

MRI of Myocardial Viability

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Introduction: Myocardial Viability as a Clinical Question

Myocardial viability is technically defined as the presence of living heart muscle cells (myocytes), irrespective of whether or not these myocytes are actually able to contract. The identification of viable myocytes which are unable to contract is an important clinical issue. For example, percutaneous intervention with the goal of revascularization is often performed with the expectation that regions of contractile dysfunction are viable and therefore will recover. Similarly, coronary artery bypass grafting is also expected to ameliorate dysfunctional regions provided that the cells remain viable. Revascularization of non-viable regions, conversely, does not improve contractile dysfunction and in this setting the procedure itself may be contraindicated by the small but finite risk of intervention.

Traditionally, myocardial viability is assessed by dobutamine echocardiography or radionuclide scintigraphy. This article discusses the potential for contrast-enhanced MRI to address the clinical question of myocardial viability.

MRI Approaches to Myocardial Viability

A number of MRI approaches to the clinical question of viability have been described in the literature, including dobutamine cine imaging performed in a manner similar to dobutamine echocardiography, spectroscopic imaging of nuclei such as phosphorus, sodium, and potassium, and straightforward geometric indices such as wall thickness and/or thickening. Recent advances in MRI techniques to visualize contrast enhancement patterns in the heart, however, have motivated more careful consideration of this approach for the specific question of myocardial viability.

A New Technique for Contrast-Enhanced MRI

Since the early use of ECG-gated spin echo imaging a number of improvements have been made. One of the most important among these was the use of segmented k-space¹ in which multiple k-space lines were acquired each cardiac cycle. This resulted in reductions in imaging times to the point where the entire image could be acquired during a single breathhold (ca. 8 sec) thereby eliminating image artifacts due to respiration. In addition, preparation of the magnetization prior to image acquisition by the use of an inversion pulse significantly increased the degree of T1-weighting in the images. In our laboratory we recently compared the use of a segmented inversion-recovery pulse sequence to nine other MRI techniques in a dog model of myocardial infarction.² Figure 1 shows MR images acquired using 10 different T1-weighted pulse sequences acquired in the same imaging session. The segmented inversion recovery sequence (SEG IR-TFL, large image in Figure 1) produced the best delineation of the hyperenhanced region (arrows). The segmented inversion recovery sequence produced the largest difference in regional myocardial image intensities of any sequence described to date. The highest contrast-to-noise ratio (CNR) was produced by this sequence as well.

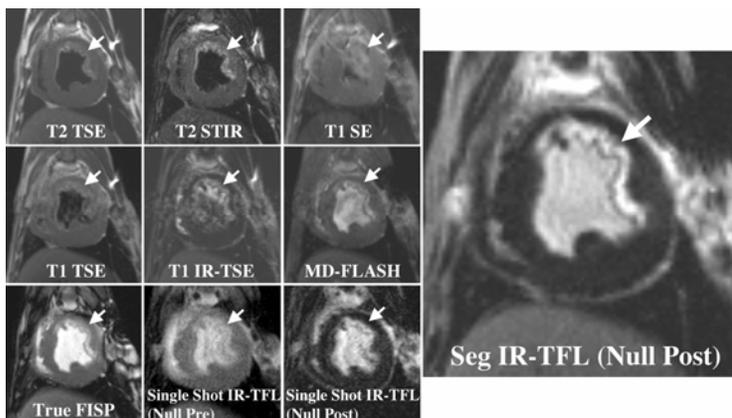


Figure 1: Contrast-enhanced images of the same heart using 10 different MRI techniques. The segmented inversion recovery technique (large image) produced the clearest delineation of the hyperenhanced region (arrows). Reprinted by permission, *Radiology* 2001;218:215-223.

Figure 2 shows the segmented inversion recovery sequence in more detail. Following the R-wave of the ECG a delay period ("trigger delay") is used to ensure acquisition of the image occurs in diastole to minimize cardiac motion. The magnetization of the heart is then prepared by a non-selective 180° inversion pulse to increase T1-weighting. The inversion delay time (TI) is then defined as the time between this 180° pulse and the center of acquisition of the segmented k-space lines (lines 1-23 in Figure 2). The TI is chosen such that the magnetization of normal myocardium is near its zero crossing, meaning that these regions will appear as dark as possible. Infarcted myocardium, however, will appear bright due to the lower T1 associated with infarcted myocardium following contrast administration.

It is important to recognize that inappropriate application of the new MRI technique will lead to an incorrect diagnosis. The two main points to consider are the timing of imaging post-contrast and the selection of the inversion time. Clearly, before 5 minutes there may be issues related to contrast agent delivery and after 30 to 40 minutes problems with contrast washout; however, in our laboratory, we have not observed significant changes in the spatial extent of hyperenhancement when imaging is performed between 5 to 30 minutes after contrast administration in patients. The longer one waits after contrast administration, however, the higher the inversion time should be set to obtain correct images. The basic premise is not that infarcted regions have static T1 (which is obviously untrue in vivo) but that the T1 is always shorter than in normal regions in a relative sense. At all time points, the highest inversion time should be selected in which normal myocardium is nulled in order to not mistakenly null regions with shorter T1 than normal myocardium.

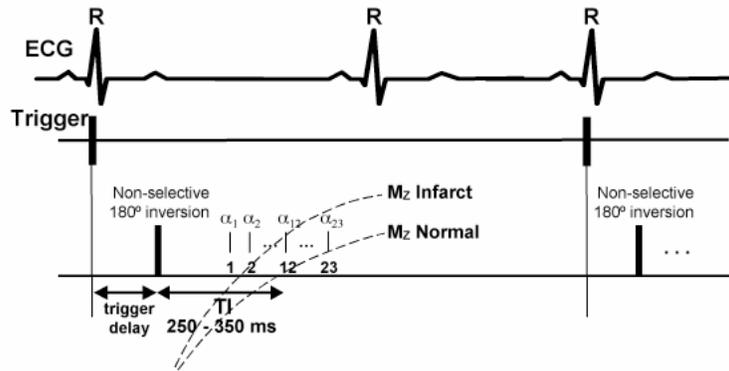


Figure 2: Timing diagram for the segmented inversion recovery turboFLASH sequence with TI set to null normal myocardium after contrast agent administration. See text for details. Adapted by permission, *Radiology* 2001;218:215-223.

Interpretation of Delayed Hyperenhancement

The phenomenon of delayed hyperenhancement, defined as myocardial regions in which post-contrast image intensities are significantly greater than those in normal myocardial regions for images acquired more than 10 min after contrast administration, was described more than 15 years ago. Data from the literature demonstrated that administration of routine MRI contrast agents resulted in regional myocardial hyperenhancement following acute infarction. The significance of delayed hyperenhancement in other clinically-relevant pathophysiologies, however, most notably in chronic infarcts and in dysfunctional but viable regions, was never established. Improved image qualities, however, afforded an opportunity to examine issues such as these in greater detail.

The basic science data appearing over the last two years strongly indicates that delayed hyperenhancement is exclusively related to irreversible injury, irrespective of contractile function or age of the injury.³⁻⁵ These findings imply a strong and inverse relationship between delayed hyperenhancement and myocardial viability: hyperenhanced regions are not viable and regions without hyperenhancement are viable. This surprisingly simple interpretation of delayed hyperenhancement appears to hold over a wide range of ischemic injuries in animal models.³⁻⁵

Acute Human Infarcts

Ultimately, improved image quality is only important if it translates into improved diagnostic capability. While prior studies have shown that acute myocardial infarction can be detected as hyperenhanced regions, typically the patients studied have had large infarcts and the transmural extent of infarction was not evaluated.⁶⁻⁸ Recently, two studies^{9,10} have distinguished between transmural and subendocardial hyperenhancement using spin-echo techniques. Although non-transmural involvement was visualized in both studies, Dendale et al.⁹ did not observe hyperenhancement in 15 (27%) of 56 infarct segments and Yokota et al.¹⁰ did not observe hyperenhancement in 6 (13%) of 44 patients with documented infarction. The infarcts that were missed were generally smaller infarcts with normal wall motion at rest⁹ and lower peak creatine kinase levels.¹⁰ The inability to detect smaller infarcts may be due to limitations in conventional spin-echo imaging which requires image acquisition over several minutes during free-breathing. Partial volume effects due to motional averaging over the respiratory cycle, image artifacts due to respiratory motion, and modest T1 weighting due to limited choices for repetition time may all decrease the conspicuity of hyperenhanced myocardium.

Recently, we evaluated eighteen consecutive patients who were referred for cardiac MR imaging who were known to have had a recent myocardial infarction.² Infarction was defined solely on the basis of an appropriate rise (> 2 times the upper limit of normal) and fall in creatine kinase-myocardial band isoenzyme (CK-MB) levels. Patients underwent MRI 19±7 days after documented enzyme elevations, and no patient was excluded for insufficient image quality or other reasons.

Figure 3 shows representative images in three patients. Starting from the left panel, infarction was due to occlusion of the left anterior descending artery, left circumflex artery, and right coronary artery respectively. Myocardial hyperenhancement is clearly visible in these patients in the appropriate infarct-related-artery (IRA) perfusion territory. Similar results were observed in the other 15 patients of the study. On average, hyperenhanced regions had image intensities that were 485±43% higher than those of normal myocardial regions. This degree of hyperenhancement was approximately 10-fold greater than that in previous reports.²

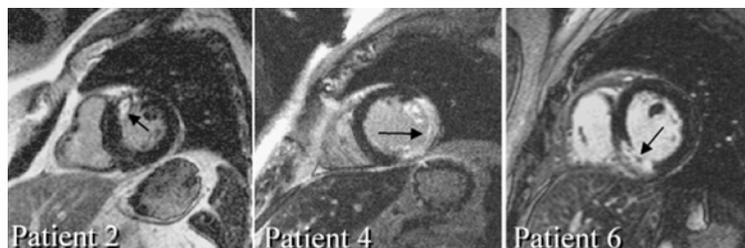


Figure 3: Short-axis images in three patients with acute myocardial infarction. The arrows point to the hyperenhanced region which was in the appropriate infarct-related artery perfusion territory. Adapted by permission, *Radiology* 2001;218:215-233.

Chronic Human Infarcts

The basic science data provide a starting point for systematic investigation in humans. A key issue to be examined is whether or not chronic human infarcts exhibit delayed hyperenhancement, an issue not resolved by previous studies. To address this, an investigation was performed in which patients with known myocardial infarction, defined by serum enzymes, were imaged by MRI after infarct healing (at 3 and 14 months).¹¹ As control groups, patients with non-ischemic cardiomyopathy and normal volunteers were randomized with the study group. All patients with non-ischemic cardiomyopathy had normal coronary arteries at catheterization.

When images from the study and control groups were randomized and scored for the presence, location, and spatial extent of hyperenhancement a clear pattern emerged. Twenty-nine of 32 patients with 3-month old infarcts (91%) and all 19 with 14-month old infarcts exhibited hyperenhancement. In patients in whom the infarct-related-artery was identified by angiography, 24 of 25 imaged at 3 months and all of 14 imaged at 14 months had hyperenhancement in the appropriate territory. None of the 20 patients with non-ischemic cardiomyopathy or the 11 healthy volunteers showed hyperenhancement. Figure 4 shows typical short- and long-axis views of three patients with hyperenhancement in different coronary artery perfusion territories. These data indicate that chronic human infarcts hyperenhance, and strongly suggest that contrast MRI can provide a permanent record of prior infarction.¹¹

Infarct Remodeling

Interestingly, it has been observed that the spatial extent of hyperenhancement decreases during infarct healing. Figure 5 shows preliminary data from a study in which the spatial extent of hyperenhancement was serially examined in animals three days, ten days, four weeks, and eight weeks after infarction. As can be seen from Panel A the size of the hyperenhanced region decreased approximately 3-fold from three days to eight weeks. During this same period, the mass of non-hyperenhanced myocardium increased. One interpretation of these observations is that the hyperenhanced region was spatially larger than the infarcted territory at three days but became smaller by eight weeks as reversibly injured regions healed and no longer exhibited hyperenhancement. This interpretation seems unlikely, however, in light of the strong correspondence between hyperenhancement and infarction defined histologically over multiple different time points.³ An alternative interpretation of finding is that infarcts shrink as the necrotic myocytes are replaced by collagenous scar. Direct evidence for infarct shrinkage can be found in the literature and the degree of infarct shrinkage measured by techniques other than MRI also suggest a three- to four-fold reduction in infarct volumes during healing. Panel B of Figure 5 shows an example of these data published in review of myocardial ischemia by Reimer and Jennings.¹² While further study of these issues is clearly warranted, there is reason to believe the changes in the sizes of hyperenhanced and non-hyperenhanced regions during infarct healing represent a perspective on the process of remodeling post-infarction.

Predicting Wall Motion Improvements Following Revascularization

The finding that chronic human infarcts hyperenhance suggests that contrast MRI may be useful in patients with chronic coronary artery disease for the prediction of recovery of contractile function following revascularization. Specifically, regions with contractile dysfunction might be subdivided into those with and without hyperenhancement (in quartiles of transmural involvement). The hypothesis was that dysfunctional regions without hyperenhancement were viable and would recover, whereas dysfunctional regions with hyperenhancement were infarcted and would not. The results of a recently published study strongly supports this hypothesis.¹³ Specifically, 78% of 329 dysfunctional segments without hyperenhancement recovered, whereas only 2% of the 58 dysfunctional segments

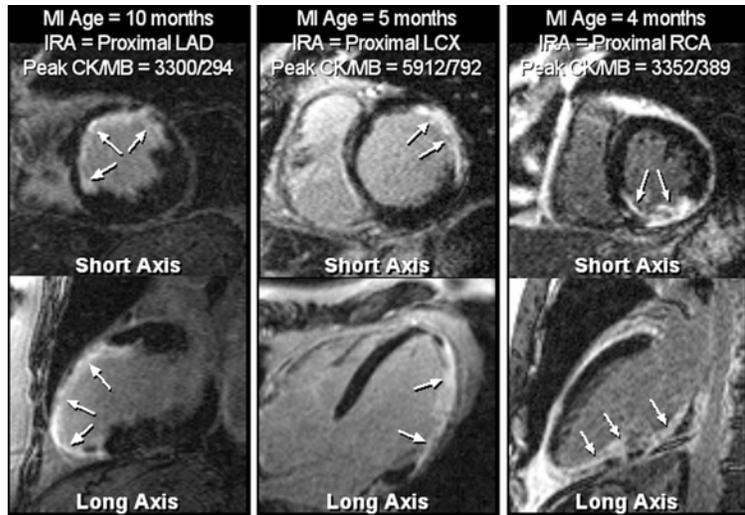


Figure 4: Typical short- and long-axis views of three patients with large transmural hyperenhancement in different coronary artery territories. Reprinted by permission, *Lancet* 2001;357:21-28.

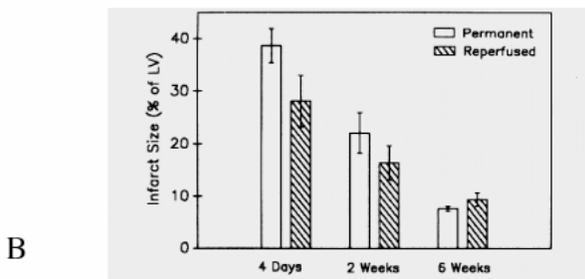
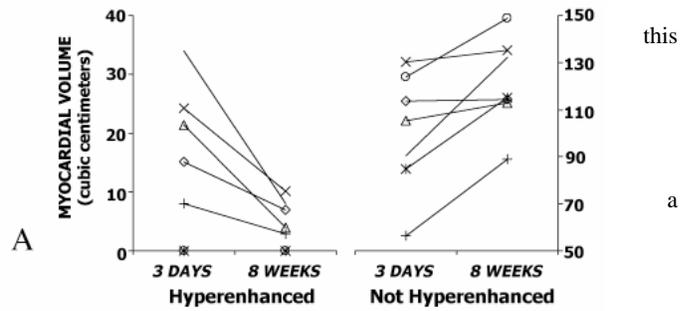


Figure 5: Panel A: Decrease in spatial extent of in vivo MRI hyperenhancement over time during infarct healing. Non hyperenhanced regions increased in spatial extent over the same time period. *Circulation*, 2000;102:1678. Panel B: Infarct shrinkage determined by histopathology. Reprinted by permission from "The Heart and Cardiovascular System, 2nd Edition". 1992.

with >75% transmural hyperenhancement recovered. These data indicate that contrast MRI is useful for the identification of viable myocardium in patients with chronic coronary artery disease.

Non-Transmural Infarction and Wall Motion Improvement

Regions with non-transmural hyperenhancement can exhibit an improvement in contractile function in the days and weeks which follow acute myocardial infarction. The middle of Figure 6 is an example of this phenomenon. Classically, myocardial viability is defined by an improvement in contractile function over time and the case of the middle row of Figure 6 it is clear

some improvement has occurred. The observation of hyperenhancement at three days following infarction (first column of Figure 6), therefore, might be suggested as evidence that hyperenhancement can occur in viable myocardium. The problem with this interpretation is that myocardial viability is being intrinsically defined as an "all-or-none" phenomenon in which a transmural segment of myocardial must be either viable (improves) or not viable (does not improve). A more likely explanation, however, is that the entire thickness of the wall was within the "area at risk" and as occlusion time increased the "wavefront" of necrosis moved outwards. Before the wavefront of necrosis reached the epicardium, however, the outer half of the heart wall was salvaged by reperfusion. In this case the improvement in contractile function could be explained by "stunning" of the viable outer half of the heart at three days which had recovered by four weeks. Because existing clinical imaging modalities which examine viability such as dobutamine echocardiography and nuclear scintigraphy cannot resolve non-transmural involvement, there has never been a compelling reason to consider viability as anything other than "all-or-none". In this setting direct application of concepts derived from other imaging modalities may effectively ignore the new information (non-transmural involvement) which is portrayed by contrast MRI. This example also demonstrates the importance of image quality in contrast MRI. The precise transmural extent of hyperenhancement was often difficult to determine using earlier MRI techniques and, as a consequence, may have lead to the erroneous impression that contractile function sometimes improves in regions of hyperenhancement.

Clinical Interpretation Algorithm

In consideration of the entire body of evidence briefly presented here, Figure 7 summarizes the algorithm for clinical interpretation of myocardial viability based on cine and contrast-enhanced images. This algorithm is primarily for patients with coronary artery disease, and is not applicable for non-ischemic forms of heart disease. Briefly, regions of the heart which are contracting normally may or may not

exhibit hyperenhancement. Hyperenhancement in the presence of normal contractile function is typical of subendocardial infarcts. For regions which do not contract normally, hyperenhancement indicates infarction (subendocardial to transmural) whereas a lack of hyperenhancement indicates viable myocardium which could be stunned, ischemic, or hibernating. For the latter two states, depending on other clinical parameters, one could consider revascularization as a therapeutic option.

Other Applications for Contrast-Enhanced MRI of the Heart

The same technique appears to be useful for clinical questions beyond those normally associated with the examination of myocardial viability. For example, other potential roles include: the assessment of patients with minor CK-MB elevation following successful percutaneous coronary intervention, the assessment of patients with new onset congestive heart failure, and the diagnosis of "silent" myocardial infarction in patients without a clinical history of myocardial infarction and without routine clinical testing indicative of prior myocardial infarction.¹⁴⁻¹⁶ Additionally, there is an abundance of emerging data concerning the use of contrast-enhanced MRI in a variety of nonischemic cardiomyopathies concerning improved diagnosis and the potential for risk stratification for future adverse cardiac events.

Summary

Contrast-enhanced MRI is emerging as a new clinical modality for the assessment of myocardial viability. Compared to existing clinical techniques to examine myocardial viability contrast-enhanced MRI does not require pharmacologic stress, allows direct

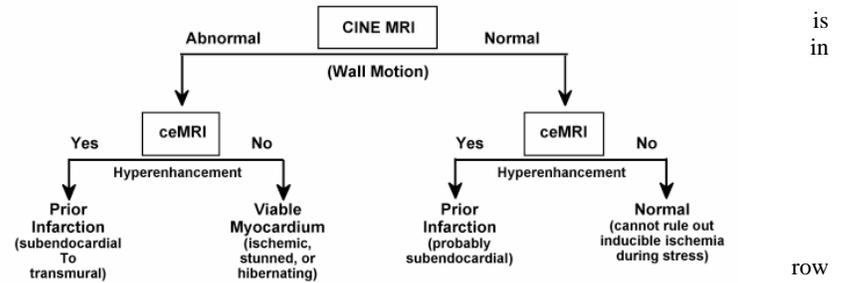


Figure 7: Combination of cine and contrast MRI to distinguish various forms of myocardial injury in patients with coronary artery disease. See text for details.

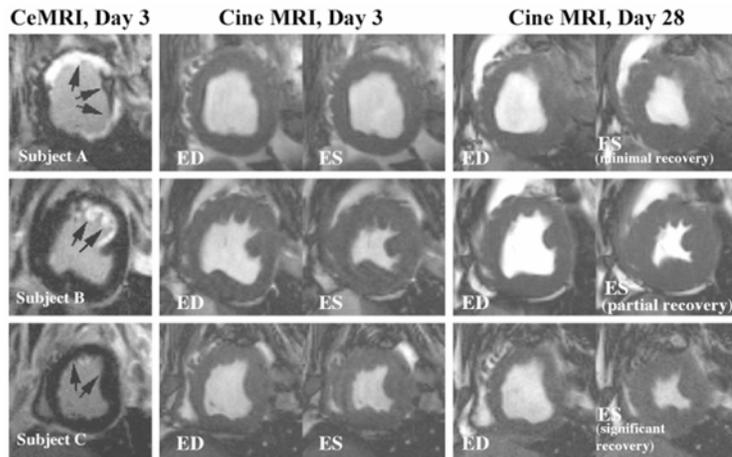


Figure 6: Contrast enhancement and wall thickening at 3 days (columns 1-3) compared to wall thickening at 28 days (columns 5-6) in three different animals (rows). See text for details. Reprinted by permission, Circulation 2000;102:1678-1683. A full-motion version of this figure can be viewed on the internet at <http://circ.ahajournals.org/cgi/content/full/102/14/1678/DC1/1>.

visualization of the transmural extent of infarction, and provides information regarding contractile function perfectly registered with the information regarding viability.

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