Evaluation of Gastrointestinal Bleeding by Red Blood Cells Labeled in Vivo with Technetium-99m

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To determine the effectiveness of abdominal imaging with RBCs labeled in vivo with Tc-99m, for the detection of gastrointestinal (GI) bleeding, 28 control subjects and ten patients with suspected bleeding underwent scintigraphy at 0–24 hr after tracer injection. Colonic activity was noted in one of the controls within 3 hr of injection, and in five of ten controls at 24 hr, all of whom had initial gastric activity. Of the ten patients with suspected GI bleeding, eight had documented active bleeding; seven of these had positive scintigrams. Nasogastric (NG) suction markedly decreased the presence of initial gastric activity in the patients with active bleeding. With this blood-pool radiopharmaceutical, frequent imaging of the abdomen over 24 hr can be done to test for active bleeding. Continuous NG suction is recommended to reduce accumulation of gastric activity. These results suggest that red blood cells labeled in vivo with Tc-99m provide a sensitive method of detecting active GI bleeding.

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The presence of active gastrointestinal bleeding can usually be diagnosed by a combination of history, physical examination, stool guaiac tests, and serial blood counts. It may be more difficult, however, actually to find the site of active gastrointestinal bleeding; this may require endoscopy and/or contrast angiography. Even then there are patients in whom the bleeding site cannot be found because the hemorrhage is intermittent. In an experimental dog model, abdominal scanning following an i.v. injection of Tc-99m sulfur colloid located areas of gastrointestinal hemorrhage with bleeding rates as slow as 0.1 ml per min (*1*). While the sulfur colloid procedure is simple to perform, the colloid is rapidly cleared from the blood pool ($t_{1/2}$ = 2 min) and it only detects bleeding that occurs at the time of tracer injection. Moreover, although bleeding sites in the lower abdomen may be identified, those in the upper abdomen may be masked by the activity in the liver and/or spleen, especially when these are enlarged.

Clearly it would be better to have a tracer that would not preferentially accumulate in the reticuloendothelial system and would remain in the circulation long enough to permit repeat imaging. The opportunity to detect intermittent bleeding over a 24-hr period would be increased, and the detection of upper gastrointestinal bleeding should be simplified. The present study evaluated red blood cells labeled in vivo with Tc-99m as a blood-pool agent to detect sites of active or intermittently active gastrointestinal hemorrhage.

MATERIALS AND METHODS

Two groups of patients were studied. The first consisted of 28 control patients, (12F + 16M), ages 28 through 65 yr, undergoing gated blood-pool scintigrams for possible cardiac abnormalities. They were studied to define the normal abdominal distribution of RBCs labeled in vivo with Tc-99m (Fig. 1). There was no history of GI bleeding in any of these patients, and their stool guaiacs on admission were negative.

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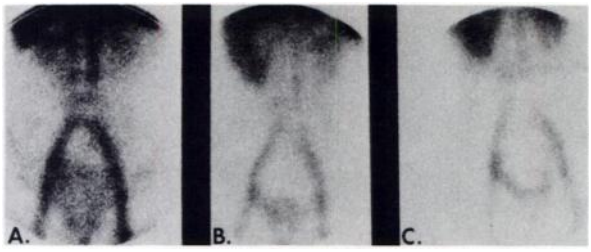


FIG. 1. Anterior abdominal scintigrams in control subject, at following times: (A) 1 hr; (B) 3 hr; (C) 24 hr. Note activity in liver, spleen, great vessels, and bladder. Bowel activity is not seen.

The second group consisted of ten adults, (4M + 6F), ages 19 through 89 yr, with a history of maroon-colored stools and/or passing blood clots per rectum. They were all referred for location of the site of bleeding in anticipation of possible angiography. Informed consent was obtained from all patients.

Images of the abdomen were recorded in the anterior position using a large-field Anger camera equipped with an all-purpose parallel-hole collimator. A 20% window was centered at 140 keV. A commercial kit* containing 1 mg stannous chloride, 10 mg pyrophosphate, and 20 mg sodium triphosphate was diluted in 3 cc of sterile saline and injected directly into an antecubital vein using a plastic syringe and 20-gauge needle. Thirty minutes later, 20 mCi of [^{99m}Tc]pertechnetate were injected directly into an antecubital vein using a 20-gauge needle to obtain in-vivo-labeled red blood cells (*2*). In the control group, 500,000-count anterior images of the abdomen were obtained 2 to 3 hr following tracer injection, and delayed 24-hr anterior abdominal views were obtained in ten patients. In the patients with suspected bleeding, sequential 500,000-count anterior images of the abdomen were obtained at 5-min intervals for 30 min, and at 1 and 2 hr. Additional oblique and lateral images were made for better triangulation of regions of abnormal tracer concentration. If the findings indicated active bleeding, the patients were immediately referred for angiography. Delayed scans were obtained on those patients with normal 2-hr images, either when the patients' clinical signs indicated renewed bleeding, or at 24 hr after initial tracer injection to monitor for recurrent bleeding not clinically suspected.

The scintigrams were prospectively interpreted before abdominal angiography. They were read as showing active bleeding sites when focal collections of activity were noted in the abdomen in regions normally free of activity.

Angiography was performed using the Seldinger technique. The specific vessels injected and the order of injections depended on the clinical presentation. The angiograms were recorded on cut film and were considered positive when extravasation of contrast material was seen.

RESULTS

Controls. The distribution of the Tc-tagged RBCs in the abdomen of 28 control patients is outlined in Table 1. On the initial images, made 2–3 hr after tracer injection, activity was always seen in the great vessels, liver, and spleen; renal, gastric, and bladder activity was noted in 60, 50, and 40% of cases, respectively. Colonic activity was noted in only one patient (4%). No Tc-99m activity was seen in the region of the duodenum, jejunum, or ileum. On delayed images obtained at 24 hr, the distribution of activity in the great vessels, liver, spleen, and

TABLE 1. INCIDENCE OF Tc-99m ACTIVITY IN SPECIFIC ABDOMINAL ORGANS IN 28 CONTROL PATIENTS AFTER IN-VIVO LABELING OF RED BLOOD CELLS

	Imaged at 2–3 hr N = 8 (%)	Imaged at 24 hr N = 10 (%)
Great vessels	100	100
Liver	100	100
Spleen	100	100
Kidneys	60	60
Stomach	50	20
Bladder	40	20
Small bowel	0	0
Colon*	4	50
Thyroid†	0	NI‡

* One patient without history of GI complaints or bleeding. Hct. 42% and stool guaiac negative.

† Three patients with gastric activity had neck area imaged for thyroid activity.

‡ NI = not imaged.

TABLE 2. INCIDENCE OF Tc-99m ACTIVITY, AFTER IN VIVO LABELING OF RED BLOOD CELLS, IN SPECIFIC ABDOMINAL ORGANS IN TEN PATIENTS WITH SUSPECTED LOWER GI BLEEDING

	Imaged at 0–10 hr N = 10 (%)	Imaged at 24 hr N = 4 (%)
Great vessels	100	100
Liver	100	100
Spleen	100	100
Kidney	70	75
Stomach	10	0
Bladder	70	100
Colon	60	50
Small bowel	30	0

TABLE 3. SUMMARY OF CLINICAL DATA IN TEN PATIENTS WITH SUSPECTED LOWER GI BLEEDING

Patient No.	History	Continuous nasogastric suction	Scintigram	Angiography	Transfusion requirement	Hospital course
1	52 yr male passing red blood clots (RBC) per rectum for 24 hr. Hematocrit (Hct) 37%, NG aspirate negative.	Yes	Positive 5 min in left lower quadrant.	Extravasation low in descending colon	1000 ml/24 hr	Treated with intraarterial (IA) pitressin (P). Good response. Barium enema (BAE) showed colonic diverticula
2	76 yr female with cirrhosis. Incarcerated small bowel; resected. Developed lower GI bleeding. Hct. 21%, NG aspirate negative	Yes	Positive 1 hr in right lower quandrant (RLQ)	Extravasation in midjejunal branch of superior mesenteric artery	3000–4000 ml/24 hr	Responded to IA P. Developed fatal sepsis and liver failure
3	75 yr female passing RBC per rectum. Hct. 23%, NG aspirate negative	Yes	Negative 1 hr; positive at 10 hr in ascending and transverse colon	Negative at 1 and 10 hr. Repeat at 36 hr showed extravasation in transverse colon	2000–3000 ml/24 hr	Poor response to IA P. Underwent colectomy for bleeding diverticulum. Good recovery
4	19 yr male with melena, negative BAE, Meckel's scan equivocal. RBC per rectum. Right hemicolectomy, but bleeding persisted. Hct. 31%, NG aspirate negative	Yes	Positive 1 hr for duodenal activity with sequential activity in small and large bowel	Negative at 24 and 48 hr	1500 ml/24 hr	Persistent bleeding without response to IA P. Endoscopy showed duodenal bleeding. Treated with vagotomy and pyloroplasty with good response
5	43 yr female with lung cancer metastatic to bowel. Partially resected. Persistent lower GI bleeding. Hct. 30%, NG aspirate negative.	Yes	Positive at 3½ hours in RLQ	Negative	500–1000 ml/24 hr	Continued slow bleeding. Received radiation therapy. Died.
6	76 yr female. RBC per rectum for 24 hr. Hct. 30%, NG aspirate negative. UGI endoscopy negative	No	Negative 1 hr; positive at 5 hr in right colon	Diffuse hyperemia of colon without focal extravasation	500–1000 ml/24 hr	Persistent slow GI hemorrhage needing transfusions. R hemicolectomy. Microscopy showed diverticulosis with superficial mucosal hemorrhage R colon

Table 3 (Continued)

TABLE 3. SUMMARY OF CLINICAL DATA IN TEN PATIENTS WITH SUSPECTED LOWER GI BLEEDING

Patient No.	History	Continuous nasogastric suction	Scintigram	Angiography	Transfusion requirement	Hospital course
7	65 yr female with a history of sigmoid resection for bleeding diverticula. Admitted for RBC per rectum. Hct. 19%, NG aspirate negative	Yes	Positive at 2 hr in LLQ	Not done	1000–1500 ml/24 hr	Maroon stools for 24 hr. Transfused 7 units. Then no further bleeding. BAE showed diverticulosis
8	20 yr female. Small-bowel obstruction from adhesions. S.B. resection, with postop. bleeding. Hct. 20%, NG aspirate negative. Transfused to Hct. 32%. No further bleeding	Yes	Negative over 24 hr	Not done	0	Clinically stable. No further bleeding. Felt to have bled at S.B. anastomosis
9	30 yr male. Upper GI bleeding 1973. Billroth II for bleeding ulcer; 3 further episodes of lower GI bleeding. Admitted with RBC per rectum 12 hr before admission. Hct. 40%, NG aspirate negative	Yes	Negative over 3 hr	Negative	0	No further bleeding. Discharged. Admitted 3 wk later with red clots per rectum. At surgery Meckel's diverticulum
10	89 yr male with iron-deficiency anemia. Multiple gastric and duodenal hamartomas on endoscopy. Stool guaiac positive. Required transfusion every 3 wk	No	Negative over 24 hr	Negative	50 ml/24 hr	Felt to have intermittent bleeding from hamartomas. No focal spot found.

kidneys appeared unchanged, but colonic activity was observed in 50% of the patients, all of whom had initial gastric activity. This colonic activity appeared similar to the activity seen in patients with positive scans for colonic bleeding, but was usually less intense. No control subjects were imaged between 3 and 24 hr. In three of the control subjects with initial gastric activity, no thyroid activity was detected in the neck at 3 hr following tracer injection.

Patients. The patients' histories, scintigraphic results, blood transfusion requirements, and hospital courses are outlined in Tables 2 and 3. Ten patients who were clinically thought to have gastrointestinal bleeding were referred for study. Eight of these had continuous drainage of gastric contents via nasogastric tubes.

Of the ten patients, seven had positive scintigrams. Of that group, all patients were subsequently shown to have continued transfusion requirements and instability of vital signs, and were considered to have continuing active hemorrhage. Three patients' scans were interpreted as

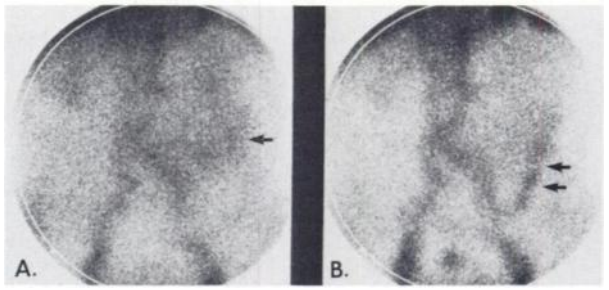
showing no evidence of active gastrointestinal hemorrhage. Two of those three had no further transfusion requirements and were totally stable. The third patient (Patient 10) continued to have a transfusion requirement of one unit of blood every 10 days over a 3-mo period.

Seven of the eight actively bleeding patients, and one of the two nonbleeding patients, were studied angiographically. Of those with positive scans, only three were subsequently found to have extravasation of contrast on selective visceral angiography: two had bleeding colonic diverticula, and one had a bleeding small-bowel anastomosis. In one patient (Patient 3), the initial scintigram was negative, as was the angiogram. At 10 hr, the scan became positive in the ascending and transverse colon, but a repeat angiogram remained negative although the patient was still requiring transfusions to stabilize her hematocrit. Another repeat angiogram at 36 hr was positive for a bleeding colonic diverticulum near the splenic flexure. At surgery, the bleeding point in the splenic flexure was found, along with fresh blood clots in the ascending and transverse colon. A subtotal colectomy was performed.

In the five remaining patients with active bleeding, four had positive scintigrams. These included two patients with bleeding diverticula, and one each with an active duodenal ulcer and metastatic tumor implants to the small bowel (proven by surgery, endoscopy, or barium contrast studies). One patient (Patient 10) with very slow bleeding from gastrointestinal hamartomas had both a negative angiogram and a negative scintigram. Two patients who had stopped bleeding clinically, one from a small-bowel anastomosis and the second from a Meckel's diverticulum, had negative scintigrams.

The radionuclide scans became positive at various time intervals following injection of tracer. Three were positive within the first hour (Patients 1, 2, and 4). These patients' transfusion requirements were approximately 1800 ml per 24 hr. The remaining four scans became positive at 2, 3½, 5, and 10 hr (Patients 7, 5, 6, and 3) respectively. Their transfusion requirements varied from 500 ml to 3000 ml per 24-hr period.

The positive scans correctly located the site of hemorrhage to the colon in the four patients with bleeding diverticula (Figs. 2 and 3). The images suggesting small-bowel hemorrhage were found in patients with a bleeding small-bowel anastomosis, bleeding metastatic implants to the small bowel, and a bleeding duodenal ulcer (Fig. 4). Of the seven scintigrams that were positive by 10 hr after tracer injection, only one had initial gastric activity.



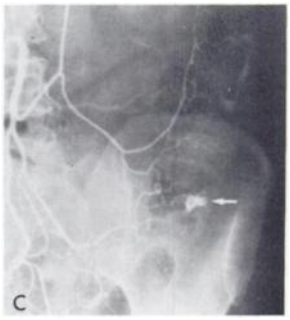
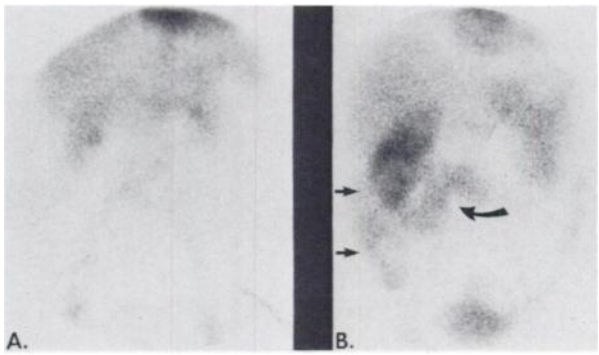


FIG. 2. Anterior abdominal scintigrams of Patient 1. (A) At 5 min abnormal tracer appears in region of left colon (single arrow); (B) at 15 min focal activity is seen in lower descending colon (double arrow). (C) Angiogram performed a short time later confirms active bleeding diverticulum in descending colon (single white arrow).



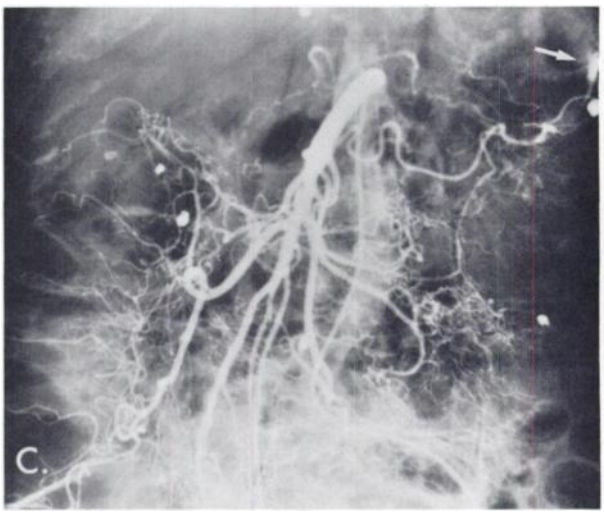


FIG. 3. Anterior abdominal scintigrams of Patient 3: (A) at 1 hr, showing normal distribution; (B) at 10 hr marked tracer activity appears in ascending (single arrows) and transverse colon (curved arrow). (C) Angiogram at 36 hr shows active extravasation in distal transverse colon (single white arrow). At surgery, bleeding point was identified along with recent clots throughout entire colon.

DISCUSSION

The advent of endoscopy and selective visceral angiography (*3*) has greatly improved the location of sites of gastrointestinal hemorrhage. Endoscopy is especially

useful in determining the site of bleeding in upper gastrointestinal hemorrhage, but the procedure is difficult to perform in the poorly prepared colon. Angiography is useful in both location and control of hemorrhage from both the upper and lower gastrointestinal tract. A large number of negative angiograms are performed in lower gastrointestinal hemorrhage because it is difficult to determine whether the patient has stopped hemorrhaging at the time of angiography. Therefore, a noninvasive technique that could detect the presence of continuing hemorrhage as well as locate the site of bleeding would be helpful in the management of acute gastrointestinal hemorrhage.

Other investigators have used tracer techniques to detect gastrointestinal bleeding. In an animal model, Cr-51-labeled red blood cells and I-131-labeled albumin have been used to demonstrate sites of gastrointestinal hemorrhage (*4*). Chromium-51-labeled red blood cells (*5*) and InCl-113m-labeled transferrin (*6*) have also been used to monitor upper gastrointestinal hemorrhage in humans by measurement of radioactivity in gastric aspirations of patients undergoing intensive medical therapy. These techniques have not gained widespread acceptance because of their cumbersome procedures and because they are primarily used to measure, rather than to locate, bleeding. The diagnosis of Meckel's diverticulum may be made following administration of pertechnetate, which is actively secreted by ectopic gastric mucosa, which may be present in 50% of such diverticula (*7*). Technetium-99m sulfur colloid in an animal model (*1*) and in humans (*8*) has also been used to detect gastrointestinal bleeding, but has been reserved to assess acute bleeding because of its rapid clearance from the blood pool. Tc-99m-labeled albumin, a blood-pool agent, has also been used to locate acute gastrointestinal hemorrhage with a bleeding rate of 2–3 ml/min in one patient with a bleeding colonic diverticulum (*9*). However, Tc-99m-labeled albumin is of limited use in evaluating abdominal gastrointestinal bleeding because of tracer accumulation in the liver (*10*), high background activity (*10*), and accumulation of from 0.3 to 20% of tracer activity in the gastrointestinal tract (*10*).

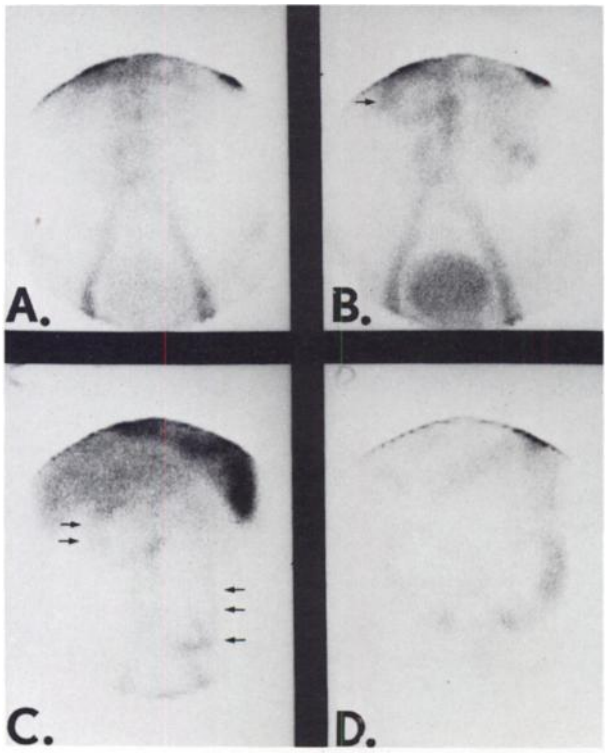


FIG. 4. Anterior abdominal scintigrams in Patient 4: (A) at 15 min, showing normal distribution of tracer; (B) at 1 hr abnormal area is seen in right upper quadrant (RUQ) (single arrow); (C) at 1¼ hr activity is more prominent in RUQ, outlining duodenum (double arrows) and proximal jejunum (triple arrows); and (D) at 24 hr activity is seen in transverse and descending colon.

In this study the radionuclide technique was successful in detecting the presence of continuing hemorrhage with transfusion requirements as small as 500 ml per 24 hr. There was a single false-negative image in a patient who was bleeding at an exceedingly slow rate. In the control group there was a single patient who showed colonic activity on the early views. Since this occurred in only one of 28 controls, its significance is unclear but this could cause false-positive interpretations.

The normal abdominal distribution of Tc-99m RBCs labeled in vivo in a control population revealed tracer activity to be present in vascular structures on all initial scans, and gastric activity was noted in 50% of these patients. Although no small-bowel activity was seen, this may have been due to the absence of imaging between 3 and 24 hr. Delayed views demonstrated that colonic activity was present in 50% of the controls with initial gastric activity. While a labeling efficiency of 96% has been reported with in vivo techniques using stannous chloride as the reducing agent (*2*), the accumulation of gastric activity in 50% of our controls indicates Tc-99m activity within the stomach or stomach wall. Such activity may not be free pertechnetate, since no thyroid activity was seen in the necks of three control patients with initial gastric activity. However, the thyroid may not have been at peak activity, since the neck image was made 3 hr after tracer injection. The delayed colonic activity may represent passage of complexed pertechnetate from the stomach to the large bowel, or secretion of pertechnetate into the bowel itself, as has been reported in an animal model (*11*). In Patient 4, duodenal activity was noted on the 1-hr images, indicating his active duodenal bleeding. Delayed 24-hr images showed passage of the extravasated labeled red cells into the colon. The discrepancy noted between the control group and bleeding patients with regard to initial gastric Tc-99m activity may be related to the fact that 80% of the bleeding patients were undergoing continuous naso-

gastric suction, which may have collected the Tc-99m activity.

It should be stressed that if tracer activity is seen in the large bowel on early views following tracer injection, active bleeding should be suspected. If there has been no initial gastric accumulation of Tc-99m activity, delayed views at 24 hr may also indicate active bleeding. However, if gastric activity is noted on the initial views, this activity may eventually accumulate in the lower small bowel and colon and may give false-positive delayed images. This problem may be minimized by keeping the patients on continuous nasogastric suction during the 24-hr imaging period. In the future, in vitro labeling of red blood cells might reduce some of the gastric activity seen with in vivo labeling methods. The tracer might be improved by labeling the RBCs with In-111, which has a longer half-life and is not excreted into the GI tract.

The data from this study suggest that red blood cells labeled in vivo with Tc-99m can provide an effective diagnostic tool in the management of patients with intermittent gastrointestinal hemorrhage, especially in patients with lower gastrointestinal bleeding. It can be particularly useful when the indications of continued active hemorrhage are equivocal. In this setting a negative scintigram is good evidence against active bleeding. Because the tracer remains in the blood pool, repeat scanning can be performed over a span of several hours to screen for active bleeding which, if present, can be further evaluated with angiography or endoscopy.

FOOTNOTE

* Pyrolite; New England Nuclear Corp., Boston, MA.

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