly, in a series of 84 postinfarction patients followed up for a mean of 23 months, Tamaki et al51 have shown that an increase in [18 F]fluorodeoxyglucose uptake was the best predictor of subsequent cardiac events.

Metabolic parameters measured by CMR also have been reported. Buchthal et al52 have evaluated cardiac metabolism using 31 P MR spectroscopy. Unfortunately, 31 P MR spectroscopy is limited by poor spatial resolution at the most commonly used field strength (1.5 Tesla), and there are as yet no known characteristic spectra for hibernating myocardium. Thus, it has not gained widespread use as a method of detecting viable myocardium. A similar limitation of spatial resolution with 23 Na MR has constrained the use of this technique in humans despite encouraging work in animal models.32,53,54 It is anticipated that with magnets of higher field strength (eg, 3.0 Tesla), interest in defining such biochemical tracers may be further stimulated.

Ionic shift resulting from loss of cellular integrity also has been used to study myocyte necrosis. Kim et al53 studied the use of Na+ imaging and found good correlation with biochemical assessment of infarct size. However, unlike perfusion and DE-MRI, the clinical utility of 23 Na and 31 P imaging has yet to be clearly defined.

A reliable noninvasive assessment of coronary flow has proved to be elusive until recently. PET studies and coronary Doppler flow wire have been the only available tools to assess coronary flow. PET imaging is not widely available,
and Doppler flow wire measurements are invasive and impractical for repeated evaluations.

Early data have suggested that CMR may have a promising role in reliably measuring absolute coronary arterial flow and flow reserve.55-57 Hundley et al56 performed cine velocity-encoded phase-contrast MRI measurements of flow in the left anterior descending coronary artery at rest and after administration of intravenous adenosine in 12 subjects and compared with intracoronary Doppler velocity and flow measurements, demonstrating good correlation between the 2 techniques (r=0.89). More recent observations by Nagel et al58 in 84 patients (without diabetes mellitus or hypertension) demonstrated that MRI-determined perfusion reserve had a sensitivity of 88% and a specificity of 90% in detecting hemodynamically significant coronary artery disease may in the near future be assessed reliably and noninvasively by this method.

Comparison of CMR With Other Techniques

Currently, there are limited prognostic data in patients with myocardial viability as assessed by cardiac MRI. However, there is a wealth of literature on the use of scintigraphic techniques (PET, single-photon emission computed tomography [SPECT]) and DSE for identifying high-risk patients whose survival could be prolonged by revascularization. In general, SPECT perfusion studies and DE-MRI have greater sensitivity but lower specificity for identifying viable myocardium compared with techniques that detect contractile reserve (ie, Dob-MRI and DSE).59,60 Data on prognosis based on Dob-MRI assessment of viability have only just begun to emerge.61 Nonetheless, results of contractile response with dobutamine protocols are essentially identical in the majority of studies for both Dob-MRI and DSE. It is therefore reasonable to project that much of the extensive prognostic data available for DSE could be extrapolated to Dob-MRI.

DE-MRI has shown excellent accuracy in the delineation of scar when compared with scintigraphic techniques. Klein et al62 studied 31 patients with ischemic cardiomyopathy and found a close correlation between the extent of myocardial scar identified by DE-MRI and PET. Though quantitative assessment of infarct mass by DE-MRI correlated well with PET infarct size (r=0.81, P<0.0001), DE-MRI identified subendocardial scar more frequently than PET. These authors also compared wall thickness (end diastolic and end systolic) and wall thickening at rest in combination with DE-MRI for viability, using PET as the gold standard, and found significantly better results for DE-MRI based on ROC analysis. These findings are concordant with those of Wagner et al63 who recently compared DE-MRI with SPECT in 91 patients. In this convincing study, both imaging modalities were also evaluated against histologically confirmed infarctions in dogs that were either transmural or subendocardial (>75% transmural or <50% transmural extent of the left ventricular wall segment, respectively). Histologically confirmed subendocardial infarcts were detected by DE-MRI in 92%, whereas SPECT detected only 28%. Moreover, in the patient series, almost half of the subendocardial infarcts were missed by SPECT as compared with DE-MRI (Figure 5).

The clinical reproducibility of infarct size by DE-MRI has been evaluated and compared with the reproducibility of SPECT imaging by Mahrholdt et al.12 In this study, the size of chronic infarcts (which were between 4% and 27% of total left ventricular mass as measured by DE-MRI) showed no significant change in size between 10 and 30 minutes after contrast administration and compared favorably with quantification by SPECT.

Although these initial data suggest a compelling role for DE-MRI in the determination of myocardial viability, there is clearly a need for larger, randomized studies comparing DE-MRI with other techniques to obtain prognostic data and a fuller understanding of its broader clinical implications.

Clinical Impact of Viability Detection by MRI

As discussed above, the excellent spatial resolution and tissue characterization afforded by CMR makes it ideal for both (1) quantification of significant areas of viable myocardium and (2) defining discrete regions of nonviability. Accurate quantification of areas of scar and viable tissue is clearly important in predicting mortality, as the benefits of revascularization rise steeply when the area of dysfunctional but viable myocardium reaches a critical size.8,9,64

The potential benefit of detecting relatively small areas of viable tissue is less well understood (Figure 6). A recent comprehensive meta-analysis indicates that revascularization of even relatively small areas of dysfunctional yet viable myocardium may be clinically beneficial in selected patients.11,65 Moreover, improved left ventricular function by itself does not appear to be an absolute prerequisite for the improvement in survival after revascularization.11 The removal of the possible adverse effects of hibernating myocardium on ventricular remodeling, electrophysiological stability, and/or diastolic dysfunction may lead to additional improved survival.66-68 The location of viable myocardium, particularly in the subepicardial location, may have an important influence on long-term ventricular geometry and function.68 Recent studies on chronically hibernating myocardium have also documented structural changes and biochem-
increase.

Nevertheless, it is apparent that the full potential of CMR has only will require larger and more definitive clinical trials. None-

maladaptive ventricular remodeling, which is expected to continue to translate directly into poorer survival.29,69,70

Figure 6. Two-chamber long-axis (left) and midventricular short-

axis (right) DE-MRI demonstrate thin subendocardial myocardial infarction (arrows) in a patient with ischemic dilated cardiomyopathy.

Conclusion

Cardiovascular MRI provides a unique tool to assess multiple interrelated clinical markers of viability in a single test. Its overall accuracy appears to be equivalent, and in several reports, superior to the currently available techniques, including PET imaging. Considering the greater spatial resolution compared with PET and the wealth of correlative pathologi-

data, DE-MRI may well represent the new gold standard compared with PET and the wealth of correlative pathologi-

data. However, DE-MRI may well represent the new gold standard compared with PET and the wealth of correlative pathologi-

data. However, more definitive clinical trials. Nonetheless, it is apparent that the full potential of CMR has only just begun to emerge, and its impact on the management of ischemic left ventricular dysfunction will continue to increase.

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