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CARDIAC MR FOR THE ASSESSMENT OF MYOCARDIAL VIABILITY

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Abstract

This article focuses on delayed contrast enhanced MRI (DE-MRI) to assess myocardial viability. We start by discussing previous literature that evaluated the potential importance of myocardial viability testing and follow up with the more recent Surgical Treatment for Heart Disease Trial (STICH) trial results. We then provide an overview of the basic concepts and technical aspects of the current DE-MRI technique and review the initial studies demonstrating that DE-MRI before coronary revascularization can predict functional improvement. Finally, we use DE-MRI as a paradigm to discuss physiological insights into viability assessment and examine common assumptions in the metrics used to evaluate viability techniques.

Background

In patients with coronary artery disease and left ventricular systolic dysfunction, determining which of them will benefit from revascularization is of obvious clinical significance. The potential importance of myocardial viability testing in determining prognosis after revascularization has been evaluated in many small single-center studies, including a meta-analysis demonstrating decreased annual mortality in patients with viability undergoing revascularization compared to those not undergoing revascularization.¹ In a meta-analysis of 24 studies that included 3,088 patients with a mean LVEF of 32%, Allman et al. concluded that in patients with significant viability, revascularization was associated with a 79.6% reduction in annual mortality compared with medical treatment (3.2% vs. 16%, $P < .001$).² Conversely, in patients without viability, mortality rates were similar for revascularization and medical therapy (7.7% vs. 6.2%, $P = \text{NS}$). However, all studies were small, not randomized, observational, and retrospective, leading to potential patient selection bias. Second, the methodology and criteria for defining viability as well as the treatment regimens were not standardized among the different studies. In part due to these limitations, the Surgical Treatment for Heart Disease Trial (STICH) was initiated.³

STICH was a randomized, multicenter, nonblinded trial funded by the National Heart, Lung, and Blood Institute.³ In this study, 1212 patients with angiographic documentation of coronary artery disease amenable to surgical revascularization and left ventricular systolic dysfunction (ejection fraction $\leq 35\%$) without medically refractory disabling angina or significant left main coronary artery stenosis were randomized to CABG with intensive medical therapy or intensive medical therapy alone. The primary endpoint of all-cause mortality after a median follow-up of 56 months occurred in 41% of patients randomized to medical therapy alone compared with 36% randomized to CABG. This difference did not reach statistical significance (HR with CABG, 0.86; 95% CI, 0.72-1.04; $P = .12$).

Post-randomization myocardial viability testing by dobutamine stress echocardiography and/or radionuclide imaging was recommended in the STICH trial. In the 601 patients who

received a viability study, there was a significant association between viability and outcome on univariate analysis but not on multivariate analysis. Surprisingly, in contrast with the prior literature, the assessment of myocardial viability did not identify patients with a differential survival benefit from CABG as compared with medical therapy alone.⁴

The authors point out that conclusions drawn from STICH are limited by a number of factors.⁴ First, slightly less than half of the 1212 enrolled patients enrolled underwent viability testing. Second, patients were not randomized to viability testing. Third, testing could have been performed prior to, on the day of, or after study enrollment. These factors may have led to patient selection/enrollment bias and influenced subsequent clinical decision-making. Additionally, only a small percentage of patients were deemed not to have viable myocardium (19%), which limited the power of the analysis to detect a differential effect of CABG, compared with medical therapy alone, in patients with myocardial viability versus those without viability. Lastly, the viability analyses were limited to SPECT and DSE imaging. While the results for SPECT and DSE were similar, caution should be taken to not extrapolate these results to other imaging modalities that were not tested in STICH, such as DE-MRI.

Despite these limitations, the STICH trial is a landmark investigation that raises an important question: Is viability assessment important? From a pathophysiologic viewpoint, it would be difficult to interpret the STICH results as concluding that live myocardium is the same as dead myocardium. On the other hand, from a clinical viewpoint, the STICH results show that using “status quo” viability methods (viability present or absent) to determine who will benefit from CABG is highly problematic. Given the results from STICH, we will explain the basic concepts and current technique of DE-MRI and use this as a model to discuss some important concepts regarding myocardial viability.

Delayed Enhancement Magnetic Resonance Imaging

Basic Concepts and Current Technique

Delayed enhancement MRI is a technique that can index cell membrane integrity. Gadolinium-based contrast media are inert

and do not cross cell membranes, however, there seems to be a direct inverse relationship between gadolinium concentration and the percentage of viable myocytes within the myocardium. Following an intravenous bolus, gadolinium distributes throughout the intravascular and interstitial space while simultaneously being cleared by the kidneys. In normal myocardium, where the myocytes are densely packed, tissue volume is predominately intracellular (approximately 75%-80% of the water space⁵). Since gadolinium is unable to penetrate intact sarcolemmal membranes,⁶ the volume of distribution is small, and one can consider viable myocytes as actively excluding gadolinium media (Figure 1). Pathophysiologic states that cause a reduced density of viable myocytes (acute and chronic AMI, nonischemic cardiomyopathies) will have an increased volume of distribution for gadolinium and higher concentration.

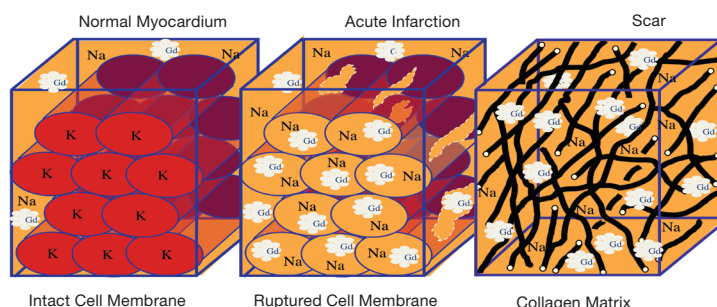


Figure 1. Mechanisms of hyperenhancement in acute and chronic myocardial infarction.

The goal of DE-MRI is to create images with high contrast between abnormal myocardial tissue, which accumulates excess gadolinium (following intravenous administration), and normal tissue in which gadolinium concentration is low. This is currently best achieved using a segmented, gradient-echo imaging engine with inversion recovery prepulse modifier to provide very strong T1 weighting.⁷⁻¹¹ Imaging is typically performed approximately 10 to 15 minutes after a one-time intravenous gadolinium dose of approximately 0.15 mmol/kg. Short- and long-axis views in the identical planes used for cine imaging are obtained during repeated 6 to 10 second breath-holds. Data acquisition (readout period) is timed with the electrocardiogram in mid-diastole to minimize cardiac motion. Only every other heartbeat is used for data collection to allow for adequate recovery of longitudinal relaxation between inversion pulses.¹²

In acute myocardial infarction, myocyte membranes are ruptured, allowing gadolinium to passively diffuse into the intracellular space. This results in an increased volume of distribution for gadolinium and thus increased tissue concentration compared with normal myocardium (Figure 1).¹³⁻¹⁵ Similarly in chronic infarction, as necrotic tissue is replaced by collagenous scar, the interstitial space is expanded and gadolinium tissue concentration is increased.¹⁵ Higher tissue concentrations of gadolinium lead to shortened T1 relaxation. Thus, when the parameters are set properly, T1-weighted sequences such as those used for DE-MRI can depict infarcted regions as bright or “hyperenhanced” whereas viable regions appear black or “nulled” (Figure 2). DE-MRI has been shown to be highly effective in identifying the presence, location, and extent of myocardial damage in both the acute and chronic setting.¹⁶

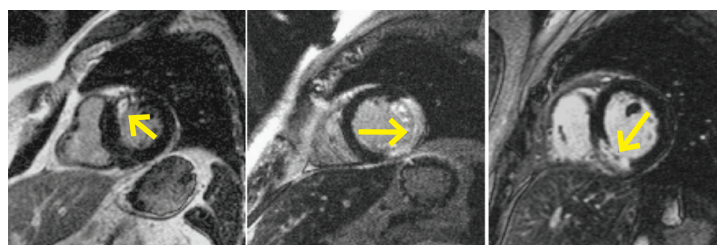


Figure 2. Short-axis DE-MRI images in three patients with acute myocardial infarction. The arrows point to the hyperenhanced territory, which was in the appropriate infarct-related artery perfusion territory. (From Radiology 2001;218(1):215–223. Reprinted with permission.⁹

Assessing Viability

Clinically, DE-MRI can be extremely useful for differentiating between patients with potentially reversible ventricular dysfunction and those with irreversible dysfunction. In patients with ischemic heart disease, it is primarily those with reversible dysfunction who will benefit from coronary revascularization. Kim et al. conducted the initial study demonstrating that DE-MRI performed before coronary revascularization could predict functional improvement. Figure 3 shows representative cine and DE-MRI images from two patients in this study. Regional wall motion analyses showed that improved contractility was inversely related to the transmural extent of infarction (Figure 4a). When the volume of dysfunctional but viable myocardium was calculated on a patient basis, this parameter predicted the magnitude of improvement in global function after revascularization (Figure 4b).

In the setting of acute myocardial infarction, early reperfusion with primary angioplasty or thrombolysis has been shown to result in salvage of ischemic but viable myocardium, long-term improvement in LVEF, and survival.¹⁷⁻²¹ However, in the immediate post-infarction setting, it is difficult to determine whether myocardial dysfunction is due to necrosis, and thus permanent, or to stunning, and thus will eventually improve. A number of studies have demonstrated the utility of DE-MRI in differentiating infarcted from viable myocardium soon after acute myocardial infarction and reperfusion therapy.^{22, 23} Similar to findings in the chronic setting, the transmural extent of infarction

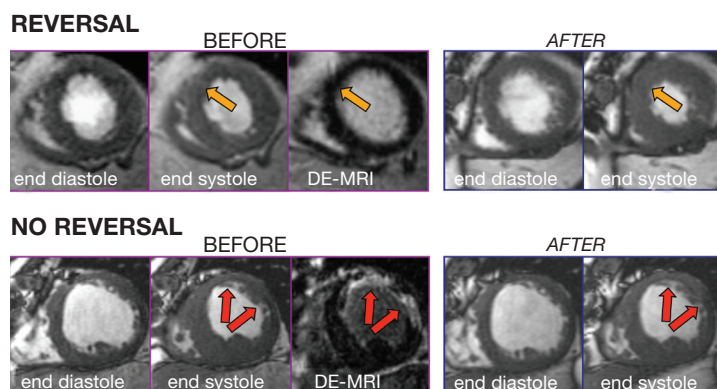
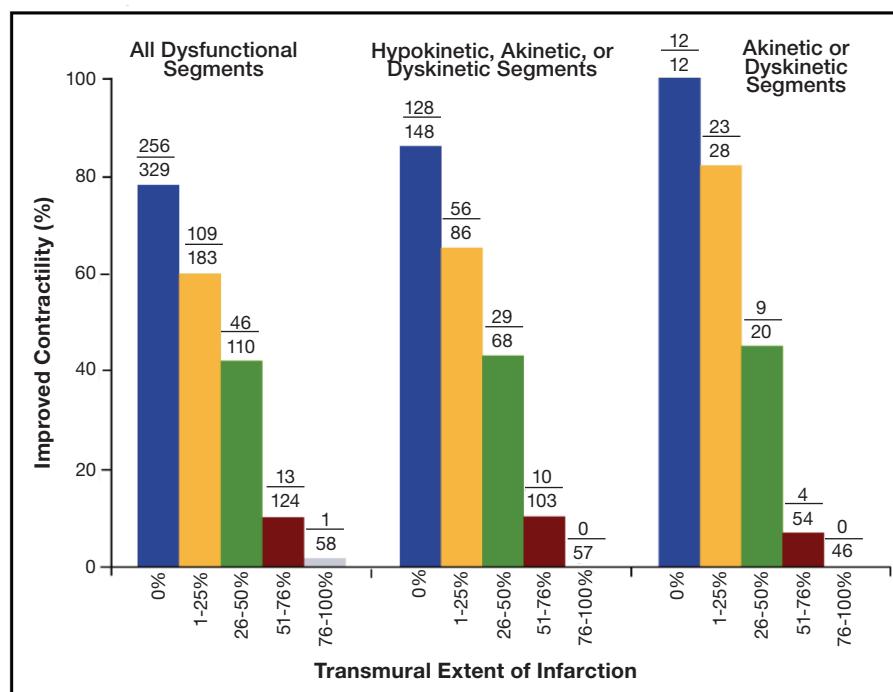


Figure 3. Representative cine and delayed enhancement images from one patient with reversible ventricular dysfunction and one with irreversible dysfunction. The patient with reversible dysfunction initially had severe hypokinesia of the anteroseptum (orange arrows). This area was not hyperenhanced prior to revascularization, and contractility improved after revascularization. The patient with irreversible dysfunction had akinesia of the anterolateral wall (red arrows). This area was hyperenhanced prior to revascularization, and contractility did not improve after revascularization. From N Engl J Med 2000;343:1445-53. Reprinted with permission.²⁶

A Regional



B Global

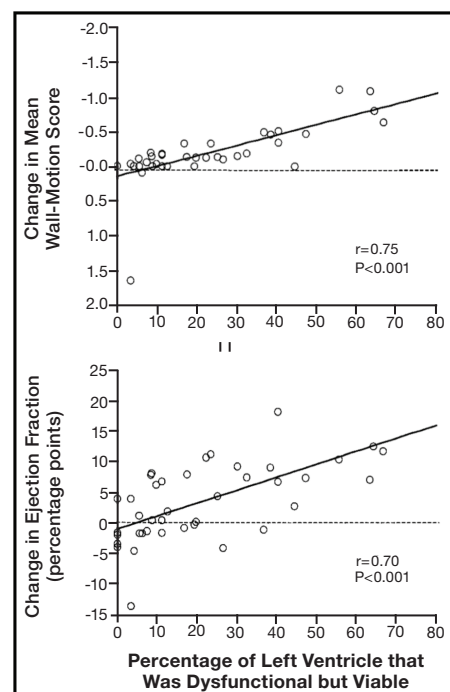


Figure 4. Prediction of improvement in regional and global systolic function by DE-MRI. (A) Relation between the transmural extent of hyperenhancement (infarction) before revascularization and the likelihood of improved contractility after revascularization. (B) Relation between amount of dysfunctional but viable left ventricle before revascularization and improvement in global function after revascularization. Decreases in wall motion scores indicate increases in contractility. From N Engl J Med 2000;343:1445-53. Reprinted with permission.²⁶

(TEI) measured by DE-MRI was found to be inversely related to improvement in segmental function in a stepwise fashion.²² In addition to predicting improvement in regional function, DE-MRI also provided the best predictor of improvement in global function: the percentage of the left ventricle that was dysfunctional but viable (i.e., $\leq 25\%$ TEI) was directly related to future changes in left ventricular (LV) wall thickening score ($r = 0.87$, $P < .001$) and LV ejection fraction ($r = 0.65$, $P = .002$).²²

Physiological Insights into Viability

A major advantage of DE-MRI is that it can visualize the transmural extent of both alive (viable) and dead (nonviable) myocardium. This has led to some interesting observations that refute traditional concepts regarding cardiac pathophysiology. Other techniques that are used to assess myocardial viability, such as nuclear scintigraphy, only visualize the viable part of the myocardium. The percentage of viability in a given segment is assessed indirectly and generally refers to the amount of viability in the segment normalized to the segment with the maximum amount of viability or to data from a sex-specific database of controls. With DE-MRI, both viable and infarcted myocardium can be visualized simultaneously, and therefore the percentage of viability can be assessed directly and expressed as the amount of viability in the segment normalized to the amount of viability plus infarction in that same segment (Figure 5A).

The ability of DE-MRI to directly visualize both alive and dead myocardium provides some important insights into myocardial thinning and the recovery of LV dysfunction. Figure 5B shows MRI images in a patient with chronic coronary disease and an akinetic anterior wall. Although the anterior wall is thinned,

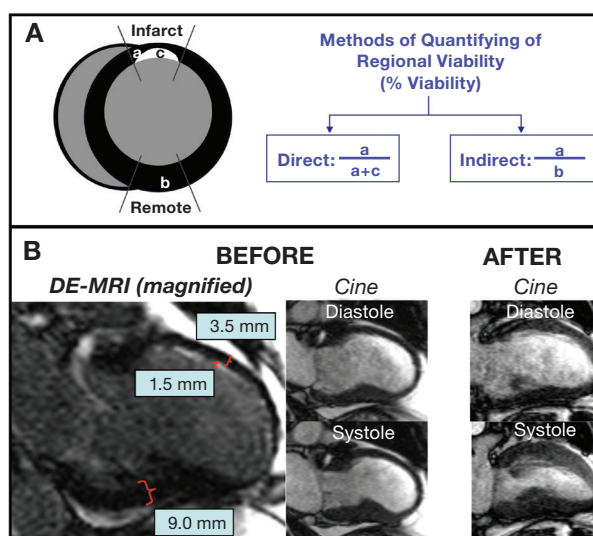


Figure 5. (A) Cartoon highlighting differences between direct and indirect method of quantifying regional viability. Viable myocardium is black, and infarct is white. "Remote" zone represents segment with maximum amount of viability. (B) Long-axis images of patient before and 2 months after revascularization. Although akinetic anterior wall is "thinned" (diastolic wall thickness 5 mm; remote zone 9 mm), DE-MRI demonstrates that there is only subendocardial infarction (1.5 mm thick). Direct assessment of viability would show that anterior wall is predominately viable ($3.5/5 \text{ mm} = 70\%$ viable), whereas indirect method would show that anterior wall is predominately nonviable ($3.5/9 \text{ mm} = 39\%$ viable). Cine views after revascularization demonstrate recovery of wall motion and diastolic wall thickness. Modified from Kim RJ et al. Fundamental concepts in myocardial viability assessment revisited: when knowing how much is "alive" is not enough. Heart. 2004;90:137-40. Reprinted with permission

only a small subendocardial portion of the anterior wall is infarcted. In this case, an indirect method would show that the anterior wall is only 39% viable (compared to the remote region), whereas a direct method would show that the anterior wall is 70% viable. The indirect method would predict absence of wall motion recovery after revascularization, whereas the direct method would predict recovery. The post-revascularization images (Figure 5B) demonstrate in this patient that the direct method is correct. This case runs against the presently accepted clinical beliefs. Prior reports have concluded that in patients with CAD and ventricular dysfunction, regions with thinned myocardium represent scar tissue and cannot improve in contractile function after revascularization.²⁴ However, this patient example indicates that thinning should not be equated with the absence of viability, and that in some patients these regions can improve after revascularization. An investigation systematically evaluating these concepts has recently been reported. Shah et al. studied 1055 patients with CAD referred for DE-MRI and found that 201 (19%) had regional wall thinning. Limited scar burden was present in 18% of thinned regions and was associated with improved contractility and resolution of wall thinning after revascularization.²⁵

Common Assumptions Regarding Viability

Intermediate Levels of Viability

The reports of predicting functional recovery with DE-MRI have shown that for any given myocardial region, there is a smooth progressive relationship between the transmural extent of viability and the likelihood of functional recovery.²⁶⁻²⁹ Therefore, with each increase in the amount of viability, there is a corresponding increment in the likelihood for functional recovery (Figures 4B, 6A). However, DE-MRI appears to have limited predictive value when intermediate levels of viability (transmural extent, 50%-75%) are present, in that only about 50% of these regions will have functional recovery. Also, since other techniques such as radionuclide imaging can also demonstrate a smooth progressive relationship between the amount of viability (tracer activity) and the likelihood for functional recovery,³⁰ how can DE-MRI provide an improved diagnosis for the clinician?

First, it is important to distinguish between what would be

desirable clinically and what can actually occur physiologically. While we may ask for an improved technique with better predictive value, perhaps in reality we are asking for a different physiological relationship—an abrupt threshold of viability below which there is virtually no chance for functional recovery and above which nearly all have functional recovery. Figure 6A demonstrates that an abrupt threshold greatly minimizes the problem of predicting an intermediate likelihood for functional recovery. Unfortunately, this physiological relationship may not exist.

Second, it is essential to remember that functional recovery is a continuum (as is viability itself) and not simply a binary—yes or no—function. Thus, part of the problem with intermediate levels of viability is expecting that these regions will or will not have functional recovery in a binary fashion. Since it more closely reflects reality, it may be better to consider most regions with intermediate levels of viability as having a high chance for an intermediate amount of improvement rather than a 50-50 chance of having either complete recovery or no improvement whatsoever.

Finally, even though two techniques can demonstrate a similar relationship between the amount of viability and the likelihood of functional recovery (like DE-MRI and radionuclide imaging), it does not mean that the techniques have the same diagnostic capability. For example, both an accurate and less accurate technique may show that, on average, 50% of segments recover function for intermediate levels of viability. Again, however, part of the problem is defining functional recovery as a binary variable. Figure 6B demonstrates the utility of expressing functional recovery as a continuous variable (e.g., millimeters of improvement in systolic wall thickening). Although the overall relationship is the same, for any given level of viability, the better technique will provide a smaller variability (smaller error bars) in the absolute amount of functional improvement than the worse technique.

Functional Recovery is the Standard of Truth

Functional recovery is currently the standard for success following revascularization. This clinical endpoint makes sense for several reasons. Since LV dysfunction portends poor prognosis, one would expect that functional recovery would be an important and beneficial clinical outcome of revascularization. Additionally, if a myocardial region recovers function, then one might confidently

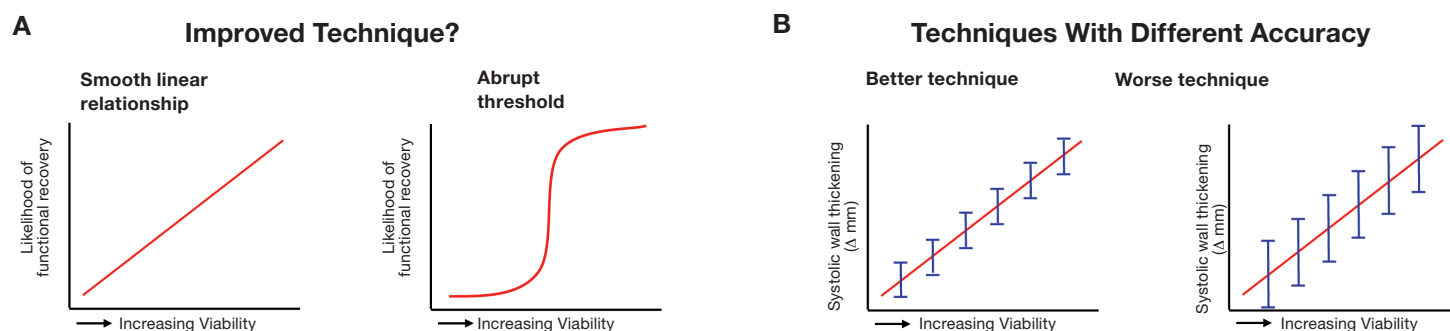


Figure 6. (Assumptions in evaluating viability techniques. (A) A technique that demonstrates a smooth linear relationship between viability and functional recovery may be considered limited in that intermediate levels of viability predict intermediate likelihood for functional recovery. With an abrupt threshold relationship between viability and functional recovery, the problem of predicting intermediate likelihood for functional recovery is greatly minimized. See text for details. (B) Two techniques with different diagnostic capability may show a similar overall relationship between viability and functional improvement. However, if functional improvement is expressed as a continuous rather than binomial variable, the better technique may reduce the variability (smaller error bars) in predicting the absolute amount of functional improvement. See text for details.

assume that the region has a substantial amount of viable myocytes.

However, a common misconception is that if a region does not have functional improvement, then this region is nonviable. In fact, Maes³¹ and Dakik³² observed that transmural needle biopsies from regions in the LV anterior wall that did not improve after revascularization still had $65 \pm 25\%$ and $69 \pm 21\%$ viability by volume, respectively.

There are several reasons why regions that are predominantly viable may not recover function following revascularization. First, revascularization may often be incomplete in patients with extensive atherosclerosis.³³ Therefore, there may be persistent areas of hibernating myocardium. Second, viable myocardium may be juxtaposed to regions with extensive scarring and unable to respond to revascularization because of tethering.³⁴ Third, there might be new perioperative myocardial necrosis in regions that were viable prior to revascularization.²⁸ Finally, the use of a single evaluation of ventricular function soon after revascularization may lead to an underestimation of the true rate of functional recovery. Bax et al.³⁵ evaluated functional recovery in 26 patients at 3 and 14 months following CABG. At 3 months, only 31% of hibernating segments recovered, whereas at 14 months an additional 61% recovered.

Even with these limitations, one could argue that functional recovery is a true standard for viability since without recovery there may be no benefit to the patient for undergoing revascularization. However, Samady et al.³⁶ showed that of 104 consecutive patients who underwent LVEF assessment before and after coronary artery bypass graft (CABG), 68 had improvement in LVEF ($>5\%$ increase) and 36 had no significant change. Surprisingly, the two groups had similar postoperative improvement in angina and heart failure scores, and there was no difference in cardiovascular mortality with a mean follow-up of 32 months. The authors concluded that a lack of improvement in LVEF after CABG is not associated with poorer outcome and speculated that many patients without improvement in LVEF may nonetheless have substantial viable myocardium that can respond to effective revascularization with beneficial effects on prognosis.

In conclusion, functional recovery is a flawed truth standard for evaluating viability imaging techniques. The primary problem is that patients without functional recovery may have substantial viability that may be important to detect clinically. This has implications for the published studies that have used functional recovery as the standard for evaluating tests of viability. Further work needs to be completed to determine how various assessments of viability predict other clinically relevant endpoints such as improvement in symptoms of angina and heart failure, improvement in exercise tolerance, and reduction in future MI, arrhythmias, and death.

Summary

A diagnostic test that can distinguish between viable and nonviable myocardium is essential in the clinical assessment and management of patients with ischemic heart disease. Delayed-enhancement MRI is a technique that can index cell membrane integrity with the use of gadolinium-based contrast media. Importantly, delayed-enhancement imaging provides simultaneous visualization of both alive and dead myocardium. The combination of cine and DE-MRI can be used in patients before revascularization procedures to predict the likelihood of

wall motion recovery following revascularization. There are many assumptions regarding viability testing, some of which arise from considering viability and/or functional recovery as a simple binary function rather than as a continuum, which more accurately reflects reality. Although an important clinical endpoint, functional recovery after revascularization is a flawed truth standard for evaluating viability techniques, since myocardium that does not recover may be predominantly viable rather than nonviable. In the end, the decision for revascularization still involves many factors besides the amount of viability.

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Keywords: cardiac magnetic resonance, ischemic heart disease, myocardial viability, hibernation, stunning, left ventricular dysfunction

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