Dynamic Graded Subtraction: A Simple Method to Background Correct and Display Multicompartmental Radiopharmaceutical Scintigrams

Michael J. Tuscan, Richard L. Wahl, and James Botti

University of Michigan Hospitals, Ann Arbor, Michigan

A common procedure to enhance the localization of a poorly localized radiopharmaceutical is to mimic and subtract its undesirable component with a second radionuclide of a different photopeak that is physiologic nonspecific. Determination of the exact amount of the nonspecific radionuclide to subtract in a single step, however, is difficult. We describe the use of a simple method to enhance an image of a poorly localized radiopharmaceutical by incrementally subtracting another image of a specific radiopharmaceutical that mimics the objectionable image data and displays the corrected image series in cinematic mode. This method of image correction and dynamic display may be useful for a variety of procedures in which there is a significant nonspecific component of the radiotracer such as in radiolabeled antibodies, or to perform selective compartmental or organ subtraction in the case of a mixed specificity radiopharmaceutical.

There are a variety of imaging procedures that depend on radiopharmaceuticals that demonstrate a significant amount of nonspecific or undesirable localization in addition to the organ of interest (*1–7*). In this situation, a method of identifying and subtracting the nonspecific or undesirable localization characteristics of the radiotracer is necessary. A commonly used method is the application of a second nonspecific radiopharmaceutical of a different photon energy in order to identify the nonspecific component of the original radiotracer (*8*). A clinical example of this is to use technetium-99m labeled human serum albumin (^{99m}Tc-HSA) to identify and to subtract the nonspecific component from an image of a radiolabeled antibody (*9–12*). In the case of the radiotracer which localizes in an undesirable compartment, as compared to the organ of interest, that compartment may be identified with an alternate radiotracer which localizes to the compartment in question and can then be subtracted. A clinical example of this is to use [^{99m}Tc]pertechnetate to identify and subtract the thyroid from ^{201}Tl activity which localizes in the parathyroid and the thyroid in an attempt to detect parathyroid adenomas (*6*). The resultant image, in both examples, is the original radiotracer minus the objectionable image data.

The difficulty in the subtraction process is to accurately determine the amount of the vascular image to subtract from the multicompartment image (*8*). This problem stems from the different imaging situations of each set of images (i.e., the administered dose, photon yield, etc.). Methods are available to calculate the appropriate correction factor, but they have the disadvantage of being a single subtraction method that may have potential errors (*3–7*).

We describe a very simple method that initially displays the raw multicompartment image, then serially and gradually subtracts a second background or single compartment image in a closed loop cinematic mode. The effect is to view the original image and then observe the undesirable compartment gradually disappear.

MATERIALS AND METHODS

All images are obtained with a wide field of view scintillation camera fitted with the appropriate collimator and interfaced to a dedicated imaging computer. All patients were immobilized in order to accurately perform the subtraction technique. In the event of patient movement, image rejustification will be necessary. Informed patient consent was obtained when necessary.

In the case of imaging ^{131}I radiolabeled antibodies, images were collected at 48 and 120 hr after administration. The photopeak is centered at 364 keV for ^{131}I with a 20% window and at 140 keV for ^{99m}Tc-HSA with a 10% window. Downscatter from the ^{131}I energy to the ^{99m}Tc window is determined with an anterior view of the chest during a 3-min acquisition immediately preceding the injection of the ^{99m}Tc-HSA. The patient is then given 1 mCi of ^{99m}Tc-HSA to mimic the nonspecific component of the radiolabeled

For reprints contact: Michael J. Tuscan, University of Michigan Hospitals, Division of Nuclear Medicine, Box 021, Ann Arbor, MI 48109.

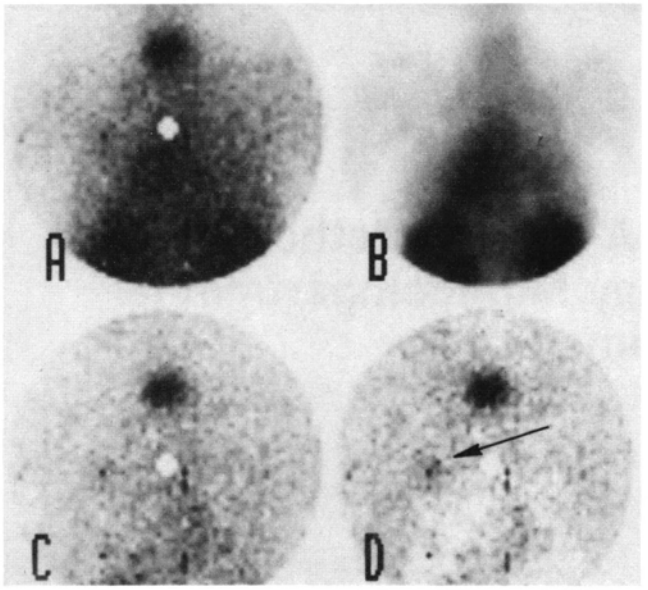

FIG. 1. (A) 20-min posterior chest image of ^{131}I-labeled murine monoclonal antibody 5F9.3 taken at 120 hr post administration. Light area in central image is acquisition artifact. (B) 20-min anterior chest image of ^{99m}Tc-HSA to localize blood pool. (C) Subtraction image of A with 50% of blood pool (image B) removed. (D) Subtraction image of A with 80% of blood pool (image B) removed.

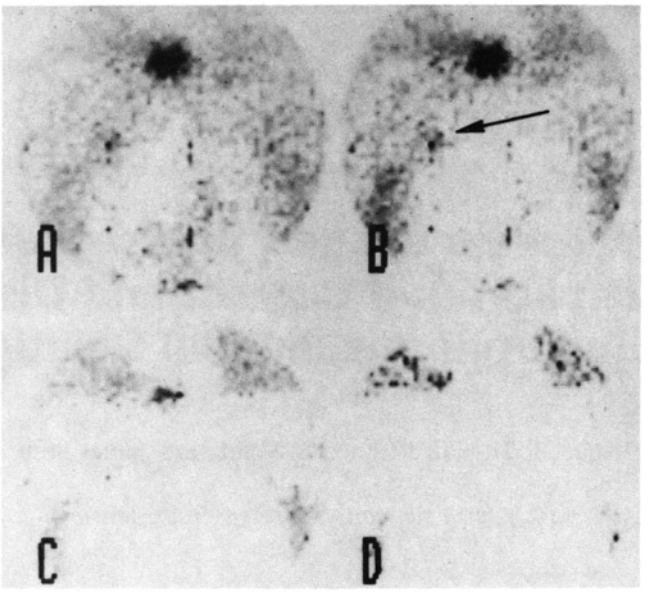

FIG. 2. (A) Subtraction image of 1A with 90% blood pool (1B) removed. (B) Subtraction image of 1A with 110% of blood pool removed. (C) Subtraction image of 1A with 150% blood pool (1B) removed. Upper left chest foci of uptake still persists. (D) Subtraction image of 1A with 200% of blood pool (1B) removed.

antibodies. Thirty minutes were allowed for complete mixing of the ^{99m}Tc-HSA prior to imaging. Images of both radiotracers are collected for 20 min over regions of suspected disease. After all images are acquired, the ^{99m}Tc-HSA images are corrected for downscatter from the ^{131}I labeled antibodies. The resultant image then becomes the input image used to estimate the nonspecific component of the radiolabeled antibody image.

Next, the amount of the ^{99m}Tc-HSA image to maximally subtract from the ^{131}I antibody image is calculated. A single region of interest is drawn over the heart in the anterior view of the ^{99m}Tc-HSA image. The same region is placed over the heart of the ^{131}I image. Respective count contributions from the heart are recorded for both images. A ratio is made that represents the relative contribution from the ^{99m}Tc-HSA image as compared to the ^{131}I antibody image. The HSA image is then multiplied by this factor. This corrected ^{99m}Tc-HSA image then approximates the nonspecific distribution of the antibody. The exact value of the correction factor used to create this image is, unlike other methods, not extremely critical due to the dynamic nature of the subtraction process.

The operator may select any one of a variety of sequential subtraction processes. The standard subtraction process will automatically perform 20 sequential subtractions. The first subtraction in the process will remove only a small fraction (5%) of the vascular image from the original images of mixed specificity. The last subtration process will remove all (100%) of the vascular image from the original image. The intermediate images are subtracted in a graded, linear fashion. More complicated subtraction schemes are available to the operator as desired. In every option, all negative pixel values that occur during subtraction are set to zero to enhance the display of the subtracted series.

The series of subtracted images are then cinematically displayed in a closed loop. Initially, in the loop, the uncorrected image is displayed and as the display dynamically proceeds, more and more of the vascular radiotracer (i.e., the ^{99m}Tc-HSA image) is removed. The operator may also set up the computer to not only sequentially subtract the vascular images, but to also show the vascular component reappearing in closed loop display. The speed of the cinematic display is controlled by the computer's joystick.

Another application of the subtraction technique is to eliminate undesirable or superimposing organ uptake such as imaging the parathyroid with ^{201}Tl in the presence of [^{99m}Tc]pertechnetate to identify the thyroid (*3–7*). In our case, the anterior chest and neck is imaged for 10 min after the intraveneous administration of 2 mCi of ^{201}Tl. The scintillation camera's photopeak is adjusted and 1 mCi of ^{99m}Tc is administered intraveneously and allowed to localize for 20 min. An image, for the subtraction process, of the pertechnetate in the thyroid is collected for 10 min. A common region of interest is drawn over the thyroid of both images to determine a correction factor to adjust the ^{99m}Tc image for the difference in relative count contribution. Again, the contribution of the ^{99m}Tc image may be slightly overestimated to assure complete subtraction in the cinematic display.

RESULTS AND DISCUSSION

Representative illustrations of the potential utility of this

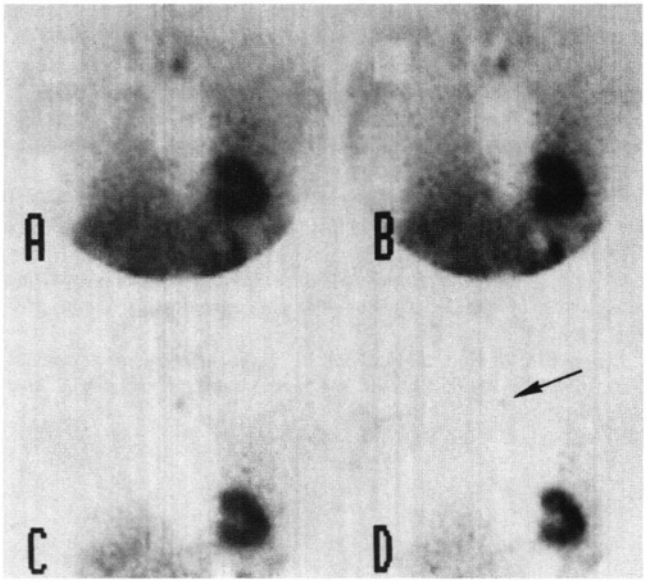

FIG. 3. (A) 10-min anterior neck and chest image of ^{201}Tl to localize thyroid and parathyroid. Dark rectangle at right shoulder is previous location of anatomical marker. (B) 10-min image of [^{99m}Tc]pertechnetate to localize thyroid. (C) Subtraction image of A with 10% of B removed. (D) Subtraction image of A with 35% of B removed.

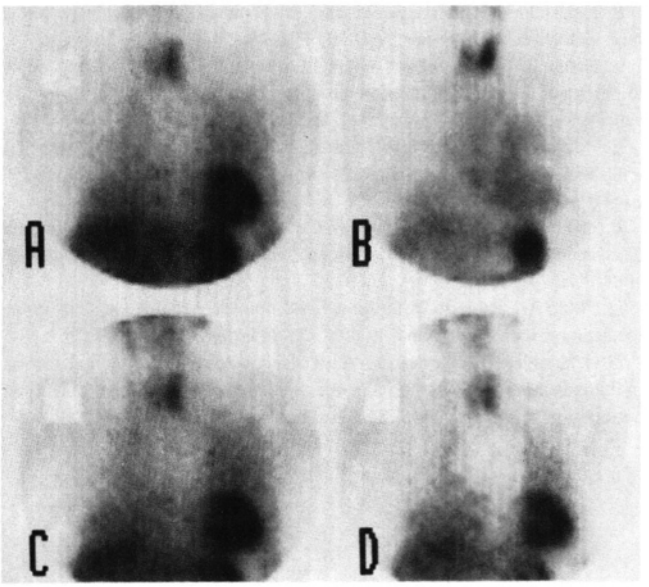

FIG. 4. (A) Subtraction image of 1A with 65% of blood pool (2B) removed. (B) 85% subtraction (3B) of image 2A. (C) 110% subtraction (3B) of image 2A. (D) 150% subtraction (3B) of image 2A. Focal uptake in neck region still persists.

approach to image correction are demonstrated in the following examples. Iodine-131 labeled murine monoclonal antibody 5F9.3, which preferentially localizes to choricarcinomas in nude mice (*13*), was injected intravenously into a patient suspected of having metastatic choriocarcinoma. A posterior 20 min acquisition view of the chest at the ^{131}I photopeak (Fig. 1A) shows considerable activity in the heart and upper abdomen which is presumedly related to blood pool activity persisting 120 hr post injection of the antibody. The 120 hr ^{99m}Tc-HSA image shows extensive blood pool activity without preferential localization to the left upper lung. Figures 1 and 2 demonstrate selected images from the cinematic display that demonstrate the disappearance of the heart blood pool activity with persistent activity in the left upper lung field (Fig. 2C). Activity remaining outside of the chest on the most highly subtracted images is due to the more extensive scattering of the ^{131}I compared to the ^{99m}Tc. In this case, the increased activity in the left lung was demonstrated at surgery to be a small ($<$ 2-cm pulmonary nodule) focus of choriocarcinoma that had been undetected until the antibody study was performed.

Figures 3 and 4 are images of the anterior neck and chest of a patient who is suspected of having a parathyroid adenoma. The series of dynamically displayed, graded subtraction images initially demonstrates the unsubtracted ^{201}Tl image (Fig. 3A). As the display proceeds, successive subtracted images (Figs. 3B–4C) illustrate the thallium image with varying amounts of the thyroid removed until the thyroid is slightly over subtracted. Remaining structures at this level of subtraction are suspicious of disease (Fig. 4D).

Currently available single background subtraction techniques to reduce nonspecific components are very difficult and theoretically limited. On the other hand, a multiple subtraction technique offers the observer a spectrum of subtracted images from which to gain an idea of the nonspecific component of the original image and to greater appreciate true foci of disease. In our limited clinical experience, we feel most comfortable diagnosing increased uptake in a region if it persists well after sufficient subtraction has been performed to remove all of the cardiac blood pool; however, a thorough prospective study of this is necessary.

The growing interest in radiolabeled antibodies and the increasing popularity of multicompartment imaging demands an improved method of correctly analyzing the data. We have not improved the theoretical complications of the subtraction technique in general, but certainly more information is available to the observer and the error of a single determination is avoided. Dynamic display of graded subtraction images may offer an alternate viewing technique to separate specific from nonspecific localization and to diagnose persistent areas of localized uptake. It may also offer an alternative method to subtract superimposing organ structures caused by the undesirable localization of an otherwise desirable radiotracer.

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