The Addition Of Subtraction In Scintigraphy: A Role In The Evaluation Of Git Bleed
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Citation

Abstract
This article reviews the application and role of subtraction scintigraphy techniques in the scintigraphic evaluation of acute lower gastrointestinal haemorrhage. A number of techniques currently utilised have been discussed and an evolving technique is introduced that offers significant potential.

INTRODUCTION
Acute lower gastrointestinal haemorrhage (LGIH) presents an interesting medical and social dilemma. The demographic structure in many developed and developing countries, has steadily changed over the last century. The aging population is evident from both numerical (absolute increase) and structural (relative increase) aging perspectives. There is an increased incidence of chronic diseases associated with this population aging. Acute LGIH is just one of many health problems faced by our increasingly aged population. Over coming decades the morbidity of old age, including acute LGIH will increase the demands on health care resources and further increase the cost of health in this age demographic. These demands on resources may be contained, in part, by improving diagnostic tools utilised for acute LGIH. Improving $^{99m}$Tc red blood cell (RBC) scintigraphy to provide earlier detection and more precise localisation of bleeding sites may facilitate its elevation to the ‘front line' diagnostic tool, filling the void left in the absence of a recognised ‘gold standard'.

SCINTIGRAPHIC EVALUATION OF ACUTE LGIH
There are a number of features which contribute to the diagnostic conundrum of acute LGIH ($^{1}$):

- the origin of bleeding may be anywhere in the gastrointestinal tract (GIT),
- bleeding is frequently intermittent,
- evidence of active bleeding may not be obvious until after bleeding has ceased,
- emergency surgery may be required for both a specific diagnosis and localisation of the bleeding site.

Furthermore, the value of an accurate diagnostic work up may vary between patients because post therapy recurrence of bleeding is common and there is no consensus on appropriate patient management ($^{1}$). Despite this, accurate localisation of the site of bleeding is crucial in treatment and patient management ($^{3}$, $^{4}$).

There are a number of sources of false positive findings in $^{99m}$Tc RBC scintigraphic evaluation of acute LGIH that generally fit one of two categories; vascular structures or concentration of $^{99m}$Tc pertechnetate following radiolabel degeneration. A significant limitation of $^{99m}$Tc RBC scintigraphy is the movement of blood in both retrograde and antegrade directions, limiting the accuracy of localisation ($^{1,3,4,5}$). A small volume of focal accumulation of radiopharmaceutical is easily detected while a large volume with rapid migration may be undetectable ($^{5}$). This is further complicated because blood is an irritant for the bowel and increases peristalsis, thus, larger bleeds may disperse more rapidly ($^{1,3,4,5}$). Regardless of the minimum detectable bleeding rate, the minimum extravasated blood volume for detection of acute LGIH is reported as 3.0 to 5.0 ml ($^{6,7}$).

It is clear that improving techniques for scintigraphic evaluation of acute LGIH would contribute to improved patient outcomes (efficient patient management, decreased morbidity, decreased mortality) while maximising efficiency of resource utilisation (decreased health care costs). A
number of methods have been employed to improve scintigraphic evaluation of the acute LGIH patient with varying success, including: a variety of radiopharmaceuticals, delayed imaging, pharmacologic intervention, radionuclide enema and subtraction scintigraphy.

**SUBTRACTION SCINTIGRAPHY**

Subtraction imaging was introduced in the 1930s by a Dutch radiologist (8). Positive copies of plain film x-rays taken immediately prior to contrast injection were superimposed on the negative contrast films taken in the same position and, thus, a subtraction image is formed displaying the contrast in the vessels (8). Today, the principle is applied in a number of imaging modalities with computer assistance. Digital subtraction angiography (DSA) is a method utilised in the assessment of, among other pathologies, gastrointestinal haemorrhage. DSA allows demonstration of vessels filled with contrast media without the superimposed background structures by subtracting images acquired prior to contrast administration (mask) from images acquired after contrast administration (1).

Subtraction imaging is also utilised in Nuclear Medicine and is termed subtraction scintigraphy. Parathyroid subtraction scintigraphy is used to delineate thyroid from parathyroid tissue. Subtraction scintigraphy is also utilised in the assessment of prosthetic joints to differentiate infection from post surgical marrow compaction mimicking infection. Less commonly, subtraction scintigraphy has been utilised in ventilation perfusion lung scanning (9) and in single photon emission computed tomography (SPECT) of the brain in epilepsy (10). Another under utilised application of subtraction scintigraphy is in $^{99m}$Tc RBC scintigraphy in the evaluation of gastrointestinal haemorrhage.

There have been a number of authors who have documented the use of subtraction scintigraphy in $^{99m}$Tc RBC evaluation of gastrointestinal haemorrhage. Ford et al. (11) and Zuckier (12) both describe the use of subtraction scintigraphy in improving image contrast. Either the first frame acquired or a summation of all images with normalisation for count density are used to represent a background image and is subsequently subtracted from each individual image (11,12). Gore et al. (13) describes the use of image subtraction in improving localisation of the bleeding site. Kouris, Adbel-Dayem and Awdch (14) used subtraction scintigraphy to overcome interpretation difficulties associated with high background activity in $^{99m}$Tc sulphur colloid studies. In Australia, only 1.1% of departments employ subtraction scintigraphy for evaluation of acute LGIH with all utilising reference frame (baseline) techniques (13).

In essence, subtracting a nominal ‘mask’ or reference image (generally an early image in the dynamic sequence) from all subsequent images provides a mechanism to view only the information contributed by accumulated bleeding. In an acquisition with ‘n’ consecutive image frames with each individual image frame given by ‘F(f)’ where ‘f’ equals (1,2,3, … … … …,n), any subtracted image in the sequence is given by:

\[
S(f) = F(f) - F(1)
\]

For example,

\[
S(10) = F(10) - F(1)
\]

Clearly ‘f’ can not equal zero and there is no ‘n+1’ and, therefore, only ‘n-2’ subtracted frames are produced. All subtraction images employed frame one as the baseline (Fig. 1) and is referred to as reference subtraction scintigraphy (RSS).

**Figure 1**

Figure 1: Schematic representation of RSS where each individual frame has subtracted from it the initial ‘reference’ frame.

This allows removal of potential sources of false positive results or removal of superimposed structures (e.g. liver, major vessels). There are, however, a number of assumptions that are not necessarily met in patient data:

- There should be minimal patient motion between the reference frame and any image to be subtracted. Using the first frame as the reference frame, the patient must be motionless for the entire acquisition (usually 60 minutes).
The biodistribution of the radiopharmaceutical is stable between the reference frame and any image to be subtracted. Normalisation of count density can accommodate physical decay of the radionuclide, however, altered biodistribution (e.g., excretion, label breakdown) may be demonstrated in image subtraction.

Sequential subtraction scintigraphy (SSS) has also been described in improving detection and localisation of LGIH \(^{(16,17,18)}\). This technique involves the subtraction of each image from the next image in the sequence and, thus, leaving only that which has changed in the interval (five minutes) between images \(^{(16,17,18)}\). In an acquisition with ‘n’ consecutive image frames with each individual image frame given by ‘F(f)’ where ‘f’ equals \((1,2,3,…,n)\), any subtracted image in the sequence is given by:

\[
S(f+1,f) = F(f+1) - F(f)
\]

For example,

\[
S(10,9) = F(10) - F(9)
\]

Clearly ‘f’ can not equal zero and there is no ‘n+1’ and, therefore, only ‘n-1’ subtracted frames are produced. In theory, ‘f+1’ will contain lower counts than ‘f’ due to decay and this may provide a limitation for the minimum detectable bleeding volume. The subtraction method should result in removal of temporally consistent image data like background to allow better visualisation of active bleeding (Fig. 2).

**Figure 2**

Figure 2: Schematic representation of SSS where each individual frame has subtracted from it the preceding frame.

The SSS technique was first described by Kouris, Adbel-Dayem and Awdch \(^{(14)}\) using five minute images to more accurately delineate fresh bleeding. Similar assumptions and limitations apply to SSS as those for RSS, however, the impact has some variation:

- Patient motion is still problematic, however, only subtracted images where there was evidence of motion between consecutive images will be affected. For example, motion in frame six will only produce artefact in the two subtracted images produced using frame six.
- Variations in biodistribution of the radiopharmaceutical, even in the presence of label breakdown, should be minimal in the period between consecutive images and, thus, have minimal negative impact on the subtracted data set.
- Similarly, normalisation is not generally required because the amount of radioactive decay between consecutive images is negligible.
- The sampling frame is crucial. One must consider the statistical certainty associated with count densities as the sampling frame becomes more rapid, particularly for slower bleeding rates. The critical volume for detection requires accommodation while optimising the interval for minimal decay, minimal alteration to biodistribution and, most importantly, minimising dispersion of blood through the bowel lumen within a single sampling frame.

SSS was trialled clinically by the first author of this paper in 1998 utilising one minute sampling intervals to remove the high background activity and superimposed activity of high count organs like the liver. This technique showed potential for earlier detection and improved localisation of bleeding sites in acute LGIH (Fig. 3).
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**Figure 3**

Figure 3: Conventional Tc RBC scintigrams (top) demonstrating diffuse ascending colon accumulation of the radiopharmaceutical without a specific bleeding site being identified. Focal accumulation of the radiopharmaceutical in the transverse colon may suggest a bleeding origin with rapid retrograde movement of blood into the ascending colon. SSS (bottom) demonstrates a proximal ascending colon bleed site.

Currently, a modified sequential subtraction technique is being trialled by these investigators in phantom and clinical studies, alternate sequential subtraction scintigraphy (ASSS). In an acquisition with ‘n’ consecutive image frames with each individual image frame given by ‘F(f)’ where ‘f’ equals (1,2,3, … … … …,n), any subtracted image in the sequence is given by:

\[ S(f) = F(f+1) - F(f-1) \]

For example,

\[ S(9) = F(10) - F(8) \]

Clearly ‘f’ can not equal zero and there is no ‘n+1’ and, therefore, only ‘n-2’ subtracted frames are produced (Fig. 4). ASSS process may allow more accurate localisation and, perhaps, earlier detection (Fig. 5). ASSS may also have a role for increasing certainty with which a diagnosis is made and more accurate localisation.

**Figure 4**

Figure 4: Schematic representation of ASSS where each new frame is produced by subtraction of its preceding frame from the subsequent frame.

\[ S(9) = F(10) - F(8) \]

**Figure 5**

Figure 5: A lack of certainty exists for this IVC bleed position in CS frames 2 and 3 (left images) while RSS (frame 2 - 1) and ASSS (frame 3 - 1) provide a certainty of ‘definitely present’.

**SUMMARY**

During \(^{99m}\)Tc RBC scintigraphy, activity at the bleeding site will steadily increase while active bleeding persists. This assumes extravasation of \(^{99m}\)Tc RBCs in a continuous manner while background activity remains relatively unchanged. It also neglects the impact of retrograde and antegrade movement of extravasated blood away from the bleed site. Subtracting sequential images should allow elimination of background activity, providing high target-to-background images of the extravasated blood (Fig. 6). In short, a dataset is produced that theoretically offers the advantages of both conventional \(^{99m}\)Tc sulphur colloid and
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CONCLUSION

Successful management of patients with acute LGIH is less reliant on the therapy than on the early diagnosis and accurate localisation of the bleed site (no. 1). Subtraction scintigraphy can be used to improve detection and localisation certainty by allowing ⁹⁹m Tc RBC scintigraphy to incorporate the advantages of imaging with ⁹⁹m Tc sulphur colloid.

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References

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