Revascularization in Patients With Severe Left Ventricular Dysfunction

Is the Assessment of Viability Still Viable?

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ABSTRACT

Myocardial viability assessment is typically reserved for patients with coronary artery disease and significant left ventricular dysfunction. In this setting, there is myocardial adaptation to an altered physiological state that is potentially reversible. Imaging can characterize different parameters of cardiac function; however, despite previously published appraisals of different imaging modalities, there is still uncertainty regarding the role of these tests in clinical practice. The purpose of this review is to reflect on the physiological basis of myocardial viability, discuss the imaging tests available that characterize myocardial viability, and summarize the current published reports on the use of these tests in clinical practice. (J Am Coll Cardiol 2016;67:2874–87) © 2016 by the American College of Cardiology Foundation.

Myocardial injury occurs through varied mechanisms, most commonly in the setting of coronary artery disease (CAD). Cardiac dysfunction consequently leads to a cascade of molecular events to maintain physiological equilibrium. Clinical heart failure may ensue secondary to pump dysfunction and arrhythmias, causing significant morbidity and mortality. Therapy is multifaceted, including revascularization paralleled with ancillary pharmacological and nonpharmacological strategies. The pharmacological armamentarium focuses on altering the neurohormonal response; the nonpharmacological approaches, primarily cardiac resynchronization therapy, focus on improving electrical synchrony. The goal is to optimize cardiovascular function, prevent progressive remodeling, allay symptoms of heart failure, and improve survival.

A challenging clinical scenario remains: the patient with severe cardiac dysfunction receiving optimal medical therapy (OMT) and carrying significant surgical risk. Can we improve symptoms? Can we improve survival? Is there a role for viability testing? Is there a standalone test, or should different modalities be used complementarily?

This review aims to elaborate on these issues that are emerging in contemporary practice. We will review the pathophysiological events in ischemic cardiac dysfunction, noninvasive strategies to image viable myocardium, and the current published reports regarding patient outcomes with decisions aided by viability testing.

THE PIVOTAL IMPORTANCE OF VENTRICULAR DYSFUNCTION AND PROGNOSIS

It has been known for close to half a century that left ventricular (LV) function is of prognostic significance in cardiovascular disease. In a 10-year follow up of survival in CASS (Coronary Artery Surgery Study), admittedly in an era when advances in medical therapeutics were only in their infancy, the presence of LV dysfunction represented an important discriminant for benefit from bypass graft surgery (1). A striking finding in the same study was the relatively low 10-year mortality of patients who had a normal ejection fraction (EF), irrespective of the number of diseased coronary vessels (1). The importance of ventricular function has been borne out in multiple investigations spanning several decades; the purported mechanisms of benefit post-revascularization being manifold, extending beyond the treatment of ischemia alone (Figure 1) (1-10).

After injury, the heart undergoes adaptive changes with alterations in geometry and function. The process of remodeling is dictated by hemodynamic and neurohormonal factors (11), which trigger a cascade of events that alter the interaction of myocytes with each other and with the extracellular matrix. Macroscopically this manifests in changes in size, shape, and wall thickness of the heart. Although initially adaptive, if unchecked, the continued stimulus for these changes leads to deleterious effects in the setting of pre-existing CAD, including progression to
symptomatic heart failure and worsening ischemia. Multiple neurohormonal mechanisms established in the pathogenesis of heart failure currently serve as important targets in medical therapy (12–17). The importance of these neurohormonal mechanisms is underscored by a recent study (18) quantifying inhomogeneity in myocardial sympathetic innervation using positron emission tomography (PET), which found this to be predictive of cardiac arrest. The study comprised 204 subjects with moderate to severe reduction in LV function. Myocardial sympathetic denervation was quantified using the tracer ¹¹C-meta-hydroxyephedrine and was predictive of sudden cardiac arrest. Interestingly, other multivariate predictors of sudden cardiac arrest included end-diastolic volume, serum creatinine, and the absence of angiotensin inhibition. These findings emphasize that the physiological milieu is critical in predicting outcomes in patients with ischemic cardiomyopathy and that evaluation of such patients must extend beyond ischemia testing alone.

Cardiac function is not a dichotomous variable; aspects of function measured using one modality might not be measureable using another. In the area of myocardial viability testing, published reports regarding the indications for revascularization in the context of the extent of potentially reversible LV dysfunction remain controversial. Under the rubric of viability, is it the EF, extent of remodeling, extent of scar, extent of ischemia, duration of dysfunction, or a combination that should drive the strategy to treat? In isolation, these parameters are useful, but their utility could be more powerful in combination (19), allowing for a more complete characterization of the entire myocardial substrate. Such an approach has been found to be of clinical utility in a small pilot study (19); however, multimodality imaging in the evaluation of myocardial viability has not been studied systematically and is not currently recommended.

**MYOCARDIAL VIABILITY: STUNNING, HIBERNATION, AND THE MYOCARDIAL SUBSTRATE**

Pathophysiologically, myocardial viability refers to those cardiomyocytes that are “alive,” defined by cellular, metabolic, and microscopic contractile function (7,20). Clinically, hibernating and stunned myocardium are subdivisions with differing but sometimes overlapping characteristics (Figure 2).

The first description of myocardial response to acute coronary occlusion was in a dog model in 1935 (21). In this experiment, ligation of a large coronary branch vessel resulted in a cyanotic and dilated heart with alterations in contractile function. Nearly half a century subsequent to this description, the notion of the “stunned” myocardium was born (22,23).

Acutely reduced blood flow initially causes contractile dysfunction that persists after blood flow is restored, and this was initially referred as the “hit, run, and stun” phenomenon (22). Although the exact mechanism remains unclear, it likely represents the response of the myocardium to metabolic aberrations created by acute ischemia. This view is supported by the lack of ultrastructural changes in myocyte appearance (23,24) and the observation of recovery of function, typically over hours to days (7).

It is clear that markedly depressed LV function in the setting of ischemic cardiomyopathy can be reversed with revascularization (9,25). Moreover, those patients with ischemic symptoms and the most severe LV dysfunction appear to benefit most from surgical revascularization. In this scenario, a high periprocedural risk must be weighed against an improvement in late mortality (Central Illustration) (26). These findings were recently confirmed in a 10-year follow-up of patients with ischemic cardiomyopathy, LV dysfunction (LVEF <35%), and CAD amenable to coronary artery bypass graft (CABG) (27). In this study, the rate of death of any cause over 10 years was significantly reduced by an absolute difference of 8% in patients who underwent CABG in addition to OMT compared with those receiving optimal contemporary medical therapy alone (27).

Hibernating myocardium was initially considered to represent an adaptation to a persistent reduction in
blood flow, significant enough to impair function but not to produce infarction per se (23). This postulate was supported by findings of reduced resting myocardial blood flow in dysfunctional myocardial segments, as measured by cardiac magnetic resonance (CMR) and PET imaging techniques (28,29). However, this mechanism is not definitive, because other investigations suggest that the pathogenesis of myocardial hibernation might be nonlinear, with examples of reductions in coronary blood flow that follow LV dysfunction rather than precede it (23,30,31). Biopsy specimens of hibernating myocardium demonstrate alterations in both cellular and extracellular structure. Observations at the cellular level include dedifferentiation to a more embryonic phenotype characterized by loss of sarcomeres and myofibrils, as well as increased storage glycogen (23,32–34). These cellular changes are coupled with fibrotic changes in the extracellular matrix. The extent of extracellular fibrosis could be linked to reversibility of hibernation, with areas of reduced or absent fibrosis predictive of functional recovery after revascularization (23,34,35). In contradistinction to stunned myocardium, functional recovery of the hibernating myocardium is more variable and is likely determined by the severity of derangements incurred at the microscopic level. The time of recovery can be as little as 10 days when the structural abnormalities are minor, or to 6 months and beyond when there is severe ultrastructural derangement, with one study documenting functional improvement extending to 14 months (32,36,37).

Although conceptually, the distinction between stunned and hibernating myocardium has important clinical implications, both can coexist, and indeed, hibernation might represent an adaptation to repetitive stunning (Figure 2) (7). Revascularization in patients with significant viability has been shown to improve outcomes, cardiac function, and functional class in many observational studies (38). In patients with significant viable myocardium (~20%) in the setting of ventricular dysfunction, mortality increases when the therapeutic strategy is medical therapy alone (39), which underscores the importance of identifying these patients to provide effective therapy.

Myocardial substrate characterization could help stratify patients who might benefit from revascularization. In a pilot study that used single-photon emission computed tomography (SPECT) to characterize myocardial function (19), the spectrum of myocardial abnormalities proved to be complex. In this study, a unique 4-step imaging protocol was implemented that took into account regional rest and stress perfusion, as well as contractile function, with dobutamine as the stress agent (19). Contractile reserve was assessed with image acquisition during low-dose dobutamine infusion. Four states of myocardial dysfunction were defined. Myocardial hibernation was defined as segments with severe systolic dysfunction with evidence of hypoperfusion at rest; myocardial stunning was defined as the presence of contractile dysfunction in the setting of normal perfusion. Myocardial remodeling included segments with regional dysfunction, with only mild to moderate resting perfusion defects and no dobutamine-inducible ischemia. Finally, myocardial scarring included segments with regional dysfunction and severe fixed perfusion defects at rest and stress. This study (19) demonstrated that even after the strict use of these definitions to distinguish myocardial substrate characteristics, different states could coexist within the same patient, and even within the same vascular territory. Moreover, each of these varied pathophysiological states will have differing tendencies to recover after revascularization, which further challenges the ability to predict response to therapy. Similarly, in a substudy comprising 399 patients (40), the presence of inducible ischemia in the setting of moderate to severe LV dysfunction was not found to predict better outcomes with surgical revascularization compared with OMT. These findings held regardless of intention-to-treat, as-treated, or per-protocol analysis. In a very large observational study comprising close to 14,000 patients (41) that used adenosine or exercise SPECT imaging, the presence of significant ischemia in patients in the

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**FIGURE 2** Hibernation and Stunning

<table>
<thead>
<tr>
<th>Mechanistic differences and similarities</th>
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</thead>
<tbody>
<tr>
<td><strong>Stunning</strong></td>
</tr>
<tr>
<td>- Adverse effect of ischemic injury</td>
</tr>
<tr>
<td>- No histopathologic abnormalities</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

Myocardial hibernation and stunning in the pathophysiology of reversible left ventricular dysfunction. These pathophysiologial entities appear to lie on a spectrum of cellular and molecular adaptations to reduced myocardial blood flow. CFR – coronary flow reserve.
setting of reduced scar burden (defined as <10% of the myocardium) predicted survival after early revascularization. This was in contradistinction to those patients who had ischemia with large scar burden, for whom a benefit from revascularization was not observed. These studies (19,40,41) highlight the importance of myocardial substrate characterization in the assessment of patients with severe ischemic heart disease. Management remains challenging, because a mixed picture of scarred, hibernating, stunned, and remodeled myocardium might confound the purported benefits of revascularization alone, which emphasizes the importance of neurohormonal pathway modification. Currently, a single imaging modality cannot both define these alterations and categorize them pathophysiologically. By identifying and characterizing abnormal myocardium, complementary multimodality imaging provides an opportunity to help determine candidacy for revascularization therapies.

**TESTS TO DETERMINE MYOCARDIAL VIABILITY**

The spectrum of viability testing includes nuclear, ultrasound, and magnetic resonance-based
techniques. These tests have variable sensitivity and specificity ranges and technical limitations; availability also influences their use in clinical practice (Figure 3, Tables 1 and 2).

**PET AND SPECT: DOCUMENTATION OF INTACT MYOCARDIAL PERFUSION AND METABOLISM.** PET identifies segments with reduced perfusion but preserved metabolism, thereby identifying viable

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**FIGURE 3** Range of Sensitivity, Specificity, PPV, and NPV of Currently Available Viability Testing Modalities

![Range of Sensitivity, Specificity, PPV, and NPV of Currently Available Viability Testing Modalities](image)

18F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging offers the greatest sensitivity, with comparable specificity to other modalities. Dobutamine echocardiography offers the greatest specificity at the cost of reduced sensitivity. The positive predictive value (PPV) is similar among the imaging modalities; however, PET appears to have a greater negative predictive value (NPV) in this pooled dataset. Data on cardiac magnetic resonance are limited by the reduced number of available studies. Adapted with permission from Schinkel et al. (64). DSE — dobutamine stress echocardiography; Tc — technetium.

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**TABLE 1** Comparison of the Ability of Imaging Techniques to Assess Ventricular Function and Characterize Myocardial Infarct Size

<table>
<thead>
<tr>
<th>Technique</th>
<th>Ventricular Functional Assessment</th>
<th>Scar Characterization</th>
</tr>
</thead>
</table>
| Echocardiography           | - Assesses both RV and LV systolic and diastolic function with quantitative and qualitative measures  
- Delineates contractile reserve with low-dose dobutamine  
- Strain imaging emerging as a complement to functional assessment  
- Can be performed at the bedside | - Scar determination based on qualitative measures including myocardial thinning, echogenicity, and regional contractility |
| Nuclear cardiac imaging    | - Assesses LV function with well-validated quantitative measures  
- Current reference standard for volumetric assessment of RV and LV  
- Delineates contractile reserve with low-dose dobutamine | - Scar quantitation techniques most robust in available published data |
| Magnetic resonance imaging | - Assesses both RV and LV function  
- Current reference standard for volumetric assessment of RV and LV  
- Delineates contractile reserve with low-dose dobutamine | - Scar quantitation is well validated and considered reference standard  
- Both infarct size and transmurality can be assessed  
- Assessment of RV involvement in the infarct  
- Microvascular obstruction assessment |
| Cardiac CT                 | - Strength in quantifying ventricular volumes | - Investigational |

CT = computed tomography; LV = left ventricle; RV = right ventricle.
TABLE 2  Comparison of Imaging Modalities Used to Test Myocardial Viability

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Radiation Exposure</th>
<th>Perfusion Imaging</th>
<th>Stress-Induced Ischemia</th>
<th>Assessment of Viability</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>201Tl SPECT</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Sarcolemmal integrity</td>
<td>Limited spatial resolution</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Highest radiation exposure</td>
</tr>
<tr>
<td>99mTc SPECT</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Mitochondrial membrane integrity</td>
<td>Limited spatial resolution</td>
</tr>
<tr>
<td>Cardiac PET</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Cellular glucose uptake capacity</td>
<td>Limited spatial resolution</td>
</tr>
<tr>
<td>Dobutamine echocardiography</td>
<td>No</td>
<td>Not approved</td>
<td>Yes</td>
<td>Contractile reserve</td>
<td>Limited acoustic windows</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Interobserver variability</td>
</tr>
<tr>
<td>CMR</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Contractile reserve</td>
<td>Avoid in patients with cardiac devices</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Avoid in patients with GFR &lt;30 ml/min/1.73 m²</td>
</tr>
<tr>
<td>PET CT</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Cellular glucose uptake capacity</td>
<td>Body habitus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not widely available</td>
</tr>
<tr>
<td>PET CMR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Cellular glucose uptake capacity</td>
<td>Need studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Contractile reserve</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Need studies</td>
</tr>
</tbody>
</table>

*PET CT and PET CMR are emerging hybrid imaging modalities that have yet to be studied. PET CT could add value by decreasing attenuation artifact by coregistration of anatomic information provided by CT with the metabolic and perfusion data provided by PET. PET CMR holds promise in its potential to combine perfusion, metabolic, and contractile information.

CMR = cardiac magnetic resonance; CT = computed tomography; GFR = glomerular filtration rate; PET = positron emission tomography; SPECT = single-photon emission computed tomography; Tc = technetium; Tl = thallium.

myocardium. PET has robust built-in attenuation correction, traditionally with line or rod sources and more recently with CT, which is particularly useful when imaging obese patients and female patients. Advances in PET technology have led to further reductions in radiation dose per scan, improved spatial resolution, and gated sequences for accurate measurement of cardiac function (23,42).

The PET imaging protocol is divided into 2 parts: the first assesses myocardial perfusion; the second assesses myocardial metabolism. Radionuclides commonly used in perfusion imaging include rubidium 82 and N-13 ammonia, the uptake of which is proportional to myocardial blood flow. Metabolic imaging with 18F-fluorodeoxyglucose (FDG) relies on a physiological milieu in which the myocardium utilizes glucose as the metabolic substrate. Under normal circumstances, the myocardium utilizes free fatty acids as the most efficient and readily available energy source; however, alterations imposed by chronic ischemia favor a substrate switch to glucose. The same carrier that transports glucose transports FDG into the cell; FDG uptake therefore represents a marker of glucose utilization, which will be normal or increased in viable myocardium. Traditionally, PET viability imaging is performed under resting conditions; however, assessment of stress-induced ischemia can be added to the protocol, because its presence affects outcomes with revascularization.

With PET viability imaging, there are 4 patterns that need consideration. The most important is a perfusion-metabolism mismatch: reduced myocardial perfusion and contractile function in the setting of relatively preserved or increased FDG uptake. This pattern suggests the presence of viable, hibernating myocardium. A second pattern includes regions of normal perfusion and normal metabolism in dysfunctional segments. In this setting, the myocardium may be normal or stunned, and in the setting of a dilated ventricle, the pattern may represent a remodeled heart. The distinction between stunned myocardium and the remodeled ventricle might not be clear from rest perfusion and metabolism images alone, and in this scenario, ischemia testing can help identify ischemic segments that typify stunned myocardium. A third pattern comprises segments of reduced perfusion and metabolism, which usually indicate presence of scar. The latter is associated with an inverse relation to improvement in LV function after revascularization (43). A final pattern, referred to as a reversed mismatch, demonstrates normal perfusion but reduced FDG uptake. Such a scenario has been observed in the setting of revascularization early after myocardial infarction, left bundle branch block, right ventricular pacing, nonischemic cardiomyopathy, and diabetes mellitus (23). Given the presence of normal perfusion, these findings are typically interpreted to mean presence of viable myocardium.

The radionuclides used in SPECT imaging include thallium-201 and technetium-99m. Although SPECT imaging is widely available and provides estimates of resting perfusion, stress-induced ischemia, extent of scar, and cardiac function, it underestimates the presence of viability. For example, a fixed defect on stress-4-h redistribution thallium-201 SPECT or
stress-rest technetium-99m SPECT could represent either severe hypoperfusion or scar (44,45). The initial uptake of thallium is flow dependent, with a high first-pass myocardial extraction fraction across physiological ranges of myocardial blood flow. The myocardial uptake of thallium-201 is a sarcosomal membrane sodium-potassium adenosine triphosphatase-dependent active process that requires cell membrane integrity and is therefore indicative of myocardial viability. Regions demonstrating redistribution of thallium correlate with regions of FDG uptake on PET imaging (46,47). There are several available protocols for viability assessment using thallium-201. Rest-redistribution protocols depend on the initial flow-dependent kinetics of thallium-201. A defect seen on an image taken soon after a rest injection is related to the resting myocardial blood flow; however, a significant percentage of resting thallium-201 defects show redistribution when reimaged several hours after injection (48,49). Segments that show a reversible resting thallium-201 defect often have improved function after revascularization, which suggests regional myocardial viability. Stress-redistribution imaging protocols may demonstrate stress-induced thallium defects that normalize on serial imaging several hours after initial image acquisition, thereby indicating viability (50). Late-redistribution imaging is predicated on the fact that under some circumstances, the redistribution of thallium-201 takes longer than the 4 h typically used in standard stress-redistribution protocols. This observation led to the development of late-redistribution protocols, which generally involve redistribution imaging 18 to 24 h after thallium-201 injection. With these protocols, thallium-201 redistribution is seen in a significant number of perfusion defects deemed fixed by imaging at 4 h (51-54). Late thallium-201 redistribution has been validated as an accurate predictor of viability, with up to 95% of segments with late redistribution showing improved stress perfusion after revascularization (54). However, as with early (3 to 4 h) redistribution, the absence of late redistribution underestimates the presence of viable myocardium in up to 37% of segments that show an improvement in function after revascularization (54). This suggests that some ischemic but viable myocardial segments might never redistribute, even with late imaging, unless blood levels of thallium-201 are increased. To circumvent some of the problems associated with redistribution imaging related to blood levels of thallium-201, reinjection protocols have also been established. Thallium reinjection performed immediately after late (24 h) redistribution in 30 patients showed defect reversibility in 40% of regions that appeared to be fixed on later redistribution in 18 patients (55). Among patients who had thallium-201 reinjection performed immediately after 3- to 4-h redistribution and subsequently underwent coronary artery revascularization, 87% of regions identified as viable by reinjection studies had normal thallium-201 uptake and improved regional wall motion after revascularization. In contrast, all regions with fixed defects after reinjection had persistent wall motion abnormalities after revascularization (56).

Sestamibi and tetrofosmin are tracer agents that are taken up and retained in the mitochondria, reflecting intact mitochondrial membranes and implying integrity of mitochondrial function, and thus are markers of cellular viability. A significant difference from thallium-201 is that these agents show minimal redistribution within the myocardium. With a few exceptions (57-69), studies comparing viability detection with technetium-99m-labeled radiotracers versus thallium-201 and FDG-PET have generally demonstrated that technetium-99m tracers underestimate myocardial viability; however, improvement in viability assessment with technetium-99m agents could be achieved through nitrate administration before rest radiotracer injection and quantification of regional radiotracer uptake (60,61).

**ECHOCARDIOGRAPHY: DOCUMENTATION OF MYOCARDIAL CONTRACTILE RESERVE.** The echocardiographic evaluation of myocardial viability includes assessment of cardiac size, shape, and wall thickness combined with regional wall motion. Areas of wall thinning and akinesis usually represent presence of scar. The addition of dobutamine infusion assesses contractile reserve, a crucial component of the examination to determine viability in dysfunctional segments. A biphasic response, which refers to an initial improvement in contractile function with low-dose dobutamine followed by deterioration with higher doses, is the most significant finding to predict recovery after revascularization (62).

Myocardial contrast echocardiography has advanced our ability to assess wall motion and myocardial perfusion. In one study, myocardial contrast echocardiography improved identification of ischemia in the left anterior descending territory and in multivessel disease compared with wall motion assessment alone (63). However, myocardial contrast echocardiography is not yet approved for myocardial perfusion imaging, and its utility in the evaluation of myocardial viability imaging is still to be determined.

**CMR: DOCUMENTATION OF MYOCARDIAL SCAR AS EVIDENCE OF NONViable TISSUE.** CMR has an emerging role in the assessment of myocardial
viability. A systematic approach that uses CMR first includes an evaluation of cardiac shape, size, wall thickness, and derivation of cardiac volumes and mass. Second is the assessment of global and regional wall motion abnormalities. The addition of low-dose dobutamine can assess contractile reserve similar to that used in echocardiography (64). Real-time perfusion imaging with intravenous gadolinium contrast allows assessment of perfusion defects. The fundamental component of the examination involves assessment for the presence of delayed myocardial enhancement after intravenous gadolinium administration. The high spatial resolution of CMR allows delineation of transmural extent of scar, which is currently not possible with nuclear cardiac imaging or echocardiography (65). The probability of improvement of regional contractile function after revascularization is directly related to the extent of transmural viability. These data suggest that recovery of function after revascularization is a continuum and is coupled to the ratio of viable to scarred myocardium within the dysfunctional myocardial region and also correlates with findings of nuclear-based imaging techniques (66).

**ROLE OF VIABILITY TESTING IN THE MANAGEMENT OF PATIENTS WITH ISCHEMIC CARDIOMYOPATHY**

Published data encompassing viability testing are weighted by small, single-center, observational studies during an era when medical therapies for ischemic heart disease have expanded markedly (8). Studies in the field have limitations in design, which results in challenges in their applicability to clinical practice. These limitations arise mostly because of differences in definition of viability, cutoffs for clinical endpoints, and differences in inclusion criteria for these studies. Furthermore, in complex CAD, a description of the completeness of revascularization is important to understanding the outcomes of revascularization (67) and could influence the utility of upstream viability testing. Further challenges are posed by the complexity of myocardial substrate abnormalities, with combinations of stunned, hibernating, remodeled, and scarred myocardium commonly being identified in the same patient (19). Therefore, there continue to be large knowledge gaps regarding application of noninvasive viability testing in patients with complex CAD and LV dysfunction.

Nevertheless, despite these challenges, 2 important initial concepts have surfaced. First, in patients with ischemic cardiomyopathy and viability noted on noninvasive testing, medical treatment alone is associated with worse outcomes, and conversely, those patients with viability detected by noninvasive testing, including SPECT, FDG-PET, and echocardiography, demonstrate significantly improved survival with revascularization compared with medical therapy alone (6–8,68–70). However, in these nonrandomized studies, medical therapy was not standardized, and adherence was not described (6,71). More recently, viability testing with CMR has paralleled the findings observed with the other modalities. In a report of 144 patients with ischemic cardiomyopathy who underwent CMR, patients deemed to have viable myocardium treated medically fared worse than those who underwent revascularization (72). Second, published reports suggest that the presence of myocardial viability on noninvasive testing predicts improvement in regional LV function, as well as heart failure symptoms and exercise capacity after revascularization (7,64,73); however, the relationship between improvement in indexes of ventricular performance and functional performance remains unclear. Furthermore, gradations of myocardial viability that could predict functional improvement, as measured by exercise capacity, remain to be delineated and may differ among the techniques.

The role of noninvasive viability testing in clinical decision making has been evaluated in only a few prospective clinical trials. CHRISTMAS (Carvedilol Hibernation Reversible Ischemia Trial: Marker of Success) was a double-blind, randomized trial of medical therapy in chronic LV dysfunction (74,75). This trial assessed the efficacy of carvedilol treatment in patients with hibernation or ischemia using both nuclear and echocardiographic techniques to identify the presence and extent of hibernation. The study found that the volume of myocardium affected by hibernation, ischemia, or both is an important determinant of the improvement of LV function (as assessed by LVEF) with carvedilol treatment (75), with little or no increase in LVEF in the absence of viability (75). Patients in the placebo arm demonstrated an increase in the number of segments with reduced viability over time, including segments that were previously classified as hibernating (75). This highlights the complexity and heterogeneity of the myocardial substrate underlying LV dysfunction caused by CAD. The role of revascularization was not specifically studied in this trial (75).

The PARR-1 (Positron Emission Tomography and Recovery Following Revascularization) study was a prospective multicenter cohort study (43). In this study, extent of scar was an independent predictor of ventricular functional recovery after...
revascularization, with smaller scar scores predicting greater improvement in LVEF (43). Small numbers (82 patients) and absence of important parameters of function, including ventricular volumes and stress-induced ischemia, limited this pilot study.

The PARR-2 study (76) was designed to assess the effectiveness of FDG-PET-assisted management in patients with severe LV dysfunction and suspected CAD compared with standard of care (Table 3). The study randomized 430 patients, with 218 patients receiving PET-assisted care and 212 receiving standard therapy (76). The study did not demonstrate a significant reduction in cardiac events with FDG-PET-directed therapy compared with the standard of care (76). Nonetheless, there are important nuances that deserve mention. First, the standard-of-care arm could include a non-PET viability test. Second, close to 25% of the FDG-PET study group were not managed according to imaging recommendations, primarily driven by the discretion of the clinician caring for the patient (76). Notably, when the analysis included only those who adhered to the PET-guided recommendations, there was a significant benefit for FDG PET. Additionally, there was benefit for FDG PET in the group without recent coronary angiography. A sub-study of the PARR-2 trial confirmed the established trend that patients with ischemic cardiomyopathy with larger amounts of perfusion-metabolism mismatch have improved outcomes with revascularization (77). In this study, if >7% of the LV demonstrated viability, there was a benefit from revascularization with regard to a composite endpoint of cardiac death, myocardial infarction, or cardiac repeat hospital stay at 1 year. Lastly, renal impairment was an independent prognosticator, as found in other studies (77, 78).

### TABLE 3 Comparison of the PARR-2 and STICH Trials

<table>
<thead>
<tr>
<th></th>
<th>PARR-2</th>
<th>STICH (Viability Substudy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Randomized controlled trial</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>Premise</td>
<td>Comparison of an imaging-guided strategy to standard care for ischemic cardiomyopathy</td>
<td>Outcome of revascularization vs. optimal medical therapy for ischemic cardiomyopathy</td>
</tr>
<tr>
<td>Number of patients</td>
<td>430</td>
<td>601</td>
</tr>
<tr>
<td>Centers</td>
<td>Multicenter (9 centers)</td>
<td>Multicenter (99 centers)</td>
</tr>
<tr>
<td>Viability test</td>
<td>PET</td>
<td>Echocardiography (SPECT)</td>
</tr>
<tr>
<td>Study endpoints</td>
<td>Primary: occurrence of cardiac death, MI, or hospital stays for cardiac cause  Secondary: time to occurrence of the primary endpoint and time to cardiac death</td>
<td>Primary: rate of death due to any cause  Secondary: rate of death due to cardiovascular causes and rate of death due to any cause or hospitalization for cardiovascular causes</td>
</tr>
<tr>
<td>Intervention</td>
<td>CABG/PCI</td>
<td>CABG</td>
</tr>
<tr>
<td>Patient characteristics, n or n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Female</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>Baseline LVEF, %</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>NYHA functional class II to IV</td>
<td>352 (82)</td>
<td>574 (96)</td>
</tr>
<tr>
<td>CCS II-IV</td>
<td>198 (46)</td>
<td>271 (45)</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>80 (19)</td>
<td>16 (3)</td>
</tr>
<tr>
<td>Prior MI</td>
<td>346 (80)</td>
<td>481 (80)</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>146 (34)</td>
<td>43 (7)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>167 (39)</td>
<td>224 (37)</td>
</tr>
<tr>
<td>Median follow-up, yrs</td>
<td>1</td>
<td>5.1</td>
</tr>
<tr>
<td>Caveats</td>
<td>25% of the FDG-PET study group were not managed according to imaging recommendations  Patients assigned to CABG had lower rates of cardiovascular death and of the composite endpoint of death of any cause or hospitalization for cardiovascular causes</td>
<td>Viability study nonrandomized  83% of subjects in the viability substudy were Caucasian compared with 54% of subjects in the STICH trial who did not have a viability test  Subgroups of patients assigned to the FDG PET group who had recent angiography or who adhered to imaging recommendations had better outcomes</td>
</tr>
<tr>
<td>Main result</td>
<td>No difference between an imaging-guided strategy and standard care</td>
<td>No incremental benefit of revascularization strategy over optimal medical therapy</td>
</tr>
</tbody>
</table>

CABG = coronary artery bypass graft; CCS = Canadian Cardiovascular Society; FDG = fluorodeoxyglucose; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; PARR = Positron Emission Tomography and Recovery Following Revascularization; PCI = percutaneous coronary intervention; STICH = Surgical Treatment for Ischemic Heart Failure; other abbreviations as in Table 2.
A study in the STICH investigation sought to examine the role of myocardial viability in identifying patients who might have a survival benefit with CABG (82). In this nonrandomized substudy, the optional viability tests included SPECT and dobutamine echocardiography (82). Notably, neither FDG-PET, which was established as the most sensitive test for viability (64) at the time of study enrollment, nor CMR were options for viability testing. Of the 1,212 patients enrolled into STICH, only 601 underwent viability testing. The assignment of presence or absence of viability was classified by use of a binary approach. In the SPECT imaging group, the presence of substantial viability was defined as those with 11 or more viable segments. For dobutamine echocardiography, this same threshold was met in those patients with 5 or more viable segments (82). Other important parameters of ventricular function, including size, shape, wall thickness, and cardiac mass, were not used in the predictive model.

In the STICH viability substudy, of the 601 patients who underwent viability testing, 487 patients were found with and 114 without substantial viable myocardium. In both groups, there was a balanced distribution of those receiving OMT alone versus OMT and CABG (82). At first glance, the investigation suggested that the presence of substantial myocardial viability portended a survival benefit, with 63% survival of patients with viability versus 49% survival of patients without viability. After adjustment for baseline variables, this significance was lost. Additionally, there was no demonstrable relationship between the viability information, treatment allocation, or patient outcome, and this was true regardless of whether patients were grouped according to intention-to-treat analysis or according to the treatment actually received. The results of this trial are controversial and remain a source of vigorous debate. There are some important limitations that must be emphasized. First, the substudy was nonrandomized, and <50% of patients enrolled in the study underwent viability testing. Second, viability testing was limited to SPECT or dobutamine echocardiography. Third, there was inherent bias regarding the decision to pursue viability testing, and the protocols for SPECT imaging varied among the multiple enrollment sites. Fourth, the presence of substantial viability was measured in a binary fashion, whereas the current published paradigm would contend that the concept of viability encompasses a wider spectrum (19). Fifth, ancillary information that is integral to understanding cardiac function, such as ventricular geometry, volumes, wall thickness, and EF, was not reported; there was no discussion regarding the association...
between SPECT tracer uptake and regional wall motion; and the biphasic response in patients who underwent dobutamine echocardiography was not used as a criterion for viability. Moreover, clinicians were not blinded to the results of viability testing, which has the potential to create an ethical dilemma regarding the enrollment of patients with ischemic heart disease and viability on the basis of noninvasive testing into a randomized clinical trial.

**FUTURE DIRECTIONS**

Myocardial viability testing in contemporary practice remains controversial. The promise of answers to important clinical questions hinged on the STICH investigation; however, several methodological issues, including the nonrandomized nature of the viability substudy and the potential for referral bias, limited this study. As it stands, the results of STICH can only truly be applied to a very small group of patients with severe LV dysfunction, a setting in which scar and deleterious remodeling could overwhelm whatever viable myocardium remains.

A recently published review highlights some of the major current challenges of trial design (83). Eliciting patient consent for randomization and recruiting centers to participate and accept randomization in the setting of clinical equipoise are some of the greatest hurdles to overcome. A spectrum exists, including stunned, hibernating, remodeled, and scarred myocardium. When the predominating abnormality is myocardial hibernation, revascularization would offer clinical benefit. Conversely, when the predominating abnormality is myocardial scarring, the benefit of high-risk procedural interventions is likely to be low. In reality, patients present with a mixture of abnormal myocardial substrates, the balance of which is challenging to define with a single imaging modality. Furthermore, although revascularization is considered the gold standard treatment, patients with intermediate pathophysiological findings might benefit from a more aggressive modification of neurohormonal and electrical activation. With the aforementioned caveats, we wait expectantly for the results of an ongoing trial, AIMI-HF (Alternative Imaging Modalities in Ischemic Heart Failure) (84). This study aims to randomize patients with ischemic heart failure to SPECT imaging, CMR, or PET to assess ischemia or viability (84), and it is hoped it will shed light on some of the current controversies.

So, is myocardial viability a viable concept in contemporary clinical practice? Viability testing might: 1) help predict the response to revascularization in selected patients with CAD and LV dysfunction; 2) be a marker of prognosis; and 3) influence response to medical therapy. Multimodality imaging could provide deeper insight into the spectrum of myocardial substrate, emphasizing not only the role of revascularization but also neurohormonal modulation and resynchronization therapy.

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**KEY WORDS** coronary artery bypass graft, coronary artery disease, myocardial hibernation, myocardial ischemia, myocardial stunning

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