In-Labeled Platelet Scintigraphy and Two-Dimensional Echocardiography for Detection of Left Atrial Appendage Thrombi

Studies in a New Canine Model

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In-labeled platelet scintigraphy and two-dimensional echocardiography were performed in 40 dogs to determine the ability of the two techniques to detect left atrial appendage thrombi. Thrombi were induced in 33 dogs that were classified into two groups, “acute” or “chronic,” according to the time of labeled-platelet injection after thrombus induction. In the acute group (17 dogs), platelets were injected 24 hours after thrombus induction. In the chronic group (16 dogs), platelets were injected 4–8 days after thrombus induction. “Sham” thoracotomies were performed on seven additional control dogs who did not receive thrombin injections. Analog and blood pool-corrected In-labeled platelet scintigraphy images were obtained 4–72 hours later. Closed-chest two-dimensional echocardiography was performed before thoracotomy and repeated at the time of scintigraphy. The location and size of each thrombus were verified at autopsy. Two-dimensional echocardiography detected three of 17 acute (mean volume, 1.2 ± 1.0 cc) and three of 10 chronic (mean volume, 0.4 ± 0.3 cc; p<0.025) left atrial appendage thrombi. In-labeled platelet scintigraphy detected all 17 acute thrombi but only two of 10 chronic thrombi. The measured radioactivity levels of the excised thrombi were 1,949 ± 1,665 cpm/clot/dose in group 1 and 228 ± 213 cpm/clot/dose in group 2 (p<0.005). In this model, In-labeled platelet scintigraphy was able to detect acute left atrial appendage thrombi that could not be identified by two-dimensional echocardiography. Both techniques showed poor sensitivity for detection of chronic thrombi. The decline in sensitivity of In-labeled platelet scintigraphy for detection of older thrombi is probably due to diminished labeled-platelet incorporation.

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Left atrial thrombi are present in 10–25% of patients with rheumatic mitral valve disease; in approximately one half of these patients, systemic embolization will occur. Autopsy studies have shown that thrombi are limited to the left atrial appendage in 41% of patients with mitral stenosis and systemic embolization. In addition, up to 50% of all left atrial thrombi are limited to the appendage.

Two-dimensional echocardiography (2-D echo) can be useful for the detection of thrombi in the left atrium, but it appears to be unreliable for detecting thrombi limited to the left atrial appendage. This is unfortunate because anticoagulation is usually instituted with detection of left atrial thrombus. Thrombus detection can also influence the choice of surgical approach used for mitral commissurotomy. Systemic embolization of left atrial thrombi during or shortly after mitral commissurotomy is a major cause of morbidity and mortality from the closed procedure. Systemic embolization can be avoided if the thrombus is evacuated during an open-heart procedure.

Although In-labeled platelet scintigraphy (In-PS) has demonstrated utility for the detection of left ventricular thrombi, the application of In-PS
Materials and Methods

Thrombus Induction

Forty mongrel dogs were intubated and ventilated with positive pressure after receiving sodium pentobarbital for anesthesia. Thirty-three dogs underwent induction of a left atrial appendage thrombus; seven additional control dogs underwent a "sham" operation. All dogs were placed in the right lateral decubitus position over a "cut-out" in the imaging table. The cut-out permitted placement of an ultrasonic transducer against the right thorax. After a baseline 2-D echo study was performed, a thoracotomy was performed, and the heart was exposed in a pericardial cradle.

The method of left atrial appendage thrombus induction that was attempted on each of the 33 dogs was developed in preliminary experiments. A polyethylene catheter was inserted into the left atrial appendage. To obtain a broad range of thrombus sizes and weights, the appendage was variably clamped between its base and its midportion. After clamping the appendage, 1,000–1,500 units thrombin and 3–7 ml blood were injected into the appendage through the catheter. One to 3 minutes after thrombin-blood injection, the clamp was removed. The presence of thrombus was confirmed by direct palpation; if no thrombus was palpated, additional thrombin-blood injections were performed until a thrombus was evident. We then reapproximated the pericardium, closed the chest, and allowed recovery for 1–7 days in a special-care facility.

The seven control dogs had also been used in a related study of experimental left ventricular thrombi. These animals underwent thoracotomy, but no thrombin was injected into the left atrial appendage or the left ventricle. As in the 33 study animals, the pericardium and chest were then closed.

Preparation of $^{111}$In-Labeled Platelets

The 33 dogs undergoing thrombus induction were divided into an "acute" group, receiving $^{111}$In-labeled platelet injection 24 hours after thrombus induction (group 1) and a "chronic" group, receiving $^{111}$In-labeled platelet injection 4–8 days (mean, 5 ± 1 days) after thrombus injection (group 2).

Group 1. Seventeen dogs received an intravenous injection of 150–290 µCi autologous labeled platelets 24 hours after thrombus induction and chest closure. Platelets were labeled with $^{111}$In by a modification of the technique described by Hawker and colleagues. Forty-three milliliters of whole blood were collected in 7 ml anticoagulant citrate dextrose solution; platelets were separated from the whole blood and incubated with $^{111}$In-labeled oxine. More than $1 \times 10^9$ platelets were labeled; the labeling efficiency averaged 75% (range, 60–92%).

Group 2. Sixteen dogs received an intravenous injection of 200–250 µCi autologous labeled platelets 4–8 days after thrombus induction and chest closure.

Scintigraphy

Group 1. After the injection of labeled platelets, each dog was imaged 4, 24, and 48 hours later (the control dogs were imaged at 24 hours only). However, once the image was unequivocally positive for clot, no additional imaging was performed. Images were obtained from a Siemens small field-of-view scintillation camera (Cherry Hill, New Jersey) fitted with a medium-energy collimator and interfaced to an ADAC DPS 2800 minicomputer (Sunnyvale, California).

The imaging protocol was as follows: 0.5 mg stannous pyrophosphate was injected intravenously; 1 mCi $^{99m}$Tc as pertechnetate was injected as pertechnetate was injected 15 minutes later. Sequential $^{111}$In and $^{99m}$Tc images of the heart were obtained in the left anterior...
oblique and right posterior oblique projections. $^{111}$In images were acquired for 200,000 counts by a 10% window centered over the 247-keV photopeak and a 5% window centered over the 173-keV photopeak. $^{99m}$Tc images were also acquired for 200,000 counts by a 5% window centered over the 140-keV photopeak. Blood pool-corrected images were generated from the $^{111}$In and $^{99m}$Tc images by a modification of the method described by Seabold and colleagues and Powers and colleagues.

Two independent observers reviewed the analog and blood pool-corrected images; they had no knowledge of the 2-D echo results, the surgical results, or the imaging time relative to the injection of $^{111}$In-labeled platelets. The images of the control dogs were intermixed at random with the images of the study dogs. An $^{111}$In-PS was interpreted as positive if discrete localization of radioactivity was identified in the region of the left atrium (Figure 1); for the statistical analysis, equivocal or uncertain studies were treated as negative interpretations. Disagreements between the two observers were resolved by consensus.

Group 2. After platelet injection, imaging was performed at 24, 48, and 72 hours. The imaging protocol and interpretation were the same as for group 1.

Two-Dimensional Echocardiography

Group 1. 2-D echo was performed within 24 hours before thoracotomy and repeated either immediately before or after the final scintigraphic examination. Real-time echocardiography was performed with an ATL-Ultramark 8 ultrasonoscope (Seattle, Washington) with a 5.0-MHz mechanical head transducer (11 dogs) or with a Toshiba SSH 10A ultrasonoscope (Tokyo, Japan) with a 2.4-MHz phased-array transducer (six dogs); each study was recorded on ¼-in. U-matic videotape. Multiple views were attempted, including views equivalent to the standard parasternal long-axis and short-axis views. Modifications of the apical four-chamber and the parasternal oblique short-axis views were also obtained.

The control and postoperative 2-D echo studies were interpreted by one independent observer who had no knowledge of the $^{111}$In-PS results, the surgical results, or the time of imaging relative to the time of thrombus induction. A 2-D echo study was interpreted as positive if a discrete echogenic mass was identified as protruding into the body of the left atrium or if an echogenic density was identified in the left atrial appendage distinct from the atrial myocardium (Figure 2).

GROUP 2. 2-D echo was performed within 24 hours before thoracotomy and within 3 days of the final scintigraphic examination. All echocardiograms were performed with the ATL-Ultramark 8 ultrasonoscope with a 5.0-MHz transducer.

Verification of Thrombus Induction

Group 1. Forty-eight hours after the injection of $^{111}$In-labeled platelets, or as soon as scintigraphy

FIGURE 2. Two-dimensional echocardiograms of a left atrial appendage thrombus (arrows) protruding into the body of the left atrium. Left panel: Parasternal long-axis view; right panel: modified short-axis view.

FIGURE 3. Photograph of left atrial appendage thrombus. Left panel: Tip of the thrombus (arrow) is visible, protruding from the left atrial appendage. Right panel: Appendage has been opened and is filled with thrombus (arrow). Length is measured in centimeters.
became unequivocally positive, each dog was killed. Immediately after death, the heart was removed from the thoracic cavity, opened, and rinsed out with saline to remove fresh thrombi. The left atrium was inspected for the presence or absence of thrombus extension into the body. An \(^{111}\text{In}-\text{PS}\) image of the excised heart was obtained for 200,000 counts. The appendage was then opened, and the thrombus was dissected free from the left atrial appendage (Figure 3); it was weighed, and its volume was determined by displacement. The thrombus was placed in a well counter (Picker Spectroscaler 4-R, Cleveland, Ohio), and 5-minute counts were recorded. The radioactivity of the thrombus was decay-corrected to the time of injection according to the formula\(^{15}\): \(A_t = A_0 e^{-0.693 \frac{t}{T_{1/2}}}\), where \(A_t\) is activity after a period of elapsed time, \(A_0\) is activity in the original sample, \(t\) is elapsed time, and \(T_{1/2}\) is half-life of \(^{111}\text{In}\) (i.e., 67 hours). The radioactivity of the thrombus was normalized to the radioactivity of the injected dose by dividing the former by the latter.

**Group 2.** One dog was killed at 48 hours, and the remaining dogs were killed after 72 hours.

**Statistical Analysis**

Data was expressed as mean ± SD. Sensitivity was defined as true positives divided by the sum of true positives and false negatives; specificity was defined as true negatives divided by the sum of true negatives and false positives. Correlations of thrombus weight and total counts per minute per clot per dose were performed with a linear regression model. Comparisons between groups 1 and 2 were evaluated with an unpaired \(t\) test. Statistical significance was considered as \(p<0.05\).

**Results**

**Group 1 (Acute) Thrombi**

A left atrial appendage thrombus was present on postmortem examination in each of the 17 dogs in which thrombus induction was attempted. The results are summarized in Table 1. The weights of the thrombi ranged from 0.2 to 3.3 g (mean, 1.2 ± 1.0 g), and the volumes ranged from 0.2 to 3.0 cc (mean, 1.2 ± 1.0 cc). The total counts per minute per clot per dose ranged from 383 to 5,510 (mean, 1,949 ± 1,665 cpm/clot/dose). There was no correlation between total counts per minute per clot per dose and thrombus weight \((r=0.28, p=0.28)\). At postmortem, six of the 17 dogs were observed to have atrial appendage thrombi that extended into the body of the left atrium.

Three of the appendage thrombi were detected by 2-D echo; in each case, the thrombi were identified as protruding into the atrial body on both 2-D echo and postmortem. 2-D echo was negative for all of

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**TABLE 1. \(^{111}\text{In}-\text{Labeled Platelet Scintigraphy and Two-Dimensional Echocardiography in Detection of Acute Left Atrial Appendage Thrombi in Group 1 Dogs**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Thrombus weight (g)</th>
<th>Thrombus volume (cc)</th>
<th>Total cpm/clot/dose (μCi)</th>
<th>Platelet scintigram after platelet injection</th>
<th>Two-dimensional echocardiogram</th>
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<td>Analog images (hr)</td>
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Mean ± SD 1.2 ± 1.0 1.2 ± 1.0 1,949 ± 1,665

All scintigrams and two-dimensional echocardiograms were negative for dogs 18–24 (sham-operated controls). -, Negative for thrombus; ±, equivocal for thrombus; +, positive for thrombus; NA, not applicable (dog killed at the time of previous scintigraphy). 

*Thrombus extending into left atrium.
TABLE 2. ¹¹In-Labeled Platelet Scintigraphy and Two-Dimensional Echocardiography in Detection of Chronic Left Atrial Appendage Thrombi in Group 2 Dogs

<table>
<thead>
<tr>
<th>Dog</th>
<th>Thrombus weight (g)</th>
<th>Thrombus volume (cc)</th>
<th>Total cpm/min/clot/dose (µCi)</th>
<th>Platelet scintigram after platelet injection</th>
<th>Two-dimensional echocardiography</th>
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<td>NP</td>
<td>-</td>
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<tr>
<td>40</td>
<td>0.7</td>
<td>0.6</td>
<td>440</td>
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</table>

mean ± SD 0.5 ± 0.3* 0.4 ± 0.3* 228 ± 213†

- Negative for thrombus; +, positive for thrombus; NP, no thrombus present.
* p<0.025 vs. group 1; † p<0.005 vs. group 1.

The 11 animals that had thrombi confined to the appendage of the left atrium. Control echocardiograms were negative in all 17 animals before the thrombus induction. Thus, 2-D echo demonstrated a sensitivity of 18% and a specificity of 100% (Table 3).

Analog ¹¹In-PS images were interpreted as positive in 14 of the 17 dogs that underwent thrombus induction, whereas blood pool–corrected images were interpreted as positive in 16 of the 17 dogs that underwent thrombus induction. One of the studies (dog 10) was positive on both analog and blood pool–corrected images obtained 4 hours after platelet injection. Analog images obtained 24 hours after platelet injection were positive in an additional 12 studies, whereas blood pool–corrected images were positive in 14. Two dogs with negative 4-hour and 24-hour ¹¹In-PS underwent 48-hour scintigraphy. One of these studies (dog 1) had positive analog and blood pool–corrected images. In the other (dog 3), 48-hour images were negative by both techniques. All of the ¹¹In-PS studies obtained in the seven sham-operated dogs were interpreted as negative. Therefore, with analog plus blood pool–corrected images, ¹¹In-PS achieved a sensitivity of 94% and a specificity of 100% for acute thrombi.

Group 2 (Chronic) Thrombi

A left atrial appendage thrombus was present at postmortem in 10 of the 16 dogs in this group. All thrombi were limited to the atrial appendage. The weights of the thrombi ranged from 0.1 to 1.0 g (mean, 0.5 ± 0.3 g, p<0.025, vs. group 1), and the volumes ranged from 0.1 to 0.8 cc (mean, 0.4 ± 0.3 cc, p<0.025, vs. group 1). The total counts per minute per clot per dose ranged from 14 to 720 (mean, 228 ± 213 cpm/clot/dose, p<0.005, vs. group 1). Compared with group 1, there was a significant but weak correlation between thrombus weight and counts per minute per clot per dose (r = 0.63, p = 0.05) (Table 2).

2-D echo detected autopsy-verified thrombi in three of 10 dogs. There was one false-positive 2-D echo. All 16 control 2-D echo examinations were negative. Thus, the sensitivity was 30%, and the specificity was 94% (Table 3).

Analog ¹¹In-PS images were interpreted as positive in only one of 10 dogs that had thrombus present at autopsy. Blood pool–corrected images were positive in only one of the 10 dogs; the analog study interpreted as positive was negative with

TABLE 3. Statistical Analysis of Data

<table>
<thead>
<tr>
<th></th>
<th>Platelet scintigraphy</th>
<th>Two-dimensional echocardiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>94% (16/17)</td>
<td>18% (3/17)</td>
</tr>
<tr>
<td>Specificity</td>
<td>100% (7/7)</td>
<td>100% (17/17)</td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>20% (2/10)</td>
<td>30% (3/10)</td>
</tr>
<tr>
<td>Specificity</td>
<td>100% (6/6)</td>
<td>94% (15/16)</td>
</tr>
</tbody>
</table>
blood pool correction. All of the $^{111}$In-PS studies in the six dogs without a thrombus were negative. Thus, $^{111}$In-PS achieved a sensitivity of 20% with a specificity of 100% in dogs with chronic thrombi.

**Discussion**

A simple animal model was developed to assess the ability of two imaging techniques to detect thrombi confined to, or arising from, the left atrial appendage. In this model, $^{111}$In-PS showed good sensitivity and specificity for detecting fresh thrombi in the appendage. However, the sensitivity of $^{111}$In-PS declined for older thrombi. The sensitivity of 2-D echo was poor regardless of thrombus age.

The inability of 2-D echo to detect thrombi limited to the left atrial appendage has been reported by others in clinical studies.3–6 Shrestha and colleagues6 performed 2-D echo on 293 patients with rheumatic heart disease. They were unable to identify left atrial thrombi in 21 of 51 patients (41%) with confirmed thrombi. Eleven of these 21 thrombi were confined to the left atrial appendage. Of the 10 remaining false-negative studies, four were very small thrombi, and three were layered mural thrombi. Similarly, Schweizer and colleagues3 were unable to detect eight of 12 left atrial thrombi (67%) that were later confirmed at surgery. Four of the eight false-negative 2-D echo studies had small thrombi confined to left atrial appendage.

In the current experimental study, many of the thrombi that could not be detected by 2-D echo were similar to those described in previous clinical studies. For instance, 11 of 17 (65%) of acute thrombi were confined to the left atrial appendage. Nine of these 11 thrombi were small, weighing less than 1.0 g or displacing less than 1 ml in volume. All of the thrombi in the chronic group were confined to the left atrial appendage and weighed 1.0 g or less. However, the canine model used in this study differs in one important aspect from the usual clinical situation. The left atrial appendage was not dilated as it usually is in patients with mitral stenosis and chronically elevated left atrial pressure. A dilated atrium and atrial appendage might facilitate echocardiographic detection of thrombi in clinical studies. It might also allow for more surface area of the thrombus to be exposed to circulating labeled platelets.

The canine 2-D echo were performed with two different transducers in the acute group; the 2.4-MHz instrument missed one of the thrombi protruding into the left atrium, whereas the 5.0-MHz instrument missed two of these large thrombi. Thus, in this study, a higher frequency instrument with higher resolution did not facilitate thrombus detection.

Clinical experience with $^{111}$In-PS for detection of left atrial thrombi is limited. Benichou and colleagues16 reported two patients with left atrial thrombi identified by both 2-D echo and $^{111}$In-PS. However, they were unable to verify the presence and location of the thrombi. Kessler and colleagues17 reported two patients with positive $^{111}$In-PS for left atrial thrombi, but one of the 2-D echo studies was negative. Again, no pathological confirmation was provided in these cases. In a study by Yamada and colleagues,18 four of five left atrial thrombi verified by surgery or autopsy were detected by platelet scintigraphy. Although age was not certain, they were presumably chronic because they were associated with mitral stenosis. Their clinical results were more encouraging than our experimental data for detection of chronic thrombi, but only two of the thrombi in their clinical study were limited to the atrial appendage, one of which was not detected by scintigraphy. In addition, three of the five thrombi were large, weighing 40–66 g, and were located along the left atrial posterior wall. Thus, their results may have been related to relatively larger thrombi located in the left atrium.

In the current experimental study, the sensitivity of $^{111}$In-PS for acute thrombi was 94%, and the specificity was 100%. Interestingly, the accuracy of $^{111}$In-PS was not influenced by acute thrombus location or size. All thrombi that protruded into the left atrium, and 10 of 11 thrombi confined to the atrial appendage were detected. One 0.8-g thrombus confined to the atrial appendage was not detected by $^{111}$In-PS. Although the size of this thrombus was smaller than the mean, other thrombi weighing between 0.2 and 0.6 g were successfully detected by $^{111}$In-PS. Failure to detect the 0.8-g thrombus was most likely due to poor incorporation of labeled platelets. This thrombus also had low $^{111}$In counts and was poorly visualized after the heart was removed, drained of blood, and reimaged.

The poor correlation between the in vitro radioactivity and the thrombus weight is probably related to labeled-platelet incorporation occurring primarily at the surface of the thrombi. Ezekowitz and colleagues11 demonstrated that for chronic thrombi, the radioactivity at the thrombus surface exceeds the activity in the deeper portions of thrombus by at least 9.7 ± 1.3 times.

In this series, two of four studies with negative 24-hour analog images had positive blood-pool corrected images. However, blood pool-corrected images may not be necessary if scintigraphy is performed more than 48 hours after platelet injection. Verheught and colleagues8 found no improvement in detection of left ventricular thrombi by using blood pool-corrected images obtained 48 hours after platelet injection. In the present study, one acute thrombus was not detected until 48-hour imaging, and both analog and blood pool-corrected images were positive. Over time, the ratio of radioactivity incorporated in the thrombus improves compared with blood-background activity, and delayed images might not require blood pool correction.12 Two factors play a major role in this improved ratio: continued accretion of labeled platelets on the thrombus surface, and a decrease in circulating blood-pool activity as platelets are
removed from circulation. Several investigators have reported that chronic ventricular thrombi are optically detected by analog images between 48 and 96 hours after injection.1-11

Improvement in the echocardiographic detection of left atrial appendage thrombi might be realized with modifications of existing 2-D echo techniques19 or by using transesophageal echocardiography. Recently, Aschenberg and colleagues20 compared transthoracic 2-D echo with transesophageal echocardiography for the detection of left atrial thrombi in 21 consecutive patients undergoing mitral valve replacement. Six patients had surgically confirmed left atrial appendage thrombi; whereas transthoracic 2-D echo was insensitive, all six thrombi were detected by transesophageal echocardiography. We attempted to use transesophageal echocardiography to visualize left atrial appendage thrombi in this experimental model with a 2.4-MHz transducer. However, we could not obtain satisfactory visualization of the left atrial appendage in a sufficient number of cases. The absence of left atrial hypertension and dilation may, in part, be responsible for this difficulty.

Computed tomography may provide an alternate imaging modality for the detection of left atrial appendage thrombi. In a clinical study by Tomoda and colleagues,21 computed tomography identified left atrial thrombi in all eight patients with pathologically verified thrombi. Two patients with negative 2-D echo had thrombi limited to the left atrial appendage.

In conclusion, 111In-PS detected most acute thrombi in the canine left atrial appendage, whereas transthoracic 2-D echo was able to detect acute thrombi only when they extended into the chamber of the left atrium. The sensitivity of 111In-PS in the detection of the chronic left atrial appendage thrombi was much less than that for acute thrombi. This difference is probably due to decreased thrombus propagation with diminished labeled-platelet incorporation as the thrombus ages. The results of this study suggest that 111In-PS is a good technique for the detection of acute or fresh left atrial thrombi but is less promising for detection of chronic thrombi. Additional clinical studies, with autopsy or surgical validation, will be necessary to confirm the results obtained in this experimental model.

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References


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