Frontiers in Cardiovascular Magnetic Resonance
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New Drugs and Technologies

Frontiers in Cardiovascular Magnetic Resonance

Valentin Fuster, MD, PhD; Raymond J. Kim, MD

Cardiovascular magnetic resonance (MR) is emerging as a multipurpose imaging modality for the assessment of cardiovascular disease in general and ischemic heart disease in particular. Currently, the pace of innovation is rapid, and the modality is changing from one that is used primarily as a research tool to one that is increasingly used in routine clinical practice. The process of innovation includes not only improvements in scanner hardware, such as coil and gradient technology, and the development of new contrast agents but also the development of novel pulse sequences. The concept of the pulse sequence, in which programming changes at the scanner can lead to fundamental changes in activating tissue, is unique to MR and gives this modality the potential to assess a vast number of biological parameters.

Cardiovascular MR promises to play an important clinical and investigational role in both vascular and cardiac systems. Current and potential future applications of cardiovascular MR will be discussed with a particular focus on ischemic heart disease. Multidetector-row computed tomography, another promising and complementary noninvasive imaging technology, will be discussed briefly in relation to cardiovascular MR for the assessment of atherothrombotic disease.

The Vasculature and Atherothrombotic Disease

Nomenclature and Evolving Imaging Assessment

Atherothrombosis is a systemic or multiterritory arterial disease that primarily affects the large- and medium systemic arteries, including the aorta and the carotid, coronary, and peripheral arteries. Although the epicardial coronary arteries appear to be the most susceptible to atherothrombosis, intramyocardial arteries are relatively resistant. The concept of multiterritory atherothrombosis has been addressed in 2 large studies of symptomatic patients that showed that at entry into the studies, 3% to 8% had symptomatic atherothrombotic disease in all 3 main arterial districts and 23% to 32% had disease in 2 districts. From a structural point of view, the 4 main components of the atherothrombotic plaques are as follows: (1) fibrocellular, or extracellular matrix of various fibril types intermixed with smooth muscle cells and other cells; (2) lipid-cellular, or lipid elements such as crystalline cholesterol and cholesteryl esters intermixed with monocyte-derived macrophages and other cells; (3) thrombotic, or deposition of platelets and/or fibrin; and (4) calcification, usually related to fibrous rather than to lipid-rich plaques. Varying proportions of these components occur in different plaques, thus giving rise to a heterogeneity or spectrum of lesions. These components mainly affect the intima, but secondary changes also occur in the media and adventitia; these presumably include growth of vasa vasorum and extravasated erythrocytes. As examples of the heterogeneity of lesions, disruption-prone plaques in the coronary arteries, the so-called vulnerable plaques, tend to have a thin fibrous cap (cap thickness ≈ 65 to 150 μm) and a large lipid core (>40% of the total lesion area). About two thirds of the acute coronary syndromes (ACS) result from disruption of a moderately stenotic vulnerable plaque, not visible by x-ray angiography, which triggers an acute thrombus formation that may result in a thrombotic occlusion. Similar observations have been made of small lipid-rich lesions of the thoracic aorta, which, after disruption and thrombosis, may result in stroke. Unlike coronary and aortic vulnerable plaques, carotid plaques prone to disruption and thrombosis are predominantly fibrotic and severely stenotic. Similar observations have been made of severely stenotic and fibrotic plaques leading to thrombotic complications (presumably favored by a hypercoagulant state) that affect the peripheral arteries and occasionally the coronary arteries, which explains approximately one third of the ACS. Therefore, in atherothrombotic disease, it has been proposed that the term “high-risk plaque” may be used interchangeably with the classic term “vulnerable plaque,” which traditionally implies the presence of a lipid-rich core. Accordingly, reliable noninvasive imaging modalities able to detect atherothrombotic disease in the various stages and regions and to characterize plaque composition are clinically desirable. Additionally, the availability of such imaging modalities will improve our understanding of the pathophysiological mechanisms underlying the atherothrombotic processes and allow us to better risk-stratify the “burden” of disease. Moreover, such tools may permit optimal tailoring of treatment and allow direct monitoring of the vascular response. Most invasive techniques, such as coronary angiography and intravascular ultrasound, identify luminal diameter or stenosis, wall thickness, and plaque...
MR and CT Angiography of the Coronary Arteries

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MDCTA indicates MDCT angiography; CE, contrast enhanced.

MR Imaging
Because atherothrombotic disease affects the entire arterial system, simultaneous assessment from supra-aortic arteries to the distal runoff vessels has been proposed with contrast-enhanced, whole-body MR angiography (MRA). Most importantly, high-resolution MRI has emerged as the potential leading noninvasive in vivo imaging modality for atherosclerotic plaque characterization.

Whole-Body, Contrast-Enhanced MRA
MRA is highly specific and sensitive compared with x-ray angiography for the detection of luminal narrowing >50%.13 Whole-body MRA excludes the intracranial and coronary arteries, for which a dedicated examination is still required. Several coronary MRA techniques have been proposed for the assessment of coronary stenosis, anomalies, and patency of bypass grafts. Thus far, the sensitivity and specificity of coronary MRA with later-generation 3D techniques are quite reasonable in select patient cohorts (Table).12-14 Coronary MRA, however, is technically challenging, and currently there are limitations in spatial coverage and resolution, temporal resolution, and image quality that preclude the routine use of coronary MRA for everyday clinical application.

Overall, it is possible that in the near future, contrast-enhanced MRA with the use of gadolinium-based contrast agents will provide complete assessment of the systemic arterial tree, whereas noninvasive CT with intravenous injection of contrast medium may replace conventional diagnostic coronary angiography in part.12 However, contrast-enhanced molecular MRA, when added to regional high-resolution MRI (ie, coronary arteries), may provide additional information in plaque characterization.

Regional High-Resolution MRI for Plaque Characterization
MR differentiates plaque components on the basis of biophysical and biochemical parameters such as chemical composition, water content, physical state, molecular motion, or diffusion. Specifically, recent improvements in MR techniques (eg, black-blood MRI, faster imaging and detection coils), conducive to high-resolution and contrast imaging, have permitted the study of the various plaque components with multicontrast MR, generated by T1- and T2-weighted, proton-density-weighted, and time-of-flight imaging.11,12,15,16 Moreover, MR provides imaging without ionizing radiation and can be repeated over time.

MRI Studies of Carotid Artery Plaques
The superficial location and relative absence of motion of the carotid arteries allows excellent delineation of plaque by MR techniques (Figure 1). Thus far, MR studies have shown the characterization of normal and pathological arterial walls, the quantification of plaque size and therapeutic regression,17,18 and the detection of fibrous cap integrity, as well as disruption-related transient ischemic attack or stroke.19 Thus, it can be predicted that MRA, which demonstrates the severity and distribution of stenotic plaques, and high-resolution MRI, which characterizes such plaques, will eventually be combined.12

MRI Studies of Aortic Plaques
The principal challenges associated with high-resolution MRI of the thoracic aorta are that attainment of sufficient sensitivity for submillimeter imaging and the exclusion of artifacts caused by respiratory motion and blood flow. Matched MRI and transesophageal echocardiography cross-sectional aortic segments showed a strong correlation for plaque thickness, whereas MRI was the best contributor to plaque characterization and therapeutic regression (Figure 2).17,20 In a recent study of asymptomatic subjects, the Framingham Heart Study showed by MRI that aortic plaque prevalence and burden (ie, plaque volume/aortic volume) significantly increased with age and were higher in the abdominal aorta than in the thoracic aorta.21 Importantly, the Framingham Heart Study coronary risk score was strongly associated with asymptomatic aortic plaques as detected by...
MRI. Such an approach may turn out to be very valuable for identification, quantification, and the therapeutic management of plaque burden, particularly in asymptomatic individuals with a high risk factor profile.12

MRI Studies of Peripheral Arteries
High-resolution MR of the femoral and popliteal arteries and of the response to balloon angioplasty has been reported.22 The extent of the plaques could be defined such that even in angiographically normal segments of vessel, lesions with cross-sectional areas ranging from 49% to 76% of potential lumen area were identified. After angioplasty, plaque fissuring and local dissection were identified easily, and serial changes in lumen diameter, blood flow, and lesion size were documented. In the future, this technology, when combined with contrast-enhanced molecular MRA as discussed later, may be of great value for the postinterventional assessment of different therapeutic strategies such as new antithrombotic or antifibrotic drugs.

MRI Studies of Coronary Artery Plaques
With a combination of multicontrast MR imaging sequences, differentiation of fibrocellular, lipid-rich, and calcified regions of the atherosclerotic coronary plaque is feasible, as shown in an ex vivo study on human coronary arteries correlated to histopathology.23 Black-blood MR methods used in the human carotid artery and aorta have been applied to imaging of the coronary arterial lumen and wall. The method was validated in swine coronary lesions induced by balloon angioplasty.24 High-resolution black-blood MR of both normal and atherosclerotic human coronary arteries was performed for direct assessment of coronary wall thickness and the visualization of focal atherosclerotic plaque in the wall (Figure 3).25 To alleviate the need for breath holding, real-time navigator for respiratory gating and real-time slice-position correction have been reported.26 Near-isotropic spatial-resolution black-blood imaging may provide a quick way to image a long segment of the coronary artery wall and may be useful for rapid coronary plaque burden measurements.27 A crucial ultimate goal of cardiovascular noninvasive imaging is to have reliable technology for plaque characterization of the coronary arteries. Guided by contrast-enhanced CT, high-resolution MRI coupled with contrast-enhanced molecular MRA promises to fulfill this goal.

Contrast-Enhanced Molecular MRI for Plaque Characterization
An alternative approach to high-resolution MRI for plaque characterization is to image plaque through the introduction of contrast agents that are targeted to specific cells, molecules, or processes that can be precisely localized and quantified.15,28–31 Examples might include the following (Figure 4): adhesion molecules (vascular cell adhesion molecule-1, intercellular adhesion molecule, and selectins), macrophages within the context of apoptosis (phosphatidylserine and synaptotagmin), fibrous cap within the context of proteolysis (matrix metalloproteinases), lipid core (nonspecific lipophilic; Figure 5), angiogenesis (integrin αvβ3), and thrombosis (fibrin and integrin αIIbβ3).15,28–31 Targeted imaging agents are generally created by chemically attaching an affinity ligand, such as an antibody, peptide, or small molecule, to a magnetic compound, such as superparamagnetic particles of iron oxide or gadolinium chelates.15,28 Our expanding understanding of cellular and molecular events within atherosclerotic plaque has been accompanied by imaginative application of imaging tools, which has led to the new field of contrast-enhanced molecular MRI. Such molecular technology, when combined with high-resolution MRI, promises complementary structural and biological information and, therefore, more detailed plaque characterization. In addition, thinner slices, such as those obtained with 3D MR acquisition techniques, and other evolving MR technologies, such as water diffusion weighting, magnetization transfer weighting, and steady-state free-precession (SSFP) sequences, all promise to further improve artery wall structural and biological imaging.

Functional Vascular MRI
Noninvasive imaging techniques such as CT and MRA allow assessment of vascular anatomy but do not provide information about blood flow. For clinical purposes, flow information is important, because anatomy and function may not be directly related. Global coherent free precession (GCFP) is a new concept in MRI that can be used to produce images that depict vascular anatomy simultaneously with vascular function (blood flow).32 Protons in moving blood are “tagged” every few milliseconds as they travel through an arbitrary region in space. Simultaneous with tagging of new blood, previously tagged blood is maintained in the GCFP state, which allows acquisition of consecutive movie frames as the heart pushes blood through the vasculature. Body tissue surrounding the moving blood is
never excited and is invisible. With this approach, pulsating blood can be seen flowing through 3D space for distances of up to 16 cm (Figure 6). Although additional technical development will be required before the full potential of GCFP MRI can be recognized, the current data demonstrate that GCFP MRI can be used to produce cine angiograms that are remarkably similar to those produced by invasive X-ray angiography, but noninvasively and without the need for contrast agents or ionizing radiation.

Future Integration of Noninvasive Coronary CT and MRI

Today, 2 different modes of CT are available. One uses nonmechanical movement of the x-ray source (ie, electron-beam CT), and another involves the motion of the x-ray source and table, combined with multiple detectors to acquire the data in spiral or helical fashion (ie, multidetector-row CT [MDCT]). Although electron-beam CT has been considered the “gold standard” for the assessment of calcified plaques, MDCT usually includes an initial nonenhanced scan for the screening and quantification of coronary artery calcium followed by CT angiography for direct visualization of coronary artery disease. Results of a number of studies concerning the use of contrast-enhanced MDCT for noninvasive coronary angiography have been published. It appears that the diagnostic accuracy is reasonable (Table), but complete assessment can be hindered by calcium deposits in the vessel wall and by motion artifacts, particularly in patients with high heart rates. Two studies with 16-slice scanners have been reported recently, each with improved accuracy.
compared with reports with 4-slice scanners (Table). The next generation of MDCT scanners will almost certainly allow for even faster gantry rotation and simultaneous acquisition of 16 slices. The breath-hold time may decrease to 10 seconds, thus reducing the volume of contrast media needed for sufficient enhancement of the coronary arteries. Temporal and spatial resolution may further improve, ideally to 100 ms and 0.6-mm slice thickness. These enhancements may help in the detection, differentiation, and reliable quantification of calcified and noncalcified coronary artery plaques. Improvement of spatial resolution and new image-reconstruction algorithms should further reduce beam-hardening artifacts and partial volume effects caused by calcifications and improve the assessment of complex mixed plaques. Further optimization of multisegmental reconstruction algorithms may allow the investigation of patients with higher heart rates without any loss in image quality.

CT and MRI together may provide unique information, such as assessment of subclinical disease, the study of atherothrombotic progression, and response to therapy. CT may first be used to localize suspicious atherothrombotic lesions in the coronary arteries within a short scan time. MRA does the same in the systemic arteries but within a much longer scan time. High-resolution MRI and contrast-enhanced molecular MRI can then be used for structural and biological plaque characterization of the problem sites. Furthermore, the role of MRI in the in vivo monitoring of therapies can be pivotal for the better understanding of new pharmacological agents before clinical trials are undergone. It can also serve as a guide to assess the vascular wall response by individual patients to proven beneficial therapies.

The Myocardium

The purpose of this section is to highlight some of the recent technical advances in cardiac MR, and in particular, to focus on how these advances may affect the clinical assessment of patients. Rather than providing a comprehensive review of the literature, we will speculate on how these new techniques could be optimally used in clinical practice, currently and in the near future. Additionally, we will discuss how some recent findings by cardiac MR provide insights into cardiac pathophysiology.

Morphology and Function

MR provides arguably the best and most comprehensive approach to evaluating the structure and function of the heart. A number of techniques have been developed, including those that can render fat or flowing blood invisible, allow rapid imaging that is free of motion artifacts even during free breathing, and, with the addition of gadolinium contrast, provide information regarding tissue perfusion, necrosis, and fibrosis. The rapid pace of innovation, however, raises some issues that are perhaps more unique to MR than to the other imaging modalities. For instance, there is often a discrepancy between the newer techniques that are quickly adopted in clinical practice and those that are described in the published literature. This problem is compounded by the fact that new techniques in MR often include new relationships between image intensity and the underlying physiology rather than just the provision of improved signal-to-noise ratio or improved resolution. It is important to realize that concepts or algorithms associated with older techniques may not apply to the newer techniques.

Consider MR for the assessment of cardiac masses. This literature is extensive; however, the vast majority of the data, even those from recent publications, were acquired by early spin-echo techniques that have several limitations. They are slow (several minutes per image) and prone to motion artifacts due to free breathing during image acquisition, and they provide limited T1 weighting. Much of this literature involved attempts at tissue characterization by comparison of image intensities on T1-, T2-, and proton-density–weighted images. Differentiation between benign and malignant masses from image intensity features, however, was usually poor.

These older spin-echo techniques are no longer used in clinical practice. Instead, at present, a typical protocol for the evaluation of a cardiac mass would consist of the following: (1) 1 or more stacks of single-shot imaging that combines rapid (0.25 seconds/slice) image acquisition with comprehensive an-
atomic coverage to quickly delineate morphology (Figure 7a); (2) cine imaging to view motion during the cardiac cycle (Figure 7b); (3) first-pass perfusion imaging during the transit of an intravenous bolus of gadolinium contrast (Figure 7c); and (4) postcontrast delayed-enhancement imaging, which accentuates differences in contrast uptake between the mass and normal myocardium and between different regions of the mass (Figure 7d). Each of these steps consists of pulse sequences that have improved significantly, even in the last 2 to 3 years. For instance, delineation of morphology with black-blood HASTE (half Fourier single-shot turbo spin-echo)34 is currently of sufficient quality that segmented black-blood sequences, which require 8- to 10-second breath holds per slice, are used sparingly.

We expect that tissue characterization of cardiac masses will be improved substantially by the performance of first-pass perfusion and delayed-enhancement imaging (also see following sections for further description of these techniques). In particular, there will be excellent discrimination between cardiac thrombus and tumors. We speculate that these techniques will become the standard approach for the noninvasive assessment of cardiac masses. Several centers are currently investigating these strategies.

One of the most significant advances in MR has been the robust implementation of SSFP sequences. SSFP (also designated as TrueFISP, FIESTA, or balanced FFE) provides substantially higher signal-to-noise ratio than can be obtained by conventional gradient-echo techniques, along with excellent contrast between myocardium and blood35 (Figure 8). Implementations include single-shot 2D versions with or without prepulses to provide rapid snapshot images to delineate morphology, first-pass perfusion, or delayed enhancement; 3D sequences to provide angiogram-like views of the vasculature without the need for contrast media; and multiphase segmented 2D sequences to provide high-resolution cine images of the heart.35 The latter is currently the “gold standard” approach to assess ventricular volumes, mass, and function.

The accuracy and reproducibility of MR in assessing cardiac morphology and function leads to low interstudy variability in quantifying these parameters. This is tumb translates into significant reductions in sample sizes that are required to test the efficacy of therapeutic interventions on these parameters.36 It is expected that the number of drug and device trials that use cardiac MR parameters as study end points will increase substantially in the future. Ultimately, however, patient outcome is the relevant clinical issue.

Future effort should be directed toward testing whether changes in cardiac parameters as measured by MR indeed translate into differences in patient outcome.

### Infarction and Viability

Recently, numerous studies have demonstrated the effectiveness of a segmented inversion-recovery gradient-echo sequence after the intravenous administration of gadolinium contrast for detecting myocardial infarction (MI) and determining viability. This technique, termed delayed contrast-enhanced MRI (DE-MRI), was first described fewer than 5 years ago,39 but there is already consideration that “DE-MRI may well represent the new gold standard in the detection of irreversibly damaged myocardium.”38

The results in the literature with DE-MRI should not be grouped with the results with older MR techniques. A major limitation of the initial techniques was insufficient image contrast between normal and infarcted myocardium. DE-MRI, on the other hand, provides image intensity differences that are 10-fold greater.39 Suboptimal image quality was a major factor in leading to the erroneous conclusion that chronic infarcts do not hyperenhance and, conversely, the speculation that viable myocytes could exhibit hyperenhancement.

There is a wealth of data in animal models of ischemic injury that directly compares DE-MRI to histopathology.37,40,41 These data demonstrate that DE-MRI can delineate between reversible and irreversible myocardial injury independent of wall motion, infarct age, or reperfusion status. Human studies demonstrate that DE-MRI is effective in identifying the presence, location, and extent of MI in both the acute and chronic settings.39,42 Additionally, DE-MRI provides scar-size measurements that are closely correlated with positron emission tomography in patients with ischemic cardiomyopathy,43,44 provides results superior to single-photon emission computed tomography (SPECT) in patients with subendocardial infarctions,45 and can be used to predict reversible myocardial dysfunction in those undergoing revascularization procedures.44,46,47

A major advantage of DE-MRI is the high spatial resolution. With a standard implementation, a group of 10 hyperenhanced pixels (voxel, 1.93×1.43×6 mm) in a typical image would represent an infarction of 0.16 g, or a region one thousandth of the left ventricular myocardial mass.45 This level of resolution, more than 40-fold greater than SPECT, allows visualization of even microinfarcts that cannot be detected by other imaging techniques.48

Besides spatial resolution, DE-MRI is different from radionuclide imaging in that it provides direct visualization of both nonviable and viable myocardium. For instance, rather than simply identifying a region of acute infarction as nonviable because of reduced tracer activity, DE-MRI can distinguish between acute infarcts with necrotic myocytes and acute infarcts with necrotic myocytes and damaged microvasculature. The latter, termed the “no-reflow phenomenon,” indicates compromised tissue perfusion despite restoration of epicardial artery patency. The incidence and extent of early no-reflow appears to be associated with worse left ventricular remodeling and outcome. Although the initial MR studies of no-reflow used single-shot perfusion sequences 1 to 2 minutes after contrast injection,49 DE-MRI performed 5 to 10 minutes after contrast
provides higher image quality and delineates regions with more profound microvascular damage (Figure 9).\(^{50}\)

The ability to simultaneously visualize nonviable and viable myocardium provides additional advantages. For example, DE-MRI can accurately assess ventricular remodeling after acute MI at an early time point before measurements of ventricular volumes, internal dimensions, and ventricular mass have changed. This is possible because DE-MRI can assess serially, concurrent directionally opposite changes such as resorption of infarcted tissue and hypertrophy of viable myocardium.\(^{51}\)

When only viable myocardium can be visualized, 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 gender-specific database of controls. Conversely, when both viable and infarcted myocardium can be visualized, 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 the same segment (Figure 10a). These differences in the way in which viability is measured can alter clinical interpretation. Figure 10b demonstrates MR images in a patient with chronic coronary disease and an akinetic anterior wall. Although the anterior wall is thinned, only a small subendocardial portion of the anterior wall is infarcted. In this case, the indirect method would show that the anterior wall is only 39% viable (compared with the remote region), whereas the direct method would show that the anterior wall is 70% viable. The indirect method would predict no recovery of wall motion after revascularization, whereas the direct method would predict recovery. The postrevascularization images (bottom right of Figure 10b) demonstrate in this patient that the direct method is correct.

The ability of DE-MRI to directly visualize the transmural extent of infarction (and viability) has led to some recent observations that appear to refute certain traditional concepts regarding cardiac pathophysiology. For example, prior studies indicate that in patients with coronary disease and ventricular dysfunction, regions of thinned myocardium represent scar tissue and cannot improve in contractile function after coronary revascularization.\(^{52}\) The patient example in Figure 10, along with data from an ongoing pilot study,\(^{53}\) however, suggest that thinning should not be equated with the lack of viability and that in some patients, these regions can improve after revascularization.\(^{54}\) Likewise, it is commonly assumed that a threshold phenomenon exists between the transmural extent of infarction and systolic wall thickening. This assumption is based on results by Lieberman et al,\(^{55}\) who demonstrated in a dog model of acute infarction that akinesia or dyskinesia is expected if infarction involves \(\geq 20\%\) of the wall thickness. Evaluation by DE-MRI in humans, however, suggests that a threshold phenomenon does not exist.\(^{56}\)\(^{57}\) These data suggest that it is unwise to extrapolate the results of Lieberman et al,\(^{55}\) who did not consider the effects of stunning or ongoing ischemia, to humans with MI who may not have residual stunning, ischemia, or hibernation. Additional studies will be needed in these controversial topics.

### Ischemia

There are a variety of MR techniques that can be used to detect myocardial ischemia. Whereas coronary MRA can provide detail concerning anatomy, stress testing with imaging of myocardial contraction or perfusion can provide information concerning the presence and functional significance of coronary lesions. Dobutamine MR to detect ische-

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**Figure 9.** No-reflow phenomenon revealed by DE-MRI. Labels refer to time after administration of gadolinium contrast. Subendocardial black zone surrounded by hyperenhancement corresponds to region of no-reflow (arrow) within acute infarction. This region can be distinguished from normal myocardium because it is encompassed in 3D space by hyperenhanced myocardium or left ventricular cavity and by the fact that it slowly becomes hyperenhanced over time. Reprinted with permission from Kim et al.\(^{50}\)

**Figure 10.** 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 MR 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 mm = 70% viable), whereas indirect method would show that anterior wall is predominately nonviable (3.5/9 mm = 39% viable). Cine views after revascularization demonstrate recovery of wall motion and diastolic wall thickness. Full-motion movies can be viewed in the online-only Data Supplement (select Movie IV). Modified with permission from Kim et al.\(^{54}\)
mia-induced wall-motion abnormalities is an established technique for the diagnosis of coronary disease. It yields higher diagnostic accuracy than dobutamine echocardiography and can be effective in patients not suited for echocardiography because of poor acoustic windows. Since the publication of these studies, MR image quality has improved with the widespread availability of SSFP imaging. Parallel imaging techniques that use spatial information from arrays of radiofrequency detector coils to accelerate imaging are expected to improve image quality further. Nonetheless, logistic issues regarding patient safety and adequate monitoring are nontrivial matters that require thorough planning and experienced personnel.

Currently, stress perfusion MR is less established for clinical application. There are convincing data that correlate MR indexes of perfusion with tissue perfusion in animal models and excellent correlations with radionuclide imaging and invasive x-ray angiography in humans. However, the published data so far do not demonstrate the feasibility of stress perfusion MR for everyday clinical use. The current studies are limited in that they were either retrospective (for patient enrollment and data analysis), required central venous catheters, imaged only 1 to 2 slices per heartbeat, or excluded patients with diabetes. Additionally, most studies required extensive interactive postprocessing after data collection, which reduces the applicability of this technique for routine clinical diagnosis.

Despite these limitations, we speculate that stress perfusion MR will not only become a routine clinical procedure but also the dominant stress MR modality in the future. Perfusion MR is promising for a number of reasons. Decreased perfusion is the first step in the ischemic cascade. Techniques that assess perfusion have the potential to be more sensitive than techniques that assess later steps. Regarding logistics, stress perfusion imaging is quick and simple. For example, we perform adenosine stress imaging as follows. After cine imaging, the patient table is pulled out partially to allow full access to the patient; adenosine is stopped, and imaging is completed. The patient then can be pulled back out of the scanner bore if necessary. The total time of imaging for stress perfusion is 30 to 45 seconds, and the total time of adenosine infusion is <3 minutes.

The pulse sequences used for stress perfusion imaging are undergoing rapid evolution. SSFP and parallel imaging techniques continue to improve image quality. These improvements are expected to allow quick visual interpretation of the perfusion images for routine clinical diagnosis (Figure 11). Moreover, there is no reason to interpret the stress perfusion images in isolation. We expect that a multiprotocol approach with incorporation of cine and DE-MRI results with the perfusion findings will not only provide a comprehensive cardiac evaluation but also improve the accuracy of MR for the detection of coronary disease. On this point, it should be noted that perfusion imaging is quite demanding in terms of scanner hardware. Images are acquired in ~100 ms rather than built up over several cardiac cycles, which is the case for conventional cine and DE-MRI imaging. Thus, the signal-to-noise ratio is substantially lower for perfusion imaging, and even with the latest improvements, artifacts can obscure diagnosis. One of our current strategies to improve the accuracy of MR for the detection of coronary disease is to incorporate rest perfusion (performed 15 minutes after stress perfusion) and DE-MRI findings with the stress perfusion results in a proscribed manner. This algorithmic approach (Figure 12) is based on the assumption that DE-MRI is the most sensitive and specific MR technique for the detection of MI and that hyperenhancement patterns on DE-MRI can be accurately classified as ischemic or nonischemic. Conceptually, it then follows that perfusion defects that have similar intensity and extent during both stress and rest (“fixed defect”) but do not have hyperenhancement (no infarct) are artifactual and should not be considered as caused by coronary disease.

This approach needs to be tested in large prospective clinical trials. We anticipate that clinical MR examinations will become increasingly comprehensive (eg, coronary MRA, cine imaging,
stress and rest perfusion, and DE-MRI) in the near future. We foresee that effort will be needed not only to improve the imaging technology but to categorize and understand the discordant results that may occur among the different MR protocols for a given patient.

Summary
Cardiovascular MR encompasses a variety of different techniques that provide a comprehensive evaluation of the range of cardiovascular disorders. Atherothrombosis throughout the vascular system can be directly imaged, quantified, and characterized according to plaque components. By providing information about vascular blood flow concurrent with vascular anatomy, the functional significance of stenotic lesions can be determined. The morphology and function of the cardiac system can be viewed in exquisite detail that rivals any other imaging modality. Pathophysiological processes such as MI and ischemia, stunning and hibernation, and scarring and fibrosis can be identified easily using quick and simple protocols. Published studies, however, describe a variety of different pulse sequences and protocols for similar imaging purposes and consist of relatively small numbers of patients. The goals of future investigation will be to refine the technology, establish standard protocols for image acquisition and interpretation, address the issue of cost-effectiveness, and validate a range of clinical applications in large-scale clinical trials.

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