The Specificity of the Diffuse Pattern of Cardiac Uptake in Myocardial Infarction with Technetium-99m Stannous Pyrophosphate

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SUMMARY To analyze the specificity of the diffuse pattern of cardiac uptake with technetium-99m stannous pyrophosphate (TcPYP), we evaluated the bone scans of 1,383 noncardiac patients and the myocardial scintigrams of 120 cardiac patients. Seventy-four (14.4%) of 483 bone scans performed on a scintillation camera revealed diffuse TcPYP cardiac uptake. Among the total 603 camera bone scans and myocardial scintigrams, the incidence of diffuse cardiac uptake was 16% among patients with clinical coronary disease but 13% among those patients without clinical symptoms. Discrete myocardial uptake was seen in 25 of 26 patients with transmural infarction. Femoral vasculature was more frequently visualized (84% vs 3%, P < 0.001) and left mastectomy occurred more often (30% vs 1%, P < 0.001) among patients with diffuse cardiac uptake than among patients with negative images, indicating possible blood pool imaging. The diffuse pattern of cardiac uptake appeared nonspecific and may be due to unintentional cardiac blood pool imaging.

SINCE ITS INTRODUCTION into clinical cardiology only three years ago, 

1, 2 cardiac imaging with technetium 99m stannous pyrophosphate (TcPYP) has been advocated with increasing frequency and prominence as a clinical tool useful in the diagnosis of recent myocardial infarction. 3, 4 Well localized TcPYP cardiac activity has been consistently correlated with documented regions of recent infarction. 5, 6 Diffuse TcPYP accumulation in the cardiac region has been said to be a sensitive and specific finding of subendocardial infarction or unstable angina pectoris. 5, 6-10 Elusive clinical entities. The diffuse pattern was thought to be caused by generalized but scattered elements of ongoing cellular necrosis in these conditions. However, early in our experience we became aware of this diffuse pattern of cardiac uptake in association with other cardiac conditions and saw it even in some patients without apparent heart disease. We sought then to determine the specificity of TcPYP cardiac imaging, especially in its diffuse pattern of uptake, and to this end we performed simultaneous retrospective and prospective studies.

Methods

In a retrospective fashion, cardiac activity was investigated in 1,383 consecutive TcPYP bone scans performed for noncardiac indications in our Nuclear Medicine Department during the last two years. Nine hundred of these studies were performed with an Ohio Nuclear Rectilinear Scanner, while the last 483 were performed with a high resolution Searle Pho Gamma IV Scintillation Camera and a low energy, all purpose collimator using a moving table and whole body imaging. All bone scans were performed in the anterior and posterior projections and taken to one million counts. Later in the course of our investigations, stationary anterior, 45° left anterior oblique (LAO), and left lateral chest images were obtained in patients where diffuse cardiac uptake was noted in the anterior whole body image.

Prospectively, 120 TcPYP myocardial scintigrams were also evaluated. All myocardial scintigrams were stationary thoracic images performed for cardiac indications, one to seven, usually three, days following the onset of chest pain. All images were performed with the Pho Gamma IV Scintillation Camera and low energy all purpose collimation in the anterior, 45° LAO, and left lateral projections, and taken to 300,000 counts.

All studies were performed at the 140 kev technetium 99m photopeak with a 20% window, 2-4 hours following the intravenous ejection of 15 mCi of TcPYP prepared in our laboratory according to a modification of the method of Hubert et al. 11 This material, prepared from reagents having a 100:1 ratio of pyrophosphate to stannous ion is quite stable and in previous studies has shown less than 3% free ionic pertechnetate. The images were interpreted independently by three observers unaware of patient history and evaluated for the presence of radioactivity in the cardiac region. Image radioactivity was called discrete if confined to a localized cardiac region and diffuse if generally apparent in all regions. Diffuse cardiac images revealed no photopenic evidence of the left ventricular cavity and showed activity from the cardiac apex to the sternum. Images were graded to conform with prior methods. 4, 6, 8 Radioactivity in the cardiac region was graded 0 to 4+ where 0 represented no increase beyond background with full observer agreement; 1+ represented slight and always indefinite increase beyond background noted by at least one but not all observers; 2+ represented definite increase beyond background but less than bone noted by all observers; 3+ represented increased activity beyond background and equal to bone noted by all observers. Images graded 2+ or 3+ were abnormal to all observers and were called positive. Images graded 1+ were included in our negative group.

Clinical parameters included age, sex, patient history, recent 12-lead electrocardiogram, chest X-ray, CBC, BUN and SMA-12 serum analysis. Additionally, among those patients studied prospectively for suspected infarction, a detailed history and physical examination, serial electrocardiograms, and serum enzymes, including creatine phosphokinase (CPK) with myocardial specific isoenzyme

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episode of heart disease into imaging in the period immediately preceding and following the scintigrams. In the latter group the electrocardiogram was always available on the day of the myocardial scintigram which was performed in the course of hospitalization for the evaluation of an acute cardiac complaint. Among those studied retrospectively, the bone scan was frequently performed as an outpatient study to evaluate the patient for the presence or distribution of malignancy. Also noted in both groups were the injection to imaging interval, the incidence and timing of prior radionuclide studies, and evidence of image vascular activity. Bone scans were evaluated for stomach, thyroid, and salivary gland activity as an index of radioisotope integrity. Dates of all studies were reviewed and compared to ensure that abnormal images were not temporally related, abnormal studies occurring only on the same or sequential dates. The occurrence of such date clustering could be evidence favoring isotope preparation, a biweekly event, as the cause for image abnormalities.

Using the information available, each patient was classified at the time of imaging according to the clinical evidence of heart disease into one of the following categories: stable angina pectoris — if exertional chest pain was present and unaltered for at least three months; unstable angina pectoris — if typical chest pain was present and recently altered in pattern and/or occurred at rest without enzyme or permanent electrocardiographic changes; acute subendocardial infarction — if pain was prolonged and associated with electrocardiographic T wave inversion and/or ST-segment depression of at least 24 hours duration with abnormal enzymes; acute transmural infarction — if the episode of prolonged chest pain and enzyme elevation was related to new electrocardiographic Q waves equal to or greater than .04 seconds; nonischemic heart disease — if the patient had myocardial, pericardial or valvular disease; no heart disease — if there was no historical, clinical, or laboratory evidence of heart disease.

Results

Examples of typical patient studies are shown in figures 1-4. Figures 1-3 show myocardial scintigrams in three projections. Figure 1 is a normal study without evidence of radioactivity between the sternum and left rib margin. Figure 2 shows discrete TcPYP activity in a patient with an acute transmural apico-septal myocardial infarction. Figure 3 shows diffuse uptake in a patient with subendocardial infarction. Figure 4 shows the anterior projections of the myocardial scintigrams performed in two patients with coronary artery disease. Both images show abnormal radioisotope activity in the cardiac region, one faint, the other more intense and are examples of diffuse TcPYP uptake.

Our results are summarized in table 1. None of the 900 rectilinear bone scans showed any evidence of cardiac uptake. Since this was probably due to poor image resolution, this group was excluded from further statistical analysis. However, 70 of 483 patients (14.4%) studied retrospectively and having whole body bone scans on the scintillation camera, showed TcPYP activity in the cardiac region. All 70 revealed diffuse cardiac uptake. Among the 120 patients studied prospectively by myocardial scintigraphy, 26 (22%) had discrete, and 12 (10%) had diffuse TcPYP activity.

Within the group having whole body camera scans, the mean age among those with diffuse uptake, 61 years, was not significantly higher than among those with negative scans.
There was little difference in sex distribution between the two populations, females comprising 53% of the diffuse cardiac uptake group and 52% of the negative image group. The incidence of clinical heart disease among those evaluated for noncardiac complaints by camera bone scan was small. Only seven of the 483 patients had confirmed clinical heart disease. Four of these, two with stable angina pectoris and two with nonischemic heart disease, had diffuse uptake while three, one with stable angina pectoris and two with nonischemic heart disease had negative scans. However, among the 120 patients evaluated for cardiac complaints by myocardial scintigraphy, 101 had documented clinical evidence of cardiac disease including 26 with transmural myocardial infarction, three with subendocardial infarction, 18 with unstable angina pectoris, 41 with stable angina pectoris and 20 with nonischemic heart disease. Table 2 shows results of imaging according to diagnosis, among the total population of 603 patients evaluated by camera bone scan and myocardial scintigrams. Discrete uptake was seen in 25 of 26 patients with myocardial infarction. Diffuse uptake was seen in each of three patients with subendocardial infarction, seven of 18 with unstable angina, four of 41 with stable angina and three of 20 with nonischemic disease. For all forms of clinical heart disease there was a 16% incidence of diffuse cardiac uptake while in those with no clinical heart disease there was a 13% incidence. There was no significant difference between the incidence of diffuse uptake among those having camera bone scans and a low incidence of heart disease and among those having myocardial scintigrams and a high incidence of heart disease. Also, when evaluated according to diagnosis there was no significant difference between the incidence of diffuse uptake among groups with and without clinical heart disease. Although diffuse cardiac uptake appeared to be more frequent among those with more severe clinical forms of coronary disease, such as subendocardial infarction and unstable angina, this trend was not significant due to the small number of patients involved.

Among bone scan subjects, other aspects of the history, laboratory and radionuclide studies were examined in an attempt to explain the occurrence of the diffuse pattern of TePYP activity. There was no significant difference in the injection to imaging interval between the diffuse uptake and negative image groups. The incidence of renal insufficiency or recent prior radionuclide study was infrequent in the two groups and did not differ significantly between them. There was no evidence of date clustering. Thyroid and parotid activity was uniformly absent. However, when all bone scans were examined carefully for evidence of vascular activity, a definite linear contour could readily be identified stretching from the inguinal region to the knee, medial to the femur bilaterally in the anterior projection of 72 (17%) studies (fig. 5). The inguinal regions of several patients having radionuclide studies with technetium 99m albumin, an intra-vascular indicator, were subsequently imaged and revealed similar linear markings. This finding strengthened our impression that such radioactivity originated in the femoral vasculature. The incidence of this vascular pattern was much greater among those patients with diffuse uptake, 59 (84%), than among the negative image group, 13 (3%), a statistically significant difference, P < 0.001 (table 3).

The diffuse uptake pattern appeared linked to the femoral vascular pattern. Seeking a clarification of this relationship, the clinical diagnosis of each bone scan patient was specifically reviewed. These diagnoses were, with rare exception, noncardiac and most frequently malignancy related.

### Table 1. TePYP Image Analysis According to Pattern of Radionuclide Cardiac Uptake

<table>
<thead>
<tr>
<th></th>
<th>Rectilinear bone scans</th>
<th>Camera bone scans</th>
<th>Camera myocardial scintigrams</th>
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<tbody>
<tr>
<td>No. of patients</td>
<td>900</td>
<td>483</td>
<td>120</td>
</tr>
<tr>
<td>Diffuse TePYP</td>
<td>0</td>
<td>70 (14%)</td>
<td>12 (10%)</td>
</tr>
<tr>
<td>uptake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discrete TePYP</td>
<td>0</td>
<td>0</td>
<td>26 (22%)</td>
</tr>
<tr>
<td>uptake</td>
<td></td>
<td></td>
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**Figure 3.** Diffuse TePYP cardiac uptake in a patient who suffered an acute subendocardial infarction. The images show diffuse radioactivity in the cardiac region.

**Figure 4.** Grades of diffuse TePYP cardiac uptake in the anterior (ANT) projection of two patients with coronary artery disease. Cardiac radioactivity appeared relatively faint but definite in the patient on the left (2+) but more intense in the patient on the right (3+). In both cases diffuse cardiac radioactivity was apparent to all observers.
TABLE 2. TcPYP Image Analysis According to Patient Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of patients</th>
<th>Discrete TcPYP uptake</th>
<th>Diffuse TcPYP uptake</th>
<th>% Diffuse uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>26</td>
<td>25</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subendocardial infarction</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>Unstable angina pectoris</td>
<td>18</td>
<td>1</td>
<td>7</td>
<td>39</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>41</td>
<td>0</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Nonischemic disease</td>
<td>20</td>
<td>0</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>All heart disease</td>
<td>108</td>
<td>26</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>No heart disease</td>
<td>495</td>
<td>0</td>
<td>65</td>
<td>13</td>
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Among these the frequency of prior left mastectomy differed significantly between the diffuse uptake and negative image groups. Table 3 reveals that the incidence of left mastectomy in the diffuse uptake group was 30% versus a 2% incidence in the negative image group (P < 0.001). Mastectomy was in all cases performed at least six months prior to imaging. Generalized increase of radioactivity over the left hemithorax likely related to decreased tissue attenuation post mastectomy was not evidence of diffuse uptake. Breast cancer itself or prior right mastectomy failed to differentiate between the two groups and there was in fact no other significant diagnostic difference between them.

TABLE 3. Evidence of Blood Pool Activity in Bone Scan

<table>
<thead>
<tr>
<th>Diffuse TcPYP uptake</th>
<th>Normal</th>
<th>P value</th>
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<tbody>
<tr>
<td>Total</td>
<td>70</td>
<td>413</td>
</tr>
<tr>
<td>Femoral activity</td>
<td>59</td>
<td>13</td>
</tr>
<tr>
<td>Females with prior left mastectomy</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Total females</td>
<td>37</td>
<td>219</td>
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Discussion

The recent literature documents the cardiac localization of TcPYP in patients with recent myocardial infarction. TcPYP accumulation is said to occur only in areas of irreversible damage, possibly due to the specific formation of an intracellular calcium containing crystalline material. Prior studies have demonstrated the sensitivity and specificity of discrete TcPYP uptake in identifying and localizing zones of recent myocardial infarction. More recently the pattern of diffuse TcPYP cardiac uptake has been identified in patients with subendocardial infarction and has thought to be specific for this condition. The diffuse pattern was also noted to be present in significant proportions of patients with unstable angina and even with stable angina pectoris. Often the pattern was associated with syndromes indicative of advanced, progressive, but apparently reversible myocardial ischemia and it was postulated that such radioisotope distribution represented widespread but patchy islands of necrosis in a sea of reversible ischemia. Such studies, however, were only performed in patients evaluated for symptoms of coronary disease with a high incidence of this condition. The present study evaluates the overall specificity of TcPYP cardiac uptake, both in its discrete and diffuse patterns, in a large non-coronary population.

Our results support the high sensitivity and specificity of discrete TcPYP images in identifying and localizing zones of myocardial infarction. Although reportedly seen as well with subendocardial infarction, ventricular aneurysms and valvular calcifications, we did not specifically study these conditions and did not note any such examples, perhaps due to the paucity of these diagnoses in our study group.

Our definition and threshold for evaluating diffuse uptake parallels established guidelines. As in other studies, among a group of patients evaluated for symptoms of coronary disease and having a high incidence of the disease, there was a significant incidence of diffuse TcPYP uptake. However, a group of patients without acute coronary symptoms and with a low incidence of coronary disease showed a similar incidence of the diffuse TcPYP cardiac pattern (table 1). Evidence presented would suggest that this patient group, evaluated for malignancy, had an incidence of coronary disease similar to that of the general population. The incidence of diffuse cardiac uptake among all those with heart disease was not statistically different from that in the group without evidence of heart disease (table 2). This pattern was seen in

FIGURE 5. Diffuse TcPYP cardiac uptake is shown in two camera bone scans. The study on the left shows diffuse cardiac uptake in the presence of femoral vascular activity (arrows). The study on the right, in a patient with prior left mastectomy, shows diffuse cardiac uptake without apparent vascular activity.
patients with subendocardial infarction and unstable angina pectoris indicating that at least some cases could be due to otherwise unappreciated focal necrosis as previously reported. Although some patients studied likely had coronary or other forms of heart disease not evident in retrospect, it is unlikely that this would explain the non-specific nature of the diffuse cardiac pattern. Alternative explanations were sought. Sex and age distribution among diffuse uptake and normal groups was similar. Factors which might alter radionuclide blood clearance were examined. The time of imaging following TcPYP administration was not different between the two groups. The presence of free pertechnetate due to an unstable preparation was unlikely, due to rigid quality control. Also, unstable preparations characteristically label the stomach, thyroid and salivary glands, not seen here. The incidence and distribution of diffuse TcPYP uptake among our prospectively studied coronary patients were in fact not different from that seen in other studies. This fact and the lack of date clustering again argue in favor of a stable preparation. It is known that recent prior radionuclide studies with technetium stannous compounds may result in binding of stannous ions within red cells. When a subsequent technetium study is performed, technetium binding to red cells may occur. The incidence of preceding imaging studies again failed to differentiate between the diffuse uptake and negative image groups. Evidence of renal disease was also rare and not significantly different between the two groups.

Finally, both femoral vascular activity and prior left mastectomy correlated with the diffuse pattern (table 3). The former may be due to endothelial adherence or, more likely, decreased blood clearance. There was no evidence that renal disease explained an altered blood clearance in patients with the diffuse pattern. However, a recent study has shown that some cases of this diffuse pattern were due to persistent TcPYP blood pool activity which was felt related to a relatively low radioisotope clearance. TcPYP clearance, in turn, varied widely and inexplicably among otherwise normal patients. This study then supports unintentional blood pool imaging and resultant visualization of cardiac chambers as a cause of some cases of diffuse uptake possibly on the basis of variations in TcPYP clearance. Also, the significantly higher frequency of left mastectomy among the diffuse uptake population might indicate that some cases of diffuse uptake represent blood pool imaging enhanced by reduced tissue attenuation. Indeed, if this premise is correct, patients with both femoral activity, indicat-ing diminished blood clearance, and left mastectomy, reducing tissue attenuation, might be expected to have a high incidence of diffuse uptake. Among seven such patients, six (86%), had the diffuse pattern.

Our findings support those of Berman and co-workers who found a 20% incidence of false positive TcPYP heart scans, all with a diffuse pattern. They also explain the findings of Soin and co-workers who reported two puzzling TcPYP bone scans, both with cardiac activity in the diffuse pattern, one with a remote left mastectomy and neither with any evidence of coronary or other form of heart disease. Our findings may also explain some recently reported cases of apparent image-documented infarction unaccompanied by diagnostic electrocardiographic changes, following coronary bypass surgery. Routine acceptance of the diffuse pattern of TcPYP cardiac uptake as the criteria for non-transmural infarction will likely lead to a large number of false positive diagnoses. Since the diffuse pattern may be due to either generalized intramyocardial or intracavitary radioactivity, methods of differentiating these causes must be developed if the diffuse pattern is to be clinically reliable. Delayed imaging, comparison with definite blood pool images, or serum isotope analysis, may be methods of such differentiation worth investigating. Routine monitoring of residual blood pool activity and blood clearance with adjustment of the injection to imaging interval, may be required to eliminate this possibility.

In summary, in spite of careful control of isotope production and imaging technique it appears that at least some cases of diffuse TcPYP cardiac uptake may be due to unsuspected blood pool imaging. Such blood pool imaging may be due to delayed radionuclide clearance, decreased tissue attenuation, or abnormal endothelial adherence. In the population studied, however, discrete TcPYP cardiac uptake was a sensitive and specific indicator of acute transmural myocardial infarction.

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References
Quantification of Infarction in Cross Sections of Canine Myocardium In Vivo with Positron Emission Transaxial Tomography and $^{11}$C-Palmitate

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SUMMARY To assess myocardial infarction quantitatively in 15 mm thick transverse sections of the canine heart in vivo we utilized a new technique, positron emission transaxial tomography (PETT) and cyclotron-produced $^{11}$C-palmitate ($^{11}$C-P) injected intravenously. Results were compared to regional myocardial creatine phosphokinase (CPK) depletion, diminished $^{11}$C-palmitate accumulation in tissue extracts, and infarction estimated morphometrically 48 hours after coronary occlusion. CPK activity and $^{11}$C-P content declined in parallel in transmural biopsies (N = 44) from normal and ischemic zones ($r = .92$) in six dogs; and infarct in 10 mm thick cross sections of the entire left ventricle estimated morphometrically (N = 26) in six other animals correlated with CPK depletion in contiguous 2.5 mm thick slices ($r = .92$). When the percentage of infarction in 15 mm thick cross sections was assessed tomographically in six other dogs 48 hours after coronary occlusion with $^{11}$C-P injected intravenously, results correlated with infarction in corresponding cross sections from the same hearts estimated morphometrically ($r = .97, N = 9$) and by analysis of CPK depletion ($r = .93, N = 9$). Thus, PETT permits estimation of infarction in cross sections of the left ventricle in vivo after intravenous injection of $^{11}$C-palmitate.

EVALUATION OF THE EXTENT OF MYOCARDIAL INFARCTION in vivo has become increasingly important because prognosis in patients appears to be influenced by infarct size and because the extent of irreversible ischemic injury may be amenable to favorable modification with interventions implemented during the early evolution of the insult. Although myocardial infarct scintigraphy is useful for detection and localization of infarction, quantification of ischemic injury with this technique may be limited because of the dependence of accumulation of tracer on the age of the infarct, and because of inherent limitations leading to disparities between the mass of injured tissue and its two-dimensional display. Precordial ST-segment elevations may reflect serial changes in the electrophysiological response of the heart to ischemia but they do not provide a direct reflection of the absolute magnitude of infarction. Chemical analysis of biopsy material permits estimation of infarct size on the basis of time-activity curves of plasma enzymes such as creatine phosphokinase suffers from the prolonged interval required for acquisition of data prior to construction of projected portions of the curves.

The present study was designed to develop and evaluate a method for quantitative estimation of the extent of myocardium undergoing infarction in vivo suitable for prompt, early, and sequential evaluation of the evolution of ischemic injury. Accordingly, we synthesized $^{11}$C-palmitate, a short-lived, positron-emitting, cyclotron-produced tracer of the predominant physiological substrate of myocardium, injected the material intravenously in closed chest dogs with myocardial infarction; and determined its distribution in ischemic myocardium with computer reconstructed images obtained by positron emission transaxial tomography in order to detect, localize, and quantify infarction in vivo. Results were compared to independent estimates of the extent of infarction based on biochemical and morphological analyses of hearts from the same animals.

This approach was predicated on several considerations. The positron-emitting tracer employed has a short half-life (20.4 min), permitting frequent sequential studies with a low total body radiation burden. Use of palmitate, a physiological substrate of the heart, permits interpretation of results in terms of the extensive information available characterizing myocardial intermediary metabolism and documenting diminished uptake and oxidation of free fatty acids.
The specificity of the diffuse pattern of cardiac uptake in myocardial infarction imaging with technetium-99m stannous pyrophosphate.

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