# The historical and conceptual evolution of radionuclide assessment of myocardial viability

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## INTRODUCTION

The assessment of whether dysfunctional myocardial tissue or regions contain predominantly viable myocytes has become an important research and clinical issue for radionuclide imaging. From a research/investigative perspective, imaging of myocardial perfusion and regional myocardial metabolism has provided important insights into the pathophysiology of hibernating and stunned myocardium. From a clinical perspective, the wealth of data built by many clinical investigators over the years has allowed noninvasive imaging of myocardial viability to occupy an important point on the decision-making spectrum for patients with heart failure, chronic coronary artery disease (CAD), and left ventricular (LV) dysfunction.

Several sources are available that document and pool the literature on the use of radionuclide imaging in patients with chronic CAD and LV dysfunction with regard to predictive values for regional functional recovery or other outcomes.[1-3] In this review we will attempt to trace the historical and conceptual pathways that led the field to its current state, to highlight what we would consider as the major achievements along that path, and finally, to identify areas for future exploration. Some of the historical milestones in this field are listed in Table 1.

## HISTORICAL PERSPECTIVE: THE RETROSPECTIVE RECOGNITION OF VIABLE DYSFUNCTIONAL MYOCARDIUM AND THE EARLY YEARS OF NONINVASIVE ASSESSMENT

Before the 1980s, impaired LV function at rest was predominantly thought to represent an irreversible process. The introduction and subsequent growth of the concepts of stunned and hibernating myocardium in the mid-1970s to early 1980s dramatically changed the application of noninvasive techniques in guiding therapeutic decisions for revascularization.

In 1975 Heyndrickx et al[4] showed that impaired regional mechanical function after coronary occlusions could persist for hours without myocardial infarction (MI). After a plethora of experimental and clinical studies, delayed recovery of contractile function after a period of ischemia was termed *stunned myocardium*.[5] Interestingly, the concept of hibernating myocardium arose initially from clinical rather than experimental observations.[6,7] In patients with chronic ischemic heart disease undergoing coronary artery bypass graft (CABG) surgery, improvements in both regional and global LV function were often observed at rest.[8,9] Approximately one third of patients with preoperative LV dysfunction manifest significant increases in ventricular function after CABG, with normalization of ejection fraction (EF) in approximately one fourth of patients.[10]

Current understanding supports the concept that the myocardium has several mechanisms of acute and chronic adaptation to a temporary or sustained reduction in coronary blood flow, known as stunning, hibernation, and ischemic preconditioning.[11] These responses to ischemia preserve sufficient energy to protect the structural and functional integrity of the cardiac myocyte. In contrast to programmed cell death, or apoptosis, the term *programmed cell survival* has been used to describe the commonality between myocardial stunning, hibernation, and ischemic preconditioning, despite their distinct pathophysiology.[12]

From the mid-1970s to early 1980s, a number of methods were introduced to assess regional LV contractile reserve in asynergic regions during invasive contrast or noninvasive radionuclide ventriculography. These included enhanced regional contractile reserve during nitroglycerin administration,[13] during postextrasystolic potentiation,[14] during low-dose catecholamine infusion,[15] or immediately after exercise.[16] However, none of these methods gained widespread clinical enthusiasm. In the meantime, thallium 201 myocardial perfusion imaging, which was introduced in 1975 for detecting CAD, gained momentum as a viability probe for differentiating viable from scarred myocardium. Experimental studies showed that extraction of Tl-201 across the cell membrane is unaffected by hypoxia, chronic hypoperfusion (hiberna-

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**Table 1.** Historical points of interest in the evolution of radionuclide assessment of myocardial viability

- Late 1970s, early 1980's: retrospective studies recognizing that dysfunctional myocardium may improve function after revascularization by CABG
- Early-mid 1980's: description of hibernating myocardium. Potential prospective identification by invasive observations of improved regional function by left ventriculogram after nitroglycerin or with post-extrasystolic potentiation
- Late 1970s-early 1980s: Initial descriptions of reversible *resting* thallium201 defects and potential implications
- Mid-1980's: initial recognition that all "fixed defects" are not all representative of infarct, and that quantitative analysis of the degree of thallium201 uptake within fixed defects correlated with the probability of improved perfusion after CABG. Opened the possibility that radionuclide imaging could prospectively identify potential improvement in perfusion or function, *noninvasively*
- Late 1980's: Prospective noninvasive evaluation of the probability of post-revascularization functional recovery by PET imaging of perfusion and metabolism
- Late 1980's: beginning of the evolution of thallium201 imaging protocols to optimize assessment of viability, including late redistribution imaging
- Late 1980's-early 1990's: initial reports of thallium201 reinjection to optimize assessment of viability
- Early-mid 1990's: Further evolution and understanding of thallium201 protocols, including quantitative assessment of defect severity after reinjection
- Early-mid 1990's: Evaluation of other PET tracers and techniques, including imaging of fatty acids and tissue perfusible index
- Mid 1990's: initial reports of the use of technetium99m agents for assessing viability in animal models and in humans
- Biopsy/tissue studies correlating SPECT and PET imaging parameters with direct measures of tissue/myocyte viability
- Mid-late 1990's: Numerous reports on predicting functional recovery. Initial reports on predicting other endpoints after revascularization, including improved symptoms and survival, as well as the prognostic importance of the presence of viability
- Mid-late 1990's: Nitrate-enhanced imaging for thallium201 and technetium99m agents
- Late 1990's: Importance of incorporating evaluation of inducible ischemia into viability evaluation
- Late 1990's-early 2000's: Other emerging techniques, such as NOGA mapping and delayed hyperenhancement cardiac MR imaging, are compared to radionuclide techniques

tion), or postischemic dysfunction (stunning), unless irreversible injury (scarred myocardium) is present.

## HISTORICAL POINTS OF INTEREST IN THE EVOLUTION OF RADIONUCLIDE TECHNIQUES FOR ASSESSING MYOCARDIAL/MYOCYTE VIABILITY

The application of radiotracer techniques for interrogating physiologic and pathophysiologic cardiopulmonary conditions actually dates back to the early 20th century. The presence of an active transport mechanism for concentrating monovalent cations in normal myocardium led to the use of radioisotopes of ionic potassium and rubidium in the 1950s for myocardial imaging. Uptake of these agents in myocardium is related to blood flow as well as to structural and functional integrity of the myocardial cell membrane, reflecting cellular (myocyte) viability. Because potassium is the major intracellular cation in muscle, and it is virtually absent in scar tissue, investigations in the 1950s concentrated on developing intravenously injected ionic myocardial perfusion tracers that have biologic properties similar to potassium. In 1954 Love et al[17] demonstrated myocardial uptake and distribution of potassium and rubidium in canine models. In 1974 a linear relationship was shown between the distribution of potassium 43 and microspheres in animal models of normal flow, ischemia, and infarction.[18] A subsequent study in 1975 showed an association between abnormalities in transmyocardial potassium flux and acute myocardial injury.[19] These favorable results in animals propelled the application of K-43 in clinical studies to identify patients with anginal chest pain and epicardial coronary artery narrowing.[20] Because Tl-201 has biologic properties similar to K-43 but with a more favorable photon energy spectrum and shorter physical half-life, in 1975 Tl-201 became the tracer of choice for clinical studies.[21,22]

## INITIAL APPLICATION OF TI-201 FOR ASSESSMENT OF VIABILITY, MODIFICATIONS OF THE STANDARD TI-201 PROTOCOL, AND USE OF TECHNETIUM 99m AGENTS

The first clinical application of stress thallium imaging for prospective distinction of scarred from viable myocardium was done in 1980 by Akins et al.[23] They performed stress-redistribution Tl-201 imaging in two angina-free patients with severe congestive heart failure to identify clinically silent areas of ischemic myocardium. Subsequent myocardial revascularization in these patients led to considerable improvement in their clinical state, postoperative nuclear scans, and rest LV dysfunc-

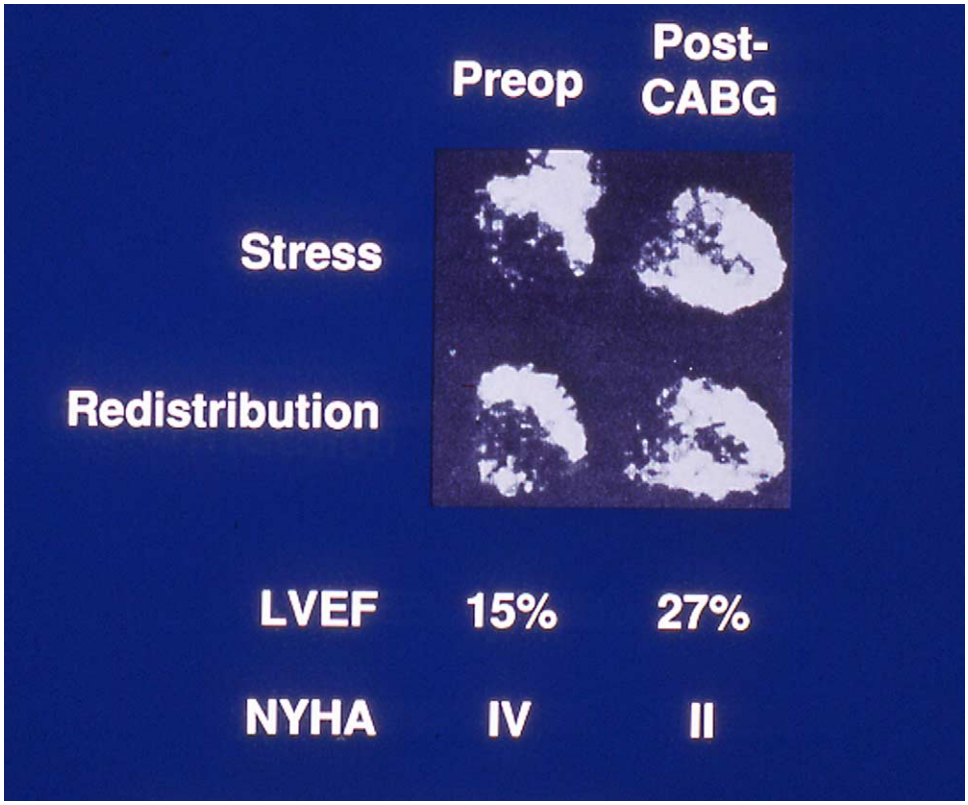


**Figure 1.** Evidence for viable myocardium in a region with an irreversible thallium defect, suggesting an underestimation of viability by the standard Tl-201 protocol. Preoperative and postoperative anterior planar thallium images demonstrate partially reversible inferior and fixed apical thallium defects preoperatively that normalize after CABG in a patient with severe LV dysfunction and heart failure but no angina. The LVEF increased from 15% before surgery to 27% after surgery, and the symptomatic state improved. (Modified and reprinted with permission from Am J Cardiol 1980;46:695-700.).

tion (Figure 1). This finding opened the era of prospective noninvasive identification of dysfunctional but viable myocardium. When such Tl-201 studies were applied in a larger number of patients with CAD undergoing revascularization, reversible defects continued to be an accurate indicator of ischemic but viable myocardium. However, the converse is not true—that is, irreversible thallium defects did not necessarily indicate scarred myocardium. Approximately 45% of regions with irreversible Tl-201 defects on stress-redistribution studies showed improved thallium uptake after revascularization.[24] This prompted investigators to develop alternative methods to assess myocardial viability, such as positron emission tomography (PET).[25] Concurrently, modifications of the standard Tl-201 protocols produced useful, clinically accurate results, generally comparable to the metabolic data with PET.

## Late Redistribution

In 1983 Gutman et al[26] introduced the concept of late redistribution imaging, performed 8 to 72 hours after the initial thallium injection at peak stress. They hypothesized that in some patients with critically stenosed coronary arteries, the initial uptake of Tl-201 in the ischemic region is low and the accumulation of the tracer from the recirculating Tl-201 in the blood is slow. If a greater amount of time is allowed for redistribution, a greater number of viable myocardial regions may be differentiated from scarred myocardium. Late Tl-201 redistribution, when present, is highly predictive of viable myocardium; however, persistent defects on late imaging have suboptimal predictive accuracy: 51% of late persistent Tl-201 defects were shown to be metabolically active by PET,[27] and 37% of such defects improved after revascularization.[28]

## Tl-201 Reinjection

Limitations of Tl-201 redistribution imaging after stress for identifying viable myocardium led to the introduction of the reinjection technique by Dilsizian et al[29] in 1990. Redistribution of thallium in a given

myocardial region depends, in part, on the concentration of the radiotracer in the blood and the rate of decline of thallium levels in the blood. During the period between stress and redistribution imaging, if the blood thallium level is low (or decreases), the delivery of thallium may be insufficient and the stress-induced thallium defect may remain irreversible even though the underlying myocardium is viable. Thus some ischemic but viable regions may show no redistribution on either early (3- to 4-hour) or late (24-hour) imaging, unless blood levels of thallium are increased. Reinjection of 1 mCi thallium at rest immediately after either stress-redistribution or stress–24-hour redistribution studies showed improved thallium uptake in a substantial proportion of "fixed" defects.[29]

In patients with chronic CAD and LV dysfunction who have been studied by both Tl-201 reinjection and PET imaging with fluorodeoxyglucose (FDG), the overall concordance between the two approaches has been excellent, especially when quantitative analysis of regional tracer activity is taken into consideration.[30,31]

### Rest-Redistribution Tl-201 Imaging

In patients with known coronary artery anatomy and LV dysfunction, rest-redistribution Tl-201 imaging is a practical approach that can yield accurate viability information without inducing myocardial ischemia. Disparity between regional and global LV dysfunction and the extent and severity of thallium uptake at rest provides insight into the likelihood of recovery of function after revascularization. In 1979 Gewirtz et al[32] were the first investigators to report that Tl-201 defects could occur on rest images in the absence of an acute ischemic process or prior MI. Moreover, they recognized that many of these defects redistribute and normalize over the next few hours. This initial report was followed by studies that evaluated the efficacy of rest-redistribution imaging in predicting the outcome of asynergic regions after revascularization.[33,34]

### Tc-99m Sestamibi and Tetrofosmin

Although initially considered to be more pure flow tracers and thus potentially underestimating viability, studies in isolated systems and animal models suggested that the actual behavior of the tracers is more complex, with evidence of relative overextraction at low flows for Tc-99m sestamibi,[35] as well as evidence of some degree of redistribution.[36,37] Clinical studies have demonstrated that the performance of these agents for predicting improvement in regional function after revascularization is in general similar to Tl-201.[38,39] Administration of nitrates to improve resting blood flow before injection of sestamibi appears has been shown to slightly improve the ability of these tracers to detect myocardial viability,[38,39] as well as with Tl-201.[40]

## MAJOR ACHIEVEMENTS IN THE INVESTIGATION OF RADIONUCLIDE IMAGING TO ASSESS VIABILITY

### Evolution of Understanding Appropriate Endpoints for Viability Studies

In parallel with the numerous studies through the 1980s reporting the retrospective observation of improved regional and/or global LV function in some patients after revascularization, seminal investigations reported the prospective identification and prediction of viability by noninvasive radionuclide imaging. Gibson et al[24] used planar Tl-201 imaging to demonstrate that preoperative Tl-201 uptake patterns could be used to predict the probability of regionally improved perfusion after bypass surgery. In this study, postoperative improvement in perfusion in an initially abnormally perfused region was used as the marker or endpoint of regional tissue viability to be predicted.

Subsequently, Tillisch et al,[41] using PET imaging of myocardial blood flow and glucose metabolism, published the seminal data predicting improved regional function after revascularization in regions that were dysfunctional preoperatively. After that publication, analysis of performance characteristics (usually positive and negative predictive values) for predicting improved regional function became the standard analysis for viability studies. Fewer studies evaluated a change in global LV function (EF), though it could be argued that changes in LVEF would be more relevant to patient-related outcomes.

Regional or global functional recovery after revascularization represents a convenient endpoint for study and, particularly with the case of changes in regional function, provides many analytic data points even with relatively few patients (as the left ventricle is divided into 9, 17, 20, or even 40 segments per patient). Although such an analysis can provide very relevant physiologic information regarding comparative aspects of different tracer techniques for assessing viability, recovery of regional or global function may be an incomplete descriptor with regard to patient-related outcomes.[42] Whereas a significant improvement in LVEF is likely to be associated with favorable clinical and prognostic outcomes, revascularization may conceivably be associated with many favorable clinical effects even in the absence of ventricular functional improvement. Such favorable effects may include relief of ischemic or heart failure symptoms, improved exercise tolerance related to

diminished inducible ischemia or improved diastolic function, and stabilization (or reversal) of remodeling and stabilization of the electrophysiologic milieu, as well as prevention of MI.[42,43] A very important observation in this regard was published by Samady et al,[44] who reported that in a group of patients with LV dysfunction undergoing bypass surgery, long-term survival rates were similar regardless of whether LVEF increased after revascularization. These data suggested that improvement in regional and/or global LV function is a sufficient but not necessary condition for improved patient outcome after revascularization and broadened the potential for outcome assessment in viability studies.

In parallel with that observation, studies through the mid-1990s to late 1990s and beyond have focused more on the performance characteristics of the noninvasive viability signals to predict outcomes more directly related to the patient—that is, improvement in symptoms and various components of short- or longer-term natural history outcomes. This approach is indeed appropriate, as the usual clinical purpose of assessing the presence and extent of myocardial viability in patients with CAD and LV dysfunction is to select those who will benefit from revascularization.

## Viability and Functional Recovery

The gold standard for imaging viability of dysfunctional myocardium in many early studies was recovery of function after revascularization. In the seminal report of Tillisch et al,[41] PET imaging in dysfunctional myocardium had positive and negative predictive values of 85% and 92%, respectively. Subsequent reports examined the utility of Tl-201 reinjection,[29] the utility of rest-redistribution Tl-201 imaging,[34] and the use of the Tc-99m agents sestamibi[45] and tetrofosmin.[46] A pooled analysis of studies reporting the performance of fluorine 18 FDG PET, Tl-201 stress-redistribution-reinjection imaging, Tl-201 rest-redistribution imaging, Tc-99m sestamibi single photon emission computed tomography (SPECT) imaging, and dobutamine echocardiography suggested high sensitivity (83%-90%) and modest specificity (54%-81%) for the prediction of recovery of regional function.[1] Radionuclide imaging had a higher sensitivity in general, whereas imaging of contractile reserve had a higher specificity and PET was slightly more accurate overall.

There have been relatively fewer studies addressing improvement in global LV function after revascularization. These studies uniformly indicate that the presence of a critical or threshold mass of viable myocardium is necessary for improvement in global LV function after revascularization. With the use of PET, in the study by Tillisch et al,[41] LVEF improved from 30% ± 11% to 45% ± 14% in patients with two or more viable segments in a 15-segment LV model. Ragosta et al[34] reported that in patients with severely depressed LV function, the presence of viability in at least 7 of 15 segments by quantitative rest-redistribution planar Tl-201 imaging was predictive of a substantial improvement in global function (LVEF improved from 29% ± 7% to 41% ± 11%) after CABG. Both studies demonstrated a lack of improvement in global LV function when a lesser extent of viability was present before revascularization.

The influence of the extent of viability in heart failure patients on the recovery of global function after medical therapy has also been assessed. In the CHRISTMAS (Carvedilol Hibernation Reversible Ischaemia Trial; Marker of Success) study,[47] the extent of hibernating myocardium defined noninvasively by SPECT sestamibi imaging correlated with the magnitude of LVEF increase seen after treatment with carvedilol.

An issue that complicates the use of regional functional recovery as a gold standard is that the timing of functional recovery is not uniform after revascularization. It has been suggested that LV function may continue to improve for many months after revascularization, and therefore a single assessment, if not timed optimally, may underestimate the full extent of functional recovery.[48]

## Viability and Remodeling

Although recovery of regional and/or global function is a relevant physiologic gold standard, revascularization may confer benefits beyond and in addition to functional recovery, including attenuation of progressive ventricular remodeling. Resting regional function is primarily determined by endocardial thickening, which is unlikely to improve despite partially preserved myocardial viability in patients who have had a nontransmural MI.[49-51] In such patients, preserved viability in the outer layers of the myocardium could prevent progressive LV dilatation, despite the lack of any improvement in resting function after revascularization. From the post-MI and heart failure literature, the prevention or reversal of adverse ventricular remodeling appears to be an important determinant of long-term natural history outcomes, and strategies that prevent or reverse remodeling generally have very favorable effects on that natural history.[52]

The relationship between infarct zone viability and remodeling has been studied in animal models. Alhaddad et al[53] created left coronary artery occlusions in rats randomized to permanent occlusion or 2, 8, or 16 hours of occlusion followed by reperfusion. On morphometric and histologic analyses performed 2 weeks later, the benefits of reperfusion on infarct expansion were related primarily to preservation and hypertrophy of small islets

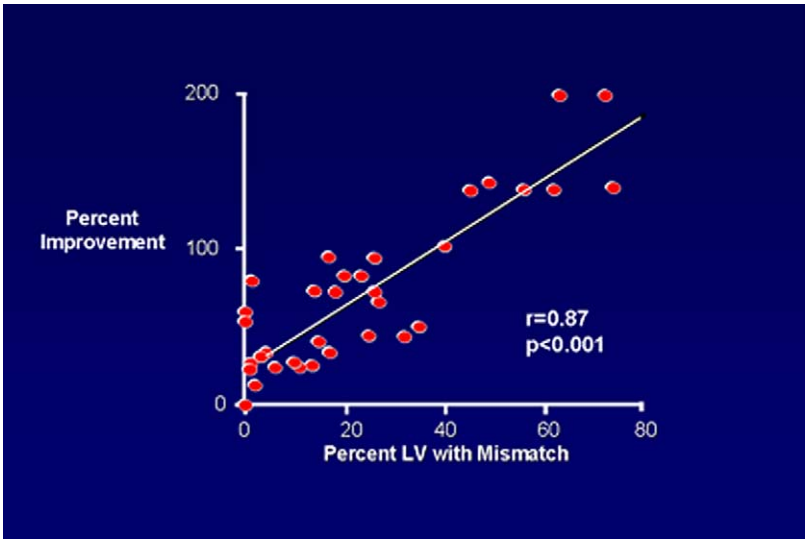


**Figure 2.** Relationship between the extent (percent LV myocardium, *x-axis*) showing viability on PET imaging (flow-metabolism mismatch) and change in functional status after CABG (percent improvement from baseline, *y-axis*), reflecting improvement in symptomatic status after revascularization. There is a strong significant correlation, suggesting that the PET viability data provided a signal of the potential magnitude of the symptomatic benefit from revascularization. (Adapted with permission from Circulation 1995;92:3436-44.)

of viable myocytes located in the subepicardium of the scar and progressively diminished with increasing periods of coronary ligation. Using a rodent model of MI, Hochman and Bulkley[54] showed that even a small rim of viable epicardial myocardium may prevent or mitigate infarct expansion.

The relative amounts of viable and necrotic myocardium within an infarct zone after MI vary widely but have been shown to be important determinants of subsequent LV remodeling.[55] Even in the presence of a high-grade stenosis or occlusion in the infarct-related artery, myocardial perfusion via collaterals can maintain infarct zone viability for prolonged periods.[56]

Few studies have examined the use of radionuclide assessment of regional viability to predict the outcome of revascularization or medical therapy on LV remodeling. An important achievement in this regard was the study of 56 patients with severe ischemic LV dysfunction by Senior et al.[57] They assessed viability (by nitrate-enhanced Tl-201 as well as nitrate-enhanced Tc-99m sestamibi imaging) at baseline, as well as LV function, size, and geometry before and again 21 months after physician-directed treatment with revascularization or medical therapy. In patients who had at least 5 viable segments in a 12-segment model (by either tracer), revascularization was associated with a prevention of remodeling, improvement in LVEF, and prevention of increasing sphericity compared with follow-up on medical therapy. On longer-term follow-up (up to 40 months), these changes with revascularization were associated with improved New York Heart Association symptom class and better survival. Thus radionuclide noninvasive evaluation of viability identified patients with ischemic cardiomyopathy in whom a strategy of revascularization was associated with both very favorable structural LV changes (prevention of remodeling) and favorable natural history outcomes.

## Viability and Improvement in Heart Failure Symptoms

In a seminal study of 36 patients with ischemic cardiomyopathy (mean LVEF, 28% ± 6%), Di Carli et al[58] found that the magnitude of improvement in heart failure symptoms after CABG was correlated with the preoperative extent of viable myocardium as determined by PET perfusion-metabolism mismatch. Patients with evidence of viability involving 18% or more of the LV myocardium had the greatest improvement in functional status. Although previous studies had demonstrated significant improvements in functional status after surgical revascularization in ischemic cardiomyopathy,[59,60] this was the first study to establish a direct correlation between the magnitude of preserved myocardial viability and the magnitude of improvement in functional status (Figure 2).

Since the publication of those data, many reports have confirmed the concept that noninvasive imaging of viability can predict the degree of symptomatic improvement in such patients, in studies involving PET[61] and

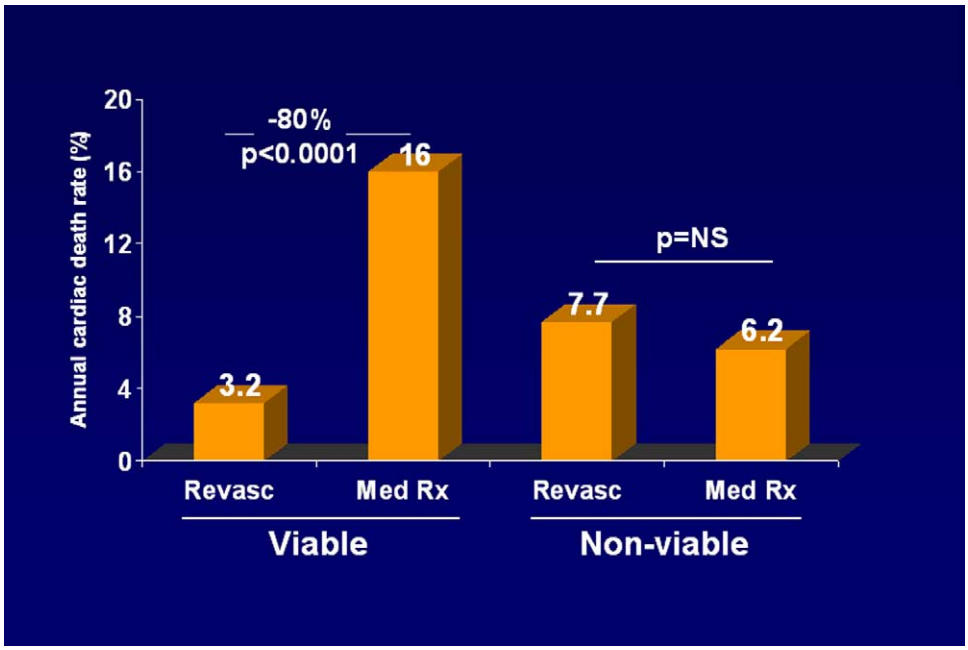


**Figure 3.** Annual cardiac mortality rates (*y-axis*) for patients with and without myocardial viability and the influence of the subsequent treatment strategy of revascularization or medical therapy (*x-axis*). Among patients with viability by noninvasive imaging treated medically, there is a 16% annual mortality rate, indicating a very high-risk group. There is an almost 80% reduction in mortality rate for similar patients with viability treated by revascularization ($P < .0001$, *left two bars*). Among patients without substantial myocardial viability, there is no significant difference in mortality rate with revascularization versus medical therapy (*right two bars*). (Adapted with permission from J Am Coll Cardiol 2002;39:1151-8.)

SPECT imaging of Tl-201 or Tc-99m sestamibi,[57] as well as identification of contractile reserve by dobutamine echocardiography.[62] Taken together, these data suggest that the extent of dysfunctional ischemic viable myocardium in heart failure patients can be used as a potential marker of the symptomatic benefit that will accrue as a result of revascularization. As revascularization in patients with significant LV dysfunction is high risk, the data suggest that viability imaging information can provide a signal of the potential benefit to inform the risk-benefit equation.

## Viability and Survival

An issue of even greater clinical relevance is the role of the presence of viable myocardium in the survival advantage offered by revascularization for patients with ischemic LV dysfunction. Management decisions are vexing in these patients and require balancing the high perioperative mortality rate imposed by severe LV dysfunction[63] with the potential for significant improvement in symptoms, functional status, and survival. In the important first studies to examine outcomes of medical therapy versus revascularization and the influence of retained viability, Eitzman et al[64] and Di Carli et al[65] concordantly reported on patients with ischemic cardiomyopathy studied with PET imaging. Among patients exhibiting a PET perfusion-metabolism mismatch pattern and classified predominantly as having viable myocardium, the survival rate was significantly higher after surgical revascularization than during medical therapy. In contrast, among patients with predominantly nonviable myocardium by PET, there was no survival benefit of revascularization compared with medical therapy.

The strength of conclusions that may be drawn from such data is limited by the small numbers of patients, raising the possibility of erroneous statistical significance or lack of significance. Since those initial publications, however, over 20 similarly designed observational studies have been published and a meta-analysis of these studies has been reported.[2] This pooled analysis consisted of 3088 patients in 24 studies reporting viability by use of radionuclide imaging, PET or dobutamine echocardiography, and long-term survival after revascularization or medical therapy. In patients with predominant viability, follow-up on medical therapy was associated with very high risk, as demonstrated by a 16% annual mortality rate. In similar patients, revascularization was associated with an 80% reduction in annual mortality rate (16% vs 3.2%, $P < .0001$), as compared with

medical therapy (Figure 3). Patients with the most severe LV dysfunction derived the greatest benefit from revascularization—that is, the survival benefit associated with revascularization of patients with viable myocardium increased proportionately with worsening LVEF. The data suggested that the presence of viable myocardium, as defined by noninvasive imaging in patients with heart failure, is a marker for very high natural history risk, and that risk appears to be significantly reduced by revascularization. These conclusions must be constrained in the context of the limitations of pooling observational cohort studies, which may bring into play unevaluable selection biases when performing a meta-analysis of published literature. More definitive conclusions may result from the ongoing STICH (Surgical Treatment of Ischemic Heart Disease) trial, in which heart failure patients without angina are randomized to revascularization or no revascularization and subsets of patients will undergo noninvasive imaging of viability before randomization.

Since the report by Allman et al,[2] other studies using Tc-99m sestamibi imaging or dobutamine echocardiography have shown concordant results,[57,66-68] demonstrating that in patients with ischemic cardiomyopathy, the presence of myocardial viability consistently predicts improved survival after revascularization.

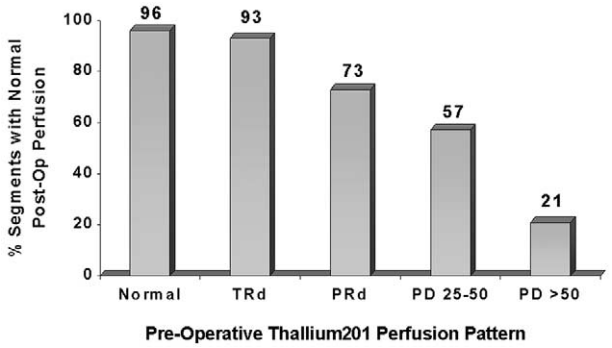


**Figure 4.** Relationship between the pattern of Tl-201 uptake on stress-redistribution imaging (*x-axis*) and the probability of post-CABG normal perfusion (as a measure of viability) (*y-axis*). Preoperative persistent Tl-201 defects (*PD*) were subclassified as to the severity of reduction in Tl-201 uptake within the fixed defect by quantitative analysis into milder (25%-50% reduction in activity [$PD_{25\text{-}50}$]) or more severe reduction ($PD_{>50}$). As the reduction in Tl-201 uptake became more severe, from totally reversible (*TRd*) to partially reversible (*PRd*) to PDs with mild and then more severe reduction in activity, the probability of postoperative viability decreased accordingly. This was the first study to suggest that (1) quantitative analysis of isotope activity helped differentiate fixed defects and (2) isotope activity represented a spectrum, related to the probability of viability. (Adapted with permission from J Am Coll Cardiol 1983;1:804-15.)

## Viability and Short-Term Management Implications

The original description of hibernating myocardium suggested that it was an adaptive steady state, potentially reversible with revascularization. Since that time, however, several reports have suggested that progressive structural and clinical deterioration may be occurring in that pathophysiologic setting, with more advanced structural changes being associated with less favorable improvement after revascularization. In a comprehensive, seminal study, Elsasser et al[69] described 38 patients with hibernating myocardium and, on myocardial biopsy, found evidence of disorganization of the contractile and cytoskeletal proteins, dedifferentiation (expression of more fetal proteins), changes in the extracellular matrix with evidence of reparative fibrosis, and evidence of fibrosis. Patients with more advanced abnormalities had less improvement in regional and global function after revascularization. These investigators suggested that hibernation was an “incomplete adaptation to ischemia” and that, once identified, prompt revascularization should occur.

Consistent with this concept are data from Beanlands et al,[70] who reported that after identification of patients with ischemic cardiomyopathy who had significant viable myocardium by PET imaging, a substantial delay in revascularization was associated with death during that delay and absence of postrevascularization LV functional improvement, as compared with similar patients undergoing more prompt revascularization.

These important studies have significant practical implications, suggesting that identification of patients with substantial ischemia and viability are not only at long-term risk, but risk in the short term as well, and that optimal reversibility of LV dysfunction and improvement in symptoms and outcome are dependent on prompt referral for revascularization.

Incorporating viability information into the database available for decision making regarding revascularization can also provide insight into the early and intermediate-term postoperative course. Haas et al[71] reported on two groups of patients with ischemic cardiomyopathy referred for bypass surgery: one group was selected on the basis of clinical and angiographic criteria, whereas the second group had PET imaging performed as part of the evaluation and selection process. The group in whom PET informed the clinical decision had a less complicated postoperative course, less need for perioperative inotropic support, and lower in-hospital and 12-month mortality rates. These important data support the concept that viability information can assist in the selection of patients with the most optimal potential outcome of revascularization.

### Assessment of "Nonviability": Radionuclide Imaging To Assess Infarct Size

A very important achievement in the field has been the extensive validation of resting Tc-99m sestamibi uptake in the early post-MI period to provide an assessment of infarct size.[72] Using an analytic threshold of 60% of peak uptake, a level derived from studies in both animal models[73] and human beings,[45] Gibbons et al[72] have found that the extent of the left ventricle that falls below this uptake level provides a clinically relevant measure of infarct size.

Infarct size as assessed by quantitative analysis of resting sestamibi uptake has been validated against many other measures of infarct size.[74] Moreover, a significant association between sestamibi infarct size and mortality rate over long-term follow-up has been demonstrated.[75] This measure is now commonly used in many clinical trials as an early post-MI surrogate endpoint to assess new agents to reduce infarct size.

## MAJOR ACHIEVEMENTS IN THE EVOLUTION OF UNDERSTANDING APPROPRIATE ANALYTIC TECHNIQUES FOR VIABILITY STUDIES

In contrast to the literature on radionuclide imaging for detection of CAD or risk stratification, in which visual scoring and semiquantitative segmental scoring have been the predominant analytic methodologies, the viability literature, almost from the beginning, has often incorporated quantitative measures of tracer uptake to more precisely map uptake patterns. The seminal study in this regard was reported by Gibson et al,[24] using quantitative analysis of the degree of Tl-201 uptake in planar images. This study provided the initial recognition that "fixed defects" are not all representative of infarct, in that regions with preoperative fixed defects could often demonstrate improved or even normal stress-redistribution Tl-201 uptake postoperatively. Moreover, quantitative analysis of the degree of Tl-201 uptake within fixed defects correlated with the probability of improved perfusion after CABG (Figure 4). These important data opened the possibility that radionuclide imaging could prospectively identify potential improvement in perfusion or function noninvasively.

Subsequently, many other reports explored and validated the importance of quantitative analysis. Dilsizian et al[29] used both visual and quantitative analysis to demonstrate the importance of Tl-201 reinjection in identifying myocardial viability. These investigators also reported that the quantitative magnitude of increase in Tl-201 uptake after reinjection was by itself an important determinant of the probability of viability and potential recovery of function.[76] Quantitative analysis of the degree of tracer uptake, as opposed to simply presence or absence, was also shown to be important for the use of Tc-99m sestamibi in assessing viability.[37,45]

A key concept that has emerged from the use of quantitative analysis of tracer uptake in viability studies is that tracer uptake represents a continuous signal rather than a dichotomous signal. That is, tracer uptake is a biologic signal that reflects the full spectrum of how much tissue viability is present in a dysfunctional region, from completely retained viability ("transmural hibernation") to transmural infarct/scar, and all admixtures in between. This concept has been confirmed by a series of very important studies representing a major achievement in this field, correlating tracer uptake with direct examination of tissue viability from myocardial biopsy samples.[77-80]

Although much of the focus in using myocardial perfusion and cell membrane integrity tracers such as Tl-201 or Tc-99m sestamibi or metabolic tracers was on predicting functional recovery after revascularization, these tracers are being imaged after uptake by individual viable myocardial cells and thus are really providing a signal of myocyte cell membrane integrity or preserved myocyte metabolism. The various thresholds or cut points that are often used to formulate predictive values for functional recovery are merely markers for a sufficient mass of viable myocardial tissue to support regional function after restoration of blood flow. In that regard, an important point of validation of these tracers for assessing myocardial viability was the correlation with the magnitude of viable myocardial cells within a dysfunctional territory.

Zimmerman et al[77] performed myocardial biopsies of dysfunctional anterior wall zones during bypass surgery in patients who had undergone planar thallium scintigraphy with thallium reinjection before operation. There was a very good correlation between the quantitated thallium regional activity within the anterior wall from the planar images after reinjection and the percent fibrosis within the biopsy specimens of those same walls (Figure 5). Similarly, in patients with chronic ischemic cardiomyopathy undergoing pretransplantation stress-redistribution-reinjection SPECT Tl-201 scintigraphy, patterns of Tl-201 defects correlated with the post-transplantation extent and distribution of collagen replacement.[81] The higher collagen content in irreversible thallium regions was associated with lower wall thickness and more severe cross-sectional coronary artery narrowing when compared with reversible and normal thallium regions.[81] These data suggest that quantitative analysis of Tl-201 uptake indeed reflects the degree of regional tissue viability.

Three key studies examined this issue by use of Tc-99m sestamibi. Medrano et al[78] injected sestamibi at rest in patients with severe ischemic cardiomyopathy just

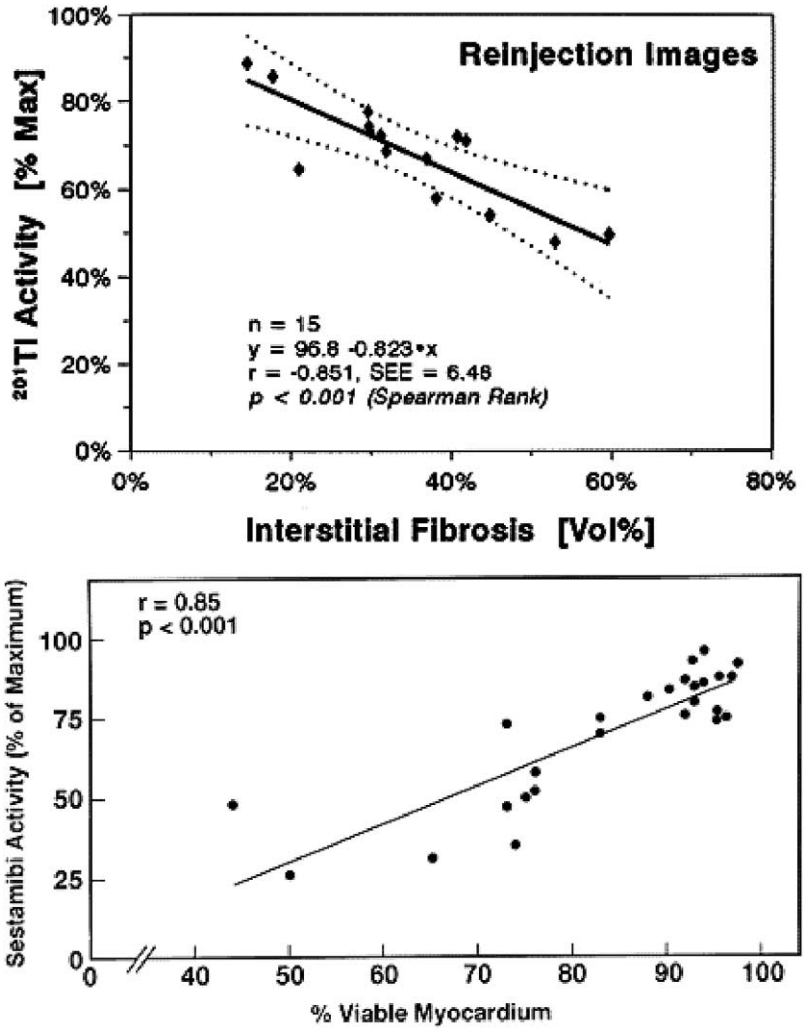


**Figure 5.** Relationship between quantitated tracer uptake and histologic measures of viability. In **A**, the relationship of preoperative quantitated Tl-201 activity after reinjection (as percent of peak counts) (*y-axis*) from planar imaging is compared with the percent interstitial fibrosis (an inverse measure of viability) taken from biopsy samples of dysfunctional anterior walls during CABG surgery. There is a strong correlation. In **B**, the relationship of preoperative quantitated SPECT Tc-99m sestamibi activity (after a rest high-dose injection) is compared with the percent viability, similarly taken from biopsy samples of dysfunctional anterior walls during CABG surgery. There is a strong direct correlation, with the same correlation coefficient as the Tl-201 study. Both of these studies documented that tracer uptake is a continuum that correlates with the direct extent of tissue viability. (Reprinted with permission from Circulation 1995;91:1016-21 and Circulation 1997;96: 2892-8.)

before heart transplantation. After explantation of the recipient's severely dysfunctional heart, these investigators found that the magnitude of sestamibi defect severity (on imaging of the sliced pathologic specimens of the explanted heart) was closely correlated to the percent of scarring within those same segments on pathologic examination (Figure 5). In addition, well counting of myocardial specimens for sestamibi activity also correlated well with the presence of viable myocardium by microscopy. These data suggest that even in the setting of severe ischemic cardiomyopathy (mean LVEF, 24% ± 6%) and dysfunctional territories supplied by severely stenosed coronary arteries, quantitative sestamibi activity correlated well with the magnitude of preserved regional tissue viability within dysfunctional territories. The data on sestamibi defect severity were, however, gathered from imaging specimens of the already explanted heart, leaving open the question of whether these elegant data could indeed be generalized to in vivo clinical planar or SPECT imaging.

However, two subsequent studies, by Dakik et al[79]

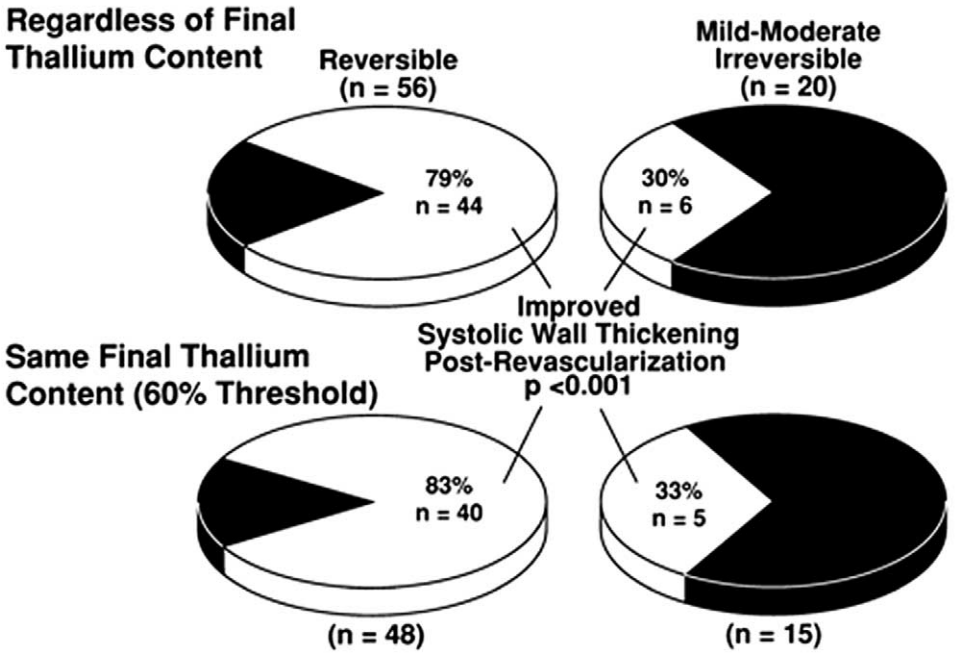


**Figure 6.** Pie chart diagram demonstrating postrevascularization functional outcome of asynergic regions in relation to prerevascularization Tl-201 patterns of reversible defects and mild-to-moderate irreversible defects via a stress-redistribution-reinjection protocol. In the *top panel*, the probability of functional recovery after revascularization was much higher if ischemia was demonstrated in contrast to a mild-to-moderate irreversible defect. In the *bottom panel*, among segments with a final Tl-201 content of at least 60% of peak (ie, even at a similar mass of viable myocardial tissue as reflected by the final thallium content), the presence of inducible ischemia was associated with an increased likelihood of functional recovery. (Adapted from Circulation 1998;98:501-8.)

and Maes et al,[80] demonstrated that similar data could indeed be derived from SPECT imaging in vivo. In both studies, 30 patients with severe left anterior descending artery stenosis and significant anterior wall dysfunction underwent resting sestamibi SPECT imaging and the data were analyzed by use of quantitative polar maps. There was a very good correlation between the quantitated sestamibi activity within the anterior wall from the preoperative SPECT images and the percent fibrosis seen in the biopsy specimens. These investigators concluded that the magnitude of sestamibi uptake is inversely related to the amount of interstitial fibrosis (and thus directly to the magnitude of preserved tissue viability) and that Tc-99m sestamibi activity reflects not only flow but also regional tissue viability. These data are concordant with animal studies suggesting that in low-flow territories, sestamibi activity is higher than one would expect based on the behavior of a pure flow tracer.[34]

The data from all of these studies emphasize the concept that regional isotope activity in dysfunctional myocardium should be viewed as a continuum of values related to the degree of tissue viability and intact myocardial cell membranes. Analytically, in published studies, quantitative cut points, such as 50% or 60% of peak uptake, are used to distinguish "viable" regions (above that cut point) from "nonviable" regions (below that cut point). It is important to note that such cut points are necessary for determining performance characteristics such as positive and negative predictive values. In light of the biopsy studies, however, whether functional recovery occurs after revascularization is related to the mass of preserved myocardial tissue, and threshold or cut points of regional isotope activity will merely reflect that sufficient mass of tissue. The concept that tracer activity is a continuous function that relates to the mass of preserved myocytes also extends to endpoints such as the probability of functional recovery—that is, the greater the amount of uptake in a dysfunctional region, the greater the probability of functional recovery after revascularization. This principle has been demonstrated for Tl-201 imaging,[82] Tc-99m sestamibi,[45,83] and PET evaluation of metabolic activity.[83,84]

Although quantitative analysis of defect severity after rest tracer injection appears to be superior to the simplified presence or absence of tracer uptake as a sign of viability, semiquantitative visual scoring across a

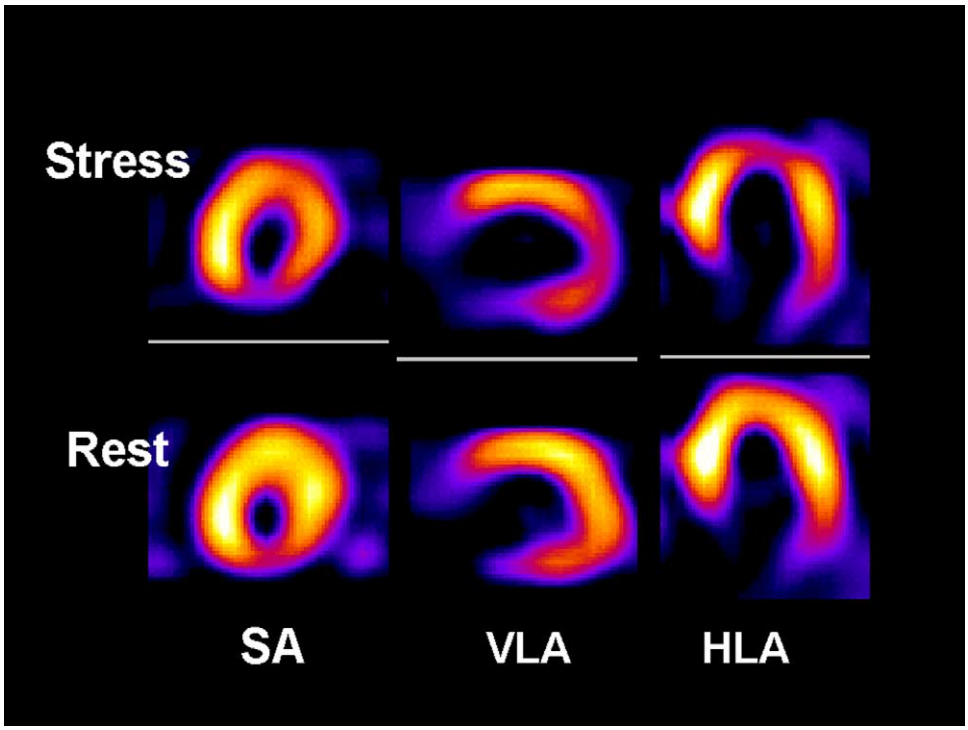


**Figure 7.** Selected short-axis (*SA*), vertical long-axis (*VLA*), and horizontal long-axis (*HLA*) images at stress and rest from a patient with severe ischemic cardiomyopathy, advanced heart failure symptoms, and minimal anginal symptoms, being considered for CABG. LVEF was 23% from the electrocardiographic-gated SPECT analysis in this 81-year-old patient with diabetes. Coronary angiography demonstrated severe 3-vessel CAD, with technically bypassable vessels. On rest imaging (*bottom row*), there is substantial tracer uptake in all areas except the inferobasal wall, suggesting retained viability. However, given the magnitude of risk associated with CABG (based on age, LV function, and presence of diabetes), as well as the severity of LV dysfunction and LV size, the clinicians requested more information. The stress images (*top row*) confirm that there is extensive inducible ischemia in the anterior, apical, lateral, and inferoapical walls. The extent of ischemia suggests substantial potential benefit from revascularization.

spectrum of uptake may provide generally similar data to fully quantitative analysis. Acampa et al[85] directly compared predictive values for functional recovery using semiquantitative visual analysis and quantitative analysis and found predictive results to be similar.

A relatively unexplored issue in the analysis of radionuclide viability studies is the relative importance of assessment of resting tracer uptake or resting metabolic activity compared with assessment of inducible ischemia via a stress-rest approach. Most studies evaluating the radionuclide techniques for assessing viability have focused on analysis of resting tracer uptake (as with Tl-201, sestamibi, or tetrofosmin) or evidence of preserved metabolic activity at rest (by FDG or carbon 11 acetate). In some patients, however, nontransmural infarction may have occurred with preservation of some degree of viability in the setting of a non–critically stenosed vessel. In this setting, evidence of uptake of the single photon tracers or metabolic activity by FDG may result in “intermediate” values, such that the role of revascularization is not clear. When this occurs, assessment of stress-induced ischemia appears to provide additional important information. In an important study, Kitsiou et al[86] demonstrated that the finding of stress-induced ischemia (a reversible perfusion defect) was a more powerful predictor of recovery of function than a “fixed” defect with a similar degree of resting tracer activity (Figure 6). Subsequently, Pasquet et al[87] showed that among patients with CAD and LV dysfunction, evidence of stress-induced ischemia by SPECT was an important prognostic factor in a multivariate analysis even when rest viability information was known. Moreover, stress-induced ischemia by radionuclide imaging correlated more powerfully with a favorable effect of revascularization on outcomes than viability data alone.

Thus, in settings in which evidence of resting tracer uptake or metabolic activity falls into an intermediate range (where the probability of recovery of function or improved outcome is itself intermediate), the addition of stress imaging to assess for the presence of stress-induced

ischemia may be helpful for informing the clinical decision making regarding revascularization (Figure 7).

## ARE THERE IMPORTANT DIFFERENCES BETWEEN NONINVASIVE TESTING MODALITIES?

The different noninvasive modalities available to assess myocardial viability interrogate distinct pathophysiologic myocyte and myocardial processes. The SPECT radionuclide tracers examine myocyte cell membrane integrity, and dobutamine echocardiography assesses regional ventricular contractile reserve. PET images myocardial blood flow and metabolism, whereas magnetic resonance hyperenhancement imaging identifies scarred myocardium. Despite these distinctions, there have not been major differences identified between the modalities that would suggest differences in patient management.

In a pooled analysis of studies reporting on rates of regional functional recovery, Bax et al[1] reported that the radionuclide agents are more sensitive and that dobutamine echocardiography was more specific, with PET having slightly higher overall accuracy for predicting functional recovery. Cardiac magnetic resonance imaging hyperenhancement data published thus far appear similar.[88]

Although some individual studies may suggest improved prediction of functional recovery by one test type over another, such data generally reflect differences in small numbers of regions or segments per patient. Whether these small differences result in different clinical decisions or different outcomes has been evaluated in two studies.

In the meta-analysis by Allman et al,[2] there was no difference in the reduction in mortality rate in patients with viable myocardium treated by revascularization, whether viability was identified by single photon radionuclide agents, PET, or dobutamine echocardiography. The most rigorous method for identifying any difference in modalities is a randomized trial. In a major achievement, Siebelink et al[89] reported on patients with CAD and LV dysfunction in whom information on the presence and extent of viability was needed to make a decision regarding revascularization. Patients were randomized to have that information provided by stress-rest SPECT sestamibi imaging or by PET imaging. There were no differences in the proportion of patients sent to revascularization, and more importantly, there was no difference in the long-term outcomes between the two randomized groups.

These data together suggest that all of the noninvasive testing modalities can provide important information on viability to inform management decisions, and major differences, sufficient to result in differential long-term outcomes, between the modalities in that regard are not apparent.

## CAVEATS REGARDING APPLICATION OF THE VIABILITY LITERATURE TO CLINICAL DECISION MAKING FOR REVASCULARIZATION

The published literature documenting the performance characteristics of radionuclide viability imaging techniques for predicting functional recovery or improvement in symptoms by its nature reflects patients who have been selected for revascularization, often on clinical grounds, who then undergo viability imaging. In other cases patient selection for revascularization is predicated on the results from viability imaging. Thus, in either scenario, there is potential for pretest or posttest referral bias to influence the performance characteristics being measured.

Perhaps the most important caveat regarding application of the viability literature to practice involves the potential extrapolation of the literature to patient subsets in practice that have more advanced degrees of LV dysfunction or more concomitant complicating conditions. Most of the studies in the literature involve patients with LVEF values in the 25% to 35% range (or higher in some studies). Particularly in centers where patients are being referred for evaluation for heart transplant, where high-risk revascularization might be considered as an option based on viability information, it would be expected that the range of LVEF values among such patients would be distinctly lower. Whether the imaging tests perform in a similar manner among patients with more dilated dysfunctional ventricles has not been carefully studied. Moreover, although one might expect that PET imaging would be superior to SPECT in patients with very dilated ventricles and generally thinner walls,[31] this has only been evaluated in small cohorts of patients.

Predicting recovery of regional and particularly global LV function in the setting of significant valvular heart disease may also be problematic. Studies of changes in regional or global LV function after revascularization usually exclude such patients from analysis, based on the complicating effect of mitral valve replacement or repair on the studied outcome, for instance. Thus, information on viability and its incorporation into benefit-risk decision-making equations should be assessed in the context of both the published literature and the individual situation at hand. Finally, as the published literature emanates from expert centers, it is important to factor in local expertise and experience in selecting the test modality for assessing viability.

## HOW OFTEN IS VIABLE MYOCARDIUM PRESENT IN PATIENTS WITH HEART FAILURE?

How often substantial viability is present among patients with heart failure and LV dysfunction has not been completely clarified by the literature. One of the barriers to such an evaluation has been the varying patient populations and selection biases among the reported studies. It would be expected that the prevalence of viability might be higher among populations already referred for revascularization on clinical grounds, in whom imaging is being performed for research purposes, whereas the prevalence might be lower among consecutive patients with advanced heart failure and severe LV dysfunction referred for transplant evaluation.

In the meta-analysis of viability outcome studies by Allman et al,[2] 42% of the 3088 patients reported in the analyzed publications had evidence of viability via noninvasive imaging (by single photon agents, PET, or dobutamine echocardiography). Auerbach et al[90] reported on PET imaging results in 283 randomly selected patients (from a sample of >700 patients referred clinically for PET imaging at University of California, Los Angeles) with varying degrees of heart failure who had ischemic LV dysfunction (mean LVEF, 26%) and found evidence of viable myocardium in 55% of patients. "Prognostically significant" viability, defined by the authors as evidence of viability in 1 to 4 segments in a 19-segment LV model, was seen in 28% of these patients, and "functionally significant" viability (≥5 segments, expected to result in an improvement in LVEF) was present in 27%.

In the CHRISTMAS trial,[47] of 489 outpatients with stable chronic heart failure due to ischemic LV dysfunction (mean LVEF, 29%), 79% had evidence of hibernation and/or inducible ischemia (as defined by the authors) representing viable myocardium as determined by Tc-99m sestamibi SPECT. Christian et al[91] reported on the prevalence of reversible LV dysfunction, as defined by postrevascularization change in LVEF, among patients with preoperative LVEF lower than 50%. One fifth of such patients had a postrevascularization EF increase greater than 8 EF units, and 33% had an EF increase greater than 4 EF units.

Thus it is difficult to definitively assess how often imaging-defined hibernation, stunning, or inducible ischemia is actually present in large heart failure populations, as the reported studies are limited in this regard by referral biases (including only patients referred for revascularization), or populations selected at random or selected for clinical trials. Nonetheless, these studies suggest that the prevalence of dysfunctional viable myocardium is potentially quite significant among patients with heart failure symptoms and ischemic LV dysfunction. An observational prevalence study of a large consecutively evaluated cohort of patients with heart failure would indeed be a "major achievement" and would be important to more fully understand how often patients with heart failure may benefit from assessment for revascularization.

## WHAT ARE THE "HOLES IN THE WALL" OF VIABILITY KNOWLEDGE?

As seen in the admittedly incomplete historical chronology in Table 1, there has been an enormous amount of literature exploring the use of radionuclide techniques for assessment of myocardial viability over the last 20 to 25 years. There are, however, issues that remain underexplored. Such a list would include the following:

- What is the true prevalence of viability or ischemia in a large, unselected heart failure population?
- How well do all of the techniques extrapolate to patients with more severe LV dysfunction, given more contemporary PET techniques (such as new crystals) and SPECT attenuation correction?
- How often does the analysis of stress-induced ischemia add incremental information to the analysis of resting tracer uptake and resting metabolic activity, particularly when the latter are in the "intermediate" range?
- Can more comprehensive outcome modeling be done for patients with ischemic cardiomyopathy, analogous to contemporary data for patients with CAD incorporating clinical, demographic, and stress test factors with imaging variables to more precisely model natural history outcomes?
- How is the viability information to be used in the setting of more complex decision making for revascularization, with concomitant valvular disease, for instance?
- Can we improve identification of remodeled myocardium that is viable by SPECT and PET but not capable of improving function by incorporating new imaging probes, such as angiotensin-converting enzyme imaging,[92] that may identify physiologic signals of irreversible remodeling?

## CONCLUSIONS

There indeed have been many major achievements in the study of radionuclide tracers for assessing viability that have in parallel shed light on the interesting and complex pathophysiologic processes of hibernation and stunning, while at the same time advancing the use of imaging to inform patient management decisions and improve outcomes. Substantial progress has been made

in understanding the pathophysiology of regional and global LV dysfunction and the states of hibernation and stunning. The clinical literature on the use of noninvasive imaging to assess myocardial viability has evolved from predicting improvement in regional LV function to predicting patient-related outcomes, including heart failure symptom improvement, survival, and differential outcomes with revascularization. Patients with heart failure, LV dysfunction, and a significant extent of ischemic viable myocardium are a very high-risk subset. A substantial body of data demonstrates that risk to be reduced by revascularization. Among patients with predominantly nonviable myocardium, there appears no clear advantage to revascularization. Ongoing randomized trials may add to and refine our understanding of these issues. Until that time, however, there is substantial evidence to suggest that noninvasive imaging of myocardial ischemia and viability can provide important prognostic information in patients with heart failure and LV dysfunction and provide a signal of the potential benefit of revascularization.

Perhaps of most interest is that the trajectory of major achievements outlined in Table 1 and by the literature in this field has been driven by the synergy that exists between the modality—radionuclide tracers that by their nature reflect physiologic processes at the cellular level—and the underlying pathophysiologic states being investigated. Somewhat in contrast to perfusion imaging in CAD—where the perfusion tracer signal is an indirect reflection of the vascular disease process under study—imaging myocardial viability is a more direct "marriage" between the physical and kinetic properties of the radionuclide tracers and the pathophysiologic perfusion, cellular, and metabolic processes underlying chronic ischemic myocardial dysfunction.

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