Positron Emission Tomography Detects Metabolic Viability in Myocardium With Persistent 24-Hour Single-Photon Emission Computed Tomography 201Tl Defects

Richard C. Brunken, MD; Freny Vaghaiwalla Mody, MD; Randall A. Hawkins, MD, PhD; Christoph Nienaber, MD; Michael E. Phelps, PhD; and Heinrich R. Schelbert, MD

Background. Four-hour 201Tl redistribution images underestimate myocardial viability in patients with coronary artery disease (CAD). Because 4-hour defects often redistribute late, delayed imaging may enhance assessment of tissue viability. Myocardial metabolic activity was therefore assessed with positron emission tomography (PET) in 26 CAD patients with impaired ventricular function (ejection fraction, 32.1±13.9%) and 24-hour single-photon emission computed tomography (SPECT) 201Tl defects.

Methods and Results. On circumferential profile analysis, PET ischemia was defined by preserved glucose metabolism in hyperperfused myocardium, and PET infarction was defined by concordant reductions in perfusion and metabolism. On 19 stress-redistribution and seven rest-redistribution SPECT studies, four observers visually scored 201Tl activity in eight segments on a scale from 0 (normal) to 3 (complete defect). Using an improvement in visual score ≥0.75 to define redistribution, there were 100 fixed, 17 partially reversible, and 12 completely reversible defects. PET identified tissue metabolic activity in 51 (51%) segments with fixed defects (21 PET ischemia, 30 PET normal) and nine (53%) segments with partially reversible defects (five PET ischemia, four PET normal). When grouped by 24-hour score, the proportion of fixed defects with metabolic activity varied from 84% (scores ≤1.4) to 15% (scores >2.6). For partially reversible defects, only 53% with scores <2.0 and one of two with scores ≥2.0 were considered metabolically viable on PET. Of 12 completely reversible defects, six (50%) were normal, five (42%) had PET ischemia, and one (8%) had PET infarction. The proportion of fixed defects with metabolic activity did not depend on whether a rest or stress study was performed or on the change in visual score used to define 201Tl redistribution (0.25, 0.50, 0.75, and 1.00).

Conclusions. In CAD patients, PET identifies glucose metabolic activity in the majority of fixed 24-hour 201Tl defects. However, very severe (near-complete) 24-hour 201Tl defects are less likely to exhibit metabolic activity on PET imaging than defects with less-pronounced reductions in segmental 201Tl activity.

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KEY WORDS • myocardial infarction • 201Tl • computed tomography • myocardial ischemia • scintigraphy • myocardium, hibernating

Today 201Tl scintigraphy plays an important clinical role in the assessment of myocardial viability. Defects that persist on early (2–4-hour) redistribution images have been attributed to completed infarction, whereas reversible defects have implied viable tissue.1–3 However, 45–75% of persistent early defects exhibit normal perfusion after revascularization,4,5 and 31–52% demonstrate improved 201Tl uptake after tracer reinfusion,6–10 indicating that conventional scintigraphic techniques underestimate myocardial viability.

Confirmation that conventional scintigraphic techniques underestimate myocardial viability has also been provided by comparative studies with positron emission tomography (PET), in which metabolic tissue viability is assessed by imaging with the glucose analogue 18F-deoxyglucose. In these studies, tissue metabolic activity has been identified in 38–58% of myocardial segments with fixed early 201Tl defects.11–14
One explanation for these observations is that 4 hours may be an insufficient period of time for 201Tl redistribution to occur in some individuals. Several investigators have proposed the use of 24-hour delayed imaging, noting that late improvement can be observed in as many as 64% of segments with early defects. These studies suggest that the 201Tl scintigraphic assessment of myocardial viability might be influenced by delayed redistribution imaging. In patients with severe coronary artery disease (CAD) and left ventricular dysfunction, we sought to determine if metabolic activity and, thus, evidence of tissue viability could be detected with PET in segments with persistent defects on 24-hour single-photon emission computed tomography (SPECT) 201Tl images.

Methods

Patient Population

Twenty-six consecutive CAD patients (23 men and three women; mean age, 59.7±10.0 years) were studied. Each had one or more previous infarctions (mean, 1.6 per patient; range, one to four) and was referred for evaluation of myocardial viability. Two patients had been treated with thrombolytic therapy at the time of their remote infarctions. Nineteen had angina, 17 had heart failure, nine required treatment for ventricular dysrhythmias, and five had had a previous cardiac arrest.

Twenty-one patients had ECG Q waves in one or more ventricular regions, whereas two had poor R wave progression with RS complexes in the anterior precordial leads. Of 38 Q wave regions, 11 were anterior, six were lateral, 13 were inferior, and eight were septal. Two other individuals had anterior ST-T changes consistent with nontransmural infarction. The remaining patient had left bundle branch block. Six individuals had a history of coronary bypass surgery, and six had prior coronary angioplasty. None had sustained an infarction within 2 weeks before study or had had revascularization for at least 3 months. Mean left ventricular ejection fraction, as determined by contrast left ventriculography (n=19), radionuclide ventriculography (n=4), or two-dimensional echocardiography (n=3), was 32.1±13.9%. Resting wall motion abnormalities were present in two to seven segments per patient (mean, 4.3 per patient). As wall motion was assessed only on right anterior oblique ventriculograms in six patients, the actual number of resting wall motion abnormalities may have been higher.

Coronary angiography was performed in each individual. The mean interval from arteriography to 201Tl scintigraphy was 7.1±6.9 weeks, and the mean interval from angiography to PET was 6.9±7.1 weeks. Lesions with >70% stenosis were considered hemodynamically significant. One individual had left main (>50% stenosis) disease, 17 had three-vessel disease, six had two-vessel disease, and two had one-vessel disease.

SPECT 201Tl Scintigraphy

Nineteen patients had exercise studies, and seven patients had rest-redistribution studies, according to the referring physician's estimate of the individual's exercise tolerance. The mean interval from SPECT to PET was 3.4±5.8 days (range, 0–25 days). Those with exercise studies achieved 76.4±15.3% of their maximal predicted heart rate and a double product of 19,100±5,500 mm Hg · beats per minute. Five had chest pain with ischemic ST segment changes, five had chest pain without ECG changes, and four had ischemic ST segment changes without pain.

Then, 3–3.5 mCi 201Tl chloride was administered intravenously 45–60 seconds before the end of exercise. SPECT imaging was begun within 14 minutes, with redistribution imaging at 4 and 24 hours. Patients were allowed to ambulate and to consume clear liquids between the stress and 4-hour studies. Twenty-four-hour imaging was performed after an overnight fast to decrease gastrointestinal activity. For the rest studies, imaging was begun 3–5 minutes after intravenous administration of 3–3.5 mCi 201Tl chloride, and redistribution imaging was performed in identical fashion.

SPECT imaging was performed over a 180° arc using a model 7500 Orbiter camera (Siemens Gammasonics Inc., Hoffman Estates, Ill.) equipped with an all-purpose, low-energy collimator. The in-plane resolution (full-width, half-maximum of a line-spread function) of this camera at a distance of 20 cm is 23 mm. For the initial and 4-hour images, 32 frames were acquired at 40 sec/frame. Acquisition times were increased to 60 sec/frame for the 24-hour images. There were 100,000–150,000 counts per frame on the initial images, 50,000–100,000 counts per frame on the 4-hour images, and 30,000–70,000 counts per frame on the 24-hour images. Short-axis, oblique sagittal, oblique coronal, and transverse images were reconstructed using a Butterworth filter (0.4 frequency cutoff, order 5). The thickness of the reconstructed transverse SPECT images was approximately 20 mm.

SPECT 201Tl Image Analysis

Four experienced nuclear cardiologists visually assessed myocardial 201Tl activity in eight segments: anterobasilar, anterior, apical, inferior, lateral, posterolateral, and inferior and superior septal. They had the four 201Tl image sets (short-axis, oblique sagittal, oblique coronal, and transverse) and the polar maps when they graded the SPECT images, but they were unaware of the PET results. For both the rest and stress studies, segmental activity was graded on the following scale: 0, normal; 1, mild but definite defect; 2, severe defect; and 3, complete defect. A grade of 1 was assigned only if a definite defect was identified, and segments with equivocal findings were considered normal. Thus, grade 1 defects would be considered moderate defects in some laboratories. Severe (grade 2) defects were defined by a pronounced reduction in segmental activity as well as identifiable myocardial activity above that of background. Complete (grade 3) defects were defined by a total absence of visible 201Tl activity (equal to background activity). Observers scored the most severe area of a defect, and defects involving contiguous segments were considered to involve both segments.

A 201Tl defect was identified if three observers assigned a score of ≥1 (mean score, ≥0.75). A defect was considered fixed if the difference between the initial and 24-hour scores was <0.75, i.e., three observers perceived a change in segmental score of less than one grade. Reversible defects were defined by an improvement in segmental score of ≥0.75 on either the 4- or the
24-hour image. Defects were considered completely reversible if the mean 24-hour score was $<0.75$ and partially reversible if the late score was $\geq 0.75$.

Early reversibility was defined by an improvement in segmental score of $\geq 0.75$ between the initial and 4-hour images plus little or no change between the 4- and 24-hour scores. Late reversibility was defined by little or no change in score between the initial and 4-hour images plus late improvement in segmental score of $\geq 0.75$. If the mean score improved by $\geq 0.75$ and this was equally or nearly equally divided between the early and late redistribution images, then the segment was said to have balanced redistribution.

ANOVA revealed no significant difference between individual readers’ scores for either initial ($F=1.007$, $p>0.50$), 4-hour ($F=1.729$, $p>0.20$), or 24-hour images ($F=1.953$, $p>0.20$), and individual scores differed from mean scores by $<0.75$ in 97.3% of the segments.

Initial stress or rest $^{201}$Tl images were analyzed quantitatively with a commercially available polar mapping technique. Relative (percent peak) $^{201}$Tl activity was calculated for each area of the entire left ventricle and compared with a sex-matched data base. Regions with relative $^{201}$Tl concentrations $<2$ SDs from normal were considered to have perfusion defects on the polar map.

**PET**

PET was performed in the resting state using an ECAT III tomograph (CTI Inc., Knoxville, Tenn.). The tomograph allows simultaneous acquisition of three cross-sectional images (two directly plus an interpolated center image). Spacing between planes was 9 mm, and the effective slice thickness of the images was approximately 14 mm. The intrinsic spatial resolution of the tomograph for $^{18}$F is 5.5–6-mm full-width half-maximum in the center of the imaging field, with an effective in-plane image resolution of 10-mm full-width half-maximum. Consistency in patient positioning was achieved by marking the chest with washable ink and aligning the marks with a low-power laser light beam from the tomograph.

Transmission images were obtained using an external ring of $^{68}$Ga to enable correction of the emission images for photon attenuation. Six or nine cross-sectional images of relative blood flow were then acquired after intravenous administration of 15–20 mCi $^{13}$N-ammonia. Acquisition times were 15 minutes for six planes (six for the first set and nine for the second set) and 30 minutes for nine planes (six, nine, and 15, respectively). The average number of true counts per cross-sectional image was 2.47±0.98 million.

Metabolic imaging was performed after intravenous administration of 5–10 mCi $^{18}$F-deoxyglucose. Forty minutes were allowed for tracer uptake; then, six to nine cross-sectional images (10 minutes per set) of relative myocardial glucose utilization were obtained in corresponding planes. True counts averaged 3.62±1.15 million per cross-sectional image.

Postprandial imaging was used to enhance myocardial glucose utilization relative to fatty acids. Patients ingested a carbohydrate-containing meal before study and were given a 25–50-g oral glucose load 1 hour before tracer administration. Each patient gave informed consent on a form approved by the UCLA Human Subject Protection Committee. The cumulative whole-body radiation dose was 0.5 rad (1.2 rad effective dose equivalent) for the PET study.

**PET Image Analysis**

Transaxial PET images were analyzed on a VAX 780 computer (Digital Equipment, Maynard, Mass.) using a circumferential count profile technique. The operator-interactive program uses a gaussian-fit edge-detection algorithm to identify the inner and outer edges of the left ventricle on the metabolic images. Image defects are included in the profile by elliptically interpolating the inner and outer borders of the nearest normal myocardium. Metabolic image contours were copied to the perfusion images, ensuring identical angular measurements for both image sets.

The ventricular contour was divided into 60 sectors of 6° each, proceeding in a clockwise fashion from the posterior limb of the long axis. Peak sectorial counts were normalized by dividing by the highest profile activity. Profile data were displayed graphically as a function of the angle around the long axis and compared with normal values obtained in 11 healthy volunteers. PET infarction was defined by concordant reductions in relative $^{13}$N and $^{18}$F activities $<2$ SDs from normal in 10 or more contiguous sectors. PET ischemia was identified by an $^{18}$F-$^{13}$N count difference $>2$ SDs from normal in 10 or more contiguous sectors. If an abnormality involved two or more segments, then both segments were considered to be affected.

**Statistical Analysis**

Reported values are given as mean±SD. Readers’ $^{201}$Tl scores were compared using ANOVA and the $F$ test. Comparison between $^{201}$Tl scores for segmental classes, as, for example, by type of $^{201}$Tl defect or PET classification, was performed with a single-factor ANOVA and the $F$ test. For significant $F$ values, the Tukey test (with correction for group size) was used to identify differences between pairs of groups. The clinical characteristics of the patients with and without PET ischemia were compared with the $\chi^2$ test (with Yates’ correction as appropriate) or with Student’s $t$ test for unpaired data. Values of $p<0.05$ were considered statistically significant.

**SPECT $^{201}$Tl Scintigraphy**

The observers identified 142 $^{201}$Tl defects in the 26 studies. Eighteen anterobasilar segments (11 with defects and seven normal) were excluded because of incomplete visualization on PET. The two septal segments in the patient with left bundle branch block were also excluded, leaving 59 normal and 129 abnormal segments for comparison with PET.

There were 100 fixed, 17 partially reversible, and 12 completely reversible $^{201}$Tl defects. In the 19 exercise studies, there were 68 fixed defects, 15 partially reversible defects (seven early, two late, and six balanced), and 10 completely reversible defects (five early, two late, and three balanced). In the seven rest studies, there were 32 fixed defects, two partially reversible defects (one early and one balanced), and two completely reversible defects (one balanced and one late). On polar maps, $^{201}$Tl defects were identified in 96 (96%) segments...
with fixed defects, 17 (100%) segments with partially reversible defects, and 11 (91.7%) segments with completely reversible defects. Thus, nearly all segments with visually identified defects had corresponding defects on polar maps of relative \( ^{201}\)TI activity.

\( ^{201}\)TI scores by defect classification (see previous “SPECT \( ^{201}\)TI Image Analysis”) are listed in Table 1. Stress study and rest study scores did not differ for any defect classification. For both the rest and stress studies, ANOVA revealed significantly different scores for each defect classification at each time (\( p<0.001 \) for each). Mean scores for completely reversible defects and normal segments did not differ on the 24-hour images; both were significantly better than the scores for segments with fixed or partially reversible defects (\( p<0.001 \) for each).

**Correlation With PET**

Only 36 of the 68 (52.9%) fixed defects on the stress studies and 13 of the 32 (40.6%) fixed defects on the rest studies exhibited PET infarction on circumferential profile image analysis (Figure 1). Eleven (16.2%) fixed defects on the stress studies and 10 (31.3%) fixed defects on the rest studies had PET ischemia (Figure 2). In 30 segments (21 stress and nine rest), relative \( ^{13}\)N-ammonia and \( ^{18}\)F-deoxyglucose concentrations were within 2 SDs of laboratory mean values, resulting in a normal PET classification. Thus, the majority (51%) of fixed \( ^{201}\)TI defects were considered metabolically viable on PET. The proportion of PET normal, ischemic, and infarcted segments did not differ between the stress and the rest studies (\( \chi^2=2.409, p=NS \)). Of 19 inferior segments with fixed defects, eight had PET infarction, four had PET ischemia, and seven were normal; the relative number of PET normal, ischemic, and infarcted segments in inferior defects did not differ from those in other ventricular segments (\( \chi^2=0.366, 2 df, p=NS \)).

Of the 17 segments with partially reversible \( ^{201}\)TI defects, eight (47.1%) had PET infarction (all stress studies). PET ischemia was noted in five segments (29.4%; three stress and two rest), whereas the remaining four segments (all stress) were normal on PET. Thus, the majority (52.9%) of partially reversible defects exhibited metabolic activity on PET imaging. Six of eight segments with early partial reversibility had metabolic activity (two PET ischemia and four normal). Only two segments (both inferior) with early partial reversibility had PET infarction. In contrast, four of seven segments with balanced partial redistribution and both segments with late partial redistribution had PET infarction. The other three segments with balanced partial redistribution had PET ischemia.

Of the 12 segments with completely reversible defects, six (50%; five stress and one rest) were normal on PET, five (41.7%; four stress and one rest) had PET ischemia, and one (8.3%; stress) had PET infarction. Three of five segments with early complete reversibility were normal, whereas one had PET ischemia and one had PET infarction. Two of four segments with balanced complete redistribution were normal, whereas two had PET ischemia. All three segments with late reversibility had preserved metabolism on PET imaging (one normal and two PET ischemia). Thus, nearly all (91.7%) segments with completely reversible defects were considered metabolically viable on PET.

Of the 59 segments normal on \( ^{201}\)TI scintigraphy, 43 (72.9%) were normal on PET. PET ischemia was noted in 11 segments (18.6%; seven stress and four rest), whereas PET infarction was present in five segments (8.5%; all stress).

<table>
<thead>
<tr>
<th>Segmental classification</th>
<th>Scores</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>4-Hour</td>
</tr>
<tr>
<td>Fixed (n=100)</td>
<td>2.18±0.59</td>
<td>2.07±0.60</td>
</tr>
<tr>
<td>Stress (n=68)</td>
<td>2.20±0.65</td>
<td>2.08±0.66</td>
</tr>
<tr>
<td>Rest (n=32)</td>
<td>2.15±0.43</td>
<td>2.06±0.44</td>
</tr>
<tr>
<td>Partially reversible</td>
<td>2.26±0.38*</td>
<td>1.60±0.57</td>
</tr>
<tr>
<td>Rest (n=17)</td>
<td>2.28±0.40*</td>
<td>1.62±0.58</td>
</tr>
<tr>
<td>Completely reversible</td>
<td>2.13±0.18†</td>
<td>1.44±0.62†</td>
</tr>
<tr>
<td>Rest (n=2)</td>
<td>1.48±0.51</td>
<td>0.66±0.62</td>
</tr>
<tr>
<td>Normal (n=59)</td>
<td>0.03±0.10</td>
<td>0.02±0.07</td>
</tr>
<tr>
<td>Stress (n=43)</td>
<td>0.03±0.11†</td>
<td>0.02±0.06</td>
</tr>
<tr>
<td>Rest (n=16)</td>
<td>0.03±0.07†</td>
<td>0.03±0.07†</td>
</tr>
</tbody>
</table>

NS, not significant; \( p \), probability value from ANOVA of the initial and 4- and 24-hour scores for each classification; Rest, segments from rest-redistribution studies; Stress, segments from stress-redistribution studies.

For the initial and 4- or 24-hour images:

\( *p=NS \) versus fixed; \( p<0.001 \) versus completely reversible in corresponding class.

\( tp=NS \) versus fixed and completely reversible in corresponding class.

\( tp<0.001 \) versus fixed, partially reversible, and completely reversible in corresponding class.

\( tp<0.001 \) versus fixed and completely reversible defects in corresponding class.

\( tp<0.02 \) versus fixed and completely reversible in corresponding class.

\( tp<0.001 \) versus fixed and partially reversible; \( p<0.05 \) versus completely reversible in corresponding class.

\( **p=NS \) versus completely reversible; \( p<0.05 \) versus fixed in corresponding class.

\( ††p<0.005 \) versus fixed and partially reversible; \( p=NS \) versus completely reversible in corresponding class.

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**Table 1. \( ^{201}\)TI Scores According to Segmental Classification**

[Table content]

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THALLIUM SCINTIGRAPHY

Panel A: Cross-sectional transaxial single-photon emission computed tomography (SPECT) 201Tl images from a 66-year-old man with prior infarction, angina, and heart failure (ejection fraction, 18%). The ventricle is dilated and extensive; fixed perfusion defects are noted in the anterior, apical, inferior, and posterolateral segments; and a partially reversible defect is present in the superior septum. Panel B: The 24-hour 201Tl images along with 13N-ammonia (NH3) perfusion and 18F-deoxyglucose (FDG) metabolic positron emission tomography (PET) images. Because of attenuation correction and the superior spatial resolution of the positron tomograph, the PET images more clearly define regional tracer concentrations (noticeable especially in the septal and inferior regions of the heart) than the SPECT images. Concordant perfusion and metabolic defects are present in the anterior and apical segments with the fixed 201Tl defects as well as the distal superior septal segment with the partially reversible 201Tl defect, denoting PET infarction. In the hypoperfused areas of the inferior and posterolateral segments, glucose metabolism is well preserved, denoting PET ischemia.

ISCHEMIC CARDIOMYOPATHY

Panel A: Stress study showing 201Tl images from the same patient as in Panel A. Panel B: 24-hour 201Tl images along with 13N-ammonia (NH3) perfusion and 18F-deoxyglucose (FDG) metabolic positron emission tomography (PET) images. Concordant perfusion and metabolic defects are present in the anterior and apical segments with the fixed 201Tl defects as well as the distal superior septal segment with the partially reversible 201Tl defect, denoting PET infarction. In the hypoperfused areas of the inferior and posterolateral segments, glucose metabolism is well preserved, denoting PET ischemia.
\textbf{THALLIUM SCINTIGRAPHY}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2}
\caption{Panel A: Cross-sectional transaxial single-photon emission computed tomography (SPECT) $^{201}$TI images from a 75-year-old man with two prior infarctions, angina, and heart failure (ejection fraction, 23\%). Fixed $^{201}$TI defects are present in the anterior, septal, and inferior segments, and the left ventricle is dilated. Panel B: The patient's 24-hour SPECT $^{201}$TI images along with the corresponding $^{13}$N-ammonia ($\text{NH}_3$) perfusion and $^{18}$F-deoxyglucose (FDG) metabolic positron emission tomography (PET) images. Although the $\text{NH}_3$ perfusion defects are similar to the $^{201}$TI defects, tissue glucose metabolism in the hypoperfused anterior and septal segments is strikingly elevated on the FDG images compared with the normally perfused posterolateral and lateral segments, denoting PET ischemia. A concordant reduction in FDG uptake is apparent in the hypoperfused inferior segment, indicating PET infarction.}
\end{figure}

\textit{Relation to $^{201}$TI Defect Severity}

$^{201}$TI scores by PET classification are listed in Table 2. Scores for the stress studies did not differ from those for the rest studies in any PET category. For both stress and rest studies, scores for PET normal, ischemic, and infarcted segments were significantly different at each time point ($p<0.001$ for all). Segments with PET infarction had scores that were significantly poorer than those for normal segments or segments with PET ischemia.

The proportion of fixed defects with preserved metabolic activity on PET imaging varied according to the 24-hour $^{201}$TI score (Figure 3). The relative number of PET segments with preserved metabolic activity did not differ between the stress and rest studies in any group of
scores ($\chi^2=0.29-2.37, p=NS$). For 24-hour $^{201}$TI scores $\leq 1.80$ (moderate defects), the proportion of segments with metabolic activity exceeded 75%. For severe defects (scores between 1.81 and 2.60), the proportion of fixed defects with metabolic activity declined to 52%. Although the likelihood of PET infarction increased with worsening defect severity, a near-complete defect (scores, $>2.6$; mean group score, 2.8±0.2) did not preclude the possibility (about one in seven) that metabolic activity would be identified with PET.

Fifteen partially reversible defects had 24-hour scores $< 2.00$, whereas two had scores between 2.00 and 2.50. Eight defects (53.3%; six stress and two rest) with scores $< 2.00$ were considered metabolically viable on PET, whereas seven had PET infarction. Of the segments with scores between 2.00 and 2.50 (both stress studies), one had PET ischemia and one had PET infarction. Thus, about half of segments with partially reversible defects exhibited criteria for PET infarction, regardless of the severity of the late $^{201}$TI score.

**Data Analysis With Differing Redistribution Criteria**

To determine if alternative definitions of $^{201}$TI redistribution would affect the results, data analyses were performed using values of 0.25, 0.50, and 1.00 as the improvement in segmental score used to define $^{201}$TI redistribution. Use of the lower thresholds (0.25 and 0.50) increased the chance that a defect with a slight change in score would be considered partially reversible and thus viable, whereas use of the higher threshold (1.00) increased the likelihood that a defect would be considered fixed and thus nonviable, according to conventional criteria.

For defects considered fixed using the differing redistribution thresholds, the proportion of segments with preserved metabolic activity ranged from 45.9% to 51.0% (Table 3). Thus, the proportion of fixed defects with metabolic activity on PET imaging was independent of the change in visual score used to define redistribution.

**Correlation With Coronary Angiography**

Significant lesions were present in the arteries supplying 94 (94.0%) segments with fixed $^{201}$TI defects. Five were supplied by stenosed vessels with patent grafts, whereas the sixth was perfused by an artery with a 50% stenosis. Of the 19 inferior segments with fixed defects, 15 were perfused by vessels with significant stenoses; three were perfused by diseased vessels with patent grafts, and the last was supplied by an artery with a 50%
TABLE 3. Relation Between the Improvement in 201TI Score Used to Define Redistribution and PET Metabolic Viability

<table>
<thead>
<tr>
<th>201TI defect classification</th>
<th>Change in 201TI score used to define redistribution</th>
<th>No. of segments</th>
<th>Percent with metabolic viability</th>
<th>Segmental PET classification (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MI</td>
</tr>
<tr>
<td>Fixed defect</td>
<td>≥0.25</td>
<td>69</td>
<td>49.3%</td>
<td>35 (51)</td>
</tr>
<tr>
<td></td>
<td>≥0.50</td>
<td>85</td>
<td>45.9%</td>
<td>46 (54)</td>
</tr>
<tr>
<td></td>
<td>≥0.75</td>
<td>100</td>
<td>51.0%</td>
<td>49 (49)</td>
</tr>
<tr>
<td></td>
<td>≥1.00</td>
<td>110</td>
<td>50.0%</td>
<td>55 (50)</td>
</tr>
<tr>
<td>Partially reversible defect</td>
<td>≥0.25</td>
<td>56</td>
<td>57.1%</td>
<td>24 (43)</td>
</tr>
<tr>
<td></td>
<td>≥0.50</td>
<td>33</td>
<td>63.4%</td>
<td>12 (36)</td>
</tr>
<tr>
<td></td>
<td>≥0.75</td>
<td>17</td>
<td>52.9%</td>
<td>8 (47)</td>
</tr>
<tr>
<td></td>
<td>≥1.00</td>
<td>7</td>
<td>71.4%</td>
<td>2 (28.5)</td>
</tr>
<tr>
<td>Completely reversible defect</td>
<td>≥0.25</td>
<td>8</td>
<td>100.0%</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>≥0.50</td>
<td>13</td>
<td>92.3%</td>
<td>1 (8)</td>
</tr>
<tr>
<td></td>
<td>≥0.75</td>
<td>12</td>
<td>91.6%</td>
<td>1 (8)</td>
</tr>
<tr>
<td></td>
<td>≥1.00</td>
<td>11</td>
<td>90.9%</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Normal</td>
<td>≥0.25</td>
<td>55*</td>
<td>92.7%</td>
<td>4 (7)</td>
</tr>
<tr>
<td></td>
<td>≥0.50</td>
<td>57</td>
<td>93.0%</td>
<td>4 (7)</td>
</tr>
<tr>
<td></td>
<td>≥0.75</td>
<td>59</td>
<td>91.5%</td>
<td>5 (8)</td>
</tr>
<tr>
<td></td>
<td>≥1.00</td>
<td>60</td>
<td>91.7%</td>
<td>5 (8)</td>
</tr>
</tbody>
</table>

PET, positron emission tomography.

*Includes one segment normal on initial 201TI images but with a score of 0.25 on 4- and 24-hour images.
†Includes two segments with fixed defects and further deterioration in 201TI visual score on 24-hour images.

Stenosis. Fifteen (88.2%) segments with partially reversible defects had significant lesions in the associated artery; two segments were supplied by narrowed vessels with patent grafts. Both of the two inferior segments with partially reversible defects were supplied by arteries with significant stenoses. Significant stenoses were present in the vessels supplying 11 (91.7%) segments with completely reversible defects. A 12th reversible anterobasilar defect was associated with a 50% proximal and a 99% mid left anterior descending coronary artery stenosis. Disease was not considered present in the vessel supplying this segment as the proximal stenosis did not exceed 70%. All segments with defects on rest studies were perfused by stenosed arteries.

Of the arteries supplying the 59 normal segments on SPECT, 22 (37%) had significant stenoses. Each of these segments were in patients with multivessel disease. Six of 16 normal segments on the rest studies were perfused by stenosed arteries. Of the 11 segments normal on SPECT with PET ischemia, seven were in the distribution of narrowed vessels and two were associated with stenosed vessels with patent grafts. Of the five segments normal on SPECT with PET infarction, four were in the distribution of narrowed vessels, and the fifth was perfused by a vessel that was diseased but previously had been successfully angioplastied.

Relation of PET Findings to Coronary Anatomy

Fifty-eight (92%) segments with PET infarction were supplied by narrowed arteries. Two were supplied by stenosed vessels with patent grafts, and two other segments were perfused by arteries with 50% stenoses. The remaining PET infarct segment was in the distribution of an angiographically normal vessel. Thirty-seven (88%) segments with PET ischemia were perfused by narrowed vessels. Two segments were supplied by stenosed vessels with patent grafts, whereas the other two were perfused by arteries that supplied significant collateral flow to adjacent segments. The final segment with PET ischemia was supplied by an anterior descending artery with a 50% proximal stenosis. Of the 83 PET normal segments, 35 (42%) were supplied by normal arteries. The other 48 segments (58%) were supplied by vessels with significant stenoses, indicating that lesion severity was insufficient to affect resting blood flow.

Clinical Correlation

Each patient had one or more fixed 201TI defects. Eighteen had four or more fixed defects, including six patients with rest studies. In 13 (72%) of these 18 patients, PET imaging identified metabolic activity in two or more fixed defects, including five individuals with rest studies. In each of 10 patients who had only fixed defects, metabolic activity was present in two or more segments with perfusion defects, including three patients with rest studies. Thus, the majority of patients with fixed or primarily fixed defects had evidence of preserved metabolic activity on PET imaging in at least two affected segments.

Nineteen (73%) patients had one or more segments with PET ischemia. PET ischemia was adjacent to an infarction in seven patients and was the only abnormality in a vascular territory in 10 patients. In two individuals, ischemia was identified in a vascular territory adjacent to an infarct in a second vascular territory. Individuals with PET ischemia were as likely as those without it to have angina (five of 19 versus five of seven, p=NS), heart failure (11 of 19 versus six of seven, p=NS), or ventricular ectopy (six of 13 versus three of seven, p=NS). Patients with PET ischemia exhibited ischemic ST segment changes with exercise as frequently as those without it (seven of 13 versus three of five, p=NS) and achieved similar double products (21,015±5,381 versus 17,150±5,726 mm Hg·beats per
minute, p=NS). The number of clinical infarcts per patient (1.7±1.0 versus 1.4±0.8, p=NS), number of fixed defects per patient (3.9±1.6 versus 4.7±1.1, p=NS), and left ventricular ejection fraction (34±15% versus 28±9%, p=NS) in individuals with PET ischemia were similar to those in individuals without PET ischemia. Thus, these clinical characteristics did not distinguish patients with from those without PET ischemia.

Discussion

In this study of 26 patients with severe CAD, PET imaging identified myocardial metabolic activity in 51% of fixed defects and 53% of partially reversible defects on 24-hour SPECT 201Tl scintigraphy. Twenty-four-hour delayed imaging did not improve the ability of 201Tl scintigraphy to discriminate viable from nonviable tissue, as defined by glucose metabolic imaging with PET. Although the probability that a fixed defect would exhibit metabolic activity declined as the severity of the 24-hour 201Tl defect became more pronounced, about one in seven of near-complete 24-hour defects did have metabolic activity on PET imaging. In contrast, about half of partially reversible defects exhibited PET infarction, despite the fact that these were incomplete defects. The relative number of fixed defects with metabolic activity did not depend on the change in visual 201Tl score used to define redistribution or on the type of SPECT study that was performed.

Study Limitations

Our patients did not undergo coronary revascularization, and this is a significant limitation of the study. Although the presence of metabolic activity on PET imaging is considered indicative of myocardial viability, it was not possible to demonstrate in our patients by an independent clinical gold standard (e.g., functional improvement after revascularization) that 201Tl scintigraphy underestimated true myocardial viability relative to PET. Clinical studies have shown that 78–85% of hyperperfused segments with metabolic activity on PET exhibit improved function after coronary artery bypass and that 78–100% of segments without metabolic activity have no functional improvement after revascularization.52,56,37 Although these previous reports indicate the usefulness of PET metabolic imaging for identifying reversible left ventricular dysfunction, it is unknown if similar functional outcomes would have been observed in our patients had they undergone coronary revascularization. Because no clinical studies have examined changes in wall motion after revascularization in segments with fixed, partially reversible, and completely reversible defects on 24-hour 201Tl scintigraphy, corresponding data for the late-redistribution SPECT studies are lacking.

A second study limitation was our inability to quantitatively compare true myocardial 201Tl concentrations with corresponding 13N-ammonia and 18F-deoxyglucose concentrations. Although tomographic imaging techniques facilitate comparison of 201Tl scintigraphy and PET, there are important differences inherent in these two methods.36 PET uses high-energy photons (511 keV) for imaging, and correction for tissue attenuation is routinely performed. In 201Tl scintigraphy, however, the photons are low energy (60–80 keV), and attenuation correction is impractical, resulting in unpredictable reductions in observed (compared with true myocardial) 201Tl concentrations.

The in-plane and z-axis spatial resolutions of the positron tomograph are better than those of the SPECT camera. Because the 201Tl images were not gated, the limited spatial resolution of the SPECT camera would have enhanced partial volume effects in areas with resting wall motion abnormalities and served to accentuate reductions in observed (compared with true myocardial) 201Tl activity. Because the PET images were not gated, the partial volume effect also caused a reduction in observed tracer concentrations in myocardial regions with wall motion abnormalities. However, the dual isotopic PET imaging technique more effectively deals with the partial volume effect, as differences in ventricular geometry and/or wall motion equally affect count recovery on both 13N-ammonia and 18F-deoxyglucose images. Subtraction of 13N profiles from 18F profiles to identify PET ischemia thus effectively eliminates partial volume effects. Because relative 201Tl concentrations obtained from circumferential profiles of transaxial SPECT images may be spuriously reduced due to attenuation and partial volume effects, a comparison of SPECT circumferential profiles to those of the PET images would have biased the study results against 201Tl scintigraphy.

Although the observers who graded 201Tl activity achieved a high level of agreement, reliance on visual determination of 201Tl redistribution also was a study limitation. Relatively high background activity was often present on the late images, and this may have caused two possible errors. Subtle redistribution might not have been appreciated, leading to the erroneous conclusion that a defect was fixed. Conversely, an apparent improvement in a defect due to higher background may have been interpreted as partial redistribution, thereby overestimating myocardial viability.

Because of these limitations, the data were separately analyzed using differing degrees of improvement in visual 201Tl score to define redistribution. These changes ranged from very sensitive (≥0.25; required one observer to perceive an improvement) to very insensitive (>1.00; required all observers to perceive an improvement). Use of a predefined change in visual 201Tl score to define redistribution is arbitrary because no clinical definition of redistribution has been “calibrated” against temporal changes in actual myocardial 201Tl concentrations. Nevertheless, the proportion of fixed defects with metabolic activity on PET was not dependent on the criterion used to define redistribution, indicating a consistency in the study’s basic findings.

Several investigators have used quantitative methods to assess 201Tl redistribution.39,40 For example, Klein et al39 developed a “reversibility bulls-eye map,” in which changes in relative 201Tl activities between stress and 4-hour delayed images are compared with a normal data base and displayed as a standard polar map. Although this quantitative method yields results that agree fairly well with those of human observers, it has not been validated in animal experiments. Furthermore, the effect of background activity on these measurements is unknown. Lear et al41 have shown that overestimation or underestimation of background can seriously affect quantitative measurements of redistribution on planar images. In addition, Hurwitz et al42 have suggested that
gated imaging may improve the quantitative assessment of $^{201}$TI redistribution. Because the software to quantitate $^{201}$TI redistribution on either ungated or gated SPECT images was unavailable to us, our results cannot be related to quantitative measurements of changes in relative $^{201}$TI concentrations.

Another limitation of PET in this investigation was its inability to visualize the entire heart. The anterobasilar segment was incompletely imaged in 18 patients, precluding comparison to $^{201}$TI scintigraphy. In addition, assessment of the inferior region of the heart on transaxial PET images is more demanding than on resliced short-axis or vertical long-axis images. Although these factors probably did not have a significant impact on the overall study results, they suggest that complete left ventricular characterization would best be achieved using newer tomographs with greater axial fields of view and resliced myocardial images orthogonal to the ventricular long axis.

**PET Image Analysis**

Thirty segments with fixed defects and four segments with partially reversible defects were normal on PET. Because most of these defects were in the distribution of a stenosed vessel (including those in the inferior segment), nearly all of the SPECT abnormalities could reasonably be attributed to CAD. Several factors may account for the discrepancies between the SPECT and PET studies. On the PET images, a perfusion defect was defined by relative $^{13}$N activity < 2 SDs from normal. Thus, even though several small foci of fibrosis or a rim of subendocardial fibrosis could reduce observed $^{13}$N counts, if the sum of all activity within a given 6° sector was within 2 SDs of the mean, then that sector was considered normal. PET perfusion defects were also defined by their anatomic extent to reduce the likelihood of a falsely positive study resulting from subtle differences in image level or in patient position. Some segments with anatomically small defects might have been classified normal on PET image analysis. Although this method of image analysis is probably more specific than sensitive for detecting ischemia and infarction, it is clinically useful for predicting improvement in segmental function after revascularization.

Thus, if a segment is normal or exhibits a perfusion–metabolism mismatch on PET, then the finding has practical clinical importance.

**Tissue $^{201}$TI Activity for Viability**

Relative myocardial $^{201}$TI concentrations have been proposed as a marker of tissue viability. A complete defect (absence of activity) implies transmural infarction, whereas an incomplete defect (diminished but observable activity) suggests residual viability (perhaps subendocardial fibrosis plus an epicardial rim of viable tissue). Mori et al. examined relative $^{201}$TI concentrations on 4-hour redistribution planar images in patients before coronary artery bypass. Fixed defects that had no functional improvement after revascularization had lower relative tracer concentrations than those with improved function after revascularization. However, the regions that did not improve had significantly poorer preoperative wall motion than those that did improve, raising the possibility that the lower observed $^{201}$TI counts in the areas without functional recovery may have reflected partial volume effects and not true differences in myocardial $^{201}$TI concentrations.

Use of relative tracer concentrations to assess myocardial viability assumes that there is no significant regional attenuation of activity, that partial volume effects do not substantially contribute to reductions in observed $^{201}$TI concentrations, that myocardial $^{201}$TI counts reflect only a viable compartment (no accumulation of tracer in “nonviable” interstitial compartments over time), and that tissue tracer concentrations predictably reflect the number of viable myocytes. As no studies have correlated relative $^{201}$TI concentrations on very late redistribution images with changes in regional wall motion after revascularization, it is unknown whether incomplete $^{201}$TI defects represent clinically important myocardial viability.

Some of our observations lend support to the hypothesis that tissue $^{201}$TI concentrations may be related to myocardial viability. PET infarct segments had significantly poorer $^{201}$TI scores than segments with metabolic activity, and the relative number of fixed defects with metabolic viability declined as the 24-hour score worsened. However, about one in seven fixed defects with near-complete defects were metabolically active on PET, suggesting that relative perfusion deficits alone may not adequately characterize the state of all hypoperfused myocardial segments. Furthermore, although late scores for partially reversible defects were significantly better than those of fixed defects, nearly half of partially reversible defects had PET infarction, including two thirds of the segments with balanced or late partial $^{201}$TI redistribution, raising the possibility that relative 24-hour $^{201}$TI concentrations may thus overestimate tissue viability in some instances. Further studies correlating myocardial $^{201}$TI concentrations on late redistribution images with functional improvement after coronary revascularization may be indicated.

**$^{201}$TI Reinjection for Viability**

Raising vascular $^{201}$TI concentrations by tracer reinjection may improve the detection of viable myocardium. Kayden et al. compared 24-hour planar redistribution images with reinjection images obtained shortly after the late redistribution images. Reinjection images were of higher quality than the 24-hour redistribution images, and the proportion of persistent 4-hour defects with reversibility increased from 21% on the late redistribution images to 52% after reinjection. Kiat et al. reasoned that longer myocardial exposure to high $^{201}$TI concentrations would reduce the frequency of late redistribution. They reinjected $^{201}$TI immediately after stress image acquisition and observed a late redistribution frequency of 24%, similar to the 22% observed in unselected patients without $^{201}$TI reinjection. In contrast, Dilsizian et al. reported that 24-hour redistribution images added little information to images obtained after reinjection at 3–4 hours.

Although it is assumed that reinjection enhances tissue tracer delivery by increasing vascular $^{201}$TI concentrations, actual plasma $^{201}$TI levels have not been reported in any of the reinjection studies. Because smaller initial $^{201}$TI doses were used in the reinjection studies (2.0–2.7 versus 3.0–3.5 mCi for the present study), it is uncertain how net tissue delivery of tracer with our protocol compares with that of the reinjection
techniques. As $^{201}$TI reinjection was not performed in the current investigation, it is unknown how the tissue characterization afforded by reinjection SPECT images would have compared with that of PET metabolic imaging in our study population.

**Twenty-four-Hour Versus 4-Hour Redistribution**

If the findings at 4 hours are analyzed, it is possible to determine if late imaging influenced the $^{201}$TI scintigraphic assessment of myocardial viability. If defects with balanced redistribution are considered partially reversible and those with late redistribution are considered fixed, then seven completely reversible, 19 partially reversible, and 105 fixed defects would have been observed at 4 hours. Of the 105 fixed defects, 54 (51.4%) exhibited metabolic activity on PET (23 PET ischemia and 31 normal). Similarly, 13 (68.4%) of 19 partially reversible defects (seven PET ischemia and six normal) and four of five (80%) completely reversible defects exhibited metabolic activity (one PET ischemia and three normal). These results parallel those of previous studies comparing 4-hour redistribution images with PET.11-14 Thus, delayed imaging did not substantially influence the $^{201}$TI scintigraphic determination of myocardial viability in our study population.

Only sixteen of 129 (12.4%) 4-hour perfusion defects exhibited late redistribution, a frequency lower than previously reported values.16-19 This may reflect differing patient populations and/or local practice. Our patients had severe disease, as indicated by angiography (92% had multivessel disease), number of prior infarcts (mean, 1.6 per patient), severity of left ventricular dysfunction (mean ejection fraction, 32.1%; 65% had heart failure), the electrical instability of these individuals (35% had serious ventricular dysrhythmias; five had prior cardiac arrest), and number of segmental perfusion defects (mean, 5.5 per patient).

In contrast, Cloninger et al17 reported that 46% of patients with prior Q wave infarctions had late redistribution on delayed imaging. However, these individuals “were selected for additional 8 to 24 h delayed imaging on the basis of incomplete redistribution in the 4 h delayed images.”17,p956 Thus, the higher incidence of late redistribution may reflect this selection criterion, as partial redistribution on 4-hour images already suggested myocardial viability.

Kiat et al18 reported that 64% of 4-hour nonreversible defects had late reversibility. Only one half of their patients had prior infarction, suggesting that their study population had less extensive coronary disease than ours. These investigators noted that “late imaging was preferentially performed in our laboratory in patients with a 4-h nonreversible defect that was considered likely to reverse late; that is patients with no prior myocardial infarction who had a positive stress electrocardiogram (ECG) or convincing symptoms of angina, or both.”18,p1457 Thus, the 64% incidence of late redistribution reflects a patient population in which late redistribution was considered likely by clinical criteria.

In an unselected population, Yang and collaborators57 observed that 22% of segments with persistent 4-hour defects exhibited late reversibility, a value closer to ours. As only half of their subjects had prior infarction, the disease severity in their population appears less marked than ours, accounting for the slightly higher incidence of late redistribution that they observed.

**Stress Versus Rest $^{201}$TI Scintigraphy**

Comparing stress-redistribution $^{201}$TI studies with resting PET studies assumes that late $^{201}$TI redistribution indicates viability in segments with stress defects. Because the 4- and 24-hour images are redistribution images, they could differ from rest images. Previous reports indicate that 4-hour redistribution images are identical to rest images in 73–78% of patients with known or suspected coronary artery disease,49,50 implying a fair agreement. A similar study comparing rest with 24-hour redistribution images has not been performed. However, the proportion of fixed defects with metabolic viability in the 19 stress studies did not differ significantly from that of the rest studies in the current investigation. Had only resting $^{201}$TI scintigraphy been used for comparison with PET, it is unlikely that there would have been a significant effect on the study results.

**Correlation With Angiographic Lesions**

SPECT imaging was 85% sensitive and 93% specific for disease detection in individual arteries. Sensitivity is slightly less than in some series51-54 since seven patients had rest studies and those with stress studies achieved only 76% of their maximal predicted heart rate. The large number of SPECT defects reflects the extensive disease in the patients studied and the fact that these individuals were referred for evaluation of myocardial viability.

Of 105 segments with PET ischemia or infarction, 95 (90%) were perfused by narrowed vessels. Four segments with stenosed vessels were considered normally perfused because of a patent graft. Thus, the PET abnormalities may reflect a myocardial event that preceded revascularization, an impairment in blood flow not apparent on angiography, or both. Three other segments were supplied by arteries with moderate (50%) stenoses, suggesting that lesion severity exceeded that predicted by the angiographic anatomy.55-57 Discrepancies between anatomic and physiological lesion severity may also explain why 58% of PET normal segments were supplied by diseased vessels; in these segments, resting blood flows were sufficient to meet local tissue oxygen demands.

**Clinical Significance of Findings**

For some individuals with CAD, treatment is straightforward and the determination of myocardial viability is not a crucial component of the clinical decision-making process. Rather, it is for the patient with ischemic heart disease and impaired left ventricular function in whom revascularization is being contemplated that the results of the current study are most germane. A clinical history of infarction and a resting wall motion abnormality do not exclude the presence of viable tissue.58-62 Because the risk of revascularization is higher in patients with impaired ventricular function, determination of the remaining amount of viable tissue is important for clinical decision making in these individuals.

Early clinical studies indicated that $^{201}$TI redistribution on 4-hour images identifies myocardium that will benefit from revascularization.23 Consistent with these reports, we also found that complete $^{201}$TI redistribution
correlated well with tissue viability as identified by PET metabolic imaging. As the limitations of 4-hour redistribution $^{201}$TI scintigraphy became apparent, some proposed more delayed redistribution imaging. In our patients with severe CAD, however, 24-hour delayed imaging did not appreciably influence the $^{201}$TI scintigraphic determination of myocardial viability as defined by PET metabolic imaging.

In concert with previous studies, this investigation supports the concept that local factors may contribute to the underestimation of myocardial viability by $^{201}$TI scintigraphy in some individuals with chronic CAD. Thus, it may be prudent to use an independent marker of myocardial viability, such as PET imaging with $^{18}$F-deoxyglucose, to assist in the clinical evaluation of patients with left ventricular dysfunction and persistent $^{201}$TI defects in whom coronary revascularization is being contemplated.

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PET Metabolism in 24-Hour SPECT 201Tl Defects


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