Viability assessment with MRI is superior to FDG-PET for viability: Con

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INTRODUCTION

Why debate modalities to assess myocardial viability? A debate is only a device to emphasize pros and cons of each modality. Any debate should be based on certain mutually accepted principles about the issue in question. There is general agreement, for example, that the goals of cardiovascular imaging are to determine the best testing strategy to answer a particular clinical question for an individual patient, while minimizing risks and costs. Optimal cardiac imaging practice should include several steps. After the referring physician orders a test, the goal of an ''imaging service'' should be to confirm that the test is appropriate, confirm the necessary pre-certification by insurance companies, perform the test safely and promptly, assuring the best possible experience for the patient, provide a prompt report that answers the clinical questions—as unambiguously as possible, while minimizing need for the referring physician to negotiate with insurance companies or with the patient regarding details of test procedure. In order to avoid canceling tests at the last minute, it is important to resolve the following issues, before the test: pacemaker/ICD, or renal insufficiency, claustrophobia and pre-certification of insurance coverage.

WHY ASSESS MYOCARDIAL VIABILITY?

In this era of healthcare reform and the need to reduce costs, it can be argued that it is more important than ever to perform myocardial viability evaluation before coronary artery bypass surgery (CABG) or percutaneous coronary intervention (PCI), whether health care reform is driven by quality of care (hopefully)[1-8] or by narrower attempts to decrease costs.[9] Both magnetic resonance imaging (MRI) and positron emission tomography (PET) are expensive, but either of these tests should be viewed as a ''gateway procedure,'' to help decide whether to undertake the risks and benefits of revascularization. A focus on quality of care for our patients requires physicians to obtain enough information to estimate the risks and benefits of the proposed procedure for that individual patient.[10] Despite the initial expense, these imaging procedures are likely to contribute less to the total expense than could the potential costs (''downstream expenses'')[7,9] of either an unnecessary revascularization procedure or of an unfavorable clinical outcome including prolonged stays in the intensive care unit and/or a rehabilitation hospital. In other words, these tests help fulfill part of the Hippocratic Oath: ''First, do no harm.'' Although there are likely to be differences between the two tests, it is difficult to calculate the cost-effectiveness of viability tests due to the many highly uncertain clinical variables that contribute to ''indirect costs.''[4,7,9] It is most important to emphasize the potentially large gains in safety, quality of care and cost-effectiveness that can be achieved by performing some reliable test to assess myocardial viability before a revascularization procedure.[4,7,9]

Patients with a large left ventricle (LV) and poor LV function have greater risk, less favorable clinical outcomes, and less benefit related to CABG or PCI—but there are numerous exceptions.[1,3,5,6,11,12] It is crucial—but difficult—to determine which patients with congestive heart failure (CHF) are most likely to respond well to revascularization. One major issue for these patients is whether the myocardium dependent on potentially revascularizable artery offers a suitable ''target tissue'' for CABG or PCI. Prior basic science work in coronary physiology[13] and experimental myocardial ischemia and infarction[3,14-18] has helped provide the background information and set the agenda for clinical assessment of myocardial viability Figure 1, which is modified from Kirk et al[17] diagrams differing results on a segment of

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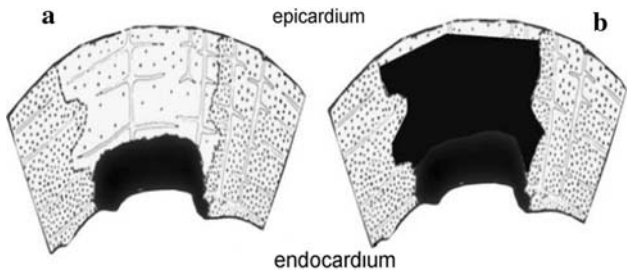

Figure 1. Diagrams of two hearts after occlusion of the LAD coronary artery to create myocardial infarctions (MI) that extend over a variable transmural thickness of the region at risk due to LAD occlusion. Density of ''speckling'' is proportional to blood flow, indicated by microsphere-tracers. **A**. The figure on the *left* shows non-viable MI (*black area*) involving about 25% of the LV wall thickness, with considerable viable myocardium in the overlying subepicardium. **B**. The figure on the *right* shows MI (*black area*) involving >75% of the LV wall thickness with a correspondingly small amount of viable myocardium in the subepicardium, overlying the MI. Figure is modified from Kirk et al[17].

myocardium after occlusion of the supplying (LAD) coronary artery. Density of speckling in Figure 1 reflects amount of blood flow to the myocardial segment. In Figure 1A, there is subendocardial MI (black area) with a considerable amount of jeopardized but viable myocardium in the subepicardium, overlying the MI. Such an anatomical/physiological substrate visualized in vivo would be expected to show the following results on imaging studies: on contrast enhanced MRI, the infarct would be contrast enhanced and the jeopardized but viable myocardium would be black (as the signal is nulled to the viable myocardium); on PET, the two dimensional representation of the segment would show a Rb-82 perfusion defect, but with increased FDG uptake due to increased anaerobic metabolism in the overlying viable but jeopardized myocardium. This segment would demonstrate the classic PET Rb-82/FDG mismatch (see Figure 3). Revascularization of the infarct-related LAD artery (IRA) would be expected to cause substantial recovery, with improved regional contraction in the ''target tissue,'' dependent on the IRA.

In Figure 1B, there is near-transmural MI (black) with very little jeopardized but viable overlying myocardium. Such an anatomical/physiological substrate visualized in vivo would be expected to show the following results on imaging studies: on ce-MRI, the contrast enhanced infarct would be near-transmural; on PET, the two dimensional representation of the segment would be a severe Rb-82 perfusion defect, with a matching severe FDG defect. This segment of predominantly non-viable myocardium, would demonstrate the classic PET Rb-82/FDG matching defects (see Figure 2). Revascularization of the IRA would be very unlikely to cause recovery or improved regional contraction in the ''target tissue,'' dependent on the IRA.

Because irreversibly injured, non-viable myocardium is dead and will not recover normal function even if arterial flow is restored,[17] the first question for the clinician, then is how much myocardium is viable? Or ''Is the horse already out of the barn?'' Imaging modalities must ''see'' a signal that is strongly related to either the viable myocardium as with FDG for PET[19-25] (see Figures 2 and 3), or both the viable myocardium and the non-viable scar [Gd-contrast for contrast-enhanced MRI[26-31]] (see Figure 4). Viable myocardium is located primarily in the subepicardium, overlying the non-viable infarction located below, in the subendocardium.[15,32] This asymmetric location of viable myocardium (illustrated in Figure 1) poses special problems for imaging, because it is located above the nonviable infracted tissue in the subendocardium, and the spatial resolution of most imaging modalities will visualize a mixture of tissue types[6,25] (see Figure 1). If there is ample viable myocardium, then the risk of revascularization appears to be lower, even in patients with poor LV function.[4-7,11,12,33,34] This discussion considers only PET performed with both a perfusion study and the FDG, and not PET FDG performed without a perfusion study or with a single photon emission computed tomography (SPECT) perfusion study. Also, we are not considering SPECT-FDG, because these procedures are subject to variable artifacts due to attenuation[35] which degrade the images. We have certainly seen patients who had this combination of findings, referred to consider CABG, with a normal PET FDG in the same region as a defect on SPECT, that was actually due to attenuation artifact. We will also not consider PET analysis of the washout of Rb-82 at rest,[36] because we found that this index did not correlate with the better-validated indicator of viability, the mismatch between

FDG and Rb-82.[37] With these considerations in mind, the remainder of this review will emphasize the advantages of PET over MRI for assessment of myocardial viability.

MRI COMPARED TO PET TO IMAGE VIABLE MYOCARDIUM

The excellent in-plane spatial resolution of MRI (1.5-2.0 mm, in the *x*-*y* plane), on slices that are 8-10 mm thick (*z*-axis) allows one to visualize what thickness/area of the LV wall is affected by infarction/scar.[26-31] Detection of scar by contrast enhanced magnetic resonance imaging (ce-MRI) is best when images are acquired with a delay of 10-20 minutes after infusion of the Gadolinium (Gd) contrast agent, because the delay allows time for Gd to washout from normal myocardium while the scar tissue will retain Gd, and show an enhanced MRI signal as an indicator of infarction.[28,30,31] The mechanism of this enhanced Gd uptake probably differs between the early, acute myocardial infarction and the late, chronic stage. Acute infarction appears to involve ''leaky'' membranes of non-viable cells that can no longer maintain their ionic gradients to keep out the Gd,[26] vs the late, chronic stage, where avid Gd binding to collagen molecules that are more easily exposed to Gd entering from the extra cellular space.[26-28] Spatial resolution and contrasting of MRI varies, depending on the sequence used to acquire the study, based on setting several imaging parameters.[30,31] The optimal protocol undergoes continuous evolution, making it a ''moving target,'' and more difficult to estimate the impact of a published method on one's own practice. In order to achieve the optimal spatial resolution and contrasting with ce-MRI, it is necessary to acquire the image with adequate electrocardiographic (ECG) gating signals (requiring a regular rhythm) and with the patient holding his or her breath long enough to acquire images for 8-10 seconds to collect images of one or two cardiac slices.[29-31,38] This procedure then needs to be repeated 5-10 times to acquire images of the entire left ventricle, from apex to mitral valve plane. Some patients cannot achieve these two conditions (stable cardiac rhythm and controlled breathing), especially in the population of CAD patients who are candidates for myocardial viability assessment due to CHF. In contrast to ce-MRI, optimal PET FDG/perfusion imaging does not require either regular rhythm or controlled breathing, so it is more easily applied to a larger number of these patients.[8,25,38-41] PET scanners seem to produce less claustrophobia than traditional MRI magnets, partly because they are not as confining as MRI, produce much less intimidating noise. Since few facilities can offer a wide bore magnet that is suitable for viability studies, claustrophobia is likely to remain a problem. PET has lower spatial resolution

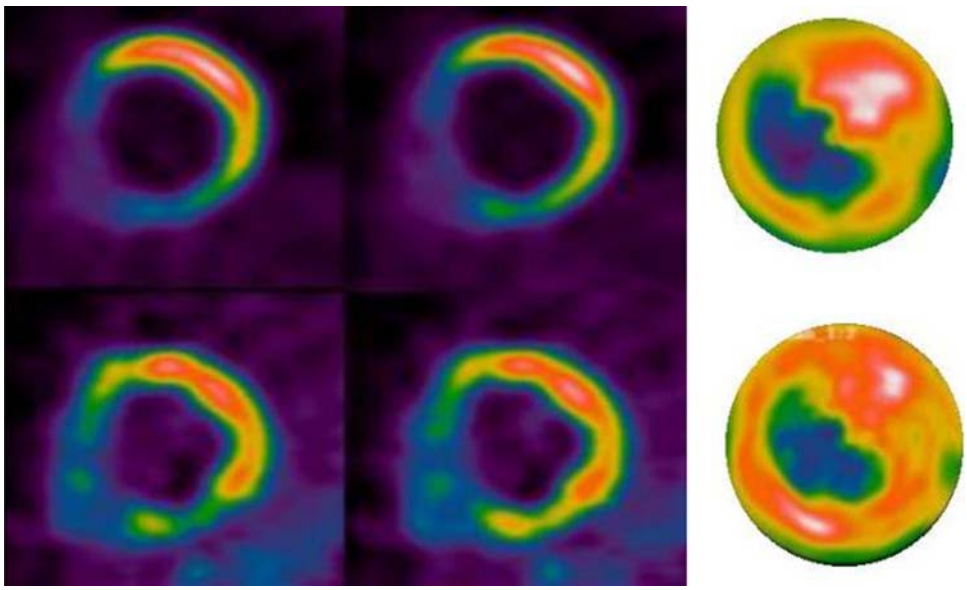

Figure 2. Two short-axis slices and one polar map, bull's-eye display of a PET FDG, above, and a PET Rb-82, below. There is a moderate to large sized, severe defect in the anterior- and inferior-septal regions that shows the same (MATCHING) severity on FDG and Rb-82 to indicate that the myocardium is no longer viable, implying a nearly transmural extent of scar tissue, as suggested by Figure 1B.

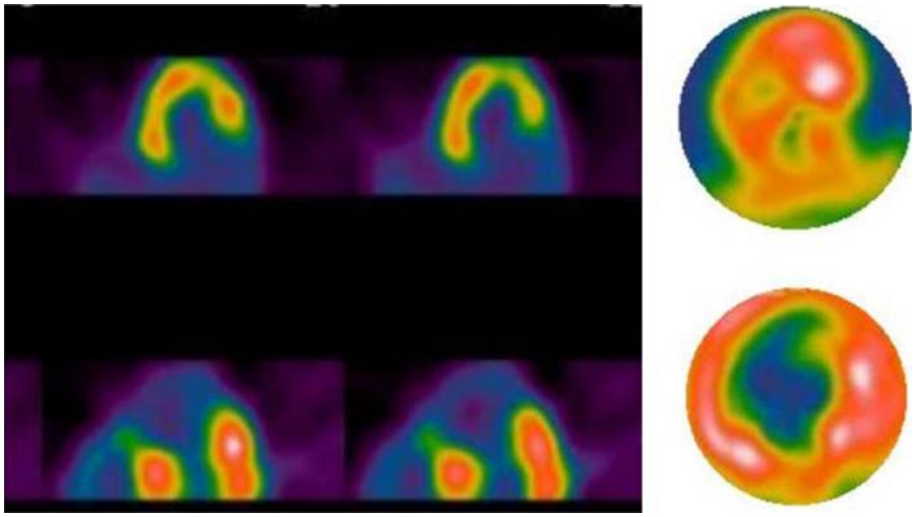

Figure 3. Two horizontal long axis slices and one polar map, bull's-eye display of a PET FDG, above, and a PET Rb-82, below. There is a moderate to large sized, severe defect in the anterior-septal-apical regions on PET Rb-82 that shows a ''hot spot,'' or dramatically more (MIS-MATCHING) intensity of FDG to indicate that the myocardium is viable, implying a limited extent of scar tissue in the subendocardium, consistent with Figure 1A.

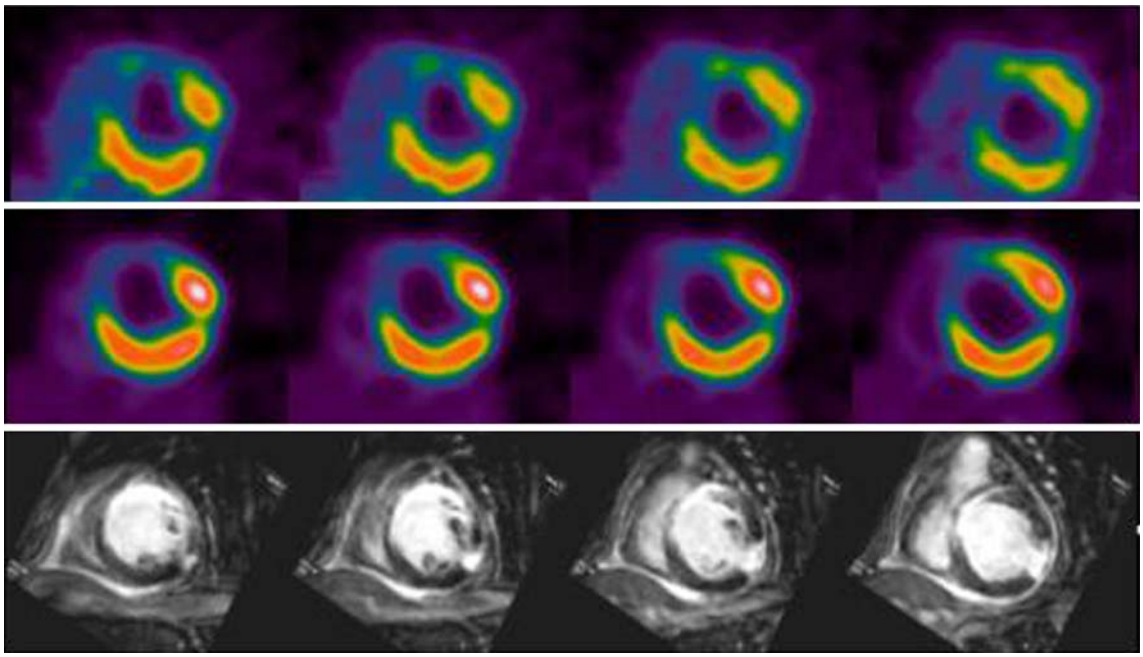

Figure 4. Four short-axis slices of a PET Rb-82 in the *top row*, above, and a PET FDG, in the *second row*. There is a moderate sized, moderately severe defect in the anterior-septal-apical regions on PET Rb-82 that shows the same (MATCHING) severity on FDG and Rb-82 to indicate that the myocardium is no longer viable. In addition, there is a second, small defect in the lateral-inferior region that also shows the same (MATCHING) severity on FDG and Rb-82 to indicate that the myocardium is no longer viable. The *bottom row* shows four short-axis MRI images that show contrast enhancement (*white*) in the same anterior septal and lateral inferior regions that are seen above on PET Rb-82 in the *top row* and PET FDG in the *middle row*. The contrast enhancement extends almost completely from endocardium to epicardium on the MRI, demonstrating a nearly transmural extent of scar tissue, consistent with Figure 1B. Thus, both PET and MRI identified the same two myocardial infarction regions as non-viable.

(7-12 mm) than does MRI, and PET uses a different signal, F-18-FDG, whose uptake is increased greatly (3- to 5-fold) in viable but jeopardized surviving myocardium, after a shift from aerobic (fatty acid substrate) to anaerobic metabolism (glucose substrate)[8,19,20,23] (see Figures 2 and 3 which explain PET: FDG/Rb-82 match/mismatch). These metabolic pathways[19-21] have been well understood for almost a century.

MRI COMPARED TO PET: ACCURACY OF RESULTS

To evaluate myocardial viability, the literature offers a longer clinical experience and hundreds of papers, in thousands of patients for PET-FDG, since 1983, and many fewer for MRI, since 2000. This evaluation should begin with the question, how does one determine the reliability of a test for myocardial viability imaging? The goal is to determine whether a viability study can predict a favorable clinical outcome. Two notes of caution are necessary, here. First, there can be registration problems for images acquired at different times and with different imaging modalities, so it is critical to identify the artery being revascularized as the artery that supplies the myocardium being tested for viability.[38,40,41] Second, it is important to confirm adequate revascularization of the region for which viability was previously defined.[42,43]

The viability outcome can be judged by one or more of following: (a) clinical improvements such as longer patient survival, fewer hospital admissions for myocardial infarction (MI), CHF or chest pain, better exercise tolerance, improvements in quality of life and fewer subsequent revascularization procedures,[4-7,12,33,39,44-47] or (b) improved regional LV function in the segments being evaluated, and improved left ventricular ejection fraction (LVEF), smaller LV end systolic volume.[2,6,33,39,43] Clearly, the most important and worthwhile outcome definitions are the most difficult to define and quantify, e.g., quality of life.[7,9,12] Indeed, almost all outcome studies encounter major barriers to completion, for example it is difficult to get patients to return for more tests, after CABG or PCI, in order to define the outcome end point. This difficulty arises not only because of the inconvenience and expense, but also because many patients are reluctant to return for more tests because they fear that the tests may reveal a recurrence of their medical problem.

Outcome studies require careful scrutiny. One study compared the outcomes of management of 430 patients by PET FDG vs no PET found no significant difference in outcomes for the groups, as a whole, but if the revascularization decision was consistent with the implications of the PET viability study, then the PET group had significantly better outcomes.[47] Other attempts to compare outcomes have included a large number of patients who had relatively normal LVEF, indicating that they were not even appropriate patients for a viability study. There are also questions for data analysis, such as the difficulty in the ''registration'' of the same myocardial regions of the LV on different imaging modalities that may be used to image viability and/or outcome indicators, such as regional LV function.[2,12,28,30,33,38,43] Also, there are questions of whether to perform analysis per patient, analysis per defect, or analysis per segment.[5] Many papers offer a small number of patients but analyze over 50 segments per patient, very few of which are even abnormal. This approach to data analysis raises questions of the validity of statistical handling of number of segments vs number of patients, since different segments within one patient are not truly independent of each other. Despite these limitations of viability studies, several publications demonstrate the value of both PET FDG/Rb-82 (or N-13-NH3) and ce-MRI in identifying viable segments at risk in patients, predicting the benefits and risks of revascularization. MRI provides better spatial resolution and better registration of the same segment if MRI is used for the follow-up study of regional LV function, as an outcome indicator.[28,30,31] Despite this advantage, PET FDG/Rb-82 and ce-MRI seem to provide similar accuracies in identifying the presence or absence of viable myocardium, as shown in the many papers previously cited, which compared one modality to recovery of LV function, or in head-to-head comparison of PET vs ce-MRI[48-50] (see Figure 4 which compares PET FDG/Rb-82 vs ce-MRI).

PROBLEMS WITH MRI: AMBIGUITY

An important, but little-discussed problem for ce-MRI is that the clinical interpretation of viability results can generate more ''shades of gray,'' or ''probable results'' rather than a ''definite result'' that is ''black or white,'' ''yes or no.'' Although ce-MRI offers the most detailed and definitive cardiac images; clinical interpretation poses challenges to the clinician who interprets the images and to the cardiovascular specialist who must decide whether or not the ce-MRI result means that one should proceed with revascularization. As will be shown from data reviewed below[28] (see Figure 5), it can be argued that MRI produces equivocal or non-diagnostic results in 293/804 (36%) of segments being tested for myocardial viability, and, thus, is ''diagnostic'' in only 64% of segments. In contrast, if FDG activity exceeds a threshold value of 50% of maximum counts in the region of the resting perfusion

defect[48-50] or a mismatch between severity of the defect on FDG vs the perfusion tracer,[8,25,37,39,40] the result gives an unambiguous result in well over 90% of patient studies.[8,39] Contrast-enhanced MRI gives a different type of answer. According to Kim et al[28] when scar is indicated by enhancement of >75% relative area of a myocardial wall segment, it is non-viable, and when there is enhancement (scar) of <25% relative area of a myocardial wall segment, it is viable, so that the segment in question will likely show improved function after revascularization.[28] On the other hand, when the enhancement involves between 25% and 75% relative area of the LV wall segment, the probability of functional recovery after revascularization is truly intermediate or a ''toss-up'' (about 50%). These segments with intermediate thickness of scar comprised 36% of Kim's study.[28] Please see Figure 5 for a more detailed look at Kim's results.[28] Those ce-MRI data are displayed as a receiver-operator characteristic (ROC) curve, which illustrates a potential problem with ambiguity in interpretation of ce-MRI. Here, we have shown a ''positive'' result of the test when it predicts the recovery of regional function in that myocardial segment after revascularization, and a ''negative'' result when the test predicts no recovery. The ROC curve shows ''no free lunch'' for changing criteria to interpret the ce-MRI as ''positive,'' as it plots the ''true positive rate,'' or sensitivity, increasing up the vertical (y) axis, and the ''false positive rate,'' or 100-specificity, increasing across the horizontal (x) axis. A ''true positive'' result means that the test predicted recovery correctly, and a ''false positive'' result means that the test predicted recovery, incorrectly, because recovery failed to occur. One must ask how much ''scar'' can be present, before the regional function will not recover after revascularization? The diagnostic threshold criterion (% relative area involved by contrast enhancement in the LV segment) must be evaluated at different levels that could be used as ''threshold values'' to decide yes or no for revascularization. As one changes this ''threshold value'' to allow more scar to be present, and yet still predicts recovery, the ''sensitivity'' increases dramatically from 60% when no scar is allowed, to 86% when scar can involve up to 25% LV segment, to 97% when up to 50% scar thickness is allowed. As one might expect, there is a dramatic decline in specificity or increase in the ''false positive rate,'' moving from left to right, as the diagnostic threshold criterion (to decide yes or no for revascularization) allows more scar. The rate of occurrence of ''false positives,'' or 100-''specificity,'' is only 19% when no scar is allowed, but increases to 39% when up to 25% scar is allowed, and to 56% when up to 50% scar is allowed, and to 85% when up to 75% scar is allowed. Conversely, to say that the negative result predicts correctly that the segment will not recover function (i.e., ''specificity'') declines from 81% when no scar is allowed, to 61% when up to 25% scar is allowed, to 44% when up to 50% scar is allowed, to 15% when up to 75% scar is allowed. These observations emphasize the need for caution in interpretation of ce-MRI to predict recovery of regional LV function after revascularization, particularly when scar involves 25-75% LV scar thickness.

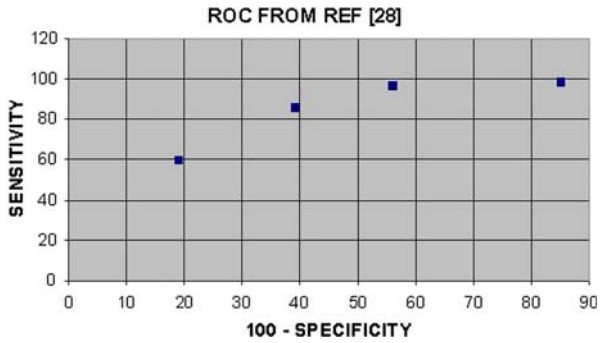

Figure 5. Receiver-operator characteristic (ROC) curve is calculated from data from Kim et al[28] for ce-MRI, illustrates a potential problem with ambiguity in interpretation of ce-MRI, where a positive result of the test predicts the recovery of regional function in that myocardial segment after revascularization, and a negative result predicts no recovery. One must ask how much ''scar'' can be present, before regional LV function will not recover after revascularization? In order to decide which criterion is best, the diagnostic threshold criterion (% relative area involved by contrast enhancement in the LV segment) must be investigated at different levels that could be used to decide yes or no for revascularization. As one changes this ''threshold value'' to allow more scar to be present—and yet still predict recovery—the ''sensitivity'' increases dramatically from 60% when no scar is allowed, to 86% when scar can involve up to 25% LV segment, to 97% when up to 50% scar thickness is allowed. As one might expect, there is ''no free lunch'' for changing criteria, because there is a dramatic decline in specificity (shown here as an increase in the rate of ''false positives'') or 100-''specificity,'' from left to right, as the diagnostic threshold criterion (to decide yes or no for revascularization) allows more scar: from only 19% when no scar is allowed, but increasing to 39% when up to 25% scar is allowed, to 56% when up to 50% scar is allowed, and to 85% when up to 75% scar is allowed. These observations emphasize the need for caution in interpretation of ce-MRI to predict recovery of regional LV function after revascularization.

In most cardiovascular testing, when a test yields a result that offers only a 50/50% chance of answering the clinical question, the result is classified as an equivocal or non-diagnostic result.[51]

These considerations support the argument to reinterpret the results of Kim's elegant paper[28] as showing that ce-MRI provides an answer to the viability question only 64% of the time, with equivocal or non-diagnostic

results in the other 36%. Although it is possible that this critique of Kim's study is only defining the reality of the underlying pathological anatomy and physiology[5,14-17,19,21,26,27,29,32,52] such an answer may not clarify how to decide whether to recommend revascularization. Even if the PET FDG/perfusion answer is ''only an accident'' of the limited resolution of the method, this ''accidental technical limitation'' appears to offer a higher likelihood of a ''yes or no answer,'' and therefore, a more effective clinical tool.

It would be desirable for ce-MRI interpretation to strive toward less equivocal, more definitive results. One approach, for example, might be to assess whether a certain thickness of viable (non-contrast enhanced) wall thickness implies that the wall is viable and will recover regional LV function after revascularization. Indeed, one study[48] compared the absolute thickness of the non-enhancing myocardial subepicardial rim to the degree of FDG uptake, noting that segments with >4.5 mm subepicardial rim of viable (non-enhancing) myocardium corresponded to regions on PET showing >50% FDG uptake. They also demonstrated functional improvement in most segments with evidence of viability by both PET and MRI following revascularization.[48] Others have also analyzed segments based on the absolute thickness of the non-enhancing myocardium and found subepicardial segments with >3 mm rim of viable (non-enhancing) myocardium agreed most closely with viability on PET-FDG (indicated by myocardial uptake that was >50% of the maximum FDG uptake).[49,50]

PET FDG and ce-MRI provide information that is, in many respects, complementary, although the costs preclude performing both tests on all patients. It seems clear that there can be a small subendocardial infarction with a substantial subepicardial viable region (Figure 1A) that will produce an ischemic defect on a stress perfusion scan, but with relatively enhanced FDG uptake, due to increased anaerobic metabolism of glucose in the viable subepicardium (Figure 3). Ce-MRI would be expected to show a small, contrast-enhanced (non-viable) region in the subendocardial infarction, but a large non-enhanced (viable) region in the subepicardium overlying this infarction.[28-31] Confirmation of the presence of a small amount of subendocardial scarring in patients with evidence of viability by PET can be ascertained from studies using biopsy material obtained intra-operatively.[32,41,42] These studies also show that the greater the evidence of viability on PET FDG, there is a corresponding decrease in the amount of scar tissue on ce-MRI.[48-50] Other studies have shown that PET FDG/perfusion mismatch occurs in the great majority of patients with ECG evidence of non-Q wave myocardial infarction.[52] ECG findings have been correlated with subendocardial (non-transmural or non-ST elevation) myocardial infarction in pathological autopsy specimens.[53] The key questions for the clinical decision-process, then, become (a) What relative or absolute thickness of viable tissue in the subepicardial rim is required to allow regional contraction to improve after revascularization? (b) What percentage of the LV must contain such jeopardized but viable tissue, in order to produce improved global LV contraction after revascularization?[5,33]

LIMITED APPLICABILITY OF CE-MRI TO PARTICULAR PATIENTS

Many advantages of PET over MRI result from problems arising when trying to acquire MRI, for example, the artifacts from pacemaker and ICD leads, and other metal in the chest.[54-58] Implantation of pacemakers (especially biventricular for cardiac resynchronization therapy) and ICDs are increasing in the same patient population that benefits most from viability assessment, i.e., CHF due to CAD. The worst fear was that older metal leads for these devices could ''heat up'' in the magnet creating heat injury to the patient.[54,55,57] Since newer pacing leads are manufactured with safer, less ferromagnetic materials, there is much less concern for this potential ''burn'' injury. For the MRI laboratory, however, there remains the issue of the time required (a) to turn off the pacing device before the patient gets in the magnet, (b) to monitor the patient and ECG carefully while in the MRI, and (c) to turn on the pacing device, promptly after the patient gets out of the magnet. Another issue is that even ''MRI-safe'' devices will distort signal and create image artifacts on MRI, with the greatest distortion for thicker ICD leads and for sites in the heart that are closest to the pacing leads, e.g., biventricular pacing leads.[54-58]

Nephrogenic systemic fibrosis (NSF) has emerged as one of the major issues that limit more widespread utilization of ce-MRI, although this disease is currently a rare complication of Gadolinium contrast agents.[59-64] NSF is a disease of connective tissue and skin that usually produces severely disfiguring scars. It was first recognized in 1997 and has a 5% mortality rate. Early symptoms and signs of NSF can be ambiguous, making it difficult to diagnose in its early phases. Unfortunately, it is easy to learn more than you ever wanted to know about such a rare disease as NSF by going to the Internet (where nephrogenic systemic fibrosis has >775,000 ''hits'' on Google), especially websites for law firms! Or by watching late night television advertisements by law firms. NSF is related to Gadolinium contrast in 95% of cases of the disease, and NSF is much more common if the dose of Gd exceeds 0.15 mmol/kg. Thus, most MRI laboratories have decreased the dose of Gadolinium to 0.10 mmol/kg. Although NSF is rare, it remains 10- to

30-fold more common if GFR is impaired,[59,61-64] and this is why it remains an important threat for many of the patients who need evaluation of myocardial viability. Patients with CHF due to CAD often have impaired renal function due to CHF.[65] In one study NSF occurred in 0.2% of almost 9000 patients after high dose [>/= 0.15 mmol/kg] Gd-contrast. NSF occurred in 8.8% of patients after high dose Gd if GFR was <15 mL/minute, and if the patient received no dialysis. In contrast, NSF occurred in only 0.4%, if the patient had dialysis shortly after Gd exposure, but NSF occurred in 15.9% of 69 patients after high dose Gd, if the patient had acute renal failure.[59-61,63,64]

For the larger population of patients who need viability testing due to CAD and CHF, but are not on dialysis, renal insufficiency is a common and important issue.[65] Renal function was impaired in over half (56%) of the patients in this prospective cohort of 754 patients with CAD and CHF. Over half (57%) of these patients had LVEF <0.35, and GFR was <60 mL/minute in 56% of patients and <30 mL/minute in 16% of patients.[65] Medical-legal concerns unquestionably exceed the medical threat that posed by Gadolinium contrast for ce-MRI, the issue of ''defensive medicine'' imposes real-world limits on utilization of ce-MRI for myocardial viability assessment. Considering the most legitimate medical issues, the threat of NSF is greatest in a patient with acute renal failure or GFR <30 L/min, who is not yet on dialysis, or any patient with hepatorenal syndrome, regardless of calculated GFR.[60-64] Despite its low incidence, NSF gets a lot of attention on the Internet and can certainly lead to time-consuming discussions with patient before the test. NSF and the even less frequent occurrence of anaphylaxis (one per 300,000-400,000)[64] are such serious problems that even their low incidence can cast a medical-legal ''shadow'' over ce-MRI. Logistical issues include the need to check renal function before ce-MRI, and if the patient is on dialysis, she or he will need dialysis.[59-64]

On the contrary, the risks of resting PET Rb-82/FDG are small. The risk of symptomatic hypoglycemia during the glucose management phase of FDG loading is small and never serious if properly monitored and treated.[8,25,37,40] PET causes an acceptably small dose of radiation, even if CT is used for attenuation correction (13-17 mSv), which is comparable to CTA.[41] The potential risk of cancer related to this radiation exposure is very unlikely to be the limiting factor for life expectancy of these high-risk patients with CAD and CHF.[11,12,38,45,47]

Problems with MRI: Claustrophobia

Thus, advantages of PET FDG/perfusion compared to ce-MRI include less need for physician-time spent on the following issues: ''negotiating'' with a patient to undergo ce-MRI, conscious sedation protocols, acquisition questions, data processing and interpretation. The ''hidden costs'' of ce-MRI must also include time spent by referring physicians and their staffs discussing ce-MRI and ''negotiating'' with the patient concerning whether he or she can tolerate the procedure, and these issues will limit enthusiasm of physicians to refer patients for MRI. Since these discussions usually occur in the office of the referring physician or in the patient's hospital room, before the patient meets MRI personnel, it is difficult to compute the true prevalence of patients who are too anxious or claustrophobic for MRI, because many never make it to the MRI laboratory. In our research study of patients referred for PET FDG/perfusion,[50] we invited most of these 141 patients who were referred for PET, to have a ce-MRI on the day they had their PET FDG/Rb, or on another day of their choosing. Only 49 (35%) patients agreed to complete the initial ce-MRI due to one or more of the following problems: the presence of ICDs or pacemakers, impaired GFR, claustrophobia or occasionally due to inconvenience of extra time spent. Finally, because most hospitals that perform ce-MRI viability studies do not have large bore magnets; claustrophobia is likely to remain a problem.

Problems with MRI: Software and Time

The major ''hidden cost'' of ce-MRI is the time required to perform post-processing and interpretation of image data, partly because the cardiac analysis software is less established and less available for ce-MRI than for PET.[5,6,8,12,25,37,40,41,66] These problems have meant that most published ce-MRI data have required that the regions of interest be ''drawn by hand'' on the computer screen,[28-31,48,49] which requires a lot of observer interaction that is time-consuming and subjective. Another issue for assessment of myocardial viability is to avoid ''missing the forest for the trees'' because MRI provides very detailed views to visualize LV wall thickness involved by scar, including trabeculae and the papillary muscles.[28-31,48,49] This issue is an important factor in the tendency of ce-MRI to provide results that do not clarify whether or not to proceed with revascularization, as discussed above. In contrast, PET provides software that is more objective, more widely available and less operator-dependent to quantify % LV myocardium that is viable vs non-viable, including using statistical comparisons on a voxel-by-voxel basis, to a ''normal file'' for many variables.[5,6,8,25,37,41,66]

Resting perfusion can strengthen interpretations, and PET and MRI both offer indexes of resting perfusion, but the PET images of Rb-82 or N-13-NH-3 are easier to interpret and offer advantages in terms of

Table 1. Comparison of several issues for assessment of myocardial viability by PET: FDG/Rb-82 vs MRI: Gd-enhanced

	PET: FDG/Rb	MRI: Gd-enhanced
Radiation risk	15-17 mSv, but less relative risk to viability study patients	None known
Pre-test requirements	Order F-18-FDG from cyclotron	Ck creatinine, or if ESRD, schedule dialysis after MRI
Spatial resolution *x-y* plane	7-12 mm	1.5-2.0 mm
Spatial resolution: *z*-axis	Same, isotropic	8-12 mm, anisotropic
Impact of arrhythmia	None on basic image	Cannot obtain optimal image quality
Need for breath-holding	None	Important for optimal image quality
Time in camera	20-35 minutes	30-50 minutes
Total time in lab	2.0-3.5 hours	45-60 minutes
Claustrophobia issues	Occasional, esp. PET/CT	Infrequent, but >PET
Pacemaker, ICD issues	No problem	Impedes performing MRI
Renal insufficiency	No problem	May exclude MRI (ARF or HRS)
Negotiation time with patient	Small	More frequent and larger issue
Impact of LBBB	Can get FDG defect despite normal perfusion: but little problem if focus only on FDG in region of PET perfusion defect	No problem
Assess worse prognosis due to ''Microvascular Obstruction''	Need to verify, but probably corresponds to more severe defects	Absence of Gd in the subendocardium of an enhanced segment indicates worse prognosis
Post-processing effort	Small due to good software	Large due to software
Interpretation effort	Small	Large due to software
Pos. predictive value to detect viable myocardium, i.e., recovers p. CABG	85-90%	Similar but what to do if scar involves 25-75% relative area of the LV wall thickness
Neg. predictive value to exclude viable myocardium, i.e., no recovery after CABG	65-85%	Similar but what to do if scar involves 25-75% relative area of the LV wall thickness
Frequency of definitive conclusion—whether viability supports CABG, PCI	>90-95%	Maybe 70-85%
Initial costs	Large	Moderate
Likelihood of catastrophic ''downstream costs'' due to unclear viability Dx	Appears very low based on 30 year experience	Much less certain, based on 10 year experience

objectivity and software to analyze severity and extent of abnormalities (% LV, by comparison to normal files).[5,6,8,25,37,41,66] The ce-MRI perfusion images require the observer to assess the intensity and rate of transit of a ''blush'' of contrast moving into and out of the myocardium, which remains a subjective procedure.[28,67] Also, deciding the indications for revascularization requires an assessment of the potential for ischemia, including regions of myocardium that have not undergone infarction. Often, it is difficult to identify the ''physiological significance'' of many anatomical stenoses on an invasive coronary arteriogram and it can be even more difficult to identify how much myocardium is actually dependent on a stenotic artery. Because of the software issues, such regions are more easily identified on PET rest/stress myocardial perfusion

imaging than on rest/stress MRI.[66,67] In addition to software issues, another advantage for PET is the superior characteristics of the tracers available to track the relative and absolute values of myocardial blood flow on PET, so that the same stress agent produces twice the increment in flow on PET (almost 4-fold), vs MRI (<2-fold).[67] The smaller increment in maximal coronary blood flow signal will create false negative results of a test that compares relative perfusion to regions dependent on normal vs stenotic coronary arteries.[68,69] Thus, it is not surprising that the rest/stress PET Rb-82 shows such outstanding sensitivity and specificity to detect CAD[69,70] although rest/stress MRI has an excellent negative predictive value, PET rest/stress perfusion imaging has outstanding sensitivity, specificity and diagnostic accuracy in patients with known coronary artery disease.[69,70]

CONCLUSION

In conclusion, there are clearly differences between the methodologies used by PET and MRI to assess myocardial viability, but both tests ''work,'' and their ''accuracy'' to identify the presence or absence of viable myocardium appears to be similar (see Table 1, for summary). The different modalities create important differences in the applicability of MRI vs PET to individual patients (pacemakers, defibrillators, renal insufficiency, and claustrophobia), thus limiting in whom the test can be performed. Four differences in the results of MRI and PET require further definition: (a) How often can the test be performed to produce an adequate study and provide a definitive conclusion as to whether the tissue in question is viable, (b) what percentage of the LV would be expected to recover its regional LV function after revascularization, and (c) would improved LV function in this region lead to improved global LV function? (d) Are there non-infracted regions of the LV that are potentially ischemic, due their dependence on stenotic coronary arteries? The critical issue is that there are many patients who could benefit from myocardial viability assessment, but may be able to have the test performed with only one, but not both of the two modalities. For this reason, both modalities must remain available to meet the needs of our patients. Based on the above considerations, however, we suggest that PET FDG and PET perfusion scans be the ''test of choice'' to assess myocardial viability.

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