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The cardiac magnetic resonance (CMR) approach to assessing myocardial viability

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Abstract

Cardiac magnetic resonance (CMR) is a noninvasive imaging method that can determine myocardial anatomy, function, perfusion, and viability in a relative short examination. In terms of viability assessment, CMR can determine viability in a non-contrast enhanced scan using dobutamine stress following protocols comparable to those developed for dobutamine echocardiography. CMR can also determine viability with late gadolinium enhancement (LGE) methods. The gadolinium-based contrast agents used for LGE differentiate viable myocardium from scar on the basis of differences in cell membrane integrity for acute myocardial infarction. In chronic myocardial infarction, the scarred tissue enhances much more than normal myocardium due to increases in extracellular volume. LGE is well validated in pre-clinical and clinical studies that now span from almost a cellular level in animals to human validations in a large international multicenter clinical trial. Beyond infarct size or infarct detection, LGE is a strong predictor of mortality and adverse cardiac events. CMR can also image microvascular obstruction and intracardiac thrombus. When combined with a measure of area at risk like T2-weighted images, CMR can determine infarct size, area at risk, and thus estimate myocardial salvage 1–7 days after acute myocardial infarction. Thus, CMR is a well validated technique that can assess viability by gadolinium-free dobutamine stress testing or late gadolinium enhancement.

INTRODUCTION

A number of methods are now clinically available for assessing myocardial viability and there is overlap in the pathophysiological mechanisms that enable each of these diagnostic findings (Figure 1). Single photon emission computed tomography (SPECT) detects viability by imaging a combination of myocardial metabolism and perfusion. ^{201}Thallium, ^{99m}Tc-sestamibi, and ^{99m}Tc-tetrofosmin are SPECT radiotracers that can be used to assess viability. ^{18}F-fluorodeoxyglucose combined with a perfusion agent such as ^{13}N-ammonia can assess metabolism, perfusion, and viability by positron emission tomography (PET). Dobutamine stress echocardiography and dobutamine stress MRI detect viability of dysfunctional myocardium on the basis of augmentation of contractility or a biphasic response to low and higher dose dobutamine. Echocardiographic bubble contrast agents represent a relatively pure intravascular perfusion assessment so do not assess myocardial viability or cell membrane integrity per se. Catheter-based

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endocardial electrocardiogram mapping can detect viability and some of the initial descriptions of inotropic reserve came from invasive ventriculography.

Cardiac magnetic resonance imaging (CMR) can characterize viability using low-dose dobutamine stress and CMR can also determine viability with late gadolinium enhancement (LGE). Iodinated contrast agents can delineate infarcted myocardium by x-ray computed tomography (CT) in ways that are analogous to LGE imaging. Gadolinium and iodinated contrast agents enhance fibrotic tissue by similar mechanisms since they distribute throughout the interstitial space. Thus, all of the major cardiac imaging methods can be used to determine myocardial viability. Considering the readership of this journal, the purpose of this review will be to focus on how CMR can be used to image myocardial viability.

LOW-DOSE DOBUTAMINE STRESS MRI TO ASSESS MYOCARDIAL VIABILITY

Although many physicians think about gadolinium enhanced CMR as a method for assessing viability, dobutamine stress CMR was the first validated method. The very concept of hibernating myocardium originated in the early days of bypass surgery when it was noticed that some patients with left ventricular dysfunction had substantial improvement of left ventricular function after revascularization.[1,2] The concept of hibernating myocardium was crystallized out of this observation of reversible, ischemic left ventricular dysfunction.[3] Many aspects of the pathophysiology of hibernating myocardium were described by 1986 and recovery of global or regional function became a central tenet in the entity.[4] The concept that hibernating myocardium showed a “biphasic response” characterized by an improvement in regional function during low-dose dobutamine infusions but ischemic deterioration at high doses of dobutamine.[5] This biphasic response has become an important refinement in the non-invasive diagnosis of the hibernating myocardium.

Dobutamine stress CMR is performed following doses and imaging protocols that are comparable to dobutamine stress echocardiography.[6] After baseline imaging, graded doses of dobutamine are infused and left ventricular function is imaged at each stage. A low-dose dobutamine stress test typically looks for improvement of regional wall motion abnormalities with a submaximal dose of the catecholamine. Some groups use low and high doses of dobutamine to have the specificity of the biphasic response as an indicator of hibernating myocardium. Most clinicians would use either type of response as a sign of viability to maximize sensitivity of the test.

Dobutamine stress CMR is accurate for detecting significant coronary artery stenosis[7–9] and for characterizing hibernating myocardium. Baer et al published a series of studies exploring the feasibility and accuracy of dobutamine stress CMR as a non-invasive test of myocardial viability. In comparisons of dobutamine stress CMR and ^{18}F-deoxyglucose PET, dobutamine induced wall thickening was a better predictor of residual metabolic activity than end diastolic wall thickness but grading a segment as viable if at least one of both CMR parameters fulfilled viability criteria improved the sensitivity of CMR to 88% for ^{18}F-deoxyglucose PET assessed metabolic activity without adversely affecting specificity (87%) or positive predictive accuracy (92%).[10] Dobutamine stress CMR and dobutamine stress echocardiography had similar diagnostic accuracy for viable myocardium relative to ^{18}F-deoxyglucose PET.[11] Dobutamine stress CMR predicted recovery of function after revascularization in patients with chronic regional wall motion abnormalities.[12] In a head-to-head comparison of dobutamine stress transesophageal echocardiography and dobutamine stress CMR for predicting functional recovery of hibernating myocardium with a reference standard that included successful revascularization of the ischemic territory, both tests were highly accurate.[13]

Thus, dobutamine stress CMR can be used to characterize the likelihood of functional recovery of regional wall motion abnormalities in patients with ischemic heart disease. One particular advantage of this method is that gadolinium contrast is not needed so the method can be used in patients with severe kidney disease. There is some evidence that dobutamine stress MRI is a better predictor of functional recovery than late gadolinium enhancement (LGE).[14] The discrepancies in predicting recovery of function may represent analogous differences between dobutamine echo and SPECT mechanisms of assessing viability as described by Arrighi and Dilsizian.[15] The use of regional wall thickening as the reference standard for assessing viability may also introduce a bias favoring dobutamine wall motion tests to assess viability. Not withstanding of these issues, dobutamine is a powerful method for enabling viability assessment by CMR.

PATHOPHYSIOLOGICAL BASIS OF LATE GADOLINIUM ENHANCEMENT

Late gadolinium enhancement has become the most widely used way of assessing viability by MRI. It has been known since 1984 that gadolinium enhances infarcted myocardium.[16] However, it took a new generation of imaging methods[17] and extensive validations to prove that LGE accurately depicts myocardial infarction.

There are important temporal aspects of gadolinium enhancement of the heart that led to the descriptive title late gadolinium enhancement (LGE). Simplistically, one can dissect the time after a bolus injection of gadolinium into three physiologically distinct time periods (Figure 2). First pass perfusion occurs within about 20 seconds of the arrival of the contrast in the heart after an intravenous injection. Perfusion can be quantified from images obtained in this earliest time period.[18] Early gadolinium enhancement (EGE) represents a period between about 1 minute and 8 minutes after injection of gadolinium. Images obtained in the EGE time period are still sensitive to severe perfusion defects such as microvascular obstruction after acute myocardial infarction.

The exact timing of what qualifies for late gadolinium enhancement is still being defined but most clinicians in 2011 have considered the time period between about 8 and 30 minutes after injection of contrast a suitable time period for LGE imaging. The key requirement is that the distribution of gadolinium into the interstitial space and blood volume are in a reasonable approximation of a steady state. Factors such as microvascular obstruction delay arrival of contrast and can leave dark patches within the core of an infarct that persist for more than 10 minutes and thus strictly speaking violate this principle but practically can simply be interpreted as a part of the infarct despite a lower signal intensity than the rest of the infarct.

In general, late gadolinium enhancement is imaged with a technique called inversion recovery. The result is an image where the technologist has adjusted the scan parameters in a way to null the normal myocardium which means the normal myocardium appears uniformly dark. Under such conditions, the infarct is brighter than normal myocardium and readily visible (Figures 2, 3).

The distribution of gadolinium-based contrast in tissue defines viability and fibrosis (Figure 3). Since most of the gadolinium-based contrast agents approved by the Food and Drug Administration are classified as extracellular agents, they rapidly enter the interstitial space after an intravenous injection but are excluded from the intracellular space by the cell membrane. Thus, gadolinium enhances normal myocardium slightly based on the size of the extracellular volume fraction which is about 25% of the tissue. Acutely infarcted myocardium enhances to a greater extent than normal myocardium since ruptured cell membranes allow gadolinium into the intracellular space of infarcted cardiomyocytes. Chronically infarcted myocardium enhances collagenous scar since that tissue has a

relatively small intracellular space and large effective extracellular volume fraction (Figure 4).

VALIDATION OF LATE GADOLINIUM ENHANCEMENT AND COMPARISONS TO SPECT OR PET

The spatial extent and localization of late gadolinium enhancement corresponds closely to the location of infarcted myocardium as determined by triphenol tetrazolium chloride (TTC) histopathology.[19] Importantly, the correlations between LGE and TTC were strong and showed almost no bias on day 1, day 3 and at 8 weeks after acute myocardial infarction in a canine model. Electron probe x-ray microanalysis showed at about a mm scale that gadolinium concentration was high in infarcted myocardium and much lower in normal myocardium.[20] Furthermore, careful analysis of LGE images showed that gadolinium was elevated primarily in the infarct and not in the area at risk or remote myocardium.[21] The spatial correlation between gadolinium enhancement and fibrosis has now been validated almost to a cellular level.[22]

The high resolution of late gadolinium enhancement translates to increased sensitivity for detection and diagnosis of infarction. For example, CMR allows detection of microinfarcts associated with side branch occlusion and embolization down stream from percutaneous interventions in patients with elevated biomarkers.[23,24] Infarcts that small were not previously detectable in patients. CMR is more sensitive to subendocardial infarcts than SPECT in head-to-head studies of animal models and in people.[25] In patients with acute myocardial infarction, infarct size as measured by CMR and SPECT correlated but SPECT had 80% sensitivity compared to CMR which had a sensitivity of 100%.[26] SPECT missed a significant percent of infarcts in a right coronary or circumflex coronary artery distribution,[26,27] a problem potentially related to lack of attenuation correction. Similarly PET and CMR measures of infarct size also correlate but Klein et al concluded that PET did not detect 55% of segments with subendocardial infarcts. CMR can also detect right ventricular infarction.[28] In practical experience, many patients with small infarcts may go undetected or described as a false positive biomarker study if studied with low resolution techniques while in fact the patient actually has minimal coronary artery disease and simply a very small myocardial infarction. Late gadolinium enhancement imaging has now been validated at the multicenter clinical trial level.[29]

PREDICTING RECOVERY OF HIBERNATING MYOCARDIUM AFTER REVASCULARIZATION

Clinical validation studies confirm that LGE images can determine myocardial viability and predict recovery of function after revascularization. The first clinical study showed that the transmural extent of infarction predicted the likelihood of functional recovery after revascularization.[30] That study was strong evidence that the increased resolution of MRI viability assessment had unique clinical impact at that time. The study results were confirmed by Selvanayagam et al.[31] Late gadolinium enhancement can also predict recovery of function downstream from chronic total occlusions.[32]

Thus, the transmural extent of late gadolinium enhancement is an index of viability in the setting of chronic ischemic heart disease. At the same time, the graded relationship between transmural extent of infarction and functional recovery means that it is difficult to predict what will happen to segments with intermediate extent of infarction. In those situations, one might consider a low dose dobutamine study to better clarify the likelihood of functional recovery. Since perfusion, function, and viability can be imaged in a single CMR examination, it may be helpful to use rest perfusion imaging to help determine whether

hibernating myocardium is supplied by severely stenotic artery.[33] One should recognize that abnormal rest perfusion findings can be relatively subtle and may require careful quantitative analysis to detect.

Realistically, the patient with clinically relevant questions regarding viability often undergoes multimodality testing. In cases where FDG PET and CMR late gadolinium enhancement have been performed, it may be useful to fuse these images for diagnostic purposes. Both FDG and late gadolinium enhancement are highly sensitive tests—FDG for residual viability and late gadolinium enhancement for scar. The combination of FDG and late gadolinium enhancement may identify viable myocardium near or adjacent to scar.

VALIDATION OF LATE GADOLINIUM ENHANCEMENT IN THE SETTING OF ACUTE MYOCARDIAL INFARCTION

Late gadolinium enhancement has also been validated in the setting of acute myocardial infarction. Infarct size correlated with biomarkers and predicted recovery of function in patients imaged 1–7 days after the acute event.[34–37] Late gadolinium enhancement is a better predictor of functional recovery after acute MI than CMR perfusion images.[36,38] The multi-center clinical trial included 282 patients studied within 16 days of acute myocardial infarction.[29] The sensitivity for detecting acute myocardial infarction was 99% at the highest dose of gadoversetamide (0.3 mmol/kg). The accuracy for determining infarct related artery, as determined by coronary angiography, was also 99% at the highest dose studied. Beyond detection of infarction and infarct sizing, early gadolinium enhancement can detect microvascular obstruction. Coupled with a CMR measure of area at risk, late gadolinium enhancement after acute myocardial infarction can allow determination myocardial salvage. These later two applications are discussed in later portions of this manuscript.

PROGNOSIS OF SCAR/FIBROSIS IMAGING

Several papers have shown that late gadolinium enhancement of the myocardium is associated with adverse clinical outcomes. Kwong et al[39] found that late gadolinium enhancement found in patients without know myocardial infarction had incremental prognostic value beyond clinical predictors, angiographically significant coronary stenosis, and left ventricular size or function. Roes et al[40] also found that late gadolinium enhancement discriminated outcomes better than left ventricular size or ejection fraction. Silent myocardial infarctions in diabetic subjects are associated with adverse events and increased mortality.[41] Other portions of the CMR exam provide additional prognostic value beyond late gadolinium enhancement such as the presence of reversible perfusion defects. Overall, late gadolinium enhancement, as a noninvasive image of myocardial scar or infarct, is a strong predictor of mortality and adverse outcomes.

OTHER CLINICALLY RELEVANT FINDINGS BY GADOLINIUM ENHANCEMENT

Beyond detecting infarction, gadolinium enhanced CMR turns out to be useful for a wide range of other conditions. For example, CMR is sensitive (88%) and highly specific (99%) for detecting intracardiac thrombus in a retrospective study of 361 patients with surgical or pathological confirmation of the presence or absence of left ventricular thrombus.[42] In that study, trans-esophageal echocardiography had a sensitivity of 40% and transthoracic echocardiography had a sensitivity of 27% while both ultrasound methods had a specificity of 96%. In particular, laminated thrombus in the atria or in left ventricular wall motion abnormalities are easier to detect on gadolinium enhanced CMR than other methods.[43]

Microvascular obstruction is frequently observed after acute myocardial infarction and has prognostic significance. Microvascular obstruction represents a residual myocardial perfusion abnormality despite an open epicardial coronary artery. In many respects, microvascular obstruction represents a severe injury. An early report by Wu et al[44] found that the presence of microvascular obstruction, as detected by CMR perfusion images, portended poor prognosis in survivors of acute myocardial infarction. Other studies also confirm the adverse prognostic significance of microvascular obstruction even though it may represent a very small percent of the left ventricular myocardium.[45] It seems that microvascular obstruction is a marker of more severe injury since it appears associated with longer ischemic times than even extensive late gadolinium enhancement.[46] Considering microvascular obstruction is relatively easy to image by CMR, this assessment should be considered a standard part of viability assessment in patients with acute myocardial infarction.

CMR can now determine ischemic area at risk and infarct size in a single examination 1–7 days after acute myocardial infarction. The difference between these measures allows determination of myocardial salvage. T2-weighted CMR helps visualize the area at risk as a hyperintense portion of myocardium relative to normal myocardium.[47] This zone represents myocardial edema which starts to form during the coronary occlusion.[48] The T2 abnormality is also present in non-reperfused infarcts.[49] T2-weighted CMR can differentiate acute from chronic myocardial infarction.[50] The T2 abnormality corresponds to the area at risk in patients[51] and correlates with SPECT estimates of area at risk.[52] The CMR estimates of area at risk also correlate with coronary angiographic estimates of area at risk and the measured myocardial salvage appropriately varies with time to reperfusion and TIMI flow post-intervention.[53]

Much is still to be learned about the prognostic value of late gadolinium enhancement. For example, a larger than median sized gadolinium enhanced border zone around infarcts is associated with increased mortality.[54] The morphology of the scar may also be a predictor of arrhythmia risk.[55]

ADVANTAGES AND DISADVANTAGES OF USING MRI TO ASSESS MYOCARDIAL VIABILITY

Despite the many advantages of using MRI to assess viability, there are also a number of disadvantages to the technology consider (Table 1). Although there is now one pacemaker is deemed conditionally safe for MRI by the Food and Drug Administration (FDA) that approval does not extend to the chest. Similarly, gadolinium-based contrast agents are not approved by the FDA for the heart as of mid-2011. Gadolinium is relatively contraindicated in patients with severe kidney disease due to the risk of developing nephrogenic systemic fibrosis. In patients that cannot receive gadolinium, dobutamine stress CMR should be considered. MRI is an expensive technology but this is partially mitigated by the fact that alternative methods for assessing viability are also expensive. Obesity and claustrophobia can limit which patients can be studied by MRI. In addition, arrhythmias can reduce image quality since the best CMR images are formed by combining several different heart beats into one better quality image. Nonetheless, there are real-time imaging methods that are good enough to characterize infarct size and detect intracardiac thrombus missed by echocardiography (see supplementary online case).

In summary, CMR is a powerful technique for assessing viability. The strengths of the technique relate to the high resolution and quality information that can be obtained. The ability assess function, perfusion, viability, and intracardiac thrombus is a highly useful set of clinical data. The technique depends on magnetic fields and radiofrequency transmissions

so do not involve ionizing radiation. The viability methods have now been validated from almost a cellular level up through multicenter clinical trials. Furthermore, CMR is now able to routinely assess microvascular obstruction and area at risk so is a particularly promising modality for assessment of viability early after acute myocardial infarction.

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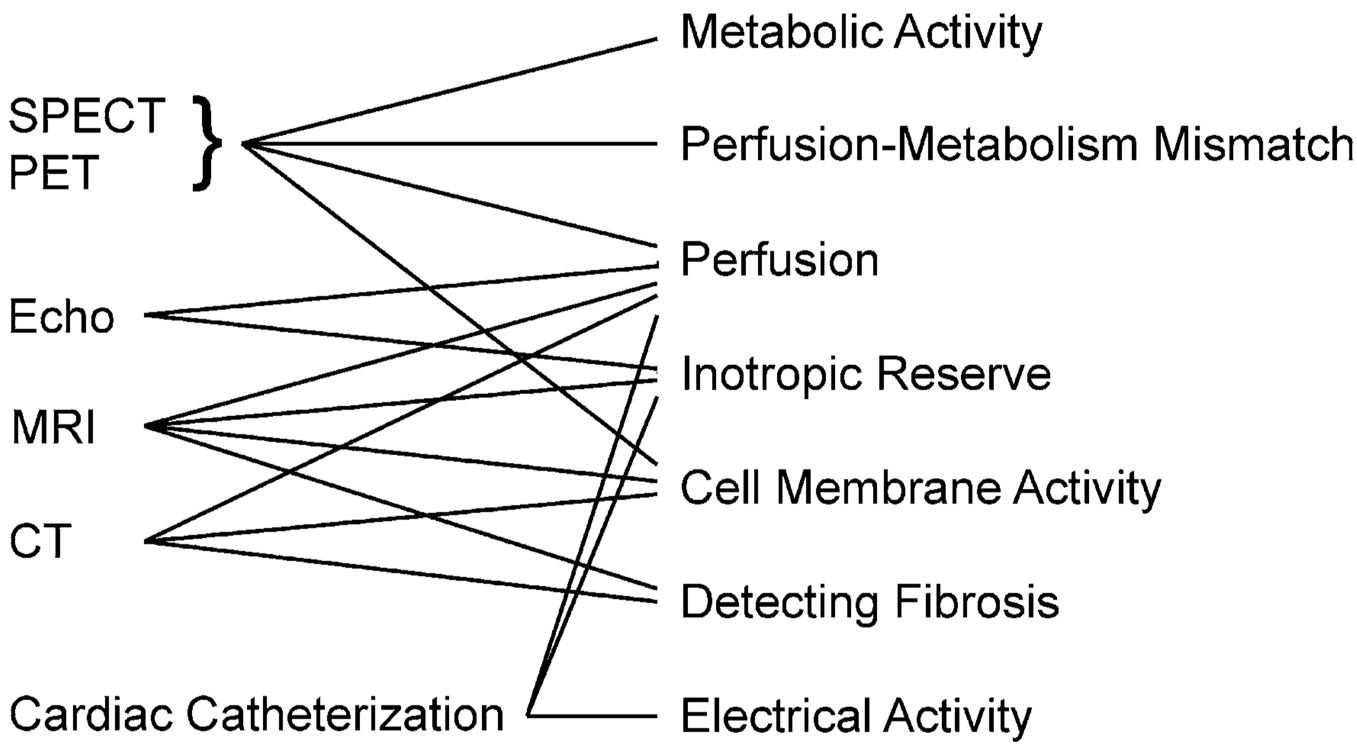

Figure 1.
Methods available for assessing myocardial viability.

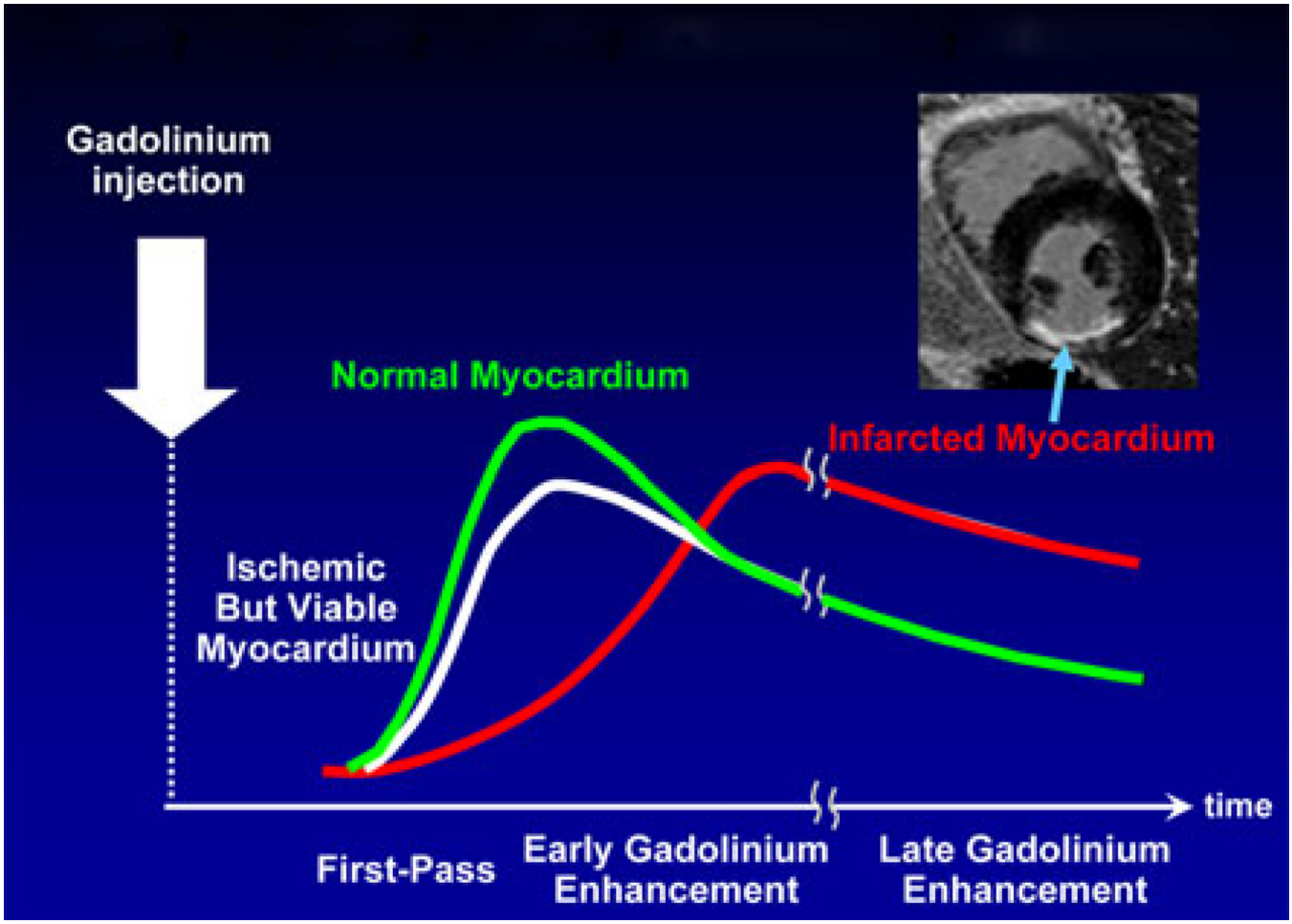

Figure 2.
Temporal aspects of late gadolinium enhancement.

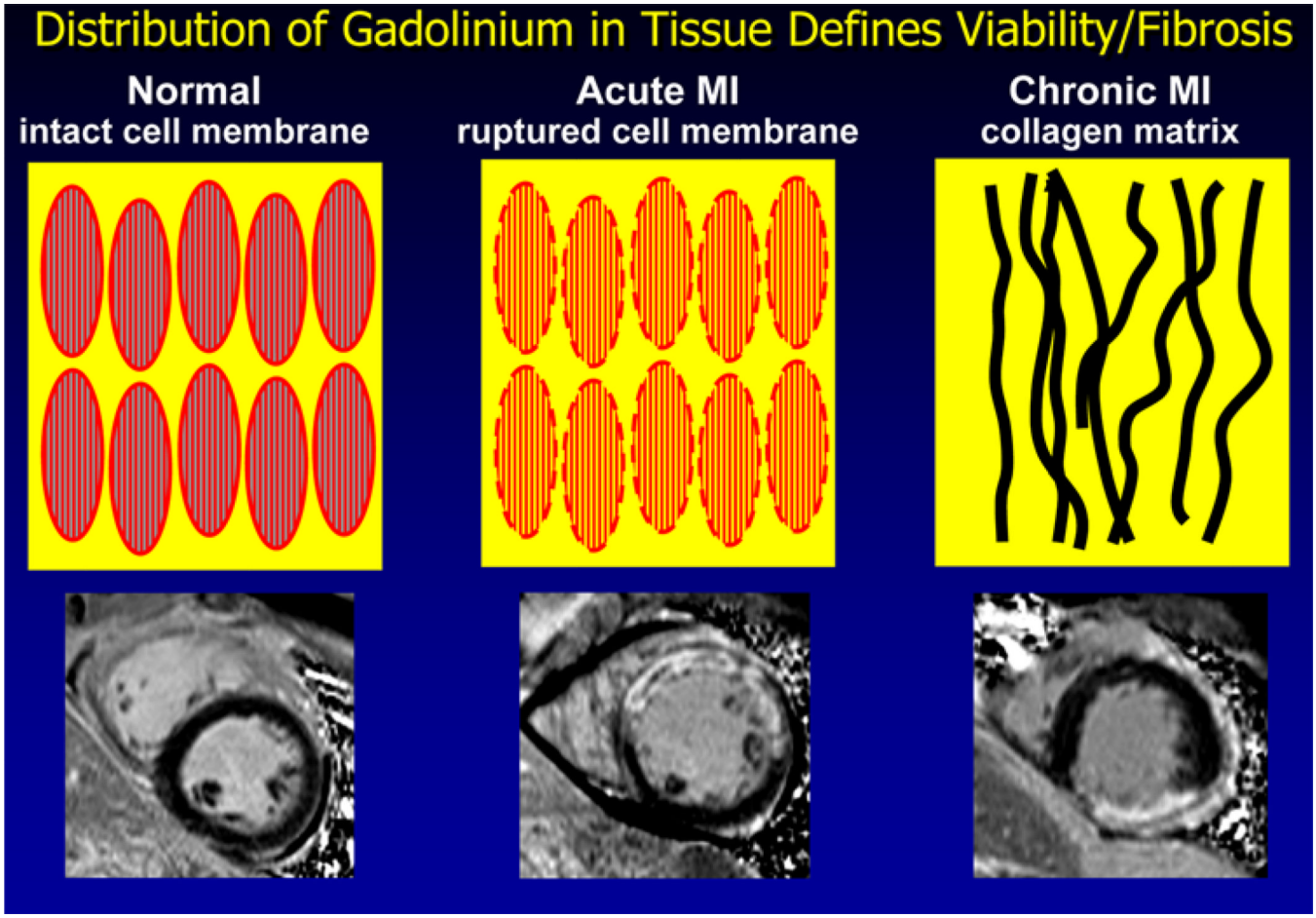

Figure 3.
The volume of distribution or extracellular volume fraction differentiates normal myocardium from acutely infarcted myocardium and chronically infarcted or fibrotic myocardium. See text for more detailed description.

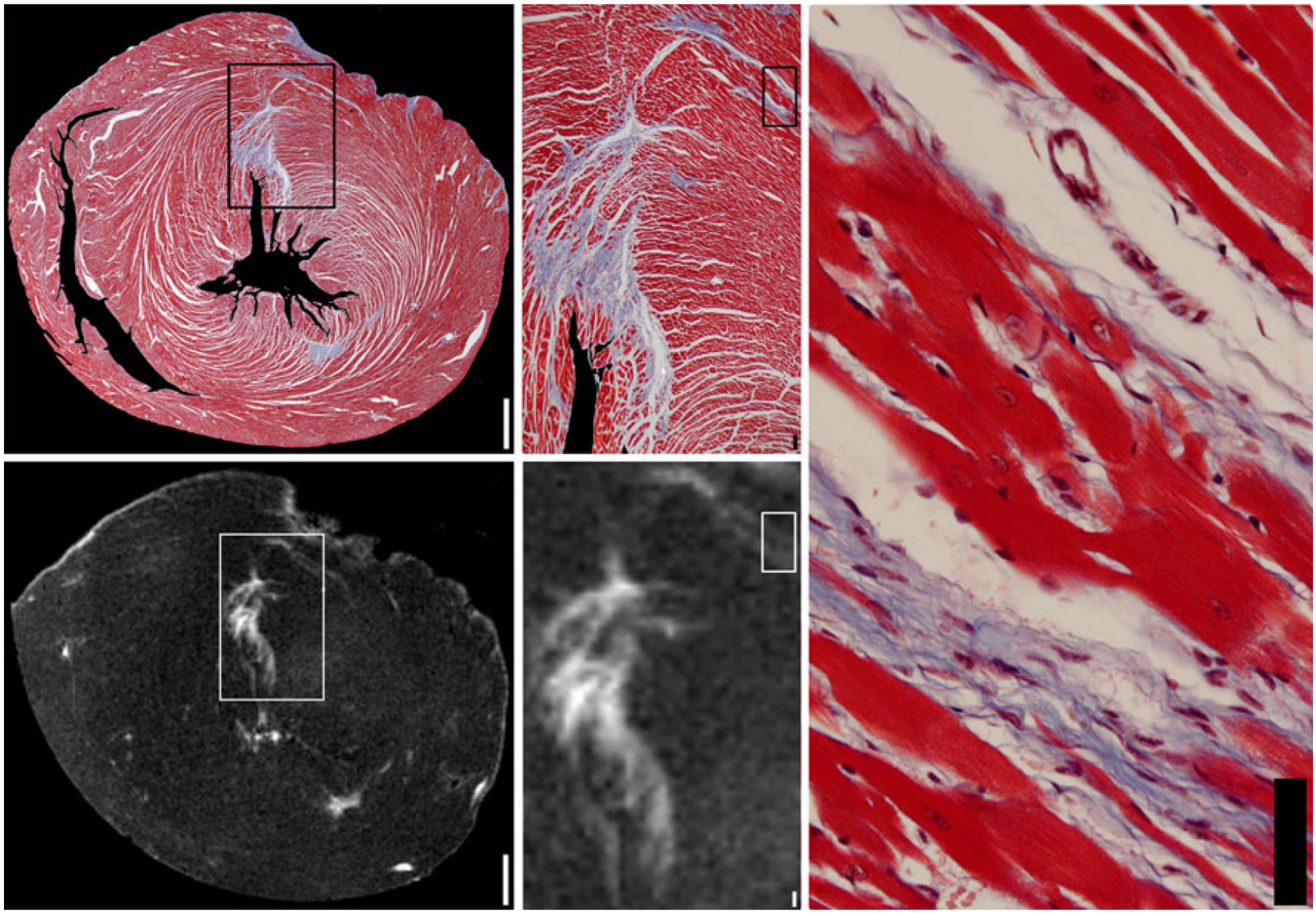

Figure 4.
Late gadolinium enhancement defines viability and fibrosis at nearly a cellular resolution. Permission to reproduce this figure was approved by circulation cardiovascular imaging[22].

Table 1

Advantages and disadvantages of using MRI to assess myocardial viability

Advantages	Disadvantages
High quality and high resolution assessment of viability	Contraindications include pacemakers, defibrillators, and many other devices
Multidimensional exam (function, perfusion, viability, thrombus)	Gadolinium is relatively contraindicated for eGFR <30 mL/min/1.73 BSA
Gadolinium no stress option vs dobutamine	Expensive
No ionizing radiation	Obesity
Validated from a cellular level up to multicenter trials	Arrhythmias
Can assess viability, area at risk, and myocardial salvage after acute MI	Claustrophobia