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 \(^{18}\text{F}\)-Fluorodeoxyglucose

Robert O. Bonow, MD; Vasken Dilsizian, MD; Alberto Cuocolo, MD; and Stephen L. Bacharach, PhD

In patients with chronic coronary artery disease and left ventricular dysfunction, the distinction between ventricular dysfunction arising from myocardial fibrosis and ischemic, but viable, myocardium has important clinical implications. By positron emission tomography (PET), enhanced fluorine-18–labeled fluorodeoxyglucose (FDG) uptake in myocardial segments with impaired function and reduced blood flow is evidence of myocardial viability. Rejection of thallium-201 at rest immediately after stress–redistribution imaging may also provide evidence of myocardial viability by demonstrating thallium uptake in regions with apparently “irreversible” defects. To compare these two methods, we studied 16 patients with chronic coronary artery disease and left ventricular dysfunction (ejection fraction, \(27\pm9\%\)), all of whom had irreversible defects on standard exercise–redistribution thallium single-photon emission computed tomography (SPECT) imaging. Thallium was reinjected immediately after the redistribution study, and SPECT images were reacquired. The patients also underwent PET imaging with FDG and oxygen-15–labeled water. A total of 432 myocardial segments were analyzed from comparable transaxial tomograms, of which 166 (38%) had irreversible thallium defects on redistribution images before reinjection. FDG uptake was demonstrated in 121 (73%) of these irreversible defects. Irreversible defects were then subgrouped according to the degree of thallium activity, relative to peak activity in normal regions. Irreversible defects with only mild (60–85% of peak activity) or moderate (50–59% of peak) reduction in thallium activity were considered viable on the basis of FDG uptake in 91% and 84% of these segments, respectively. In contrast, in irreversible defects with severe reduction in thallium activity (<50% of peak), FDG uptake was present in 51% of segments. In such severe defects, an identical number of segments (51%) demonstrated enhanced uptake of thallium after reinjection. In these severe “irreversible” defects, data on myocardial viability were concordant by the two techniques in 88% of segments, with 45% identified as viable and 43% identified as scar on both PET and thallium reinjection studies. These observations suggest that thallium imaging can be used to identify viable myocardium in patients with chronic coronary artery disease and left ventricular dysfunction. Most irreversible defects with only mild or moderate reduction in thallium activity represent viable myocardium as confirmed by FDG uptake. In myocardial regions with severe irreversible thallium defects on standard exercise–redistribution thallium imaging, thallium reinjection identifies as viable or nonviable, with few exceptions, the same regions as does PET imaging with FDG. (Circulation 1991;83:26–37)

In patients with chronic coronary artery disease and impaired left ventricular function, the distinction between ventricular dysfunction arising from myocardial fibrosis and ischemic, but viable, myocardium has important clinical implications.

Metabolic imaging with positron emission tomography (PET) has emerged as a new and promising method for assessing myocardial viability in regions.

From the Cardiology Branch, National Heart, Lung, and Blood Institute and the Department of Nuclear Medicine, Clinical Center, National Institutes of Health, Bethesda, Md.

Address for correspondence: Robert O. Bonow, MD, Building 10, Room 7B-15, National Institutes of Health, Bethesda, MD 20892.

Received April 17, 1990; revision accepted September 11, 1990.
with impaired function and reduced blood flow in such patients.\textsuperscript{1–7} It has been demonstrated that 38–47\% of myocardial regions with irreversible perfusion defects according to exercise–redistribution thallium-201 scintigraphy are metabolically active, and hence viable, by PET.\textsuperscript{8–11} However, recent studies show that reinjection of thallium after redistribution imaging may result in enhanced thallium uptake within apparently irreversible thallium defects, which is compatible with viable myocardium.\textsuperscript{12,13} Moreover, the frequency of increased thallium uptake after reinjection (31\% to 49\%) in such “irreversible” defects is similar to the frequency of preserved metabolic activity reported with PET. Revascularization studies also show a similar frequency of improved perfusion and wall motion after revascularization in regions identified as viable or nonviable by both PET\textsuperscript{5,7} and thallium reinjection\textsuperscript{12,14} techniques. In the present study, we directly compared the results of metabolic PET imaging with fluorine-18–labeled fluorodeoxyglucose (FDG) and those of exercise thallium scintigraphy with rest reinjection in patients with chronic coronary artery disease and left ventricular dysfunction.

\section*{Methods}

\subsection*{Patient Selection}

We studied 16 patients with angiographically proven chronic multivessel coronary artery disease and left ventricular dysfunction. There were 15 men and one woman, ranging in age from 45 to 79 years (mean, 60±10 years). Patients were selected for study on the basis of left ventricular dysfunction and at least one irreversible thallium perfusion defect on standard tomographic exercise–redistribution thallium scintigraphy. Left ventricular ejection fractions by radionuclide angiography ranged from 16\% to 47\% (mean, 27±9\%) at rest. Although all patients had evidence of previous myocardial infarction, we studied only patients with chronic stable coronary artery disease; no patient had an acute myocardial infarction or unstable angina within 6 months of the study. Coronary arteriography demonstrated significant stenosis (≥50\% reduction in luminal diameter) of all three major epicardial coronary arteries in 10 patients and of two coronary arteries in the other six patients. All patients had at least one totally occluded epicardial coronary artery, and 10 patients had at least two totally occluded arteries. Patients underwent thallium scintigraphy and PET imaging after withdrawal of all antianginal medications.

\subsection*{Thallium SPECT Imaging}

All patients underwent exercise thallium-201 single-photon emission computed tomography (SPECT) as previously described.\textsuperscript{12} After an overnight fast, patients underwent treadmill exercise according to a standardized multistage exercise protocol, with continuous monitoring of heart rate and rhythm, blood pressure, and symptoms. Eleven patients achieved more than 85\% of maximal predicted heart rate during exercise. At peak exercise, 2 mCi thallium-201 was injected intravenously, and the patient continued exercise for an additional 30–45 seconds. After termination of exercise, thallium images were obtained with a wide-field-of-view rotating gamma camera equipped with a low-energy, medium resolution, high-sensitivity collimator centered on the 68 keV photo peak with a 20\% window. The camera was rotated through a 180° arc in an elliptical orbit about the patient’s thorax from 40° right anterior oblique to 40° left posterior oblique at 6° increments for 30 seconds each. Redistribution images were obtained at rest 4 hours after the injection of thallium by identical imaging methods. During the period between the exercise and redistribution acquisitions, patients were ambulatory and remained in the fasting state. Immediately after redistribution imaging, all patients received an additional 1 mCi thallium-201 at rest, and a third set of images was reacquired within 10–15 minutes of the second administered dose by use of the same imaging protocol. From the raw scintigraphic data, the exercise, redistribution, and reinjection data were reconstructed as tomographic images oriented along the three standard orthogonal planes of the left ventricle. The data were also displayed separately as a series of whole body transaxial tomograms for direct comparison with the corresponding PET images as described below.

\subsection*{Positron Emission Tomography}

Patients underwent PET studies to assess regional myocardial perfusion with oxygen-15–labeled water and exogenous glucose utilization with FDG. Imaging was performed with a whole body PET camera producing 21 contiguous tomograms spaced 5.1 mm apart with a slice thickness of 13 mm and an in-plane resolution of 7 mm. Images were obtained perpendicular to the long axis of the body to create a series of transaxial tomograms.

Patients were studied after an overnight fast. Before imaging, patients ingested a solution containing 50 g glucose and then underwent a 20-minute transmission scan to correct for attenuation. Two separate injections of 12–15 mCi \textsuperscript{15}O-water were then administered intravenously, 12 minutes apart. For each \textsuperscript{15}O-water study, dynamic PET data were acquired continuously, beginning immediately before the injection and for the next 5 minutes (ten 3-second scans, followed by six 10-second scans, followed by seven 30-second scans) to determine the left ventricular blood pool and myocardial time–activity curves of the tracer. At least 15 minutes after the second \textsuperscript{15}O-water injection, we administered 5 mCi FDG with continuous acquisition of data for the next 60–75 minutes. The data acquired at 30 minutes after injection, corresponding to the final 30–45 minutes of data acquisition, were reconstructed to create tomographic images of regional myocardial FDG uptake. Careful attention was focused on maintaining constant patient position within
the scanner for the duration of the study, from the beginning of the transmission scan until the completion of FDG data acquisition.

Data Analysis

In each patient, corresponding transaxial tomograms from the three sets of thallium images representing the exercise, redistribution, and reinjection studies were aligned for direct comparison. These, in turn, were then aligned with the corresponding transaxial tomographic images of myocardial FDG uptake from the PET study. Thus, multiple, corresponding myocardial slices from the PET and SPECT data were analyzed for each patient, with an average of six tomographic planes evaluated per patient. The regional FDG and corresponding thallium activities were then graded by three observers on a five-point scale, in which grade 0 represents absent activity and grade 4 represents normal or peak activity.

To facilitate and objectify the comparison of relative regional FDG and thallium activity, myocardial regions of interest were constructed on each FDG tomogram and the three corresponding thallium images. Regional FDG and thallium activities were then computed within each region of interest. Five regions were drawn on each tomographic image, representing the posterolateral, anterolateral, anteropical, anteroapical, and posteroseptal myocardium (Figure 1); in the more cephalal tomographic planes, in which the interventricular septum is shortened, a single region was drawn to encompass the entire septum, resulting in a total of four regions of interest per tomographic slice. A total of 432 myocardial regions were evaluated, averaging 27 per patient.

Regional myocardial thallium activity. In each patient, the myocardial region of interest with the maximum counts on the exercise thallium study was used as the normal reference region for that patient. The corresponding regions in the redistribution and reinjection thallium studies were identified and used as the reference region for those studies. The thallium activity in all other myocardial regions was then expressed as a percentage of the activity measured in the reference region for each of the exercise, redistribution, and reinjection image series.

For each exercise study, thallium activity in any myocardial region measuring less than 85% of the normal reference region was considered reduced and defined as a thallium perfusion defect. On the basis of previous reproducibility measurements in our laboratory, we defined a regional perfusion defect with exercise as reversible if relative thallium activity increased by 10% or more on the subsequent redistribution image. Such reversible defects were further classified as completely reversible on the redistribution study if thallium counts in that region achieved 85% or more activity relative to the reference region and as partially reversible if relative thallium activity remained less than 85% of the activity in the reference region. Perfusion defects on exercise were defined as irreversible if relative thallium activity was unchanged or increased less than 10% on the subsequent redistribution study. For purposes of comparison with the PET data, these irreversible thallium defects on redistribution imaging were subgrouped on the basis of the severity of reduction in thallium activity: mild (60–84% of peak activity), moderate (50–59% of peak), and severe (<50% of peak) thallium defects. Examples of these three types of irreversible perfusion defects are shown in Figure 2. Irreversible defects classified as mild or moderate had visually apparent, albeit reduced, thallium uptake on visual analysis of the tomographic images (grades 1–3), whereas thallium uptake was visually absent (grade 0) in severe irreversible defects (Figure 2).

Similar methods were used for objective analysis of the thallium reinjection data. Regions with either irreversible defects or partially reversible defects on the redistribution study were considered to have enhanced thallium uptake after reinjection of the
isotope if relative thallium activity increased more than 10% compared with the redistribution data and were considered unchanged if thallium activity was unaltered or increased by less than 10% after reinjection. In addition, a severe irreversible defect on redistribution imaging was also considered irreversible after reinjection, regardless of the magnitude of increase in thallium activity, if the activity in that region after reinjection remained less than 50% of the normal reference region.

Regional myocardial FDG uptake. Relative regional FDG uptake was assessed using analogous methods to those used for analysis of the thallium tomograms. The myocardial region on the FDG image series that corresponded to the normal reference region on the thallium exercise image series was used as the normal reference region for relative FDG uptake. FDG activity in all other myocardial regions was then expressed as a percentage of the activity in this reference region. The quantitative regional FDG data were interpreted by relating the FDG activity to regional blood flow values as described below.

Regional myocardial blood flow. We computed absolute regional myocardial blood flow from the dynamic $^{15}$O-water data. The FDG image series was reviewed for each patient to identify the appropriate tomographic levels in which the left ventricular cavity was well defined. An average of four such tomographic levels were identified per patient. Left ventricular cavity regions of interest were manually constructed on these FDG tomograms and were then applied directly to the corresponding tomographic $^{15}$O-water data to derive a composite ventricular blood pool time–activity curve of the tracer. This ventricular time–activity curve was then used as the $^{15}$O arterial input function. Previous studies in our laboratory and others demonstrate that the blood pool time–activity curve computed in this manner accurately represents instantaneous arterial concentrations of $^{15}$O-water.

The myocardial regions of interest previously constructed on the FDG images for measurement of regional FDG activity were then applied to the corresponding tomographic $^{15}$O-water data to derive the regional myocardial $^{15}$O time–activity curve. Using the $^{15}$O arterial input function, the myocardial $^{15}$O time–activity curve, and an assumed partition coefficient for $^{15}$O-water of 0.92, absolute regional myocardial blood flow was computed by a modification of the methods of Fida et al. and Herrero et al. that automatically accounts for partial volume and spill-over effects. In regions judged to have normal thallium uptake on both exercise and redistribution studies, the regional blood flow values by $^{15}$O-water ranged from 0.74 to 1.59 ml/g/min (mean, 1.00±0.18 ml/g/min), which is similar to previous data reported for normal human subjects.

Regional FDG uptake relative to blood flow. The regional FDG data were then interpreted in relation to regional myocardial blood flow. FDG activity in each region of interest was classified as normal (≥80% of activity in the normal reference region associated with normal blood flow), reduced (50–79% of normal reference activity with proportionately reduced blood flow), absent (<50% of normal reference activity), or ischemic (normal or increased FDG activity associated with reduced myocardial blood flow). All regions with absent FDG activity were considered to indicate myocardial fibrosis. Because FDG uptake was evident in regions with reduced FDG uptake, these regions were considered to represent a mixture of viable and fibrotic myocardium. Regions with relative increases in FDG uptake were considered normal rather than ischemic if there was a proportionate increase in regional myocardial blood flow.

Blood flow and FDG to blood flow ratio images. Tomographic images of regional myocardial blood flow were then created to correspond to each FDG tomogram, by use of the myocardial regions of interest previously drawn on the FDG images. By assigning the appropriate blood flow value, corrected for partial volume and spillover effects, to each myocardial region of interest, we constructed functional images depicting regional myocardial blood flow.
TABLE 1. Regional FDG Uptake on PET and Thallium Uptake on Stress–Redistribution Imaging

<table>
<thead>
<tr>
<th>Imaging</th>
<th>Myocardial regions (n)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regional FDG uptake on PET imaging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>180</td>
<td>42</td>
</tr>
<tr>
<td>Ischemic</td>
<td>78</td>
<td>18</td>
</tr>
<tr>
<td>Reduced</td>
<td>111</td>
<td>26</td>
</tr>
<tr>
<td>Absent</td>
<td>63</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>432</td>
<td>100</td>
</tr>
<tr>
<td>Regional thallium uptake on stress–redistrib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tion imaging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>86</td>
<td>20</td>
</tr>
<tr>
<td>Completely reversible defect</td>
<td>75</td>
<td>18</td>
</tr>
<tr>
<td>Partially reversible defect</td>
<td>105</td>
<td>24</td>
</tr>
<tr>
<td>Irreversible defect</td>
<td>166</td>
<td>38</td>
</tr>
<tr>
<td>Reduction in thallium activity within irreversible defects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (60–84% of peak)</td>
<td>53</td>
<td>12</td>
</tr>
<tr>
<td>Moderate (50–59% of peak)</td>
<td>45</td>
<td>10</td>
</tr>
<tr>
<td>Severe (&lt;50% of peak)</td>
<td>68</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>432</td>
<td>100</td>
</tr>
</tbody>
</table>

FDG, fluorine-18–labeled fluorodeoxyglucose; PET, positron emission tomography.

addition, by dividing FDG activity within each myocardial region of interest by the corresponding blood flow value, we constructed functional images of the ratio of regional FDG uptake to blood flow.

Statistical Analysis

The comparison of regional uptake of thallium and of FDG uptake relative to blood flow was performed with χ² analysis.

Results

Regional FDG Activity

Of the total 432 myocardial regions evaluated in the 16 patients, 180 (42%) had normal FDG uptake and regional blood flow, 78 (18%) had an ischemic pattern with increased FDG uptake relative to reduced regional blood flow, 111 (26%) had reduced FDG uptake, and 63 (14%) had absent FDG uptake (Table 1). All 63 regions with absent FDG uptake by objective analysis also had reduced myocardial blood flow; by visual analysis, 56 of these 63 regions (89%) also had no discernible FDG uptake (grade 0), and the other seven regions had greatly reduced FDG activity (grade 1). These 63 regions were considered to represent myocardial fibrosis by PET. In the 111 regions with reduced FDG activity, 101 regions (91%) had FDG uptake that was visually apparent though reduced (grades 1–2). Because FDG uptake was evident in these regions, these regions were interpreted as representing a mixture of viable and fibrotic myocardium, and they were grouped together with the regions with normal and ischemic FDG–blood flow patterns as regions with viable myocardium. Thus, only those regions with absent FDG uptake were considered metabolically inactive and nonviable.

Regional Thallium Activity

On the basis of the standard exercise–redistribution thallium studies (Table 1), 86 of the 432 myocardial regions (20%) were considered normal, 75 (18%) had perfusion defects during exercise that were completely reversible, and 105 (24%) had perfusion defects with exercise that were partially reversible. Thallium uptake in these regions, with exercise or on redistribution imaging, was interpreted as evidence for viable myocardium by standard thallium imaging. This was confirmed by FDG uptake in 94% of these regions. The remaining 166 myocardial regions (38% of the total) had thallium defects during exercise that were irreversible on the redistribution study. Of these 166 regions with irreversible thallium defects (Table 1), 53 had mild reduction in thallium activity (with a mean activity of 74% of peak activity), 45 had moderate reduction in thallium activity (mean, 56% of peak activity), and 68 had severe reduction in thallium activity (mean, 33% of peak activity). We then turned our attention to evidence of viable myocardium within these fixed perfusion defects.

Evidence for Viable Myocardium Within Irreversible Thallium Defects

The results of FDG imaging in the 166 segments with irreversible thallium defects on redistribution images are shown in Table 2. FDG uptake occurred in 121 of these regions (73%). However, the frequency of FDG uptake depended on the severity of the thallium defect. FDG uptake occurred in 48 (91%) of the 53 regions with only mild reduction in thallium activity and in 38 (84%) of the 45 regions with moderate reduction in thallium activity. In contrast, FDG uptake occurred in only 35 (51%) of the 68 regions with severe reduction in thallium activity (Table 2). The frequency of FDG uptake in these latter, severe thallium defects was significantly less than that observed in defects with mild or moderate reduction in thallium activity (both p<0.001).

The results of thallium reinjection in the segments with irreversible thallium defects on redistribution imaging are also presented in Table 2. Increased thallium activity after thallium reinjection was evident in 78 of the 166 regions (47%), which is significantly less than the frequency of FDG uptake (p<0.001). In particular, 52 of 88 regions (59%) with no increase in thallium activity after reinjection had FDG uptake. These apparently discordant results between FDG uptake and thallium uptake after reinjection were then explored by accounting for the severity of the irreversible thallium defect (Table 2). This discordance was greatest in those regions with irreversible thallium defects with only mild or moderate reduction in thallium activity after redistribution, in which the vast majority manifested FDG uptake.
TABLE 2. Irreversible Thallium Defects on Redistribution Imaging: Patterns of FDG Uptake and Thallium Uptake After Reinjection

<table>
<thead>
<tr>
<th>Defect</th>
<th>Total</th>
<th>+</th>
<th>–</th>
</tr>
</thead>
<tbody>
<tr>
<td>All irreversible thallium defects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With FDG uptake</td>
<td>121</td>
<td>69</td>
<td>52</td>
</tr>
<tr>
<td>Without FDG uptake</td>
<td>45</td>
<td>9</td>
<td>36</td>
</tr>
<tr>
<td>Total</td>
<td>166</td>
<td>78</td>
<td>88</td>
</tr>
<tr>
<td>Severity of irreversible thallium defects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (60–84% of peak activity)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With FDG uptake</td>
<td>48</td>
<td>18</td>
<td>30</td>
</tr>
<tr>
<td>Without FDG uptake</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>22</td>
<td>31</td>
</tr>
<tr>
<td>Moderate (50–59% of peak activity)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With FDG uptake</td>
<td>38</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Without FDG uptake</td>
<td>7</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>Severe (&lt;50% of peak activity)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With FDG uptake</td>
<td>35</td>
<td>31</td>
<td>4</td>
</tr>
<tr>
<td>Without FDG uptake</td>
<td>33</td>
<td>4</td>
<td>29</td>
</tr>
<tr>
<td>Total</td>
<td>68</td>
<td>35</td>
<td>33</td>
</tr>
</tbody>
</table>

FDG, fluorine-18-labeled fluorodeoxyglucose; +, enhanced thallium uptake after reinjection; –, no enhanced thallium uptake after reinjection.

In contrast, among the myocardial regions with irreversible thallium defects characterized as having severe reduction in thallium activity, the results of thallium reinjection were identical to those of FDG imaging: enhanced thallium uptake after reinjection occurred in 35 (51%) of the 68 regions (Table 2). There was a concordance of data regarding myocardial viability by both FDG and thallium reinjection studies in 60 regions (88%), with 31 (45%) identified as viable and 29 (43%) identified as scar (Table 2). In the eight regions (12%) with discordance between the thallium reinjection and FDG data, an equal number of regions had FDG uptake alone or thallium uptake alone after reinjection (four regions each). Corresponding tomographic PET and thallium images in two patients with severe irreversible thallium defects on redistribution imaging are shown in Figures 3 and 4, demonstrating the comparable nature of the FDG and thallium reinjection data.

FDG activity in severe irreversible thallium defects. We then examined the pattern of FDG activity in these severe irreversible defects on redistribution imaging (Figure 5). FDG uptake was absent in 33 regions. A pattern of normal or ischemic FDG activity occurred in only 11 regions, all of which showed increased thallium activity after reinjection. FDG uptake was present, but reduced, in the other 24 regions. Thus, in regions with severe irreversible thallium defects on redistribution imaging, FDG uptake, when present, was usually reduced in proportion to reduced blood flow rather than increased relative to blood flow. The ischemic pattern of enhanced FDG uptake in relation to blood flow (that is, FDG–blood flow “mismatch”) occurred in only six of the 35 regions (17%) with FDG uptake.

Thallium Activity in Relation to Patterns of FDG Uptake

Regions with FDG–blood flow mismatch. An ischemic pattern of FDG uptake was observed in 78 myocardial regions (Table 3). Most of these regions (64%) were not associated with irreversible thallium defects; stress–redistribution thallium imaging revealed normal regional thallium uptake in seven regions (9%), completely reversible perfusion defects in 16 regions (20%), and partially reversible defects in 27 regions (35%). Among the remaining 28 regions (36%) that did have associated irreversible defects on redistribution studies, 16 had mild reduction in thallium activity, six had moderate reduction in thallium activity, and only six (8%) had severe reduction in thallium activity. All six of these regions with severe irreversible thallium defects had enhanced uptake of thallium after reinjection. These results were similar to those observed in regions in which FDG uptake was normal (Table 3).

Regions with reduced versus absent FDG uptake. We classified the 111 regions with reduced FDG activity (50–79% of normal reference activity) as representing viable myocardium. This was supported by the thallium data in most regions (Table 3). Exercise–redistribution thallium imaging revealed either normal uptake or reversible ischemia in 60 regions (54%). Of the remaining 51 regions (46%) with irreversible defects, only 24 were associated with severe reduction in thallium activity, and 20 of these 24 regions showed enhanced uptake of thallium after reinjection. In comparison, regions with absent FDG activity (<50% of normal reference activity) had a higher prevalence of irreversible thallium defects, most of which were associated with severe reduction in thallium activity that did not increase after thallium reinjection.

Discussion

In many patients with chronic coronary artery disease, impaired left ventricular function under resting conditions arises, at least in part, from regions of ischemic or hibernating myocardium rather than from myocardial fibrosis.20–22 In such patients, ventricular function may improve considerably, and even normalize, after revascularization procedures.1,2,3,23–26 Thus, left ventricular dysfunction in chronic coronary artery disease may represent a potentially reversible instead of an irreversible process, and the identification of ischemic, but viable, myocardium has important clinical implications.

The assessment of myocardial viability by using standard imaging techniques is often imprecise. No criteria have been identified to accurately distinguish hibernating myocardium from myocardial fibrosis on the basis of regional ventricular function measure-
ments obtained by contrast ventriculography, radionuclide angiography, or echocardiography. Moreover, several studies have demonstrated that between 25% and 50% of patients with apparently irreversible perfusion defects on exercise-redistribution thallium imaging will manifest normal thallium uptake and improved regional wall motion at rest after revascularization. Thus, thallium scintigraphy, as routinely performed as an exercise study followed by a 3–4-hour redistribution study, may be inadequate in identifying viable myocardium.

In contrast to these relatively poor results with standard thallium imaging, metabolic imaging using PET technology has emerged as a promising method for identifying viable myocardium in patients with compromised left ventricles. Of note, some of these studies included patients with recent myocardial infarctions rather than studying only patients with chronic coronary artery disease and left ventricular dysfunction. The demonstration by PET of maintained or enhanced glycolytic activity, as estimated by the uptake of FDG, in regions with impaired function and reduced blood flow, has been shown to be accurate for the differentiation of viable myocardial tissue from scar in patients with coronary artery disease, with a positive predictive value of 78–85% and a negative predictive value of 78–92% for predicting improvement in regional left ventricular function after revascularization.

Metabolic imaging with PET has also been shown to be superior to standard exercise–redistribution thallium imaging in such patients. In studies comparing the results of metabolic PET imaging with FDG to those obtained using tomographic thallium imaging in which regional thallium uptake could be compared directly with regional FDG uptake from matched tomographic planes, 38–47% of regions with apparently irreversible thallium defects exhibited evidence of preserved glycolytic activity, and hence viability, by PET, with either normal FDG–blood flow relations or an ischemic pattern of increased FDG uptake relative to reduced blood flow.

There are two considerations regarding these three previous studies comparing the results of PET and thallium SPECT imaging that should be addressed. First, in these studies thallium defects were clas-
sified as being completely reversible, partially reversible, or irreversible on the redistribution images, but the severity of the reduction in thallium activity within the irreversible defects was not investigated. Our data suggest that this is a potentially important consideration that could explain the high prevalence of metabolic activity in irreversible thallium defects in these previous studies, as irreversible defects with only a mild or moderate reduction in thallium activity relative to normal myocardial regions almost uniformly demonstrate evidence of preserved metabolic activity as indicated by FDG uptake (Table 2). Because such irreversible defects also show visually apparent thallium activity on both exercise and redistribution images (Figure 2), from the clinical viewpoint the level of thallium activity alone in these regions may serve as evidence of viable myocardium. It is irreversible defects with severe reduction in regional thallium levels (<50% of peak normal activity), associated with no visually discernible thallium activity, in which viability is in question and in which FDG uptake would provide clinically important data.

A second issue regarding the previous comparisons of thallium SPECT imaging and metabolic imaging with PET relates to thallium redistribution. In these studies,9–11 only a single redistribution study was performed at rest 3–4 hours after the injection of thallium during exercise. It has now been shown in several investigations that late thallium redistribution imaging at 8–72 hours will detect thallium uptake in a large number of myocardial regions that appear to have irreversible defects at 3–4 hours.28–30

As an alternative approach to this issue, we recently demonstrated that the re-injection of thallium at rest immediately after 3–4 hours of redistribution imaging results in enhanced thallium uptake in 49% of regions with apparently irreversible defects on the redistribution images.12 That this increased regional thallium activity after re-injection represented viable myocardium was confirmed by the results of coronary angioplasty in a subset of patients. Improvement in regional thallium uptake and regional ventricular function at rest after coronary angioplasty occurred in 87% of irreversible defects manifesting enhanced thallium activity after re-injection on the preangioplasty studies.

**FIGURE 4.** Tomograms showing concordance of PET and thallium reinjection data. Two tomographic imaging planes are shown for one patient, with format similar to Figure 5. An irreversible thallium defect involving the septum and left ventricular anterolateral wall that remains irreversible after reinjection is confirmed by reduced blood flow and absent FDG uptake by PET. PET, positron emission tomography; SPECT, single-photon emission computed tomography; FDG, fluorine-18–labeled fluorodeoxyglucose; MBF, myocardial blood flow; Ex, exercise; RD, redistribution; RI, reinjection.

**FIGURE 5.** Nomogram of FDG uptake in 68 regions with severe “irreversible” thallium defects on redistribution imaging. FDG uptake, when present, usually represented a reduction in FDG activity in proportion to reduced blood flow rather than an ischemic pattern of increased FDG uptake relative to blood flow. All but four regions with FDG uptake also had enhanced thallium uptake after reinjection. FDG, fluorine-18–labeled fluorodeoxyglucose.
whereas such improvement in regional perfusion and function after angioplasty occurred in none of the regions that remained irreversible after thallium reinjection before angioplasty. These findings have been confirmed by the results of Ohtani et al.

Further evidence that regions with enhanced thallium uptake after reinjection represent viable myocardium is provided by recent preliminary data in our laboratory using a combination of thallium SPECT, PET imaging with FDG, and gated magnetic resonance imaging in patients with coronary artery disease and left ventricular dysfunction, in which corresponding thallium, PET, and magnetic resonance tomograms were directly compared. Regions with irreversible thallium defects that improve with reinjection had regional systolic wall thickening by magnetic resonance imaging that was not significantly different from segments with normal thallium uptake but that was significantly greater than regions with irreversible defects that did not manifest enhanced thallium uptake after reinjection.

The similarity between the results with thallium reinjection and the published results with PET, in reference both to the percentage of irreversible thallium defects identified as viable by both techniques and to the improvement in perfusion and function after revascularization in regions so identified, led us to the present study in which we directly compared the results of metabolic imaging with PET and those of exercise thallium scintigraphy with reinjection in patients with chronic coronary artery disease and left ventricular dysfunction.

Our results, according to an objective method of evaluating regional thallium uptake and FDG uptake relative to blood flow, indicate that in severe irreversible thallium defects on standard exercise-redistribution imaging, thallium reinjection provides information regarding myocardial viability that is comparable to that provided by FDG uptake by PET. Similar to the findings of previously published series, we identified metabolic activity with FDG in 51% of regions demonstrating severe irreversible thallium defects on redistribution images. The results with thallium reinjection were identical: 51% of severe irreversible thallium defects demonstrated enhanced thallium activity after reinjection, which is in keeping with our previous experience. Thallium reinjection identified as viable or nonviable, with few exceptions, the same myocardial regions as did PET imaging with FDG, and the reinjection images tended to mirror the information in the FDG images (Figures 3 and 4).

Differences exist between our study and previous studies relating to this subject in interpreting the thallium and FDG data, and these differences should also be addressed because they can influence conclusions. First, we assessed the severity of the reduction of thallium activity within irreversible thallium defects, which (as noted previously) is an important issue not considered in the previous investigations. In addition, our evaluation of regional FDG uptake relative to blood flow also differed. Regional FDG activity in previous studies has been defined as normal, ischemic (increased FDG uptake relative to reduced flow), or scar (proportionate decrease in FDG relative to reduced flow). We considered two categories to describe relative reductions in FDG uptake proportionate to reduced blood flow, based on the assumption that mild-to-moderate reductions in regional blood flow and glucose utilization represented evidence of viable myocardium (perhaps admixed with fibrous tissue) rather than transmural fibrosis. We, therefore, differentiated between regions with mild-to-moderate and those with severe decreases in FDG uptake. Our supposition that the former regions represent viable myocardium and that the latter regions represent nonviable myocardium is
supported by the corresponding regional thallium activity. Most regions with severe reduction in FDG uptake (absent FDG activity) were associated with irreversible thallium defects, and most of these thallium defects were severe in nature and did not improve after reinjection (Table 3). In contrast, regions with a mild-to-moderate reduction in FDG uptake in proportion to blood flow (reduced FDG activity) corresponded to those regions in which thallium activity indicated viable myocardium (Table 3). Most regions had thallium uptake on standard stress-redistribution images; most of the irreversible defects that did occur had only mild or moderate reduction in thallium activity, and most of the severe irreversible defects manifested enhanced thallium uptake on reinjection at rest.

A similar analysis is useful in evaluating the significance of an ischemic pattern of enhanced FDG uptake relative to reduced blood flow. In our patients, this FDG–blood flow mismatch pattern occurred predominantly in regions without irreversible thallium defects on redistribution imaging (Table 3). Moreover, when an irreversible thallium defect was observed in a region with FDG mismatch, the thallium activity within the defect was usually only mildly reduced and rarely severely reduced. These findings suggest that the pattern of FDG–blood flow mismatch on PET imaging identifies viability in mild thallium defects (in which the level of thallium activity itself may be considered evidence of viability) but is less useful in identifying viable myocardium within severe irreversible thallium defects on redistribution studies. In these severe irreversible thallium defects, FDG uptake is usually moderately or severely reduced (Figure 5), and the increase or lack of increase in thallium activity after thallium reinjection segregates regions according to the presence or absence of metabolic activity by FDG imaging (Tables 2 and 3).

In comparison to these results of thallium reinjection in severe irreversible thallium defects, the reinjection of thallium often failed to show enhanced thallium activity after reinjection in irreversible defects that were only mild or moderately severe in nature, despite metabolic evidence of viability by PET (Tables 2 and 3). We believe, as noted previously, that the actual level of thallium activity in such defects is itself a marker of viable myocardium (which is confirmed by the FDG uptake in these regions); although thallium activity is not enhanced after reinjection in many such regions, the thallium levels both at redistribution and after reinjection are sufficient to indicate viability. Nonetheless, the apparent lack of augmentation in thallium activity after reinjection is a potential limitation and cause for concern. However, this apparent discordance between the FDG and thallium reinjection findings in mild irreversible defects may be reconciled further by considering the relative nature of the thallium measurements. Regional thallium activity in each of the exercise, redistribution, and reinjection images was expressed relative to the activity in a normal reference region. An irreversible defect on redistribution imaging would appear to not improve after reinjection, even if the underlying myocardium was viable, if the increase in activity in the normal reference region after reinjection was disproportionately greater than the increased activity in the region with the thallium defect. Preliminary data in our laboratory addressing the magnitude of increase in absolute thallium activity after reinjection indicate that mild irreversible defects with no apparent increase in relative thallium activity after reinjection manifest a significantly greater increase in thallium activity with reinjection (74 ± 19% of the increase observed in normal regions) than do severe irreversible defects with no relative increase in thallium activity after reinjection (41 ± 18% of the increase in normal regions). This indicates that quantitative analyses of the changes in thallium levels that occur within defects after rest reinjection, in addition to the thallium activity present on the redistribution study, may be useful in identifying viable myocardium.

There are limitations of the present study on identifying viable myocardium. Our data were obtained in patients with chronic coronary artery disease and, thus, may not apply to the evaluation of patients with acute ischemic syndromes, especially those patients undergoing thrombolytic therapy or revascularization procedures in whom the distinction between stunned and necrotic myocardium may be an important clinical issue. Our series also consisted of a relatively small number of patients, only one of whom underwent successful revascularization, and given this sample size, conclusions regarding the overall efficacy of thallium reinjection compared with PET in predicting improvement in regional and global ventricular function after revascularization require further experience in a larger series. Although 80% or more of myocardial regions identified as viable by FDG or thallium reinjection imaging may improve after revascularization, the number of patients who benefit from such salvage may be much lower because this is likely to depend on the mass of jeopardized myocardium that is successfully revascularized. Hence, definitive statements regarding the use of thallium scintigraphy or PET in the management of patients with left ventricular dysfunction are not possible from our data.

Our data, however, do permit an evaluation of thallium scintigraphy in comparison with PET imaging in the assessment of myocardial viability. Our analysis involved a wide range of ventricular dysfunction and a large number of myocardial regions with a variety of thallium perfusion defects. Because the level of thallium activity in mild or moderate irreversible thallium defects and the level of enhanced thallium activity after reinjection in severe irreversible defects identified the same regions as viable or nonviable (with few exceptions) as did PET imaging with FDG, our data suggest that exercise thallium scintigraphy with rest.
reinjection provides information comparable to that obtained by PET in identifying viable myocardium in patients with chronic coronary artery disease and left ventricular dysfunction.

**Acknowledgments**

We acknowledge the excellent technical assistance of Wendy R. Smeltzer and Raymond Dextras in performing the thallium studies and Karyn Lloyd-Hontz and Calvin Miller in performing the PET studies.

**References**


29. Yang LD, Berman DS, Kiat H, Resser KJ, Friedman JD, Rozanski A, Maddahi J: The frequency of late reversibility in


**KEY WORDS**  
- coronary artery disease  
- fluorodeoxyglucose  
- left ventricular dysfunction  
- myocardial viability  
- positron emission tomography  
- thallium-201 scintigraphy
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 18F-fluorodeoxyglucose.
R O Bonow, V Dilsizian, A Cuocolo and S L Bacharach

Circulation. 1991;83:26-37
doi: 10.1161/01.CIR.83.1.26

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/83/1/26

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/