Revascularization for heart failure

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Coronary artery disease is the most common underlying cause of heart failure, yet there is little consensus on the role of revascularization in the management of patients with ischemic cardiomyopathy. The concept of recovery of dysfunctional but viable myocardium forms the pathophysiologic basis for the benefit of revascularization. Data from observational studies suggest that patients with coronary disease and left ventricular dysfunction may have improved outcomes after surgical revascularization or percutaneous coronary intervention (PCI) compared to medical treatment. Viability testing may be useful in selecting a population of patients who will receive differential benefit. In the clinical management of patients with heart failure, clinicians face challenging decisions about whether to recommend revascularization especially in patients who do not have angina. As data from randomized trials are awaited, PCI and coronary artery bypass grafting may be considered as complimentary revascularization approaches. Registry data suggest a benefit of coronary artery bypass grafting over PCI in patients with reduced ejection fraction; however, in patients with focal disease and comorbidities including previous surgery, PCI is reasonable, especially if complete revascularization is possible. (Am Heart J 2007;153:S65-S73.)

Background

Heart failure (HF) is a worldwide public health problem of major and ever-expanding proportions. In the United States, 5 million patients have HF,[1] and annually, more than 1 million are hospitalized with HF,[2] making it the most common diagnosis related group.[3] Moreover, more than 50 000 patients in the United States die each year with HF as a primary diagnosis[1] and, despite many therapeutic advances in treatment, clinicians are frustrated by the overall poor prognosis of these patients.[4]

Coronary artery disease (CAD) is the most common cause of HF in the United States. Almost 60% of patients in the ADHERE Registry had a history of coronary artery disease.[5] Similarly, of patients enrolled in chronic HF clinical trials, most patients (68%) had ischemic heart disease recorded as their HF etiology.[6]

In the presence of CAD, without valvular disease, HF is most commonly caused by left ventricular (LV) systolic dysfunction. Coronary revascularization in the form of coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) has been exhaustively studied and analyzed over the years as a treatment of acute and chronic CAD, yet definitive studies that address the role of revascularization in patients with CAD and LV dysfunction are not available. The management of patients with ischemic cardiomyopathy, but without angina, is particularly challenging, yet no randomized trials have been completed in this group.

This article will review the existing data concerning revascularization as a treatment of HF in patients with CAD. An attempt will be made to refine the clinical approach especially in regard to the role of PCI in this patient population. Viability testing for identifying patients most likely to benefit from revascularization therapy will be discussed.

Pathophysiology of functional recovery after coronary revascularization in patients with ischemic dysfunction

Revascularization may potentially improve the outcome of patients with ischemic LV dysfunction by several mechanisms. Viable but dysfunctional myocardial cells can be explained by the concepts of hibernating[7] or stunned myocardium.[8] Hibernating myocardium is chronically dysfunctional tissue related to inadequate coronary blood flow and may demonstrate better function after improvement in perfusion. Recovery occurs over a prolonged course with only about one third of hibernating segments showing early improvement, but nearly two thirds demonstrating late recovery after 14 months on serial evaluation after revascularization.[9] Apoptosis appears to play a role in hibernation and suggests that early revascularization may be essential to avoid irreversible dysfunction.[10] Stunned myocardium refers to dysfunction in viable myocardium related to transient ischemia. After ischemia is relieved, serial noninvasive imaging suggests that recovery may occur early with nearly two thirds of stunned segments, demonstrating early functional recovery at 3 months

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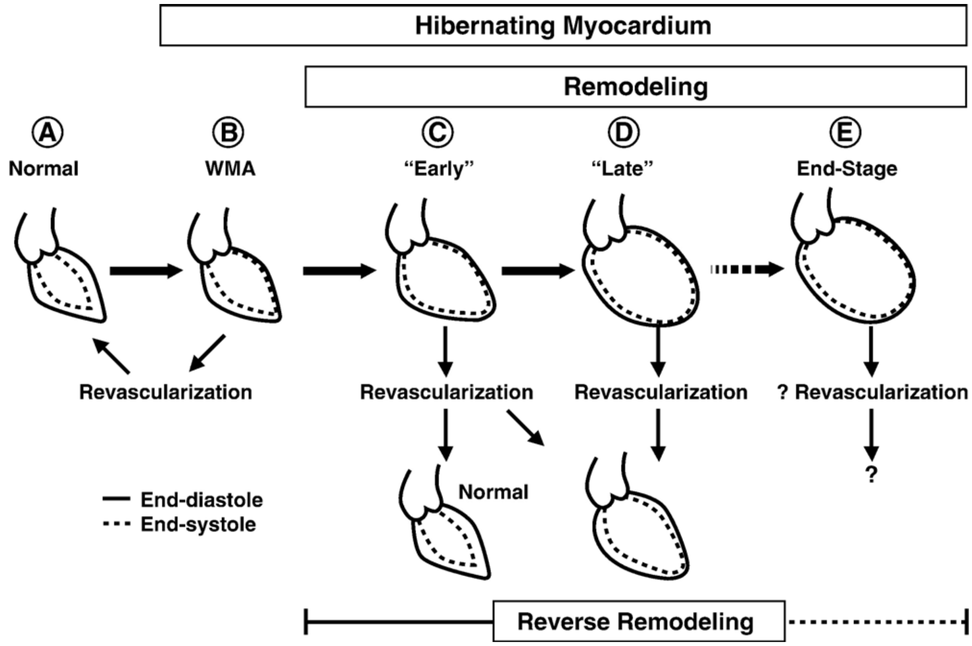
doi:10.1016/j.ahj.2007.01.026

Figure 1



Diagrammatic representation of postulated progressive changes in a patient with hibernating myocardium and (**A**) no remodeling (**B**), mild to moderate remodeling (**C** and **D**), and end stage (**E**) of the disorder. *WMA*, Wall-motion abnormality. Reprinted with permission from *J Am Coll Cardiol* 2006;47:978-80. Copyright 2006, The American College of Cardiology Foundation.

after revascularization, and only one tenth showing late improvement at 14 months.[9]

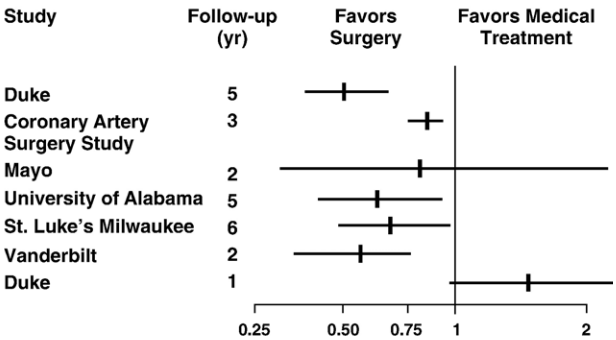
In practice, the distinction between hibernating and stunned myocardium blurs, and the 2 processes probably often coexist. Both contribute to progressive systolic dysfunction, remodeling, and the development of HF. Up to 60% of ischemic LV dysfunction has been attributed to dysfunctional but viable myocardium,[11] and thus, there is a potential opportunity to improve outcome in many patients. Rahimtoola et al[12] have recently suggested a unifying concept of hibernation and remodeling with emphasis on the importance of early revascularization (Figure 1). Other potential benefits of revascularization, independent of functional improvement, may include prevention in further deterioration in LV function and reduction in the risk of sudden death.[13]

Another consideration is that of postinfarction remodeling, which involves the replacement of nonviable myocardium with scar tissue and is accompanied by secondary pathologic changes in shape and size of the LV. This process contributes to the progression of systolic dysfunction, and may also be reversed by revascularization.[14] Remodeling appears to progress over time and the ability to reverse the process may also be time-sensitive.[12]

Surgical coronary revascularization in patients with LV dysfunction: observational data

The evidence supporting the clinical benefit of surgical coronary revascularization is based on observational data. The Duke Cardiovascular Disease Databank is a unique database for the evaluation of surgical revascularization in patients with ischemic cardiomyopathy. O'Connor et al[15] reported the 25-year experience of 1391 patients with systolic dysfunction and ischemic heart disease. Of these, 1052 patients were treated medically and 339 underwent CABG. After adjusting for disease severity and other prognostic factors, the CABG-treated patients had a significantly lower mortality beyond 30 days as compared with the medically treated patients. Survival after CABG exceeded medical therapy at 1 year (83% vs 74%, $P < .0001$) 5 years (61% vs 37%, $P < .0001$) and 10 years (42% vs 13%, $P < .0001$). The survival advantage was present regardless of ejection fraction (EF), age, New York Heart Association functional class, or the presence of angina. Recently, an update of more than 18000 patients entered into the Duke Databank from 1986 to 2000 confirmed the survival

Figure 2



Relative risk of mortality for CABG compared to medical therapy in moderate-to-severe LV systolic dysfunction, ranked in order of study quality. Studies were observational, most patients had limiting angina, and preoperative viability testing was not routinely performed. Reprinted with permission from *J Am Coll Cardiol* 2005;46:567-74. Copyright 2005, The American College of Cardiology Foundation.

benefit of revascularization in patients with CAD and reduced EF.[16]

The potential improvement in mortality from revascularization in patients with ischemic LV dysfunction was seen in other studies, but the apparent benefit in patients without angina is at odds with other data sets.[17,18] The surgical operative mortality in these early series ranged from 5% to 30% depending on LV function and comorbidities. The most recent series suggest that most patients demonstrate improvement in functional status, but given the risk of the surgical procedure, it is unfortunate these late outcomes of the procedures are not better defined.[18] Similarly, these observational series suggest an improvement in LV function after revascularization, but the numbers of patients with severe dysfunction is small.[18] The mortality data from nonrandomized studies comparing CABG with medical therapy are summarized in Figure 2.

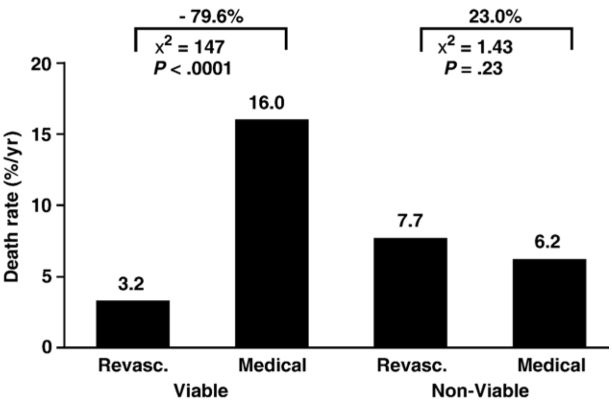
A more recent observational series confirmed the mortality benefit of revascularization seen in earlier series and emphasized the benefit of early treatment. Tarakji et al[19] analyzed the outcomes of 765 patients with a LVEF <35% who underwent positron emission tomography (PET)/fluorodeoxyglucose (FDG) study at the Cleveland Clinic between 1997 and 2002. Of the 765 patients, 230 (30%) underwent early intervention (mostly CABG within the first 6 months of the viability study). Of the 230 patients, using 39 demographic, clinical, and PET/FDG variables, 153 were propensity matched with 153 patients who did not undergo early intervention. Early intervention was associated with a 3-year mortality rate of 15% versus 35% for the medically treated group ($P < .0004$). There was benefit seen irrespective of the amount of viability seen on the PET/FDG study.

Role of PCI in patients with HF

Recently, observational data supporting the benefit of PCI to treat acute HF, presumably related to myocardial stunning, has been reported. The GRACE Registry provided an opportunity to evaluate the characteristics and outcomes of patients who developed HF in the setting of an acute coronary syndrome from a contemporary data set (1999-2001).[20] The registry enrolled 16166 patients, of which 1788 had HF at the time of hospital admission. Patients with HF were significantly less likely to undergo cardiac catheterization (46.5% vs 54.2%, $P = .0001$) and PCI (26% vs 31.8%, $P = .0001$) compared with patients who have acute coronary syndrome without HF. The rate of CABG was similar between groups. The combined risk of inhospital and postdischarge 6-month mortality was significantly higher in patients with HF on admission (20.7% vs 5.9%, hazard ratio 3.8, 95% CI 3.33-4.36, $P < .001$). Patients with HF who underwent inhospital revascularization (predominantly PCI) had a significantly lower rate of postdischarge 6-month mortality (14% vs 23.7%, $P < .0001$). This finding persisted after adjusting for baseline differences and other prognostic factors (hazard ratio 0.5, 95% CI 0.37-0.68, $P < 0.0001$). Low utilization of cardiac catheterization in patients with acute HF was also confirmed in the ADHERE Registry.[5]

The data on PCI in chronic ischemic LV dysfunction is even more meager than that for surgical revascularization. Revascularization of chronic total occlusions has been shown to have beneficial effects on LV function and volumes.[21] Percutaneous revascularization with stenting can be safely performed in patients with low EF with acceptable late major adverse cardiac event rates.[22] A single small, randomized trial comparing PCI with CABG in a low EF population concluded that outcomes were similar with the 2 revascularization approaches.[23] In contrast, a large registry report from the State University of New York suggested better outcomes for patients with impaired LV function who underwent CABG compared with those who underwent stenting. They compared 37212 patients with multivessel disease who underwent CABG (26% with EF <40%) and 22102 patients with multivessel disease who underwent PCI (18.5% with EF <40%) from January 1, 1997, to December 31, 2000.[24] For the patients with an EF <40% and with 2- or 3-vessel disease with involvement of the proximal left anterior descending coronary artery, the hazard ratios strongly favored CABG over stenting. The hazard ratios were not significantly different for other patients with 2-vessel disease. Concerns about the validity of comparisons

Figure 3



Death rates for patients with and without myocardial viability treated by revascularization or medical therapy. There is 79.6% reduction in mortality for patients with viability treated by revascularization ($P < .0001$). In patients without myocardial viability, there was no significant difference in mortality with revascularization versus medical therapy. Reprinted with permission from *J Am Coll Cardiol* 2002;39:1151-58. Copyright 2002, The American College of Cardiology Foundation.

of PCI and CABG outcomes in registries have been recently emphasized.[25]

The role of viability testing

Observational series suggest that viability testing may be useful to identify a subset of patients with ischemic LV dysfunction who are likely to benefit from cardiac revascularization procedures. Viability may be evaluated by an assortment of techniques including single-photon emission computed tomography, PET, dobutamine echocardiography, and most recently, magnetic resonance imaging (MRI).

Recently, several meta-analyses have been consistent in predicting improved survival in patients who demonstrated viability in the setting of ischemic dysfunction and who subsequently underwent revascularization.[26-30] Allman et al conducted a meta-analysis of 24 studies of viability testing in 3088 patients with CAD and systolic dysfunction. Among patients with demonstrated viability, 1-year mortality was 16% in the medically treated patient and 3.2% in patients who underwent revascularization ($P < .0001$). There was no difference in mortality among the patients who did not demonstrate viability (Figure 3). In contrast to these studies, the report of Tarakji et al[19] from the Cleveland Clinic discussed previously showed no relationship between the degree of viability on PET/FDG and outcome. Early intervention was associated with better survival regardless of the amount of myocardium thought to be nonfunctional but viable. The numerous limitations of these observational studies of viability testing in patients with ischemic LV dysfunction have been well summarized by the Mayo Clinic Group.[11,31]

Contrast-enhanced magnetic resonance imaging (CMR) may also be a useful strategy to determine response to revascularization in patients with HF. Capitalizing on the outstanding spatial resolution of this technique and the increased uptake of gadolinium in areas of infarction ("hyperenhancement") allows accurate delineation of viable versus nonviable myocardium and makes CMR a practical tool to quantify the transmural extent of irreversible myocardial damage. Kim et al[32] studied 50 patients who underwent MRI before revascularization. Magnetic resonance imaging was repeated after revascularization to determine improvements in regions of myocardial dysfunction. Of the original study cohort, 41 patients had repeat MRI an average of 79 days after revascularization. After revascularization, 53% of the segments with abnormal contractility improved. The likelihood of improvement in contractility was related to the extent of hyperenhancement. As hyperenhancement increased, the proportion of segments with improved contractility significantly decreased. This relationship was observed after adjustment for repeated measures and other prognostic factors (Figure 4). Clinicians are beginning to consider CMR as the gold standard for viability testing, but more data are needed linking CMR viability with clinical outcomes before its true role in clinical decision making can be defined.[33]

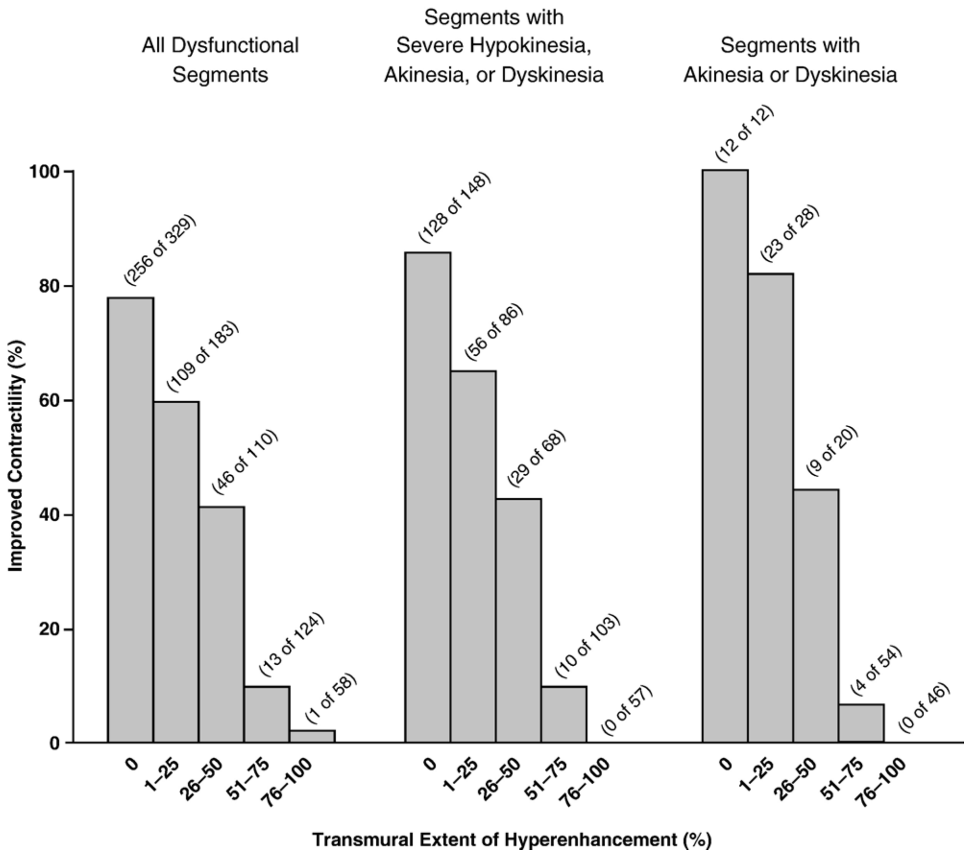
Randomized trials in progress

There are many limitations of the observational studies evaluating the effect of revascularization and the predictive value of viability testing in patients with ischemic LV dysfunction. The possibility of a selection bias cannot be ruled out in any of these studies. Imaging and revascularization techniques have improved over time, and earlier series may not accurately predict current outcomes. Medical therapy was not optimal in the early series and was not standardized in any of the studies. In addition, the impact of limited use of defibrillators is unknown. Fortunately, at least 3 randomized trials are underway to evaluate the effect of revascularization in patients with ischemic dysfunction: the STICH trial,[34] the HEART,[35] and the PARR-2 study.[36] In addition, these trials are designed to determine the role of viability testing in patient selection.

Guideline-based clinical practice

Decisions about the uncertain benefits of revascularization in high-risk patients with ischemic LV dysfunction have challenged clinicians since the early days of coronary revascularization. The benefits of pharmaco-

Figure 4



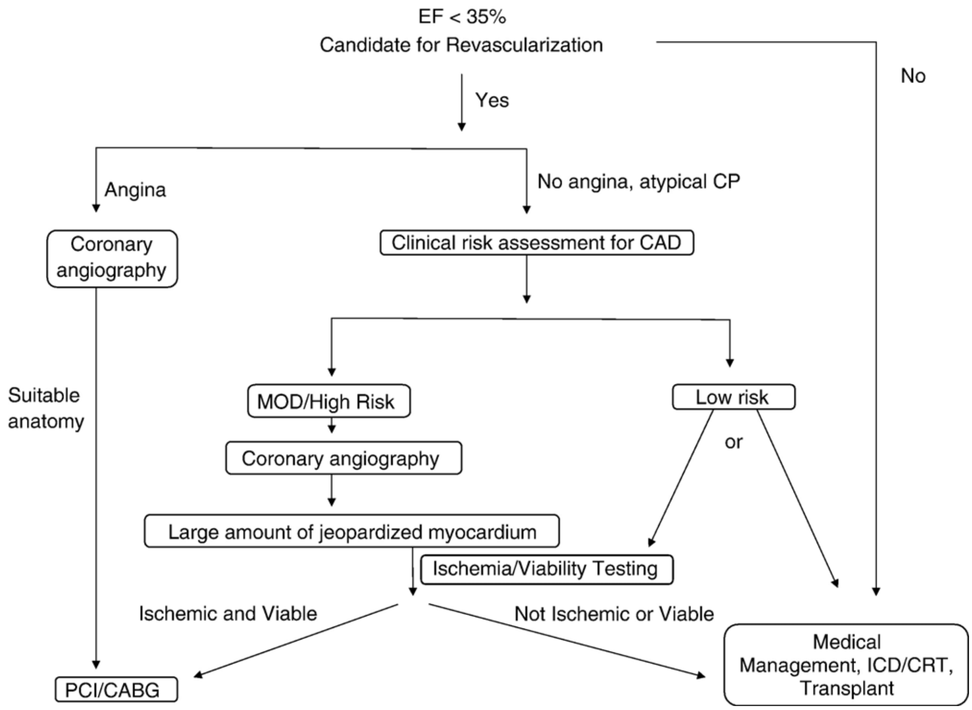
Relation between the transmural extent of hyperenhancement before revascularization and the likelihood of increased contractility after revascularization. Data are shown for all 804 dysfunctional segments and separately for the 462 segments with at least severe hypokinesia and the 160 segments with akinesia or dyskinesia before revascularization. For all 3 analyses, there was an inverse relation between the transmural extent of hyper enhancement and the likelihood of improvement in contractility. Reprinted with permission from *N Engl J Med* 2000; 343;1445-53. Copyright 2000, Massachusetts Medical Society.

logic management are strongly evidence-based, and all patients should be placed on medical management with recommended agents according to the 2005 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines Update for the Diagnosis and Management Chronic Heart Failure.[37] In addition, device therapy with defibrillators and possibly cardiac resynchronization therapy should be considered in many of these patients.

The ACC/AHA guidelines provide several recommendations on the role of coronary angiography. A class I recommendation is given to patients presenting with HF and angina or significant ischemia, unless the patient is not a candidate for any type of revascularization.[37] Coronary angiography is a class IIa recommendation in patients with HF who have chest pain that may or may not be of cardiac origin, whose coronary anatomy is unknown. It is also a class IIa recommendation in patients with HF and known or suspected CAD but who do not have angina, despite the concerns in the guidelines about the effectiveness of revascularization in these patients.

In practice, if not previously performed, many clinicians believe it is reasonable to consider cardiac catheterization in all patients who present with HF who are candidates for revascularization. Coronary angiography is usually necessary to reliably demonstrate or rule out the presence of CAD because perfusion deficits and segmental wall-motion abnormalities identified on noninvasive testing cannot reliably distinguish those with ischemic LV dysfunction from those with nonischemic cardiomyopathy. Accordingly, noninvasive testing to define the likelihood of CAD in patients with HF and LV dysfunction has a class IIb recommendation in the guidelines.[38]

Figure 5



Management algorithm for patients with LV dysfunction and suspected coronary disease. *SPECT*, Single-photon emission computed tomography; *Echo*, echocardiography; *CABG*, coronary artery bypass surgery; *ICD*, implantable cardioverter/defibrillator; *CRT*, cardiac resynchronization therapy.

Coronary angiography is important not only in determining candidacy for revascularization but also because decisions regarding medical therapy for patients with HF depend on the presence or absence of CAD. It is not recommended to use aspirin in patients without obstructive coronary disease and HF unless there are other indications. In contrast, patients with CAD should be treated with vasculoprotective medications including aggressive therapy with statins. Finally, the choice of angiotensin-converting enzyme inhibitor may be affected by the type of HF based on the presence or absence of significant CAD.

The guidelines state that noninvasive imaging to detect myocardial ischemia and viability is reasonable in patients with HF and known CAD without angina (class IIa recommendation).[37] Despite observational data suggesting the value of revascularization for patients with viability, the studies are not yet considered pivotal in clinical decision making. Thus, viability testing may be used to refine revascularization decisions but viability is not required as a prerequisite to revascularization in patients who are otherwise good candidates.

The 2005 ACC/AHA guidelines also provide recommendations for revascularization.[37] Revascularization in patients who have HF symptoms and angina pectoris is a class I recommendation. The management of patients with HF but no angina is not straightforward, and the guidelines state that, despite theoretical arguments in favor of revascularization, the benefit is unproven. The 2004 ACC/AHA guidelines for CABG address patients with poor LV function with an emphasis on the amount of jeopardized myocardium and assign a class I recommendation for patients with LV dysfunction and left main, left main equivalent, and proximal left anterior descending coronary artery disease with 2- or 3-vessel disease without regard to symptoms or viability.[38] A class IIa recommendation is given to patients with LV dysfunction with a myocardium that can be significantly revascularized without the class I anatomical patterns, but again, without regard to symptoms. The 2005 guidelines for PCI do not address recommendations for patients with clinical HF or LV dysfunction.[39]

In practice, HF patients with ischemic dysfunction and angina are offered revascularization if feasible. Although clinical data are inconsistent, revascularization is often considered in patients without angina, given the high mortality associated with medical treatment. Thus, the practice patterns of many clinicians approximate the

CABG guidelines, and patients without angina, but who have large amounts of jeopardized myocardium suitable for revascularization, are strongly considered for revascularization. Stress testing is challenging in this patient population, but a decision in favor of revascularization may be supported if a large amount of ischemia can be convincingly demonstrated. The role of viability testing varies among institutions depending on availability of techniques and clinical experience. Decision making in patients who have no angina, borderline coronary anatomy, or significant comorbidities can be assisted by viability testing with the finding of large amounts of viability supporting a decision for increased-risk revascularization as shown in Figure 5. Knowledge of the pathophysiology of hibernating myocardium plus observational data would suggest that revascularization is time-sensitive, and a "wait-and-see approach" is rarely appropriate. The eagerly awaited results of randomized trials should clarify the role of revascularization and viability testing especially for patients who have no angina.

There are no strict criteria to determine which patients are "too sick" to be considered for revascularization. Many of these are patients with advanced age or who have compelling comorbidities such multiorgan failure, and conservative management is obvious. Unfortunately, clinicians not uncommonly face difficult decisions concerning younger patients including the dilemma in which the choice between the periprocedural mortality of high-risk revascularization must be balanced against the uncertainty of organ availability and risks of transplantation.

Patient selection for PCI

Percutaneous coronary intervention is the most common revascularization technique for coronary disease worldwide based on the efficacy of bare metal and, more recently, drug-eluting stents. Fundamentally, PCI differs from CABG in that PCI addresses a focal stenosis, whereas CABG treats an entire myocardial segment. In the former case, a current culprit is being treated, whereas in the latter case, future culprit lesions may be revascularized. This concept has been used to explain the more favorable outcomes with CABG compared to PCI in the New York State Registry.[40]

In everyday practice, PCI and CABG may be considered as complementary rather than competitive approaches in patients with ischemic cardiomyopathy. A history of previous bypass surgery is a common reason to prefer PCI over CABG, whereas the need for concomitant mitral valve repair makes a surgical approach more appealing. A number of anatomical and clinical factors are summarized in Table I. The ability to achieve complete revascularization is often an important issue in choosing between PCI and surgical revascularization with some believing that late outcome is influenced more by completeness of revascularization than by method.[11] It especially seems reasonable to try to achieve revascularization of all viable segments. Finally, PCI is often the procedure of last resort for patients who have been denied surgery. In those patients with compromised LV function and in whom technically challenging lesions are approached, the risk versus benefit in terms of the potential for cardiovascular collapse and other risks of the PCI procedure including intra-aortic balloon pump support must be considered.

Table I. Factors influencing choice of CABG versus PCI in patients with LV dysfunction and CAD

	PCI	CABG
Anatomic		
Focal lesions	+	
Diffuse lesions		+
Complex lesions including chronic total occlusion		+
Clinical		
Prior CABG	+	
Advanced age	+	
Multiple comorbidities	+	
Need for concomitant mitral surgery		+

Conclusions

Currently, revascularization decisions in patients with ischemic cardiomyopathy cannot be based on randomized clinical trial data. The outcomes of multiple observational studies support the benefit of revascularization in patients with ischemic cardiomyopathy and angina. Revascularization may be an emerging concept in patients without angina but who have appropriate coronary anatomy and no contraindications. Viability testing can identify patients who may have hibernating or stunned myocardium, and may play a supportive role in decision making. The choice of revascularization technique should be made on the basis of anatomical, clinical, and patient preference issues. Ongoing randomized clinical trials should better define the role of revascularization and viability testing and allow the development of more comprehensive clinical guidelines for management.

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