Noninvasive Imaging of Myocardial Viability
Current Techniques and Future Developments
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Abstract—Complete knowledge of myocardial structure, metabolism, and function is crucial to understanding the response of the heart to injury such as ischemia. Increasingly, this type of knowledge is required at multiple levels, from that of the isolated myocyte to the functioning organism, to provide basic scientists and clinical investigators a common framework for translation of findings and information feedback. This article focuses on the utilization of imaging methods to assess myocardial viability in vivo. It discusses the advantages and pitfalls of different imaging techniques, with particular emphasis on available data in humans and large animal models. Because of their novelty and potential for accurate phenotyping of human pathophysiology, magnetic resonance modalities will be highlighted. (Circ Res. 2003;93:1146-1158.)

Key Words: cardiac magnetic resonance imaging ■ myocardial viability ■ myocardial metabolism

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The clinical recognition that myocardial dysfunction in patients with coronary artery disease was potentially reversible preceded basic science investigations into pathophysiologic mechanisms of viability. Because it was first recognized as a clinical phenomenon, the concepts of viability and functional recovery have been used interchangeably, particularly in many of the existing clinical studies. In fact, these two terms may not be synonymous. A complete assessment of viability may in truth require comprehensive evaluation of perfusion and metabolism in addition to global and regional function. This has become increasingly apparent from basic research investigations exploring potential mechanisms for viability. These pathophysiological hypotheses will be reviewed to serve as background for discussion of the relative merits of the present clinical applications of diagnostic imaging in viability assessment.

Pathophysiological Mechanisms of Myocardial Hibernation and Stunning
In the 1970s, it was observed that in patients with chronic ischemic cardiomyopathy, regions with abnormal wall motion often recovered contractility after coronary artery bypass grafting (CABG). Furthermore, inotropic stimulation transiently enhanced regional or global function and could...
identify those individuals who later experienced left ventricular (LV) functional improvement after CABG. The term “hibernating myocardium” was subsequently coined5,6 to characterize this chronic situation of “resting LV dysfunction due to reduced coronary blood flow that can be partially or completely reversed by myocardial revascularization and/or by reducing myocardial oxygen demand” (page 211). Chronically reduced perfusion was thought to downregulate metabolism, thus decreasing energy demand and limiting necrosis.

Paralleling these observations, reversible global LV dysfunction was observed in experimental animals after brief coronary occlusion and reflow.7 This phenomenon was called myocardial stunning. It is characterized as prolonged mechanical dysfunction after coronary reflow despite resumption of normal perfusion and lack of permanent tissue damage.7 The basic mechanisms for myocardial stunning are better understood8 than those underlying hibernation. Stunning seems to result from alterations in contractile proteins in response to sublethal ischemic insults. There are presently two dominant pathogenetic hypotheses. The oxyradical hypothesis proposes that oxidant stress resulting from the generation of reactive oxygen species impairs contractility.10,11 The calcium hypothesis postulates that stunning results from disturbed cellular calcium homeostasis.11–13 Specifically, ischemia may lead to decreased responsiveness of the contractile protein machinery to calcium, calcium overload, and excitation-contraction uncoupling because of sarcoplasmic reticulum dysfunction.11 The two hypotheses may not be mutually exclusive and may represent components of the same process.9

Stunning can occur in several settings, including after acute reperfused myocardial infarction (MI) and after CABG. In humans, the return of functional recovery may require days to weeks.9 This may relate to the slow synthesis of new contractile proteins.12 Hence, diagnostic methods to distinguish stunning from necrosis are particularly relevant for clinical investigation and patient management in patients with acute, severe LV dysfunction or cardiogenic shock after revascularization.

In the case of hibernating myocardium, fewer data are available regarding mechanisms of chronic dysfunction with recovery after revascularization. Although several studies support the traditional view that underperfusion downregulates local contractile performance,9,14–20 recent studies have questioned this concept by demonstrating relatively normal regional perfusion in hibernating segments21–23 as well as normal oxidative metabolism.24 Despite relatively normal resting perfusion, however, perfusion reserve has been found to be profoundly abnormal in hibernating segments.21 It has thus been postulated that repetitive intermittent ischemic episodes leading to a chronic myocardial stunned state could underlie the baseline contractile dysfunction of hibernating myocardial segments.8,21,25 Whether myocardial hibernation and stunning represent a continuous spectrum or are distinct entities remains unresolved and controversial.9

Histopathological features of hibernating myocardium are profound but potentially reversible.5,26 A substantial proportion of cardiac myocytes has sarcolemmal loss, but this is not accompanied by reduced cell volume. Instead, there is replacement by glycogen. The extracellular matrix is characterized by increased collagen and proteoglycan content. In fact, hibernating myocytes seem to dedifferentiate and adopt an embryonic phenotype.28 Presumably, functional recovery is associated with correction of some cellular dedifferentiation. When advanced histopathologic changes are present, prognosis for recovery may be poor.9

Detecting viable myocardium, whether hibernating or stunned, is of clear scientific and clinical significance. For example, the ability to distinguish hibernation from stunning could potentially elucidate the prevalence, natural history, and relative importance of these two entities in the development of heart failure associated with ischemic heart disease.9 One major limitation for detailed myocardial phenotyping in clinical investigation at the present time, however, is the lack of a true gold standard for defining viability. Histopathological verification of viability in patients is impossible. Thus, the ideal methodology to assess myocardial viability would provide accurate noninvasive measurements of perfusion, metabolism, and cellular membrane integrity in addition to systolic and diastolic function, with sufficient spatial and temporal resolution for a detailed reconstruction of the entire LV as it contracts and relaxes in 3-dimensional space. Increasingly, attempts at assessing multiple aspects of viable myocardium are being made with the various noninvasive technologies. This review summarizes the present status of these techniques and explores future developments.

Echocardiography

Echocardiography enjoys wide popularity because it is relatively economical, portable, and widely available. In present clinical applications, the technique requires pharmacological stress, either with an inotrope (dobutamine) or a vasodilator (typically, dipyridamole). The hallmark of echo viability is the presence of stress-induced contractile reserve. With increasing doses of dobutamine, viable tissue exhibits a biphasic response with improved contractility at low doses (5 to 10 μg/kg per minute) and regression to abnormal wall motion at higher doses (>15 μg/kg per minute).29 Dipyridamole leads to transiently increased coronary flow, which leads to improved contractility in viable myocardium.29 Although dipyridamole was the prototype of stress echo tests, its use is limited in the United States but remains popular abroad.

Several small studies have used dobutamine echo to predict improved regional contractile function after revascularization.30 Pooled analysis totaling 448 patients reveals an average sensitivity of 84% and specificity of 81%.30 A small study comparing dipyridamole with dobutamine revealed 93% concordance.31 Combined dipyridamole-dobutamine (low-dose dipyridamole followed by low-dose dobutamine) has also been proposed and found in a small cohort to have improved sensitivity of 90% and specificity of 92%.32 The broad applicability of this approach remains to be seen.

Prospective, randomized trials studying the prognostic value of stress echo in detecting viability are lacking. Several observational studies examined prognosis at 16 to 40 months using dobutamine.33 All consistently showed improved prognosis in patients with viable myocardium treated with revascularization compared with medical therapy.34 A study of 337 patients using low-dose dipyridamole also demonstrated significant survival benefit at 36 months in patients with viability who underwent...
coronary revascularization compared with those without viability (97.6% versus 77.4%, P<0.01).32

Stress echo has numerous limitations that impair its sensitivity. Optimal acoustic windows are often difficult to obtain. Echocardiography is generally assessed qualitatively with high interobserver variation. Lastly, diagnostic accuracy is reduced in the setting of increasing extents of regional and global LV dysfunction.35 Recent innovations have been proposed to improve accuracy. One approach is tissue Doppler imaging (TDI), which is a modification of conventional Doppler and measures myocardial velocity.36 In theory, viable tissue retains enough sufficient active contraction that is detected as positive velocities by TDI. TDI has been used to differentiate transmural from nontransmural infarction after reperfusion.37 TDI has recently been shown to improve the accuracy of dobutamine echo in detecting hibernating myocardium.39

Another approach is myocardial contrast echo (MCE). Instead of assessing contractile reserve, microbubbles are injected to assess patency of the microvasculature as a marker of viability. For details of the technique, the reader is referred to an in-depth review.40 MCE has theoretical advantages over stress echo in detecting stunned after reperfused MI. Detecting contractile reserve is adversely affected by the extent of residual coronary stenosis, myocardial flow reserve, extent of necrosis and fibrosis, energy stores, and adrenergic receptors. In contrast, none of these factors affect MCE. However, in predicting functional recovery, specificity with dobutamine echo tends to be higher, although sensitivity is lower.40 Recently, MCE was able to detect hibernating myocardium in a small cohort with comparable sensitivity to thallium and contractile reserve in predicting recovery, although specificity was lower.41 Combining MCE and dobutamine echo information may improve diagnostic performance.40–42

**Single-Photon Emission Computed Tomography**

Nuclear scintigraphy with single-photon emission computed tomodraphy (SPECT) is used with radiopharmaceuticals, primarily 201thallium (201TI), to assess perfusion and cell membrane integrity as hallmarks of viability. 201TI is a potassium analog that is actively transported into myocytes by a Na+/K+-ATPase–dependent mechanism. Its uptake thus requires an intact, functional cell membrane. Myocardial 201TI is then exchanged continuously with the reservoir of systemic 201TI, with net efflux from the myocardium over time. 201TI kinetics are directly proportional to tissue blood flow. Hence, normal tissue has more rapid uptake and washout than underperfused, viable tissue. 201TI redistribution in regions that initially had a 201TI defect is the hallmark of viability by this technique. Numerous viability protocols have been described, including rest or stress distribution followed by early (3- to 4-hour) or late (8- to 72-hour) redistribution. 201TI reinjection after stress or 3- to 4-hour redistribution imaging significantly improves viability assessment, as does semiquantitation of 201TI activity.43 Pooled analysis of 201TI viability studies assessing postrevascularization functional recovery reveals high sensitivity (88%) but low specificity (49%).40 This suggests overestimation of recovery by 201TI. Whether specificity can be improved with the development of gated SPECT, which allows quantitation of regional and global function, remains to be seen.

Compared with stress echo, SPECT is more sensitive but less specific in predicting functional recovery.30 A positive inotropic response likely requires more viable, functional myocytes than needed for thallium uptake.44 Also, in patients with two- and three-vessel coronary artery disease, ischemia can often be induced at dobutamine doses as low as 2.5 µg/kg per minute, thus additionally decreasing the sensitivity of commonly used stress echo protocols.44 However, meta-analysis of patients with chronic ischemic cardiomyopathy shows a similar mortality benefit with 201TI SPECT identification of viability as with stress echo.33

**Positron Emission Tomography**

The best-validated positron emission tomography (PET) method for detecting viability assesses both regional metabolism and perfusion. Metabolism is measured by uptake of [18F]-fluorodeoxyglucose, which is a glucose analogue. It is transported into the cell and is subsequently converted into a compound that is trapped within the myocardium. Perfusion is assessed with [15N] ammonia, [15O]H2O, or rubidium-82. Normal myocardium is characterized by normal flow, normal glucose uptake, and preferential metabolism of fatty acids over glucose. Infarcted, nonviable myocardium has both decreased flow and glucose uptake. Viable myocardium has normal or increased glucose uptake and either reduced resting flow or decreased perfusion reserve in response to dipyridamole.

From a pooled analysis of studies investigating the value of preserved [18F]-fluorodeoxyglucose uptake in predicting functional recovery, sensitivity was 88% and specificity was 73%.30 In several studies, simultaneous perfusion assessment was not obtained, possibly accounting for the relatively low specificity. In a meta-analysis, revascularizing patients with PET-identified viability significantly improved prognosis, but this was similar to that with stress echo and thallium-SPECT.33

Although long considered the gold standard for viability assessment, PET has not been widely available, largely because of its high equipment and operational costs. In addition, more widespread clinical use would likely require evidence that it is prognostically more valuable than the other techniques. It remains an important research tool.

**Magnetic Resonance**

**Contractile Reserve**

Similar to echocardiography, cine magnetic resonance imaging (MRI) allows real-time visualization of cardiac motion but is characterized by superior endocardial border definition, facilitating more accurate wall motion assessment. Contractile reserve can be assessed with cine MRI using low-dose dobutamine. Several semiquantitative parameters for measuring MRI wall motion recovery have been described.45–46 They compared favorably to PET viability in 35 patients with chronic ischemic cardiomyopathy, with sensitivity of 88% and specificity of 87%.47 In predicting functional recovery on an individual-patient basis, dobutamine MRI was 89% sensitive and 94% specific.45 On a segmental basis, the positive and negative predictive values were 85% and 68%.46 Al-
though these values are suboptimal even compared with echocardiography, they do not account for the fact that MRI can be performed in patients with poor echo images. Given its high spatial resolution, semiquantitative assessment of wall motion by MRI has a potential role.

Semiquantitative assessments are of course limited. Transmural variations in mechanical function cannot be evaluated. MRI tissue tagging is thus particularly advantageous because it can quantify local myocardial segmental shortening. Tagging uses selective radiofrequency excitation to saturate the magnetization in a thin planar region perpendicular to the imaging plane before acquiring image data. The altered magnetization in the tagged region appears as a dark line in the subsequent image, where it intersects the imaging plane, persisting during systole and most of diastole. If the underlying tissue moves between the times of tagging and imaging, the altered magnetization of the tag line deforms with it. Hence, motion of the tag line faithfully follows underlying tissue motion (Figure 1).

The improved performance of dobutamine-tagged MRI in detecting chronic hibernation was examined in 10 patients with ischemic cardiomyopathy. The presence of contractile reserve by dobutamine MRI was 89% sensitive and 93% specific for functional recovery at 4 to 8 weeks after revascularization. The detection of stunning was reported in a cohort of 20 patients with first acute reperfused MI who were studied acutely and at 8 weeks after infarction. Tagged MRI had a sensitivity of 89%. Moreover, because of the spatial resolution of MRI, contractile reserve in the different layers across the myocardial wall could be assessed. Recently, quantitative stress-tagged MRI was directly compared with qualitative assessment of echocardiographic contractile reserve in 22 patients 3 days after acute reperfused MI. The outcome variable was 8-week postinfarct functional improvement by echocardiography. Echocardiography and MRI were concordant in 76% of the segments. Compared with echo, MRI had similar sensitivity (82% versus 86%) but lower specificity (69% versus 87%). However, the overall accuracy of MRI and echo was 76% and 85%, respectively, which was not statistically different. One reason for the lower specificity includes difficulties in cross-registering locations between the two modalities. Also, the subendocardial response to dobutamine by MRI is known to be lower. To more directly compare with echo, this study averaged the MRI response across the three transmural layers, likely amplifying the difference.

In addition to assessing two-dimensional shortening, tagged MRI can be applied in three dimensions to assess regional function not only in the circumferential but also the radial and longitudinal directions (Figure 1). The sequential tag positions during the cardiac cycle can be fitted to a finite element model of heart wall deformation. The components of strain (deformation) can then be separated from rigid body motion (translation and rotation). This approach accurately and precisely measures mechanical function. Importantly, it accounts for conformational changes of the heart during systole, such as the base to apex shortening and twist.

Resting and low-dose dobutamine 3-dimensional tagged MRI was performed in seven dogs 48 hours after acute reperfused MI. Strains in the infarcted regions were reduced compared with remote \( P < 0.001 \) and were dobutamine-unresponsive. Risk regions were dysfunctional at rest but responsive to dobutamine. Receiver operating curves demonstrated that radial strain analysis most accurately identified viable myocardium, with a sensitivity of 94% for a specificity of 80%.

Widespread clinical application of stress MRI, particularly with tagging, has been limited by relatively long imaging times and time-consuming postprocessing and offline analyses. New approaches are available that decrease imaging and postprocessing time and potentially provide online quantitative assessment of wall motion in near real time. This
may prove beneficial in detecting ischemia with higher sensitivity and at an earlier point in the stress protocol, improving both accuracy and patient safety.

Delayed Hyperenhancement
Contrast-enhanced MRI (ceMRI) with gadolinium-DTPA was described in 1984 in a canine acute MI model. Compared with normal myocardium, infarcted myocardium demonstrates significantly greater T1 shortening after contrast, resulting in tissue hyperenhancement. With the advent of ultrafast MRI sequences in the early 1990s, studying myocardial perfusion patterns and tissue damage by MRI in humans became practical and investigations into the pathophysiological mechanisms followed. In an early application to patients with acute MI, Lima et al described the ceMRI patterns in 22 individuals 8 days after MI. Virtually all patients had increased signal intensity at 10 minutes after contrast bolus in the region perfused by the infarct-related artery. This MRI region correlated well with fixed thallium defect size, potentially indexing infarct size.

The mechanisms of the delayed hyperenhancement in both acute and chronic infarction have been investigated. In acute MI, myocyte necrosis results in membrane rupture and interstitial edema. Because gadolinium-DTPA is primarily an extracellular, interstitial agent, the volume of distribution for the contrast molecules increases within the infarcted imaging voxel. The increased gadolinium concentration within infarcted tissue shortens the T1 relaxation time. Hence, infarcts appear hyperenhanced (Figure 2). Another contributory mechanism is abnormal contrast molecule kinetics within infarcts. In a rabbit model of ischemia/reperfusion in which gadolinium was continuously infused in stepwise concentrations, washout time constants within the infarcted regions were markedly prolonged compared with normal regions. By electron microscopy, the hyperenhanced regions not only had extensive myocardial cell membrane rupture but also a 37-fold increase in the number of capillaries with erythrocyte stasis. Hence, the reduced functional capillary density could prolong contrast washout by two mechanisms: the smaller effective capillary surface area decreases the rate of solute transport and increases the distance that solute has to travel to diffuse out of the affected region. Because diffusion time is directly proportional to the square of the distance traveled, modest decreases in capillary density significantly lengthen washout times.

Chronic infarcts also display hyperenhancement, although the mechanisms are somewhat different. Similar to acute infarcts, chronic infarcts have increased gadolinium concentrations and tissue-blood partition coefficients. This suggests that the extracellular space is increased in collagenous scars and explains the increased volume of distribution for gadolinium in chronic infarction. Reduced capillary density in chronic scars also reduces contrast washout, leading to the hyperenhancement.

The accuracy of ceMRI in quantifying infarct size has been investigated and compared with histopathology. Initial studies demonstrated a strong correlation (r=0.88 to 0.93) but suggested that ceMRI overestimated pathology by 8% to 15%. This led to the hypothesis that perhaps tissue edema in the infarct periphery explained the overestimation (ie, that hyperenhancement can also occur in reversibly injured areas surrounding acute necrosis). Recent data, however, suggest that when thin, 0.5-mm LV cross sections are imaged with MRI, there is near-identity between the hyperenhanced and necrotic regions at all stages after infarction and that the overestimation results from the partial volume effect of imaging relatively thick slices. Furthermore, reversibly injured myocardium does not exhibit increased gadolinium concentrations, nor does it enhance. Thus, regions of hyperenhancement denote nonviable myocardium. ceMRI has recently been applied to identifying reversible ischemic injury in humans. Fifty patients with ischemic LV dysfunction were studied before and after revascularization with ceMRI and cine MRI. Segmental wall thickening was analyzed semiquantitatively. The extent of hyperenhancement within each segment (expressed as percent of the total segmental area) was graded on a 5-point scale, with 0 indicating no enhancement; 1, 1% to 25% tissue involvement; 2, 26% to 50%; 3, 51% to 75%; and 4, 76% to 100%. Increasing transmural extents of infarction correlated with a reduced likelihood of functional recovery after revascularization (Figure 4). Of the segments with no hyperenhancement (ie, viable by ceMRI),
Figure 3. A, Triphenyltetrazolium chloride (TTC)-stained slices compared with corresponding ex vivo MR images from an animal 3 days after acute reperfused anterior infarct. There is close agreement between the extent of TTC-negative regions and MRI hyperenhancement at all stages of infarct healing (B). Reprinted from Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O, Bundy J, Finn JP, Klocke FJ, Judd RM. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation. 1999;100:1992–2002, by permission of the American Heart Association ©1999.
78% experienced functional recovery. Moreover, functional recovery was seen in 86% of the nonenhanced segments that had at least severe hypokinesia before revascularization and 100% of the akinetic or dyskinetic segments. Thus, unlike dobutamine echocardiography and nuclear scintigraphy, ceMRI had better accuracy in the presence of more severe dysfunction. Of the segments with >75% transmural hyperenhancement, only 1.7% experienced improved contractility after revascularization. The rate of functional recovery was 10% in the 51% to 75% group, 42% in the 26% to 50% group, and 60% in the 1% to 25% group. Hence, there was no single cutoff on which to base predictions of functional recovery. On average, the mean transmural extent of hyperenhancement in segments with improved function was 10±7% compared with 41±14% in the segments that did not improve function. Nonetheless, revascularization when there is an intermediate degree of viability (ie, an epicardial rim of viable myocardium exists) may be beneficial even though overall resting function is not improved, although this remains to be confirmed. Transmural extent can also identify stunned myocardium after acute reperfused MI. Decreasing extents of transmurality are the best correlates of improved long-term regional contractile function and overall ejection fraction. ceMRI is unique in its ability to assess transmurality because of its greater spatial resolution.

Using MRI, complex regional differences in response to dobutamine within the hyperenhanced regions have been demonstrated in a canine model of acute reperfused MI. In the center of the hyperenhanced zones, where transmural enhancement averaged 66±3%, there was no significant inotropic reserve. In the periphery of the hyperenhanced zone, the extent of transmural hyperenhancement averaged 38±3%, and those segments had mild dobutamine-induced improvement in shortening, which actually reflected reduced passive stretch rather than increased active shortening. This can be explained by the patchy, less-transmural involvement in the peripheral zones compared with the infarct core. The better contractile function seen in the periphery may result from the combination of the contractile improvement shown by the viable cardiomyocytes as well as the interaction with and functional recruitment of adjacent noninfarcted regions, previously reported by others. Hence, these data additionally support the notion that hyperenhancement represents nonviable myocardium.

Infarct size by ceMRI has been compared with other modalities. In one study, 20 chronic infarct patients underwent two consecutive ceMRI and two resting SPECT examinations. The average difference between the two methodologies was −0.5% of the LV mass, with MRI infarct size underestimating that measured by SPECT. The average difference between the two MR scans was −0.1% of the LV compared with −1.3% for the SPECT scans. Hence, ceMRI compared favorably with SPECT and was reproducible.

The underestimation of MRI relative to SPECT, moreover, is attributable to the latter’s low spatial resolution (10×10×10 mm full-width half maximum for SPECT versus 1.5×2.0×8 mm for MRI, a 42-fold difference). Hence, it was hypothesized that ceMRI may detect nontransmural, subendocardial infarcts missed by SPECT. To address this, 91 patients underwent both stress-rest dual-isotope SPECT and ceMRI. A segmental, semiquantitative analysis approach was used. For segments with large transmural extents of infarction (>75%), there was complete agreement between ceMRI and SPECT (Figure 5A). However, in detecting subendocardial infarcts, there was a marked discordance (Figure 5B). Among the segments with <50% transmural hyperenhancement by ceMRI, SPECT did not detect a fixed perfusion defect in 47%. These findings were confirmed by histopathological animal data.

ceMRI has recently been compared with PET in patients with ischemic cardiomyopathy. Sensitivity and specificity
of ceMRI for detecting nonviable myocardium by PET were 96% and 84%, respectively. Quantitative infarct size by MRI correlated well with but tended to underestimate that by PET (18 ± 16% versus 20 ± 18%, r = 0.81, P < 0.0001). There are several potential explanations. MRI has a higher spatial resolution than PET, which may have allowed subtler infarct detection and border definition. In support of this, 55% of segments with subendocardial infarcts by MRI were missed by PET. Gadolinium allows detection of necrosis, whereas fluorodeoxyglucose-PET evaluates cellular metabolism. Small islands of viable myocytes may exist in the infarct periphery but may not contribute to active contraction. The relative predictive value of MRI and PET remains unknown.

**Microvascular Obstruction**

In addition to hyperenhancement, acutely infarcted territories often demonstrate marked heterogeneity by ceMRI, which reflects the status of the microvasculature. In the first few minutes after contrast bolus, some patients develop a hypoenhanced region with decreased signal intensity in the subendocardial layer of the myocardium that later enhances (Figure 6). Hypoenhancement correlates with an increased incidence of total coronary occlusion at initial angiography after MI, electrocardiographic Q-waves, and greater regional dysfunction by echocardiography. However, up to half of the patients with hyperenhancement ultimately have a widely patent infarct-related artery after revascularization. Hence, it has been postulated that these regions represent the no-reflow phenomenon or regions of microvascular obstruction described in experimental studies and in humans by nuclear and echocardiography techniques.

No-reflow was first described in the heart by Kloner et al. in a canine model of ischemia/reperfusion. Despite complete restoration of epicardial coronary artery flow, within the core of the necrotic region, progressive flow impairment and tissue hypoperfusion may occur. This happens at the capillary level, which, by electron microscopy, is characterized by intravascular neutrophil occlusion and marked intracapillary erythrocyte stasis.

MRI-hypoenhanced regions have microsphere-measured flow rates less than half that of remote regions after reperfusion and correlate in anatomic location and spatial extent to pathologic no-reflow. Potential mechanisms have been examined. By MRI, subendocardial no-reflow regions had delayed contrast wash-in times compared with the delayed contrast wash-out of the hyperenhanced region. Both delays in contrast kinetics are potentially explained by the obstructed capillaries. Decreased functional capillary density prolongs the time for gadolinium molecules to penetrate the infarct core leading to the dark, low signal intensity early after contrast bolus.

Microvascular obstruction (MO) after revascularization is actually a progressive phenomenon. In canine acute infarct models, MRI hypoenhancement increased 3-fold during the first 48 hours after reperfusion. MRI hyperenhancement or infarct size also increased, but only by 33% at 48 hours. Between 2 and 9 days after infarct, both MO extent and infarct size stabilize and are unchanged. From previous human studies, MO disappears by 6 months after infarct. Hence, this suggests that MO extension could result from reperfusion injury that peaks within 48 hours and stabilizes for a period of time thereafter, gradually resolving as neovascularization occurs and the occluded microvessels are replaced by fibrous tissue.

MO has potential long-term implications. In patients with acute reperfused MI, it is associated with an increased rate of cardiovascular complications (Figure 7), independent of infarct size. Although it correlates with patency status of the infarct-related artery, MRI MO was present in 17% of patients with brisk, TIMI 3 flow after revascularization. It is
also associated with increased end-diastolic and end-systolic volumes and increased rates of myocardial fibrous scar formation at 6-month follow-up. Hence, a potential mechanism for the worse clinical prognosis associated with MO is its adverse effect on postinfarct LV remodeling.

This was investigated in a canine model of acute reperfused infarction using ceMRI and tagged MRI at 6 and 48 hours after reperfusion. Increasing amounts of MO correlated significantly with altered myocardial strains both in the infarcted and adjacent, noninfarcted myocardium. Areas with MO comprising >35% of the infarct had significantly less passive stretch versus regions with less MO. In adjacent myocardium, subendocardial thickening was significantly decreased when the adjacent infarcted territory had >35% MO. Interestingly, there was a time differential in the occurrence of the strain alterations, with the changes occurring at 48 hours after reperfusion in the noninfarcted region versus 6 hours in the infarcted territory. Hence, infarcted regions with widespread MO experience reduced elasticity early after reperfusion. This potentially increases local wall stress in the adjacent noninfarcted regions and lengthens those segments, a phenomenon previously described and that could explain the worse remodeling seen with MO.

ceMRI has been compared with MCE in a canine model. MO quantification by both techniques correlates well with histopathology and radioactive microspheres. However, the absolute extents are different: MO by MCE systematically overestimates histopathology, which in turn overestimates ceMRI. Compared with radioactive microsphere flow maps, MRI detects regions of MO where blood flow is <40% of remote compared with <50% for histopathology and <60% for MCE. Differences between MCE and MRI likely result from the different characteristics of the contrast used. Microbubbles are purely intravascular, whereas gadolinium is an interstitial agent. Microbubbles are also heterogeneous, with variable size diameters, and may become trapped in larger microvessels that would allow passage of gadolinium. Both of these reasons could explain the larger region measured by MCE. Direct comparison in humans is lacking.

**MR Spectroscopy**

MR spectroscopy (MRS) assesses viability by quantifying regional myocardial metabolism and chemistry. Instead of using the $^1$H nucleus as the signal source (as in MRI), MRS can detect and quantify the concentrations of $^{31}$P-, $^{23}$Na-, and $^{13}$C-nuclei that are components of normal cardiac energetics. $^{31}$P MRS detects high-energy phosphate compounds, such as adenosine triphosphate (ATP) and creatine phosphate (PCr), which are essential for myocardial contractile function. $^{23}$Na MRS detects high-energy phosphate compounds, such as adenosine triphosphate (ATP) and creatine phosphate (PCr), which are essential for myocardial contractile function. $^{23}$Na MRS can quantify total, intracellular, and extracellular sodium content. $^{13}$C-MRS allows analysis of metabolic path-
ways, such as glycolysis, β-oxidation, and the tricarboxylic acid cycle.

For myocardial viability assessment, predominantly 31P spectroscopy has been used. Myocyte necrosis is associated with the loss of intracellular high-energy phosphates and total creatine stores. In patients with recent anterior MI, reduced PCr to inorganic phosphate ratios at rest without changes in the PCr/ATP ratio has been described.95 Moreover, infarcted regions are characterized by significantly reduced absolute levels of PCr (50% decrease) and ATP (65% decrease).96 Significantly lower PCr content is also seen in patients with and without reversible thallium defects.97 ATP concentration, however, was significantly depressed only in those with an irreversible defect (ie, nonviable). Hence, 31P spectroscopy provides unique viability information.

The disadvantages of 31P spectroscopy include the relatively low total concentrations of 31P in the heart and decreased sensitivity, which require relatively large imaging voxels averaging 30 mL. This reduces spatial resolution and depth penetration, restricting studies to the anterior ventricular wall. 1H MRS has much higher sensitivity (a 20-fold improvement) and also allows detection of the total pool of myocardial phosphorylated plus unphosphorylated creatine. (Note that creatine levels are important for calculating ADP levels and the free energy of ATP hydrolysis.) Voxel sizes below 10 mL can thus be interrogated, allowing imaging of all myocardial regions. This approach was recently validated in a canine model of nonreperfused infarction and applied to 10 healthy volunteers and 10 patients with remote MI.98 By MRS, mean total creatine content in infarcted and noninfarcted regions agreed with fluorometric quantification. In humans, MRS detected similar mean total creatine concentrations in the myocardium of the healthy volunteers compared with the noninfarcted regions of the infarct patients. In contrast, the infarcted myocardium of the patients had significantly reduced total creatine (Figure 8). Hence, this methodology potentially allows the metabolic means of distinguishing healthy from infarcted, nonviable myocardium.

**Sodium Imaging by MRI**

Another recent MRI approach detects increased total sodium concentrations ([Na+]i) in regions of irreversible injury. With normal myocyte function, active outward transport pumps maintain an electrochemical gradient with much lower intracellular compared with extracellular [Na⁺]. Cellular injury disrupts this gradient to varying extents. Reversible ischemia transiently increases intracellular [Na⁺], which returns to baseline with reperfusion.99 Irreversible ischemia, however, permanently raises intracellular [Na⁺]. However, to assess local viability, it may not be necessary to separate the sodium content in the different compartments but rather document the increased total regional [Na+]i associated with injured myocardium. Under normal conditions, because myocardial tissue volume is primarily intracellular, comprising ~75% of the water space, extracellular sodium levels far exceed a weighted average of intracellular and extracellular sodium. In the extreme situation in which all the myocytes in a nonviable region become necrotic and unable to maintain a sodium gradient, the total tissue [Na⁺] would reach that of the extracellular level, an increase of >200% above normal. This increase is potentially detectable on 23Na images.100 In fact, increased 23Na image intensity by MRI was described as early as 1986 in animals subjected to ischemia/reperfusion and imaged ex vivo.100 Because increased [Na⁺]i in infarcted regions require sodium delivery,99 this approach is limited to situations in which there is reperfusion or at least some residual coronary flow.

The potential of 23Na imaging to detect nonviable myocardium has been demonstrated, however, in animal models of ischemia/reperfusion using a high-field 4.7 T system.101,102 Nonviable regions are characterized by significantly elevated 23Na image intensity. In fact, the extent of regions with elevated 23Na signal intensity are nearly identical to areas of necrosis. Concurrent 23Na spectroscopy demonstrated a 142±7% increase in [Na+]i in the nonviable compared with the viable areas, supporting the notion that the increased 23Na MR image intensity results from differences in myocardial [Na⁺]. Furthermore, infarcted territories also have a significantly increased intracellular sodium/potassium ratio, which is associated with only minor increases in extracellular volume. This additionally suggests that the mechanism for the increased 23Na signal intensity after reperfused infarction is the loss of myocyte ionic homeostasis, which causes intracellular sodium retention.

Recently, 23Na and contrast-enhanced 1H MRI were combined in a canine model to relate the time course of myocardial sodium accumulation after acute reperfused MI to microvascular integrity.103 Up to 9 hours after reperfusion, infarcted regions with MO by ceMRI are characterized by significantly slower time course of 23Na signal intensity rise compared with regions without MO. However, regions with total coronary occlusion had an even more markedly delayed increase. This suggests that the time course of 23Na accumulation depends on sodium delivery and requires both patent microvasculature as well as a patent epicardial artery. Combining both 23Na imaging and ceMRI thus potentially allows full characterization of tissue viability and perfusion.

Recently, 23Na imaging was adapted for a clinical 1.5T MR scanner104 and validated against atomic absorption spectrophotometry as an accurate measure of [Na+]i in a canine model of acute reperfused MI.105 23Na MRI at 1.5 T has been applied to a human cohort of subacute (8-day) and chronic (6-month) MI.106 23Na signal intensity was increased at both time points and correlated with the extent of wall motion abnormalities by cine MRI. Larger-scale human studies are required to fully assess the potential of 23Na MRI clinically.

**Future Developments**

Presently, the field of myocardial viability assessment suffers from important knowledge gaps. First and foremost is the lack of large-scale, randomized, prospective studies demonstrating that the a priori identification of viable myocardium improves prognosis. Existing studies lack protocol standardization and uniform definitions of viability and are thus difficult to directly compare. Second, the mechanisms of improved prognosis observed after revascularizing patients with ischemic cardiomyopathy remain unclear. Do the benefits result from improved LV remodeling with accompanying reductions in the incidence of malignant arrhythmias and recurrent ischemia or do they pri-
marily derive from enhanced LV function? Answers to these questions will in part determine how these diagnostic techniques are used in the future. It is likely that these answers will depend on the availability of comprehensive strategies to assess perfusion, function, and metabolism.

The present noninvasive techniques themselves have numerous limitations. Echocardiography is obviously attractive because of its portability and wide availability. However, its low spatial resolution will always represent significant limitations. Nuclear techniques have greater sensitivity but lower specificity compared with techniques based on functional recovery. MRI is presently limited by its lack of wide availability and relatively long study times. The high spatial resolution of MRI, however, is a strong advantage, particularly if a complete assessment of perfusion, metabolism, and function can be performed as part of a single examination. cMRI is very attractive as an adjunct to functional and perfusion studies. New approaches to tagged MRI analysis have been recently proposed that decrease imaging time, minimize the need for human subjective interaction, and potentially provide online quantitative assessment of wall motion in near real time. Recent advances in spectroscopy include the ability to combine 1H and 31P MRS for a more complete assessment of myocardial pH, PCR, ATP, and creatine. With the advent of high-field 3 Tesla clinical scanners, the potential for spectroscopy and sodium imaging can be even greater. Imaging at 3 Tesla improves the signal to noise ratio, decreases imaging times, and increases spatial resolution. Hence, one would potentially be able to detect metabolites in lower concentration (ie, inorganic phosphate) or nuclei with smaller chemical shift separations.

Ultimately, however, the predominance of one technique over the others for investigative and clinical purposes will be driven by proof of its superior diagnostic and prognostic performance. Until then, clinician investigators and practitioners will have to judiciously select and interpret the incomplete data from the presently available studies to not only support clinical decision making but also design the much-needed studies to eventually elucidate the role of tissue viability on the pathogenesis of ventricular remodeling and heart failure.

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