Received:
10 April 2018

Revised:
16 September 2018

Accepted:
25 September 2018

<https://doi.org/10.1259/bjr.20180336>

Cite this article as:

Gurajala RK, Fayazzadeh E, Nasr E, Shrikanthan S, Srinivas S, Karuppasamy K. Independent usefulness of flow phase ^{99}Tc -red blood cell scintigraphy in predicting the results of angiography in acute gastrointestinal bleeding. *Br J Radiol* 2019; **91**: 20180336.

FULL PAPER

Independent usefulness of flow phase ^{99}Tc -red blood cell scintigraphy in predicting the results of angiography in acute gastrointestinal bleeding

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Objective: In acute gastrointestinal bleeding, despite positive dynamic phase ^{99}Tc -red blood cell scintigraphy, invasive catheter angiography (CA) is frequently negative. In this study, we investigated the value of flow phase scintigraphy in predicting extravasation on CA.

Methods: Institutional review board approval with a waiver of informed consent was obtained for this retrospective study. A total of 173 scintigraphy procedures performed in 145 patients with GIB between January 2013 and August 2014 were analysed. Scintigraphy had two phases: flow (1 image/s for 1 min) followed by dynamic (1 image/30 s for 1 h). Patients who underwent CA within 24 hours of positive scintigraphy were assessed. Each scintigraphy phase was randomly and independently reviewed by two nuclear medicine physicians blinded to the outcomes of the other phase and of CA.

Results: A total of 42 patients (29%) had positive scintigraphy. Of these patients, 29 underwent CA, and extravasation was seen in 6 (21%). In all, dynamic phase scintigraphy was positive. 13 of the 29 patients also had

positive flow phase scintigraphy. The sensitivity, specificity, positive-predictive value, and negative-predictive value of flow phase scintigraphy for extravasation on CA were 100, 70, 46, and 100%, respectively. Specificity and positive predictive value were higher when CA was performed within 4 hours of positive flow phase scintigraphy.

Conclusions: Negative flow phase scintigraphy can identify patients who will not benefit from CA despite positive dynamic phase scintigraphy. The likelihood of extravasation on CA is higher when performed soon after positive flow phase scintigraphy.

Advances in knowledge: Negative flow phase scintigraphy identifies patients who will not benefit from invasive catheter angiography despite positive results on subsequent dynamic phase scintigraphy. Increasing the delay between positive red blood cell scintigraphy and catheter angiography progressively reduces the likelihood of identifying extravasation, which is required to target embolization.

KEY POINTS

- (1) In patients with acute GIB, flow phase RBC scintigraphy should be routinely performed and the results should be reviewed immediately while the dynamic phase is being acquired.
- (2) Negative flow phase scintigraphy identifies patients who will not benefit from invasive catheter angiography despite positive results on subsequent dynamic phase scintigraphy.
- (3) When flow phase scintigraphy is positive, catheter angiography should be performed immediately to allow identification of extravasation and to target therapy.
- (4) Increasing the delay between positive RBC scintigraphy and catheter angiography progressively reduces the

likelihood of identifying extravasation, which is required to target embolization.

INTRODUCTION

Each year, nearly 180 patients per 100,000 of population in the USA are hospitalised for gastrointestinal bleeding (GIB), with an annual mortality exceeding 16,000.¹ In 1997, the median cost of each hospitalisation to manage acute upper GIB ranged from 2856 to 5379 USD.² Most cases of GIB resolve spontaneously; however, 25% require immediate medical attention due to continued bleeding.³ Locating the bleeding source can be challenging, and up to 35% of patients may be discharged without a diagnosis.⁴ Endoscopic evaluation is the first step of the diagnostic

work-up.³ however, this procedure may fail to locate the bleeding source if it is not accessible, if it is covered by excessive blood, or if the bowel preparation was poor. In such cases, alternative modalities such as nuclear scintigraphy, CT angiography,⁵ and catheter-directed digital subtracted angiography (CA) may be required. Avoiding the overuse of such resources could reduce the costs of managing GIB without compromising outcomes.⁶

Scintigraphy can detect bleeding at a rate as low as 0.1 ml min^{-1} ¹⁷ with a minimum of 2–3 ml of labelled blood needed,⁸ whereas CA may successfully locate the causable branch when the bleeding rate is greater than 0.5 ml min^{-1} .³ This relatively higher threshold for CA has caused debate regarding when CA should be used in cases of acute GIB. In one retrospective review, nearly 8 of 10 CA procedures were negative and deemed unnecessary in the diagnostic workup of acute GIB.⁹ Although some have advocated for the use of scintigraphy as a screening tool to precede invasive CA,¹⁰ one study found that scintigraphy failed to localise bleeding in 85% of cases, implying its inadequacy as a screening tool.¹¹ However, another retrospective review found that scintigraphic screening increased the diagnostic yield by a factor of 2.4.¹² Hence, the potential role of scintigraphic screening before CA in acute GIB is still evolving.

^{99m}Tc-red blood cell (RBC) scintigraphy is routinely performed in two phases at Cleveland Clinic: (1) flow phase imaging, acquired after injection of ^{99m}Tc-labelled autologous RBCs at a higher frame rate with lower count density per image; and (2) dynamic phase imaging, acquired at higher count densities and lower frame rates. Additionally, delayed phase imaging was available but was seldom required and was not evaluated in this study. The Society of Nuclear Medicine and Molecular Imaging and the European Association of Nuclear Medicine practice guidelines for GIB management underplay the role of initial flow phase imaging (radionuclide angiography) and consider it optional because of its questioned usefulness.¹³ However, the temporal resolution of flow phase scintigraphy performed at the rate of 1 frame/s for 60 s during the initial flow of the tracer is closer to the temporal resolution of CA (acquired at a rate of 2–3 frames/s during the flow of contrast in a selected arterial territory for approximately 30–40 s) than to that of dynamic phase scintigraphy (acquired at the rate of 1 frame/30–60 s for 60 min). In this study, we sought to evaluate the independent role of ^{99m}Tc RBC flow phase scintigraphy as a predictor of extravasation during subsequent CA in patients presenting with acute GIB.

METHODS AND MATERIALS

Study type and patients

After institutional review board approval with a waiver of informed consent was obtained, we conducted a retrospective study to assess the results of planar scintigraphy and CA performed in patients referred to our institution between January 2013 and August 2014. Inclusion criteria were signs and/or symptoms of GIB (including haematemesis, coffee-ground emesis, melena, or haematochezia) with no affirmative findings on upper/lower GI endoscopy. Patients with unstable haemodynamic status, those with a known background of GI varices, and

Figure 1. The study flow algorithm. A total of 145 patients were initially evaluated for acute GIB. Dynamic phase scintigraphy was positive in 42 scintigraphy procedures. Among these patients, 29 underwent catheter-directed digital subtracted angiography (CA) within 24 h and were included in this study (red box). Extravasation was observed and treated in 6 patients. CA, catheter angiography; GIB, gastrointestinal bleeding.

those in whom angiography was delayed for more than 24 h were excluded from the study.

Study flow and procedural technique

The study algorithm is shown in Figure 1. Autologous RBCs were tagged by 20.0 mCi (740 MBq) of ^{99m}Tc pertechnetate *in vitro* using an Ultratag kit (Mallinckrodt Pharmaceuticals, St. Louis, MO). Radiolabelled RBCs were then injected back into the patient after the patient had been placed in a supine position on an imaging table, covering from the level of the diaphragm to below the urinary bladder. A large field-of-view gamma camera (Symbia S, Siemens Healthcare GmbH, Erlangen, Germany) equipped with a low-energy high-resolution collimator was used (setup: window, 15%; energy selection, 140 keV; matrix, 128 × 128; and magnification, 1×).

Immediately after reinjection of the RBC radiotracers, the scintigraphic evaluation was initiated with the acquisition of sequential images of the abdomen and pelvis in movie mode at the arterial flow phase (1 image/s for 1 min), followed by the blood pool dynamic phase (1 image/30 s for 60 min). All images were obtained on the coronal plane. Two nuclear medicine

board-certified specialists, each with more than 5 years of clinical experience, reviewed the images independently. The data obtained from each phase were interpreted separately. The results were considered positive for the flow phase if there was a focus of abnormal activity (immediate blush) and were considered positive for the dynamic phase if there was a focus of increased activity that changed in location and increased in intensity over time (delayed blush). In these cases, the time of appearance of radionuclide blush was recorded. If the two reviewers disagreed on the interpretation of scintigraphy findings, they examined the results together to reach a consensus.

Positive scintigraphy cases underwent subsequent selective CA of the mesenteric arteries within 24 h. For this purpose, the femoral artery was cannulated via the Seldinger technique. The catheter was advanced to the arterial branch feeding the territory of radionuclide blush observed on scintigraphy. An interventional radiologist blinded to the RBC scan findings reviewed the angiography data from patients' electronic medical records.

Data analysis

Data were analysed using GraphPad Prism 7 statistical software (GraphPad Software Inc., San Diego, CA). Quantitative data are presented as mean $\pm$ standard deviation. With conventional angiography used as the gold-standard, the sensitivity, specificity, and overall accuracy of flow phase scintigraphy for the detection of GIB were calculated. Post-scintigraphy probabilities of positive and negative angiographies were determined by the predictive values of flow phase scintigraphy outcomes. A modified Wald method was used to compute 95% confidence intervals (CIs) for specificity, accuracy, and positive-predictive value (PPV) of flow phase scintigraphy. For the sensitivity and negative-predictive value (NPV), a simple method described previously was used to calculate 95% CIs for binomial proportions where no events are observed.¹⁴ Subgroup analysis was also performed for patients who underwent CA within 12 h ($n = 27$) or within 4 h ($n = 17$) of scintigraphy to evaluate the effect of a delay. Quantitative data were analysed with Student's *t* test. Two-tailed Fisher's exact test was used for comparisons between positive and negative flow phases. *P* values <0.05 were considered statistically significant.

RESULTS

A total of 173 ^{99m}Tc RBC scintigraphies were performed in 145 patients with suspected acute GIB. Results were positive in 42 (29%) patients, indicative of bleeding at the upper GI (12% of cases), small intestine (excluding proximal duodenum) (35%), ascending colon (14%), transverse colon (18%), and left colon (21%). Among the 29 patients (18 males, 11 females; mean age, 67.9 ± 17.1 y; age range, 4–88 y) who subsequently underwent mesenteric CA within 24 h (mean time interval, 345 ± 279 min; range, 130–1279 min), extravasation during CA (positive CA) was seen in 6 (21%) cases. The locations of bleeding detected by CA in these cases matched with the presumptive sites seen on scintigraphy and were treated successfully by coil embolization. Flow phase scintigraphy was positive in 13 (45%) patients, and in all of these cases, dynamic phase results were also positive. There was no significant difference in the average time interval between scintigraphy and CA among positive flow phase and negative flow phase groups (259 ± 69 min vs 367 ± 309 min; $p = 0.14$). Radionuclide blush was first observed after 32 ± 19 s (range, 7–59 s) in positive CA cases and after 9.45 ± 11.84 min (range, 0.27–56 min) in negative CA cases ($p = 0.0016$). Table 1 shows the predictive values of flow phase scintigraphy for CA outcomes. Angiographic extravasation was only detected in cases with positive results at the flow phase of the RBC scan [46%; 95% CI (23–71%); $p = 0.0036$] (Figure 2).

Time was an important factor in the detection of extravasation on CA. The sooner CA was performed after positive scintigraphy, the more likely CA was to be positive. This was especially significant in cases with positive flow phase scintigraphy (Figure 3). The specificity and PPV of flow phase scintigraphy for the detection of extravasation were higher in patients who underwent CA within 4 h (Figure 4). None of the patients who underwent CA after 6 h demonstrated extravasation.

DISCUSSION

Although catheter-directed embolization has a very high success rate for controlling acute GIB,¹⁵ complications such as access site haematoma, pseudoaneurysm, arterial dissection, bowel ischaemia, and contrast-induced nephropathy or allergic reaction can occur.¹⁶ Targeted embolization requires accurate identification of the extravasation site. Because of the frequent failure of CA studies to display extravasation,⁹ identifying patients who are unlikely to

Table 1. Distribution of outcomes of CA based on results of preceding flow phase scintigraphy with positive dynamic phase in patients with suspected acute GIB

Scintigraphy (positive dynamic phase)	CA			
	Positive	Negative	Total	
Positive flow phase	6	7	13	PPV: 6/13 [46%; 95% CI (23–71%)]
Negative flow phase	0	16	16	NPV: 16/16 [100%; 95% CI, (83–100%)]
Total	6	23	29	
	Sensitivity: 6/6 [100%; 95% CI, (61–100%)]	Specificity: 16/23 [70%; 95% CI, (49–85%)]	Accuracy: 22/29 [76%; 95% CI: (58–88%)]	

CA, catheter-directed digital subtracted angiography; CI, confidence interval; GIB, gastrointestinal bleeding; NPV, negative-predictive value; PPV, positive-predictive value;

Figure 2. A 53-year-old female presented with bright red bleeding per rectum. (A) Serial RBC scintigraphy images included flow and dynamic phases. Radionuclide blush was detected during flow phase imaging (15 s after the study was initiated) (black arrow); this blush persisted through the dynamic phase, suggesting the presence of bleeding near the splenic flexure. (B) Catheter-directed digital subtracted angiography (CA) in the same patient obtained after SMA catheterization within 4 h of positive flow and dynamic phase scintigraphy revealed active extravasation (white arrow) from the distal middle colic artery. CA, catheter angiography; RBC, red blood cell; SMA, superior mesenteric artery.

benefit from CA will decrease the number of unnecessary procedures and their associated morbidities. In the present study of patients with positive dynamic phase scintigraphy, a negative flow phase examination accurately identified those who would not benefit from CA.

Radionuclide scintigraphy for the detection of active GIB has been used for more than 40 years.¹⁷ Since then, this procedure has proven to be a highly sensitive, specific, noninvasive,

low-risk, and cost-efficient method for assessing intermittent bleeding.^{18,19} However, guidelines on scintigraphy protocols continue to underplay the significance of the flow phase,¹³ and this aspect continues to be overlooked during scintigraphy interpretation.²⁰ In this study, we demonstrated the unique advantage of flow phase scintigraphy in predicting extravasation on subsequent CA. We found that nearly 80% of CA procedures performed within 24 h of positive dynamic phase failed to demonstrate extravasation. However, if the flow phase was

Figure 3. The percentage of angiographic extravasation in cases of positive dynamic phase scintigraphy irrespective of the outcome of flow phase (blue line) versus positive flow phase scintigraphy (red line) within 4, 12, and 24 h after scintigraphy.

Figure 4. Specificity (blue line) and PPV (red line) of flow phase scintigraphy in predicting angiography within 4, 12, and 24 h after scintigraphy. PPV, positive-predictive value.

positive, 46% of CA procedures demonstrated extravasation, thus aiding in subsequent targeted embolization (Table 1).

Previous studies have demonstrated the PPV of scintigraphic blush in predicting the results of CA in acute GIB. In a retrospective review, although clinical factors such as intensive care unit admission, number of transfusions, and presence of hypotension or tachycardia failed to predict the outcome of CA, the elapsed time before scintigraphic blush was negatively correlated with positive CA. However, the authors did not report the individual significance of detecting early blush during a prolonged planned scintigraphy.²¹ In another study in which imaging was performed every 2 min, 60% of patients with blush on scintigraphy observed within 2 min after injection of ^{99m}Tc -labeled RBCs had positive CA, whereas only 7% had positive CA when blush appeared after 2 min.²² All positive CA cases in our study were preceded by scintigraphic blush that appeared during the flow phase acquired at higher temporal resolution during the first minute after radio-tracer injection. This demonstrates the critical value of the flow phase in this patient population.

In a study of 120 patients with acute lower GIB, the duration between the beginning of RBC scan and observation of positive result affected the rate of subsequent positive CA.²³ When scintigraphy was positive within 9 min, the sensitivity, specificity, PPV, and NPV for a positive CA were 92, 35, 27, and 94%, respectively. In our study, when scintigraphy was positive in ≤ 1 min, the sensitivity, specificity, PPV, and NPV for a positive CA were 100, 70, 46, and 100%, respectively (Table 1). This indicates that the blush appearing within 1 min has a higher specificity and PPV for subsequent CA, whereas when blush is absent, subsequent CA is likely to fail to demonstrate extravasation. In the above-mentioned study, the authors acquired flow phase images of the abdomen at 2 s intervals for a duration of 60 s; however, the flow phase was not independently reviewed or reported and the median time to positive scintigraphy was approximately 5 min (range, 1–90 min). In another study of 135 patients with lower GIB, positive RBC scintigraphy (without distinction between flow and dynamic phases) within 12 min followed by CA within 24 h demonstrated sensitivity, specificity, PPV, and NPV for positive CA of 92, 63, 57, and 94%, respectively; the mean time to positive scintigraphy was 7.8 ± 9.5 min for cases of positive CA.²⁴ However, the authors did not report whether flow phase in the first minute of scintigraphy was acquired and/or reviewed independently. In our study, blush during positive scintigraphy was observed as early as 7 s (range, 7 s–56 min), thus indicating the usefulness of assessing the flow phase individually and early while the dynamic phase is being acquired.

We also demonstrated a mean time to positive scintigraphy of 32 s for cases of positive CA, with all patients demonstrating radionuclide blush within the first 60 s. Unlike prior reports, our study clearly defines the role of flow phase scintigraphy in identifying patients who are unlikely to benefit from CA and those who are likely to exhibit extravasation when CA is performed shortly after scintigraphy. As a result, positive flow phase outcomes during a scintigraphic procedure should be reported to the angiography suite as soon as possible while

scintigraphy is still running until the site of bleeding is accurately localised.

Previous studies have also demonstrated that the time elapsed between positive scintigraphy and CA is negatively correlated with positive CA.^{21,23} Similarly, we observed that after positive dynamic phase scintigraphy, the rate of positive CA increased from 21% (when performed within 24 h) to 24% (when performed within 4 h). These rates improved from 46 to 57% when the flow phase of scintigraphy was positive (Figure 3). One of the previous studies also reported that none of the CA studies performed later than 10 h after positive scintigraphy demonstrated extravasation²³; similarly, we observed no angiographic extravasation when CA was performed more than 12 h after positive scintigraphy (Figure 3). These studies indicate a lack of correlation between positive scintigraphy and the prediction of positive CA when CA is delayed for several hours.

It is important to emphasize that the high temporal resolution of the flow phase can detect tracer accumulation that occurs within a few seconds after tracer injection, whereas in the dynamic phase, each image represents at least 1 min of tracer activity. However, this high temporal resolution results in lower count densities in each flow phase image, thus making the detection of tracer accumulation more difficult.²⁵ This partially explains why flow phase imaging is considered suboptimal and optional.¹³ Our study suggests that despite the limited image quality, flow phase imaging has an advantage over dynamic phase imaging in predicting outcomes of subsequent CA. Additionally, certain methods can overcome the drawbacks of flow phase imaging. In one study, using cinematic playback viewing of 60 images, each obtained for 15 s, improved localisation and detection of bleeding when compared with viewing a set of high-resolution static images, each representing 1 min duration of counts every 5 min.²⁶ We propose that by reformatting counts acquired every second during the flow phase into longer (3–5 s) overlapping frames, one could improve the spatial resolution of each frame without significantly reducing its temporal resolution, thus improving its ability to detect abnormal tracers. Other methods such as subtraction scintigraphy could also be used as supplements to conventional datasets to improve the detectability of abnormal tracer.²⁵ After identifying a blush during planar scintigraphy, SPECT/CT can be used to accurately locate the site of blush. In one study, adding SPECT/CT to planar scintigraphy had a significant effect on the final outcomes in approximately one-third of the study population, mostly due to precise localisation of the bleeding foci.²⁷

In our study, the PPV of flow phase scintigraphy was 55% for detecting extravasation when CA was performed within 12 h, which suggests that a large number of angiographic studies would still be negative despite a positive flow phase RBC scan. This may be largely due to the intermittent nature of GIB as angiographically demonstrated by Sos et al.²⁸ Thus, the importance of scintigraphic identification of patients who are more likely to benefit from CA becomes more evident. For instance, because most cases of ulcer-related bleeding stop

spontaneously without any specific interventions,²⁹ identification of these patients, who are not likely to benefit from CA, is important. In these contexts, flow phase scintigraphy is more beneficial than the dynamic phase.

Our study has several limitations, including its retrospective observational nature and the relatively small sample size. Differences in screening and workup of GIB between our practice and previous studies make the comparison of findings rather difficult. Because our accuracy estimates are based only on patients who had a positive scintigraphy and underwent CA within 24 h, the results may be subject to selection and/or verification biases. Another challenge is the relatively lower resolution of flow phase images, making interpretation of the results complex when compared with the higher resolution of dynamic images reported in previous studies. Subtraction scintigraphy and reformatting methods were not used in our study to improve the resolution of flow images. Prospective multicentre studies with larger sample sizes using various methods of image reconstruction are needed to address these limitations. This study has a limited aim of predicting the

outcome during angiography, not assessing the diagnostic quality of scintigraphy.

CONCLUSION

Evaluation of images from the flow phase of scintigraphy acquired at high temporal resolution for 1 min after ^{99m}Tc RBC injection greatly increases the likelihood of detecting extravasation on subsequent CA. A negative flow phase accurately predicts which patients are unlikely to benefit from CA in spite of positive dynamic phase scintigraphy. In addition, a shorter time lag between positive flow phase scintigraphy and CA increases the PPV of scintigraphy in angiographic localisation of extravasation. We recommend that review committees consider these findings when framing future guidelines regarding the role of flow phase scintigraphy in GIB.

ACKNOWLEDGMENT

We thank Megan Griffiths for her assistance in reviewing the manuscript, Matthew Kiczek for initial data collection, and Jennifer Bullen for providing assistance with the statistical review of data.

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