Technetium-99m Stannous Pyrophosphate Myocardial Scintigraphy

Reliability and Limitations in Assessment of Acute Myocardial Infarction

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SUMMARY Two hundred-three patients had technetium 99m (stannous) pyrophosphate myocardial scintigrams for the evaluation of chest pain and suspected acute myocardial infarction. In addition to routine imaging at 60-90 minutes after injection of the radiopharmaceutical, the blood pool was imaged immediately in each patient for comparison with routine anterior, left anterior oblique, and left lateral views. Further delayed studies were obtained when residual blood pool activity was identified. Seventy patients had acute myocardial infarction by clinical, electrocardiographic, and enzymatic (CK-MB) criteria. Sixty-five of these 70 patients with acute infarction had positive myocardial scintigrams, with one technically unsatisfactory study. Only four of the 70 patients had negative scintigrams when imaged 18-72 hours after infarction in this study. Technically satisfactory scintigrams were recorded in 125 patients without evidence of infarction. Ninety-six had negative scintigrams at 60-90 minutes, while 19 patients (15%) had precordial activity at 60-90 minutes which was identical in distribution to early blood pool images and cleared with further delay. With these included, the true negative incidence was 92%. Ten of 125 patients had false positive scintigrams; two had recent cardioversion with resultant chest wall damage. The other eight patients had previous infarction 1½ to 72 months earlier and had akinetic segments shown angiographically in the areas of the persistently positive scintigrams.

Myocardial scintigraphy correlates well with the presence of other evidence of acute infarction, as well as with the absence of acute infarction when residual blood pool activity is identified. False positive scintigrams can occur following cardioversion and in patients with previous myocardial infarction and resultant ventricular wall motion abnormalities.

THE OBSERVATION THAT THE BONE IMAGING RADIOPHARMACEUTICAL TECHNETIUM-99M (STANNOUS) PYROPHOSPHATE (99mTc-PYP) accumulated in acutely infarcted myocardium has been well established,1 but the clinical usefulness and limitations of these studies remain to be defined. Initial reports describing this scintigraphic technique indicated both specificity and sensitivity for the detection of acute myocardial infarction.2 More recently, scintigraphic findings in some patients have correlated poorly with other objective evidence of myocardial infarction. Abnormal myocardial scintigrams have been reported in as many as 35% of patients with unstable angina pectoris without evidence of acute infarction,3 and in patients with postinfarction left ventricular wall motion abnormalities.4 This study reviews our experience with 99mTc-PYP myocardial scintigraphy in 203 patients studied for the evaluation of symptomatic coronary artery disease and discusses the results and potential sources of interpretive error encountered.

Materials and Methods

All patients were admitted to the University of Alabama in Birmingham Hospital (UAB); patients with a clinical diagnosis of unstable angina pectoris or suspected acute myocardial infarction were admitted to the Specialized Center of Research for Ischemic Heart Disease. All patients with suspected infarction had serial electrocardiograms and serum enzyme determinations, including creatine kinase MB isoenzyme assayed according to the technique of Mercer,5 ECG evidence of transmural myocardial infarction required ST-segment elevation, T wave inversion, and the development of 0.04 see Q waves in appropriate ECG leads. Subendocardial infarction demonstrated only ST-segment depression and T wave inversion associated with elevated serum CK-MB levels. Unstable angina was defined as crescendo (increased frequency, duration, or severity of angina or development of rest pain) or pre-infarctional (pain of more than 30 min duration with previous stable angina).

Myocardial scintigrams were performed initially within 18-36 hours of admission or onset of symptoms and repeat scintigrams were obtained 48 hours later in 80 of the 203 patients. Fifteen patients had additional scintigrams 3-4 weeks after their initial studies to determine persistence of abnormal 99mTc-PYP myocardial uptake. When persistently abnormal scintigrams were identified, serial follow-up images were obtained. Imaging was performed at the patient's bedside with an Ohio Nuclear mobile gamma camera equipped with a high resolution collimator. The camera was set on the Tc-99m 140 keV photo peak utilizing a 20% window. A thoracic transmission scintigram utilizing a flat lucite source of Tc-99m pertechnetate was recorded initially to

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Two hundred and three patients underwent $^{99m}$Tc-PYP myocardial scintigraphy. Seventy patients had clinical evidence of acute myocardial infarction substantiated by electrocardiographic and enzymatic criteria. Five patients demonstrated evidence of extension of infarction during the initial 3-5 days. The myocardial infarction site by electrocardiographic localization was anterior or anterolateral in 50 and inferior or posterior in 20 patients. Transmural myocardial infarction was diagnosed in 57 patients (40 anterior, 17 inferior) and subendocardial myocardial infarction in 13 patients (10 anterior, 3 inferior).

Myocardial scintigrams were positive in 65 of 69 patients (94.2%) with infarction, and one patient with infarction had a technically unsatisfactory scintigram. Scintigrams were positive in 49 of 50 patients (98%) with anterior infarction and in 16 of 19 patients (84.2%) with inferior infarction (table 1). Each patient with evidence of extension by ECG and enzymatic criteria developed new areas of abnormal $^{99m}$Tc-PYP uptake on restudy. Fifty-three of 56 patients (94.6%) with transmural infarction had discrete positive scintigrams which corresponded to the ECG site of infarction. Twelve of the 13 patients (92.3%) with subendocardial infarction had positive scintigrams. Of these twelve, six had discrete localized activity indistinguishable from that seen in transmural infarction. However, six patients had diffuse activity (2+ in the grading scale of Parkey et al.) which was in all cases smaller in size than the early blood pool images. Four of 70 patients (3.8%) with documented acute infarction (one anterior, three inferior) had definitely negative scintigrams. Each of the latter was imaged at the appropriate initial time 18-36 hours after onset of infarction and each of three imaged 48 hours later remained negative.

All had technically satisfactory scintigrams with excellent skeletal detail. The one patient with anterior infarction and negative scintigrams (fig. 1) had experienced no prior symptoms of ischemic heart disease and presented with electrocardiographic evidence of anterolateral infarction, accompanied by marked elevation of serum enzymes (peak CPK — 4000 I.U.; normal 50–150 I.U.) and this patient subsequently

Table 1. Results with $^{99m}$Tc-PYP Myocardial Scintigraphy

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myocardial infarction</td>
<td>70</td>
<td>94.2%</td>
</tr>
<tr>
<td>anterior</td>
<td>50</td>
<td>98%</td>
</tr>
<tr>
<td>inferior</td>
<td>20</td>
<td>84.2%</td>
</tr>
<tr>
<td>Positive scintigrams</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>anterior</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>inferior</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Negative scintigrams</td>
<td>4</td>
<td>5.8%</td>
</tr>
<tr>
<td>anterior</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>inferior</td>
<td>3</td>
<td>15.8%</td>
</tr>
<tr>
<td>Technically unsatisfactory scintigrams</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No acute myocardial infarction</td>
<td>133</td>
<td>92%</td>
</tr>
<tr>
<td>Negative scintigrams</td>
<td>115</td>
<td></td>
</tr>
<tr>
<td>Definite negative</td>
<td>96</td>
<td>76.8%</td>
</tr>
<tr>
<td>Residual Blood Pool</td>
<td>19</td>
<td>15.2%</td>
</tr>
<tr>
<td>Positive scintigrams</td>
<td>10</td>
<td>8%</td>
</tr>
<tr>
<td>Technically unsatisfactory scintigrams</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

Results

scintigrams recorded one (left) and five days (right) after unequivocal myocardial infarction as an initial coronary event. Note excellent sternal and rib detail and no evidence of abnormal uptake in the region of the anterolateral wall of the left ventricle on either study.

identified anatomical reference sites. Twelve to fifteen mCi of $^{99m}$Tc-PYP were then injected intravenously and polaroid images of blood pool activity were generated 2-5 minutes later in the anterior, left anterior oblique, and left lateral views, accumulating 400,000 counts in each projection. Imaging at 60-90 min after injection was performed in the same views; if residual blood pool activity was identified, further delayed views at 2-5 hours were obtained.

Delayed scintigrams were interpreted as positive when localized myocardial $^{99m}$Tc-PYP was present or when diffuse precordial activity was recorded which was distinguishable from persistent blood pool activity by comparison with early (2-5 min) images. Scintigrams were classified as negative when there was no detectable $^{99m}$Tc-PYP uptake or when diffuse activity was identified as persistent blood pool activity. Residual blood pool activity was considered present when 60-90 minute images demonstrated activity identical in size and distribution to early images in the anterior or left anterior oblique views. Scintigrams were considered technically unsatisfactory when there was poor resolution of images and/or reference skeletal uptake was indistinct.
developed severe left ventricular dysfunction. The three additional patients with acute infarction and negative scintigrams each had inferior myocardial infarction. One of these patients had experienced acute anterior infarction four months earlier and scintigrams at that time were characteristic for transmural anterior infarction (fig. 2). This patient had an inferior infarction two weeks following saphenous vein coronary artery bypass surgery and repeated scintigrams performed at optimal imaging intervals were negative.

One hundred thirty-three patients developed no clinical, enzymatic, or electrocardiographic evidence of myocardial infarction. Ninety-six (76.8%) had unequivocally negative scintigrams, 19 (15.2%) had definite diffuse 99mTc-PYP activity, ten patients had well localized 99mTc-PYP activity, and eight patients had technically unsatisfactory scintigrams.

In all 19 patients with diffuse activity, the images obtained at the usual 60-90 min interval were indistinguishable from early blood pool images in pattern and distribution of activity, although the amount of activity was decreased in all instances (fig. 3). When graded according to the classification of Parkey et al., 1 ten had 2+ and nine had 3+ activity. In 12 instances activity extended to the right of the sternum in the anterior view, making that view of the blood pool useful. Patients re-imaged with further delayed views demonstrated disappearance of this activity at post-injection intervals ranging from 2-5 hours (fig. 4).

Comparison of the clinical profiles in patients with persistent blood pool activity and the 96 with unequivocally negative scintigrams revealed similar clinical features (table 2). There were no differences in frequency of unstable or stable angina or in the frequency, extent or severity of coronary artery disease (defined as greater than 70% luminal narrowing of at least one major vessel). A similar percentage of both groups had normal coronary arteriograms.

Inclusion of these 19 patients with persistent blood pool activity and no evidence of myocardial infarction with the 96 patients having unequivocally negative scintigrams increased the true negative incidence in this series from 76.8% to 92%.

Definite positive myocardial scintigrams in the absence of any evidence of acute myocardial infarction occurred in 10 of the 125 patients (8%), two following cardioversion and eight in patients with previous myocardial infarction. Cardioversion had been performed to treat ventricular tachycardia occurring at cardiac catheterization in one patient, who received two direct current shocks of 400 joules each; the other patient had developed ventricular fibrillation during a treadmill exercise test, and sinus rhythm was restored on the first attempt at defibrillation using 400 joules. Both developed evidence of chest wall skeletal muscle damage with elevated CK-MM and negative CK-MB fractions, and had 99mTc-PYP uptake localized to the region of the anterior chest wall (fig. 5).

The other eight patients with positive myocardial scintigrams and no evidence of acute myocardial infarction had experienced previous myocardial infarction; six had recent infarction ranging from 6-22 weeks prior to evaluation and imaging at this institution, while two had experienced myocardial infarction 1½ and 6 years previously (table 3). None
had evidence of re-infarction during the intervening period prior to their evaluation at UAB, although five patients had recurrence of angina (2 unstable, 3 stable). Two of the six patients with recent prior infarction were admitted with unstable angina pectoris and both had $^{99m}$Tc-PYP uptake corresponding to the electrocardiographic localization of prior documented infarction 8 and 12 weeks earlier. One additional patient had clinical and angiographic evidence of ventricular aneurysm. The abnormal $^{99m}$Tc-PYP uptake was in the area of dyskinesia and persisted until surgical repair; following aneurysm resection a negative scintigram was recorded (fig. 6). Two of the remaining three patients with recent infarction had stable angina pectoris and one had symptoms of left ventricular dysfunction following infarction (fig. 7). The two patients with remote infarction and positive scintigrams both had ventricular aneurysm by clinical and angiographic criteria. One had stable angina and one had no chest pain. In these eight patients with previous myocardial infarction and positive scintigrams, the abnormal $^{99m}$Tc-PYP uptake corresponded in each to the electrocardiographic location of the previous infarction (anterior in 7, inferior in one.)

Of the 65 patients with acute myocardial infarction and positive $^{99m}$Tc-PYP scintigrams, six patients were identified to have persistently positive myocardial scintigrams at 10–20 weeks (mean — 14 weeks) following infarction. Each had a large anterior or antero-lateral infarction by clinical and enzymatic criteria and demonstrated angiographic wall motion abnormalities with akinetic segments corresponding to the location of the persistently positive scintigrams.

In addition nine patients had unsatisfactory myocardial scintigrams which demonstrated diffuse precordial activity and indistinct skeletal uptake at 60–90 min after injection. Additional delayed views showed progressive increases in tissue background activity. Chromatography of the radiopharmaceutical, as well as the serum of selected patients with this finding, demonstrated abnormal amounts of unbound pyrophosphate. The resultant free pertechnetate may explain the unsatisfactory scintigrams in such patients.

### Discussion

Our experience with $^{99m}$Tc-PYP myocardial scintigraphy in 203 patients confirms the usefulness of this agent in identifying acute myocardial infarction, but also identifies several problem areas in its clinical application. Myocardial scintigraphy correctly identified acute infarction in 94.2% of patients, while 92% of patients without infarction had negative scintigrams. In patients with proven myocardial infarction in this series, 57 were transmural and 13 were subendocardial. Of those with transmural infarction, which included one unsatisfactory study, 94.6% had discretely positive scintigrams. In the subendocardial group, 12 had positive scintigrams (92.3%). Of these 12, six had diffuse uptake as described by Willerson et al., but six had discrete up-
take similar to the scintigraphic pattern of transmural infarction. In those with diffuse activity, the activity pattern was in each case smaller than the early blood pool pattern. Scintigraphy thus correlates well with the clinical presence or absence of acute myocardial infarction. However, using current standard imaging intervals and techniques, disparate clinical and scintigraphic results can occur, which include false negative scintigrams, apparent false positive scintigrams due to residual blood pool activity, and “true” false positive scintigrams in patients with previous myocardial infarction.

False Negative Myocardial Scintigrams

Although false negative scintigrams were uncommon, occurring in only 5.8% of patients imaged at optimal times, they do represent a significant clinical limitation of this technique. The false negative scintigrams could not be attributed to technical factors, since high quality images were obtained in each patient. In addition, there was no apparent relation between infarct size and negative scintigrams, since two of the four patients with negative scintigrams had clinically large infarctions with significant CK-MB isoenzyme release. The significance of false negative scintigrams is unknown, but they may well represent true absence of flow to the involved areas of the myocardium.

Diffuse False Positive Scintigrams

Most reported cases of positive scintigrams in the absence of infarction have had faint, diffuse precordial activity. Some of these patients have had unstable angina, and it has been suggested that scintigraphy may be a more sensitive indicator of myocardial necrosis than the clinical criteria which were used to determine infarction. The current availability of CK-MB assay has provided a more sensitive index of infarction, and this method was used in the present study.

In our experience these patients with apparent diffuse myocardial activity and no clinical evidence of infarction (including CK-MB assays) have residual blood pool activity when imaged at the usual standard time of 60–90 minutes. These images would all have been classified as 2+ or greater with the grading system described by Parkey et al. Residual blood pool activity can be suspected when radiopharmaceutical activity is present over the entire precordium, including the area of the right cardiac chambers, and can be confirmed if immediate blood pool images have been obtained for comparison. Disappearance of precordial activity in these patients when re-imaged with additional delayed views (at 2–5 hours) further supports residual blood pool activity as the cause of these “false positive” images. This scintigraphic pattern of persistent blood pool was observed in 15.2% of patients who had no evidence of infarction and in 9.4% of all patients undergoing 99mTc-PYP myocardial scintigraphy. Since only 76.8% of patients without infarction had unequivocally negative scintigrams at 60–90 min, failure to recognize this additional 15% of patients with residual blood pool activity would have significantly lowered the resultant sensitivity and specificity of this technique.

Clearance of blood pool activity is determined by several factors. Pharmacokinetic studies have demonstrated that 99mTc-PYP is loosely bound to plasma proteins and red blood cells, and variation in this binding may explain differences in clearance of blood pool activity in certain

Table 3. Patients with False Positive 99mTc-PYP Scintigrams

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Angina</th>
<th>ECG Infarct Location</th>
<th>Angiographic Location of Akiness/Dyskinesis</th>
<th>Time of Scintigrams After MI (months)</th>
<th>99mTc-PYP Uptake Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>43/M</td>
<td>0</td>
<td>Ant</td>
<td>Ant</td>
<td>1 1/2–3</td>
<td>Ant</td>
</tr>
<tr>
<td>50/M</td>
<td>0</td>
<td>Ant</td>
<td>Ant</td>
<td>1 1/2–3</td>
<td>Ant</td>
</tr>
<tr>
<td>47/M</td>
<td>stable</td>
<td>Ant</td>
<td>Ant</td>
<td>2–4</td>
<td>Ant</td>
</tr>
<tr>
<td>58/M</td>
<td>unstable</td>
<td>Ant</td>
<td>Ant</td>
<td>2–3 1/2</td>
<td>Ant</td>
</tr>
<tr>
<td>55/M</td>
<td>stable</td>
<td>Ant</td>
<td>Ant-Inf</td>
<td>5–7</td>
<td>Ant</td>
</tr>
<tr>
<td>41/M</td>
<td>0</td>
<td>Ant</td>
<td>Ant</td>
<td>72</td>
<td>Ant</td>
</tr>
<tr>
<td>52/F</td>
<td>stable</td>
<td>Ant</td>
<td>Ant</td>
<td>18–28</td>
<td>Ant</td>
</tr>
<tr>
<td>56/M</td>
<td>unstable</td>
<td>Inf</td>
<td>Inf</td>
<td>3</td>
<td>Inf</td>
</tr>
</tbody>
</table>
patients. In addition, blood pool radiopharmaceutical clearance is dependent on cardiac output and urinary excretion, and may be significantly delayed in low cardiac output states or renal failure. The finding that 15.2% of patients without infarction and more than 9% of the entire group had diffuse precordial activity and apparently “false positive” scintigrams related to residual blood pool radiopharmaceutical activity indicates the importance of both early blood pool images as well as further delayed imaging in the complete scintigraphic evaluation using 99mTc-PYP. Use of these additional views should eliminate a potentially significant source of interpretive error and increase the reliability of this technique.

Discrete False Positive Scintigrams

Ten patients without evidence of acute myocardial infarction had definite positive myocardial scintigrams with well localized 99mTc-PYP uptake. Two of these had undergone high energy direct current cardioversion to revert ventricular arrhythmias. Precordial activity was localized to the anterior chest wall on the lateral views in both of these patients. Similar observations in experimental animals have been described by Pugh et al., and the potential difficulty in subsequent scintigraphic identification of acute infarction has been discussed.

The other eight patients with false positive 99mTc-PYP scintigrams had previous myocardial infarction ranging from 6 weeks to 6 years prior to scintigraphic study and none had evidence of subsequent ischemic injury. Although positive scintigrams have been reported in unstable angina, only two of these patients had this syndrome (table 3). Stable angina occurred in three others. In contrast, all eight had previous infarction and angiographic evidence of akinesis or dyskinesis corresponding to the location of abnormal 99mTc-PYP uptake (table 3). These data suggest a relation to the prior infarction rather than to a particular chest pain syndrome. Ahmed et al. have reported localized 99mTc-PYP uptake indistinguishable from the pattern of acute myocardial infarction in nine patients with ventricular aneurysm by angiography and in two patients without aneurysm but with akinesis on angiography. Two of our patients with remote infarction and positive scintigrams had angiographic dyskinetic segments. Six of these eight patients with false positive scintigrams in our series were documented to have serial scintigrams which remained positive for up to 10 months after their initial abnormal study. Although our results are compatible with those of Ahmed et al., the greater number of patients without aneurysm in our group suggests that the wall motion abnormality and not aneurysm per se may be related to false positive images and may be a determinant of the abnormal 99mTc-PYP myocardial uptake.

Persistently Positive Scintigrams Following Acute Infarction

In a prospective attempt to estimate the frequency of persistently positive myocardial scintigrams, six of 65 patients with acute infarction and positive scintigrams in this series (including 12% of those with acute anterior infarction) were identified to have persistently abnormal scintigrams with serial study for 10-20 weeks after acute infarction. Since all patients with acute infarction did not have late scintigrams, these figures represent a minimal estimate of the frequency of this finding. All six had large anterior or anterolateral infarction by clinical criteria, and all had angiographic akinetic segments which corresponded to the location of per-
sistent scintigraphic abnormality. This demonstration of persistently abnormal \textsuperscript{99}Tc-PYP scintigrams from the occurrence of acute myocardial infarction to several months later is similar to the finding of discrete false positive myocardial scintigrams in eight of our patients (6.4%) without acute infarction but with previous recent or remote infarction. Both may represent the same phenomenon and false positive scintigrams in patients with prior myocardial infarction may actually represent persistence of positivity from a previous infarction as the cause of the false positive images.

The cause of this continued \textsuperscript{99}Tc-PYP myocardial uptake in the absence of acute myocardial infarction or ventricular aneurysm is unknown. Since serial, late scintigrams were obtained only in selected patients, the incidence of persistently positive myocardial scintigrams is also unknown. The duration of persistent positivity in patients with previous infarction (with or without ventricular aneurysm) is still uncertain, but our observations suggest that scintigrams indistinguishable from acute infarction occur for as long as six months after infarction when aneurysm is not present and for up to six years with ventricular aneurysm. The occurrence of persistently positive scintigrams may explain a certain number of the false positive results in other series. This finding appears to occur with sufficient frequency to warrant caution in interpreting positive \textsuperscript{99}Tc-PYP myocardial scintigrams as indicative of acute infarction in patients who have had previous infarction.

**Conclusion**

\textsuperscript{99}Tc-PYP myocardial scintigraphy in over 200 patients confirms the usefulness of this technique in correlation with clinical findings for the evaluation of chest pain and suspected acute myocardial infarction. However, certain limitations of myocardial scintigraphy are identified. Residual blood pool activity can occur in a significant number of patients (9% in this series) and provides a potentially important source of interpretative error. The usefulness of blood pool images and further delayed views in the recognition of residual blood pool activity and subendocardial infarction is discussed. In addition, the occurrence of false positive scintigrams in patients with previous myocardial infarction is documented, as well as the persistence of abnormal \textsuperscript{99}Tc-PYP uptake following acute infarction. Their possible relationship is considered and their importance as causes of false positive scintigrams is emphasized.

Recognition of these pitfalls and limitations of \textsuperscript{99}Tc-PYP myocardial scintigraphy should further increase the reliability and usefulness of this technique.

**References**

Technetium-99m stannous pyrophosphate myocardial scintigraphy. Reliability and limitations in assessment of acute myocardial infarction.

M J Cowley, J A Mantle, W J Rogers, R O Russel, Jr, C E Rackley and J R Logic