Assessment of Myocardial Viability: Review of the Clinical Significance

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The identification of myocardial viability in patients with coronary artery disease and left ventricular dysfunction (LVD) has important clinical and prognostic implications. Two terms commonly used to define clinical conditions of potentially reversible contractile dysfunction are stunned myocardium *and* hibernating myocardium. *Stunned myocardium refers to transient depression of contractile function secondary to an acute ischemic insult. Hibernating myocardium is a form of contractile dysfunction of living myocytes in the setting of chronic ischemia or chronically reduced flow reserve. Numerous observational studies have shown improved clinical outcomes after revascularization of patients with LVD and evidence of myocardial viability, although patients with nonviable myocardium have not been shown to have the same benefits. The use of noninvasive techniques to determine myocardial viability provides important information to guide clinicians in deciding which patients with LVD are likely to receive benefit from a revascularization procedure. Positron emission tomography, single-photon emission computed tomography, dobutamine echocardiography, and cardiac magnetic resonance imaging each have advantages and limitations.*
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Key words: Myocardial viability • Stunned myocardium • Hibernating myocardium • Positron emission tomography • Single-photon emission computed tomography • Dobutamine echocardiography • Cardiac magnetic resonance imaging

Potentially viable myocardium denotes tissue that is metabolically active but exhibits contractile dysfunction. Cardiac myocytes may be viable in the setting of reduced or absent contractile function that is caused by either an acute or chronic reduction in perfusion. This article will review clinical definitions of potentially viable myocardium, prognostic implications of myocardial viability, and modalities for detection of viability.

Clinical Definitions

Two terms commonly used to define clinical conditions of potentially reversible contractile dysfunction are *stunned myocardium* and *hibernating myocardium*. Stunned myocardium refers to transient depression of contractile function secondary to an acute ischemic insult. Myocardial adenosine triphosphate (ATP) concentrations are depleted to 50% of normal levels after 15 minutes of myocardial ischemia, and they remain at below-normal levels for days after reperfusion.[1] Ventricular dysfunction in stunned myocardium is expected to improve several hours to several days or weeks after reperfusion is established, and it has been seen to mirror the repletion of myocardial ATP in the ischemic zone. This process has been shown in dog models in which short periods of coronary artery ligation lead to acute functional limitation of the ventricle, followed by improvement hours to days later. In humans, it is often seen in patients with acute myocardial infarction who receive prompt revascularization.[2,3]

Hibernating myocardium is a form of contractile dysfunction of living myocytes in the setting of chronic ischemia or chronically reduced flow reserve. Repeated episodes of myocardial stunning can lead to hibernation or permanent necrosis.[2] On the cellular level, there is dedifferentiation rather than degeneration of myocytes, with cells regressing to characteristics of embryonic developing myocytes.[4] Chronic reduction in perfusion leads to the down regulation of metabolism and function, with a reduction in T-tubules and small mitochondria, increased intramyocyte glycogen, and a reduced myofibril amount. Alterations in mitochondrial NADH oxidase and ATPase activity are also seen.[4]

Although caused by different mechanisms, stunned myocardium and hibernating myocardium lead to the similar endpoint of contractile dysfunction, and clinically the 2 are very hard to distinguish. There is a continuum that includes acutely stunned myocardium, chronically ischemic hibernating myocardium, and infarcted, fibrosed myocardium, each with varying degrees of cellular function and metabolism. This spectrum of myocardial injury may be seen in the same patient and in the same myocardial region.

Clinical Significance of Myocardial Viability

The identification of myocardial viability in patients with coronary artery disease and left ventricular dysfunction (LVD) has important clinical and prognostic implications. Numerous observational studies have shown improved clinical outcomes after revascularization of patients with LVD and evidence of myocardial viability, but patients with nonviable myocardium have not been shown to have the same benefits.[5-8] At this time, there are few randomized data supporting improved outcomes from revascularization in patients with viability, although there are trials currently underway addressing this issue.

There is risk inherent to both coronary artery bypass surgery and percutaneous coronary intervention, especially for patients with severe LVD. Patients with LVD, particularly if there is stunned or hibernating myocardium, have the most to gain from these procedures. For this reason, the use of noninvasive techniques to determine myocardial viability provides important information to guide clinicians in deciding which patients with LVD are likely to receive benefit from a revascularization procedure.

Positron Emission Tomography

Positron emission tomography (PET) has played a very important role in viability assessment, since early research showed that a perfusion-metabolism mismatch correlated with improved wall motion and improved outcomes postrevascularization.[5,9,10] Whereas the gold standard of viability has been evidence of improved contractile function postrevascularization, PET historically has been the gold standard of viability testing prior to revascularization. The strength of PET lies in the use of metabolic tracers that can be imaged and quantified in their areas of uptake. Glucose utilization, a marker for myocyte metabolic activity and, thus, viability, is evaluated with the injection and myocardial uptake of 18F-fluoro-2-deoxy-D-glucose (FDG). In comparison, regional myocardial perfusion is assessed with N13-ammonia, rubidium-82, or O15-labeled water.[11]

A relative increase in FDG uptake compared with regional hypoperfusion leads to a perfusion-metabolism mismatch and indicates a region of viable myocardium. Conversely, a concordant reduction in FDG uptake and myocardial perfusion (match pattern) is indicative of nonviable myocardium. Areas of normal FDG uptake and perfusion indicate normal myocardium. In a meta-analysis of 20 studies that included 598 patients undergoing PET followed by revascularization, PET assessed myocardial viability with a mean sensitivity of 93% and a mean specificity of 58%.[12] The mean positive predictive value (PPV) was 71%, and the mean negative predictive value (NPV) was 86%.

Disadvantages of PET are its lack of widespread availability, high cost, and the need to control for glucose metabolism in patients with insulin resistance or diabetes mellitus. Most

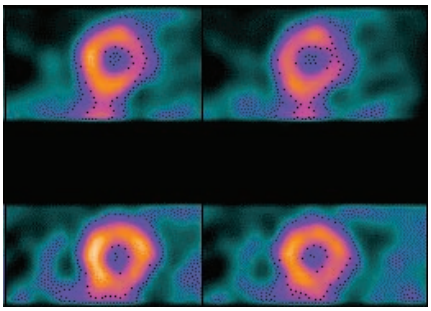

Figure 1. *Thallium-201 single-photon emission computed tomography (SPECT) short-axis image, comparing rest study (top) with delayed study (bottom). There is a lateral defect on the rest images and comparative redistribution on the delayed images, implying viability of the lateral wall.*
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positron emitters have a very short half-life and require an expensive on-site cyclotron. High-energy collimators can be added to single-photon emission computed tomography (SPECT) cameras to image positron emitting tracers. As a result, "hybrid" techniques combining the metabolic assessment with 18F-FDG and perfusion testing with SPECT have been tested and compare favorably with PET and other imaging modalities.[7,13,14] Slart and colleagues[15] studied 47 patients with technetium-99m (Tc-99m)-sestamibi/18F-FDG dual-isotope simultaneous acquisition (DISA) SPECT and 13N-ammonia/18F-FDG PET prior to revascularization and found no significant difference in sensitivity or specificity for predicting improvement in regional wall motion, global left ventricular function, or left ventricular reverse remodeling.

SPECT: Thallium-201

The widespread availability of SPECT imaging has led to its use for the assessment of viability. Thallium-201 is a radionuclide analog of potassium, and its initial uptake after injection depends on regional blood flow (Figures 1 and 2). The sustained uptake of thallium requires the integrity of the cell membrane and thus implies myocardial viability. Many protocols have been described, and robust data have shown SPECT to be comparable with PET in assessing viability.[12]

The 2 most common protocols for assessing viability via SPECT are the rest-redistribution and stress-redistribution-reinjection protocols. A rest-redistribution protocol involves the injection of thallium-201 at rest, followed immediately by a first set of imaging. A second set of imaging is acquired 3- to 4-hour later, allowing the tracer to redistribute. An area of decreased thallium uptake on initial rest imaging implies a perfusion defect. Redistribution of the tracer, seen as increased uptake in the area of the initial deficit in the later imaging set, implies viability; the most commonly used threshold for viability in a fixed defect has been defined as an increase in tracer activity of more than 10%.[16] There is some evidence that redistribution may continue after 3 hours and that images acquired 24 hours after injection may increase detection of viable myocardium.[17] Stress-redistribution-reinjection protocols involve a radionuclide injection during peak stress, with a first set of images acquired immediately after exercise, and a second set of images acquired 3 to 4 hours later to allow for redistribution. Then a smaller dose of thallium-201 is reinjected, and a third set of images is obtained later. This protocol allows for the testing of both perfusion and viability, and allows for the additional redistribution of the tracer that may occur after the initial 3- to 4-hour window. The criterion for viability is a defect reversibility (redistribution) or a minimum level of tracer activity detection (usually $>$ 50%) in a dysfunctional segment.[12]

Figure 2. *Thallium-201 single-photon emission computed tomography (SPECT) long-axis image, comparing rest study (top) with delayed study (bottom). There is a lateral defect on the rest images and comparative redistribution on the delayed images, implying viability of the lateral wall.*
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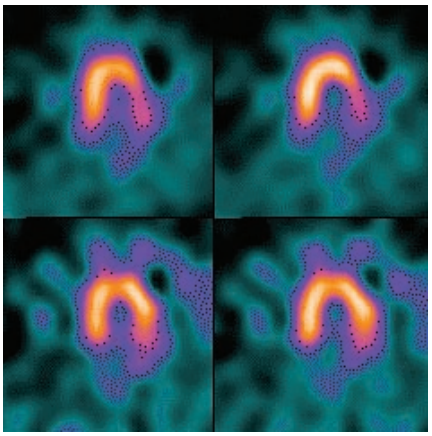

Many studies have evaluated the utility of different SPECT protocols in predicting recovery after revascularization. A meta-analysis of 22 studies involving 557 patients using the rest-redistribution protocol found a mean sensitivity of 86% and a mean specificity of 59%, with a mean PPV of 69% and a mean NPV of 80%.[12] Of these, 11 studies of 301 patients using reinjection protocols (3 of which were stress-reinjection protocols) found a mean sensitivity of 88% and a mean specificity of 50%, with a mean PPV of 57% and a mean NPV of 83%.

SPECT: Technetium-99m

Technetium-based tracers are an alternative to thallium and can be used in viability imaging. Technetium is lipophilic and is passively taken up across the myocardial membrane. It has a shorter half-life, enabling the use of higher doses of tracer and a higher energy. This attribute results in less scatter as compared with thallium, which may be associated with better image quality.[11] Its short half-life would seemingly result in minimal redistribution potential and possible underestimation of viability. A study compared the regional activities of thallium and technetium and the ability of each technique to predict

recovery of ventricular function in 31 patients with ischemic cardiomyopathy. The PPV (75% for thallium vs 80% for sestamibi) and NPV (92% for thallium vs 96% for sestamibi) for recovery of regional ventricular dysfunction after revascularization was noted to be similar for the 2 agents.[18] Similarly, a comparative study of 30 patients undergoing rest-redistribution thallium-201 imaging and rest electrocardiogram (ECG)-gated Tc-99m imaging found similar rates of sensitivity (95% vs 96%, respectively), specificity (59% vs 55%, respectively), PPV (88% vs 87%, respectively), NPV (78% vs 80%, respectively), and predictive accuracies (86% vs 86%, respectively).[19] Technetium scans have the advantage of assessing ventricular function by ECG-gated Tc-99m SPECT, which may improve sensitivity. Some recent studies have shown that viability assessment using Tc-99m–labeled tracers can be improved by administration of nitrates, which cause vasodilatation and increased tracer flow to viable segments.[20,21]

Dobutamine Echocardiography

Dobutamine echocardiography has been well studied as a method of assessing myocardial viability and has been shown to predict improved survival postrevascularization.[6] Dysfunctional but viable myocardium is characterized by systolic dysfunction at rest, with improvement in contractility during dobutamine infusion. A low-dose dobutamine infusion (5-10 µg/kg/min) is used to assess improvement in contractile function. To further improve the assessment of viability, a high-dose dobutamine stress protocol (with dosages up to 40 µg/kg/min and the addition of atropine) has been studied. This protocol allows for assessment of the biphasic response: an initial improvement of contractility during low-dose dobutamine stress and worsening of contractile function during high-dose dobutamine infusion, believed to be caused by stress-induced ischemia. The 3 other responses are sustained improvement in function, immediate worsening in function, or no change in function. Thus, the low-dose and high-dose protocols performed together allow for the assessment of both viability and perfusion. Contractile reserve during dobutamine echocardiography correlates inversely with the extent of interstitial fibrosis and directly with rest-redistribution thallium uptake.[22]

Cornel and colleagues[23] studied 61 patients with ischemic LVD prior to and at 3 months and 14 months after surgical revascularization. They found that the diagnostic accuracy depended on the use of the low- and high-dose protocol, the severity of regional dyssynergy, and the timing of reevaluation. A similar study found that use of the low- and high-dose protocol provided a more optimal evaluation, and of the 4 possible responses to dobutamine, the biphasic response had the highest predictive value for recovery of function.[24] A meta-analysis of 1090 patients using dobutamine echocardiography to predict functional outcome after revascularization found a sensitivity of 81%, specificity of 80%, PPV of 77%, and NPV of 85%.[12] Of these 29 studies, only 4 used a high-dose dobutamine protocol.

There are limitations to the information derived from dobutamine echocardiography. In some patients, it is not possible to acquire satisfactory images because of body habitus. Resolution and border definition can be suboptimal. Most studies have focused on prediction of recovery of segments with severe wall motion abnormalities. However, there is evidence that some hypokinetic segments exhibiting contractile reserve during low-dose dobutamine did not improve in function after revascularization.[25] This finding may be attributed to the mixture of subendocardial scar with normal tissue; during dobutamine infusion, the normal myocardium may become hyperkinetic, whereas the subendocardial scar remains akinetic, resulting in normokinesia. Another explanation may be a tethering effect by the adjacent akinetic segments that causes irreversible hypokinesia.[26,27]

Cardiac Magnetic Resonance

With its uniquely high spatial resolution, cardiac magnetic resonance (CMR) imaging is potentially the gold standard of myocardial viability assessment (Figure 3). Contrast-enhanced CMR (ceCMR) and dobutamine magnetic resonance (MR) are 2 techniques used in the assessment of viability. CeCMR involves the injection of gadolinium-based contrast agents followed by acquisition of images after a delay of 15 to 20 minutes. Contrast material enters lysed muscle cell and extracellular space much more readily than it enters living myocardium. Hyperenhancement of tissue implies the extracellular accumulation of contrast in regions of infarcted, nonviable muscle. The high resolution of MR allows for the quantification of the extent of transmural hyperenhancement. Dobutamine MR is similar to dobutamine echocardiography, as detection of contractile reserve from cine images implies viability.

Three studies have looked at the ability of ceCMR to predict improvement after coronary revascularization in patients with chronic coronary artery disease. Kim and colleagues[28] studied 50 consecutive patients with LVD who underwent surgical or percutaneous revascularization. Cine MR imaging was repeated approximately

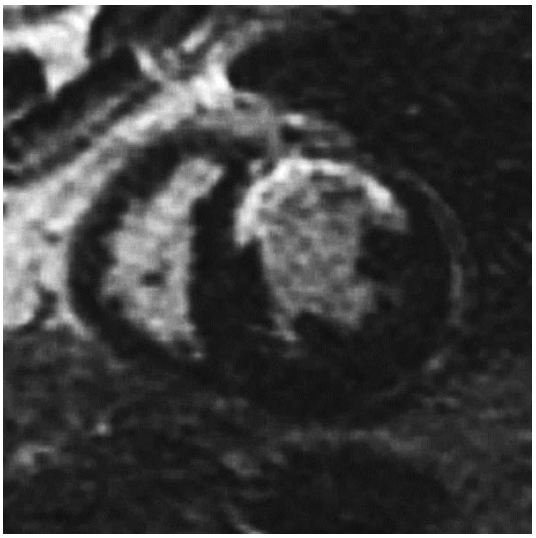

Figure 3. *This midventricular short-axis view of the left ventricle in a patient postmyocardial infarction shows a pattern of hyperenhancement suggestive of a transmural infarction of the anterior wall and a subendocardial infarction of less than half the wall thickness in the anteroseptal segment. Dysfunction in the anteroseptal segment would likely respond to revascularization; the anterior segment is most likely nonviable.*
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3 months after revascularization to document changes in regional wall motion. Segments with a transmural extent of infarction of less than 50% were more likely to recover function following coronary artery bypass grafting. Regional wall motion recovered in the 78% of segments with no hyperenhancement, whereas only 8% of segments with nearly transmural (50% to 100%) hyperenhancement recovered. The authors demonstrated that the likelihood of improvement in regional contractility after revascularization progressively decreased as the transmural extent of hyperenhancement increased. A cutoff value of 25% of the transmural extent of hyperenhancement corresponded to a PPV and NPV of 71% and 79%, respectively, for tissue with any degree of contractile dysfunction, improving to 88% and 89%, respectively, in regions with akinesia or dyskinesia. A study by Selvanayagam and colleagues[29] of 60 patients scheduled for surgical revascularization with ceCMR found that 82% of the dysfunctional segments without hyperenhancement that were identified before the procedure improved on cine MR imaging 6 months later. Using the 25% hyperenhancement cutoff, PPV was 73% and NPV was 69%. The finding of improved predictive accuracy in more dysfunctional segments was again seen, with PPV of 81% and NPV of 72%, when only severely dysfunctional, akinetic, or dyskinetic segments were considered. Gutberlet and coworkers[30] studied 20 patients with severe LVD with multiple imaging modalities, including ceCMR, before and after revascularization and found a sensitivity of 99% and an NPV of 99% when a 50% hyperenhancement cutoff value was used.

Studies comparing ceCMR with other modalities of viability testing have shown favorable results. Klein and colleagues[8] studied 31 ischemic heart failure patients with PET and ceCMR and found close agreement between the 2 modalities, with the increased spatial resolution of ceCMR allowing for better delineation of scar tissue. Lee and coworkers[31] found superior detection of subendocardial infarct with ceCMR compared with Tc-99m SPECT.

Dobutamine MR has the advantage of providing superior endocardial border definition on cine images, which helps to more accurately assess regional wall motion and end-diastolic wall thickness as compared with other modalities. Baer and colleagues[32] compared dobutamine MR with FDG-PET in patients with LVD and found sensitivity, specificity, and PPV of 88%, 87%, and 92%, respectively, when either preserved end-diastolic wall thickness or contractile reserve was seen. As compared with dobutamine transesophageal echocardiography, dobutamine MR had a higher sensitivity and specificity for detecting FDG-PET–defined myocardial viability in 43 patients with LVD.[33] Gunning and coworkers[34] and Sandstede and colleagues[35] found lower sensitivities (50% and 60%, respectively) but strong specificities (81% and 90%, respectively) when comparing dobutamine MR with other modalities.

Limitations of MR include the need for a prolonged breath hold, the inability to image patients with devices such as defibrillators or pacemakers, and problems associated with gating in patients with arrhythmias.

Overall Comparison of Imaging Techniques

The analysis of pooled data from 77 studies revealed that the sensitivity for predicting functional recovery was high for PET, SPECT, and dobutamine echocardiography techniques (Table 1).[12] FDG-PET had the highest sensitivity, and dobutamine echocardiography had the highest specificity. Dobutamine echo had the highest PPV, and FDG-PET had the highest NPV. A pooled analysis of the 2 studies in which ceCMR was used in patients undergoing revascularization yielded a sensitivity of 82%, specificity of 63%, PPV of 72%, and NPV of 75%, when the 25% hyperenhancement cutoff of all dysfunctional segments was used.[28,29] When considering only the segments

Table 1
Comparison of Imaging Techniques

	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
FDG-PET[12]	93	58	71	86
SPECT[12]	86	59	69	80
Dobutamine Echocardiography[12]	81	80	77	85
ceCMR[28,29]	82	63	72	75

FDG-PET, fluoro-2-deoxy-D-glucose–positron emission tomography; SPECT, single-photon emission computed tomography; ceCMR, contrast-enhanced cardiac magnetic resonance.

with severe hypokinesia, akinesia, or dyskinesia, the pooled results yielded a PPV and NPV of 80% and 79%, respectively. A hyperenhancement cutoff of less than 50% increased sensitivity and negative predictive values.[28] Dobutamine MR has compared well with other modalities but has not been studied against the standard of improvement after revascularization.

Summary

With the rising prevalence of ischemic cardiomyopathy, the assessment of myocardial viability for the prediction of functional recovery after revascularization has become an important clinical issue. Different noninvasive imaging techniques have been developed to identify hibernating myocardium. Dobutamine echocardiography and nuclear imaging have been extensively used for the assessment of hibernating myocardium, and newer techniques such as MR imaging will further enhance the assessment of viability with high spatial resolution, relative freedom from artifacts, and simultaneous information on contractile function. Integrated information obtained from these techniques can optimize patient selection for revascularization, with the possibility of improved outcome and long-term survival after revascularization. Because each technique has its own benefits and limitations, clinical sense and local expertise dictate which modality is best for each individual patient. ■

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Main Points

- Stunned myocardium refers to transient depression of contractile function secondary to an acute ischemic insult.
- Hibernating myocardium is a form of contractile dysfunction of living myocytes in the setting of chronic ischemia or chronically reduced flow reserve.
- Positron emission tomography (PET) historically has been the gold standard of viability testing prior to revascularization. The strength of PET lies in the use of metabolic tracers that can be imaged and quantified in their areas of uptake.
- Robust data have shown single-photon emission computed tomography to be comparable with PET in assessing viability.
- Dobutamine echocardiography has been well studied as a method of assessing myocardial viability and has been shown to predict improved survival postrevascularization.
- Cardiac magnetic resonance, with its uniquely high spatial resolution, is potentially the gold standard of myocardial viability assessment.

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