Left ventricular dysfunction may be reversible if due to hibernating or stunned myocardium. There are several imaging techniques that help identify such patients in whom coronary revascularization may improve left ventricular function, quality of life, and prognosis. This paper will discuss some of these techniques.

RAHIMTOOLA first used the word hibernating to describe a condition of chronic reduction in coronary blood flow leading to decrease in contractile function that can be reversed by improving the coronary blood flow. It is now clear that even severe regional and global left ventricular (LV) dysfunction in patients with coronary artery disease (CAD) can be reversible. Irreversible dysfunction results from myocardial necrosis and scar tissue formation while reversible contractile dysfunction may be caused by stunning or hibernation. In hibernating myocardium, the chronic reduction in myocardial blood flow is thought to be matched by a "down regulation" of contractile function associated with alterations in substrate metabolism. Both the reduced contractile function and the altered metabolism have been considered to represent measures for reducing energy expenditures to ensure myocyte survival. Myocardial stunning, on the other hand, is a state of altered metabolic and contractile function that follows an ischemic episode (produced by either a decrease in supply or an increase in demand) and occurs despite restoration of myocardial blood flow. Stunning and hibernation may, in fact, coexist in many patients. Further, both types of contractile dysfunction may also coexist with normal myocardium or scar tissue in the same myocardial region. Metabolic activity is maintained as long as there is some residual myocardial blood flow to supply substrate and to remove inhibitory metabolites.

An important reason for the interest in detecting myocardial viability is related to the prognosis of patients with CAD and LV dysfunction. Medical therapy in these patients carries a high risk. In the CASS study, the seven-year survival was 35% with medical therapy and 63% with coronary artery bypass surgery. In those with ejection fraction (EF), survival is less than 25%, 15% with medical therapy, and 68% with surgery. It is, therefore, important to identify the patients who have reversible LV dysfunction. The decision for revascularization in most patients with CAD is based on symptoms, coronary anatomy, and LV function. However, in some patients, the knowledge that LV dysfunction is due to hibernating myocardium and, thus, reversible may also be important. Identification of viable myocardium is not in and of itself an indication of revascularization; nevertheless, improvement in EF after revascularization depends on several factors such as the extent of reversible dysfunction, suitability of coronary anatomy, peri operative events, and long-term patency of the conduits used in surgery (Table 1).

Methods of Assessment of Myocardial Viability

Positron Emission Tomography

One of the methods of assessing myocardial viability is positron emission tomography (Table
Currently, F-18 Fluorodeoxyglucose (FDG) is most commonly used for metabolic studies, although the study of oxidative metabolism using C-11 acetate may prove to be an even more attractive alternative.

Table 1. Factors affecting improvement in left ventricular function after coronary revascularization.

<table>
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<th>Factor</th>
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<td>Presence and extent of preoperative hibernation or stunning</td>
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<tr>
<td>Presence of suitable coronary anatomy</td>
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<td>Completeness of coronary revascularization</td>
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<td>Lack of perioperative necrosis</td>
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<td>Patency of the grafts</td>
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<td>Reliable method to detect improvement</td>
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<td>Left ventricular size</td>
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<td>Associated (unrelated) primary cardiomyopathy</td>
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Table 2. Methods of assessment of myocardial viability.

<table>
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<th>Method</th>
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<tr>
<td>Positron emission tomography</td>
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<tr>
<td>Single-photon imaging</td>
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<tr>
<td>Alternative imaging techniques: magnetic resonance imaging, echocardiography</td>
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<tr>
<td>Cardiac catheterization</td>
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<tr>
<td>Clinical evaluation including the electrocardiogram</td>
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<tr>
<td>Others</td>
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The traditional method for positron emission tomography (PET) studies in assessing viability is based on the use of two different tracers, one for measuring myocardial blood flow (Rb-82, 0-15 water, or N-13 ammonia) and the other for measuring myocardial glucose utilization (FOG). With PET, the abnormal area has a positive signal (increased FDG uptake) which is easier to detect than a negative signal (decreased uptake) as seen with thallium studies. The FDG is transported from the blood to the myocardium in proportion to glucose level, and it then competes with intracellular glucose for hexokinase. The phosphorylated tracer (FOG-6-phosphate) becomes trapped in the myocardium because it is a poor substitute for glycogen synthesis, glycolysis, dephosphorylation, and because the cell membrane is relatively impermeable to it. Approximately 40 to 60 min after the FOG injection, the tissue concentration represents the rate of the glucose utilization. The rate of regional utilization can be obtained using appropriate tracer models. Based on regional flow and FOG uptake, two patterns may be seen, flow-metabolism mismatch and flow-metabolism match. A mismatch pattern represents regionally reduced blood flow with increased glucose extraction. Conversely, a reduction in blood flow associated with normal glucose extraction (e.g., proportionately reduced blood flow and glucose utilization) is consistent with an admixture of normal and scar tissue. In the mismatch zones, the FOG uptake is equal or less than the normal myocardium but is greater relative to the regional flow. A match pattern represents reduction in both the flow and glucose uptake. Obviously, a normal myocardium also has normal flow and glucose uptake and, hence, represents another example of a match pattern. This pattern, however, is not an issue in viability assessment.

In 1986 Tillisch et al first reported the results of PET metabolic imaging in predicting reversibility of wall motion abnormality in patients with CAO. They used F-18 FDG/N-13 ammonia in 17 patients who subsequently had coronary artery bypass surgery. There were a total of 41 asynergic segments with a mismatch pattern (viable myocardium), and of those, 35 improved after surgery (positive predictive value, 85%). There were 26 segments with a matched decrease in perfusion and flow (scar), and of those, 24 did not improve after surgery (negative predictive value, 92%). In this study, Q-waves on the electrocardiogram predicted irreversibility in only 43% of the patients. In 1987 Brunken et al from the same group compared the results of FOG to thallium-201 in 12 patients. Fifteen of the 36 fixed defects on thallium (42%) had evidence of viability by PET. Since then, a number of studies have been done with similar conclusions (positive and negative predictive values of 80% to 85% each).

Single Photon Imaging

The regional concentration of thallium-201 depends on regional flow as a function of the cardiac output (fractionation or Sapirstein principle), the extraction fraction, clearance, and the partial volume effect. The last factor is important in regions of abnormal perfusion pattern due to ischemia or scar. For example, ischemia results in a decrease in wall thickening causing a partial volume effect, where the true
tissue concentration is underestimated. The degree of underestimation increases nonlinearly as the wall thickness decreases.

Since Pohost and associates introduced the single-injection technique in thallium imaging in 1977, the stress/4-h redistribution protocol has been widely used to characterize perfusion defects as fixed, partially reversible, or reversible. It was clear that the 4-h redistribution images underestimated reversibility and overestimated scar when compared to separate rest studies. Almost one-half of fixed perfusion defects may show improvement after coronary artery bypass surgery. Finally, as discussed earlier, there was clear evidence of presence of viability as assessed by metabolic imaging in areas of fixed thallium defects.

There are two modifications (which are not necessarily exclusive of each other) that have been thoroughly investigated and have received wide acceptance. These are the 24-h delayed imaging and the reinjection technique. In 1988 it was suggested that delayed thallium imaging obtained 12 to 24 h after stress showed improvement in reversibility in some fixed defects noted on the conventional 4-h delayed images. Late reversibility was detected in one or more segments in 62 of 118 patients (53%) and in two or more segments in 41 patients (35%). A total of 164 segments showed late reversibility. This constitutes 7% of total segments (normal and abnormal), 16% of all abnormal segments, (reversible or irreversible), and 22% of nonreversible segments alone. In these same patients, there were an additional 285 segments showing reversibility on the 4-h images. These segments constituted 27% of all abnormal segments. In 26 patients, there was an average of 4.5 late reversible segments per patient, representing 20% to 25% of LV myocardium. Thus, roughly 20% of patients had late reversibility of sufficient degree to be clinically relevant in patient management. The precise reason for continued improvement in the 24-h delayed images is not clear. However, it has been suggested that due to a very slow process of redistribution which is incomplete at four hours, tight coronary stenosis causes a decrease in the resting coronary blood flow. The drawbacks of the 24-h delayed imaging include patient inconvenience, increased imaging time, difficulty in identifying patients who are likely to benefit from such studies, and, more importantly, the low counts in the 24-h delayed images resulting in noisy and suboptimal image quality in many patients.

In 1990 Dilsizian, Rocco, and their associates described the reinjection technique. There are several modifications of this protocol. The reinjection technique is based on the principle that redistribution is affected by blood-thallium concentration. To increase the blood-thallium concentration, an additional dose of thallium-201 is injected prior to delayed imaging. This dose is smaller, roughly 30% to 50% of the initial dose injected. This technique therefore can be viewed as having features of both the stress/redistribution (the one-day) protocol and the stress/rest (two day) protocol. Dilsizian et al studied 100 patients with CAD, 92 of them had perfusion defects on the exercise study. Two mCi of thallium-201 was used for the exercise SPECT imaging and 1 mCi for the reinjection technique. There was a total of 260 defects on the stress images, 85 were fixed and the remaining were reversible. Of the 85 fixed defects on the 4-h redistribution images, 42 (49%) showed improvement with reinjection. A subset of 20 patients underwent balloon angioplasty. In these patients, 13 of 15 defects that were classified as viable by the reinjection technique had normal thallium and normal wall motion after angioplasty. On the other hand, eight of eight segments (100%) classified as fixed by the reinjection technique did not improve after angioplasty. A number of other studies have confirmed these observations. It appears that fixed defects, if mild or moderately severe, denote the presence of underlying viable myocardium, and metabolic imaging in these areas will almost always show activity consistent with viability. On the other hand, only 50% of severe fixed defects showed evidence of viability, and in these zones the reinjection and PET provided comparable results.

Rest-Redistribution Thallium Imaging

Several studies have suggested that in some patients with CAD, perfusion defects are seen in rest-thallium images that appear to be partially or completely reversible, consistent with resting
hypo-perfusion (hibernation). In general, these defects occur in segments subserved by coronary arteries with severe stenosis. A stress study is only necessary in the detection of ischemia and may not be relevant in patients with severe LV dysfunction if the dysfunction is due to hibernating myocardium or scar. Dilsizian et al found concordance between stress-reinjection and rest-redistribution thallium imaging in 72% of 594 segments in 41 patients. We studied 26 patients with CAD and LV dysfunction using rest-redistribution thallium images before and after coronary revascularization. The patients with normal thallium images or reversible resting perfusion defects showed improvement in EF after revascularization.

Ragosta et al studied 21 patients with LV dysfunction (mean ejection fraction of 27%), before and after coronary artery bypass surgery, using rest-redistribution thallium-201 (planarquantitative method) and radionuclide ventriculography. Their definitions of viability were as follows: normal viability implied normal initial uptake or complete redistribution; mild reduction of viability implied mild defect with or without partial redistribution or severe defect with partial redistribution, and severe reduction of viability implied severe defect with no redistribution. Segments with normal wall motion or mild hypokinesia had a pattern of normal or mild reduction of viability. Of interest is that of segments with severe wall motion abnormality, only 27% had a pattern of severe reduction of viability. Almost 60% of segments with normal or mild reduction of viability improved after surgery compared to 23% of segments with severe reduction of viability. As discussed earlier, functional improvement depends on viability and adequacy of revascularization. For example, when only viability criteria were used, the predictive value for functional improvement was 57%, but when adequacy of revascularization was also considered, the predictive value was 73%. The greatest improvement in EF after surgery occurred in patients with multiple viable segments. In patients with severe reduction in viability or only a few viable segments, there was no significant improvement. These findings may provide guidelines for recommending coronary revascularization in patients with CAD with evidence of LV dysfunction who have minimal or no symptoms of angina pectoris.

Sabia et al found that the amount of thallium in the redistribution image in the infarct zone to correlate with baseline wall motion abnormality and to predict improvement in wall motion after coronary revascularization. These results were obtained in patients with acute myocardial infarction and occluded infarct-related arteries. An important observation from these studies, therefore, is that incorporation of wall motion assessment improves the ability to characterize myocardial viability. For example, the presence of normal or only mild hypokinesia in segments showing fixed defects is, in itself, an indication of myocardial viability. On the other hand, the presence of dyskinesia or akinesis may be due to scar, or to viable but stunned or hibernating myocardium. Inotropic stimulation (nitroglycerin, dobutamine, or both), postextrasystolic potentiation, and improvement in wall motion in post-exercise recovery period have been suggested as alternative techniques for detecting viable myocardium. Wall motion assessment provided by contrast ventriculography, echocardiography, or radionuclide angiography should be incorporated in the algorithm in myocardial viability assessment. Segments showing improvement in regional function with small doses of dobutamine have viable myocardium and show improvement after revascularization. On the other hand, segments remaining akinetic or dyskinetic during dobutamine infusion do not show any improvement.

We examined the importance of viability as a clinical issue in 532 patients with angiographically proven CAD who underwent exercise SPECT thallium imaging. Conventional 4-h delayed images were used to differentiate scar from ischemia based on analysis of 20 segments per patient. There were 90 patients (17%) with normal images, 274 patients (52%) with reversible defects, and 168 patients (31%) with fixed defects, with or without associated reversible defects. The patients with fixed defects were subdivided according to the number of segments with fixed defects and the number of additional reversible defects. There were 114 patients with fixed defects alone or more fixed than reversible defects.
Contrast ventriculography in these 114 patients revealed normal wall motion or EF in 50 patients. On the basis of results of thallium imaging alone, the issue of viability would have been considered important in 114 patients or 21% of the total population; however, when the wall motion data were also included, the issue was significant only in 64 patients or 12% of the total population.

**Technetium Agents**

In animal models, there is a good correlation between infarct size and sestamibi images. More recently, a similar good correlation was seen in excised hearts in patients undergoing cardiac transplantation. In these patients, sestamibi was injected a few hours before removal of the heart. The heart was then examined histologically and imaged. There was excellent correlation between infarct size and sestamibi images in the intact heart and on slice per slice analysis. These results and the experimental data suggest that sestamibi should be a useful agent to study viability. On the other hand, teboroxime appears to be a flow agent only.

There is good agreement between sestamibi and thallium-201 imaging in characterizing perfusion defects as normal, reversible, and nonreversible in patients undergoing exercise studies. Sestamibi-gated images (planar or SPECT) permit assessment of perfusion pattern, wall thickening, wall motion, and EF. Also, simultaneous first-pass radionuclide angiography allows assessment of wall motion and EF. It should be noted that viability (by FDG) may exist in regions with reduced wall thickness or even no systolic thickening. Marzullo et al studied 14 patients and found that sestamibi overestimated scar as compared to thallium. Cuocolo et al studied 20 patients with LV dysfunction. These patients had a total of 122 fixed defects by thallium-201 redistribution imaging. Of those, 100 appeared fixed and 22 reversible by sestamibi imaging.21 When the reinjection thallium technique was used, 57 of the 122 fixed thallium defects at 4 h showed reversibility (47%) and the remaining 65 (53%) remained unchanged. Therefore, of the total 122 fixed defects, 57 were reversible by the reinjection technique and only 22 by sestamibi. This study also suggested that thallium imaging is preferable to sestamibi in assessing viability.

Recent evidence, however, suggests that although sestamibi does not show as much redistribution as thallium-201, some redistribution may occur. One may take advantage of this phenomenon in rest studies and obtain the images 3 to 4 h (rather than 1 h) after injection. The delayed sestamibi rest images may show better evidence of viability than the conventional rest images. It is, therefore, conceivable that modification of the imaging technique, quantitation of the severity of the perfusion abnormality, and additional information from gated imaging and wall motion abnormalities may, indeed, improve the ability of sestamibi to characterize perfusion defects. Rest images (gated or ungated) have also shown more reversibility after sublingual nitroglycerin administration. For example, nitrate administration may enhance detection of reversibility. More work needs to be done to select the best imaging protocol and best parameters to assess viability with sestamibi.

**Radiolabeled Fatty Acids**

The prototype for cardiac imaging is 1-123 para-phenyl-penta-decaonic acid (IPPA). In canine studies, approximately 95% of the myocardial IPPA uptake occurs in the first 2 to 3 min after intravenous injection. The clearance is biexponential. The early phase has a half-life of 5 to 10 min and reflects beta-oxidation. A late phase has a half-life of over 120 min and reflects turnover and incorporation of fatty acid into triglyceride and phospholipid pools. Maurray and colleagues have recently evaluated 1-123 IPPA as a myocardial viability agent and correlated the results with transmural myocardial biopsy in 15 patients with CAD and LV dysfunction.23 The patients underwent imaging using 1 mCi of 1-123 IPP A injected intravenously and imaged with a multicrystal camera and results were correlated with transmural myocardial biopsy specimens. Resting akinesis or dyskinesia was present in 20 of 22 infarcted territories but 16 of the 22 segments (73%) were metabolically viable. Compared to biopsy results, metabolic evidence for viability had a sensitivity of 92% and a specificity of 86%. It remains to be determined whether a rapid imaging protocol with a multihead SPECf detector can more clearly define the regional
uptake and clearance rates. We examined the ability of dynamic SPECf I-123-IPPA imaging to detect myocardial viability in 18 patients with LV dysfunction due to CAD (EF, 35 ± 12%). Serial 1800 SPECT images (five sets, 8 min each) were obtained starting at 4 min after injection of 2 to 6 mCi of IPP A at rest. The uptake in each of 20 segments per patient was compared to that of rest/ redistribution thallium-201 images. The IPP A images showed 11 I 15 abnormal segments per patient. Of the 191 abnormal segments, 118 were reversible and 73 were fixed on serial imaging (29 mild-to-moderate and 44 severe). The rest! redistribution thallium images showed 10 I 5 segmental perfusion defects per patient. Of the total of 171 perfusion defects, 36 were reversible, 47 were mild to moderately fixed, and 88 were severely fixed. There was a 91% agreement between IPP A and thallium (normal versus abnormal) (kappa = 0.81 I 0.03) and 71% agreement for all categories (normal, reversible, and fixed) (kappa = 0.55 I 0.04). In 11 patients, the EF was repeated after coronary revascularization, and it improved from 31 I 12% to 37 I 12% (P < 0.01); the EF improvement was more in patients with multiple IPP A defects. Thus, dynamic I-123-IPPA imaging is a new technique to assess myocardial viability.

Cardiac Catheterization

Although coronary angiography and contrast ventriculography are the "gold standard" for assessment of LV function and CAD, they have limited applications for the study of myocardial viability. As addressed earlier, viability is not an issue in patients with normal or near normal wall motion. The degree of coronary stenosis and extent of CAD are of little help in detecting and assessing viability. Sabia and associates assessed collaterals using contrast echocardiography with sonicated contrast material (containing micro bubbles of air with a mean diameter of 6 micrograms) in patients with recent infarction and occluded infarct arteries. 19 They observed collateral flow in many patients who had no angiographically visible collaterals. Restoration of the antegrade flow with revascularization improved regional function provided that the degree of collateralization was adequate. The degree of improvement in the regional function was dependent on the percent of the occluded bed perfused by the collateral flow.

The degree of LV dilation, which is a compensatory mechanism to the declining contractile function, has not been adequately studied as a marker of viability. Intuitively, LV dilation may occur as a response to a decrease in EF and remodeling regardless whether that is due to scar or hibernation. It is of interest to note, nevertheless, that LV volume is an important prognosticator in patients with CAD.

As discussed earlier, the electrocardiogram is also not a reliable predictor of viability. Similarly, the clinical manifestations may not be very helpful. The patients with LV dysfunction, whether due to scar or hibernation, may be asymptomatic or may have symptoms of congestive heart failure. Mahmarian et al studied 100 patients with acute myocardial infarction and showed thallium redistribution in 60% of the infarct zones.25 Similar to the study of Sabia et al, infarct artery patency did not predict redistribution. In fact, 77% of the occluded vessels with collaterals had evidence of thallium redistribution. Thus, collateral blood flow may be sufficient to maintain viability for many weeks after acute infarction in some patients.

Conclusion

LV dysfunction, even if severe, may be reversible after coronary revascularization if due to viable myocardium. In such patients, myocardial hibernation and stunning are the pathophysiologic mechanisms for dysfunction. Coronary revascularization in properly selected patients results in improvement in functional class and survival. The current scintigraphic methods for detection of viable myocardium depend on measurements of myocardial blood flow, metabolism, and cell membrane integrity. The rest-distribution thallium imaging is a cost-effective method that is widely available. The choice of a given technique depends on viable resources and local expertise. Assessment of wall motion and thickening during dobutamine infusion may also be useful.
References
