TECHNOLOGISTS' SECTION

Use of myocardial perfusion imaging to assess viability

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With advances in our ability to effectively treat and decrease initial mortality from acute cardiac events, such as myocardial infarction, the numbers of patients with chronic heart conditions related to left ventricular dysfunction are increasing. These patients are at high risk for subsequent cardiac death and severe morbidities, such as episodes of pulmonary edema and cardiac arrhythmias necessitating hospitalization. These patients often have severe limitations in life-style and well being.

In patients with chronic heart disease, left ventricular dysfunction is the strongest predictor of subsequent mortality.[1] While there have been significant advances in medical therapy for these patients, including angiotensin-converting enzyme inhibitors,[2] nitrates,[3] hydralazine,[3] β-blockers,[4] and more recently spironolactone,[5] the mortality from congestive heart failure/left ventricular dysfunction nevertheless remains extremely high, with an annual mortality rate of 16% and a yearly sudden death rate of 8%.[6]

It has been known for some time that left ventricular dysfunction is not always the result of irreversible myocardial scarring. In some cases left ventricular dysfunction is the result of "stunned myocardium," defined as myocardium that has become dysfunctional because of a transient coronary occlusion, has been salvaged by coronary reperfusion, and yet exhibits prolonged but transient postischemic dysfunction, lasting hours to weeks.[7] In myocardial stunning there is a flow-contraction mismatch. Stunned myocardium, global or regional, often occurs after acute myocardial infarction, as well as after cardioplegic arrest during heart operations.

Examples of stunned myocardium were demonstrated in a 1985 study by Topol et al.[8] Myocardial functional recovery was evaluated in 20 consecutive patients with acute myocardial infarction who received thrombolytic therapy and, in some cases, coronary angioplasty. After revascularization of infarcted areas, while there was no immediate or 24-hour improvement in wall motion, after 10 days 28 of 33 reperfused infarct zone segments demonstrated improved wall motion compared with 6 of 20 nonreperfused infarct segments ($P = 0.01$).

In other cases left ventricular dysfunction is the result of "hibernating myocardium," defined as a state of persistently impaired left ventricular function at rest caused by reduced coronary blood flow that can be partially or completely restored to normal if the myocardial oxygen supply/demand relationship is favorably altered, either by improving blood flow or by reducing demand, or with both methods.[9] By this definition, hibernating myocardium is a flow-contraction match. However, recent data suggest that blood flow in hibernating myocardial segments is not decreased to the extent that would account for the degree of cardiac dysfunction. Thus some believe that hibernating myocardium is actually a manifestation of repeated myocardial stunning, perhaps the result of impairment in coronary flow reserve.[10]

Regardless of the mechanism, it is important to identify hibernating myocardium because ventricular function will improve after revascularization. For example, in 1982 Rahimtoola[11] reported the case of a patient with an occluded left anterior descending coronary artery, an akinetic anteroapical wall, and a global ejection fraction of 37%. After bypass, function of the anteroapical region returned to normal and the ejection fraction increased to 76%.

CLINICAL IMPORTANCE OF IDENTIFYING VIABLE MYOCARDIUM

Patients with depressed left ventricular function have a worsened prognosis. In the CASS (Coronary Artery Surgical 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 approximately 60%

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J Nucl Cardiol 2000;7:72-80.

1071-3581/2000/$12.00 + 0 **43/1/103725**

for those with an ejection fraction of 35% to 49%, and 30% for those with an ejection fraction less than 35% ($P < 0.001$).[12]

Patients in whom the left ventricular dysfunction is the result of hibernating or stunned myocardium, that is, in whom the myocardium is viable, appear to have a worse prognosis than patients whose left ventricular function is the result of myocardial scarring. Gioia et al[13] performed rest-redistribution thallium imaging in 81 medically treated patients with coronary artery disease and left ventricular dysfunction (left ventricular ejection fraction <40%). For patients with evidence of myocardial viability, the death rate (over 31 ± 24 months) was 58%, compared with 26% ($P = 0.03$) for patients without significant viability.

DiCarli et al[14] performed positron emission tomographic (PET) imaging on 93 consecutive patients with coronary artery disease and a mean left ventricular ejection fraction of 25%. As shown in Figure 1, patients receiving medical therapy who had PET evidence of myocardial viability had a markedly lower annual survival (50%) than patients without evidence of viability (92%, $P = 0.007$). Patients with evidence of myocardial viability who underwent revascularization had a higher survival rate than those treated medically (88% vs 50%, $P = 0.03$).

Conversely, patients with left ventricular dysfunction who do not have significant viability do poorly if they undergo surgical revascularization. Haas et al[15] studied 76 patients with advanced coronary disease and left ventricular dysfunction who were being considered for coronary bypass operations. Compared with patients who were first evaluated for viability with PET imaging (which resulted in patients being held back from the surgical procedure), patients operated on who did not have a viability assessment had a significantly worse postoperative course, including a lower 12-month survival rate: 79% versus 97% ($P = 0.01$).

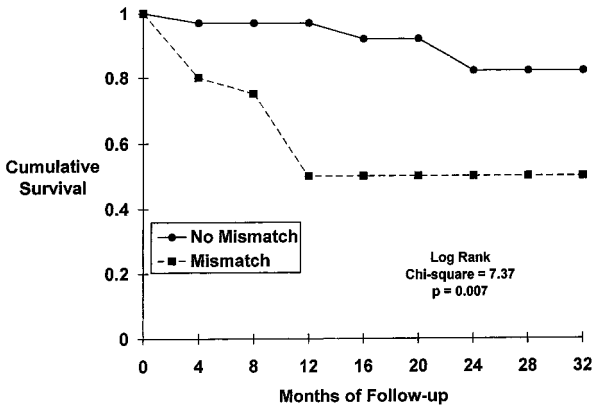

Figure 1. Cumulative survival in 50 patients receiving medical therapy in relation to the presence (*mismatch*) or absence (*no mismatch*) of PET evidence of myocardial viability. Modified from DiCarli MF, Davidson M, Little R, Khanna S, Mody FV, Brunken RC, et al. Am J Cardiol 1994;73:527-33, with permission from Excerpta Medica, Inc.

USE OF PERFUSION IMAGING TO ASSESS MYOCARDIAL VIABILITY

Stress-Delayed Thallium-201 Imaging

Thallium-201 was introduced as an agent to assess myocardial perfusion by Lebowitz et al[16] in 1975. At first, as per previous work by Zaret et al[17] with potassium-43, two separate studies were performed: a study in which Tl-201 was injected intravenously during exercise and a second study in which Tl-201 was administered at rest. Defects present on the stress but not on the rest images were considered to represent myocardial ischemia, whereas defects on both the stress and rest images were considered to represent scar from myocardial infarction. In 1976 Pohost et al[18] saw that with serial images over 4- to 6-hour intervals in patients who received injections of Tl-201 during exercise, certain zones of decreased myocardial uptake present on initial images resolved, a phenomenon termed *thallium redistribution.* Redistribution was thought to represent zones of ischemic, but viable, myocardium, whereas fixed, nonredistributing defects were thought to represent nonviable, fibrotic scar.

As more experience was obtained with stress-delayed Tl-201 imaging, it became clear that the situation was more complex than at first thought. In 1983 Gutman et al[19] reported that in the presence of severe stenoses, defects that appear fixed at 3 to 6 hours might show redistribution at 24 hours. Kiat et al[20] reported that late (18 to 72 hour) imaging often showed thallium redistribution in defects that were fixed at 4 hours and that the later images were better predictors of viability, as demonstrated by stress image improvement after coronary angioplasty.

Liu et al[21] followed up 52 patients with single-vessel disease who underwent coronary angioplasty. Although most who had redistribution on preangioplasty stress-delayed thallium imaging were subsequently shown to have viability (ie, image normalization after the procedure), 12 of 16 patients with fixed defects also had myocardial viability.

Gibson et al[22] performed Tl-201 scintigraphy on 47 consecutive patients before and after coronary bypass grafting. Of 42 persistent defects thought to represent myocardial scar before bypass, 19 (45%) demonstrated normal perfusion after operation. Interestingly, classifica-

tion of persistent defects according to the quantitative reduction in thallium activity helped predict which segments would improve after revascularization. Whereas 57% of persistent defects with a 25% to 50% reduction in relative thallium activity demonstrated normal thallium uptake after operation, only 21% of fixed defects with a greater than 50% reduction in activity showed improved perfusion after bypass ($P = 0.02$).

Evidence thus was growing that fixed defects on stress-delayed Tl-201 imaging often contain viable myocardium. In 1986 Tillisch et al[23] reported that myocardial imaging with the metabolic positron-emitting tracer fluorine 18 deoxyglucose was a powerful method of assessing viability. For 17 patients with left ventricular dysfunction who underwent bypass grafting, assessment of fluorine 18 deoxyglucose uptake had a positive predictive value of 85% and a negative predictive value of 92% in predicting postoperative improvement in ventricular function. Subsequently, Brunken et al[24] saw that 58% of fixed Tl-201 defects demonstrated fluorine 18 deoxyglucose uptake, consistent with viability.

Thus it was clear that a significant proportion of fixed defects on stress-delayed Tl-201 imaging contain viable tissue and that other methods must be used to assess these segments. Because the quality of 24-hour delayed images is often poor as a result of low counts, and because PET imaging is not available to most facilities, a new method of viability assessment was sought. In 1990 Dilsizian et al[25] reported on the technique of Tl-201 reinjection. In this technique, for fixed images, immediately after acquisition of the delayed image an additional dose of Tl-201 is injected at rest. It was reported that 49% of apparently irreversible defects demonstrated normal thallium uptake after the second injection of thallium. Additionally, of 15 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, whereas all 8 regions with fixed defects on reinjection before angioplasty had abnormal thallium uptake and abnormal regional wall motion after angioplasty.

Subsequently, Bonow et al[26] reported that thallium reinjection imaging has an 88% concordance with fluorine 18 deoxyglucose PET imaging. They 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 fluorine 18 deoxyglucose uptake. For severe, irreversible thallium defects, thallium reinjection identifies as viable or nonviable, with few exceptions, the same regions as does imaging with fluorine 18 deoxyglucose.

Technetium-99m–Labeled Sestamibi as a Viability Agent

In 1990 the Food and Drug Administration approved the use of the first technetium-99m compounds for myocardial perfusion imaging, Tc-99m–labeled teboroxime and Tc-99m–labeled sestamibi. Because teboroxime rapidly diffuses out of myocardium and is thus technically difficult to image with tomographic (single photon emission computed tomography; SPECT) techniques, most technetium imaging procedures use Tc-99m–labeled sestamibi. Compared with Tl-201, Tc-99m–labeled sestamibi emits higher energy photons, and the shorter half-life of Tc-99m allows administration of a higher dose. Thus the counts in Tc-99m–labeled sestamibi images are higher than those in Tl-201 images, resulting in clearer images and the ability to assess left ventricular function by either first-pass or gating techniques. Several studies have shown a higher specificity with Tc-99m–labeled sestamibi imaging compared with Tl-201.[27,28] Of 5.2 million studies done in the United States in 1997, approximately 60% used Tc-99m–labeled sestamibi.[29]

Unlike Tl-201, however, Tc-99m–labeled sestamibi does not exhibit significant myocardial redistribution. Thus stress imaging with Tc-99m–labeled sestamibi requires separate stress and rest injections, either on the same day (1-day protocols) or on different days (2-day protocols). Thus from the advent of sestamibi use, there was concern that stress imaging with this radiopharmaceutical might not provide viability information comparable to that obtained with Tl-201.

In 1992 Cuocolo et al[30] compared the results of Tl-201 reinjection with those of Tc-99m–labeled sestamibi in 20 patients with coronary artery disease and left ventricular dysfunction. Of 122 regions with irreversible defects on stress-delayed thallium imaging, 18% showed reversibility with stress-rest sestamibi imaging. However, 47% showed evidence of viability with reinjection thallium imaging, and thus the authors concluded that thallium imaging, when combined with rest reinjection, is superior to sestamibi imaging in identifying myocardial viability.

In the same year, Marzullo et al[31] performed rest Tc-99m–labeled sestamibi imaging in 14 patients with previous myocardial infarction referred for revascularization. Whereas 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—sestamibi images overestimated rest 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."

More recently, in 1997 Marcassa et al[32] compared sestamibi uptake with rest-redistribution thallium uptake in 48 patients with ischemic heart disease and regional wall motion abnormalities. Whereas uptake of the two 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 might be less sensitive for detecting viable myocardium.

In contrast to the aforementioned studies, there are several other reports suggesting that Tc-99m–labeled sestamibi is, in fact, an excellent viability imaging agent. Udelson et al[33] compared rest and delayed Tl-201 images with rest Tc-99m–labeled sestamibi images in 31 patients with coronary disease and left ventricular dysfunction. Quantified sestamibi activity 1 hour after rest injection was found to parallel redistribution Tl-201 activity, suggesting that the uptake and handling of sestamibi is more complex than can be explained by its being solely a flow tracer. Importantly, for patients who underwent revascularization procedures, as depicted in Figure 2, Tl-201 and Tc-99m–labeled 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 et al.[34] Twenty patients with a mean left ventricular ejection fraction of 33% underwent early and 3-hour delayed rest Tl-201 imaging and rest Tc-99m–labeled sestamibi imaging. Uptake of Tc-99m–labeled sestamibi and Tl-201 were comparable in myocardial zones of asynergy as identified by rest 2-dimensional echocardiography. Defect magnitude, by quantitation, was similar for the two tracers for regions of both mild and severe reduction in tracer uptake.

Medrano et al[35] administered intravenous Tc-99m–labeled sestamibi to 15 consecutive patients with ischemic cardiomyopathy 1 to 6 hours before transplantation. Excised hearts were imaged and analyzed histologically, and a good correlation was found between tissue Tc-99m–labeled 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 et al[36] prospectively studied 30 patients with coronary disease and wall motion abnormalities who were referred for bypass grafting. Each patient underwent rest sestamibi imaging and PET imaging with N-13 ammonia (a flow agent) and fluorine 18 deoxyglucose (a metabolic agent), as well as transmural biopsy. Significantly higher sestamibi uptake was found in patients with evidence of viability by PET imaging 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.

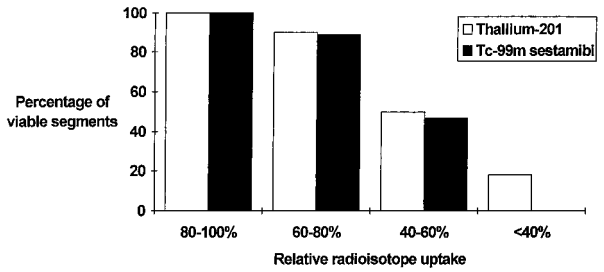

Figure 2. Percentages of segments that were viable in relation to relative uptake of Tl-201 or Tc-99m–labeled sestamibi. The likelihood of viability was related to the magnitude of regional activity rather than the radiotracer used. Modified from Udelson JE, Coleman PS, Metherall J, Pandian NG, Gomez AR, Griffith JL, et al. Circulation 1994;89:2552-61.

Rest-Delayed Thallium Imaging to Assess Myocardial Viability

Another commonly used technique to assess myocardial viability is rest-delayed thallium imaging. Although at first it was thought that a defect on rest Tl-201 imaging could only represent scar, Berger et al[37] predicted that in the presence of a severe coronary stenosis without infarction, a defect would be present on a rest image that would, over time, resolve by redistribution. They proposed that rest-delayed imaging could help differentiate underperfused but viable myocardium from infarction or scar, and they performed this protocol in 14 patients with unstable angina and 15 patients with stable angina. An initial defect was present in 90% of patients, and 76% of segments with a defect showed redistribution on the delayed images. In patients who underwent subsequent bypass grafting, 77% of segments with redistributing defects reverted toward normal initial uptake after operation, although 13 of 18 segments with fixed defects also improved.[37]

Iskandrian et al[38] performed rest and redistribution thallium imaging in 26 patients with coronary disease and left ventricular dysfunction before bypass grafting. Of 16 patients with normal or transient thallium defects, 12 (75%) showed improved ejection fraction after opera-

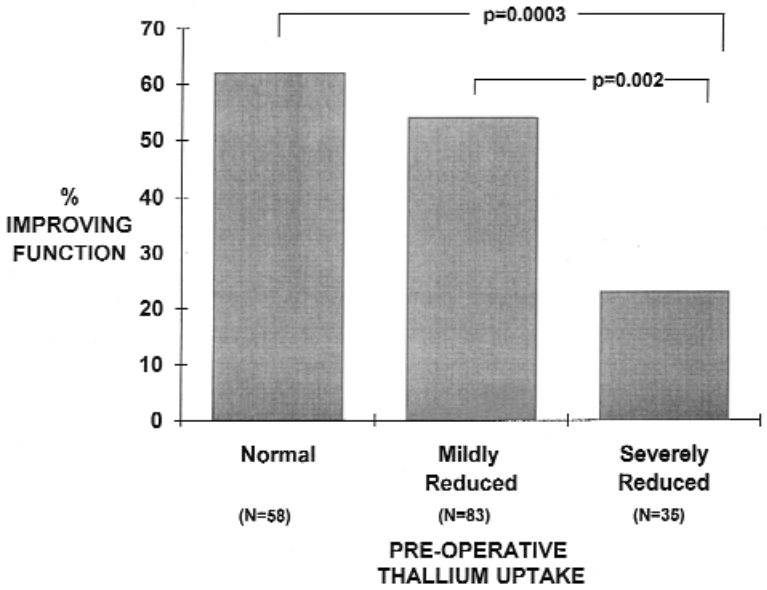

Figure 3. The correlation between improvement in regional function after coronary bypass grafting and assessment of viability by preoperative rest-redistribution Tl-201 imaging in segments with severe asynergy (severe hypokinesis, akinesis, or dyskinesis). Modified from Ragosta M, Beller GA, Watson DD, Kaul S, Gimple LW. Circulation 1993;87:1630-41.

tion, 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 et al,[39] who performed this imaging procedure in 21 patients with left ventricular dysfunction (mean ejection fraction 27%) who subsequently underwent bypass grafting. Myocardial segment viability was assessed both by quantitative analysis of defect severity and by the presence of redistribution. As shown in Figure 3, 62% of severely asynergic segments with normal viability and 54% with mildly reduced viability had improved function after the operation compared with only 23% with severely reduced viability (P = 0.002). For patients in which there was viability in 7 or more of the 15 segments analyzed, mean left ventricular ejection fraction increased significantly after bypass.

The importance of assessing viability with regard to predicting and improving clinical outcome was reported by Pagley et al.[40] Seventy patients with multivessel coronary disease and a left ventricular ejection fraction less than 40% underwent rest-delayed thallium imaging before bypass grafting. A viability index based on image findings was assessed for each patient. Figure 4 shows the relationship of event-free survival to the viability index. The viability index was significantly related to 3-year event-free survival, independent of other variables including left ventricular ejection fraction. Thus use of rest-delayed thallium imaging helps to identify patients who are more likely to benefit from bypass grafting.

There are conflicting data in the literature regarding whether the presence of defect reversibility or thallium uptake of 50% or more of peak counts is the better indicator of viability. In a study of 35 patients with left ventricular dysfunction, Sciagrà et al[41] found that redistribution activity is more important than reversibility when differentiating viable from nonviable myocardium. In contrast, Kitsiou et al[42] have presented preliminary data showing that reversible defects more accurately predict functional recovery after revascularization.

One must consider that for revascularization to improve ventricular function, the ventricle must be ischemic from a stenosis in an artery perfusing the dysfunctional territory, and this situation is best depicted by defect reversibility. In the setting of a ventricle impaired by cellular dysfunction related to a cardiomyopathy, one could see satisfactory myocardial thallium uptake, but in this situation revascularization would not be expected to improve function.

COMPARISON OF PERFUSION IMAGING WITH OTHER IMAGING MODALITIES

Positron Emission Tomography

As discussed earlier, PET imaging with fluorine 18 deoxyglucose is useful in detecting myocardial viability and predicting improvement in left ventricular function

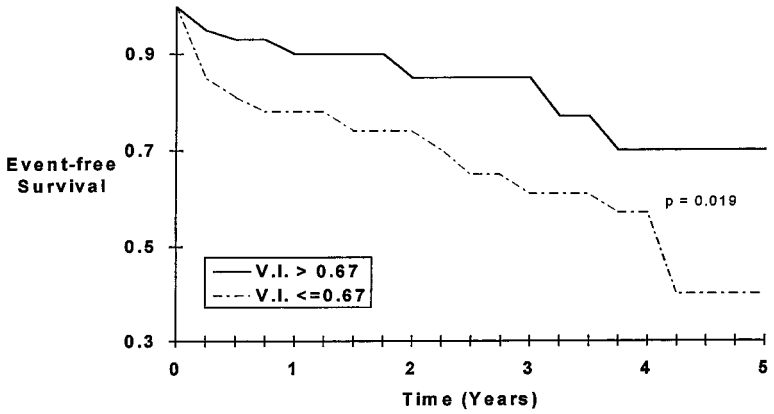

Figure 4. Survival free from cardiac events (cardiovascular death or heart transplantation) in relation to viability index (*V.I.*). Modified from Pagley PR, Beller GA, Watson DD, Gimple LW, Ragosta M. Circulation 1997;96:793-800.

after revascularization.[23,24] The clinical application of this technique has been limited by the high cost of PET cameras. However, with the advent of high-energy collimators for SPECT imaging,[43] it is now possible to image fluorine 18 deoxyglucose with a conventional gamma camera. Srinivasan et al[44] compared the images generated by rest Tl-201 imaging, rest fluorine 18 deoxyglucose SPECT, and rest fluorine 18 deoxyglucose PET in 28 patients with chronic coronary disease and reduced ventricular function (ejection fraction 33% ± 15%). In general, there was good concordance among the three techniques, but in patients with an ejection fraction of 25% or less, thallium tended to underestimate viability compared with both PET and SPECT fluorine 18 deoxyglucose imaging, particularly in the inferior wall. Nevertheless, fluorine 18 deoxyglucose SPECT would occasionally (27% of the time) suggest viability when the other imaging techniques did not. In an accompanying editorial, Udelson[45] discusses many unresolved issues in these different imaging methods. It is not at all clear which technique is best for which clinical situation and whether perhaps a technique such as thallium imaging will be significantly improved with incorporation of new technologies, such as attenuation correction. However, the advent of fluorine 18 deoxyglucose SPECT promises to make metabolic myocardial imaging more widely available.

Stress Echocardiography

Assessment of resting left ventricular function by echocardiography has been shown to add significant information to rest-delayed thallium imaging in identifying myocardial viability.[46] It has been suggested that dobutamine stress echocardiography might be as good as or better than perfusion imaging techniques in assessing myocardial viability. Perrone-Filardi et al[47] performed dobutamine echocardiography and rest/4-hour/24-hour thallium imaging in 40 patients with dysfunctional, hypoperfused myocardium and related these results to left ventricular function before and after revascularization. Whereas concordance between thallium and dobutamine echocardiography was 82% in hypokinetic segments, it was 43% in akinetic segments. Although both techniques helped to identify patients whose ventricular function would improve with revascularization, dobutamine had a higher positive predictive accuracy than thallium (92% vs 72%), whereas thallium imaging had a better negative predictive accuracy (100% vs 65%). In an accompanying editorial, Bonow[48] combined the results of multiple studies reporting on the accuracies of fluorine 18 deoxyglucose PET, thallium SPECT, and dobutamine echocardiography in ventricular function improvement after revascularization. As illustrated in Figure 5, compared with the other techniques, thallium imaging had the lowest positive predictive value in terms of functional improvement, but at the same time identified more patients who would benefit from revascularization. Bonow[48] suggests that these findings may in part be related to methodologic factors. For example, because left ventricular functional improvement is assessed with echocardiography, one would expect that echocardiographic testing before revascularization would more closely predict results. Use of an echocardiographic technique to evaluate a perfusion imaging technique might be impaired by anatomic misalignment. In addition, for most of the studies reviewed by Bonow,[48] postrevascularization echocardiography was done a short time after revascularization. Because the myocardium may be stunned, assessment in these patients at a later time might show additional improvement of ventricular function, which could improve the positive predictive value of thal-

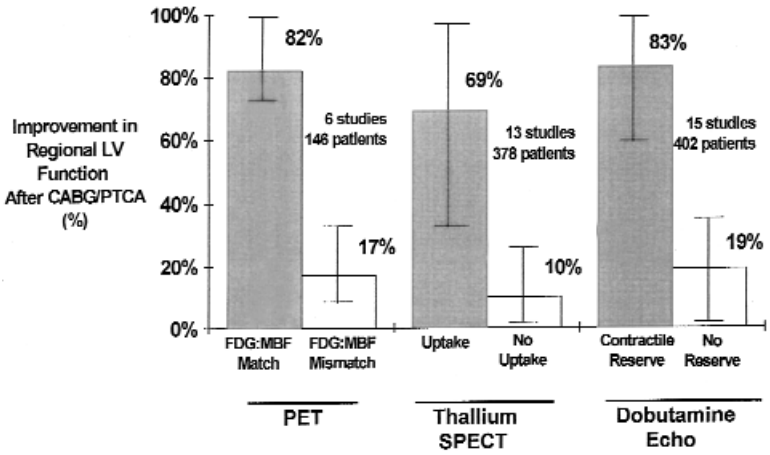

Figure 5. Improvement in left ventricular (*LV*) function after revascularization in relation to results of noninvasive testing to detect myocardial viability. *Horizontal bars* connected by *vertical lines* indicate the range of reported values. *Shaded bars* represent the positive predictive values, and the *open bars* represent the inverse of the negative predictive values. *CABG,* Coronary artery bypass grafting; *PTCA,* percutaneous transluminal coronary angioplasty; *FDG,* fluorine 18 deoxyglucose; *MBF,* myocardial blood flow; *echo,* echocardiography. Modified from Bonow RO. Circulation 1996;94:2674-80.

lium imaging. Finally, it is somewhat unclear which response to dobutamine echocardiography indicates viability. Recent studies suggest that a biphasic response (improvement in ventricular function at lower dobutamine dosages, followed by deterioration at higher dosages) is the most accurate, but published studies have used a variety of criteria.

A recent study by Baumgartner et al[49] does suggest that there may be a pathophysiologic basis to the differences among the results of the different noninvasive tests used to assess myocardial viability. The hearts of 12 patients with coronary disease and severely reduced ventricular function who underwent cardiac transplantation were assessed with rest-delayed thallium imaging, fluorine 18 deoxyglucose PET, and dobutamine echocardiography, and the explanted hearts were assessed histopathologically. More histologically viable cells were required for a segment to exhibit viability by stress echocardiography than were required by the radionuclide imaging techniques. Segments with less than 25% viable myocytes showed echocardiographic evidence of viability in only 19% of cases, compared with 33% for fluorine 18 deoxyglucose PET and 38% for thallium SPECT. Thus there might 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 might require fewer viable cells to assess viability that in many cases might be insufficient to, at least initially, show functional improvement after revascularization. Nevertheless, it is unclear whether functional improvement is necessary for a patient to benefit from revascularization.[45] It is possible that preservation of the small areas of viability detected by perfusion imaging techniques might 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 dilatation and remodeling. Thus perfusion and functional imaging techniques might provide complementary data, and both might help in clinical decision making.

CONCLUSIONS AND FUTURE DIRECTIONS

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 as a result of coronary disease, it will become increasingly important to identify patients who will benefit from aggressive intervention, 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–labeled sestamibi imaging, and metabolic imaging with fluorine 18 deoxyglucose PET and fluorine 18 deoxyglucose SPECT (and perhaps in the future techniques that incorporate gated SPECT image data)—are helpful in making clinical decisions, but they all have limitations. Competing techniques, such as stress echocardiography, also have limitations, but might provide important complementary information. Larger, carefully conducted prospective

studies are needed to more effectively evaluate the various tests singly or in combination, and the studies must incorporate newer technologies, such as attenuation correction. These studies should be undertaken on the different subsets of patients in whom viability is an issue, for example, patients with coronary disease and severe ventricular dysfunction who have symptoms of heart failure, similar patients with angina, similar patients who are free of symptoms, patients who have had one or several myocardial infarctions, and so on.[50] It is important to consider that medical therapy is improving and might influence the risk/benefit ratio of surgical procedures in many cases. Gene therapy and angiogenesis techniques might revolutionize the way patients with these types of cardiovascular disease are treated. Nevertheless, one would expect that radionuclide imaging techniques will continue to play an important role in assessment of myocardial viability.

References

1. Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. N Engl J Med 1983;309:331-6.
2. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.
3. Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration cooperative study. N Engl J Med 1986;314:1547-52.
4. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al, for the US Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 1996;334:1349-55.
5. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al, for the Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341:709-17.
6. Stevenson WG, Stevenson LW, Middlekauff HR, Fonarow GC, Hamilton MA, Woo MA, et al. Improving survival for patients with advanced heart failure: a study of 737 consecutive patients. J Am Coll Cardiol 1995;26:1417-23.
7. Kloner RA, Bolli R, Marban E, Reinlib L, Braunwald E. Medical and cellular implications of stunning, hibernation, and preconditioning: an NHLBI workshop. Circulation 1998;97:1848-67.
8. Topol EJ, Weiss JL, Brinker JA, Brin KP, Gottlieb SO, Becker LC, et al. Regional wall motion improvement after coronary thrombolysis with recombinant tissue plasminogen activator: importance of coronary angioplasty. J Am Coll Cardiol 1985;6:426-33.
9. Rahimtoola SH. The hibernating myocardium. Am Heart J 1989;117:211-21.
10. Wijns W, Vatner SF, Camici PG. Hibernating myocardium. N Engl J Med 1998;339:173-81.
11. Rahimtoola S. Coronary bypass surgery for chronic angina—1981: a perspective. Circulation 1982;65:225-41.
12. Emond M, Mock M, Davis K, et al. Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) registry. Circulation 1994;90:2645-57.
13. Gioia G, Milan E, Giubbini R, DePace N, Heo J, Iskandrian AS. Prognostic value of tomographic rest-redistribution thallium 201 imaging in medically treated patients with coronary artery disease and left ventricular dysfunction. J Nucl Cardiol 1996;3:150-6.
14. DiCarli MF, Davidson M, Little R, Khanna S, Mody FV, Brunken RC, et al. Value of metabolic imaging with positron emission tomography for evaluating prognosis in patients with coronary artery disease and left ventricular dysfunction. Am J Cardiol 1994;73:527-33.
15. Haas F, Haehnel CJ, Picker W, Nekolla S, Martinoff S, Meisner H, et al. Preoperative positron emission tomographic viability assessment and perioperative and postoperative risk in patients with advanced ischemic heart disease. J Am Coll Cardiol 1997;30:1693-700.
16. Lebowitz E, Greene MW, Fairchild R, Bradley-Moore PR, Atkins HL, Ansari AN, et al. Thallium-201 for medical use: I. J Nucl Med 1975;16:151-55.
17. Zaret BL, Strauss HW, Martin ND, et al. Noninvasive evaluation of regional myocardial perfusion with radioactive potassium: study of patients at rest, exercise, and during anginal pectoris. N Engl J Med 1973;288:809-12.
18. Pohost GM, Zir LM, McKusick KA, Moore RH, Guiney TE, Beller GA. Differentiation of transiently ischemic from infarcted myocardium by serial imaging after a single dose of thallium-201. Circulation 1977;55:294-302.
19. Gutman J, Berman DS, Freeman M, Rozanski A, Maddahi J, Waxman A, et al. Time to completed redistribution of thallium-201 in exercise myocardial scintigraphy: relationship to the degree of coronary artery stenosis. Am Heart J 1983;106:989-95.
20. Kiat H, Berman DS, Maddahi J, Yang LD, Van Train K, Rozanski A, et al. Late reversibility of tomographic myocardial thallium-201 defects: an accurate marker of myocardial viability. J Am Coll Cardiol 1988;12:1456-63.
21. Liu P, Kiess MC, Okada RD, Block PC, Strauss HW, Pohost GM, et al. The persistent defect on exercise thallium imaging and its fate after myocardial revascularization: does it represent scar or ischemia? Am Heart J 1985;110:996-1001.
22. Gibson RS, Watson DD, Taylor GJ, Crosby IK, Wellons HL, Holt ND, et al. Prospective assessment of regional myocardial perfusion before and after coronary revascularization surgery by quantitative thallium-201 scintigraphy. J Am Coll Cardiol 1983;1:804-15.
23. Tillisch J, Brunken R, Marshall R, Schwaiger M, Mandelkern M, Phelps M, et al. Reversibility of cardiac wall-motion abnormalities predicted by positron tomography. N Engl J Med 1986;314:884-8.
24. Brunken R, Schwaiger M, Grover-McKay M, Phelps ME, Tillisch J, Schelbert HR. Positron emission tomography detects tissue metabolic activity in myocardial segments with persistent thallium perfusion defects. J Am Coll Cardiol 1987;10:557-67.
25. Dilsizian V, Rocco TP, Freedman NMT, Leon MB, Bonow RO. Enhanced detection of ischemic but viable myocardium by the reinjection of thallium after stress-redistribution imaging. N Engl J Med 1990;323:141-6.
26. Bonow RO, Dilsizian V, Cuocolo A, Bacharach SL. Identification of viable myocardium in patients with chronic coronary artery disease and left ventricular dysfunction: comparison of thallium scintigraphy with reinjection and PET imaging with ^{18}F-fluorodeoxyglucose. Circulation 1991;83:26-37.
27. Taillefer R, DePuey EG, Udelson JE, Beller GA, Latour Y, Reeves F. Comparative diagnostic accuracy of Tl-201 and Tc-99m sestamibi SPECT imaging (perfusion and ECG-gated SPECT) in detecting coronary artery disease in women. J Am Coll Cardiol 1997;29:69-77.
28. Miller DD. The growing flood of technetium-99m myocardial perfusion agents. More water . . . or more mud? Circulation 1995;91:555-8.
29. Cohen MC. A snapshot of nuclear cardiology in the United States. Am Soc Nucl Cardiol Newsletter 1998;5:13.

30. Cuocolo A, Pace L, Ricciardelli B, Chiariello M, Trimarco B, Salvatore M. Identification of viable myocardium in patients with chronic coronary artery disease: comparison of thallium-201 scintigraphy with reinjection and technetium-99m methoxyisobutyl isonitrile. J Nucl Med 1992;33:505-11.
31. Marzullo P, Sambuceti G, Parodi O. The role of sestamibi scintigraphy in the radioisotopic assessment of myocardial viability. J Nucl Med 1992;33:1925-30.
32. Marcassa C, Galli M, Cuocolo A, Scappellato F, Maurea S, Salvatore M. Rest-redistribution thallium-201 and rest technetium-99m-sestamibi SPECT in patients with stable coronary artery disease and ventricular dysfunction. J Nucl Med 1997;38:419-24.
33. Udelson JE, Coleman PS, Metherall J, Pandian NG, Gomez AR, Griffith JL, et al. Predicting recovery of severe regional ventricular dysfunction: comparison of resting scintigraphy with ^{201}Tl and ^{99m}Tc-sestamibi. Circulation 1994;89:2552-61.
34. Kauffman GJ, Boyne TS, Watson DD, Smith WH, Beller GA. Comparison of rest thallium-201 imaging and rest technetium-99m sestamibi imaging for assessment of myocardial viability in patients with coronary artery disease and severe left ventricular dysfunction. J Am Coll Cardiol 1996;27:1592-7.
35. Medrano R, Lowry RW, Young JB, Weilbaecher DG, Michael LH, Afridi I, et al. Assessment of myocardial viability with ^{99m}Tc sestamibi in patients undergoing cardiac transplantation: a scintigraphic/pathologic study. Circulation 1996;94:1010-7.
36. Maes AF, Borgers M, Flameng W, Nuyts JL, Van de Werf F, Ausma JJ, et al. Assessment of myocardial viability in chronic coronary artery disease using technetium-99m sestamibi SPECT. J Am Coll Cardiol 1997;29:62-8.
37. Berger BC, Watson DD, Burwell LR, Crosby IK, Wellons HA, Teates CD, et al. Redistribution of thallium at rest in patients with stable and unstable angina and the effect of coronary artery bypass surgery. Circulation 1979;60:1114-25.
38. Iskandrian AS, Hakki A, Kane SA, Goel IP, Mundth ED, Hakki A, et al. Rest and redistribution thallium-201 myocardial scintigraphy to predict improvement in left ventricular function after coronary arterial bypass grafting. Am J Cardiol 1983;51:1312-6.
39. Ragosta M, Beller GA, Watson DD, Kaul S, Gimple LW. Quantitative planar rest-redistribution ^{201}Tl imaging in detection of myocardial viability and prediction of improvement in left ventricular function after coronary bypass surgery in patients with severely depressed left ventricular function. Circulation 1993;87:1630-41.
40. Pagley PR, Beller GA, Watson DD, Gimple LW, Ragosta M. Improved outcome after coronary bypass surgery in patients with ischemic cardiomyopathy and residual myocardial viability. Circulation 1997;96:793-800.
41. Sciagrà R, Bisi G, Santoro GM, Zerauschek F, Sestini S, Pedenovi P, et al. Comparison of baseline-nitrate technetium-99m sestamibi with rest-redistribution thallium-201 tomography in detecting viable hibernating myocardium and predicting postrevascularization recovery. J Am Coll Cardiol 1997;30:384-91.
42. Kitsiou AN, Srinivasan G, Quyyumi AA, Bacharach SL, Summers RM, Dilsizian V. Stress-induced reversible and mild-moderate irreversible thallium defects: are they equally accurate for predicting recovery of function after revascularization [abstract]? J Nucl Med 1996;5:25P.
43. Van Lingen A, Huijgens PC, Visser FC, Ossenkoppelle GJ, Hoekstra OS, Martens HJ, et al. Performance characteristics of a 511-keV collimator for imaging positron emitters with a standard gamma camera. Eur J Nucl Med 1992;19:315-21.
44. Srinivasan G, Kitsiou AN, Bacharach SL, Bartlett ML, Miller-Davis C, Dilsizian V. ^{18}[F]Fluorodeoxyglucose single photon emission computed tomography: can it replace PET and thallium SPECT for the assessment of myocardial viability? Circulation 1998;97:843-50.
45. Udelson JE. Steps forward in the assessment of myocardial viability in left ventricular dysfunction. Circulation 1998;97:833-8.
46. Petretta M, Cuocolo A, Nicolai E, Acampa W, Salvatore M, Bonaduce D. Combined assessment of left ventricular function and rest-redistribution regional myocardial thallium-201 activity for prognostic evaluation of patients with chronic coronary artery disease and left ventricular dysfunction. J Nucl Cardiol 1998;5:378-86.
47. Perrone-Filardi P, Pace L, Prastaro M, Squame F, Betocchi S, Soricelli A, et al. Assessment of myocardial viability in patients with chronic coronary artery disease: rest–4-hour–24-hour ^{201}Tl tomography versus dobutamine echocardiography. Circulation 1996;94:2712-9.
48. Bonow RO. Identification of viable myocardium. Circulation 1996;94:2674-80.
49. Baumgartner H, Porenta G, Lau Y, Wutte M, Klaar U, Mehrabi M, et al. Assessment of myocardial viability by dobutamine echocardiography, positron emission tomography and thallium-201 SPECT: correlation with histopathology in explanted hearts. J Am Coll Cardiol 1998;32:1701-8.
50. Rahimtoola SH. Importance of diagnosing hibernating myocardium: how and in whom? J Am Coll Cardiol 1997;30:1701-6.