

## A new subtraction method for obtaining myocardial perfusion images with oxygen-15 water and positron emission tomography

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The myocardial positron emission tomograms which are obtained during the perfusion phase following bolus injection of O-15 water ( $H_2^{15}O$ ) intravenously require subtraction of the blood pool activity overlaid upon the myocardium. Subtraction has been carried out using the blood pool images obtained in the same position following single inhalation of O-15 labeled carbon monoxide gas ( $C^{15}O$ ). However, because a difference in activity exists between the left ventricular (LV) cavity and the right ventricular (RV) cavity, simple subtraction of the LV cavity activity using  $C^{15}O$  blood pool images induced significant over-subtraction in the right-side heart including the interventricular septum and RV wall. We developed a new method, "two-component subtraction," in which the  $C^{15}O$  blood pool images were decomposed into the right-side and left-side components using the early phase images of the  $H_2^{15}O$  dynamics under the assumption that the whole activity of that phase was distributed in the right-side heart homogeneously. Thus we subtracted the blood pool spillover from RV and LV separately. This method provided myocardial perfusion images of high quality which were well correlated with N-13 ammonia images.

**Key words:** Positron emission tomography, Myocardial perfusion, O-15 labeled water, Subtraction

AS A POSITRON EMITTING MYOCARDIAL PERFUSION AGENT, N-13 ammonia ( $^{13}NH_3$ ) has a high extraction fraction, is efficiently trapped as ammonium ion or glutamine, and is rapidly cleared from blood so that it gives myocardial perfusion images of high quality.<sup>1-4</sup> However, the extraction decreases at high flow, and since its trapping mechanism is of metabolic fashion, the  $^{13}NH_3$  kinetics considerably depends on the myocardial metabolic integrity and hydrogen ion concentration, which altogether make it difficult to quantitate the regional blood flow.<sup>1,5,6</sup>

On the other hand O-15 water ( $H_2^{15}O$ ) has been used to quantitate the regional cerebral blood flow as a freely diffusible tracer.<sup>7-9</sup> The term "diffusible" implies that the extraction is nearly 100% and that it is washed out in proportion to the regional blood

flow. Because the kinetics are not affected by metabolism,  $H_2^{15}O$  may provide a more accurate means to evaluate regional myocardial blood flow (rMBF).<sup>10-13</sup>

To quantitate rMBF using  $H_2^{15}O$  we have three problems to solve.

- (i) How to obtain the input function to the organ or the arterial time activity curve.
- (ii) How to subtract the cardiac blood pool activity.
- (iii) How to correct for the partial volume effect of the heart muscle including the motion effect.

In this paper we focused on the second problem, the subtraction of the blood pool activity, and presented a new subtraction method.

Unlike  $^{13}NH_3$ , which is trapped and retained in the myocardium,  $H_2^{15}O$  promptly begins to be washed out as it enters the heart muscle.<sup>7,10</sup> Thus a large amount of activity from the blood pool contaminates the myocardial perfusion phase images.

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The blood pool activity is usually subtracted using the blood pool images obtained by single inhalation of 0–15 or C-11 carbon monoxide gas ( $C^{15}O$  or  $^{11}CO$ ) which labels red blood cells.<sup>11,12</sup>

However, in the myocardial phase following intravenous bolus injection of  $H_2^{15}O$ , the left ventricular (LV) cavity has much higher activity than the right ventricular (RV) cavity, so that the simple subtraction of the blood pool image to take away LV activity would bring about oversubtraction in RV, and, due to the partial volume effect, underestimation of the myocardial activity in the interventricular septum and the RV wall.

We have developed a new subtraction method “two-component subtraction”. We assumed that all the activities in the early-phase image following intravenous bolus injection of  $H_2^{15}O$  are distributed only in the right-side blood pool homogeneously and not in the left side. Under this assumption we decomposed the  $C^{15}O$  blood pool image into the right and left components, thus subtracting the blood pool activity from the right chamber and left chamber separately. The goal of the study is to evaluate the validity of the two-component subtraction method in clinical studies in comparison with the conventional simple subtraction using  $^{13}NH_3$  images as a reference.

## MATERIALS AND METHODS

**Subjects:** The positron tomography was performed in one normal volunteer and one patient with anterior wall myocardial infarction. All subjects gave written consent.

**Radionuclides:**  $H_2^{15}O$  was produced in a baby cyclotron (CYPRIS) by bombarding nitrogen gas with deuterons followed by palladium-catalyzed reduction of  $^{15}O_2$  gas with hydrogen gas and obtained as a saline solution. The radiochemical purity was greater than 99%, and 15 mCi was administered in a clinical study.  $C^{15}O$  was produced by bombarding nitrogen gas containing 0.5% of oxygen with deuterons. The gas mixture was then passed rapidly over activated charcoal at 1,000°C and through a soda lime trap to remove uncovered  $CO_2$ . The radiochemical purity was greater than 99%, and the concentration was less than 0.3%. Twenty to 30 mCi of  $C^{15}O$  was inhaled from the bag.  $^{13}NH_3$  was produced by bombarding water with protons followed by reduction of oxides of  $^{13}N$  with titanium trichloride, and was obtained in a saline solution. The radiochemical purity was greater than 99%, and 15 mCi was administered.

**Imaging device:** The whole-body seven-slice PET scanner, Positologica III, was used giving 7 tomographic images at an interval of 16 mm.<sup>14</sup> Since the detectors rotate continuously on the principle of

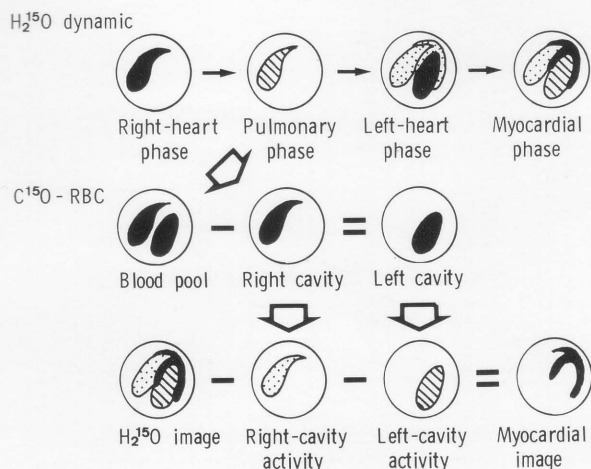
“positology”, the minimum sampling time required for a complete data acquisition is 2.25 sec. The spatial resolution was 9 mm FWHM in the center of the field of view in the reconstruction condition of this study. The axial resolution was 12 mm. The sensitivity for a 20 cm diameter cylindrical phantom was 34 and 52 kcps/ $\mu Ci/ml$  for true and cross planes, respectively.<sup>14</sup> The deadtime losses were corrected using single photon events.<sup>15</sup> The photon attenuation was corrected using the transmission scan with an external source. The sensitivity was calibrated against the well counter with a cylindrical phantom filled with  $^{68}Ga$ -EDTA solution.

**Data acquisition:** The subject was positioned supine in the gantry and the transmission scan was performed. Then a blood pool scan was performed for 3 min starting 5 min after the inhalation of 50 mCi of  $C^{15}O$  gas. At the beginning, midtime and end of the scan, the venous blood was sampled and its activity concentration was counted in the well counter. After the activity decreased, 15 mCi of  $H_2^{15}O$  was i.v. injected as a bolus and a serial dynamic scan was performed at 4.5 sec/frame. A reference perfusion scan was performed for 5 min starting 3 min after i.v. injection of 15 mCi of  $^{13}NH_3$ .

**Data analysis:** The images were reconstructed after the correction for deadtime, photon attenuation and sensitivity among slices and were presented in terms of counts (well counter) per ml. The recovery coefficient (RC) images were created from the  $C^{15}O$  blood pool images divided by the activity concentration of the blood samples under the assumption that the activity concentration of the peripheral venous blood pool is equilibrated with the cardiac blood chambers during the scan period. The RC images represent the degree of partial volume effect in each pixel in the blood pool images due to the insufficient resolution and the cardiac beating as well as the respiratory motion. The square region of interest (ROI) with 4 by 4 pixels (10 by 10 mm) was taken in the center of each chamber so that it contained the pixels with 85% or larger RC values. These ROI's were used later to determine the activity of each cardiac chamber or to adjust the gain of the images.

The  $H_2^{15}O$  perfusion phase images were obtained by adding 6 or 8 frames (27–36 sec) in the myocardial phase starting from the next frame showing the peak activity in the left ventricle. The blood pool activity was subtracted by the conventional simple subtraction method or the two-component subtraction method.

In the simple subtraction method, the  $C^{15}O$  blood pool images were gain-adjusted and subtracted from the myocardial perfusion images so that the ROI's in the center of the left cardiac chambers showed zero activity.



**Fig. 1** Schematic presentation of the two-component subtraction method.

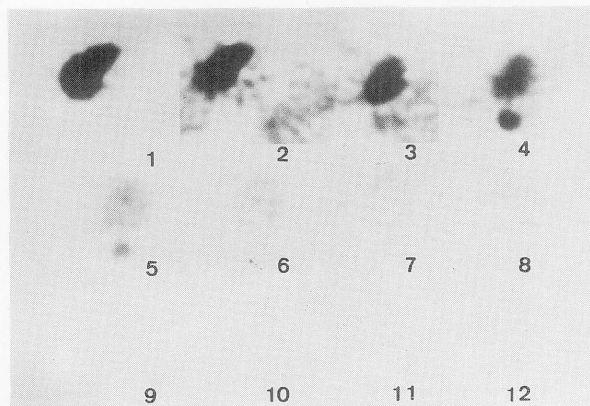
In the two-component method (Fig. 1), we picked up the early phase images (frame No. 1 or No. 2) of the  $H_2^{15}O$  dynamic scan and used as the right-side cardiac blood pool images, which were then subtracted from the  $C^{15}O$  images to generate the left-side blood pool images by scaling the activity in the ROI's of the right cardiac chambers. Thus, the  $C^{15}O$  blood pool images were decomposed into those of the right and the left sides. The blood pool activity was subtracted from the  $H_2^{15}O$  myocardial perfusion phase images using each of the decomposed blood pool images by adjusting each of the cardiac chamber ROI values.

All the additions and subtractions were carried out in the pre-reconstruction projection data (sinograms) to prevent noise expansion in image arithmetics.<sup>12</sup>

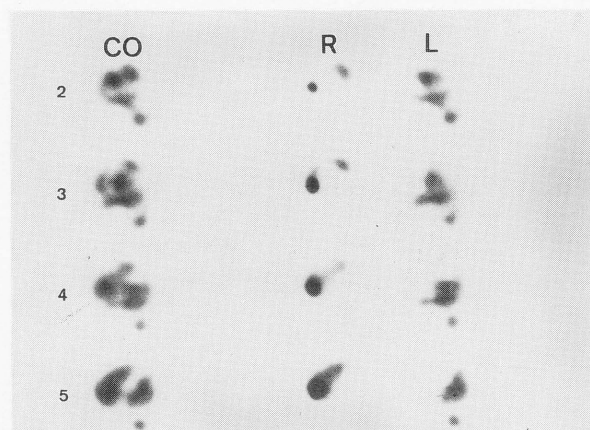
To validate our method, the myocardial activity in each subtraction method and that in  $^{13}NH_3$  study were compared by taking square ROIs with 4 by 4 pixels (10 by 10 mm) in the right ventricular wall and left ventricular septal, anterior, lateral and posterior walls.

## RESULTS

Figure 2 shows a set of serial dynamic tomographic images at the level of the cardiac ventricle following an intravenous bolus injection of  $H_2^{15}O$  into the median cubital vein of a normal subject. The transfer of the activity was clearly delineated as it passed through the right ventricular cavity, the lungs, the left ventricular cavity and the aorta, followed by the visualization of the myocardium. Because the first frame showed activity only in the right-side heart, it was adopted as the right-side blood pool images and was used to decompose the  $C^{15}O$  images into the



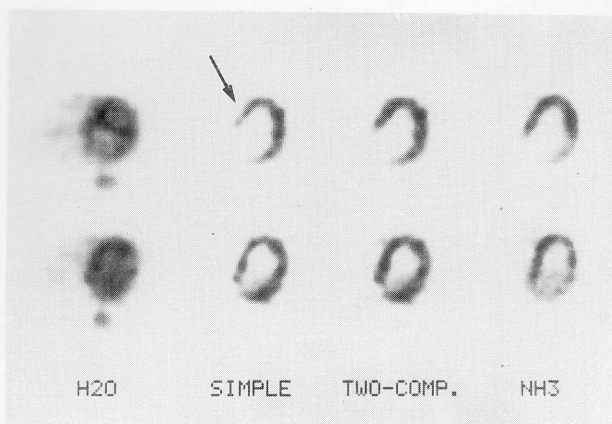
**Fig. 2** Serial dynamic tomograms acquired at 4.5 sec/frame following intravenous bolus injection of  $H_2^{15}O$  in a normal subject. Numbers indicate the frame numbers.



**Fig. 3** Decomposition of  $C^{15}O$  blood pool images (CO) into right (R) and left (L) components. Numbers indicate the slice numbers. The blood pool lumens are successfully separated into the two anatomical components except for the inferior vena cava.

right-side and left-side components (Fig. 3). The right component included the superior vena cava (SVC), the right atrium (RA), the right ventricle (RV) and the pulmonary artery (PA). The left component included the pulmonary veins (PV), the left atrium (LA), and left ventricle (LV), and ascending and the descending aorta (aAO and dAO). Although the inferior vena cava (IVC) belongs to the right side anatomically, it was visualized in the left component.

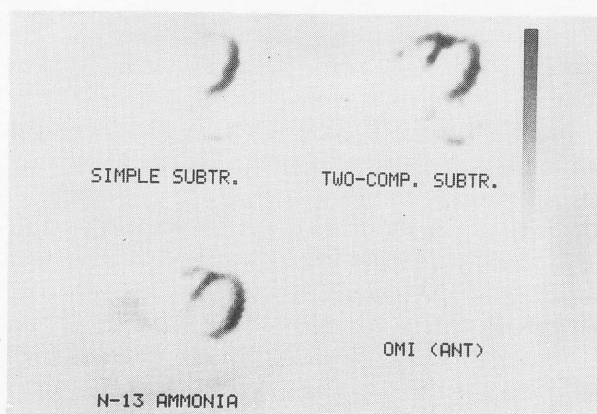
Then the blood pool activity was subtracted from the myocardial phase  $H_2^{15}O$  images. Figure 4 shows the subtracted myocardial images of a normal volunteer with a simple subtraction method and two-component subtraction method, and the  $NH_3$  images as a reference. The simple subtraction images showed decreased activity in the intraventricular septum due to oversubtraction on the right side, which has been induced by the activity difference between the left and right chambers. On the other hand, the two-com-



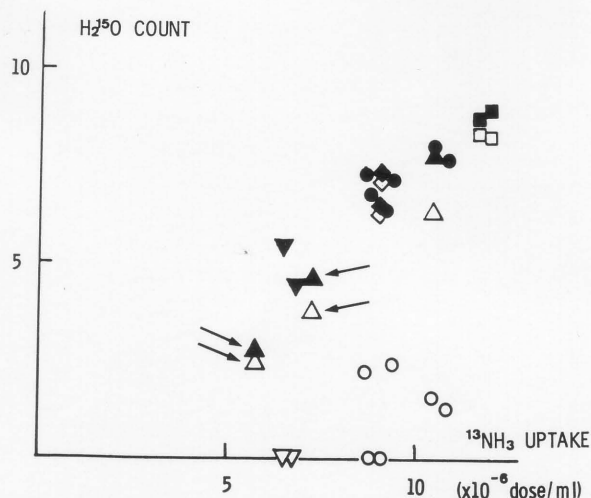
**Fig. 4** Blood pool activity contaminates the myocardial images acquired in the myocardial perfusion phase following injection of  $H_2^{15}O$  ( $H_2O$ ). Simple subtraction (SIMPLE) and two-component subtraction (TWO-COMP.) are compared using  $^{13}NH_3$  images as a reference ( $NH_3$ ). The simple subtraction shows decreased activity in the interventricular septum due to oversubtraction in the right side (arrow).

ponent subtraction showed homogeneous activity in the septum and the free wall. The  $NH_3$  images made sure that the septum has no perfusion abnormality.

Figure 5 shows the subtracted myocardial images of a patient with anterior wall infarction contrasting the two subtraction methods and with the  $^{13}NH_3$  images as a reference. The RV wall and the septum completely disappeared in the simple subtraction images but were clearly observed in the two-component images in exactly the same way as the  $^{13}NH_3$  images. The regional activity of each myocardial segment in the  $H_2^{15}O$  images of the two methods was plotted against the  $^{13}NH_3$  uptake (Fig. 6). The two-component subtraction showed good correlation



**Fig. 5** Simple subtraction and two-component subtraction  $H_2^{15}O$  myocardial images compared with the  $^{13}NH_3$  images of the same slice in the patient with anterior wall myocardial infarction. Note a wide discrepancy between simple subtraction and  $^{13}NH_3$  in the septum and RV wall.



**Fig. 6** Regional counts at RV wall ( $\nabla$ ), septum ( $\circ$ ), anterior ( $\triangle$ ), lateral ( $\square$ ) and posterior wall ( $\diamond$ ) in  $H_2^{15}O$  images of the two methods plotted against the  $^{13}NH_3$  uptake in the case shown in Fig. 5. Open symbols stand for simple subtraction and closed symbols two-component subtraction. Arrows indicate the infarcted segments.

against the  $^{13}NH_3$  in all segments including the infarcted areas, whereas the simple subtraction showed extremely underestimated activity in the RV wall, septum and a part of the anterior wall compared with that of  $^{13}NH_3$  due to oversubtraction on the right side.

## DISCUSSION

The blood pool subtraction is a prerequisite for imaging myocardial perfusion using  $H_2^{15}O$ , which promptly begins to be washed out as it enters the tissue so that strong activity remains within the LV cavity and the aorta in the myocardial perfusion phase following i.v. bolus injection. The subtraction was performed with the blood pool images obtained by the inhalation of  $C^{15}O$  or  $^{11}CO$  gas which labelled hemoglobin in the red blood cells.<sup>11,12</sup> However, the time difference makes a large activity difference between the LV cavity and the RV cavity in the myocardial phase following i.v. administration. Therefore, the simple subtraction of LV blood pool activity with  $C^{15}O$  gas would bring about oversubtraction in the RV wall, septum and the anterior wall. The results of the present study indicated decreased activity in the RV wall, septum and part of the anterior LV wall in the simple subtraction images, which were in clear contrast to the  $^{13}NH_3$  images (Figs. 4–6). Although the  $H_2^{15}O$  and  $^{13}NH_3$  images might not necessarily coincide with each other, these discrepancies are probably the artifacts induced by the oversubtraction in the simple subtraction method.

A slow injection technique or continuous infusion technique would diminish this inconvenience but would increase the statistical errors because the blood pool would have more activity in those techniques.<sup>12</sup> Several studies regarding the cerebral blood flow measurement have also disclosed that far more errors are involved in the continuous administration method due to non-linearity in flow-activity relationships.<sup>7,16</sup>

We developed a new subtraction method, "two-component subtraction," for myocardial imaging with  $\text{H}_2^{15}\text{O}$ . We assumed that the whole activity in the early phase images following an i.v. bolus injection are distributed homogeneously and only in the right blood pool, with no activity on the left side. On this assumption, the  $\text{C}^{15}\text{O}$  images were decomposed into the right and the left components scaling the counts in the right chamber. Thus we subtracted the blood pool from the right and the left chamber separately. According to the results of our study, the two-component subtraction showed the septum and the free wall with approximately equal activity in a normal subject (Fig. 4). In a patient with anterior wall infarction, the new method provided myocardial images of high quality showing a good correlation with  $^{13}\text{NH}_3$  images (Figs. 5, 6). Since the myocardial phase activity of the  $\text{H}_2^{15}\text{O}$  scan and the uptake of  $^{13}\text{NH}_3$  are both determined primarily by the regional blood flow, the regional counts of the two images of the same subject should trace a positive correlation in all segments. Thus our results indicate the inappropriateness of the conventional simple subtraction due to the oversubtraction in the right side and the superiority of the two-component method in that aspect.

We had assumed that the whole activity is distributed homogeneously in the right blood pool in the early phase of  $\text{H}_2^{15}\text{O}$  dynamics. A condition contradicting this assumption makes the decomposition unsuccessful. If strong activity remained in the SVC, an artifact develops in the SVC region due to a cold spot in the left component. To prevent this, a bolus administration technique should be introduced so that a hot spot in the SVC should disappear following the appearance of the tracer in the LA. For the same reason, a low output heart and an R-L shunting heart are resistant to this method. Even with the ideal dilution in the SVC and the right chambers, the IVC is sorted into the left component in the brachial administration resulting in a less significant artifact (decreased activity) in the nearby area.

Another important problem is how to scale the two images on subtraction. We sampled the blood to measure the absolute activity concentration in the  $\text{C}^{15}\text{O}$  scan and generated the recovery coefficient (RC) images. If the center of each chamber has full

recovery ( $\text{RC}=100$ ), accurate scaling and subtraction could be realized by scaling the count for that area. Moreover, the arterial time-activity curve (input function) can be determined noninvasively by measuring the activity of that region in a fast dynamic scan. This is not the case due to the partial volume effect induced by the insufficient resolution and the beating and respiratory motion. When the RC at the center of the LV is 90%, for instance, the residual 10% may be a spillover from the LV wall, and scaling the area to zero leads to oversubtraction to that degree. This error is inevitable unless a full recovery area is obtained in each chamber. In spite of these problems involved in the subtraction procedure, the two-component subtraction method should be superior to the conventional simple subtraction and help improve the myocardial perfusion study qualitatively and quantitatively.

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