Effect of EHDP on Calcium Accumulation and Technetium-99m Pyrophosphate Uptake in Experimental Myocardial Infarction

L. Maximilian Buja, M.D., Andrew J. Tofe, Ph.D., Robert W. Parkey, M.D., Marion D. Francis, Ph.D., Samuel E. Lewis, M.D., Padmakan V. Kulkarni, Ph.D., Frederick J. Bonte, M.D., and James T. Willerson, M.D.

SUMMARY Ethane-1-hydroxy-1,1-diphosphonate (EHDP) inhibits bone mineral growth. This study was performed to test the hypothesis that EHDP would interfere with the process of calcium uptake and deposition in evolving myocardial infarction and thereby influence other parameters, including technetium-99m pyrophosphate (Tc-99m PYP) uptake and scintigraphic visualization of the infarcts. Permanent occlusion of the left anterior descending coronary artery (LAD) was produced in beagles. In seven dogs, serum EHDP was maintained at 10-15 μg/ml for 24 hours by continuous i.v. infusion, and seven control dogs were infused with saline. The Tc-99m PYP was injected 2 hours before sacrifice. EHDP-treated dogs showed a mild decrease (20%) in mean calcium content of infarcted myocardium (102.4 ± 6.4 μg [± SEM] per gram wet weight [n = 51] vs 126.7 ± 5.9 [n = 49] p < 0.05). These dogs showed a prominent decrease (37%) in mean Tc-99m PYP content of infarcted myocardium (18.2 ± 1.4 [% dose/g × 105] [n = 46] vs 28.9 ± 4.3 [n = 46] p < 0.005) and a marked decrease (65%) in infarct-to-normal ratio (6.1 ± 0.9 [n = 6] vs 15.9 ± 3.7 [n = 6] p < 0.05). Positive relationships were demonstrated between myocardial Tc-99m PYP and calcium levels in the EHDP-treated dogs (r = 0.69) and the control dogs (r = 0.77). Infarct size and regional myocardial blood flow changes were similar in the EHDP-treated and control dogs. The average grade (0-4+) of the Tc-99m PYP myocardial scintigrams for infarcts greater than 3.5 g was 2.4 ± 0.2 for control dogs and 1.1 ± 0.4 for EHDP-treated dogs (r < 0.05). Thus, EHDP infusion at the dose tested produced a mild decrease in calcium accumulation in canine infarcts; however, it produced a greater reduction in Tc-99m PYP uptake in the infarcts, probably by complexing with Tc-99m PYP binding sites and by dilution of Tc-99m PYP in the circulating diphosphonate pool. These findings suggest that calcification inhibitors, and possibly other calcium-blocking agents, may alter the sensitivity of Tc-99m PYP myocardial scintigraphy, but the specific effects of each calcium antagonist must be evaluated.

PHOSPHATES (general chemical formula [P-O-P]n) and phosphonates (general chemical formula [P-C-P]n) have an affinity for various calcific species associated with biologic calcification, including hydroxyapatite.1-4 Substitution of a carbon for oxygen renders the phosphonates more stable than the polyphosphates in vivo by decreasing the susceptibility of the compounds to enzymatic degradation.1-4 Phosphonates, including ethane-1-hydroxy-1,1-diphosphonate (EHDP), inhibit skeletal and soft tissue calcification.1-4 Polyphosphates, including pyrophosphate (PYP), and phosphonates also have an affinity for acutely necrotic muscle; radiopharmaceuticals of these agents tagged with technetium-99m (99mTc) accumulate in acute myocardial infarcts and necrotic skeletal muscle.6-11 This uptake of the radiopharmaceuticals is at least in part related to an affinity for calcific deposits that develop in areas of damaged muscle with significant resident perfusion.6-11 Several studies indicate that alterations of calcium homeostasis, including altered calcium flux and calcium accumulation, can induce irreversible myocardial injury.13-16 Drugs that interfere with transmembrane calcium movements may reduce the extent of myocardial damage.13-16 The present study was undertaken to evaluate the effect of continuous infusion of EHDP on the process of calcium uptake and deposition during evolving experimental myocardial infarction and to evaluate the effect of altered calcium deposition on other parameters, including subsequent uptake of 99mTc-PYP and scintigraphic visualization of the infarcts.

Materials and Methods

Protocol

Purebred beagles, 9-12 kg, were tranquilized with an i.v. injection of 0.5 ml xylazine (20 mg/ml) (Rompun) and 1 ml ketamine (100 mg/ml) (Vetalar) and anesthetized with an i.v. injection of 1.5-4.5 ml of sodium thiamylal (5 g/100 ml) (Surital). Each dog was placed on a Harvard respirator and ventilated with room air. Cannulas were inserted into a carotid artery and the right and left jugular veins. An infusion was begun through one of the venous catheters of either normal saline (12 dogs) or EHDP (12 dogs). The study was performed such that control dogs were interspersed with EHDP dogs. The infusion was begun with a Harvard infusion pump and, after the surgical procedure was completed, subsequently maintained until the end of the study with a small infusion pump.
(Cormed Inc.) placed in a backpack and strapped to the animals. Solutions of 14C-labeled EHDP were used at concentrations calculated to maintain serum levels of 10–15 μg/ml. A 0.7% 14C EHDP solution was used with the Harvard infusion pump (20-ml syringe, setting 7) and a 2% 14C EHDP solution with the backpack pump. Venous blood samples were collected from a jugular venous catheter at 1, 3 and 24 hours after the start of the infusion. Serum levels of 14C EHDP were assayed by direct liquid scintillation counting in Triton X-100.

After a thoracotomy and pericardiotomy, a left atrial catheter was inserted. Radioactive microspheres (7–10 μ) were injected through the left atrial catheter and arterial blood samples were collected for subsequent measurement of myocardial blood flow.20–22 The radioactive microsphere blood flow measurements were made with a standard dose (approximately 1,000,000), which has not been associated with significant hemodynamic alterations or microvascular obstruction.20–22 Thirty minutes after the infusion of saline or EHDP was begun, the proximal left anterior descending coronary artery (LAD) just distal to the origin of the first major septal and lateral branches was ligated. Fifteen minutes after LAD ligation, a second dose of microspheres was injected. The thoracotomy was closed, and a vest with the backpack infusion pump was secured to the dog. The dog was allowed to recover from anesthesia.

The next day, the dog was again tranquilized and anesthetized as described above. An i.v. injection of 3–4 mCi of Tc-99m PYP was given 22 hours after LAD occlusion. Two hours later, myocardial scintigrams were obtained in the three standard views (anterior, left anterior oblique and left lateral) using a Searle 37-tube scintillation camera with a 16,000-hole, high-resolution collimator. The camera was set at 140 keV with a 20% window. The Tc-99m PYP myocardial scintigrams were graded according to a standard protocol without knowledge of the treatment group on a scale of 0–4+, with grades 2–4+ considered positive and 0–1+ negative.8

With the dog anesthetized and on the respirator, the final microsphere injection was performed. The saline or EHDP infusion was discontinued, and the dog was sacrificed 24–25 hours after LAD occlusion with a large dose (more than 60 mg/kg) of i.v. pentobarbital.

The protocol was repeated in an additional seven dogs that received higher doses of 14C EHDP so as to maintain serum levels in the range of 100 μg/ml.

Tissue Sampling and Processing

The heart was removed and cut into four or five transverse rings. Slice weights, heart weight and left ventricular weights were obtained. Small samples (100–200 mg) were obtained for 99mTc-PYP, 14C EHDP and calcium analyses from the subepicardium and subendocardium of the noninfarcted posterior left ventricle and from the anterior left ventricle, including peripheral and central regions of grossly damaged myocardium. Larger samples (0.5–1 g) were obtained from the same areas for radioactive microsphere measurements. Wet weights on all the samples were obtained.

The ventricular slices were incubated in a solution of 1% triphenyl tetrazolium chloride in phosphate buffer until the noninfarcted tissue stained bright red.23 The slices were then fixed in 10% phosphate-buffered formalin and photographed. Representative tissue blocks were obtained and processed for histologic examination. Photographic prints of the slices were made. Total areas and infarcted areas were traced on the photographic prints and digitized for subsequent calculation of infarct size.

Multiple determinations were made on the 100–200-mg samples. The 99mTc-PYP levels were determined by gamma scintillation counting. After decay of 99mTc, samples were combusted in quartz cups (to collect ash residue for calcium analyses), trapped in a solution of Carbo-Sorb and Permafluor-I and radioassayed for 14C by liquid scintillation counting. The residual ash was digested in nitric acid and the calcium levels were quantitated by atomic absorption as previously described.7 Cross-contamination from combustion of the 99mTc, 85Sr and 47Sc microspheres was investigated and found to be negligible.

Radioactive microsphere levels in tissue and blood samples were quantitated by gamma spectroscopy several days after sacrifice when 99mTc activity was negligible. A standard computer program was used to correct for cross-contamination from the three isotopes (121I, 85Sr and 47Sc) and to calculate myocardial blood flows (ml/min/g).

Statistical Analysis

Comparisons of infarct size, blood flow and tissue levels of calcium and 99mTc-PYP between groups of dogs were performed with a two-tailed group t test (tables 1–3). Correlations of 99mTc-PYP, 14C EHDP and calcium levels within groups were made using Pearson's correlation coefficient (table 4). A chi-square analysis was used to compare the number of positive scintigrams (table 5) and the group t test for the average scan grade (table 5).

Results

Of the 12 dogs in the control group, five were excluded, including four that died overnight and one that became moribund when reanesthetized before 99mTc-PYP injection. Of the 12 dogs in the EHDP (10–15 μg/ml) group, five were excluded, including two that

| Table 1. Infarct Size in Dogs Administered Saline or Diphosphonate (EHDP) During Left Anterior Descending Coronary Artery Occlusion for 24 Hours |
|---|---|
| Infarct wt. (g) | % LV infarcted |
| Saline dogs | 6.5 ± 1.33 | 14.1 ± 2.91 |
| EHDP dogs | 8.3 ± 0.54 | 19.4 ± 0.80 |
| p < 0.50 | p < 0.20 |

Values are mean ± SEM.
died overnight, one that became moribund when re-anesthetized before injection of $^{99m}$Tc-PYP, one that did not receive an appropriate amount of drug due to a pump malfunction and one that had relatively well preserved blood flow (30–60% of normal) in the LAD bed and did not have a gross infarct. Thus, the study groups consisted of seven control dogs and seven EHDP dogs with serum levels of 10–15 μg/ml confirmed by measurements of blood samples.

The control group and 10–15-μg/ml EHDP group

Table 3. Calcium, Technetium-99m Pyrophosphate and $^{14}$C EHDP Levels in Dogs Administered Saline or Diphosphonate (EHDP) During Left Anterior Descending Coronary Artery Occlusion for 24 Hours

<table>
<thead>
<tr>
<th></th>
<th>Calcium (ppm)</th>
<th>$^{99m}$Tc-PYP (% dose/g × 10$^3$)</th>
<th>$^{14}$C EHDP (% dose/g × 10$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Saline dogs</td>
<td>EHDP dogs</td>
<td>Saline dogs</td>
</tr>
<tr>
<td>Normal LV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epi</td>
<td>23.4 ± 2.6</td>
<td>29.3 ± 5.4</td>
<td>1.9 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>(n = 7)</td>
<td>(n = 7)</td>
<td>(n = 6)</td>
</tr>
<tr>
<td></td>
<td>(p &lt; 0.50)</td>
<td></td>
<td>(p &lt; 0.05)</td>
</tr>
<tr>
<td>Infarct periphery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epi</td>
<td>109.4 ± 38.0</td>
<td>86.4 ± 17.2</td>
<td>30.7 ± 9.7</td>
</tr>
<tr>
<td></td>
<td>(n = 7)</td>
<td>(n = 7)</td>
<td>(n = 6)</td>
</tr>
<tr>
<td></td>
<td>(p &lt; 0.80)</td>
<td></td>
<td>(p &lt; 0.50)</td>
</tr>
<tr>
<td>Endo</td>
<td>120.0 ± 20.2</td>
<td>92.5 ± 13.5</td>
<td>26.7 ± 4.4</td>
</tr>
<tr>
<td></td>
<td>(n = 7)</td>
<td>(n = 7)</td>
<td>(n = 6)</td>
</tr>
<tr>
<td></td>
<td>(p &lt; 0.50)</td>
<td></td>
<td>(p &lt; 0.10)</td>
</tr>
<tr>
<td>Infarct center</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epi</td>
<td>129.9 ± 22.6</td>
<td>113.9 ± 17.2</td>
<td>33.8 ± 6.6</td>
</tr>
<tr>
<td></td>
<td>(n = 7)</td>
<td>(n = 7)</td>
<td>(n = 6)</td>
</tr>
<tr>
<td></td>
<td>(p &lt; 0.80)</td>
<td></td>
<td>(p &lt; 0.20)</td>
</tr>
<tr>
<td>Endo</td>
<td>135.9 ± 15.1</td>
<td>110.8 ± 17.3</td>
<td>22.5 ± 3.0</td>
</tr>
<tr>
<td></td>
<td>(n = 7)</td>
<td>(n = 7)</td>
<td>(n = 6)</td>
</tr>
<tr>
<td></td>
<td>(p &lt; 0.50)</td>
<td></td>
<td>(p &lt; 0.01)</td>
</tr>
<tr>
<td>Average infarct</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>values</td>
<td>122.3 ± 20.1</td>
<td>99.9 ± 13.3</td>
<td>28.2 ± 4.8</td>
</tr>
<tr>
<td></td>
<td>(n = 7)</td>
<td>(n = 7)</td>
<td>(n = 6)</td>
</tr>
<tr>
<td></td>
<td>(p &lt; 0.50)</td>
<td></td>
<td>(p &lt; 0.10)</td>
</tr>
<tr>
<td>Infarct/normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ratio</td>
<td>5.5 ± 0.9</td>
<td>3.6 ± 0.3</td>
<td>15.9 ± 3.7</td>
</tr>
<tr>
<td></td>
<td>(n = 7)</td>
<td>(n = 7)</td>
<td>(n = 6)</td>
</tr>
<tr>
<td></td>
<td>(p &lt; 0.10)</td>
<td></td>
<td>(p &lt; 0.05)</td>
</tr>
<tr>
<td>All infarct samples</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>126.7 ± 9.5</td>
<td>102.4 ± 6.4</td>
<td>28.9 ± 4.3</td>
</tr>
<tr>
<td></td>
<td>(n = 49)</td>
<td>(n = 51)</td>
<td>(n = 46)</td>
</tr>
<tr>
<td></td>
<td>(p &lt; 0.05)</td>
<td></td>
<td>(p &lt; 0.005)</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
All values are reported in units per gram wet weight. Parts per million (ppm) is equal to micrograms per gram.
showed no significant differences in infarct size (table 1) or in absolute or percent reductions in myocardial blood flow in the ischemic region (table 2). Levels of calcium, \(^{99}\text{Tc-PYP}\) and \(^{14}\text{C EHD\textup{P}}\) in the two groups are shown in table 3. Calcium levels were measured in each dog in both groups, whereas \(^{99}\text{Tc-PYP}\) levels were measured in six of the seven dogs in each group. The average values for calcium in the normal left ventricle were similar for saline- and EHD\textup{P}-treated dogs. When infarct calcium levels in the saline and EHD\textup{P} dogs were compared using mean calcium values for the various infarct regions or the average of all values for each infarct, significant differences were not observed in infarct calcium levels, probably because of the large variation in the mean values from dog to dog in each group. However, the infarct-to-normal ratios for calcium in the EHD\textup{P} dogs tended to be lower than those in the control dogs (\(p < 0.10\)). Further, when all infarct samples were compared, the EHD\textup{P} dogs showed a 20% reduction in infarct calcium (\(p < 0.05\)) (table 3).

The EHD\textup{P} dogs showed a significantly higher \(^{99}\text{Tc-PYP}\) level in normal left ventricle compared with the controls (\(p < 0.05\)) (table 3). The average infarct levels for \(^{99}\text{Tc-PYP}\) tended to be lower in the EHD\textup{P} dogs (\(n = 6\)) than in the controls (\(n = 6\)) (\(p < 0.10\)). The most significant difference in \(^{99}\text{Tc-PYP}\) levels between the two groups was in the central subendocardium (\(p < 0.01\)), but the levels tended to be lower in other infarct regions of the EHD\textup{P} dogs. The mean infarct-to-normal ratio for \(^{99}\text{Tc-PYP}\) was significantly reduced in the EHD\textup{P} dogs (\(p < 0.05\)). When all infarct samples for \(^{99}\text{Tc-PYP}\) were compared between the two groups, the EHD\textup{P} dogs showed significantly lower \(^{99}\text{Tc-PYP}\) levels (\(p < 0.005\)).

Correlations between myocardial tissue levels of calcium, \(^{99}\text{Tc-PYP}\) and \(^{14}\text{C EHD\textup{P}}\) are shown in table 4. All samples with available measurements from normal and infarcted tissue were included in the analyses. There was a good correlation between \(^{99}\text{Tc-PYP}\) and calcium levels in the control dogs (\(r = 0.77\)). In the EHD\textup{P} dogs, significant correlations also occurred between calcium and \(^{99}\text{Tc-PYP}\) (\(r = 0.69\)) and between calcium and \(^{14}\text{C EHD\textup{P}}\) (\(r = 0.66\)) levels. The \(^{99}\text{Tc-PYP}\) and \(^{14}\text{C EHD\textup{P}}\) levels showed a strong correlation (\(r = 0.94\)), indicating that both agents have an affinity for similar tissue-binding sites.

The results of myocardial scintigraphy are summarized in table 5. The myocardial scintigrams were interpreted on a scale of 0–4+ without knowledge of the treatment received by the dogs. Consistent with the reported sensitivity of approximately 3 g, two control dogs with small infarcts of 2.1 and 3.4 g showed positive \(^{99}\text{Tc-PYP}\) myocardial scintigrams, whereas all five with larger infarcts had positive scintigrams (fig. 1). All EHD\textup{P}-treated dogs had infarcts of more than 3.5 g. Myocardial scintigrams in the EHD\textup{P}-treated group, however, generally showed high background activity and decreased visibility of specific infarct uptake. Myocardial scintigrams were read as positive in only four of the seven dogs in the EHD\textup{P}-treated group (table 5). The average grade (0–4+) of the \(^{99}\text{Tc-PYP}\) myocardial scintigrams for infarcts greater than 3.5 g was 2.4 ± 0.2 for the control dogs and 1.1 ± 0.4 for the EHD\textup{P}-treated dogs (\(p < 0.05\)). Five of the seven high-dose (100 \(\mu\text{g/ml}\)) EHD\textup{P} dogs completed the protocol. All five had gross myocardial infarcts with calcium and \(^{99}\text{Tc-PYP}\) levels similar to those in the saline controls. The high-dose EHD\textup{P} dogs also showed higher levels of \(^{99}\text{Tc-PYP}\) and calcium in normal left ventricle than either the control dogs or low-dose EHD\textup{P} dogs.

**Discussion**

When continuously infused at a serum level of 10–15 \(\mu\text{g/ml}\) for 24 hours of coronary occlusion, EHD\textup{P} did not effect a detectable reduction in infarct size and did not prevent abnormal calcium accumulation in the ischemic region, but did produce a 20% decrease in the calcium content of the infarcted myocardium. These results suggest that the major effect of EHD\textup{P} on ischemic myocardium is to retard progres-

**Table 4. Relationship Between Tissue Levels of Calcium, Technetium-99m Pyrophosphate and 14C EHDP in Dogs Administered Saline or Diphosphonate (EHD\textup{P}) During Left Anterior Descending Coronary Artery Occlusion for 24 Hours**

<table>
<thead>
<tr>
<th></th>
<th>(n)</th>
<th>(p)</th>
<th>(r)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Saline dogs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium vs (^{99}\text{Tc-PYP})</td>
<td>51</td>
<td>&lt;0.001</td>
<td>0.77</td>
</tr>
<tr>
<td>EHDP dogs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium vs (^{99}\text{Tc-PYP})</td>
<td>52</td>
<td>&lt;0.001</td>
<td>0.69</td>
</tr>
<tr>
<td>(^{99}\text{Tc-PYP}) vs (^{14}\text{C-EHDP})</td>
<td>58</td>
<td>&lt;0.001</td>
<td>0.66</td>
</tr>
<tr>
<td>(^{99}\text{Tc-PYP}) vs (^{14}\text{C-EHDP})</td>
<td>52</td>
<td>&lt;0.001</td>
<td>0.94</td>
</tr>
</tbody>
</table>

**Table 5. Technetium-99m Pyrophosphate Myocardial Scintigraphy in Dogs Administered Saline or EHD\textup{P} During Left Anterior Descending Coronary Artery Occlusion for 24 Hours**

<table>
<thead>
<tr>
<th></th>
<th>No. positive scans</th>
<th>Scan grade (0–4+)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Saline</td>
<td>EHDP</td>
</tr>
<tr>
<td>Infarcts 2.1–3.4 g</td>
<td>0/2</td>
<td>0/0</td>
</tr>
<tr>
<td>Infarcts 4.0–10.7 g</td>
<td>5/5</td>
<td>4/7</td>
</tr>
<tr>
<td>((p = 0.20))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All infarcts</td>
<td>5/7</td>
<td>4/7</td>
</tr>
<tr>
<td>((p = 0.58))</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The scintigrams were graded without knowledge of the treatment group on a scale of 0–4+, with grades 2–4+ considered positive.

*Values are mean ± SEM.
sion of pathologic calcification without inhibiting initial stages of altered transmembrane calcium flux and calcium accumulation. Amelioration of these initial calcium alterations probably is more important in reducing the severity of ischemic myocardial damage. This is suggested by results with other agents, such as D-600, verapamil, nifedipine and chlorpromazine, with ischemic injury and catecholamine-induced necrosis.\(^{(10-19)}\) However, Rosenblum et al. observed a protective effect of EHDP against myocardial and vascular degeneration and calcification produced by administration of dihydrotestosterol.\(^{(9)}\)

Significant correlations were obtained between \(^{99m}\)Tc-PYP and calcium levels in the control dogs and between \(^{99m}\)Tc-PYP, \(^{14}\)C EHDP and calcium levels in the EHDP dogs. These results provide further evidence that complexing of \(^{99m}\)Tc-PYP with calcium deposits is an important mechanism in the scintigraphic detection of necrotic myocardium with this agent.\(^{(6-11)}\) EHDP infusion, however, produced an adverse effect on \(^{99m}\)Tc-PYP myocardial scintigraphy characterized by a significant decrease (37%) in the uptake of \(^{99m}\)Tc-PYP in infarcted myocardium, increased (58%) background activity in normal myocardium, decreased (65%) infarct-to-normal ratio and reduced visualization of infarcts on \(^{99m}\)Tc-PYP myocardial scintigrams. Infusion of EHDP at a higher dose (100 \(\mu g/ml\) serum levels) resulted in further deterioration of the infarct-to-normal ratio of \(^{99m}\)Tc-PYP. These effects of EHDP may be explained by partial saturation of \(^{99m}\)Tc-PYP binding sites by EHDP and dilution of \(^{99m}\)Tc-PYP in the circulating diphosphonate pool at the time of \(^{99m}\)Tc-PYP injection.

The clinical implication of these findings is that significant impairment of diagnostic accuracy of \(^{99m}\)Tc-PYP myocardial scintigraphy may result from disease states, metabolic alterations or drugs that increase the background level and reduce the infarct-to-normal ratio of \(^{99m}\)Tc-PYP. One such condition is chronic renal failure, which may be associated with increased serum phosphate levels, altered pyrophosphate metabolism and, possibly, decreased renal excretion of radiopharmaceuticals.\(^{(24,25)}\) This study also raises the concern that impaired scintigraphic accuracy may occur in patients receiving various calcium antagonists. This is an important problem because more patients with various ischemic heart disease syndromes are being treated with these agents.\(^{(26)}\) Each of the calcium antagonists, however, will have to be evaluated with respect to individual effects on \(^{99m}\)Tc-PYP myocardial scintigraphy. Finally, our study reinforces the important point that myocardial scintigrams with unacceptably high background and blood pool levels should not be read as positive or negative, but should be considered uninterpretable and repeated until technically adequate.

**Acknowledgment**

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