Revascularization is a treatment option for moderate-to-severe ischemic cardiomyopathy. Limitations of the current literature, lack of completed randomized trials, and higher periprocedural risks create significant uncertainty about the optimal treatment strategy. This review focuses on the available literature describing the effect of revascularization on outcome and the role of noninvasive viability testing. It attempts to identify a subset of patients likely to benefit from therapy. (J Am Coll Cardiol 2005;46:567–74) © 2005 by the American College of Cardiology Foundation

Heart failure (HF) is a global epidemic of cardiovascular disease in the 21st century and is the most common Medicare diagnosis-related group. Annual HF hospital stays in the U.S. approximated 2.6 million during the last decade and might double in the next 40 years (1). In the older population, particularly women, survival after HF diagnosis has changed minimally (2).

Left ventricular (LV) systolic dysfunction underlies the traditional HF paradigm. In developed nations, the leading cause of LV dysfunction is coronary artery disease (CAD) (3). Established treatment options for ischemic HF include medical therapy, revascularization, and cardiac transplantation. Device therapy is a recent addition for eligible patients, but other modalities are investigational (4). Despite therapeutic advances, outcome of medical therapy in severe HF is poor (3). In specific subsets of patients, the potential benefits of revascularization must be weighed against the high periprocedural risks. We review the role of revascularization in moderate-to-severe LV systolic dysfunction and attempt to identify patients likely to benefit from this therapy.

CLINICAL RELEVANCE OF DYSFUNCTIONAL BUT VIABLE MYOCARDIUM WITH POTENTIAL FOR FUNCTIONAL RECOVERY

“Viable” describes myocardial cells that are alive, defined often by cellular, metabolic, and contractile functions. Although viable myocardium encompasses normally contracting and hypococontractile tissue, “viability” has been used interchangeably with “contractile recovery,” a clinical focus of ischemic HF; however, revascularization might provide long-term benefits even without contractile recovery by preventing further functional decline, additional infarctions, progressive LV dilation, and sudden cardiac death (5).

The dysfunctional viable myocardial states, “hibernating” and “stunned” myocardium, have distinct definitions and morphological characteristics with different implications for revascularization. “Hibernating myocardium” is chronically hypocontractile tissue due to persistently low flow with the potential to improve function after restoration of blood supply (6), although apparently conflicting data support both reduced and normal resting flow (7). Hibernating myocardium might represent adaptation to both impaired coronary flow reserve (repetitive ischemia and stunning) and reduced resting coronary blood flow (7). Biopsies of human hibernating myocardium demonstrate histologic changes of cellular dedifferentiation and an embryonic phenotype (7). The severity of ultrastructural changes correlates directly with the time course of functional recovery, but correction of cellular changes after the restoration of flow or flow reserve is likely only partial (7,8). These observations, and evidence that apoptosis is important in hibernation, underscore the importance of early revascularization in this dynamic transition from reversible to irreversible contractile dysfunction (7). Furthermore, in an animal model of hibernating myocardium, despite no pathologic infarction in most hearts, a high rate of sudden cardiac death parallels the poor clinical survival of medical therapy in hibernating myocardium (9).

“Stunning” is contractile dysfunction in viable myocardium resulting from transient ischemia, followed by restoration of perfusion (10). Pathogenesis likely involves oxyradicals and calcium. Dysfunction might persist from hours to days, but generally improves with time. An exception is “repetitive stunning,” defined as repeated episodes of ischemia producing prolonged post-ischemic contractile dysfunction (7), which is similar to hibernation in that revascularization has the potential to improve contractile function. Theoretically, hibernation and stunning are different pathophysiologic states; practically, they are often
indistinct, appear to coexist in varying degrees in the same patient or myocardial region, and represent a continuum of the same process. The interplay of this process and many other factors contributes to remodeling, progression of systolic dysfunction, and HF (Fig. 1).

The timing of functional recovery after revascularization appears to differ between stunned and hibernating myocardium. In an echocardiographic and radionuclide imaging study, nearly two-thirds of stunned segments exhibited early contractile recovery 3 months after revascularization, and only one-tenth showed late improvement at 14 months (8). In contrast, only about one-third of hibernating segments exhibited early improvement, but nearly two-thirds showed late recovery. These observations suggest that many published studies might have assessed contractile recovery too late. These studies have focused on advanced LV systolic dysfunction, and HF (Fig. 1).

Effects of surgery on survival. There are no completed randomized controlled trials of coronary artery bypass grafting (CABG) in patients with moderate-to-severe LV systolic dysfunction (left ventricular ejection fraction [LVEF] <35%) and in patients without angina as the predominant symptom. Therefore, nonrandomized cohort and registry studies have focused on advanced LV systolic dysfunction and HF. Present practice decisions are based largely on surgical studies performed nearly two decades ago, because of a paucity of data from contemporary therapy. In the two largest series, Coronary Artery Surgery Study registry (420 medical patients and 231 surgical patients) (12) and Duke University Cardiovascular Database (409 medical patients and 301 surgical patients) (13), CABG provided a significant long-term survival advantage over medical therapy, but surgical survival benefits were greatest for patients with the most severe LV systolic dysfunction (LVEF <25%), most extensive CAD, and most severe angina. Although these and other smaller studies, overall, favored surgery over medical therapy (Fig. 2), important limitations include the selection bias underlying the decision to treat surgically, the outdated medical therapy in both medical and surgical groups, under-use of internal mammary artery grafts, small number of patients (particularly with predominant HF symptoms), and lack of routine preoperative viability assessment (14).

Effects of surgery on functional status. Only observational data on quality of life and symptoms are available for advanced LV dysfunction. Early observational series reported lack of consistent symptomatic benefit with CABG, and functional improvement was observed in only 9% to 25% of patients (14). Most subsequent observational studies, however, demonstrated that HF symptoms improved in 59% to 92% of surviving patients after CABG (14).

Effects of surgery on LV systolic function. Only one small randomized study has examined the effect of CABG on LVEF (15). A nonsignificant increase in LVEF occurred at five years in both surgical (n = 102) and medical (n = 92) groups. Observational series have shown significant improvement in LVEF after CABG, but had few patients (n = 9 to 38) with moderate-to-severe LV systolic dysfunction (14).

Promising and adjunctive surgical approaches to LV systolic dysfunction, including mitral valve repair, surgical ventricular restoration, cardiac restraint devices, and prolonged mechanical decompression with LV assist devices, are being investigated (1,16).

Percutaneous transluminal coronary angioplasty (PTCA) in LV systolic dysfunction. A few case series have suggested that PTCA alone can relieve angina and improve LVEF or regional contraction (17). Coronary stenting shows promise, but has not been systematically investigated (17).

CABG versus percutaneous coronary intervention in LV systolic dysfunction. In a recently concluded trial (18), 36-month survival for randomized percutaneous coronary intervention patients with LVEF <35% was similar to survival of the CABG group (72% vs. 69%; p = NS).
Registry findings in patients with LV dysfunction paralleled randomized data, although most patients presented with angina and acute coronary syndromes. Earlier observational series favored CABG over percutaneous coronary intervention for LV systolic dysfunction, suggesting improved LVEF, fewer cardiac events, and reduced repeat revascularization with CABG (19,20); however, late outcome after both procedures was influenced primarily by the completeness of revascularization, not the mode.

**Procedural risks and LV systolic dysfunction.** Perioperative mortality rates for CABG in LV systolic dysfunction vary widely, from approximately 5% in younger adults to >30% in older adults with more severe LV systolic dysfunction and comorbidities (14). Similarly, PTCA alone in LV systolic dysfunction is associated with a high periprocedural mortality of 2.5% to 5% (17). In a reported registry (before stents), 18.2% of patients with LVEF <25% required emergency CABG, and 7.5% with LVEF between 25% and 35% experienced nonfatal myocardial infarction and acute closure (21).

**VIABILITY IMAGING TECHNIQUES**

Although published series allude to potential survival benefits of revascularization in ischemic cardiomyopathy, limitations in study design and higher periprocedural risk have created uncertainty about the optimal treatment strategy. This has provided the rationale for noninvasive viability testing, which, based mainly on observational studies, has potential value before revascularization in moderate-to-severe ischemic cardiomyopathy.

The most widely used clinical viability techniques are single-photon emission computed tomography (SPECT), positron emission tomography (PET), and dobutamine echocardiography. Magnetic resonance imaging (MRI) shows promise. Left ventriculography, with or without nitroglycerin or catecholamine administration, has a potential role, especially in conjunction with coronary angiography (22). Angiographic indices of microvascular perfusion have predictive and prognostic values after acute myocardial infarction (23), but their role in chronic LV dysfunction has not been defined. The most established techniques have generally been compared with contractile recovery after revascularization, a widely used but imperfect surrogate of viability (Fig. 3) (24).

**Nuclear imaging techniques.** Single-photon emission computed tomography and PET rely predominantly on the demonstration of cellular (intact cell membrane and mitochondria) and metabolic functions (preserved glucose utilization), respectively, to identify viable myocardium. With SPECT, both stress-induced perfusion abnormalities and resting isotope uptake >50% to 60% predict functional recovery (3). Compared with PET, SPECT underestimates viability (25,26); SPECT is widely available, but its lower-energy tracers, lower spatial resolution, and lack of built-in attenuation correction limit its diagnostic accuracy.

The most established PET technique for assessing viability is the combined examination of myocardial perfusion (with either N-13 ammonia or rubidium-82), and myocardial glucose metabolism (with F-18 fluorodeoxyglucose [FDG]). The most specific pattern for functional recovery is PET mismatch (reduced perfusion, preserved metabolism) (27). Hypocontractile regions with >50% FDG uptake (compared with normal or remote regions) also might recover contractile function after revascularization, but at a lower frequency, likely because of subendocardial scarring (27). With its built-in attenuation correction, greater temporal and spatial resolution, and higher-energy tracers, PET has superior image quality and high diagnostic accuracy. Its disadvantages are limited availability, cost, complexity, and dependence of FDG uptake on the patient’s metabolic state.

**Echocardiography.** The most commonly used echocardiographic technique for assessing viability relies on demonstrating contractile reserve with dobutamine administration. Dobutamine increases heart rate, blood pressure, and contractility, hence, myocardial oxygen demand and coronary blood flow. Functional improvement in hypocontractile segment(s), with or without subsequent contractile deteri-
oration (biphasic response), indicates viability and ischemia and predicts functional recovery (28). When conventional echocardiographic imaging does not provide adequate images, both harmonic imaging (29) and intravenous blood pool contrast (30) can improve endocardial definition. Although widely available and less technically complex, echocardiography is limited by its qualitative assessment, with high interobserver and intercenter variation, and inadequate acoustic windows in a substantial number of patients, even with harmonic imaging and contrast (24).

MRI. The two main MRI approaches to viability detection are the use of paramagnetic contrast agents to assess the microcirculation (delayed contrast enhancement) and the demonstration of contractile reserve with dobutamine, similar to that with echocardiography (31). In contrast enhancement, acute and chronic infarcts display hyperenhancement, providing an assessment of the overall (and transmural) extent of scar tissue (31). The postulated mechanisms have been discussed elsewhere (31). Functional recovery is less likely with increasing extent of hyperenhancement (31). Dobutamine MRI is interpreted by visual analysis in a manner similar to dobutamine echocardiography. In one study, dobutamine MRI appeared to have superior diagnostic accuracy for functional recovery compared with MRI delayed enhancement (32). The main advantages of MRI are its potential to provide near-simultaneous information on anatomy, function, and perfusion and its superior spatial resolution. Its limitations include lower temporal resolution, need for breath-holding sequences during acquisition, poor images with irregular rhythm, and implanted metallic devices.

Viability imaging and potential benefits of revascularization. Several meta-analyses have examined the relative accuracies of PET, SPECT, and dobutamine echocardiography in predicting benefits after revascularization (3,24,33,34). Most studies have important limitations (Table 1) (24,34,35).

Table 1. Limitations of Current Reports on Noninvasive Viability Testing

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<td>Nonrandomized studies</td>
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<td>Technique under investigation served as gold standard for contractile measurements</td>
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<td>Varied protocols, even for the same technique</td>
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<td>Arbitrary definition/criterion for viability</td>
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<td>Limited systematic comparison with invasive viability testing</td>
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<td>No evaluation of graft/vessel patency at time of follow-up functional assessment</td>
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<td>Unknown duration of dysfunctional but viable myocardium before revascularization</td>
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<td>Unknown severity of left ventricular remodeling before revascularization</td>
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Limitations notwithstanding, promising key findings on the impact of viability imaging in ischemic cardiomyopathy include the following:

- **Medically treated patients with defined viability by any noninvasive imaging technique have the lowest survival rate.** This was observed with individual modalities and in pooled meta-analysis of various techniques (3,33,36). In a meta-analysis of 3,088 patients (mean LVEF, 32 ± 8%), annual mortality was 16% in medically treated patients with viability by SPECT, PET or echocardiography versus only 6.2% in the medically treated nonviable group (33).

- **Patients with defined viability by any noninvasive imaging technique demonstrate significantly improved survival with revascularization compared with medical therapy.** This was demonstrated with individual modalities (28,37–42) and in pooled meta-analyses of various techniques (3,33). A meta-analysis of 24 nonrandomized studies demonstrated an 80% relative reduction in death and a 51% relative reduction in all other events with revascularization compared with medical therapy when viability was present (16% vs. 3.2%, p < 0.0001), but no benefit when viability was absent (7.7% vs. 6.2%, p = NS) (Fig. 4) (33). When the meta-analysis was limited to the nine studies with sufficient data to calculate the treatment–viability interaction odds ratio, revascularization still had the largest effect on long-term mortality compared with medical therapy in patients with viable myocardium (Fig. 5) (34), although the magnitude of the effect was far lower than for the larger cohort. Most studies found no difference in survival between the treatment groups when viability was not present (3,33). Only two studies have shown a survival benefit with revascularization in the absence of viability; however, one study included patients with LVEF >50% (43).

In patients with ischemic cardiomyopathy, improvement in HF symptoms and exercise capacity after revascularization appears to be at least modestly related to the preoperative presence and/or extent of dysfunctional but viable myocardium. Receiver operator characteristics curves with PET suggested that improvement in functional status after revascularization was best predicted by viable, but dysfunctional, myocardium of at least 18% of the LV (44). In another study, the extent of PET viability correlated with post-revascularization change in exercise capacity; however, with viability by echocardiography, this correlation was not present (3). Other observational studies have also shown functional class improvement in a greater proportion of patients with SPECT viability than in patients without viability (3).

- **Viability imaging predicts improvement in regional LV function after revascularization.** Mean sensitivity and specificity for each technique is as follows: thallium–201 imaging, 86% and 59%; SPECT with technetium–99m labeled tracers, 81% and 66%; FDG PET, 93% and 58%; and dobutamine echocardiography or MRI, 81% and 80% (24). Values are not corrected for the effects of post–test referral bias, however, which likely artificially increases sensitivity.
and decreases specificity (45). Nuclear imaging techniques tend to have higher sensitivity and lower specificity compared with echocardiography. Although this apparent difference was greater when the two techniques were compared directly in the same patients (3), it might be explained partly by different levels of referral bias for the two techniques (45). Diagnostic accuracy of echocardiography might be reduced by increasing severity of regional and global LV systolic dysfunction (46).

Viability imaging predicts improvement in global LVEF after revascularization. Published studies consistently show LVEF improvement after revascularization in viable patients identified by the aforementioned techniques (3); however, the data on MRI in this regard are limited. The more important question is the extent of viability required to observe an improvement in LVEF after revascularization. The threshold extent varies from 8% to 67% of the LV (27). Studies using receiver operator characteristics curves with various imaging modalities have provided cutoff extent in the range of 25% to 30% of LV for improvement in LVEF after revascularization (3).

There are no published randomized controlled trials, however, and most published studies have major limitations (Table 1)(35). Furthermore, studies with positive results are more likely to be published than ones with negative results (35). Hence, despite promising results, limitations of the literature have created considerable uncertainty and reluctance to apply these results, based on more selected patients, to larger unselected HF populations. Over the past decade at our institution, less than 15% of patients with HF and large areas of ischemia on SPECT imaging underwent revascularization, reflecting not only the presence of comorbidities and poor target vessels, but also the clinicians’ uncertainty about whether revascularization would improve outcomes (47).

Larger, more rigorous observational studies and randomized controlled trials are needed to determine outcome with revascularization versus medical therapy and to define the role of viability testing in moderate-to-severe ischemic cardiomyopathy. Three such studies are underway: the Surgical Treatment for Ischemic Heart Failure (STICH) trial (35), the Heart Failure Revascularization Trial (HEART) (48), and the PET and Recovery Following Revascularization-2 (PARR-2) study (49). Until results from these trials are available, clinicians must rely on available observational data to make decisions about revascularization of dysfunctional but viable myocardium.

CLINICAL IMPLICATIONS

Limitations of the literature are reflected in the absence of class I recommendations in current practice guidelines. The American College of Cardiology/American Heart Association (ACC/AHA) 2001 HF guidelines assigned noninvasive imaging and coronary angiography as class IIa recommendations with level C evidence for patients with known or suspected CAD without angina who are candidates for revascularization (1). Although the HF guidelines considered revascularization in patients with HF and CAD but without angina as a class IIb recommendation with level B evidence, the ACC/AHA 2004 Guideline Update for CABG incorporated viability in its class IIa recommendation that “CABG might be performed in patients with poor LV function with significant viable noncontracting, revascularizable myocardium.” and recognized that a subgroup of patients might experience benefit (50). On the basis of the available literature, we suggest that when 25% to 30% of the LV is dysfunctional but viable by noninvasive testing, revascularization might be considered (Fig. 6). The decision to proceed with revascularization should also consider comorbidities, prior revascularization, and patient preference. Because of current uncertainty, patients should be considered for and approached about ongoing randomized trials whenever possible.

The timing of coronary angiography is important for patients whose comorbidities and preferences do not preclude revascularization. Although the authors of one study advocate performing noninvasive viability testing before coronary angiography to prevent the “oculo-stenotic” reflex (48), defining coronary anatomy before proceeding with viability testing is often useful in clinical practice. If anatomy is not suitable for coronary revascularization, viability
testing, although prognostically useful, is unlikely to alter management. Moreover, noninvasive testing without prior coronary angiography in patients with LV systolic dysfunction might incorrectly suggest nonischemic cardiomyopathy in the presence of underlying CAD. For these reasons, initial coronary angiography seems appropriate for potential revascularization candidates.

Another clinical issue is whether to initially embark on a trial of medical therapy, and if unsuccessful, then consider revascularization. Randomized clinical trials have documented the extensive benefits of optimal medical therapy compared with placebo for ischemic HF (16); however, trials did not compare medical therapy with revascularization, and few examined the potential effects of viability on response to medical therapy (11). On the basis of these factors, the higher mortality for viable patients with delayed compared with earlier revascularization (51,52) and pathologic evidence of a dynamic process of hibernation that can progress rapidly to apoptosis, early revascularization seems appropriate (until randomized trial results are available).

In addition to optimal medical therapy and revascularization, device interventions are routinely considered for advanced HF and LV systolic dysfunction. Implantable cardioverter defibrillators have mortality benefits for both primary and secondary prevention of sudden death (16). In selected patients, cardiac resynchronization therapy has salutary effects on symptoms, hemodynamics, and perhaps mortality (16). The interaction of these benefits and viability status has not been investigated systematically, but viability testing might have a potential role in patient selection and predicting response to therapy (53).

The choice of viability technique depends on many factors, including availability, expertise, cost, and body habitus. Although reported diagnostic accuracies differ among techniques for predicting functional recovery, there are no data to meaningfully compare individual techniques with respect to patient outcome.

In summary, no completed randomized trials provide definitive data on the relative value of revascularization over medical therapy for patients with moderate-to-severe ischemic cardiomyopathy without angina. Observational studies report conflicting prognostic results in the absence of noninvasive viability testing. Reasonable observational evidence indicates that viability testing, despite varying diagnostic accuracies, can identify a subset of patients with reversible LV dysfunction who have improved outcome and symptomatic benefit after revascularization. Although the current literature has many limitations, revascularization should at least be considered in patients with moderate-to-severe ischemic cardiomyopathy who have a significant amount of dysfunctional, but viable, myocardium. Randomized trials

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**Figure 6.** Proposed clinical algorithm. CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; MRI = magnetic resonance imaging; PET = positron emission tomography; SPECT = single-photon emission computed tomography.
are needed, are ongoing, and, potentially, can better define the role of noninvasive viability testing and the value of revascularization over medical therapy for LV systolic dysfunction and HF.

Reprint requests and correspondence: Dr. Panithaya Chareonthaitawee, Division of Cardiovascular Diseases, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905. E-mail: chareonthaitawee.panithaya@mayo.edu.

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