

# Technetium-99m Sestamibi for the Assessment of Myocardial Salvage Following Reperfusion Therapy in Acute Myocardial Infarction

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## Abstract

**Introduction:** Reperfusion therapy with either thrombolysis or angioplasty has been shown to be beneficial in acute myocardial infarction. Tc-99m sestamibi is a myocardial tracer that can be used to assess myocardial salvage because of its property of very limited redistribution. **Materials and Methods:** To assess the feasibility of this technique locally, Tc-99m sestamibi was injected before and after reperfusion therapy with angioplasty (n = 11) or streptokinase (n = 18) in 29 patients with acute myocardial infarction (anterior = 25, inferior = 4). Single-photon emission computed tomography (SPECT) was performed within 4 hours of reperfusion and repeated 5 to 7 days later. **Results:** Initial perfusion defect size ranged from 6% to 78% (mean  $36.3 \pm 18.7\%$ ), and final defect size from 0% to 50% of the left ventricle (mean  $23.7 \pm 14.8\%$ ,  $P < 0.001$ ). Patients with proximal left anterior descending artery (LAD) lesions had larger defects compared to those with mid LAD lesions (mean defect size 52% for pLAD versus 28% for mLAD,  $P < 0.013$ ). However, there were wide variations in initial defect size (myocardium at risk) for a given infarct-related artery location. The mean decrease in defect size was 12% in the 28 patients with patent arteries compared to only 2% in the patient with an occluded artery (47% to 45%). There was no significant difference in amount of salvage between patients who had thrombolysis (mean 13%,  $P = 0.0003$ ) and patients who had percutaneous transluminal coronary angioplasty (PTCA) (mean 12%,  $P = 0.005$ ). **Conclusions:** Assessment of myocardial salvage is feasible using Tc-99m sestamibi SPECT imaging. It allows for quantitation of myocardium at risk and the amount of myocardial salvage, which is not possible by angiography alone.

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**Key words:** Myocardial salvage, Quantitative defect severity, Reperfusion therapy, Single-photon emission computed tomography

## Introduction

Reperfusion therapy for acute myocardial infarction is feasible with thrombolytic therapy as well as acute percutaneous transluminal coronary angioplasty (PTCA). Both modalities of treatment have been proven to improve long-term survival.<sup>1,2</sup> The extent of improvement, however, depends directly on the amount of myocardial salvage obtained. The assessment of efficacy of either therapy is complicated by the fact that arterial patency does not allow for assessment of the amount of myocardial salvage, which varies with the time to reperfusion and the area supplied by the infarct-related artery (IRA).

Tc-99m sestamibi single-photon emission computed tomography (SPECT) imaging has been advocated as a

means of overcoming this problem. Tc-99m sestamibi is a synthetic lipophilic cationic SPECT myocardial perfusion agent that is initially distributed in the myocardium according to blood flow. It actively and passively distributes across sarcolemmal and mitochondrial membranes and 90% of Tc-99m sestamibi activity can be found in the mitochondria as the original free cationic complex, showing negligible redistribution over time.<sup>3,4</sup> The property of minimal redistribution is useful in the initial assessment of the amount of myocardium at risk, as injection of this tracer prior to reperfusion therapy will allow for assessment of the amount of at risk myocardium, even when imaging is performed several hours later,<sup>5-8</sup> without any inhibition to reperfusion therapy. A second injection following

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reperfusion will allow for assessment of the final amount of myocardial salvage, by comparison with the initial image, using objective polar map quantitation.

## Materials and Methods

### *Aims of Study*

To study the feasibility of using Tc-99m sestamibi for assessment of myocardial salvage in our local setting, we performed imaging before, and 5 to 7 days after PTCA ( $n = 11$ ) or thrombolytic therapy ( $n = 18$ ) in 29 patients who had diagnosis of acute myocardial infarct on ECG, enzymatic and clinical grounds. The study period lasted from January 1993 through February 1996. All patients selected were informed of the risks and benefits of both procedures. As a secondary objective, we studied the relationship between angiographic findings and the extent of defect by polar map quantitation.

Patients were excluded if they had any absolute contraindication to PTCA or thrombolytic therapy or refused consent to either procedure. Patients with a prior history of myocardial infarct or had ECG evidence of prior infarct were also excluded as assessment of the myocardium at risk would be confounded by the presence of prior infarct.

### *Thrombolytic Protocol*

All patients in this protocol were given 300 mg of aspirin prior to thrombolytic therapy.  $1\frac{1}{2}$  million units of intravenous streptokinase was administered over 1 hour, with intravenous hydrocortisone given prior to streptokinase infusion, to prevent allergic complications.

### *PTCA Protocol*

All patients in this protocol were also given 300 mg of aspirin prior to PTCA. Following diagnostic angiography, the IRA was identified and dilated according to standard protocols. Coronary stenting of the IRA was performed at the discretion of the interventionist if balloon angioplasty alone did not achieve adequate results. Intravenous heparin was given post-angioplasty at a rate of 10 units/kg/hour for at least 24 hours.

### *Imaging Protocol*

Preparation of unit doses of Tc-99m sestamibi were made on a daily basis and kept in a lead shielded syringe and lead box in the coronary care unit (CCU). On admission of a patient with an acute myocardial infarct to the CCU, assessment of suitability for reperfusion therapy was made, and consent both for treatment and imaging was taken if the patient was found suitable.

Injection of sestamibi (15 to 20 mCi) was performed upon diagnosis of acute myocardial infarction but prior to reperfusion therapy.

SPECT imaging was performed 1 to 4 hours after injection, after completion of the reperfusion therapy and stabilisation of the patient. Repeat injection of Tc-99m sestamibi and imaging was performed 5 to 7 days later before discharge of the patient from the hospital. Twenty-three patients also had pre-discharge angiography to determine the degree of residual stenosis in the IRA. The other 6 patients did not agree to further angiographic studies.

### *SPECT Data Acquisition and Processing*

Post-injection acquisition in the supine position was begun within 1 to 4 hours, both for initial and repeat rest images. Step and shoot SPECT acquisition was done with a dual head system, with 64 projections ( $64 \times 64$  matrix) over a  $180^\circ$  anterior arc, using a low energy all-purpose collimator. Acquisition time was set at 20 seconds per frame.

Reconstruction was performed using filtered back-projection algorithm (Butterworth filter; order 5, cut-off 0.3). Reorientation was then performed to display the images in the standard short axis, and vertical and horizontal long axis cuts. Quantitative analysis was performed using the commercially available CEQUAL software program and customised normal databases.

The initial and final defect sizes were defined as the percentage of left ventricle with counts less than 2.5 standard deviations below counts of the normal database, using the respective images.

The change in defect size was defined as the initial defect size minus final defect size.

The percent change in defect size was defined as the change in defect size divided by the initial defect size multiplied by 100.

### *SPECT Interpretation*

Quantitative analyses of the SPECT images were done by an experienced observer blinded to the results of the angiography and type of reperfusion therapy.

### *Statistical Analysis*

The relationships between quantitative SPECT defect severity and infarct-related artery occlusion and degree of residual stenosis were analysed by linear regression analysis (Pearson's  $r$ ). All continuous variables were expressed as mean (M)  $\pm$  standard deviation (SD).

The alpha ( $\alpha$ ) level of significance was set at 0.05 and all computations were performed using SPSS® statistical software.

## Results

### *Demographic Data*

Twenty-nine patients (25 males, 4 females, age  $51.4 \pm$

9.0 years, range 31 to 67 years) were included in the study. Twenty-five patients had anterior infarction and 4 had inferior infarctions. Eleven patients underwent PTCA (all anterior) and 18 patients underwent thrombolysis (14 anterior, 4 inferior).

The site of infarct, type of reperfusion therapy, angiographic and initial and final image quantitative characteristics of the study cohort are shown in Table I.

#### PTCA Patients

All PTCAs in this study were successful with no procedure-related deaths. However, 1 patient was found to have an occluded infarct-related artery at pre-discharge angiography. The mean initial defect size was  $38.9 \pm 17.9\%$  (range 6% to 76%) and this decreased to  $27.3 \pm 13.4\%$  (range 0% to 45%) after acute angioplasty. The mean change in defect size was  $11.6 \pm 10.8\%$  (range 1% to 33%). The change in defect sizes in this patient group is shown in Figure 1.

#### Thrombolysis Patients

The mean initial defect size was  $34.7 \pm 19.5\%$  (range 7%

to 78%) and this decreased to  $21.4 \pm 15.9\%$  (range 0% to 50%) after acute thrombolysis. The mean change in defect size was  $13.2 \pm 12.4\%$  (range 3% to 57%). The change in defect sizes in this patient group is shown in Figure 2.

#### Complications

During the initial (acute infarct) imaging which was carried out in the Department of Nuclear Medicine, SGH, patients were monitored by a cardiologist. No acute deaths or major complications were observed in this study during the imaging procedure.

#### Initial Defect Size and Angiographic Findings

The initial defect size or myocardium at risk for the group as a whole ranged from 6% to 77% (mean  $36.3\% \pm 18.7\%$ ) and was correlated with the infarct-related artery occlusion, as shown in Table II and Figure 3.

#### Change in Defect Size

The mean initial defect size was  $36.3\% \pm 18.7\%$  (range 6% to 78%). The mean final defect size was  $23.7\% \pm 14.8\%$  (range 0% to 50%). The decrease in defect size was

TABLE I: PATIENT CHARACTERISTICS, DEFECT SIZES AND FINAL ANGIOGRAPHIC RESULTS

| No. | Age | Sex | Site of infarct | Treatment | Initial size | Final size | Change in size | Final angio findings |
|-----|-----|-----|-----------------|-----------|--------------|------------|----------------|----------------------|
| 1   | 53  | M   | Anterior        | PTCA      | 6            | 0          | 6              | MidLAD25             |
| 2   | 42  | M   | Anterior        | PTCA      | 47           | 36         | 11             | MidLAD90             |
| 3   | 60  | M   | Anterior        | PTCA      | 47           | 45         | 2              | MidLAD100            |
| 4   | 44  | M   | Anterior        | PTCA      | 76           | 43         | 33             | ProxLAD20            |
| 5   | 41  | M   | Anterior        | PTCA      | 56           | 26         | 30             | ProxLAD50            |
| 6   | 58  | M   | Anterior        | PTCA      | 36           | 35         | 1              | MidLAD25             |
| 7   | 38  | M   | Anterior        | PTCA      | 37           | 29         | 8              | ProxLAD40            |
| 8   | 50  | M   | Anterior        | PTCA      | 30           | 23         | 7              | ProxLAD20            |
| 9   | 46  | M   | Anterior        | PTCA      | 27           | 12         | 15             | MidLAD70             |
| 10  | 63  | F   | Anterior        | PTCA      | 32           | 19         | 13             | No angiogram         |
| 11  | 60  | M   | Anterior        | PTCA      | 34           | 32         | 2              | No angiogram         |
| 12  | 56  | F   | Anterior        | IVSK      | 62           | 49         | 13             | ProxLAD99            |
| 13  | 49  | M   | Anterior        | IVSK      | 78           | 50         | 28             | ProxLAD80            |
| 14  | 45  | M   | Anterior        | IVSK      | 7            | 2          | 5              | MidLAD95             |
| 15  | 56  | M   | Inferior        | IVSK      | 7            | 0          | 7              | ProxLCx90            |
| 16  | 57  | F   | Anterior        | IVSK      | 67           | 10         | 57             | LeftMain50           |
| 17  | 60  | M   | Anterior        | IVSK      | 23           | 6          | 17             | MidLAD90             |
| 18  | 50  | M   | Anterior        | IVSK      | 38           | 27         | 11             | MidLAD50             |
| 19  | 67  | M   | Anterior        | IVSK      | 26           | 18         | 8              | MidLAD40             |
| 20  | 65  | F   | Anterior        | IVSK      | 18           | 3          | 15             | MidLAD90             |
| 21  | 47  | M   | Anterior        | IVSK      | 35           | 28         | 7              | MidLAD80             |
| 22  | 31  | M   | Inferior        | IVSK      | 31           | 18         | 13             | MidRCA90             |
| 23  | 47  | M   | Anterior        | IVSK      | 42           | 29         | 13             | No angiogram         |
| 24  | 41  | M   | Inferior        | IVSK      | 14           | 3          | 11             | DistalRCA50          |
| 25  | 63  | M   | Anterior        | IVSK      | 26           | 22         | 4              | No angiogram         |
| 26  | 42  | M   | Inferior        | IVSK      | 31           | 22         | 9              | No angiogram         |
| 27  | 55  | M   | Anterior        | IVSK      | 34           | 31         | 3              | No angiogram         |
| 28  | 58  | M   | Anterior        | IVSK      | 49           | 39         | 10             | LeftMain25           |
| 29  | 47  | M   | Anterior        | IVSK      | 36           | 29         | 7              | ProxLAD95            |

F: female; IVSK: intravenous streptokinase; LAD: left anterior descending artery; LCx: left circumflex artery; M: male; Prox: proximal; PTCA: percutaneous transluminal coronary angioplasty; RCA: right coronary artery

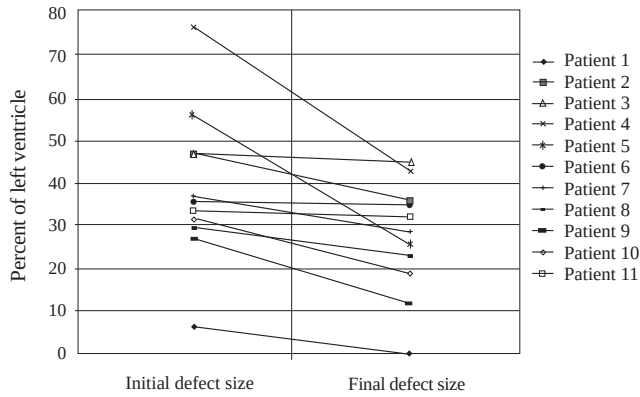


Fig. 1. Initial and final defect sizes in PTCA patients.

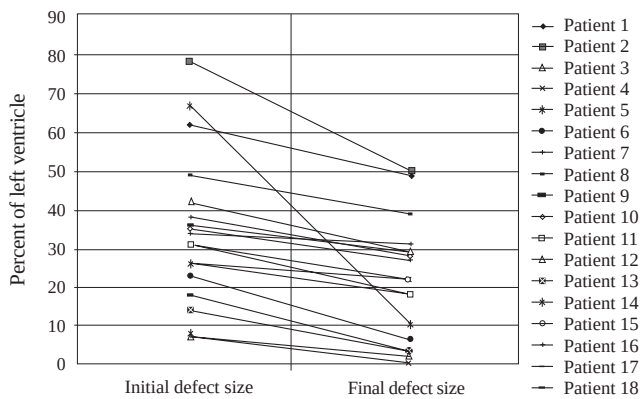


Fig. 2. Initial and final defect sizes in thrombolysis patients.

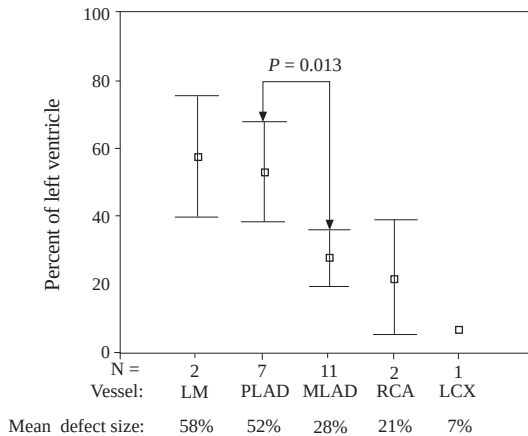


Fig. 3. Relationship of initial defect size and angiographic findings.

$12.6\% \pm 11.6\%$  (range 1% to 57%), and this represented a statistically significant improvement ( $P < 0.001$ ) over the initial defect size. The average percentage change in defect size was  $40.6\% \pm 28.7\%$  (range 3% to 100%).

#### Change in Defect Size and Patency of Infarct-Related Artery (IRA)

In the patients with patent IRA on pre-discharge

TABLE II: RELATIONSHIP BETWEEN INITIAL DEFECT SIZE AND ANGIOGRAPHIC FINDINGS

| Site of occlusion  | No. of patients | Mean defect size |
|--------------------|-----------------|------------------|
| Left main coronary | 2               | 58%              |
| Proximal LAD       | 11              | 52%*             |
| Mid LAD            | 6               | 28%              |
| Mid RCA            | 2               | 21%              |
| Distal LCx         | 1               | 7%               |

\*  $P = 0.013$  versus mid LAD mean defect size

LAD: left anterior descending artery; LCx: left circumflex artery; RCA: right coronary artery;

angiography, perfusion defect size decreased by a mean of  $18.3\% \pm 16.1\%$  (range 1% to 57%), and mean percentage change in defect size was  $53.2\% \pm 32.3\%$  (range 3% to 100%). In the 1 patient with a completely occluded mid LAD lesion on pre-discharge angiography, perfusion defect size decreased by only 2% (initial defect size 47%, final defect size 45%). There was, however, no statistically significant correlation between the amount of myocardial salvage and the degree of residual stenosis on pre-discharge angiography ( $P = 0.11$ ).

Figures 4a and 4b show an example of myocardial perfusion imaging in a patient during acute anterior myocardial infarct and 6 days after successful reperfusion therapy, showing a significant reduction in defect size at late imaging.

#### Angioplasty versus Thrombolysis (IVSK)

Both PTCA and IVSK sub-groups showed statistically significant changes in defect size. However, no statistically significant difference could be found in the initial and final defect sizes, nor in the change in defect size (i.e. amount of salvage) between the two sub-groups. The results of the 2 groups are shown in Table III.

#### Discussion

##### Quantitation of Myocardial Infarction and Salvage Using Tc-99m Sestamibi

Our study is the first to demonstrate the feasibility of acute infarct imaging in the local setting. There was a significant decrease in defect size from initial to final imaging in patients who had patent IRAs on pre-discharge angiography, indicating myocardial salvage. In contrast, in the patient with a re-occluded IRA at pre-discharge angiography, a minimal change in defect size was noted, demonstrating the importance of maintaining patency as well as the ability of the technique to demonstrate salvage. There was, however, a wide variation in the amount of salvage obtained by either revascularisation strategies, as seen in Figures 1 and 2.

Similarly, there was a statistically significant correlation

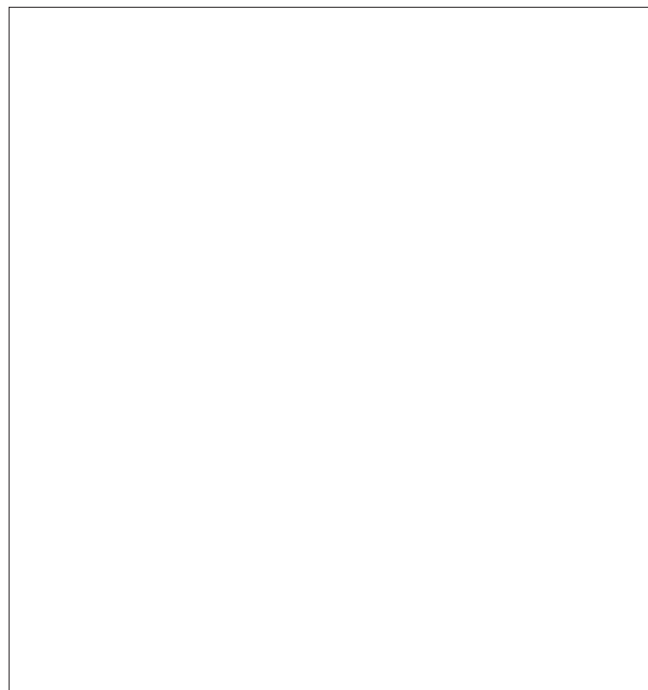


Fig. 4a. Example of myocardial perfusion scan performed before revascularisation in a patient with a large acute anterior myocardial infarct. Note the large defect in the anterior and apex of the left ventricle.

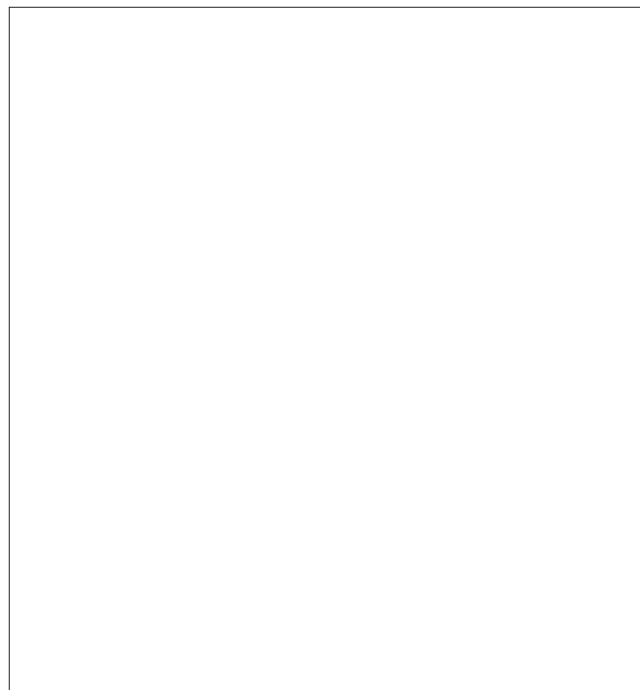


Fig. 4b. Example of myocardial perfusion scan performed 6 days after successful revascularisation in the same patient with anterior infarct. The defect is now much smaller compared to the initial image.

TABLE III: RESULTS OF ANGIOPLASTY VS THROMBOLYSIS

|                                 | PTCA              | IVSK              |
|---------------------------------|-------------------|-------------------|
| No. of patients                 | 11                | 18                |
| Initial defect size (% of LV)   | 38.9% $\pm$ 17.8% | 34.7% $\pm$ 19.5% |
| Final defect size (% of LV)     | 27.3% $\pm$ 13.4% | 21.4% $\pm$ 15.5% |
| Change in defect size (% of LV) | 11.6% $\pm$ 10.8% | 13.2% $\pm$ 12.3% |
| % change in defect size         | 34.2% $\pm$ 28.7% | 43.9% $\pm$ 28.9% |
| P value                         | 0.005             | 0.0003            |

IVSK: intravenous streptokinase; LV: left ventricle

PTCA: percutaneous transluminal coronary angioplasty;

P values reflect the significance of change in defect size versus initial defect size in the PTCA and IVSK groups. There was no significant difference in the change in defect size between the 2 groups.

between the site of IRA occlusion on angiography and the initial defect size (myocardium at risk). However, for a given IRA and site of occlusion, there was a large difference in the size of myocardium at risk. Thus, we cannot predict the amount of myocardium at risk or the amount of salvage based on the site of occlusion from angiography alone, again emphasising the importance of SPECT imaging in providing such additional information. Furthermore, apart from the absence or presence of IRA patency, there was an overall poor correlation between the degree of residual stenosis and the amount of salvage. These findings show that coronary angiography, though important in demonstrating patency, has limited ability to assess myocardial salvage and myocardium at risk.

Since Tc-99m sestamibi is taken up by viable myocardium, it is ideal for quantitating salvage as shown by our study. There are several reports in the literature regarding quantitation of myocardial infarct size and salvage. In 1988, Verani et al<sup>9</sup> first reported myocardial imaging with Tc-99m sestamibi as a means of assessing myocardial infarct size during coronary occlusion and to quantify the extent of salvaged myocardium following reperfusion in 31 dogs. The authors showed that the scintigraphic perfusion defect size correlated well with the pathologic infarct size ( $r = 0.85$  and  $0.95$  by planar and tomographic imaging, respectively). The uptake of Tc-99m sestamibi in the ischaemic myocardium also increased significantly 48 hours after reperfusion ( $P < 0.003$ ) and correlated with the increase in regional myocardial blood flow, as assessed by radioactive microspheres ( $r = 0.83$ ,  $P < 0.01$ ). They thus concluded that myocardial imaging with Tc-99m sestamibi allowed for accurate estimation of infarct size and quantitation of extent of salvage after coronary reperfusion. Sinusas et al<sup>10</sup> also investigated Tc-99m sestamibi uptake before and after reperfusion in 17 dogs undergoing LAD occlusion and reperfusion. As with the previous study, the risk area defined by perfusion imaging correlated well with the post-mortem risk area ( $r = 0.94$ ).

Wolfe et al<sup>11</sup> further showed that SPECT of Tc-99m sestamibi could accurately measure perfused left ventricular

mass in non-ischaemic, ischaemic and reperfused myocardium in canine models.

Thus, the use of this technique in assessment of myocardium at risk and salvage is very well validated in animal studies.

### *Clinical Studies on Myocardial Salvage*

Kayden et al<sup>12</sup> first showed the feasibility of such a technique in a patient with antero-septal myocardial infarction undergoing thrombolytic therapy. Other authors have also reported on the clinical feasibility of such techniques.<sup>13,14</sup>

Berman et al<sup>15</sup> further alluded to the advantages of Tc-99m sestamibi over thallium-201 for the assessment of arterial patency and myocardial salvage immediately after thrombolytic therapy, including higher quality images, lack of redistribution, and the ability to assess first-pass ventricular function. Several other authors<sup>16-20</sup> have also described the advantages of different tracers in nuclear perfusion imaging in acute myocardial infarction.

Santoro et al<sup>5,6</sup> first investigated the use of SPECT with Tc-99m sestamibi and echocardiography as a method to evaluate the results of intravenous thrombolytic therapy in 14 patients with acute myocardial infarction. In a protocol similar to our present study, the authors showed a good correlation between the 5-day scintigraphic estimate of infarct dimension and enzymatic infarct size ( $r = 0.907$ ,  $P < 0.00002$ ). That study showed the initial defect size ranging from 9% to 42% of the left ventricle and an improvement ranging from 51% to 73% when the patients were successfully thrombolysed. These results, as well as results from various other studies,<sup>21-24</sup> are comparable with our present findings. They also showed that the reduction in defect size predicted late functional improvement that was demonstrated by echocardiography performed 1 month later ( $r = 0.89$ ,  $P < 0.00005$ ). Faraggi et al<sup>8</sup> also showed the potential use of MIBI-SPECT to investigate the initial perfusion status in acute myocardial infarction in 39 patients in a European multi-centre study group. They showed that SPECT improvement demonstrated myocardial salvage earlier than wall motion studies. Other authors have reported the usefulness of perfusion imaging for the evaluation of primary PTCA or thrombolysis in the setting of acute myocardial infarction.<sup>21-24</sup>

### *PTCA versus Thrombolysis in Myocardial Salvage*

Several studies have evaluated the relative efficacies of PTCA versus thrombolysis in the setting of myocardial salvage in acute myocardial infarct. Gibbons et al<sup>25</sup> studied 108 acute infarct patients randomised to either immediate angioplasty and thrombolysis with intravenous tissue plasminogen activator (TPA) and found no significant

difference in the amount of myocardial salvage achieved by the 2 modalities of treatment. Similarly, our study was also unable to show any significant difference in salvage rates between PTCA and thrombolysis, but the patients were not randomised.

### *Limitations*

Several limitations should be mentioned. First, our study did not show a significant difference in salvage rates between PTCA and thrombolysis. This could be attributed to the small numbers of patients in this study, and the fact that there was no randomisation in this study. Due to logistic constraints such as the availability of radio-tracers and gamma camera time, the numbers are small. Another reason could be the delay in performing acute PTCA due to logistical reasons. Secondly, 6 patients refused pre-discharge angiography, and this could have compromised our study results. Thirdly, none of the patients with inferior infarcts were in the angioplasty arm, and thus the 2 arms were not comparable. Finally, we did not assess the influence of ECG-gating on measurements of myocardium at risk and infarct size during acute infarct. However, Christian et al<sup>26</sup> had previously reported that although gated images consistently reported a significantly greater perfusion defect size, the increment was small and clinically insignificant. It thus appeared that the partial volume effects had minimal impact on the quantitation of myocardium at risk and infarct size in clinical tomographic imaging during acute myocardial infarction.

### *Conclusion*

Our study clearly shows that the assessment of myocardial salvage by Tc-99m sestamibi is a feasible technique in the local setting, and can be safely and expeditiously performed in the setting of acute myocardial infarction. This technique allows for measurement of the amount of myocardium at risk and myocardial salvage, which has long-term prognostic implications, and which is difficult to assess from angiography alone, demonstrating the importance of reperfusion.

We were unable to demonstrate a difference in efficacy between thrombolytic therapy and PTCA, but this was not a randomised study.

Although this method is safe and feasible, we do not advocate that this be performed in all patients presenting with acute infarctions. The logistics and manpower involved are somewhat prohibitive. However, it is a powerful research tool to study the beneficial effects of various therapies on acute myocardial infarction.

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