Contrast Magnetic Resonance Imaging in the Assessment of Myocardial Viability in Patients With Stable Coronary Artery Disease and Left Ventricular Dysfunction

Kishin Ramani, MD; Robert M. Judd, PhD; Thomas A. Holly, MD; Todd B. Parrish, PhD; Vera H. Rigolin, MD; Michele A. Parker, MS; Cathy Callahan; Steven W. Fitzgerald, MD; Robert O. Bonow, MD; Francis J. Klocke, MD

Background—The utility of contrast MRI for assessing myocardial viability in stable coronary artery disease (CAD) with left ventricular dysfunction is uncertain. We therefore performed cine and contrast MRI in 24 stable patients with CAD and regional contractile abnormalities and compared MRI findings with rest-redistribution 201 Tl imaging and dobutamine echocardiography.

Methods and Results—Delayed MRI contrast enhancement patterns were examined from 3 to 15 minutes after injection of 0.1 mmol/kg IV gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA). Comparable MRI and 201 Tl basal and midventricular short-axis images were subdivided into 6 segments. Segments judged nonviable by quantitative and qualitative assessment of 201 Tl scans showed persistent, systematically greater MRI contrast signal intensity than segments judged viable (P≤0.002). Delayed contrast hyperenhancement also occurred in segments judged nonviable by dobutamine echocardiography (P≤0.03). The presence or absence of hyperenhancement correlated most closely with nonviability and viability, respectively, in segments that were akinetic or dyskinetic under resting conditions (83% concordance with 201 Tl in both cases). In segments with resting hypokinesis, 58% of segments showing hyperenhancement were judged viable by 201 Tl and may have represented an admixture of scar tissue and viable myocardium.

Conclusions—Delayed (by 3 to 15 minutes) hyperenhancement of Gd-DTPA contrast–enhanced MRI images occurs frequently in dysfunctional areas of the left ventricle in patients with stable CAD. Hyperenhancement is associated with nonviability by rest-redistribution 201 Tl scintigraphy and dobutamine echocardiography, particularly in regions exhibiting resting akinesis/dyskinesis. The absence of hyperenhancement correlates with radionuclide and echocardiographic determinations of viability, regardless of resting contractile function. (Circulation. 1998;98:2687-2694.)

Key Words: coronary disease ■ echocardiography ■ heart failure ■ magnetic resonance imaging

The identification of patients with coronary artery disease (CAD) who have viable but hypocontractile myocardium that is likely to benefit from revascularization continues to be based on assessments of regional contractile function (dobutamine echocardiography) or perfusion and metabolism (PET and radionuclide imaging). MRI can in principle address function and perfusion in a single setting, with excellent spatial resolution and the potential for in vivo spectroscopic assessment of metabolism. However, its value for assessing the viability of chronically dysfunctional myocardium is not yet clear.

The present study was undertaken to define the behavior of gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA), a commonly used paramagnetic contrast agent, in chronically dysfunctional areas of the left ventricle (LV) in patients with stable CAD. To place MRI findings in context with other imaging approaches used to assess myocardial viability, patients were also studied with rest-redistribution 201 Tl imaging and dobutamine echocardiography.

Methods

Patient Population
We prospectively studied 24 ambulatory patients with stable CAD and LV dysfunction (identified by previous angiographic, echocardiographic, and/or radionuclide studies). The group included 22 men and 2 women ranging from 35 to 75 years (mean, 64 years) of age. Ten were diabetic, 13 had a history of hypertension, 13 had a history of hypercholesterolemia, and 16 had a history of cigarette smoking. CAD was confirmed in all patients by coronary arteriography; 14 showed ≥70% reduction in the luminal diameters of ≥2 major coronary arteries, whereas 10 had triple-vessel disease. Seven had undergone CABG, and 3 had coronary angioplasty. Twenty-two patients had a history of myocardial infarction. In 18 patients, the...
infarction occurred >6 months before study. One patient was studied 4 months after infarction. The remaining 3 patients had infarctions producing persistent wall motion abnormalities >6 months before study and were studied 1, 2, and 4 weeks after recurrent ischemic episodes associated with minor elevations in creatine kinase and/or no demonstrable change in wall motion. Fifteen patients had abnormal Q waves on ECGs. All patients were in NYHA functional class II or III at the time of study. LV ejection fraction averaged 0.33 (range, 0.15 to 0.45). No patient had a hemodynamically significant valvular abnormality.

Of the 24 patients, 21 underwent rest–4-hour redistribution. 201TI single-photon emission computed tomography (SPECT) and contrast-enhanced MRI. 1 additional patient had only a rest 201TI study. Eighteen patients also underwent dobutamine echocardiography. MRI, 201TI SPECT, and echocardiographic studies were performed within an interval of 12±2 days (mean±SEM).

Imaging Protocols

Magnetic Resonance Imaging

All images were acquired on a 1.5T MRI unit (Siemens Vision, Siemens Medical Systems) with patients in the supine position with a flexible torso surface radiofrequency coil for signal reception. ECG-gated cine MRI images were acquired at 6 to 8 base-apex short-axis locations during repeated breath-holds (~15 seconds). From the cine images, 4 short-axis locations exhibiting regional myocardial dysfunction were selected for further study. Delayed contrast enhancement patterns were examined by imaging at all 4 locations every 2 minutes from 3 to 15 minutes after bolus injection of Gd-DTPA (0.1 mmol/kg IV). Imaging parameters included image data acquisition gated to end diastole, 3 cardiac cycles per image, 60 nonselective 30° radiofrequency pulses before image acquisition, repetition time of 6 ms, echo time of 2 ms, and voxels of 1.1×2.8×10 mm.$^1$

201TI Imaging and Dobutamine Echocardiography

Patients underwent SPECT imaging after the administration of 3 mCi 201TI IV under resting conditions. Rest images were acquired 15 minutes after 201TI administration; redistribution images were acquired 4 hours after 201TI injection. Transthoracic echocardiographic images were acquired at rest and during dobutamine infusion by use of a standard clinical protocol.$^2$

Registration of Images for Comparative Analyses

MRI and 201TI images were displayed side by side on a Macintosh computer with the software package NIH Image 1.60 (National Institutes of Health). The entire series of contrast-enhanced short-axis MRI images at 4 base-apex levels, the cine short-axis MRI images at 6 to 8 levels, and 201TI short-axis images at 12 to 13 levels were examined. MRI short-axis images, 1 at the midventricular level and 1 at the base of the heart, were selected for further study by consensus of 2 observers. (Apical images were not analyzed because they were not obtained in all patients.) Two short-axis 201TI images corresponding to the basal and midventricular short-axis MRI locations were then selected (at rest and at redistribution). Each MRI and 201TI image was subdivided into six 60° segments, yielding a total of 264 segments in the 22 patients evaluated with both techniques. MRI images could not be assessed further in 7% of segments because of inadvertent erasure of raw data in 2 patients, regions of interest were manually drawn to encompass each segment, and 201TI image intensity was measured. The myocardium within each segment was considered viable if segmental 201TI activity was ≥50% of activity in the segment (of any slice) with greatest 201TI activity. Because of inadvertent erasure of raw data in 2 patients, quantitative analyses of 201TI activity were derived from 20 rather than 22 patients.

Magnetic Resonance Imaging

201TI Imaging

MRI and 201TI images were displayed side by side on a Macintosh computer with the software package NIH Image 1.60 (National Institutes of Health). The entire series of contrast-enhanced short-axis MRI images at 4 base-apex levels, the cine short-axis MRI images at 6 to 8 levels, and 201TI short-axis images at 12 to 13 levels were examined. MRI short-axis images, 1 at the midventricular level and 1 at the base of the heart, were selected for further study by consensus of 2 observers. (Apical images were not analyzed because they were not obtained in all patients.) Two short-axis 201TI images corresponding to the basal and midventricular short-axis MRI locations were then selected (at rest and at redistribution). Each MRI and 201TI image was subdivided into six 60° segments, yielding a total of 264 segments in the 22 patients evaluated with both techniques. MRI images could not be assessed further in 7% of segments because the patient began to breathe during the scan, resulting in image artifacts.

201TI Quantitative Analysis

By consensus of 2 observers, each segment was independently classified as becoming hyperenhanced or not becoming hyperenhanced by examination of all postcontrast images (3 to 15 minutes). Cine MRI

Regional wall motion for each segment analyzed for contrast enhancement was characterized by examining the cine MRI images at the same location. Each segment was rated by consensus of 2 observers as showing normal, hypokinetic, or akinetic/dyskinetic wall motion.

201TI Qualitative Analysis

For qualitative assessment of myocardial viability, rest and redistribution 201TI images were examined by consensus of 2 experienced nuclear cardiologists blinded to the clinical and other imaging data. Each segment was scored as viable or nonviable, with the severity of any resting defect and the presence or absence of redistribution at 4 hours taken into account.

Echocardiographic Images

Echocardiographic images were analyzed off-line from videotape and digitized cine-loop playback by 2 experienced echocardiographers unaware of the 201TI and MRI results. LV regional wall motion was analyzed and graded semiquantitatively.$^3$ A segment with a baseline wall motion abnormality was considered viable if it showed improvement in wall motion score by at least 1 grade during dobutamine infusion or if ischemia became evident (wall motion deteriorated). Segments with normal resting wall motion were also categorized as viable.

Statistical Analyses

Comparisons of MRI image intensity between segments exhibiting viability and segments exhibiting nonviability by the various modalities were made by use of 2-sample t tests. Comparisons of MRI image intensity between viable and nonviable segments within patients were made by use of paired t tests. Agreement between MRI hyperenhancement and nonviability by 201TI or dobutamine echocardiography was assessed using K values and McNemar’s test. Differences in categorical variables were assessed by use of the χ$^2$ test statistic. All statistical tests were 2 tailed; P<0.05 was regarded as statistically significant.

Results

Comparison of Regional MRI Signal Intensity and Regional 201TI Activity

Regional MRI signal intensity after contrast administration was evaluated relative to baseline signal intensity, and the signal

Data Analysis

Magnetic Resonance Images

MRI Quantitative Analysis of Contrast Enhancement

MRI image intensity was measured in each segment at 2-minute intervals from 3 to 15 minutes after contrast administration by use of manually drawn regions of interest encompassing each segment. Care was taken to avoid endocardial and epicardial pixels that might have been affected by partial volume effects. MRI image intensity was expressed as a percent of baseline (precontrast) image intensity.

MRI Qualitative Analysis of Contrast Enhancement

By consensus of 2 observers, each segment was independently classified as becoming hyperenhanced or not becoming hyperenhanced by examination of all postcontrast images (3 to 15 minutes).
The intensity in each region was compared with the $^{201}$Tl activity in that region. Figure 1 presents images from an illustrative case. Figures 2 and 3 show pooled MRI data compared with 3 different approaches for assessing $^{201}$Tl activity: measured activity at rest (Figure 2, top), measured activity on redistribution images (Figure 2, bottom), and visual assessment of regional viability or nonviability (Figure 3).

In segments with severely reduced $^{201}$Tl activity on initial resting images (<50% of normal as defined by maximum segment activity), MRI signal intensity was significantly greater than in segments with $^{201}$Tl activity >50% at rest (Figure 2, top). This difference in the degree of MRI enhancement persisted throughout the 15-minute MRI acquisition period. MRI signal intensity was also greater in segments with severely reduced $^{201}$Tl activity (<50% of normal) on redistribution images (Figure 2, bottom), an effect that again lasted throughout the MRI imaging period. A somewhat greater separation of the MRI enhancement data between regions with <50% and >50% $^{201}$Tl activities was apparent on redistribution images than on rest images. This resulted from a greater degree of contrast enhancement in segments with $^{201}$Tl activity <50% on redistribution and rest images. Similar results were observed when the $^{201}$Tl data were analyzed by visual assessment of viability versus nonviability (Figure 3), with greater contrast enhancement in regions judged to be nonviable than in those judged to be viable. Table 1 compares the visual assessment of $^{201}$Tl viability and qualitative MRI analysis of contrast enhancement.

Because the mean data in Figures 2 and 3 do not represent paired data, this analysis could conceivably obscure individual responses and individual variability. Thus, a paired analysis was performed in individual patients comparing MRI signal intensity in regions considered viable or nonviable by qualitative $^{201}$Tl imaging (Figure 4). At each point in time after contrast administration, there was significantly greater MRI enhancement in regions in which $^{201}$Tl imaging suggested nonviability.

MRI Signal Intensity, Regional Wall Motion, and $^{201}$Tl Activity
The relation between MRI signal enhancement and regional $^{201}$Tl activity was further analyzed in relation to regional wall

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**Figure 1.** Short-axis MRI images obtained after contrast administration compared with corresponding short-axis $^{201}$Tl tomograms at rest and after redistribution (REDIST). Persistent MRI hyperenhancement develops in inferolateral wall, corresponding to severe irreversible $^{201}$Tl defect in same region. Inferior wall also demonstrates substantial perfusion defect at rest but shows redistribution, indicating myocardial viability; MRI images in this area show lesser degree of hyperenhancement than in area of irreversible injury.
motion assessed by cine MRI (Figure 5). The likelihood of increased MRI signal intensity was significantly greater in akinetic or dyskinetic (43%) than in hypokinetic (22%) or normal (9%) segments ($P < 0.0001$). Among myocardial regions with normal systolic function, 95% had evidence of myocardial viability by $^{201}$Tl imaging regardless of the presence or absence of hyperenhancement (Figure 5, left). In hypokinetic regions, 58% of regions with MRI hyperenhancement were considered viable on the basis of $^{201}$Tl imaging regardless of the presence or absence of hyperenhancement (Figure 5, middle). In regions with akinetic or dyskinetic wall motion, 83% of segments not showing MRI hyperenhancement were viable by $^{201}$Tl criteria compared with only 17% of segments with MRI hyperenhancement (Figure 5, right).

**Comparison of Regional MRI Signal Intensity and Dobutamine Echocardiography**

The relation between MRI hyperenhancement and nonviable myocardium identified by dobutamine echocardiography was similar to that observed in comparisons of MRI hyperenhancement and $^{201}$Tl data. Segments assessed as nonviable during dobutamine administration showed significantly greater MRI contrast enhancement than those segments judged to be viable (Figure 6). The difference was observed when all myocardial regions were analyzed together (Figure 6, top) and when only regions with baseline wall motion abnormalities were analyzed (Figure 6, bottom). In both cases, the difference again persisted throughout the 15-minute MRI acquisition period. Figure 7 shows a paired analysis in individual patients comparing MRI signal intensity in regions considered viable and nonviable by dobutamine echocardiography. Table 2 compares the qualitative MRI analysis of contrast enhancement with the dobutamine echocardiography assessment of viability.

**TABLE 1. $^{201}$Tl Nonviability Versus MR Hyperenhancement in Individual Segments**

<table>
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<tr>
<th>Thallium Viability</th>
<th>MR Hyperenhancement</th>
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<th>$95%$ CI</th>
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$kappa=0.47$ (95% CI, 0.33 to 0.62); $P=0.64$ by McNemar’s test.
Discussion

MRI Assessment of Myocardial Viability

Van der Wall and colleagues have recently reviewed MRI studies in acute myocardial ischemia and infarction. Prolongation of $T_1$ and $T_2$ relaxation times without contrast infusion has been suggested to indicate loss of viability after myocardial infarction. Because of the excellent spatial resolution of MRI, measurements of regional wall thickness have also been of interest in assessing myocardial viability in chronic ischemic heart disease. Baer et al found excellent concordance between segment viability graded by end-diastolic wall thickness and SPECT $^{99m}$Tc–methoxyisobutyl-isonitrile uptake. Although thin, asynergic myocardium can represent irreversibly scarred tissue, Perrone-Filardi et al found many thin, akinetic segments on spin-echo–gated MRI to be metabolically active by fluorodeoxyglucose-PET imaging. That study underscored the need for further refinement of MRI techniques for predicting myocardial viability.

Use of contrast agents has enhanced the ability of MRI to distinguish infarcted from viable myocardium. Intravenous administration of Gd-DTPA and other paramagnetic compounds results in a shortening of both $T_1$ and $T_2$ relaxation times, with the former predominating. The signal enhancement caused by these agents is proportional to the tissue concentration. Tissue contrast depends on differences in tissue perfusion, blood content, size of extracellular space, and myocardial contrast agent distribution. Gd-DTPA diffuses into the extracellular fluid with $\sim 50\%$ clearance from the intravascular space on initial capillary transit. Areas of edema and inflammation have greater accumulation and slower clearance of Gd-DTPA because of increased capillary permeability and expansion of the interstitial space. The signal enhancement in an area of infarct is probably related to increased uptake of Gd-DTPA and/or delayed washout.

Early studies using contrast-enhanced MRI were limited by spin-echo imaging, which required several minutes to obtain each cardiac image. Nevertheless, hyperenhancement of acutely injured myocardium was sometimes described, both clinically and experimentally. More recently, the advent of fast MRI methods has permitted acquisition of MRI

Figure 4. Paired data comparing MRI signal intensity in individual patients in segments considered viable and nonviable by $^{201}$Tl imaging (qualitative). Image intensities for viable and nonviable segments within same patient were averaged. Nonviable regions by $^{201}$Tl have significantly greater MRI enhancement at each point in time after contrast administration. (Not shown are 6 patients without nonviable regions at short-axis levels of LV chosen for analysis.)

Figure 5. Relationship of MRI contrast hyperenhancement (qualitative analysis) to regional wall motion and evidence of viable or nonviable myocardium by $^{201}$Tl imaging (also qualitative analysis). Likelihood of MRI hyperenhancement increases from 9% in segments with normal wall motion (left) to 22% in segments with hypokinetic wall motion (middle) to 43% in segments with akinetic or dysskinetic wall motion (right) ($P < 0.0001$ for relationship between worsening wall motion and hyperenhancement). In akinetic/dyskinetic segments showing hyperenhancement, 83% are nonviable by $^{201}$Tl criteria. Although >50% of regions with akinesia or dyskinesia did not manifest MRI hyperenhancement, most (83%) are considered viable by $^{201}$Tl criteria. Regardless of severity of wall motion disturbance, segments failing to show MRI hyperenhancement have $^{201}$Tl findings indicating myocardial viability.
tomograms during a breath-hold. This allows study of the influence of paramagnetic contrast agents on myocardial signal intensity with much greater temporal resolution. In a study of recent infarction in humans, Lima et al. showed that in the first few minutes after contrast administration, large infarcts were characterized by central dark zones surrounded by regions of hyperenhancement, whereas smaller infarcts were characterized by hyperenhancement alone. In both cases, hyperenhanced regions correlated with fixed Tl scintigraphic defect. In a related study of dogs subjected to 2-day-old reperfused infarction, dark regions were shown to relate to the “no-reflow” phenomenon, whereas hyperenhanced regions correlated with nonviable areas histologically.

Few other studies of contrast MRI have been performed in nonacute settings. Those using spin-echo technology reported that regional contrast enhancement abates within the first few weeks after acute infarction. A recent experimental fast MRI study also noted a decreasing pattern of contrast enhancement in the first few weeks after acute infarction. Conversely, Fedele et al. have reported that chronically infarcted areas judged to be “necrotic” on the basis of Tl-phenylpentadecanoic acid scintigraphy show relatively enhanced MRI signal intensity 8 to 30 minutes after contrast administration. A preliminary report from Roberts et al. also indicates that hyperenhancement can persist for up to 6 months after Q-wave myocardial infarction.

Limitations of MRI Analysis in This Study
The choice of a surface radiofrequency receiver coil rather than a body coil represented a compromise between improved image signal-to-noise ratio and homogeneity of the radiofrequency field. Although the surface coil introduces inhomogeneities resulting in higher image intensities closer to the coil, they are expected to be similar before and after contrast administration. Normalization of MRI signal intensity after contrast administration to the precontrast image intensity in the same segment should correct, at least to the first order, for radiofrequency inhomogeneities. Pooling of data from multiple patients implies that all patients received the same amount of contrast agent, that hemodynamics were similar in all patients, and that the slope of the relationship of MRI image intensity to contrast concentration was similar in all cases. To minimize these variables, all patients received the same contrast dosage on a body mass basis, and care was taken to choose identical MRI imaging parameters such as flip angle. Despite these procedures, it remains likely that patient-to-patient variation increased the variability of MRI image intensity after contrast administration. Because patient-to-patient variability would tend to mask differences in MRI image intensity between viable and nonviable myocardium, this study cannot provide a specific cutoff point between normal and irreversibly damaged tissue. In addition, the acquisition of postcontrast images at 2-minute intervals permitted only 4 short-axis views, and apical segments were not studied. Nonetheless, this study does demonstrate a systematically greater elevation in MRI image intensity in nonviable segments than in other areas.

Relationship of Delayed Contrast Enhancement to Rest-Redistribution Tl SPECT and Dobutamine Echocardiography Assessments of Myocardial Viability
As shown in Figure 5, the absence of MRI hyperenhancement appears to be a specific finding for viable myocardium with the Tl criteria, regardless of the severity of regional dysfunction. The presence of MRI hyperenhancement correlates with Tl evidence of nonviable myocardium when regional systolic function is severely depressed (Figure 5, right) but correlates less well when systolic function is only mildly abnormal (Figure 5, center). MRI hyperenhancement is an uncommon finding in regions with normal wall motion (Figure 5, left) and may not be an accurate marker of nonviable tissue in such regions. Several previous studies have validated the use of rest-redistribution Tl imaging for
predicting myocardial viability by use of a cutoff of ≤50% to 60% of maximal $^{201}$Tl activity to define nonviable tissue.25,26

Our echocardiographic criteria for viability were intended to separate living myocardium from scar tissue and therefore included segments with resting wall abnormalities that responded to dobutamine with sustained improvement, initial improvement followed by deterioration, or deterioration alone. As with $^{201}$Tl imaging, Gd-DTPA contrast enhancement was systematically greater in segments failing to show viability by echocardiography.

Recent studies have compared $^{201}$Tl rest-redistribution scintigraphy and dobutamine echocardiography in patients with chronic CAD and LV dysfunction.27,28 Perrone-Filardi et al27 and Qureshi et al28 have found that dobutamine echocardiography has a greater positive predictive accuracy for functional recovery after revascularization, whereas negative predictive accuracy is superior with $^{201}$Tl. Although information concerning functional responses to revascularization in hypocontractile segments studied with MRI contrast enhancement is not yet available, the present findings suggest that the predictive characteristics of hyperenhancement correspond more closely to those of $^{201}$Tl than dobutamine. Information about other end points, eg, improved exercise tolerance, a reduction in ischemic events, or improved survival, remains limited for all technologies being used to assess viability.

Mechanism(s) of MRI Hyperenhancement

The mechanism(s) responsible for delayed hyperenhancement on MRI remain unclear. As discussed previously, there is considerable evidence that the concentration of Gd-DTPA is increased in regions showing hyperenhancement during acute injury. It is often argued that this increase reflects an increased volume of distribution, resulting from Gd-DTPA (molecular weight, 800 Da) entry into the intracellular space after myocyte membrane rupture. However, in a study of isolated acutely infarcted rabbit hearts subjected to step changes in contrast concentration, the primary mechanism of hyperenhancement appeared to be prolonged washout of Gd-DTPA.11 In a long-term setting, myocardium that has been irreversibly injured in the past is presumably replaced by scar tissue. The present findings suggest that delayed enhancement may have special value in evaluating fibrotic or scar tissue. Delayed enhancement correlated closely with fixed $^{201}$Tl defects in akinetic segments and was infrequent in akinetic segments judged viable by $^{201}$Tl. The somewhat poorer concordance of delayed enhancement and $^{201}$Tl nonviability in hypocontractile segments could reflect an admixture of viable myocardium and scar tissue. The potential importance of scar tissue is highlighted by studies demonstrating an inverse relationship between magnitude of fibrosis and chances of functional recovery after revascularization in coronary patients with regional ventricular dysfunction.29,30 It is possible that hyperenhancement results, at least in part, from a relatively larger extracellular space (and therefore a larger volume of distribution for Gd-DTPA) in scar tissue than viable myocardium.

Conclusions

In patients with stable CAD, delayed (3 to 15 minutes) hyperenhancement of Gd-DTPA contrast–enhanced MRI images occurs frequently in LV regions showing contractile dysfunction. The presence of hyperenhancement is associated with evidence of nonviability by rest-redistribution $^{201}$Tl imaging and dobutamine echocardiography, particularly in regions exhibiting akinesia/dyskinesia under resting conditions. The absence of hyperenhancement correlates closely with evidence of viability, regardless of resting contractile

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$\kappa$=0.34 (95% CI, 0.14 to 0.54); $P=0.85$ by McNemar’s test.
function. Delayed hyperenhancement may be useful in evaluating scar tissue in stable CAD.

References


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Circulation. 1998;98:2687-2694
doi: 10.1161/01.CIR.98.24.2687
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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