Feasibility of Tomographic $^{99m}$Tc-Hexakis-2-Methoxy-2-Methylpropyl-Isonitrile Imaging for the Assessment of Myocardial Area at Risk and the Effect of Treatment in Acute Myocardial Infarction

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$^{99m}$Tc-hexakis-2-methoxy-2-methylpropyl-isonitrile (Tc-Sestamibi), a new myocardial perfusion radiopharmaceutical, was injected intravenously in 11 patients within 4 hours of the onset of acute myocardial infarction before treatment with intravenous tissue-type plasminogen activator and 6–14 days later. Five patients with acute myocardial infarction who did not receive intravenous thrombolytic therapy underwent a similar injection of radiopharmaceutical. The absence of redistribution of Tc-Sestamibi permitted imaging with single-photon emission computed tomography up to 6 hours after intravenous injection to assess the distribution of myocardial perfusion at the time of administration. The region of hypoperfused myocardium on the initial images varied widely from 9% to 68% of the left ventricle and was significantly greater in anterior than in inferior infarcts ($p<0.01$). The region of hypoperfused myocardium on the final images varied widely from 0% to 63% of the left ventricle and was also greater in anterior infarcts ($p<0.01$). The final hypoperfused region correlated ($r=-0.82$) with the late resting ejection fraction and with the late regional wall motion score in the infarct segment for both anterior ($r=-0.74$) and inferior ($r=-0.97$) infarcts. There was a significant decrease ($-13\pm11\%$, $p<0.003$) in the extent of hypoperfused myocardium between the initial and final studies in the patients who received thrombolytic therapy compared with an insignificant increase ($4\pm6\%$, $p>0.5$) in the patients who did not receive thrombolytic therapy. Tomographic imaging with Tc-Sestamibi permits determination of the amount of hypoperfused myocardium “at risk” in acute myocardial infarction. The change in myocardial perfusion determined by Tc-Sestamibi before and after therapy in acute myocardial infarction is a promising tool for assessing treatment. (Circulation 1989;80:1277-1286)

Randomized trials have clearly shown that acute intervention with thrombolytic therapy reduces mortality in acute myocardial infarction. Although this beneficial effect is presumably due to a reduction in myocardial necrosis as a result of clot lysis in the infarct-related artery, previous attempts to show a reduction in infarct size by thrombolytic therapy have yielded less consistent results. Some trials have not shown any treatment benefit, whereas others have found that significant benefit is restricted to patients with anterior infarction. The end points used to assess therapeutic efficacy have included the resting ejection fraction after infarction and thallium defect size after infarction and the change in the resting ejection fraction measured during and after infarction. Using intracoronary injections of $^{99m}$Tc-
macroggregated albumin and gated planar imaging, Feiring et al\textsuperscript{13} showed that the amount of myocardium “at risk” during acute myocardial infarction is highly variable, even when the coronary occlusion occurs in a similar location. On the basis of these findings, they suggested that the determination of the amount of myocardium at risk was therefore crucial in the assessment of acute intervention in myocardial infarction.

\textsuperscript{99m}Tc-hexakis-2-methoxy-2-methylpropyl-isonitrile (Tc-Sestamibi) is a new radiopharmaceutical that appears useful for myocardial perfusion imaging.\textsuperscript{14-20} Like \textsuperscript{201}Tl, Tc-Sestamibi is rapidly cleared from the blood pool and accumulates in normal myocardium in direct proportion to blood flow.\textsuperscript{14} In the setting of acute coronary occlusion, a close relation exists between the distribution of microspheres and the circumferential count profile on tomographic Tc-Sestamibi images.\textsuperscript{19} Unlike \textsuperscript{201}Tl, Tc-Sestamibi has a very slow washout from the myocardium with minimal redistribution.\textsuperscript{14} Imaging can therefore be delayed for up to 6 hours and still provide information about the distribution of myocardial perfusion at the time of administration. This radiopharmaceutical should therefore be ideal in assessing the amount of myocardium at risk in acute myocardial infarction without requiring any delay in the administration of thrombolytic therapy. This pilot study was designed to assess the feasibility of using this radiopharmaceutical for this purpose and to determine its potential role in assessing the effect of treatment in myocardial infarction.

\textbf{Methods}

\textbf{Study Population}

The thrombolysis group consisted of 11 patients who were enrolled in Phase IIB of the Thrombolysis in Myocardial Infarction study (TIMI). The eligibility criteria for the study are described in detail elsewhere.\textsuperscript{21} In brief, the inclusion criteria were 1) chest pain of at least 30 minutes in duration, 2) electrocardiographic ST segment elevation of 0.1 mV or more in at least two leads, and 3) initiation of intravenous tissue-type plasminogen activator therapy within 4 hours of the onset of chest pain. There were 19 specific exclusion criteria for the TIMI trial, which were related primarily to contraindications to thrombolytic therapy. There were three additional exclusion criteria for this study: 1) evidence of previous myocardial infarction, 2) any nuclear medicine study with \textsuperscript{99m}Tc within 48 hours of presentation, and 3) clinical instability preventing transport within 6 hours of Tc-Sestamibi administration to the Nuclear Cardiology Laboratory for tomographic imaging.

The conventional treatment group consisted of five patients who were admitted during the same time period with chest pain of at least 30 minutes in duration and ST elevation of 0.1 mV or more in at least two electrocardiographic leads and who were not treated with thrombolytic therapy. These patients were excluded from entry into the TIMI trial because they either had chest pain of more than 4 hours in duration (four patients) or had a contraindication to thrombolytic therapy (one patient). Two patients in the conventional treatment group had an unsuccessful attempt at acute percutaneous transluminal coronary angioplasty (PTCA) (Table 1). The remaining three patients did not undergo attempted revascularization within 24 hours of presentation.

Eleven patients (six in the treatment group and five in the control group) were enrolled at the Mayo Clinic. Five patients in the treatment group were enrolled at Baylor College of Medicine.

The location of the infarction was assigned (anterior, inferior, or lateral) according to the location of the electrocardiographic leads with ST elevation.

\textbf{Clinical Care}

All patients were admitted to the Coronary Care Unit and received conventional therapy, including oxygen, nitrates, and morphine, as required.

In the thrombolysis group, patients received 100 mg intravenous recombinant tissue-type plasminogen activator during 6 hours: 60 mg during the 1st hour, 20 mg during the 2nd hour, and 5 mg during each of the next 4 hours. These patients also received prophylactic lidocaine, intravenous heparin, and low-dose aspirin according to predetermined guidelines. In accordance with the TIMI Phase IIB protocol, patients in the thrombolysis group were randomized to (1) acute intravenous metoprolol therapy or no acute \( \beta \)-blocker therapy and (2) early cardiac catheterization at 18 to 48 hours with PTCA of the infarct-related artery or cardiac catheterization at 8–10 days unless necessary sooner for the management of recurrent ischemic events.

In the conventional treatment group, patients received additional therapy, including heparin, aspirin, \( \beta \)-blockers, cardiac catheterization, and PTCA, according to the judgment of their staff cardiologist.

\textbf{Radionuclide Acquisition}

Tc-Sestamibi was prepared using a sterile, nonpyrogenic, lyophilized kit. After \textsuperscript{99m}Tc was added, the mixture was boiled for 10 minutes. After subsequent cooling, radiochemical purity was confirmed using thin-layer chromatography. The total preparation time was approximately 30 minutes. Kits were prepared every 6 hours on a routine basis so that they were immediately available for injection.

After giving informed consent, each patient received 20–30 mCi of Tc-Sestamibi intravenously before the initiation of thrombolytic therapy. Radionuclide acquisitions were performed 1–6 hours later with a commercially available rotating gamma camera (Elsinfect, Haifa, Israel or Adac Laboratories, Sunnyvale, California). Thirty images (64\times64 matrix) were acquired for 40 seconds each, at every 6\textsuperscript{6}
TABLE 1. Data of the 11 Patients in the Thrombolysis Group and the Five Patients in the Conventional Treatment Group

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Myocardial infarction location</th>
<th>Time to T-PA/Tc-Sestamibi (min)*</th>
<th>Infarct-related artery</th>
<th>Hypoperfused region time (%L.V)</th>
<th>Late rest ejection fraction</th>
<th>Late regional wall motion score$</th>
<th>Late rest</th>
<th>Late regional wall motion score$</th>
</tr>
</thead>
<tbody>
<tr>
<td>57</td>
<td>M</td>
<td>Anterior</td>
<td>88</td>
<td>LAD (proximal)</td>
<td>90 PTCA</td>
<td>55</td>
<td>58</td>
<td>25</td>
<td>0.43</td>
</tr>
<tr>
<td>66</td>
<td>F</td>
<td>Lateral</td>
<td>215</td>
<td>RCA (proximal)</td>
<td>70 PTCA</td>
<td>38</td>
<td>49</td>
<td>33</td>
<td>-16</td>
</tr>
<tr>
<td>72</td>
<td>M</td>
<td>Inferior</td>
<td>118</td>
<td>RCA (proximal)</td>
<td>100 CABG</td>
<td>48</td>
<td>9</td>
<td>4</td>
<td>-5</td>
</tr>
<tr>
<td>57</td>
<td>M</td>
<td>Inferior</td>
<td>120</td>
<td>RCA (distal)</td>
<td>99 PTCA</td>
<td>7</td>
<td>21</td>
<td>14</td>
<td>-7</td>
</tr>
<tr>
<td>64</td>
<td>M</td>
<td>Anterior</td>
<td>215</td>
<td>LAD (proximal)</td>
<td>95 PTCA</td>
<td>6</td>
<td>58</td>
<td>54</td>
<td>-4</td>
</tr>
<tr>
<td>44</td>
<td>M</td>
<td>Anterior</td>
<td>200</td>
<td>LAD (mid)</td>
<td>95 PTCA- unsuccessful†</td>
<td>48</td>
<td>22</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>56</td>
<td>F</td>
<td>Inferior</td>
<td>152</td>
<td>RCA (proximal)</td>
<td>95 None</td>
<td>—</td>
<td>15</td>
<td>0</td>
<td>-15</td>
</tr>
<tr>
<td>64</td>
<td>M</td>
<td>Anterior</td>
<td>127</td>
<td>LAD (proximal)</td>
<td>50 None</td>
<td>—</td>
<td>68</td>
<td>35</td>
<td>-3</td>
</tr>
<tr>
<td>71</td>
<td>M</td>
<td>Anterior</td>
<td>225</td>
<td>LAD (mid)</td>
<td>100 None</td>
<td>—</td>
<td>38</td>
<td>35</td>
<td>-3</td>
</tr>
<tr>
<td>57</td>
<td>F</td>
<td>Inferior</td>
<td>75</td>
<td>RCA (proximal)</td>
<td>100 None</td>
<td>—</td>
<td>60</td>
<td>38</td>
<td>-22</td>
</tr>
<tr>
<td>53</td>
<td>F</td>
<td>Anterior</td>
<td>136</td>
<td>LAD (proximal)</td>
<td>20 None</td>
<td>—</td>
<td>66</td>
<td>41</td>
<td>-25</td>
</tr>
<tr>
<td>Mean±SD</td>
<td></td>
<td></td>
<td>152±54</td>
<td></td>
<td></td>
<td>42±22</td>
<td>30±19</td>
<td>13±11</td>
<td>0.43±0.14</td>
</tr>
</tbody>
</table>

Conventional treatment group

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Myocardial infarction location</th>
<th>Time to T-PA/Tc-Sestamibi (min)*</th>
<th>Infarct-related artery</th>
<th>Hypoperfused region time (%L.V)</th>
<th>Late rest ejection fraction</th>
<th>Late regional wall motion score$</th>
<th>Late rest</th>
<th>Late regional wall motion score$</th>
</tr>
</thead>
<tbody>
<tr>
<td>52</td>
<td>M</td>
<td>Inferior</td>
<td>706</td>
<td>LCx (proximal)</td>
<td>100 PTCA- unsuccessful CABG</td>
<td>12</td>
<td>11</td>
<td>15</td>
<td>+4</td>
</tr>
<tr>
<td>67</td>
<td>M</td>
<td>Inferior</td>
<td>300</td>
<td>RCA (proximal)</td>
<td>100 CABG</td>
<td>36</td>
<td>18</td>
<td>14</td>
<td>-4</td>
</tr>
<tr>
<td>68</td>
<td>M</td>
<td>Anterior</td>
<td>409</td>
<td>LAD (mid)</td>
<td>100 None</td>
<td>—</td>
<td>58</td>
<td>63</td>
<td>+5</td>
</tr>
<tr>
<td>47</td>
<td>M</td>
<td>Inferior</td>
<td>435</td>
<td>RCA (proximal)</td>
<td>100 None</td>
<td>—</td>
<td>14</td>
<td>25</td>
<td>+11</td>
</tr>
<tr>
<td>74</td>
<td>M</td>
<td>Inferior</td>
<td>112</td>
<td>RCA (proximal)</td>
<td>100 PTCA- unsuccessful CABG</td>
<td>4</td>
<td>41</td>
<td>Died in low output state at 30 hours</td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td></td>
<td></td>
<td>392±217</td>
<td></td>
<td></td>
<td>28±20</td>
<td>29±23</td>
<td>+4±6</td>
<td>0.48±0.16</td>
</tr>
</tbody>
</table>

LV, left ventricle; LAD, left anterior descending; RCA, right; LCx, left circumflex; PTCA, percutaneous transluminal angioplasty; CABG, coronary artery bypass graft.

*t-PA for the thrombolysis group and Tc-Sestamibi for the conventional treatment group.

†Wall motion and perfusion abnormalities present in both inferior and lateral walls.

‡Inadequate views of inferior wall due to severe dilatation of right ventricle.

§Computed for appropriate infarct area.

††Attempted PTCA led to occlusion of left anterior descending coronary artery.

throughout a 180° arc beginning 45° right anterior oblique and ending 45° left posterior oblique.

Before discharge 6–14 days later, injection of Tc-Sestamibi was repeated, and an acquisition was repeated 1–6 hours later.

Resting radionuclide angiography was performed 1 day after the final Tc-Sestamibi study using modified in vivo labeling and previously described techniques. Data from this study are subsequently designated as "late."

Radionuclide Processing

Phantom validation. Tomographic acquisitions were performed on a static cardiac phantom (Capintec, Ramsey, New Jersey) with the same acquisition protocol described above. The myocardial portion of the phantom was filled with a solution of $^{99m}$Tc that provided a myocardial count density comparable to that observed in patient studies. Solid plastic pieces were introduced into the myocardial portion of the cardiac phantom to simulate 13 hypoperfused areas of different size (range, 4–71% of the left ventricle) and location that were representative of clinical situations; acquisitions were repeated.

Images were reconstructed with standard back-projection algorithms and a Ramp-Hanning filter. Short-axis slices of the left ventricle were obtained every pixel (6 mm) and normalized to the peak counts in the heart for each set of images. Circumferential count profiles were generated for three representative apical, midventricular, and basal slices by identifying the peak counts in every 6° sector around the left ventricle. Each pixel in this circumferential count profile was normalized by the peak value in the profile. The apical slice was chosen by selecting the slice where the left ventricular cavity was first visible and by moving one slice farther toward the base of the ventricle. The basal slice was chosen by selecting the slice where a decrease in septal activity was first visualized and by moving two slices farther toward the apex of the ventricle. The midventricular slice was chosen halfway between the apical and basal slices. When
sizable apical defects were present, the absence of the apex was confirmed by inspection of the horizontal and vertical long-axis slices, and the location of the apex was estimated visually. A circular region of interest was overlaid on each slice to determine the radius of the slice at a point midway between the endocardial and epicardial borders. When a large portion of a slice was absent, a symmetrical shape was assumed. The ventricle was assumed to consist of a hollow cylinder at the base and midventricle and a hollow cone at the apex. The relative volume of each geometrical cylinder and cone was estimated using the radius of the representative slice and standard geometrical formulas, assuming an equal myocardial thickness throughout. The hypoperfused portion of the left ventricle was estimated for different threshold values of the normalized counts in the circumferential count profile as described by Tamaki et al. A threshold value of 60% of peak counts yielded the best agreement between the true defect size as a percentage of left ventricular volume and the measured defect size (Figure 1), with a correlation coefficient of 0.99 and a regression line near the line of identity [measured defect=1.00(true defect)−1.07]. Additional experiments with all short-axis slices did not improve this correlation despite the potential “under-sampling” in the three-slice method. The three-slice method was therefore used throughout for computational simplicity.

The phantom data did suggest a small (<5%) systematic error in that anterior infarcts were overestimated compared with inferior infarcts. Given the small magnitude of this error and the difficulty of defining an accurate correction factor for infarcts of all sizes and locations, no correction was applied.

Patient studies. The initial and final patient images were reconstructed and processed with the same procedure described for the phantom studies by an observer unaware of patient treatment and outcome. Pixels in the circumferential count profile with less than 60% of peak counts were identified as hypoperfused, and the percentage of hypoperfused left ventricle was calculated. The contrast between normally perfused and hypoperfused areas was excellent, permitting easy visual confirmation of the hypoperfused area (Figure 2). Intraobserver and interobserver variabilities were assessed by repeat processing of 10 patient studies several weeks later.

The resting ejection fraction was determined from the resting radionuclide angiogram using standard techniques.

Regional wall motion was assessed subjectively on the resting radionuclide angigram by two observers unaware of the patient’s treatment and outcome using a 5-point grading system (4=normal, 3=mild hypokinesia, 2=moderate hypokinesia, 1=severe hypokinesia, and 0=akinesia or dyskinesia). A total of 10 segments were graded (three on the anterior view, five on the left anterior oblique view, and two on the left lateral view). The three anterior and two septal segments were assigned to the territory of anterior infarcts; the two lateral segments were assigned to lateral infarcts; the two inferior segments were assigned to inferior infarcts. A wall motion score in the infarct territory was computed as the average of the appropriate segmental scores of the two observers.

Coronary Angiography

Coronary angiography was performed as indicated by the TIMI Phase IIB protocol and as necessary for the management of recurrent ischemia. Standard percutaneous femoral or brachial cut-down approach was used. Multiple selective contrast injections were performed into the left main and right coronary arteries. Left ventriculography was performed by a simultaneous biplane technique. The infarct-related artery was identified by analysis of the electrocardiographic ST segment changes, left ventriculogram, and coronary angiogram. The infarct-related artery was judged to be patent or occluded by previously established criteria.

Statistical Analysis

The initial and final hypoperfused regions for each patient were compared using a paired t test. Comparisons between groups and between anterior and inferior infarcts were made with an unpaired t test. Simple linear correlation was performed between the hypoperfused region (initial, final, and change), the resting ejection fraction, and the regional wall motion score. A p value less than 0.05 was considered significant. All values are expressed as mean±SD.

Human Studies

The protocol and consent form was approved by the institutional review board at each of the participating institutions.
Results

Clinical Course

The clinical characteristics of the thrombolysis group and conventional treatment group are shown in Table 1.

In the thrombolysis group, patients received t-PA 152±54 minutes after the onset of chest pain. All patients underwent coronary angiography (seven within 48 hours and four before discharge), which showed a patent infarct-related artery in eight patients and an occluded infarct-related artery in three patients. Five patients received t-PA only, without PTCA or bypass grafting. Five patients underwent attempted PTCA at 6–55 hours. Four of these attempts were successful; one resulted in occlusion of a previously patent vessel. One patient underwent coronary artery bypass grafting at 48 hours.

In the conventional treatment group, patients received Tc-SeStamibi 392±217 minutes after the onset of chest pain. All of the patients underwent coronary angiography within 48 hours, which showed an occluded infarct-related artery in all cases. As mentioned previously, two patients underwent early PTCA, which was unsuccessful. One patient in this group, with an inferior infarct and hypoperfusion of 41% of the left ventricle, died at 30 hours in a low-output state.

Reproducibility of Measurement of Hypoperfused Region

The intraobserver variability for the determination of the percentage of hypoperfused left ventricle in patients was small, −1±3% with a range of −5% to +5% (r=0.97 for the two determinations). The interobserver variability in patients was similar, −1±3% with a range of −6% to +3% (r=0.98 for the two determinations).

Amount of Hypoperfused Myocardium on the Initial Study

The amount of hypoperfused left ventricle on the initial study before therapy varied widely from 9% to 68% of the left ventricle (Figure 3). Inferior myocardial infarctions had generally less hypoperfused myocardium than anterior infarctions (24±18% vs. 53±17%, p<0.01), but there were individual exceptions (patients 6, 10, and 16). The single patient with a lateral infarction by electrocardio-
dium (49%), which included both lateral and inferior walls. There was a significant correlation ($r = -0.68$, $p=0.005$) between the initial amount of hypoperfused myocardium and the late resting ejection fraction.

Within infarct categories, there was a wide range of hypoperfused myocardium (9–60% for inferior myocardial infarctions and 22–68% for anterior myocardial infarctions). The location of the coronary occlusion could account for only a portion of this variability. For example, although the largest hypoperfused region in the patients with inferior infarcts (60% in patient 10 and 41% in patient 16) occurred in the presence of both right coronary and left circumflex involvement, the single patient (patient 4) with distal right coronary occlusion had a hypoperfused region of 21% compared with a range of 9–18% for the four patients with proximal right coronary occlusions.

**Amount of Hypoperfused Myocardium on the Final Study**

The amount of hypoperfused left ventricle on the final study varied widely from 0% to 63% of the left ventricle. Inferior infarctions had less hypoperfused myocardium than anterior infarctions (16±13% vs. 43±17%, $p<0.01$), but there were individual exceptions (patients 6, 10, and 15). There was a significant correlation ($r = -0.82, p=0.0002$) between the final amount of hypoperfused myocardium and the late resting ejection fraction (Figure 4), but the ejection fraction was variable in patients with hypoperfusion of less than 40% of the left ventricle. For both inferior and anterior infarcts, there was a correlation between the final amount of hypoperfused myocardium and the late regional wall motion score ($r = -0.97, p<0.01$; and $r = -0.74, p=0.055$, respectively). The final amount of hypoperfused myocardium did not differ significantly between the thrombolyis and conventional treatment groups (30±19% vs. 29±23%). The final amount of hypoperfused myocardium was closely related to the initial amount of hypoperfused myocardium ($r=0.85, p=0.0001$). For example, the eight patients with initially more than 25% of the left ventricle hypoperfused had a much larger final amount of hypoperfused myocardium (44±14%) than the seven patients with less than 25% of the left ventricle hypoperfused on the initial study (13±9%).

**Change in Hypoperfused Myocardium**

Ten of the 11 patients in the thrombolysis group had a decrease in the amount of hypoperfused myocardium between the initial and final Tc-
Sestamibi studies (Figure 5). The remaining patient, who had occlusion of the left anterior descending coronary artery during attempted PTCA, was unchanged. The change in hypoperfused myocardium for the thrombolysis group (mean, −13%; range, 0% to −33%) was significant (p<0.003). Three of the four patients in the conventional treatment group had a slight increase in the amount of hypoperfused myocardium between the initial and final Sestamibi studies. There was no significant change for the group as a whole (mean, +4%; range, −4% to +11%; p>0.5).

The change in hypoperfused myocardium did not correlate with the initial amount of hypoperfused myocardium (r=0.37), the final amount of hypoperfused myocardium (r<0.1), or resting ejection fraction (r<0.1).

Discussion

Tc-Sestamibi is a promising new myocardial perfusion imaging agent, which has a very slow washout from the myocardium with minimal redistribution.14 This property permits the administration of the radiopharmaceutical before the injection of thrombolytic therapy and subsequent imaging up to 6 hours later to determine myocardial perfusion at the time of administration.14-26 As shown in this study, this radiopharmaceutical can therefore assess the amount of hypoperfused myocardium during acute infarction without any delay in the administration of thrombolytic therapy.

Many animal studies have shown that the amount of myocardium supplied by an occluded coronary artery is highly variable.27-29 Using intracoronary injections of macroaggregated albumin, Feiring et al13 showed that patients with acute infarction have great variability in the amount of myocardium at risk, even when the coronary occlusion occurs in a similar location. This broad spectrum presumably reflects variability in the actual territory supplied by the native coronary vessels and the variable effect of collaterals in patients with long-standing coronary artery disease. Our results confirm the variability in the amount of myocardium at risk with a more practical method. Tc-Sestamibi can be easily injected intravenously before thrombolytic therapy without any delay. Unlike 201TI, immediate imaging is not required because Tc-Sestamibi does not redistribute significantly within the myocardium. The higher energy gamma ray of 99mTc compared with 201TI and the greater radioactivity that can be administered (30 vs. 4 mCi) provide higher-count density images that are ideally suited to tomographic quantification.

More important, if the uptake of Tc-Sestamibi on the final images is an accurate representation of viable, perfused myocardium, the change in hypoperfused myocardium between the initial and final images would permit assessment of the efficacy of acute therapy. The assessment of myocardial viability after reperfusion is a matter of some controversy. Although the uptake of 30Ti is generally an indicator of myocardial viability, animal studies have suggested that the uptake of 201TI early after reperfusion could be misleading30-32 presumably because of reactive hyperemia. However, clinical studies33,34 have not found evidence of reactive hyperemia and thus have not substantiated the reservations implied by the animal studies. Although the uptake of Tc-Sestamibi usually parallels that of 201TI,15,16 in one report, Tc-Sestamibi distinguished areas of infarction and ischemia, whereas 201TI did not. Animal studies of permanent coronary occlusion20 have shown a close correlation between pathologic infarct size and tomographic defect size by Tc-Sestamibi, but the findings in reperfusion models have been more variable.35,36

The present study suggests that the uptake of Tc-Sestamibi 6–14 days after infarction does indicate “functional” myocardium. The final amount of hypoperfused myocardium inversely correlated with the late resting ejection fraction despite the potential confounding effects of preexisting myocardial dysfunction or of delayed mechanical recovery on this relation. In addition, late regional wall motion score in the infarct area was inversely correlated with the final amount of hypoperfused myocardium for anterior and inferior infarctions. Thus, global
and regional function after infarction are closely related to the uptake of Tc-Sestamibi on the final images. However, the poorly functioning myocardium that does not accumulate Tc-Sestamibi could still be viable; future studies with positron emission tomography could help to clarify this issue.

Previous assessments of therapy in acute myocardial infarction have used measurements of resting ejection fraction and thallium defect size measured after infarction or of the change in resting ejection fraction measured during and after infarction. Perfusion or function measurements obtained after infarction are clearly dependent on the amount of myocardium at risk initially as demonstrated by Feiring et al and by this study. The variability in the amount of myocardium at risk will therefore be a potential obstacle in the detection of any treatment benefit, except in large randomized trials where the amount of initially hypoperfused myocardium will presumably be similar in treated and control patients. In the present study, neither late resting ejection fraction nor the final amount of hypoperfused myocardium were significantly different in the thrombolysis group compared with the conventional treatment group. In this small number of patients, any treatment effect on these end points was presumably obscured by the wide variation in myocardium at risk.

The use of the change in resting ejection fraction measured during and after infarction could provide some adjustment for the amount of initially hypoperfused myocardium. Simoons et al and Guerci et al found that the change in ejection fraction showed a more significant treatment effect than the ejection fraction after infarction. However, the resting ejection fraction measured during infarction is influenced by many factors other than the amount of hypoperfused myocardium, including preload, afterload, duration of myocardial ischemia, and hyperkinesis in normal segments. These factors could contribute to the large spontaneous changes that occur in ejection fraction during the first 24 hours of acute myocardial infarction. Measurement of acute resting ejection fractions were not obtained in the present study. However, Feiring et al showed that these ejection fractions did not correlate with the amount of myocardium at risk. Thus, the end points previously used to assess acute intervention in myocardial infarction probably do not adequately adjust for the variable amount of initially hypoperfused myocardium. This could account for the failure to show significant myocardial salvage in studies or subgroups that involved relatively small numbers of patients. The change in hypoperfused region assessed by tomographic imaging with Tc-Sestamibi appears to be a promising measurement tool, which adjusts for the variable amount of initially hypoperfused myocardium. Possibly, the final images can be obtained much earlier after therapy to assess efficacy. Further studies are needed to determine the relation between Tc-Sestamibi uptake early after myocardial infarction and myocardial blood flow and viability.

The wide range in the change in the amount of hypoperfused left ventricle could be related to many factors, including the presence and timing of acute reperfusion. Because angiography during the acute conditions was not routinely performed, we could not determine whether or not thrombolysis produced successful reperfusion, and we could not determine the timing of this event. There was no correlation between time to therapy and the change in hypoperfused myocardium in the thrombolysis group. The three patients in the thrombolysis group (patients 3, 6, and 9) with documented occlusion 48 hours after therapy had the smallest amount of change ( 5, 9, and 3, respectively). None of the conventional treatment patients had spontaneous reperfusion, which might have altered the final amount of hypoperfused myocardium.

The quantitative method used in the present study has several limitations. Its validation is based on a static cardiac phantom, which does not take into account cardiac motion, areas of low but not absent flow, variable patient background, and variable myocardial shape and thickness. The count density in Tc-Sestamibi images is sufficient to permit the future use of gated tomographic imaging that would minimize motion. The close correlation (r=0.95) between pathologic and tomographic infarct size in a permanent occlusion animal model with a similar threshold technique would suggest that the error due to areas of low flow is minimal. The variability in background and myocardial shape and thickness in individual patients contribute to possible error. There is also a potential error due to under-sampling using this three-slice method compared with a method in which all slices are analyzed.

The percentage of hypoperfused myocardium for several of the patients who survived anterior myocardial infarctions exceeded 50%, which appears to conflict with the widely accepted notion that cardiogenic shock occurs with infarction of more than 40% of the left ventricle. Of note, however, this figure is based on the study of Page et al, which was an autopsy series that concluded that patients who died in cardiogenic shock had more than 40% of the left ventricle involved; no survivors of myocardial infarction were included in their study. Clinical experience with echocardiography, radionuclide angiography, and contrast ventriculography suggests that many survivors of myocardial infarction with large left ventricular aneurysms have considerably more than 50% of the ventricle infarcted. The data of Feiring et al tend to confirm this impression; five of their 13 patients with anterior myocardial infarctions had involvement of more than 40% of the left ventricle.

The Tc-Sestamibi methodology used here offers promise as an adjunct in clinical decision making for individual patients with acute myocardial infarc-
tion. However, there are several practical difficulties that must be overcome to permit its widespread clinical application. First, the preparation kit currently used requires 30 minutes for preparation. It does not contain any bacteriostatic agent and must therefore be administered within 6 hours. To permit the rapid administration of Tc-Sestamibi without delaying thrombolytic therapy, kits must be prepared routinely four times daily. Such frequent preparation is clearly impractical. The addition of a suitable bacteriostatic agent should help to reduce the frequency of preparation. Second, the acquisition of tomographic images requires equipment that is not currently available in many community hospitals and includes potential hazards involved in the transportation of critically ill patients. Planar imaging could provide a reasonable alternative to tomographic imaging but would do so at the cost of some loss of localization and perhaps quantitative accuracy. Analysis of the planar studies performed as part of this multicenter trial is currently underway; these studies will be the subject of a separate report. Although these practical issues could limit the widespread clinical utilization of tomographic imaging with Tc-Sestamibi in acute myocardial infarction, we believe that these data show its feasibility and promise as a measurement tool for assessing acute intervention strategies in any future clinical trials.

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References


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Feasibility of tomographic 99mTc-hexakis-2-methoxy-2-methylpropyl-isonitrile imaging for the assessment of myocardial area at risk and the effect of treatment in acute myocardial infarction.

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