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Assessment of Myocardial Viability

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The prevalence of left ventricular (LV) dysfunction and resultant congestive heart failure is increasing. Patients with this condition are at high risk for cardiac death and usually have significant limitations in their lifestyles. Although there have been advances in medical therapy resulting in improved survival and well being, the best and most definitive therapy, when appropriate, is revascularization. In the setting of coronary artery disease, accounting for approximately two thirds of cases of congestive heart failure, LV dysfunction often is not the result of irreversible scar but rather caused by impairment in function and energy use of still viable-myocytes, with the opportunity for improved function if coronary blood flow is restored. Patients with LV dysfunction who have viable myocardium are the patients at highest risk because of the potential for ischemia but at the same time benefit most from revascularization. It is important to identify viable myocardium in these patients, and radionuclide myocardial scintigraphy is an excellent tool for this. Single-photon emission computed tomography perfusion scintigraphy, whether using thallium-201, Tc-99m sestamibi, or Tc-99m tetrofosmin, in stress and/or rest protocols, has consistently been shown to be an effective modality for identifying myocardial viability and guiding appropriate management. Metabolic imaging with positron emission tomography radiotracers frequently adds additional information and is a powerful tool for predicting which patients will have an improved outcome from revascularization, including some patients referred instead for cardiac transplantation. Other noninvasive modalities, such as stress echocardiography, also facilitate the assessment of myocardial viability, but there are advantages and disadvantages compared with the nuclear techniques. Nuclear imaging appears to require fewer viable cells for detection, resulting in a higher sensitivity but a lower specificity than stress echocardiography for predicting post-revascularization improvement of ventricular function. Nevertheless, it appears that LV functional improvement may not always be necessary for clinical improvement. Future directions include use of magnetic resonance imaging, as well as larger, multicenter trials of radionuclide techniques. The increasing population of patients with LV dysfunction, and the increased benefit afforded by newer therapies, will make assessment of myocardial viability even more essential for proper patient management.

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There is an increasing number of patients with disabling heart conditions related to left ventricular dysfunction. In the developed world, two thirds of cases of left ventricular dysfunction are the result of coronary artery disease,[1] and the improved ability to treat and decrease the initial mortality from acute coronary syndromes has contributed to the increased prevalence of this condition. Not only are these patients at high risk for subsequent cardiac death, severe morbidities, and recurrent hospitalizations for congestive heart failure, they also frequently have severe limitations in their lifestyles and well being. The estimated annual treatment cost in the United States is more than 10 billion dollars per year.[2]

Although there have been significant advances in medical therapy for left ventricular dysfunction and resulting symptoms of heart failure, including angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, nitrates, hydralazine, β-blockers, aldosterone blockade, natriuretic peptides and, most recently, biventricular pacing,[3-9] the prognosis from heart failure remains extremely poor, with an annual mortality ranging from 10% to 50% per year. The total number of deaths has risen 148% between 1979 and 2000.[10]

It has been known for some time that left ventricular dysfunction is not always the result of irreversible myocardial

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necrosis and scarring. After an initial ischemic injury, various processes can occur that lead to left ventricular dysfunction, including left ventricular remodeling, impairment of energetics, myocyte dysfunction, and cell death via necrosis and/or apoptosis.[11] Other than cell death, these processes are, to an extent, reversible, and left ventricular function often can be improved, resulting in better patient outcome. Although medical therapy can be extremely beneficial, revascularization in the appropriate patient often is the best therapy.

Left ventricular dysfunction, in some cases, is the result of "stunned myocardium," which is defined as myocardium that has become dysfunctional because of a transient coronary occlusion, has been salvaged by coronary reperfusion, yet exhibits prolonged but transient postischemic dysfunction, lasting hours to weeks.[12] Thus, in myocardial stunning, blood flow has been restored but contraction has not returned to baseline, ie, there is a flow-contraction mismatch.

Stunned myocardium, global or regional, often occurs in the setting of acute myocardial infarction that has been followed by spontaneous or induced reperfusion. Stunning also can occur after cardioplegic arrest during open heart surgery, as well as after exercise-induced ischemia. Episodes that lead to stunning can be single or multiple, brief or prolonged, but by definition are not severe enough to result in myocardial necrosis.

Topol and coworkers evaluated myocardial functional recovery in 20 consecutive patients with acute myocardial infarction who received thrombolytic therapy and, in some cases, coronary angioplasty.[13] Although there was no immediate or 24-hour improvement in wall motion after revascularization of infarcted areas, after 10 days, 85% of reperfused infarct zone segments demonstrated improved wall motion compared with 30% of nonreperfused segments ($P = 0.01$).

The exact pathogenesis of myocardial stunning is unclear and may be caused by a variety of factors, including the presence of oxygen free radicals and/or calcium overload.[14] Structural changes in collagen, including the collagen present in myocyte to myocyte struts, also have been seen in stunned myocardium.[11]

Left ventricular dysfunction, in other cases, is the result of "hibernating myocardium," which is defined as a state of persistently impaired left ventricular function at rest as the result of reduced coronary blood flow. It is hypothesized that the deprived myocytes are preferentially using the energy that they are able to generate to preserve cellular integrity at the expense of contractile function. Myocyte function can be partially or completely restored to normal if the myocardial oxygen supply/demand relationship is favorably altered, either by improving blood flow and/or by reducing demand.[15] By this definition, hibernating myocardium is a flow-contraction match. One of the first reported cases was in 1982, when Rahimtoola[16] described a patient with an occluded left anterior descending coronary artery, an akinetic anteroapical wall, and a global ejection fraction of 37%. After bypass surgery, function of the anteroapical region returned to normal, and the ejection fraction increased to 76%.

However, recent data suggest that resting blood flow in hibernating myocardial segments is not decreased to the extent that would account for the degree of cardiac dysfunction, but rather it is flow reserve that is impaired.[17,18] Some investigators contend that hibernating myocardium is actually a manifestation of repetitive myocardial stunning.

Observations suggest that hibernation may be a temporal progression of chronic, repetitive stunning with an initial state of normal or near-normal flow but reduced flow reserve, leading eventually to decreased resting flow.[19] Over time, there also appears to be structural changes in the myocardium, including alteration of structural proteins, metabolism to a more fetal form, disorganization of the cytoskeleton, loss of myofilaments, occurrence of large areas filled with glycogen, and sarcomeric instability. There also may be progressive apoptosis.[20]

Regardless of the mechanism, it is important to identify hibernating myocardium because ventricular function will generally improve after revascularization or other therapies. In the recently published Christmas trial (Carvedilol Hibernation Reversible Ischemia Trial), 59% of patients with class I-III heart failure (most class II) were found to have hibernating myocardium, on average, affecting 30% of the myocardium. Patients without hibernating myocardium had no improvement in ejection fraction after carvedilol treatment, whereas patients with 5 or more segments affected had an absolute 7% increase in ejection fraction.[21,22]

If indicated, it appears that revascularization should be undertaken as soon as possible to prevent progressive morphologic changes that can become irreversible.[23] Beanlands and coworkers[24] showed improved left ventricular function and lower mortality in patients who underwent revascularization within 35 days of diagnosis compared with patients who were revascularized later.

Clinical Importance of Identifying Viable Myocardium

Patients with depressed left ventricular systolic function have a worsened prognosis. In the CASS (Coronary Artery Surgery Study) registry, for the cohort of patients treated with medical therapy, those with a left ventricular ejection fraction of 50% or greater had a 10-year survival of approximately 90%, compared with a survival of 60% for those with an ejection fraction of 35% to 49%, and a survival of 30% for those with an ejection fraction less than 35% ($P < 0.001$).[25]

The principal goal of myocardial viability assessment is to identify patients whose symptoms and natural history may improve after revascularization. Recent publications have consistently shown that among patients with abnormal left ventricular systolic function, those with hibernating, ie, viable myocardium, have the poorest prognosis if they are not referred for a revascularization procedure. Comparable patients whose left ventricular function is predominantly the result of myocardial scarring appear not to be helped with revascularization and with medical therapy alone have a better prognosis than patients with viable myocardium.

For example, Gioia and coworkers[26] performed rest-redistribution thallium imaging in 81 medically treated patients

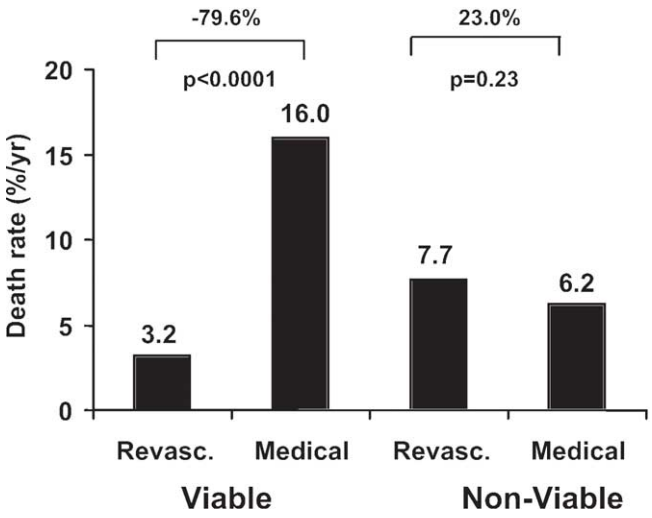

Figure 1 Death rates with and without myocardial viability treated by revascularization and medical therapy. Patients with viability had a significantly decreased death rate with revascularization, whereas patients without viability did not benefit from revascularization. Modified and reprinted with permission from Allman and coworkers.[28]

with coronary artery disease and left ventricular dysfunction (left ventricular ejection fraction <40%). Patients with evidence of myocardial viability had a death rate (over 31 ± 24 months) of 58%, compared with 26% ($P = 0.03$) for patients without significant viability.

DiCarli and coworkers[27] performed positron emission tomographic (PET) imaging on 93 consecutive patients with coronary artery disease and a mean left ventricular ejection fraction of 25%. Medically treated patients who had PET evidence of myocardial viability had a markedly lower annual survival of 50%, compared with 92% for patients without evidence of viability ($P = 0.007$). Patients with evidence of myocardial viability who underwent revascularization had a higher survival rate than those treated medically (88% versus 50%, $P = 0.03$).

In a meta-analysis of 3088 patients with decreased ejection fraction who underwent a viability study using a variety of methods, Allman and coworkers[28] reported that the yearly death rate for patients with viability who were treated medically was 16%, compared with 3.2% for patients who underwent revascularization ($P < 0.0001$), illustrated in Figure 1. Revascularization improved survival for patients with viable myocardium by 79.6%. This pattern held regardless of the technique that was used to assess myocardial viability. Conversely, for patients without viable myocardium, there was a trend toward increased mortality in patients who underwent revascularization, 7.7% versus 6.2% ($P = 0.23$).

Haas and coworkers[29] studied 76 patients with advanced coronary disease and left ventricular function who were being considered for coronary bypass surgery. Compared with patients who were first evaluated for viability with PET imaging, patients sent to surgery who did not have a viability assessment had a significantly worsened postoperative course, including a lower 12-month survival rate, 79% versus 97% ($P = 0.01$). This study concluded that the forgoing of a viability study resulted in too many high-risk patients without viability being sent for bypass surgery, resulting in a worsened prognosis.

Use of Perfusion Imaging to Assess Myocardial Viability

Thallium-201 Imaging

There are numerous imaging procedures available to assess myocardial viability. Among the most commonly used is imaging with thallium-201, a radionuclide tracer that assesses not only myocardial perfusion but also myocyte cell membrane integrity. In a meta-analysis of 33 studies with 858 patients, Bax and coworkers[30] found that thallium imaging using rest and/or stress protocols had a sensitivity of 86% and a specificity of 59% in predicting improvement of regional function post-revascularization. Specificity varied depending on the criteria used to classify viability, better if a higher percentage of thallium uptake was used as the threshold. In addition, as will be discussed in more detail later, a patient may have sufficient myocardial viability in a region to benefit prognostically with revascularization without there necessarily being an improvement in ventricular systolic function.

A review of the history of myocardial perfusion imaging is helpful in understanding current thallium protocols used to assess myocardial viability. At its initial clinical introduction in 1975 for the detection of coronary artery disease and stress induced ischemia, patients had two separate studies performed: one study in which thallium-201 was injected intravenously during exercise stress, and a second study in which thallium-201 was administered at rest.[31] Defects present on the stress but not on the rest images were considered to represent myocardial ischemia, while defects on both the stress and rest images were considered to represent scar from myocardial infarction. In 1976, Pohost and coworkers[32] observed that in patients injected with thallium-201 during exercise, on serial images obtained at 4- to 6-h intervals, certain zones of decreased myocardial uptake present on initial images improved or resolved totally, a phenomenon termed "redistribution." Redistribution was thought to represent zones of ischemic and, therefore, viable myocardium, whereas fixed, nonredistributing defects were interpreted as nonviable, fibrotic scar.

However, with increased experience using stress-delayed thallium-201 imaging, it became clear that the situation was more complex than first thought. In 1983, Gutman and coworkers reported that in the presence of severe stenoses, defects that appeared fixed at 3 to 6 h often showed redistribution at 24 h.[33] Kiat and coworkers reported that late (18- to 72-h) imaging often showed thallium redistribution in defects that were fixed at 4 h and that the later images were better predictors of myocardial viability, as demonstrated by stress image imaging after coronary angioplasty.[34]

Liu and coworkers followed 52 patients with single vessel disease who underwent coronary angioplasty.[35] Although most who had redistribution on preangioplasty stress-delayed thallium imaging were subsequently shown to have

viability (ie, image normalization postprocedure), 75% of patients with fixed defects also had myocardial viability.

Gibson and coworkers performed thallium-201 scintigraphy on 47 consecutive patients before and after coronary bypass surgery.[36] Of 42 persistent (fixed) defects observed before surgery, which were thought to represent myocardial scar, 19 (45%) demonstrated normal perfusion postoperatively. Interestingly, classification of persistent defects according to the quantitative reduction in thallium activity helped predict which segments would improve post-revascularization. Although 57% of persistent defects with a 25% to 50% reduction in relative thallium activity demonstrated normal thallium uptake postoperatively, only 21% of fixed defects with greater than 50% reduction in activity showed improved perfusion after surgery ($P = 0.02$).

Thus, evidence had accumulated that fixed defects on stress-delayed thallium-201 imaging often contain significant viable myocardium. In 1986, Tillisch and coworkers reported that myocardial imaging using the metabolic positron emitting tracer, ^{18}F-2-deoxyglucose (^{18}FDG), was a powerful method of assessing viability.[37] For 17 patients with left ventricular dysfunction who underwent bypass surgery, assessment of ^{18}FDG uptake with PET had a positive predictive value of 85% and a negative predictive value of 92% in predicting postoperative improvement in ventricular function. Subsequently, Brunken and coworkers showed that 58% of fixed thallium-201 defects demonstrated ^{18}FDG uptake, consistent with viability.[38]

Thus, it was clear that a significant proportion of fixed defects on stress-delayed thallium-201 imaging contain viable tissue and, therefore, stress/delayed thallium imaging alone was insufficient to fully assess myocardial viability in regions with a 4-h fixed perfusion defect. Because the quality of 24-h delayed images often is poor as a result of low counts, a new method of viability assessment was sought. In 1990, Dilsizian and coworkers reported on the technique of thallium-201 reinjection.[39] In patients with fixed defects or redistribution images, immediately following acquisition of the delayed images, an additional dose of thallium-201 was injected at rest. It was observed that 49% of irreversible defects demonstrated normal thallium uptake after the second injection of thallium. Of myocardial segments with defects on redistribution images that were identified as viable by reinjection studies, 87% had normal thallium uptake and improved regional wall motion after angioplasty.

Subsequently, Bonow and coworkers reported that thallium reinjection imaging has an 88% concordance with ^{18}FDG PET imaging.[40] This group concluded that with stress/delayed thallium imaging, most irreversible defects with only mild-to-moderate reduction in thallium activity represent viable myocardium as confirmed by FDG uptake. For severe, irreversible thallium defects, with few exceptions, thallium reinjection identified as viable or nonviable the same regions as ^{18}FDG.

Rest-Delayed Thallium Imaging to Assess Myocardial Viability

Another commonly used technique to assess myocardial viability is rest-delayed thallium imaging. Although initially it was thought that a defect on rest thallium imaging could only represent scar, Berger and colleagues observed that in the presence of a severe coronary stenosis without infarction, a defect present on early rest thallium imaging would often resolve on delayed images.[41] Of 14 patients with unstable angina and 15 patients with stable angina, 90% had a defect on the initial rest images, 76% of which showed redistribution on the delayed images. In the subgroup that underwent subsequent bypass surgery, 77% of segments with redistributing defects reverted toward normal initial uptake postoperatively, but 72% (13/18) of segments with fixed defects also improved.

Iskandrian and coworkers performed rest and redistribution thallium imaging on 26 patients with coronary disease and left ventricular dysfunction before bypass surgery.[42] Twelve of 16 patients with normal or transient thallium defects (75%) showed improved ejection fraction after surgery compared with only 2 (20%) of 10 patients with fixed defects.

The usefulness of rest-redistribution thallium imaging in identifying myocardial viability was further supported by Ragosta and coworkers, who studied 21 patients with left ventricular dysfunction (mean ejection fraction = 27%) who subsequently underwent bypass surgery.[43] Myocardial segment viability was assessed both by quantitative analysis of defect severity and the presence of redistribution. 62% of severely asynergic segments with normal viability and 54% with mildly reduced viability improved function after surgery, compared with only 23% that had severely reduced viability ($P = 0.002$). There was viability in 7 or more of the 15 segments analyzed, mean left ventricular ejection fraction increased significantly after bypass surgery.

The importance of assessing viability for predicting an improved clinical outcome was reported by Pagley and coworkers.[44] Seventy patients with multivessel coronary disease and a left ventricular ejection fraction less than 40% underwent rest-delayed thallium imaging before bypass surgery. A viability index based on image findings was assessed for each patient. Figure 2 shows the relationship of event free survival to the viability index. Those patients who underwent bypass surgery with at least about two thirds viable myocardium (viability "index" >0.67) had a significantly enhanced 3-year event-free survival compared with patients who had less viability. In these patients event-free survival was independent of other variables, including left ventricular ejection fraction. Thus, rest-delayed thallium imaging can help identify patients who are likely to benefit from bypass surgery.

There are conflicting data in the literature regarding whether defect reversibility or thallium uptake of 50% or greater of peak counts is the best indicator of viability. In a study of 35 patients with left ventricular dysfunction, Sciagrà and coworkers found that tracer activity in a delayed thallium image was more important than defect reversibility for differ-

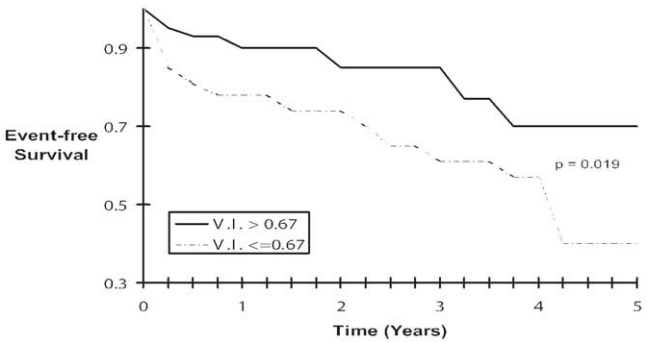

Figure 2 Survival free from cardiac events (cardiovascular death or heart transplantation) in relation to viability index. Modified and reprinted with permission from Pagley and coworkers.[44]

entiating viable from nonviable myocardium.[45] In contrast, Kitsiou and coworkers showed that reversible defects more accurately predict functional recovery after revascularization than fixed defects with similar resting tracer activity.[46] As in Figure 3, although 63% to 96% of reversible defects showed improved wall thickening post-revascularization, only 30% of mild-moderate severity fixed defects showed functional improvement.

For revascularization to improve ventricular function, the ventricle must be ischemic from a stenosis in the artery perfusing the dysfunctional territory(s), and this situation is best depicted by defect reversibility. For example, a myocardial region that is dysfunctional from myocardial damage after a non-ST segment elevation infarction and is perfused by a nonstenotic vessel may show sufficient tracer uptake on resting thallium imaging to indicate viability, but will not show improved function after revascularization. In another setting, ventricular contraction may be depressed because of cellular dysfunction related to a cardiomyopathy, in which case one might see satisfactory myocardial thallium uptake, but revascularization would not be expected to improve function. The situation becomes particularly complex in patients who may have both coronary artery disease and nonischemic cardiomyopathy, such as diabetics. In these instances a rest/delayed thallium imaging study may be insufficient, and additional imaging with stress may be needed to identify the presence of myocardial ischemia to decide on revascularization.[47] In fact, there is little lost by performing stress/rest-redistribution studies in all patients sent for assessment of myocardial viability as this will not only provide information regarding viability but also provide an assessment of exercise or pharmacologic induced ischemia.

Technetium-99m Sestamibi as a Viability Agent

In 1990, the Food and Drug Administration approved the use of Tc-99m sestamibi for myocardial perfusion imaging. Compared with thallium-201, technetium-99m sestamibi emits higher energy photons, and the shorter half life of Tc-99m allows the administration of a higher dosage. As a result of higher counts as well as better tissue penetration, attributable to the 142 keV emission energy, imaging with Tc-99m sestamibi results in sharper images. Several studies have shown a higher specificity with Tc-99m sestamibi imaging compared with thallium-201.[48,49] Of the perfusion imaging studies performed in the United States, approximately 60% use Tc-99m sestamibi.[50]

Unlike thallium-201, however, technetium-99m sestamibi does not exhibit significant myocardial redistribution. Thus,

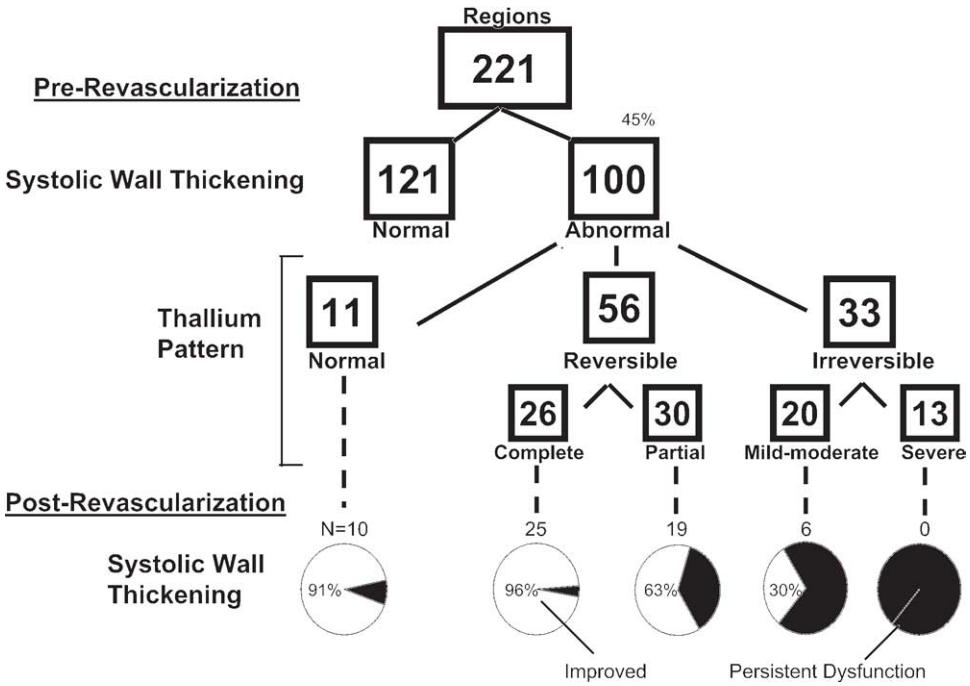

Figure 3 Post-revascularization systolic function in relation to prerevascularization function and thallium image results. Modified and reprinted with permission from Kitsiou and coworkers.[46]

imaging with Tc-99m sestamibi requires separate stress and rest injections, either on the same (1 day protocols) or different (2 day protocols) days. Thus, from the advent of sestamibi use, there was concern that stress imaging with this radiopharmaceutical may not provide viability information comparable to that obtained with thallium-201.

In 1992, Cuocolo and coworkers compared the results of thallium-201 stress/delayed/reinjection imaging with Tc-99m sestamibi stress/rest imaging in 20 patients with coronary artery disease and left ventricular dysfunction.[51] Of 122 regions with irreversible defects on stress-delayed thallium imaging, 18% showed viability with stress/rest sestamibi imaging. However, 47% showed evidence of viability with reinjection thallium imaging leading the authors to conclude that thallium-201 imaging, when combined with rest reinjection, is superior to Tc-99m sestamibi imaging for identifying myocardial viability.

In the same year, Marzullo and coworkers performed rest Tc-99m sestamibi imaging on 14 patients with previous myocardial infarction referred for revascularization.[52] Tc-99m sestamibi imaging had high diagnostic accuracy for predicting improvement in wall motion after revascularization: sensitivity, specificity, and positive predictive accuracy were 83%, 71%, and 79%, respectively. However, sestamibi images overestimated perfusion defects in 25% of territories supplied by stenotic coronary arteries that had normal wall motion at rest. The authors concluded that sestamibi "appears to be primarily a perfusion agent that can provide limited information regarding viability."

Marcassa and coworkers compared sestamibi uptake with rest-redistribution thallium-201 uptake in 48 patients with ischemic heart disease and regional wall motion abnormalities.[53] Although uptake of the 2 tracers was comparable in normal segments and in segments with fixed thallium defects, in segments with reversible thallium defects sestamibi uptake was significantly lower than redistribution thallium uptake, again suggesting that sestamibi may be less sensitive for detecting viable myocardium.

Nevertheless, as uptake and retention of sestamibi is dependent on cell membrane integrity and mitochondrial function, many investigators believe that sestamibi is an effective viability tracer provided that protocols and methods of interpretation are adjusted to take into account the unique properties of sestamibi. For example, Udelson and coworkers found that if sestamibi images are interpreted quantitatively, they can predict ventricular function improvement after revascularization.[54] Sestamibi activity one hour after rest injection was found to parallel redistribution thallium-201 activity. Importantly, as illustrated in Figure 4 for patients who underwent revascularization procedures, thallium-201 and Tc-99m sestamibi regional activities were similar in segments with reversible as well as irreversible ventricular dysfunction. The severity of the defect was the important variable in predicting improvement in revascularization rather than which tracer was used.

Similar findings were reported by Kauffman and coworkers[55] Patients with a mean left ventricular ejection fraction of 33% underwent early and 3 hour delayed rest thallium-201 imaging, and rest Tc-99m sestamibi imaging. Uptake of Tc-99m sestamibi and thallium-201 were comparable in myocardial zones of asynergy as identified by rest 2-dimensional echocardiography. Defect magnitude, by quantitation, was similar for the 2 tracers for regions with both mild and severe reduction in tracer uptake.

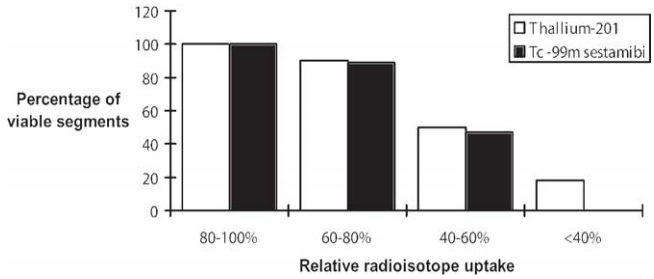

Figure 4 Percentages of segments that were viable in relation to relative uptake of thallium-201 or Tc-99m sestamibi. The likelihood of viability was related to the magnitude of regional activity rather than the radiotracer used. Modified and reprinted with permission from Udelson and coworkers. [54]

Medrano and coworkers administered intravenous Tc-99m sestamibi to 15 consecutive patients with ischemic cardiomyopathy 1 to 6 h before transplantation.[56] Excised hearts were imaged and analyzed histologically, and a good correlation was found between tissue Tc-99m sestamibi activity and histologic evidence of myocardial viability. The authors concluded that sestamibi can accurately quantify myocardial scarring and that it is a good indicator of myocardial viability determined with microscopy.

Maes and coworkers prospectively studied thirty patients with coronary disease and wall motion abnormalities who were referred for bypass surgery.[57] Each patient underwent rest sestamibi imaging and PET imaging with $^{13}NH_3$ (a flow agent) and ^{18}FDG (a metabolic agent), as well as transmural biopsy. Significantly higher sestamibi uptake was found in patients with evidence of viability by PET than in those without. There was a linear relation between sestamibi uptake and fibrosis in the biopsy specimen. Sestamibi uptake was able to predict ventricular functional improvement after bypass, with positive and negative predictive values of 82% and 78%, respectively.

Finally, Siebelink and coworkers compared Tc-99m sestamibi single-photon emission computed tomography (SPECT) with $^{13}NH_3$/^{18}FDG PET imaging-guided patient management.[58] For 103 patients with left ventricular dysfunction who were being considered for revascularization, management decisions for those randomized to SPECT imaging were comparable to those randomized to PET, and event free survival was the same. This study concluded that in a clinical setting, sestamibi imaging was comparable to what many consider the viability "gold" standard, FDG-PET, in deciding whom to send for revascularization. However, this study is limited by there being only one third of patients with an ejection fraction less than 30%, and inclusion of relatively stable patients who had their image studies over the course of 30 to 40 days. Thus, whether these results apply to patients who are sicker and more unstable is unclear.[59]

In an analysis of 20 published studies including 488 pa-

tients studied with technetium-99m sestamibi, (7 with nitrate enhancement, discussed below), Bax and coworkers reported a sensitivity of 81%, a specificity of 66%, a positive predictive value of 71%, and a negative predictive value of 77% in predicting post-revascularization improvement of regional ventricular function.[30] For most of these studies, segments were classified as viable if activity exceeded a certain threshold, frequently 50-60%.

Sometimes combining stress sestamibi with rest/delayed thallium imaging, in a dual-isotope protocol, can provide a comprehensive assessment of the entire clinical scenario. The extent of reversible defects on the stress sestamibi images can assess the amount of myocardial ischemia, while the rest/delayed thallium images can provide additional information on myocardial viability. Sharir and coworkers performed rest thallium/stress sestamibi dual isotope studies on 458 patients and noted that 37% of segments with defects on rest thallium imaging had redistribution on 18- to 24-h thallium images.[60] The presence of late thallium redistribution above an investigationally determined quantitative threshold predicted a significantly increased cardiac mortality with medical therapy alone, suggesting that such patients may benefit from revascularization.

Methods to Enhance the Use of Tc-99m Sestamibi as a Viability Agent

Early during the introduction of sestamibi for clinical use, Dilsizian and coworkers noted that tracer uptake was poor in territories supplied by an occluded artery with poor collateral flow.[61] Although thallium can redistribute and slowly fill-in a defect in such a region, it may be difficult to detect potential viability using sestamibi. Because nitrates improve collateral blood flow to hypoperfused areas, demonstrated in several studies using thallium-201 imaging,[62-64] Bisi and coworkers proposed that nitrates might have a role in improving the ability of sestamibi imaging to predict myocardial viability.[65] This group used quantitative rest sestamibi imaging during baseline conditions and during intravenous nitrate administration to study 19 patients with previous myocardial infarction and left ventricular dysfunction scheduled for revascularization. Patients whose ventricular function improved after revascularization showed a 37% decrease in defect size with nitrate infusion, compared with no change or a slight increase in patients whose ventricular function did not improve ($P < 0.0005$). In a subsequent study by this group, Sciagrà and coworkers observed that nitrate enhanced sestamibi imaging was at least as good as rest/redistribution thallium in detecting viable myocardium and predicting post-revascularization recovery.[45] In the meta-analysis by Bax and coworkers, defect reversibility after nitrate-enhanced sestamibi imaging yielded a sensitivity of 86% and a specificity of 83% in predicting myocardial viability.[30]

Another potential method to enhance the ability of sestamibi imaging to detect viability is concomitant assessment of ventricular function using ECG-gated SPECT imaging. Levine and coworkers reported that combining sestamibi defect scoring with assessment of regional wall motion improved the accuracy of predicting functional improvement post-revascularization.[66] In a novel approach, Iskandrian and coworkers described acquiring ECG-gated SPECT images at baseline and during low dose dobutamine infusion, looking not only at tracer uptake, but also at changes in wall motion to assess contractile reserve.[67] However, this is a difficult protocol requiring dobutamine infusion for an extended period during SPECT acquisition, and is not in common use at this time. Attempts also have been made to examine potential enhancement of ECG-gated SPECT wall motion after nitroglycerin, but changes in function were found to be too subtle to be assessed effectively.[68] A study by Leoncini using combined nitrate and low dose dobutamine enhancement of ECG-gated SPECT images reported reliable wall motion evaluation and comparable results to low dose dobutamine echocardiography; however, no confirmation of myocardial viability was provided in this study.[69]

Tc-99m Tetrofosmin

Given its similarity to Tc-99m sestamibi, one would not expect important differences in using Tc-99m tetrofosmin to evaluate myocardial viability, although data are limited. Matsunari and coworkers reported that myocardial tetrofosmin uptake correlated well with thallium uptake on rest-delayed images.[70] Gunning and coworkers found that tetrofosmin imaging was similar to thallium and dobutamine magnetic resonance imaging (MRI) in predicting post-revascularization functional recovery.[71] He and coworkers reported that rest uptake of tetrofosmin in dysfunctional myocardial segments, after administration of sublingual isosorbide dinitrate, correlated with metabolic activity as assessed by ^{18}FDG.[72] Stollfuss saw that combining tetrofosmin perfusion and ECG-gated SPECT parameters helped identify (sensitivity = 87%) segments that showed improved wall motion post-revascularization as assessed by MRI.[73] Although the specificity of tetrofosmin uptake was limited (42%), the use of gated SPECT improved the positive predictive value.

Positron Emission Tomography (PET)

PET has several theoretical advantages over SPECT techniques for the detection of myocardial viability. These include the intrinsically quantitative aspect of PET since attenuation correction can be performed accurately; the higher energy of positron emitters (511 keV) providing better tissue penetration; and the ability to incorporate positron-emitting isotopes into substances of physiological interest. In addition to providing both qualitative and quantitative estimates of myocardial perfusion and metabolism, there are several tracers utilized with PET that can provide information regarding tissue viability.[74]

PET has been considered "gold-standard" for assessment of myocardial viability using metabolic tracers. With the use of metabolic tracers, several patterns of metabolism can be delineated in combination with knowledge of both perfusion

Table 1 Outline of the PET Classification of Myocardial Regions Based on Their Function, Level of Perfusion, and Metabolic Activity

Tissue Classification	Function	Perfusion	Metabolism/flow
Normal	Normal	Normal	Normal
Stunned	Diminished	Normal	Variable
Hibernating	Diminished	Diminished	Preserved or increased
Infarcted	Diminished	Diminished	Diminished

and assessment of regional function to classify myocardium (Table 1). Normal tissue shows normal function, perfusion and metabolism. Stunned myocardium shows diminished function but relatively normal perfusion and a variable metabolic pattern (glucose uptake as assessed with FDG can be normal, increased, or decreased). Hibernating myocardium can be identified by diminished perfusion and function with upregulation of glucose metabolism relative to flow and relatively preserved oxygen utilization. Infarcted myocardium can be identified by reduced function, perfusion and metabolism.

To define viability with PET, assessment of perfusion must also be made. For assessment of myocardial perfusion, tracers include oxygen-15 (^{15}O) water, nitrogen-13 (^{13}N) ammonia, and rubidium-82 (^{82}Rb) chloride. Both ^{15}O water and ^{82}Rb chloride may also provide information on both blood flow and viability.

Perfusion Tracers Used for Viability Assessments

^{15}O Water

^{15}O water is a freely perfusable tracer. Its uptake and release from myocardium is nearly solely dependent on myocardial perfusion.[75,76] Some studies have demonstrated the ability of ^{15}O water to assess myocardial viability based on specific model-related functions, such as the fractional volume of a given region of interest occupied by myocardium that is capable of rapidly exchanging water or perhaps the heterogeneity of transmural flow as assessed by this tracer.[77,78] Yamamoto and coworkers and De Silva and coworkers applied this approach to patients with ischemic heart disease and demonstrated a lower perfusion index in patients with heart disease compared with volunteers and demonstrated a certain level of this index below which recovery of function did not occur after revascularization.[79,80] However, the limited diagnostic utility of ^{15}O water and the requirement for an on-site cyclotron as well as the additional computer modeling required have limited the use of this approach.

Rubidium-82 (^{82}Rb)

^{82}Rb is attractive because it is generator produced and commercially available. Because rubidium is a potassium analog, the retention of this tracer may also be an index of myocardial viability.[81] Gould and coworkers demonstrated that decreased retention of ^{82}Rb correlated with increased uptake of FDG, suggesting that the kinetics of this tracer may be used to delineate cellular viability.[82] However, this approach has not been widely used or validated.

Metabolic Assessments With PET

Under aerobic conditions, the heart uses predominantly fatty acids, but after carbohydrate loading, the inhibitory effect of insulin on release of fatty acids from adipocytes diminishes circulating fatty acids and up-regulates glucose use by the heart. Similarly, with ischemia, fatty acid metabolism is diminished and glucose uptake is enhanced.[74] Thus, assessment of diminished fatty acid use or normal (relative to flow) or enhanced glucose metabolism serves as the metabolic signature of ischemic myocardium. Stunned or hibernating myocardium also demonstrate preserved oxygen use relative to perfusion and function.[83]

Because the diminished use of fatty acids is a key metabolic feature of myocardial ischemia, early interest with PET focused on the use of fatty acids such as ^{11}C palmitate.[84] However, because of its relatively complicated synthesis, the need for on-site cyclotron, and the complex tracer kinetics, this tracer is not used currently for identification of viable myocardium. More recently, a single-photon congener, β-methyl-p-[^{123}I]-iodophenyl-pentadecanoic acid, has been used for identification of viable myocardium. This agent is not available in the United State. Thus, its use will not be described further. However, it is extensively used in Japan for early identification of myocardial viability.[85]

Fluorodeoxyglucose (FDG)

FDG is the most extensively used tracer in PET because of the central role of glucose metabolism in delineation of metabolism in the heart as well as for studies of the brain and for tumor imaging. The 110-minute physical half-life allows convenient synthesis at a site remote from the scanner. For most studies using FDG, glucose loading either by oral glucose administration or by insulin clamp is essential. ^{13}N ammonia is typically used for assessment of perfusion in sites with cyclotrons. Patterns of myocardial perfusion and FDG uptake have been the mainstay for delineation of viable from nonviable myocardium. Scar (infarction) is identified by a matched decrease in perfusion and FDG uptake whereas hibernating myocardium is identified as regions with preserved or enhanced glucose metabolism compared with flow (Fig. 5). Dysfunctional segments with relatively normal flow but either enhanced or decreased FDG uptake are also felt to represent viable myocardium.

Imaging with FDG for delineation of viability is superior to that achievable with thallium scintigraphy.[86-88] These studies have demonstrated that approximately 30% to 50% of seg-

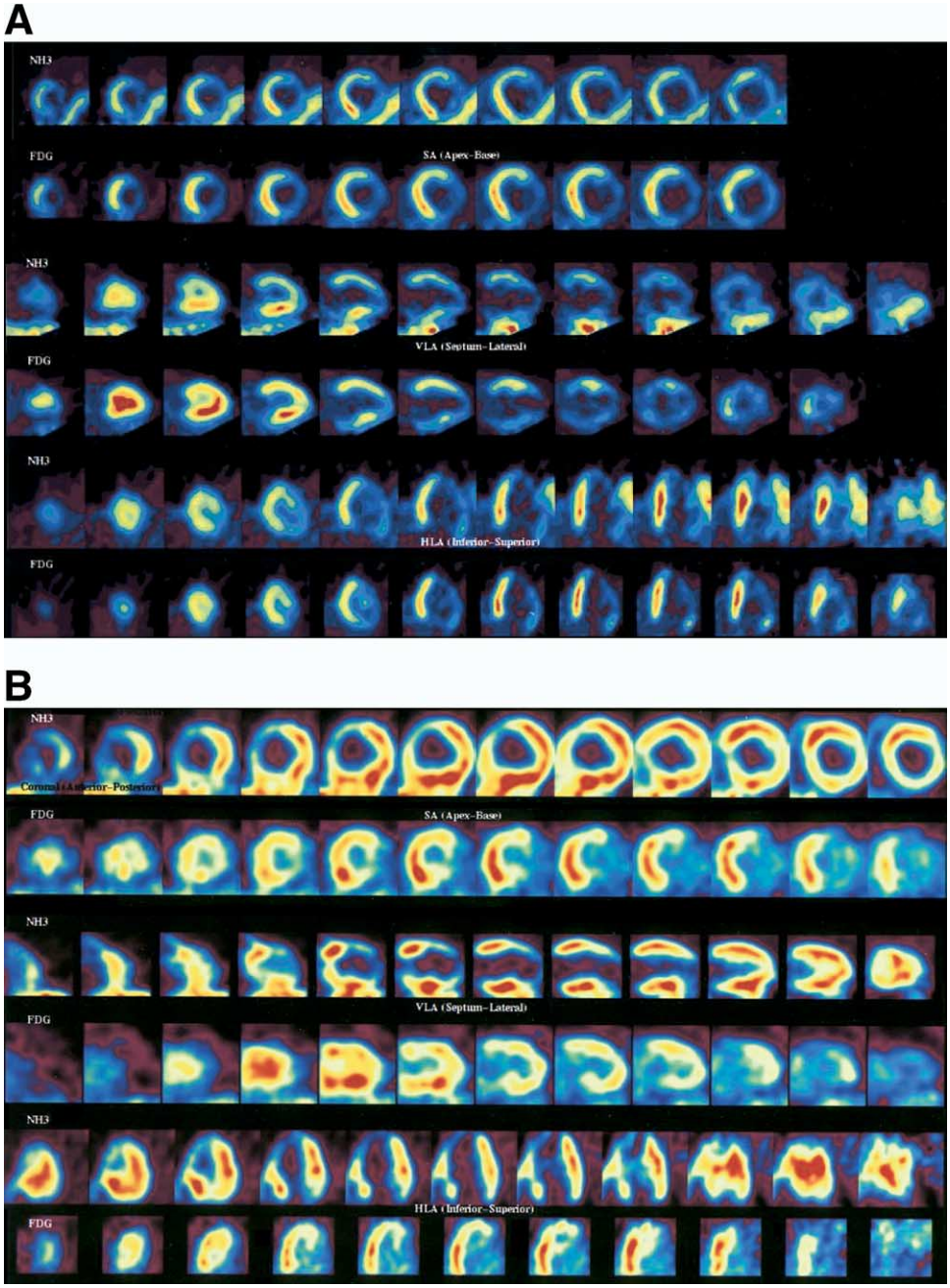

Figure 5 PET tomograms obtained showing standard reconstructions with resting ^{13}N ammonia images on the top and ^{18}F FDG images below. In this color scheme, red represents the highest counts with blue–black representing the lowest counts per pixel. A, PET image of infarction. Patient with large anterolateral and inferior perfusion defects that have concordantly decreased FDG uptake consistent with a large circumflex and/or right coronary artery infarction. In the ^{13}N ammonia images, the uptake seen at the lower right represents ^{13}N ammonia uptake into lungs, which frequently is seen in patients with congestive heart failure. There is some evidence of viability in the left anterior descending coronary artery territory with diminished perfusion and slightly increased FDG uptake. B, PET images of significant viable myocardium. There are large anteroapical and lateral perfusion defects seen in the ^{13}N ammonia study with intense FDG uptake in areas of hypoperfusion representing near complete viability in these areas.

ments felt to represent scar by delayed thallium imaging demonstrate uptake of FDG suggesting viability.

DiCarli and coworkers demonstrated that the size of the PET defect representative of hibernating myocardium was predictive of the functional recovery after revascularization.[89] This is important because patients that have the poorest ventricular function are most at risk for perioperative morbidity or mortality but also are those that typically show the most improvement when they undergo revascularization. Analysis of data of patients show that global left ventricular function increases significantly after revascularization in patients with viable myocardium based on PET.[87,90]

Table 2 The Rate (%) of Major Adverse Cardiac Events (Death or Nonfatal Myocardial Infarction) Based on Pooled Analysis of Data From 4 Studies[87,90-92]

	Infarction	Hibernating
Medical therapy	14 (n = 130)	47 (n = 85)
Revascularization	7 (n = 58)	11* (n = 130)

The table is based on major adverse cardiac event rate and patients with either infarction or hibernating myocardium as assessed by PET and observing the 1-year event rate in those maintained on medical therapy compared with those undergoing revascularization. The number of patients per group is in parenthesis.

*$P < 0.001$ compared with patients with evidence of viability remaining on medical therapy.

PET also has been shown to have to have important prognostic implications based on the findings of viable versus nonviable myocardium (Table 2). Patients who are identified as having scar based on PET who do not undergo revascularization have a 14% 1-year incidence of major adverse cardiac events compared with a 7% incidence in patients with scar who underwent revascularization. In contrast, patients with viable myocardium based on PET who did not undergo revascularization had a 1-year event rate of 47%, which was markedly reduced (to 11%) if patients underwent revascularization.[87,91-93] This is despite the fact that recent studies were performed in patients with very severe left ventricular dysfunction. For example, in the study of Rohatgi and coworkers, the pre-PET mean ejection fraction was 22%.[87] It appears that viable myocardium represents a vulnerable substrate for ischemia and arrhythmia that lead to cardiac events. When a significant amount (approximately 20-25% of contiguous myocardium) of viable myocardium can be identified by PET, revascularization has significant salutary effect. The finding of viability on PET is critical in recommending patients for revascularization.

Centers that perform heart transplants often use PET to determine those patients in whom coronary artery bypass grafting can be performed rather than transplantation. It has been the experience of several centers that approximately 30 to 50% of patients referred for transplantation have hibernating myocardium based on PET.[94-96] These patients do well when revascularized.

Because of the utility of FDG with PET, a number of centers now use FDG with SPECT systems with or without high-energy collimation.[97] However, because of issues related to resolution and sensitivity, use of FDG with dedicated PET is still preferred.

Alternative Tracers

A number of other approaches to assess viability have been made with tracers such as ^{11}C acetate. However, this tracer requires a cyclotron in addition to the assessment of the myocardial kinetics of wash-out, thereby making this somewhat less useful for most centers. It should be recognized that acetate may in fact be more sensitive in assessing viable myocardium compared with FDG.[98-100] A number of other tracers, such as hypoxic sensitizers (which assess the level of tissue oxygenation), have been developed for delineation of ischemic but viable myocardium,[101,102] although these have not yet reached clinical utility.

Dobutamine Stress Echocardiography

Another way to assess myocardial viability is to evaluate ventricular contractile reserve. As discussed above, some investigators have used the response of left ventricular function to low dose dobutamine infusion during ECG-gated SPECT acquisition as a method of identifying viability. More commonly, however, ventricular contractile reserve is measured with transthoracic echocardiography at various stages of either a low dose or higher dose prolonged dobutamine infusion protocol.[103] Infusions typically begin at 5 μg/kg/min for 3 min, increasing every 3 min to 10, 20, 30, and 40 μg/kg/min, often with atropine given at peak infusion to achieve target heart rate. Images are acquired at each stage to determine new wall motion abnormalities, worsening of preexisting wall motion abnormalities, or enhanced wall motion. While enhancement of wall motion during low dose dobutamine infusion has commonly been used to predict functional recovery following revascularization, a higher predictive value is obtained with higher infusions while looking at both enhancement and worsening of wall motion.[104]

Bax and coworkers performed meta-analysis of 29 studies using dobutamine echocardiography and 3 using dobutamine MRI of ventricular function to predict improved ventricular function after revascularization.[30] For the 1090 patients analyzed, the sensitivity and specificity were 81% and 80%, respectively, and the positive and negative predictive values were 77% and 85%, respectively. However, only 4 of these studies used a high-dose protocol. Using the high-dose protocol allows one to better distinguish between 4 wall motion response patterns: (1) biphasic response (initial ventricular function improvement followed by deterioration of function), (2) worsening of ventricular function, (3) sustained functional improvement, and (4) no change in function. Although there has been demonstrated post-revascularization functional improvement with responses 1, 2, and 3, Cornel and coworkers reported that the biphasic response 1 had the highest positive predictive value, 75%, for predicting functional improvement at 14 months, compared with 9% for response 2 and 22% for response 3, whereas only 4% of patients with response 4 improved after revascularization.[105] Similarly, Afridi and coworkers saw that the positive predictive value of a biphasic response was 72% compared with 35% for worsening function, 15% for sustained improvement, and 13% for no change.[104]

Although there may be differing opinions regarding the ideal dobutamine stress echocardiographic protocol and the degree to which the various ventricular responses to dobutamine predict functional recovery, as with radionuclide imaging techniques, stress echocardiography can predict patient outcome. In a study by Afridi and coworkers patients who had evidence of viability on dobutamine echocardiogra-

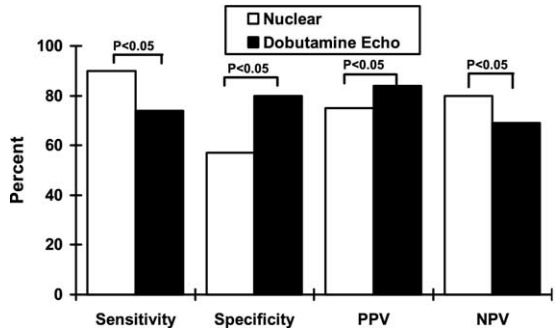

Figure 6 Comparison of nuclear perfusion image and dobutamine stress echocardiography testing for prediction of ventricular function results after revascularization. Data for figure are from Bax and coworkers.[30]

phy had a significantly improved survival with revascularization compared with medical therapy alone, 92% versus 78% at 2 years ($P = 0.01$).[106] Patients without viability did poorly with either revascularization or medical therapy alone.

Comparison of Nuclear and Echocardiographic Studies

In an analysis of 563 patients in 18 studies directly comparing patients who underwent viability assessment with a nuclear technique (thallium-201 or ^{18}FDG PET) versus dobutamine echocardiography, Bax and coworkers reported that pooled results indicate a higher sensitivity and negative predictive value for the nuclear technique, and a higher specificity and positive predictive value for dobutamine echocardiography, with post-revascularization improvement in ventricular function used as the judging standard.[30] When nuclear studies with a stress component and echocardiographic studies using high dose dobutamine were excluded (thus excluding components of stress-induced ischemia), respectively the sensitivities of nuclear imaging and dobutamine echocardiography were 90% and 74% ($P < 0.05$), the specificities were 57% and 80% ($P < 0.05$), the positive predictive values were 75% and 84% ($P < 0.05$), and the negative predictive values were 80% and 69% ($P < 0.05$), shown in Figure 6. Studies consistently show that although nuclear imaging identifies more viability, missing fewer patients who would benefit from revascularization, nuclear imaging may indicate viability more often than dobutamine echocardiography in a setting in which ventricular function does not improve after revascularization.

Various explanations have been proposed for differences between nuclear techniques and dobutamine echocardiography in predicting post-revascularization functional improvement. Bonow suggests that the differences may in part be methodological.[107] For example, because left ventricular functional improvement is assessed with echocardiography, one would expect that prerevascularization echocardiographic testing would more closely predict results that are measured with the same technique. Using an echocardiographic technique to evaluate a perfusion imaging technique has limitations because of anatomic misalignment, ie, the orientation of the heart is inherently different between the techniques. This would cause a significant bias for analyses done on a segmental basis.

In addition, in many cases post-revascularization echocardiography had been performed a short time after revascularization. As the myocardium may be stunned, assessment of patients at a later time may show additional improvement of ventricular function, which could improve the positive predictive value of thallium imaging.

A recent study by Baumgartner and coworkers suggests that there may be a pathophysiologic basis to the results of the different noninvasive tests used to assess myocardial viability.[108] The hearts of 12 patients with coronary disease and severely reduced ventricular function who were referred for cardiac transplantation were assessed with rest-delayed thallium imaging, ^{18}FDG PET, and dobutamine echocardiography, and the explanted hearts were assessed histopathologically. More histologically viable cells were found to be required for a segment to exhibit viability by stress echocardiography than by the radionuclide imaging techniques. Segments with <25% viable myocytes showed echocardiographic evidence of viability in only 19% of cases, compared with 33% for ^{18}FDG PET and 38% for thallium-SPECT. Thus, there may be a critical mass of myocardium that needs to be viable in order for there to be contractile reserve detectable by stress echocardiography and for there to be functional improvement after revascularization. Radionuclide imaging techniques may require fewer viable cells to show viability, which in many cases may be insufficient to, at least initially, show functional improvement after revascularization.

MRI

One of the newest methods of assessing myocardial viability is contrast-enhanced MRI (ce-MR). Gadolinium-based contrast agents have been shown to enhance nonviable tissue better than viable tissue, perhaps because of contrast accumulation in the extracellular space in the former (cellular membranes not intact).[109] Kim and coworkers used ce-MR to study 50 patients with ventricular dysfunction before bypass surgery.[110] Of 329 segments without contrast enhancement, 78% showed improved contractility after bypass, compared with only 2% of segments with hyperenhancement of more than 75% of tissue ($P < 0.001$). The percentage of myocardium that was both dysfunctional and not hyperenhanced was strongly related to global wall motion improvement after revascularization.

The high spatial resolution of MR allows more precise assessment of the extent of myocardial viability. In a recent study by Kneusel and coworkers, ce-MR was found to complement metabolic imaging with ^{18}FDG in predicting post-revascularization functional recovery. Most often, ce-MR viability wall thickness correlated with FDG uptake.[111] Of segments with both a thick viable rim (>4.5 mm) on ce-MR and PET viability, 85% improved function, compared with only 13% of segments with only a thin viable rim and no PET viability. However, for patients with mixed pictures (one of

the techniques showing "no" viability), only 24% to 36% improved function. Thus, in this study viability needed to be demonstrated by both techniques to reliably predict functional improvement. Larger, longitudinal studies (such as those described below) are needed to further assess this issue.

Putting Things Into Perspective

Preservation of myocardial viability exists as a spectrum, from complete transmural infarction with no viability, to transmural hibernation or stunning with potential of full recovery. An important principle demonstrated by biopsy studies is that tracer uptake represents a continuous variable, with the magnitude of tracer uptake directly reflecting the magnitude of preserved viability.[47] Thus it may be misleading to consider viability simply on a yes or no basis.

The extent of viability needed for a patient to benefit from revascularization is unclear and may vary in different clinical circumstances. Patients can have various mixtures of stunned, hibernating, ischemic, and fibrotic myocardium, in a variety of arrangements. From one viewpoint, even when there is substantial normal and/or reversibly dysfunctional myocardium (in which case a nuclear technique may indicate viability), if more than 30% to 35% of myocardium is fibrotic (in which case dobutamine echocardiography would suggest minimal to no viability), then segmental wall motion would unlikely be improved after revascularization.[112] A study by DiCarli and coworkers demonstrated that the larger the area of myocardial viability, the greater the percent improvement in ventricular function after revascularization.[89]

It is not clear that improvement of ventricular function, regional or global, is necessary for there to be patient benefit. Samady and coworkers saw no difference in survival between ischemic cardiomyopathy patients who did or did not have improved left ventricular ejection fraction following bypass surgery.[113] In addition, postoperative improvement in angina and heart failure were similar between the two groups. Thus, even without improvement in ventricular systolic function, there may be important clinical benefits. Preservation of the small areas viability detected by perfusion imaging techniques may improve clinical outcome by stabilizing the electrical milieu and preventing lethal arrhythmias, by preventing a subsequent myocardial infarction, and by improving symptoms and functional capacity through prevention of deleterious myocardial dilation and remodeling.[114] These concepts need further investigation.

With the continued aging of the population and the predicted greater prevalence of patients with chronic diseases such as congestive heart failure and left ventricular dysfunction attributable to coronary disease, it will become increasingly important to identify patients who will benefit from interventions such as revascularization. It will be important to more accurately identify myocardial viability. Currently available radionuclide imaging techniques: stress-delayed and rest-delayed thallium imaging, Tc-99m sestamibi imaging, metabolic imaging with PET, dobutamine stress echocardiography, and MRI techniques, are all helpful in making clinical decisions, but all have limitations. Larger, carefully conducted prospective studies will need to be performed to more effectively evaluate the various tests singly or in combination, and they will need to incorporate newer technologies, such as attenuation correction. These studies will need to be undertaken on the different subsets of patients in whom viability is an issue, eg, patients with coronary disease and severe ventricular dysfunction who have symptoms of heart failure, similar patients with angina, patients who are asymptomatic, patients who have had one or several myocardial infarctions, etc.[115] Among the current ongoing investigations is the UK Heart trial (Heart Failure Revascularization Trial) that will randomize 800 patients with ischemic heart failure to either best medical therapy or revascularization (CABG or PCI), correlating patient outcome with the extent of myocardial viability.[116] A similar trial called STITCH (Surgical Treatment for Ischemic Heart Failure) is being undertaken in the United States, also assigning patients of various types to CABG or medical therapy, correlating outcome with the extent of myocardial viability (as assessed by rest-redistribution thallium or nitrate enhanced sestamibi imaging).[21]

It is important to consider that medical therapy is improving and may influence the risk benefit ratio of revascularization in these ongoing trials and in clinical practice. In addition, newer procedures, such as therapeutic coronary angiogenesis and stem cell repair techniques, may revolutionize the way patients with these types of cardiovascular disease are managed.[117,118] Nevertheless, one would expect that radionuclide imaging techniques will continue to play an important role in assessment of myocardial viability.

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