Bleeding Rates Necessary for Detecting Acute Gastrointestinal Bleeding with Technetium-99m-Labeled Red Blood Cells in an Experimental Model

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Proponents of [^{99m}Tc]sulfur colloid for GI bleeding studies argue that, although labeled red blood cells are useful for intermittent bleeding, they are not capable of detecting low bleeding rates. Studies of dogs with experimental GI bleeding have indicated bleeding rates of 0.05 ml/min can be detected with [^{99m}Tc]sulfur colloid. Since similar data in the dog model were unavailable for ^{99m}Tc-labeled red blood cells, we undertook this study. To simulate lower GI bleeding, catheters were inserted into the bowel lumen. Each dog's blood was labeled with ^{99m}Tc using an in vitro technique. Venous blood was then withdrawn and re-infused into the lumen of the bowel using a Harvard pump. Fourteen dogs were studied, ten receiving a bleeding rate from 4.6–0.02 ml/min in the descending colon and four with proximal jejunal bleeds of 0.20–0.02 ml/min. Bleeding rates of 4.6–0.2 ml/min were detected within 10 min in the colon and bleeding rates as low as 0.04 ml/min were seen by 55 min. Slower bleeding rates were not detected. Similar findings were noted for proximal jejunal bleeds. Based on the time of appearance, a minimum volume of ~2–3 ml labeled blood was necessary to detect bleeding. We conclude that ^{99m}Tc-labeled RBCs are sensitive for low bleeding rates in the dog model. The rates are comparable to those described for [^{99m}Tc]sulfur colloid in this experimental setting. The time of appearance of activity is related to the bleeding rate.

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The successful management of acute gastrointestinal hemorrhage depends on accurate localization of the bleeding site (*1*). Radionuclide techniques have been developed to noninvasively detect and localize the site of gastrointestinal bleeding. There are two competing radionuclide techniques; one uses a radiopharmaceutical with rapid blood clearance, [^{99m}Tc]sulfur colloid, the other uses a blood-pool agent, ^{99m}Tc-labeled red blood cells (RBCs). Which of these two is the better method to use is controversial (*2*).

Proponents of [^{99m}Tc]sulfur colloid for GI bleeding studies argue that, although ^{99m}Tc-labeled red blood cells are useful in intermittent bleeding, they are not capable of detecting low GI bleeding rates due to high background activity (*3*). Technetium-99m sulfur colloid has been shown to be very sensitive. In experimental GI bleeding studies in dogs, bleeding rates as low as 0.05 ml/min were detected (*4*). Since similar data were unavailable for ^{99m}Tc-labeled red blood cells, we undertook a study to determine the sensitivity of ^{99m}Tc-labeled RBCs in detecting acute gastrointestinal bleeding in a dog model similar to that used for [^{99m}Tc]sulfur colloid.

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MATERIALS AND METHODS

Fourteen dogs, each weighing 15–25 kg, were anesthetized with sodium pentobarbital. A catheter was inserted and secured into the lumen of the descending colon through a midline abdominal incision in ten dogs and in the proximal jejunum in four dogs.

Autologous dog red blood cells were labeled using the Brookhaven method (*5*). The ^{99m}Tc-labeled red blood cells were then withdrawn from the vial, assayed in a dose calibrator and injected into the animal. Following a 20-min delay, 10–20 ml of venous blood was withdrawn from the animal for infusion through the intraluminal bowel catheter.

The labeling efficiency of the ^{99m}Tc red blood cells was determined just prior to reinjection and in a venous sample 20 min following injection. This was done by placing two drops of blood in a test tube and mixing it with 2 ml normal saline (*6*). The cells and supernatant were then separated by centrifugation and assayed using a scintillation probe counter. The percent binding was determined by the following formula:

$$\% \text{ labeling yield} = \frac{\text{RBC activity} \times 100}{\text{RBC activity} + \text{supernatant activity}}.$$

To simulate GI bleeding, venous blood was withdrawn from the animal and infused through the intraluminal bowel catheter using a precalibrated Harvard pump with a variable rate setting. The extension tubing and syringe used to inject the labeled RBCs were filled with 4,000 USP units of heparin to prevent clotting at slow infusion rates.

Ten dogs were studied with the catheter in the descending colon at bleeding rates ranging from 4.6-0.02 ml/min and four dogs with proximal jejunal bleeds were studied at rates from 0.2-0.02 ml/min. Serial, 1-min images were obtained for 90 min using a standard field-of-view scintillation camera with a general, all-purpose collimator interfaced to a computer. A 20% window was centered on the 140-keV photopeak. Four baseline 1-min images were obtained before the experimental bleeding was started. At the end of each study, 1–2 mCi of [^{99m}Tc]pertechnetate were injected through the intraluminal catheter to verify the location of the bleeding site.

Scintigraphic images were read independently by two experienced nuclear medicine physicians to determine the bleeding site location and time interval after the onset of experimental bleeding when the study was first noted to be positive. This was done without knowledge of the pertechnetate flow study images. The results were then correlated with the catheter flow study.

RESULTS

Results are shown in Table 1. There was no disagreement as to the site of bleeding. In only two cases did the readers disagree on the time of appearance of bleeding and in each case the longer time was chosen. Bleeding rates from 4.6-0.2 ml/min were all detected within 10 min after the onset of GI bleeding in the descending colon bleeds. The slowest bleeding rate detected was 0.04 ml/min. This bleeding rate was seen by 55 min in one experiment and by 63 min in another. Slower bleeding rates were not detected within the 90-min period. No significant differences in appearance time were noted with proximal jejunal bleeds. In every experiment, the site of GI bleeding determined by the observers on the earliest views correlated with the location of the intraluminal catheter as determined by the injection of free [^{99m}Tc]pertechnetate at the end of each experiment. Based on the time of appearance of bleeding and the bleeding rate, a minimum volume of ~2–3 ml of labeled blood was necessary to scintigraphically detect bleeding. Examples of studies are shown in Figs. 1–4. The average labeling efficiency was 97.5% prior to injection and during the study averaged 95.2% (Table 1).

DISCUSSION

In 1977, Alavi developed a method for detecting and localizing GI bleeding using [^{99m}Tc]surfur colloid (*4*). Based on dog studies with experimental GI bleeds produced by catheter infusion, he was able to detect GI bleeding rates as low as 0.05 ml/min. Clinical studies with [^{99m}Tc]sulfur colloid have shown the greater sensitivity of sulfur colloid for detecting GI bleeding compared to contrast angiography (*1,3,7*).

Although [^{99m}Tc]sulfur colloid is sensitive for slow GI bleeds, questions have been raised about its usefulness in patients with intermittent GI bleeding (*8*). For that reason, ^{99m}Tc-labeled RBCs have been used in GI

TABLE 1

Dog no.	Bleed rate (ml/min)	+/−	Time to + (min)	Accumulated blood volume to time + (ml)	Efficiency (%) of label	
					Before inject	During study
Colonic bleed						
1	4.6	+	1	<4	98.8	98.0
2	2.0	+	1	2	98.1	95.2
3	0.8	+	4	3	98.8	98.7
4	0.43	+	3	1.3	93.5	—
5	0.20	+	8	1.6	98.9	93.1
6	0.085	+	14	1.2	98.6	95.7
7	0.04	+	63	2.4	90.8	87.6
8	0.04	+	55	2	98.6	98.2
9	0.02	−	—	—	98.6	97.4
10	0.02	−	—	—	98.5	98.0
Jejunal bleed						
11	0.20	+	14	2.8	98.4	95.3
12	0.085	+	22	2.2	98.2	93.0
13	0.04	+	34	1.2	97.2	95.1
14	0.02	−	—	—	99.1	93.2

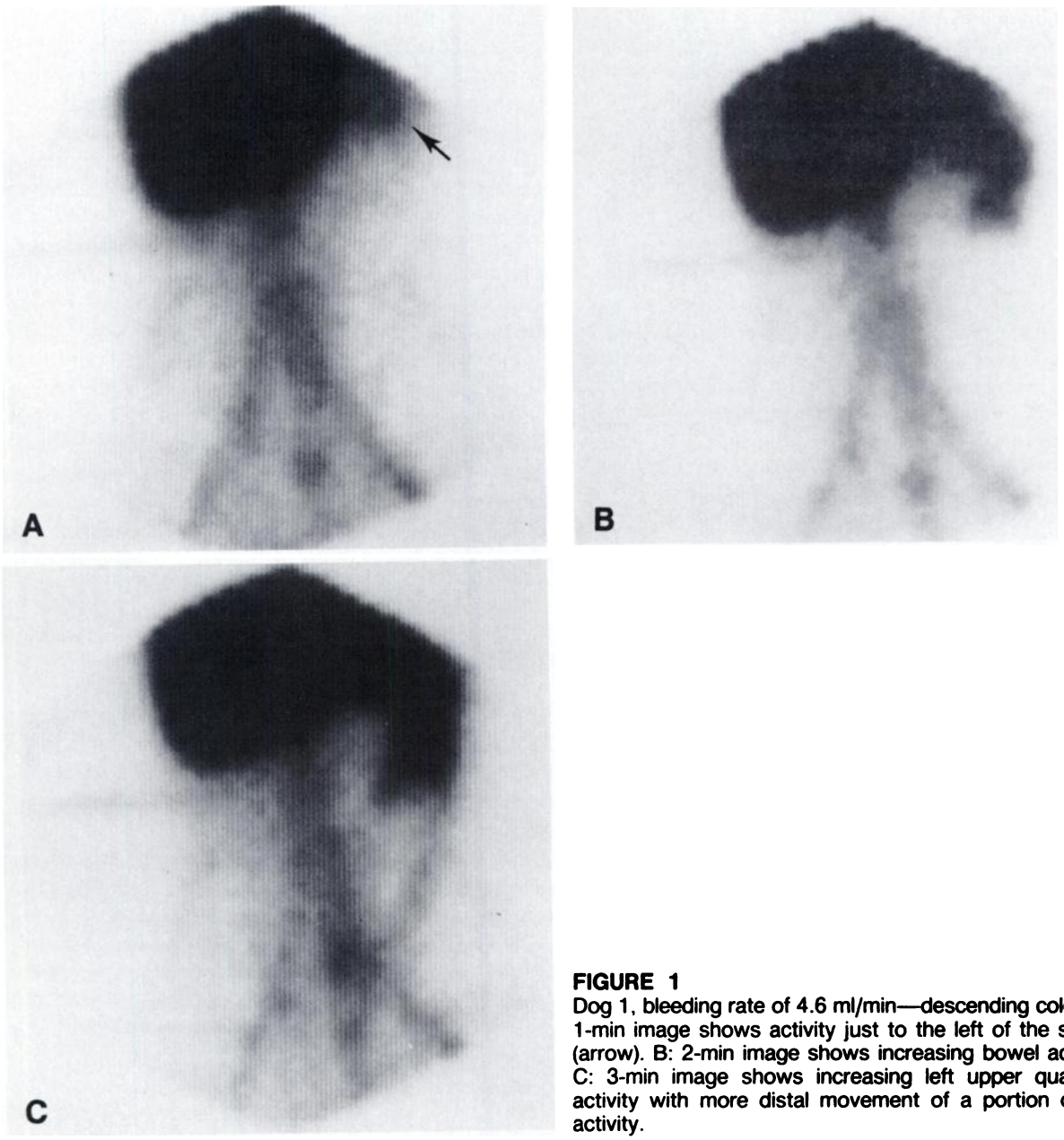

FIGURE 1
Dog 1, bleeding rate of 4.6 ml/min—descending colon. A: 1-min image shows activity just to the left of the spleen (arrow). B: 2-min image shows increasing bowel activity. C: 3-min image shows increasing left upper quadrant activity with more distal movement of a portion of the activity.

bleeding. Clinical studies with labeled RBCs have confirmed their utility in diagnosing and localizing the site of gastrointestinal bleeding (*8–12*). Serial scanning over 24 hr has allowed intermittent gastrointestinal bleeds to be detected (*8–10*).

Proponents of [^{99m}Tc]sulfur colloid have argued that, although labeled RBCs are useful for intermittent bleeding, they are not capable of detecting low bleeding rates (*1,3*). However, to our knowledge, similar data on the minimum bleeding rate that can be detected in dogs using ^{99m}Tc-labeled blood cells is not available. For this reason, we undertook this study.

Using an experimental protocol similar to the one used by Alavi (*4*), we detected and localized GI bleeding rates as low as 0.04 ml/min with labeled red cells. This bleeding rate was visualized within 55–63 min after the onset of simulated bleeding. Bleeding rates from 4.6–0.2 ml/min were all detected within 10 min. Based on the time of appearance, a minimum volume of ~2–3 ml of labeled blood was found to be necessary to detect bleeding in this experimental model. These findings indicate that labeled red blood cells are as sensitive as [^{99m}Tc]sulfur colloid in experimental bleeding. Although it may be argued that with time, even the slowest bleeding rates would become positive, we were able to correctly detect bleeding rates as low as 0.2 ml/min within 10 min and rates as low as 0.04 ml/min by 1 hr. Imaging of patients with gastrointestinal bleeding for 60 min is clinically feasible in most circumstances.

Colonic bleeds were studied since the colon is the

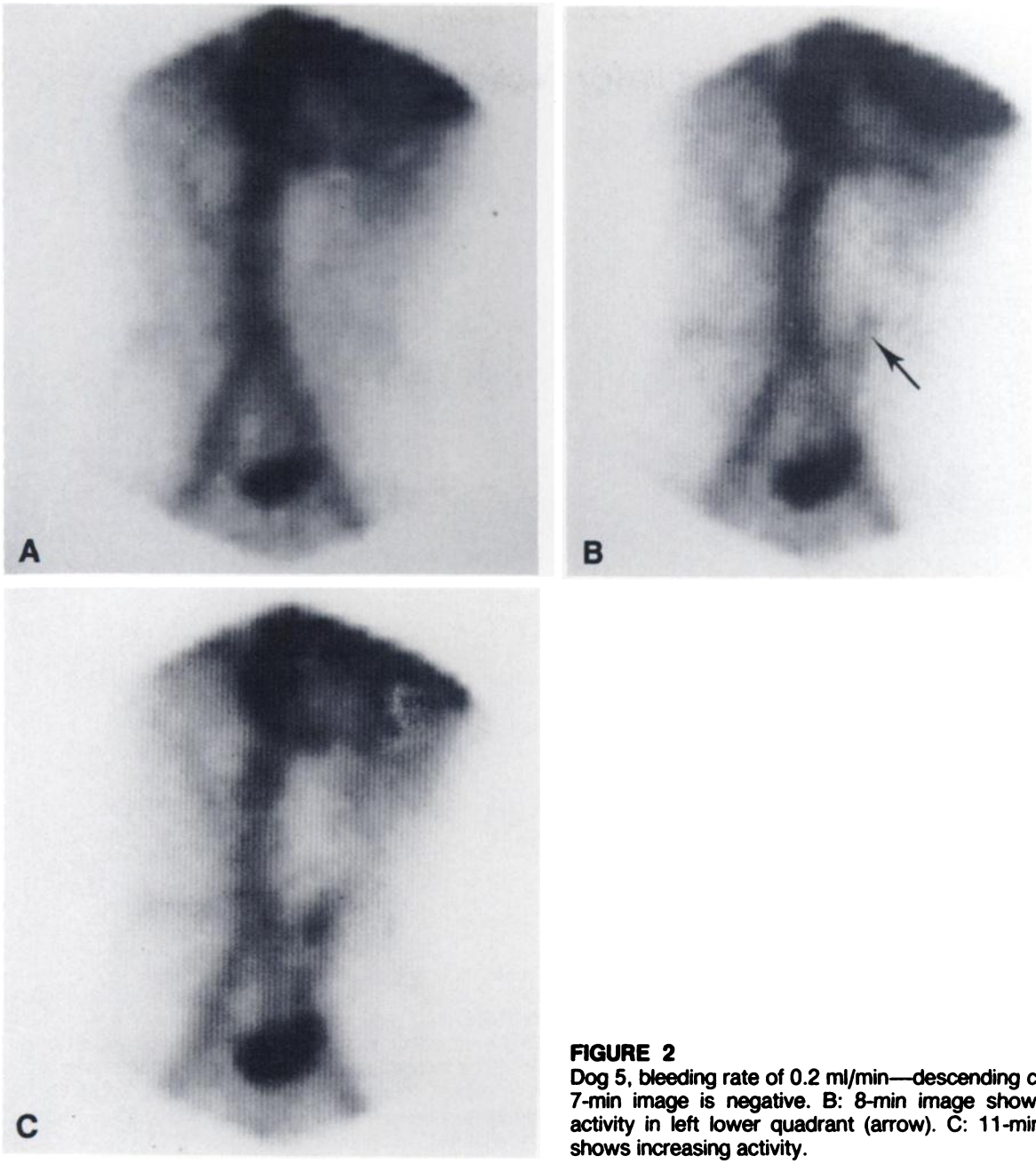

FIGURE 2
Dog 5, bleeding rate of 0.2 ml/min—descending colon. A: 7-min image is negative. B: 8-min image shows linear activity in left lower quadrant (arrow). C: 11-min image shows increasing activity.

usual site for which RBC bleeding studies are used. Upper GI bleeds are usually evaluated with endoscopy (*1*). Jejunal bleed studies of 0.20–0.02 ml/min were also performed to be certain there was no difference in detectability between proximal small bowel bleeds and colon bleeds. This might occur if there were significant differences in background. However, no significant differences in detectability were found. This isn't surprising since the dog's abdominal cavity is small and the small bowel and descending colon are in the same relative positions.

Our data conflict with that presented in an abstract by Dann et al. (*13*). Although details of their study are not given, they indicate that bleeding rates of 5–10 ml/min were necessary to detect experimental bleeding in dogs with labeled RBCs within 10–20 min. These authors also indicated that 30–60 ml of extravasated blood was necessary to produce positive images.

Several studies support our findings. One would expect the bleeding rate sensitivity of the technique to be less in the human. However, Smith showed that in a single human volunteer, as little as 5 ml of ^{99m}Tc-labeled RBCs could be detected when swallowed (*14*). Winzelberg, using transfusion requirements in patients with lower GI bleeding, found that labeled red blood cell scans were positive in patients with transfusion requirements as low as 500 ml/24 hr (*10*). Finally, although Som et al. was unsuccessful in detecting GI bleeding in

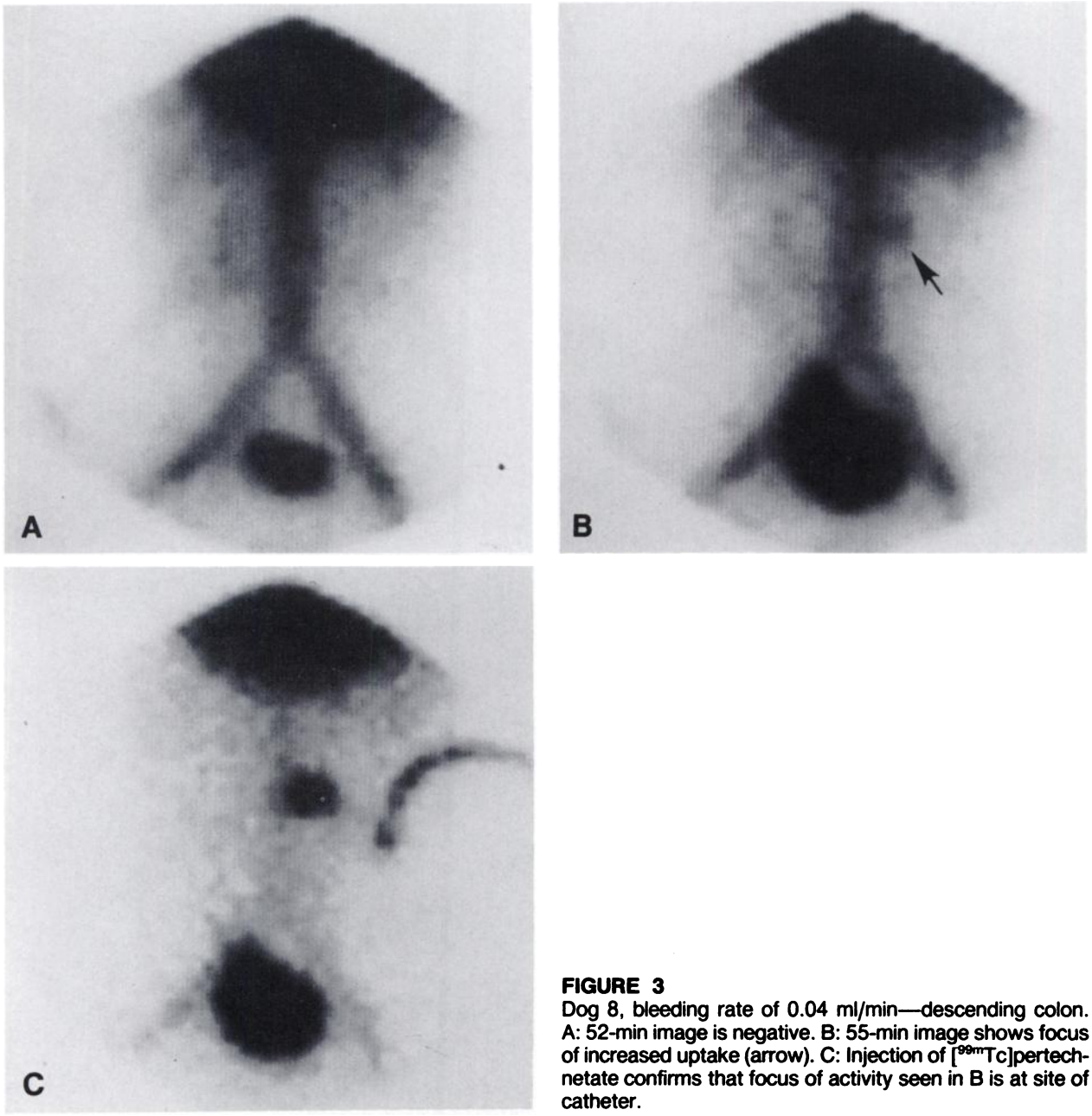

FIGURE 3
Dog 8, bleeding rate of 0.04 ml/min—descending colon. A: 52-min image is negative. B: 55-min image shows focus of increased uptake (arrow). C: Injection of [^{99m}Tc]pertechnetate confirms that focus of activity seen in B is at site of catheter.

dogs with undamaged labeled RBCs, they were able to localize experimental GI bleeding using heat-damaged RBCs at a bleeding rate of 0.12 ml/min (*15*). The time necessary to image this bleeding rate was not given.

In a large clinical series comparing [^{99m}Tc]sulfur colloid to ^{99m}Tc-labeled RBCs, Bunker et al. found that labeled red blood cells detected GI bleeding in a larger number of patients than [^{99m}Tc]sulfur colloid (*16*). These authors point out that ^{99m}Tc-labeled RBCs are more suited to detect intermittent GI bleeds due to the ability to scan over a 24-hr period. In addition, labeled red blood cells are more sensitive in detecting upper GI bleeding and in detecting bleeding in hepatic and splenic flexures than sulfur colloid since there is less interference from liver and spleen activity than with colloid (*8*).

The data from our study are useful in comparing the sensitivity of ^{99m}Tc-labeled red cells to [^{99m}Tc]sulfur colloid *in the dog model.* It does *not* indicate what the bleeding rate sensitivity is in humans. Anesthesia and laparotomy decreases bowel peristalsis making detection much easier. Likely, this is why the activity was detected at the site of the catheter in our study. However, this study does allow a comparison of the sensitivity of [^{99m}Tc]RBC to Tc-sulfur colloid in the same experimental setting.

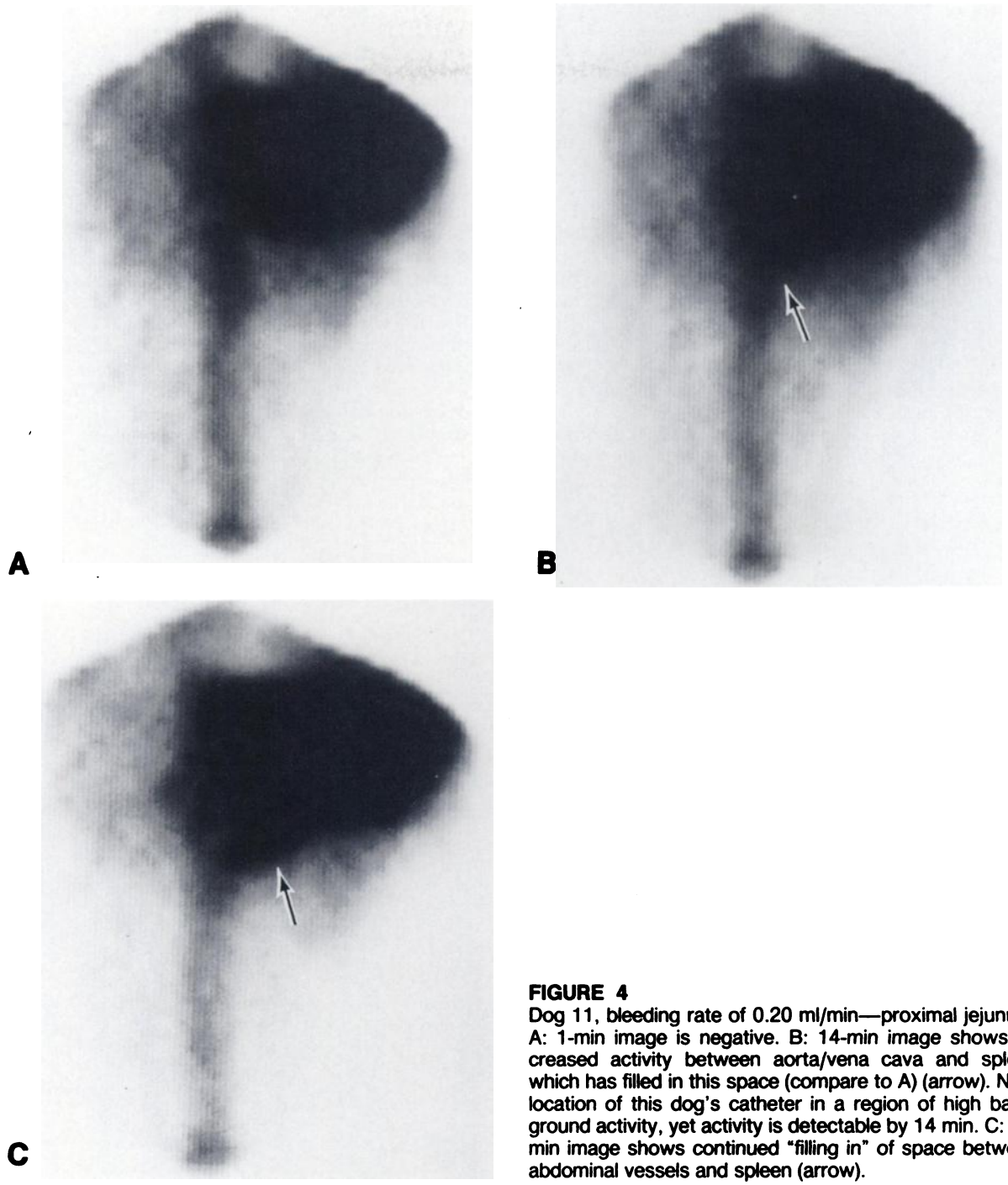

FIGURE 4
Dog 11, bleeding rate of 0.20 ml/min—proximal jejunum. A: 1-min image is negative. B: 14-min image shows increased activity between aorta/vena cava and spleen which has filled in this space (compare to A) (arrow). Note location of this dog's catheter in a region of high background activity, yet activity is detectable by 14 min. C: 33-min image shows continued "filling in" of space between abdominal vessels and spleen (arrow).

We conclude that ^{99m}Tc-labeled RBCs are sensitive for detecting low GI bleeding rates in the dog model. Our studies indicate a sensitivity similar to [^{99m}Tc]sulfur colloid in this experimental setting. With slow bleeding rates, the time required for the study to become positive is dependent on the accumulation of a minimum volume of labeled blood.

REFERENCES

1. Alavi A, McLean GK. Radioisotopic detection of gastrointestinal bleeding: an integrated approach with other diagnostic and therapeutic modalities. In: Freeman LM, Weissmann HS, eds. Nuclear medicine annual 1980. New York: Raven Press, 1980:177–218.
2. Hattner R, Engelstad BL. An advance in identification and localization of gastrointestinal hemorrhage. *Gastroenterology* 1982; 83:484–492.
3. Alavi A. Detection of gastrointestinal bleeding with ^{99m}Tc-sulfur colloid. *Semin Nucl Med* 1982; 12:126–138.
4. Alavi A, Dann RW, Baum S, Biery DN. Scintigraphic detection of acute gastrointestinal bleeding. *Radiology* 1977; 124:753–756.
5. Smith RD, Richards P. A simple kit for the prepara-

tion of ^{99m}Tc-labeled red blood cells. *J Nucl Med* 1976; 17:126–132.
6. Srivastava SC, Chervu LR. Radionuclide-labeled red blood cells: current status and future prospects. *Semin Nucl Med* 1984; 14:68–82.
7. Alavi A. Scintigraphic demonstration of acute gastrointestinal bleeding. *Gastrointest Radiol* 1980; 5:205–208.
8. Winzelberg GG, McKusick KA, Froelich JW, et al. Detection of gastrointestinal bleeding with ^{99m}Tc-labeled red blood cells. *Semin Nucl Med* 1982; 12:139–146.
9. Wenzelberg GG, McKusick KA, Strauss HW, et al. Evaluation of gastrointestinal bleeding by red blood cells labeled in vivo with Tc-99m. *J Nucl Med* 1979; 20:1080–1086.
10. Wenzelberg GG, Froelich JW, McKusick KA, et al. Radionuclide localization of lower gastrointestinal hemorrhage. *Radiology* 1981; 139:465–469.
11. Miskowiak J, Nielsen SL, Munck O. Scintigraphic diagnosis of gastrointestinal bleeding with ^{99m}Tc-labeled blood-pool agents. *Radiology* 1981; 141:499–504.
12. McKusick KA, Froelich J, Callahan RJ, et al. ^{99m}Tc red blood cells for detection of gastrointestinal bleeding: experience with 80 patients. *Am J Roentgenol* 1981; 137:1113–1118.
13. Dann R, Alavi R, Baum R, et al. A comparison of in vivo labeled red blood cells with Tc-sulfur colloid in the detection of acute gastrointestinal bleeding [Abstract]. *J Nucl Med* 1980; 21:P75.
14. Smith RK, Aterburn G. Detection and localization of gastrointestinal bleeding using Tc-99m-pyrophosphate in vivo labeled red blood cells. *Clin Nucl Med* 1980; 5:55–60.
15. Som P, Oster ZH, Atkins HL, et al. Detection of gastrointestinal blood loss with ^{99m}Tc-labeled heat-treated red blood cells. *Radiology* 1981; 138:207–209.
16. Bunker SR, Lull RJ, Tanasescu DE, et al. Scintigraphy of gastrointestinal hemorrhage: superiority of ^{99m}Tc red blood cells over ^{99m}Tc sulfur colloid. *Am J Roentgenol* 1984; 143:543–548.