2 Surgical Revascularization in the Management of Heart Failure and Ischemic Left Ventricular Dysfunction

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INTRODUCTION

More than 5 million Americans have congestive heart failure, and 550,000 new cases are diagnosed each year. This condition results in almost 1 million hospital discharges and more than 50,000 deaths a year at a cost of $28.8 billion *(1)*. Coronary artery disease (CAD)

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remains a leading cause of heart failure. Since the early trials of surgical vs medical management of coronary artery disease in the late 1970s, there have been substantial changes in the surgical techniques and the medical management of chronic CAD, acute coronary syndromes, and heart failure.

Despite these advances, the optimal role of surgical revascularization in the management of heart failure and ischemic left ventricular (LV) dysfunction remains unclear and primarily anecdotal. There is still no large prospective randomized experience with coronary artery bypass graft (CABG) surgery for patients with heart failure in the current era of mechanical revascularization. Although retrospective surgical series have suggested benefit for this population, these studies have rarely included the most recent advances in medical, surgical, and device therapies for heart failure *(2–8)*. Furthermore, basic questions about bypass surgery and heart failure remain, including the optimal methods for assessing viability, the most appropriate end points (other than mortality) that should be targeted, and whether cost considerations and quality-of-life (QoL) measures should be paramount. Nonetheless, surgical revascularization remains one of the therapeutic cornerstones in the management of advanced heart failure from CAD.

CORONARY BYPASS SURGERY AND HEART FAILURE: THE CLINICAL EXPERIENCE

There are no randomized, controlled trials of patients with multivessel CAD and significant LV dysfunction because most early clinical trials of surgical revascularization excluded patients with advanced heart failure because of their high perioperative mortality. However, the three large randomized trials of bypass surgery vs medical management of the 1970s, the Veterans Administration Cooperative Study (VACS), the European Cooperative Coronary Study (ECSS), and the Coronary Artery Surgery Study (CASS), did include some patients with decreased LV function. Therefore, some insight into the role of CABG in these patients can be gleaned from a review of these trials (Table 1).

Randomized Trials

The VACS was the first large, multicenter, randomized controlled trial of medical therapy vs CABG for patients with stable angina. A total of 686 patients were randomized between 1972 and 1974. LV dysfunction was defined as an ejection fraction (EF) less than 50%. A minority of patients in either group had LV dysfunction, 35% in the medical arm and 31% in the CABG arm. A subgroup of patients with

Table 1
Comparison of Major Characteristics From the Three Large, Randomized Trials of Coronary Bypass Surgery vs Medical Management

	VACS	*ECSS*	*CASS*
Number of patients	686	768	780
Inclusion criteria			
Age (years)	≤65	≤65	≤65
Male sex (%)	100	100	90
EF (%)	>35	>50	>30
Significant stenosis (%)	≥50	≥50	≥70
Baseline characteristics (%)			
CHC class I/II angina	42[a]	57	74
β-Blockers	12	75	43
EF < 50%	26 (<45%)	0	21
Three-vessel disease (≥50% stenosis)	50	53[b]	51
Randomized to surgery			
Operative mortality (%)	5.8	3.3	1.4
Grafts/patient in three-vessel disease	2.3	2.4	2.8
Graft patency (%)			
12–18 months	70	75	90
60 months	67	69	82
Randomized to medical therapy (%)			
CABG by 10–12 years	38	36	38

CABG, coronary artery bypass graft surgery; CASS, Coronary Artery Surgery Study; ECSS, European Cooperative Coronary Study; EF, ejection fraction; CHC, Canadian Cardiovascular Association Classification; VACS, Veterans Administration Cooperative Study.

[a]Twenty-six percent were asymptomatic after myocardial infarction or had nonexertional chest pain.

[b]Eight percent of patients had left main coronary artery disease with lumen narrowing of 50% or more. (Adapted from ref. *16*.)

three-vessel disease and impaired LV dysfunction (but without left main CAD) was defined as having high angiographic risk. In this subgroup, the 7-year survival was 52% in the medically treated group vs 76% in the CABG group ($p = 0.002$). The survival advantage of bypass surgery was sustained at 11 years (38% medical vs 50% surgical, $p = 0.026$) *(9,10)*, but not by 18 years (23% medical vs 24% surgical, $p = 0.49$) *(11)*.

The ECSS was the second large, multicenter, randomized controlled trial of medical therapy vs CABG for patients with stable angina. It enrolled 768 patients from 1973 until 1976, but excluded any patient with an EF less than 50% *(12)*.

CASS was the third large, multi-center, randomized controlled trial of bypass surgery for stable angina. Patients in New York Heart Association (NYHA) class III/IV or with an EF less than 35% were specifically excluded. A total of 780 patients were randomly assigned from 1975 to 1979. There were, however, 160 patients with an EF less than 50%; in this subgroup, there was a survival benefit to bypass surgery at 7 years (70% medical vs 84% surgical, $p = 0.01$). Importantly, most of the survival advantage was in those patients with triple-vessel disease, whose survival was 65% with medical therapy and 88% with CABG ($p = 0.009$) *(13)*. A survival benefit was also seen in those with LV dysfunction in combination with more severe angina and left main coronary disease *(14,15)*. Although there was no difference in overall survival for all patients at 10 years, patients with an EF less than 50% had a survival benefit with surgery (61% vs 79% for the medical and CABG groups, respectively) *(16)*.

In summary, the landmark randomized trials of coronary bypass surgery did demonstrate a survival benefit to patients with advanced CAD and decreased LV function, but it is important to note that these studies were primarily trials of angina and not heart failure. Moreover, they were conducted in an era when surgical mortality was much higher than it is today, and medical therapy for both atherosclerosis and heart failure was essentially nonexistent. In fact, some have argued that the trials have no relevance in today's practice.

Contemporary Retrospective Studies

With improvements in surgical techniques and a growing perception that CABG benefits ischemic LV dysfunction, more contemporary experiences have been reported and are arguably more reflective of current practices. Duke University reported 710 patients with an EF of 40% or less, 301 of whom had CABG. After adjusting for differences between those who did and did not receive operations, the 3-year survival was 86% in the surgical group and 68% in the medical group. The benefits were greatest in the subgroup with the worst tertile of LV function *(17)*.

Yale University reported 83 consecutive patients with an EF of 30% or less who underwent CABG, half of whom had heart failure as the indication for surgery. The survival in this cohort at 3 years was 80%, with concomitant improvements in symptoms (by one NYHA functional class) and ventricular function (EF improved from a mean of 24.6 to 36%, $p < 0.001$) *(18)*.

Finally, in a review of 12 retrospective surgical series, bypass surgery improved 3-year survival by 30 to 50% in patients with LV

dysfunction *(19)*, but at the cost of a higher surgical mortality. This increase in surgical mortality was, not surprisingly, consistent across studies. In a study of 12,471 patients undergoing bypass surgery, the operative mortalities with an EF above 40%, from 20 to 40%, and less than 20% were 2.3, 4.8, and 9.8%, respectively ($p < 0.001$) *(20)*. In fact, this surgical mortality paradox is often the clinical dilemma of whether to accept the high perioperative mortality for the potential long-term mortality benefit.

ISCHEMIC HEART DISEASE AND HEART FAILURE: PATHOPHYSIOLOGY

Historically, the prevailing perception was that LV dysfunction was the consequence of nonviable scar from myocardial infarction. Yet, early surgical revascularization experience with advanced CAD and concomitant LV dysfunction resulted in improvements in overall ventricular performance, and this improvement was not easily explained by the concept of a scarred hypocontractile ventricle. By the early to mid-1980s, the phenomenon of painless ischemia at rest and myocardial viability began to supplant the previous notion of an irreversibly scarred heart *(21)*. This concept that chronic resting hypoperfusion could result in resting wall motion abnormalities without infarction and was reversible with revascularization was termed *hibernating myocardium (22,23)*.

In a related manner, some areas of myocardium, although well perfused at rest (therefore not hibernating), may easily become ischemic because of a tenuous blood supply from severe epicardial CAD. With repeated bouts of episodic ischemia, the myocardium may become dysfunctional, a process referred to as *stunning*. Although these entities are thought of as clinically distinct (stunning in acute ischemic events and hibernation in chronic stable coronary disease), they often coexist in the same patient and even in the same myocardial territory *(24)*. Most important, both conditions are potentially reversible with revascularization.

Hibernation is an adaptive response of the myocyte to a level of perfusion sufficient for the preservation of the low-energy demands of maintaining cellular integrity, but inadequate for the high-energy demands of contractile function *(25)*. Although the myocyte can maintain cellular integrity when blood flow is reduced by 40–60%, greater reductions in blood flow usually result in membrane dysfunction *(26)*. In the setting of hypoxia, the myocyte shifts to glucose utilization to meet its metabolic demands. However, glycolysis can only be maintained if there is enough

blood flow to ensure the supply of glucose and the removal of inhibitory metabolites, such as lactate *(27,28)*. Thus, hibernating myocardium exists in a delicate balance between blood flow adequate enough to avert cellular death, but insufficient for contractile function.

Although cellular integrity may be maintained, intracellular functions may be altered. Hibernating myocardium at the time of bypass surgery demonstrates characteristics of dedifferentiation with loss of contractile elements and an increase in the interstitial space *(29)*. Subsequent investigations have shown cytoskeletal disorganization, interstitial fibrosis, and markers of apoptosis, but not signs of ischemic cell death. Therefore, the hibernating myocyte is not merely a normal cell with reduced metabolic activity *(30)*. It eventually undergoes a process of architectural disorganization and extracellular fibrosis that may lead to apoptotic signaling. Hence, the time from restoration of flow to clinically detectable improvement in contractile function depends on the severity of the intracellular alterations that have occurred. If hypoperfusion is allowed to persist long enough, there may be myocyte loss, irreversible cell damage, or an unfavorable extracellular matrix that may diminish the magnitude of any potential improvement in contractile function *(31)*. However, if hibernation (and/or stunning) can be identified before irreversible cell damage or death, restoring adequate blood flow by revascularization should improve myocardial function. This concept of recoverable myocardial function in the setting of compromised blood flow is known as *myocardial viability.*

ASSESSMENT OF MYOCARDIAL VIABILITY

Early techniques to assess myocardial viability were primitive but important because perioperative morbidity and mortality could be prohibitive if clinical improvement was not likely. Early strategies included the use of ventriculography or echocardiography to assess improvements in regional ventricular contractility after nitrate administration *(32–34)* or after provoked extrasystoles *(35,36)*. Other provocative methods have used inotropic agents *(37)* and exercise *(38)*. In contemporary practice, detection of myocardial viability employs one of three strategies: (1) identifying metabolically active myocardium (i.e., radionuclide perfusion imaging), (2) assessing contractile reserve (i.e., dobutamine echo), or (3) quantifying myocardial scar (i.e., cardiac magnetic resonance imaging [MRI]).

Positron Emission Tomography

The determination of viability with positron emission tomography (PET) scanning involves the independent assessments of myocardial

blood flow and cell viability. Blood flow to the myocardium is most commonly measured with ^{13}N-ammonium, but ^{15}O-water, ^{82}Rb, and other single-photon emission computed tomography (SPECT) perfusion tracers have been employed *(39)*. Metabolically active myocytes, especially hypoperfused myocytes that rely more heavily on glycolysis, will transport glucose intracellularly; thus, myocardial cell viability is inferred by uptake of ^{18}F-deoxyglucose (FDG) *(40)*. The perfusion scan is then matched with the metabolism scan. Normal myocardium will have normal perfusion and metabolism. Scar will have both decreased perfusion and decreased metabolism. Hibernating and viable myocardium will have decreased perfusion, but normal metabolism *(41)*. For these reasons, PET is often considered the gold standard for the noninvasive assessment of viability. Unfortunately, the lack of wide availability of this technology has limited its clinical utility.

A landmark study by Tillisch et al. in 1986 first applied PET to the assessment of myocardial viability and found an accuracy of 92% for the prediction of postoperative improvements in LV wall motion *(42)*. Their observations have been confirmed in numerous subsequent studies of PET in the prediction of viability. A meta-analysis of 17 such studies (including 462 patients) demonstrated an overall positive predictive accuracy of 76% and a negative predictive accuracy of 82% for improvement of wall motion after revascularization *(41)*. Furthermore, in a multivariate model for predicting improvement in LV function, PET viability was a strong independent predictor of recovery *(43)*.

Thallium Perfusion Imaging

There are two basic protocols for assessing viability with thallium 201 (Tl 201), rest–redistribution and stress–redistribution–reinjection. Thallium 201, a potassium analogue, is actively transported into the myocardium by a sodium–potassium pump. After injection, the tracer initially distributes into viable cells based on the distribution of blood flow. After several hours, thallium can be redistributed into myocardium independent of blood flow and thus is a marker of preserved cellular metabolism and hence viability *(44)*. During a rest–redistribution scan, Tl 201 is injected at rest, and baseline images are obtained. Hypoperfusion is manifested by a defect on the resting scan. The redistribution images are obtained 3 or 4 hours later. The resting scan is then compared to the redistribution scan. Viability is inferred by defects in Tl 201 uptake at rest that "fill in" on the redistribution scan.

However, this technique may incorrectly identify scar as viable myocardium. Both hibernating myocardium and nontransmural scar

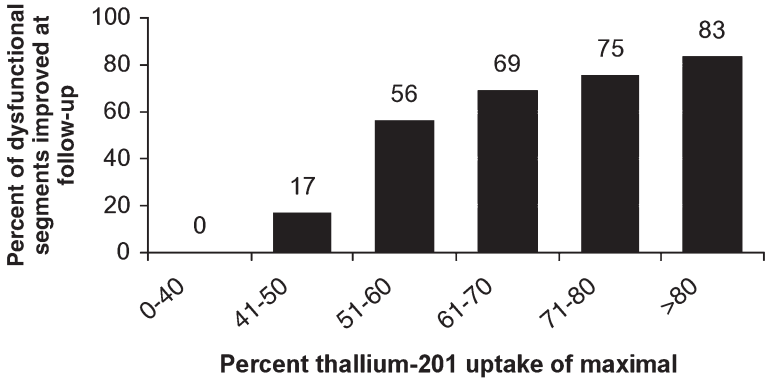

Fig. 1. Improvement in dysfunctional segments after revascularization based on the level of Tl 201 uptake after 4 hours of redistribution. (Adapted with permission from ref. *53*.)

can produce an area of decreased perfusion that redistributes (fills in) and is associated with a resting wall motion abnormality *(45)*. Conversely, the lack of uptake after redistribution does not necessarily equate with scar *(26,46,47)*. When the redistribution phase is lengthened from several hours to as long as 8–48 hours, there is greater distinction between scar and hibernating myocardium *(48)*. Unfortunately, longer intervals between rest and redistribution scans lead to poor image quality because of tracer decay or washout *(49)*. A second injection of Tl 201 has been used to overcome this loss of tracer intensity and substantially improves viability detection *(50–52)*. As many as half of fixed defects in a redistribution scan can show enhancement after reinjection *(51)*.

Because Tl 201 activity in the myocardium is present across a continuum of values, a minimum value is often arbitrarily used as a cutoff to determine clinical viability. Myocardial defects with counts below this cutoff are therefore labeled "irreversible." Although there is no ideal single value, 50% of the maximal tracer uptake is commonly used as this cutoff. However, viability is not binary at a prespecified cutoff value, although the chance of functional recovery decreases progressively as thallium counts fall (Fig. 1) *(53)*. Moreover, the ability of thallium techniques to predict functional recovery at a particular activity value for viability is worse in areas of akinesis than hypokinesis *(53)*. Therefore, it is possible that irreversible defects by TI 201 may still be viable, especially when assessed by PET. Only the most severe perfusion defects correlate well with PET nonviability *(54)*. These cutoff values are important to note and

may account for the variable diagnostic accuracy of this technique in the literature.

The diagnostic accuracy of Tl 201 scintigraphy can be improved with exercise. In areas with equivocal viability by tracer uptake, the finding of reversible ischemia on stress imaging predicts recovery of function *(55)*. Exercise stress imaging also provides the additional prognostic information of exercise capacity. Finally, combining various features of Tl 201 scintigraphy, such as stress-induced ischemia, wall motion abnormalities, late redistribution activity, and the use of absolute of tracer counts, can refine the interpretation of viability.

Despite these technical issues, Tl 201 scintigraphy is sensitive. Pooled data from several studies showed that the use of Tl 201 for viability has a sensitivity of 86–90% and specificity of 47–54% for predicting improvement in postrevascularization wall motion *(40)* and compares favorably to PET *(56)*.

Technetium-99 Perfusion Imaging

The technetium-based tracers ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin have also been used for the assessment of myocardial viability. Technetium-based agents cross cell membranes passively and then bind to mitochondria. These tracers distribute according to perfusion and viability of the myocardium *(44,57)*, but do not redistribute as extensively as Tl 201. However, they are similar to Tl 201 in their ability to demonstrate viability and predict recovery of function *(58–61)*. Pooled data from seven studies of ^{99m}Tc-sestamibi showed a sensitivity of 81% and specificity of 60% for the detection of functional recovery after revascularization and can be improved with the administration of nitrates *(40)*. Finally, in one series, ^{99m}Tc-tetrofosmin had a sensitivity of 96% and specificity of 30% for predicting viability *(58)*.

In summary, the primary advantages to the use of thallium- or technetium-based scintigraphy are their widespread availability and high sensitivity. The tracers are generally similar in their ability to predict improvement in LV function. Drawbacks to the technology include motion artifacts, attenuation of counts from other organs, and the time to obtain, process, and interpret the data. Continuous technological improvements are helping to minimize these disadvantages.

Dobutamine Echocardiography

In early studies of myocardial viability, inotropic agents often improved the function of hypokinetic or akinetic myocardial segments. Although the hibernating myocyte may have a perturbed cytoskeletal structure and a decreased quantity of contractile fibers,

it is often still capable of responding to inotropic agents through β-receptor stimulation.

Low-dose dobutamine stress echocardiography (LDSE) can demonstrate this contractile reserve and imply viability. During infusion of low-dose dobutamine (<5 μg/kg/min), hypocontractile viable myocardium is stimulated to contract (via adrenergic β-1-receptors), but not to a level at which the increased oxygen demand outstrips its supply. The sensitivity, specificity, and diagnostic accuracies of LDSE to predict postoperative improvements in LV function are variable and range from 71 to 97%, 63 to 96%, and 70 to 91%, respectively *(62)*. When compared to Tl 201, LDSE generally shows a higher specificity and lower sensitivity for viability *(63,64)*.

The lower sensitivity may be because of the inability to deliver the substrate necessary to increase contractile function when there is advanced cytoskeletal disarray, so the dobutamine stress results in an ineffectual or absent contractile response *(24)*. Echocardiography is also better at predicting functional recovery of hypokinetic rather than akinetic segments *(65)*, although this is true of thallium imaging as well *(24)*. As noted by Bonow *(24)*, the ability of LDSE to predict postrevascularization improvements in wall motion more accurately than PET or SPECT may not be surprising because viability is typically defined by improvements in echocardiographically assessed wall motion.

The specificity of dobutamine stress echocardiography (DSE) for the detection of viability is improved by a phenomenon known as the *biphasic response*. The biphasic response is an improvement in wall motion at low doses of dobutamine, but a diminution in function with higher doses *(66)*. It was postulated that this represented a mismatch between limited perfusion because of coronary disease and the increasing metabolic demand from dobutamine, resulting in myocardial ischemia and dysfunction. Hence, at low doses there is improved contractile function (as in LDSE), but at higher doses of dobutamine, the myocardium becomes ischemic and dysfunctional as the demands of contractile function surpass the supply of metabolic substrate. The presence of a biphasic response increases the specificity of DSE for predicting functional recovery to 73% *(67)* and improves the concurrence with radionuclide imaging *(68)*.

In summary, dobutamine stress echocardiography is widely available and is generally lower in cost compared to both PET and SPECT. It also can be performed quickly and even portably. Concomitant echocardiography also provides other details about ventricular and valvular structure and function. Disadvantages include poor acoustic windows from lung disease, obesity, or immobility. Interpretation can

be difficult if the endocardium is not well delineated or if there is tethering from adjacent abnormal segments *(69)*. Some of these technical issues can be ameliorated with the use of echocontrast agents. Finally, as compared to scintigraphic techniques, it has greater specificity, although less sensitivity.

Cardiac MRI

Cardiac MRI is playing an increasingly important role in the assessment of viability. Improvements in contrast-enhanced MRI have led to the ability to detect myocardial perfusion and scar with high spatial resolution. Ischemic wall motion is detected via a dobutamine protocol similar to DSE. Quantification of a gadolinium-based contrast material in the myocardium is used to measure myocardial blood flow. Scar is manifest by hyperenhancement in the ventricular myocardium. Hyperenhancement is seen after myocardial infarction, but not in patients with nonischemic cardiomyopathies or in normal volunteers *(70)*. In the first large study of contrast-enhanced MRI by Kim et al., 78% of nonhyperenhancing dysfunctional segments improved after revascularization *(71)*. Furthermore, MRI was more predictive of improvement in ventricular segments with akinesia and dyskinesia than in areas of hypokinesia, which is just the converse of PET and SPECT. There was also an inverse relationship between the burden of hyperenhancement and the likelihood of improvement in wall motion after revascularization.

Contrast-enhanced dobutamine MRI will likely become an important tool in the detection of myocardial viability. The advantage of contrast-enhanced dobutamine stress MRI is the ability to combine measures of baseline and stress wall motion and myocardial perfusion with myocardial scar visualization. Disadvantages include lack of wide availability and the inability to accommodate patients with metallic hardware common to this population, such as pacemakers and implantable defibrillators.

In summary, PET still is considered the test to which other modalities are compared for predicting viability. The other radionuclide agents are similar to PET and provide excellent sensitivity, but dobutamine echocardiography and MRI have superior specificity (Fig. 2).

Problems in Assessing the Accuracy of Methods to Detect Myocardial Viability

If recovery of ventricular systolic function defines viability, then the gold standard for judging the accuracy of a diagnostic technique rests solely on the assessment of postrevascularization ventricular function *(72)*. However, it is not clear when to assess the impact of surgical

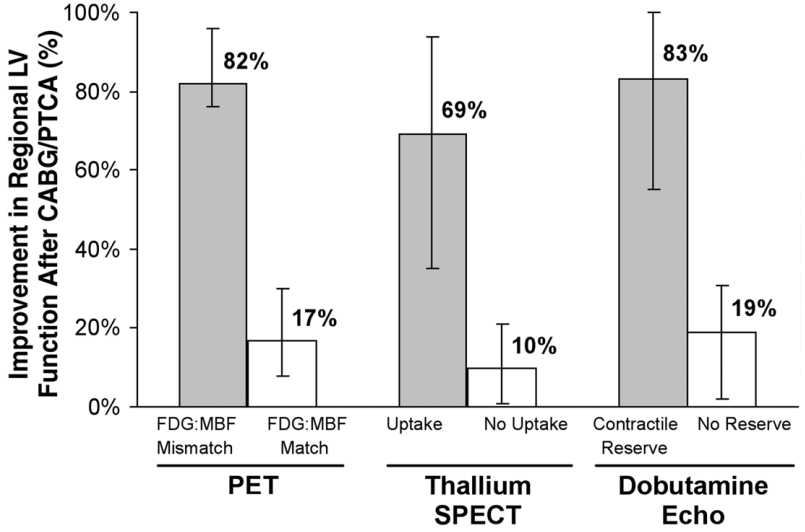

Fig. 2. Analysis of sensitivity and specificity of various modalities for predicting improvement in LV function after revascularization from multiple studies. The positive predictive value of each test is represented by the gray bars, and the inverse of the negative predictive value is represented by the open bars. CABG, coronary artery bypass graft surgery; Echo, echocardiography; FDG, ^{18}F-deoxyglucose; LV, left ventricular; MBF, myocardial blood flow; PET, positron emission tomography; PTCA, percutaneous transluminal coronary angioplasty; SPECT, single-photon emission tomography. (Reproduced with permission from ref. *24*.)

revascularization on ventricular function in the postoperative period, despite the fact that most studies base the accuracy of preoperative viability testing on assessments of ventricular function soon after surgery. Given the potential severity of the cytoskeletal disarray in hibernating myocardium, it is not surprising that full functional recovery may take months. Several studies have demonstrated such delayed recovery after revascularization does take place *(73,74)*. Conversely, viable segments may improve in function without a substantial impact on overall LV function *(75)*. In fact, in one series, the survival of patients undergoing bypass surgery without preoperative viability testing was independent of postoperative improvements in their EF *(76)*.

Completeness of revascularization will also have an impact on the predictive accuracy of tests for postoperative improvements in LV function (Table 2). If there is hypoperfusion of the myocardium from poor runoff, stenosis at the anastomotic site, development of graft atherosclerosis, or progression of native coronary disease distal to the anastamosis, there may not be functional recovery. Similarly, if the graft fails

Table 2
Factors Affecting Improvement in Left Ventricular Function After Coronary Artery Revascularization

1. Presence and degree of preoperative myocardial hibernation or stunning
2. Coronary anatomy
3. Completeness of revascularization
4. Presence and degree of intraoperative or postoperative myocardial infarction
5. Graft patency
6. Method for determining ventricular function
7. Left ventricular size
8. Time from revascularization to assessment of ventricular function
9. Presence of concomitant myopathy

Adapted from ref. *75.*

and the myocardium becomes infarcted, there will be a lack of functional recovery *(45)*. Trials have shown the predictive accuracy of rest–redistribution Tl 201 is improved with the exclusion of inadequately revascularized segments *(77)*. However, few trials address the completeness of revascularization.

OTHER BENEFITS OF SURGICAL REVASCULARIZATION IN HEART FAILURE

In multivariate models used to predict postrevascularization ventricular function *(43)*, preoperative myocardial viability only accounts for 36% of the variability in the postsurgical EF *(78)*. Therefore, some have questioned whether recovery of ventricular function is the most clinically relevant end point for patients with advanced CAD and heart failure. Statistical improvements in the contraction of segments of myocardium or even in total EF may not easily translate into tangible benefits unless they impact on symptom relief, QoL, or survival. Various studies have examined such end points in addition to postoperative ventricular systolic function.

Symptoms

The identification of viability may identify those most likely to derive symptomatic benefit from surgery. In a study of 36 patients with symptomatic heart failure (a third also had angina) and poor ventricular function (mean EF 28%), the total extent of PET mismatch corresponded

linearly with postoperative symptomatic improvement. In fact, those with the largest mismatch had the greatest degree of benefit *(79)*. Improvement in symptoms also paralleled an improvement in survival *(80)*.

Other techniques to identify viability also predict symptomatic improvements. Bax et al. *(81)* used DSE to assess viability in 62 patients, more than half of whom had heart failure as the indication for revascularization. For those patients with four or more viable segments by DSE, the mean NYHA functional class improved from 3.2 to 1.6 ($p < 0.01$) after revascularization and corresponded to an increase in the EF from 27 to 33% ($p < 0.01$). There were no improvements in symptoms or ventricular function in patients with less than four viable segments.

Quality of Life

QoL was investigated in a study of 73 patients (mean EF 28% and mean NYHA class 2.6) who had both PET and DSE prior to bypass surgery. Improvement in exercise capacity correlated with amount of viability by PET but not by echo. The mean NYHA functional class improved from 2.6 to 1.9, but correlated weakly with the viability assessments. Interestingly, QoL scores improved significantly with no correlation to viability *(82)*. The presence of viability contributed to improved symptoms, but QoL may be too complex a measure to be driven solely by symptomatic improvement. In fact, the contribution of the placebo effect of surgery cannot be discounted and was an important confounder in the transmyocardial laser revascularization studies of chronic medically refractory angina.

Survival

Early studies of PET showed 3-year survival was similar to cardiac transplantation with surgical revascularization when viability was present *(83)*. Revascularization of PET-viable territories also decreased nonfatal ischemic events compared to those who were treated medically *(84)*. Other studies have demonstrated decreased incidence of myocardial infarction, cardiac arrest, and death when PET viability was present before revascularization *(85)*. Tl 201 viability has also been shown to improve survival after revascularization *(86–89)* and is independent of age, EF, and number of diseased vessels *(90)*.

Scintigraphic techniques appear comparable when trying to predict survival. For example, ^{13}N-ammonia/^{18}FDG PET and stress/rest ^{99m}Tc-sestamibi SPECT were compared in 103 patients with a mean NYHA class of 2.5 and advanced LV dysfunction (a third had EF <30%). The

revascularization team was blinded to the specific test, and the patients received either percutaneous transluminal coronary angioplasty or CABG if there was demonstrable viability; otherwise, they received medical management. The cardiac event-free survival 28 months after revascularization was improved to the same degree regardless of whether SPECT or PET was used to determine viability *(91)*.

Improvements in ventricular geometry may also predict survival and make the use of echocardiographic techniques to assess viability attractive. Using LDSE, an improvement in ventricular geometry predicted a twofold increase in 4-year survival *(92)*. Along with improvements in NYHA class and EF, LDSE viability predicts survival with surgical revascularization when compared to medical management alone *(81,86,93,94)*. Furthermore, LDSE viability was the strongest predictor of survival in a multivariable analysis *(95)*. Lack of echocardiographic viability also predicts an absence of survival benefit with revascularization. In one investigation (Fig. 3), survival from cardiac death after a mean of 40 months was 97% for patients with viability who had revascularization, 69% for those with viability with medical treatment, 50% for those without viability who had revascularization, and 56% for those without viability who were treated medically *(93)*.

A meta-analysis of 24 studies of viability with PET, thallium perfusion, or dobutamine echocardiography was performed to compare the impact of viability testing on prognosis. More than 3000 patients with a mean EF of 32% were followed for more than 2 years. Annual mortality after revascularization with viable myocardium was 3.2% compared to 16% with medical treatment ($p < 0.0001$). If there was demonstrable viability, then the patients with the worst preoperative EF had the greatest degree of benefit. Last, patients with viable myocardium who were treated medically had a death rate of 16% compared with 6.2% (Fig. 4) for patients who had no viability and were treated medically *(96)*.

To conclude, testing for viability to assess suitability for subsequent revascularization of patients with CAD and LV function appears to predict not only improvements in LV function, but also improvements in symptoms and survival. However, the published data to date, as Bonow noted, are generally derived from small, single-center observational trials, with viability treated in a binary fashion and using a mix of surgical and percutaneous revascularization in patients with various degrees of heart failure and angina *(97)*. Furthermore, these studies by and large are retrospective and subject to significant bias because the decision to proceed with surgery was rarely randomized.

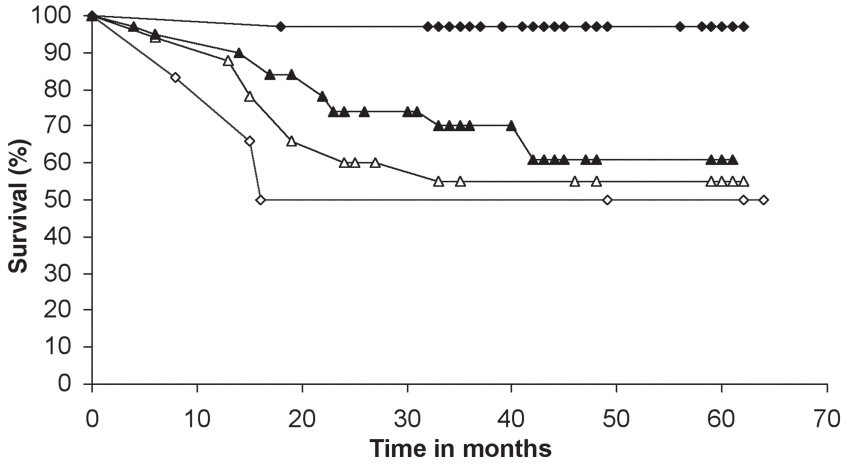

Fig. 3. Effect of myocardial viability by dobutamine echocardiography on survival in 87 consecutive patients with a mean of 2.3 diseased arteries and a mean EF of 25%. Solid diamond, viable myocardium and revascularization; solid triangle, viable myocardium and medical therapy; open triangle, no viable myocardium and medical therapy; open diamond, no viable myocardium and revascularization. (Reproduced with permission from ref. *93*.)

Nonetheless, for the patient with advanced coronary artery disease (and suitable anatomy for revascularization), LV dysfunction, and heart failure, but without angina, revascularization is likely beneficial if viability can be demonstrated. Viability demonstrated by thallium scintigraphy, PET, or dobutamine echocardiography predicts symptomatic improvement, and these modalities are similar in their ability to predict survival after revascularization (Fig. 5). Equally important, patients who lack significant myocardial viability probably do not benefit, and are potentially harmed, from surgery when compared to contemporary medical and device therapies for heart failure.

This body of evidence has contributed to the current recommendations by the American Heart Association/American College of Cardiology (AHA/ACC) for CABG *(98)* in patients with LV dysfunction (*see* Table 3). The choice of method for the preoperative assessment of myocardial viability is ultimately dependent on local expertise and familiarity because the various modalities appear to be comparable (Table 4). Some centers use more than one modality to take advantage of the high sensitivities of certain techniques (i.e., scintigraphic tests) and the high specificities of others (i.e., dobutamine echocardiography or cardiac stress MRI).

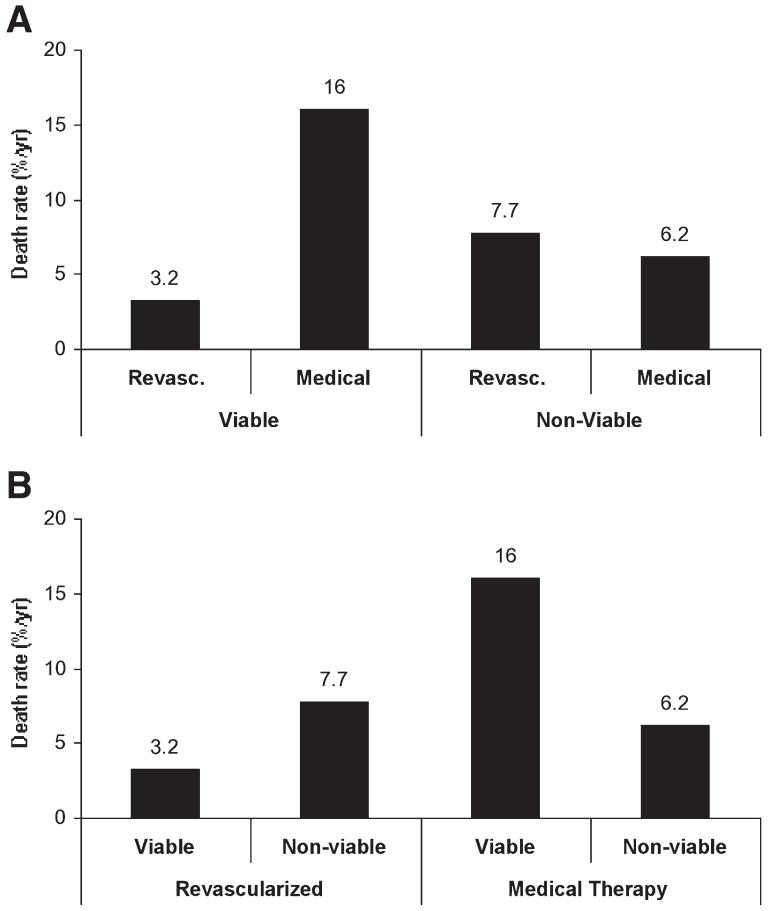

Fig. 4. The results of a meta-analysis of 24 studies using positron emission tomography, thallium 201 perfusion, or dobutamine echocardiography to assess viability in patients with coronary artery disease and left ventricular dysfunction. **(A)** Death rates for patients with and without myocardial viability treated by revascularization (Revasc.) or medical therapy. **(B)** Death rates for patients treated by revascularization or medical therapy with and without demonstrable viability. (Adapted from ref. *96*.)

SURGICAL VENTRICULAR REMODELING

Surgical remodeling of the ventricle, especially when significant ventricular distortion is present, can improve ventricular function and can be performed concomitantly with coronary bypass grafting *(99)*. This procedure, as modified by Dor, involves decreasing the scar size by apposing the surrounding viable myocardium directly or through a pericardial patch *(100)*. By maintaining LV geometry at a lower

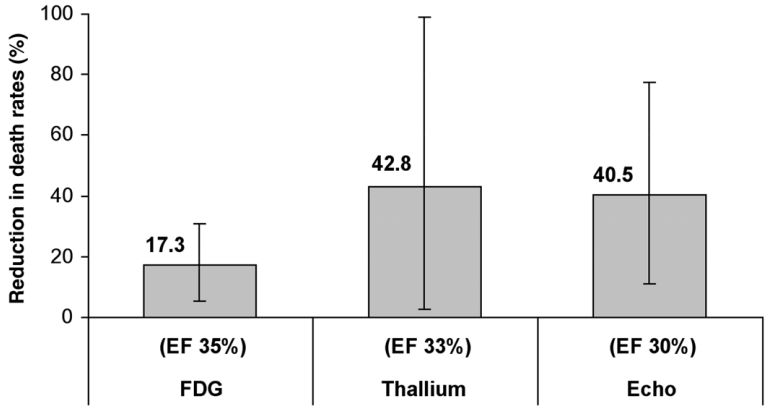

Fig. 5. The results of a meta-analysis of 11 studies of F-18 fluorodeoxyglucose (FDG) positron emission tomography, 6 studies of thallium 201 perfusion imaging, and 7 studies of dobutamine echocardiography on survival in patients with coronary artery disease and LV dysfunction. The mean EF of the patients is listed in parentheses above the modality used to assess viability. The mean decrease in mortality after the revascularization of viable myocardium is represented by the bar graph; the lines represent the 95% confidence intervals. The decrease in mortality is not statistically significantly different between the three modalities for detecting viability. (Adapted with permission from ref. *96*.)

volume, many of the adverse consequences of LV dilation can be pacified *(101,102)*. A study reviewed this approach in 439 patients, 89% of whom had simultaneous bypass surgery, from a variety of surgical centers. Both ventricular function and geometry improved, with the mean EF increasing from 29 to 39% ($p < 0.0001$), and the end systolic volume decreasing from 109 mL/m^2 to 69 mL/m^2 ($p < 0.005$). Most important, in the mortality at 18 months was an acceptable 10.8% *(103)*.

THE FUTURE OF MECHANICAL REVASCULARIZATION IN HEART FAILURE

It still remains that no prospective randomized trial exists to address the problem of revascularization for heart failure and ischemic LV dysfunction. Although current retrospective literature is supportive of surgery in this clinical situation, the evidence is far from definitive. In response to this dilemma, the National Institutes of Health is sponsoring a multicenter prospective randomized trial, the Surgical Treatment for Ischemic Heart Failure (STICH) study. It is recruiting patients with

Table 3
ACC/AHA/ASNC Consensus Recommendations for Radionuclide Techniques to Assess Myocardial Viability

Indication	*Test*	*Class*	*Level of evidence*
1. Predicting improvement in regional and global LV function after revascularization	Stress–redistribution–reinjection	I	B
	Rest–redistribution imaging	I	B
	Perfusion plus PET FDG imaging	I	B
	Resting sestamibi imaging	I	B
	Gated SPECT sestamibi imaging	IIa	B
	Late Tl 201 redistribution imaging (after stress)	IIb	B
2. Predicting improvement in heart failure symptoms after revascularization	Perfusion plus PET FDG imaging	IIa	B
3. Predicting improvement in natural history after revascularization	Tl 201 imaging (rest–redistribution and stress–redistribution–reinjection)	I	B
	Perfusion plus PET FDG imaging	I	B

ACC, American College of Cardiology; AHA, American Heart Association; ASNC, American Society of Nuclear Cardiology; LV, left ventricular; PET, positron emission tomography; FDG, ^{18}F-deoxyglucose; SPECT, single-photon emission computed tomography; Tl 201, thallium 201.

Recommendation class: I, conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective; IIa, the weight of evidence or opinion is in favor of the procedure or treatment. IIb, usefulness/efficacy is less well established by evidence/opinion.

Level of evidence B: Data derived from a single randomized clinical trial or nonrandomized studies. (Adapted from ref. *49*.)

Table 4
ACC/AHA Guidelines for the Indications for CABG in Patients With Poor LV Function

Class I
1. Significant left main coronary artery stenosis
2. Left main equivalent: significant (≥70%) stenosis of the proximal LAD and proximal left circumflex artery
3. Proximal LAD stenosis with two- or three-vessel disease
Class IIa
Poor LV function, with significant viable noncontracting revascularizable myocardium and without any of the above anatomic patterns
Class III
Poor LV function, without evidence of intermittent ischemia and without evidence of significant revascularizable viable myocardium

ACC, American College of Cardiology; AHA, American Heart Association; CABG, coronary artery bypass graft surgery; LV, left ventricular; LAD, left anterior descending coronary artery.

Recommendations class: I, conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective; IIa, the weight of evidence or opinion is in favor of the procedure or treatment; III, conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases can be harmful. (Adapted from ref. *98*.)

ischemic LV dysfunction with an EF less than 35%, CAD amenable to surgical revascularization, and NYHA class 2–4 heart failure at 50 centers with a goal enrollment of 2800 patients. The overall study design is to randomly assign patients, stratified by presence or absence of angina and by the presence or absence of a large akinetic territory, either to surgery or to continued medical therapy. Those with large akinetic territories will be eligible to undergo surgical ventricular restoration (SVR; i.e., surgical remodeling).

Patients without angina will be divided into two groups: 1600 patients with SVR-ineligible anatomy and 600 patients who are SVR eligible. The SVR ineligible will be randomly assigned to medical therapy vs CABG alone. The SVR eligible will be randomly assigned to one of three arms: medical therapy, CABG alone, or CABG and SVR. Finally, in a subgroup study of 600 patients with angina, those with heart failure and a large area of akinesis will be randomly assigned to conventional CABG alone or CABG and SVR.

The trial will have a minimum follow-up of 3 years. The study has an 89% power to demonstrate a 20% reduction in the combined end point of all-cause death for CABG compared to medical therapy. For SVR-eligible patients, the study has a 90% power to detect a 20% difference in the end point of survival free of hospitalization for cardiac causes when compared to CABG alone or medical therapy. All screened patients who meet inclusion criteria for any of the trial's arms but who refuse study entry will be followed in a registry.

The study will also include an investigation of the noninvasive assessment of viability with cardiac MRI, radionuclide imaging, and echocardiography. There will be postoperative assessments of LV function at 4 months and 2 years. The modalities will be assessed for their ability to predict clinical outcomes both individually and in comparison to one another. Substudies will analyze cost, QoL, neurohormonal mediators, proinflammatory cytokines, natriuretic peptides, and polymorphisms in genotype expression. When completed, this study will surely be a landmark effort in refining the evaluation of patients with ischemic heart failure and defining the roles of medical therapy, revascularization, and surgical ventricular remodeling in their subsequent management.

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