Regional Cerebral Blood Flow Imaging: A Quantitative Comparison of Technetium-99m-HMPAO SPECT with $C^{15}O_2$ PET

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The aim of this study was to compare technetium-99m-hexamethylpropyleneamineoxime (^{99m}Tc-HMPAO) single-photon emission computed tomography (SPECT) with regional cerebral blood flow (rCBF) imaging using positron emission tomography (PET). As investigation of dementia is likely to be one of the main uses of routine rCBF imaging, 18 demented patients were imaged with both techniques. The PET data were compared quantitatively with three versions of the SPECT data. These were, first, data normalized to the SPECT cerebellar uptake, second, data linearly corrected using the PET cerebellar value and, finally, data Lassen corrected for washout from the high flow areas. Both the linearly-corrected ($r = 0.81$) and the Lassen-corrected ($r = 0.79$) HMPAO SPECT data showed good correlation with the PET rCBF data. The relationship between the normalized HMPAO SPECT data and the PET data was nonlinear. It is not yet possible to obtain rCBF values in absolute units from HMPAO SPECT without knowledge of the true rCBF in one reference region for each patient.

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There has been considerable interest in the clinical potential of the new cerebral imaging agent technetium-99m-hexamethylpropyleneamineoxime (^{99m}Tc-HMPAO), which, when used with single-photon emission computed tomography (SPECT), may permit the imaging of regional cerebral blood flow (rCBF) on a routine basis (*1*). Although there is already evidence of the clinical value of ^{99m}Tc-HMPAO SPECT in several areas, for example in stroke, epilepsy, and cerebral tumours (*2–4*), one of the most exciting applications is in dementia (*5*). The possibility of differentiating between dementia of the Alzheimer type (DAT) and multi-infarct dementia (MID) is of considerable importance given the increase in the numbers of demented patients in the developed world and the fact that therapeutic trials for both DAT and MID are beginning to emerge. The appearances seen with ^{99m}Tc-HMPAO SPECT in DAT patients are similar to those seen using positron emission tomography (PET) (*6–9*), which is, of course, a much more expensive and elaborate procedure and so unsuitable for routine clinical use.

Despite the similarity between ^{99m}Tc-HMPAO SPECT images and PET images in the demented patient, there is still a need to compare the data quantitatively. Such a comparison will help both to validate ^{99m}Tc-HMPAO and to show whether ^{99m}Tc-HMPAO can be used to measure rCBF in absolute units. In this study, a quantitative method is used to compare rCBF images obtained using $C^{15}O_2$ PET with images obtained using ^{99m}Tc-HMPAO SPECT in a group of demented patients.

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MATERIALS AND METHODS

Patients

A total of 18 demented patients was investigated. The mean age was 62.7 yr (s.d. 8.7 yr) and there were 11 females and 7 males. The group comprised 10 MID patients and 8 DAT patients, classification being made using the American Psychiatric Association Diagnostic and Statistical Manual (*10*). All patients were assessed clinically in accordance with the criteria laid down by the Medical Research Council (MRC) working party on Alzheimer's Disease (an informant's corroboration of behavioral change indicating the presence of dementia) and the Folstein Mini Mental State examination (MMSE) (*11*). In addition, laboratory exclusion of endocrinologic, biochemical, and infective causes of dementia was carried out (*12*) and the Hachinski ischemic score was applied

(*13*), a score of <4 indicating DAT and >7 indicating MID. Those patients diagnosed as DAT had a mean age of 66.3 yr (s.d. 6.3 yr) and a mean MMSE score of 16.1 (s.d. 9.5). Those diagnosed as MID had a mean age of 59.8 yr and a mean MMSE score of 20.0 (s.d. 5.7). Permission for the study was obtained from the Joint Ethical Committee of the Grampian Health Board and the University of Aberdeen. Consent was obtained prior to the study from the patient and the nearest relative.

Imaging Procedure

The PET rCBF images were obtained using the equilibrium method of continuous inhalation of oxygen-15-labeled carbon dioxide with arterial blood sampling (*14*). The labeled carbon dioxide was administered into a face-mask at 14 μCi/min in a nitrogen gas stream containing 1% carbon dioxide at a rate of 500 ml/min. This was mixed in the face-mask with ambient air. The patient was allowed to breathe the gas mixture for 9 min before imaging began, by which time a steady-state had been reached. The method permits functional images of rCBF to be obtained. The PET imager used was an EG&G Ortec ECATII single section instrument. All data were corrected for attenuation by the prior acquisition of transmission images using a germanium-68 ring source and images reconstructed with the medium resolution Shepp filter.

Absolute rCBF estimates from PET require a knowledge of arterial blood tracer concentration levels. These were obtained by taking three arterial blood samples from the left radial artery during steady-state imaging, and measuring these in a well counter. The mean specific activities were reproducible within ~3% (coefficient of variation). The well counter was calibrated with respect to the ECATII by imaging a phantom containing ^{68}Ge and measuring an aliquot of the contents of the phantom in the counter. The blood/brain partition coefficient was assumed to be 0.96. Functional rCBF images were then calculated from the primary PET images using the model described in detail elsewhere (*14*). All subsequent reference to PET images in this paper is to such functional images.

SPECT rCBF images were obtained using ^{99m}Tc-HMPAO (Ceretec, Amersham, Intl.). Technetium-99m-HMPAO (750 MBq) was injected intravenously and data acquisition started 15 min postinjection. Sixty-four by 25 sec frames were collected on a 64 × 64 matrix using a high resolution collimator fitted to an IGE 400ACT rotating gamma camera interfaced to a Link Analytical MAPS 5050 data processor. Reconstruction was by back-projection of profiles filtered by a Hanning-weighted ramp filter and the first-order Chang method of attenuation correction was used (*15*).

Three PET images were obtained for each patient; one section through the cerebellum, one at the level of the ventricles, and a section above the ventricles. Acquisition times were between 5 and 10 min for each image. The level of the obitomeatal (OM) line was marked on the scalp with an indelible marker and the position of each of the three sections relative to the OM line was determined anatomically using magnetic resonance imaging prior to the PET study. Accurate positioning of the patient for the PET study was then achieved using a pair of cross-line laser beams.

The SPECT study was carried out within 48 hr of the PET study, and on the SPECT images the OM plane was marked with three cobalt-57 markers. After reconstruction, the SPECT data were adjusted so that the transaxial sections were parallel to the OM plane. Since the distance between adjacent transaxial sections was known to be 6.4 mm, the section corresponding to a particular PET image was easily determined. Where the level lay between two sections, the average of the two sections was used for the comparison.

Method of Quantitative Analysis

The PET data were transferred to the MAPS 5050 system where quantitative analysis of both PET and SPECT data was carried out. The SPECT data were interpolated to 128 × 128, corresponding to an element size of 3.2 × 3.2 mm, and the PET data were formatted to a 128 × 128 matrix of the same element size. The method of analysis was as follows. Having decided which PET and SPECT images matched, the operator outlined the brain on the SPECT image with a region of interest (ROI). A second ROI was then inscribed at a distance of 7 pixels (22.4 mm) within the first by the computer. The second ROI was subtracted from the first leaving an ROI which included most of the cerebral cortex. This ROI was then divided into 10 equal sized smaller ROIs as shown in Figure 1. This method was used for analysis of the mid-ventricular and higher sections. The cerebellar image was only used for data correction as described below. The identical ROI was applied to both the PET and SPECT images. The average counts per pixel for each of the 10 ROIs was then recorded. For the PET images, this gave rCBF in ml/min/100 ml directly, but the values obtained from the SPECT data depended on any further image processing employed.

In this study, three different methods of calculating rCBF from the SPECT data were used. First, the counts in the SPECT ROIs were expressed as a percentage of the counts in the cerebellum on the appropriate SPECT section. In the second method, the percentages calculated in the first method were converted to rCBF, in ml/min/100 g, using the value of the rCBF of the cerebellum in the PET image; in this paper this is referred to as linear correction. In the final method, the

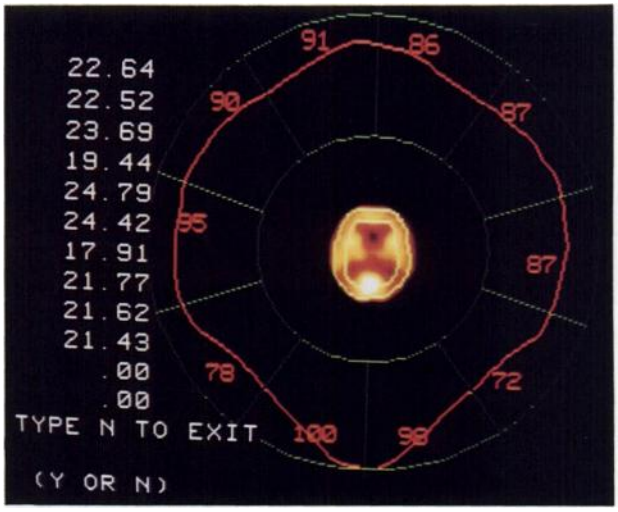

FIGURE 1
The ROI over the cortex is divided into 10 smaller ROIs as shown for quantitative analysis. The data used in the quantitative analysis is displayed on the left.

PET cerebellar value was also used to apply to so-called Lassen correction (*16*) to the SPECT data. This correction is based on a three-compartment model and corrects for washout from high flow areas. The algorithm employed is:

$$\frac{F}{Fc} = \frac{\alpha \cdot C/Cc}{1 + \alpha - C/Cc},$$

where C and Cc are the count densities in the ROI and the cerebellum, respectively, F and Fc are the rCBF in the same regions and α is a constant of value 1.5 (*16*).

RESULTS

Each of the three versions of the SPECT data was compared with the equivalent PET image and the results are shown in Figures 2, 3, and 4. For each patient, two PET images were available, and hence 20 data points were produced. In one patient, two mid-ventricular PET images 1 cm apart were acquired, and so, for this patient 30 data points were produced. Consequently there are 370 data points in each of Figures 2, 3, and 4.

Regression analysis was performed on the data in Figures 3 and 4, and the line of best fit is shown in each case. Both sets of data show a significant fit ($p < 0.01$, F ratio test) to the regression line, the correlation coefficients being 0.81 and 0.79, respectively. The gradients of the regression lines are 0.96 and 0.93, and the intercepts are 6.66 and 4.8, respectively. Linear regression analysis was not carried on the data in Figure 2 as it was clearly nonlinear.

DISCUSSION

Technetium-99m-HMPAO was developed to give images showing rCBF on a routine basis but it is already clear that the mechanism of HMPAO uptake is complex and so the images will not simply show the distribution of rCBF (*17–19*). The aim of this study was to validate ^{99m}Tc-HMPAO SPECT using PET imaging with ^{15}O-labeled CO_2, an established method of rCBF tomography, as the "gold standard." In an investigation into the accuracy of the inhalation technique, it was shown that errors as large as 30% in rCBF measurements can occur (*20*). The largest source of error, potentially well over 20%, is the effect of tissue heterogeneity, i.e., the mixture of grey and white matter in each pixel, caused by the relatively poor spatial resolution of the PET imager. It was, however, shown that the size of this error will depend on the rCBF value and the proportion of grey matter in the ROI used for the PET measurement. Under the present circumstances where the cortical rCBF is less than 40 ml/min/100 g and assuming that the proportion of grey matter in the ROI is 70% ± 10%, then this source of error will be of the order of 5% (*20*). Including other sources of error, such as inaccuracies in tissue count data and in arterial radiotracer concentration (*20,21*), the rCBF values measured by PET in this investigation should be accurate to 10%.

This study was carried out on a group of demented subjects, as this was one of the groups of patients most likely to benefit from routine rCBF imaging. Although it is clear that the two methods produce subjectively similar images (Fig. 5), particularly using the Lassen correction, a quantitative comparison is also required and the results of this are shown in Figures 2, 3, and 4. In this investigation, the absolute rCBF values for the cerebral cortex as measured by PET are quite low. However the mean cerebellar rCBF in this study was 40.0 ml/min/100 g (s.d. 9.4 ml/min/100 g), which is similar to the value of 44.8 ml/min/100 g (s.d. 6.7 ml/min/100 g) for the mean cerebellar rCBF in a group of

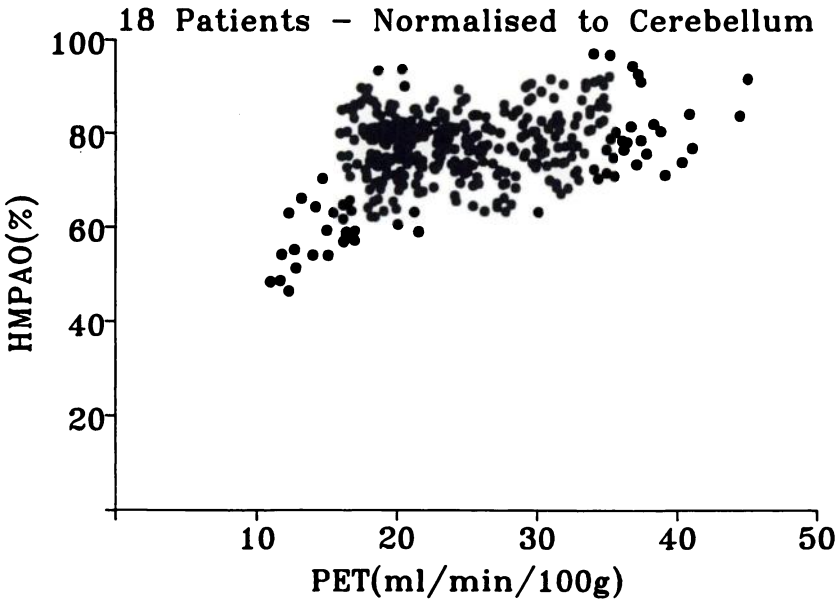

FIGURE 2
Comparison of the normalized HMPAO SPECT data with the PET rCBF data. In the normalized SPECT data, the counts per pixel in each ROI are expressed as a percentage of the counts per pixel in the cerebellum for that patient.

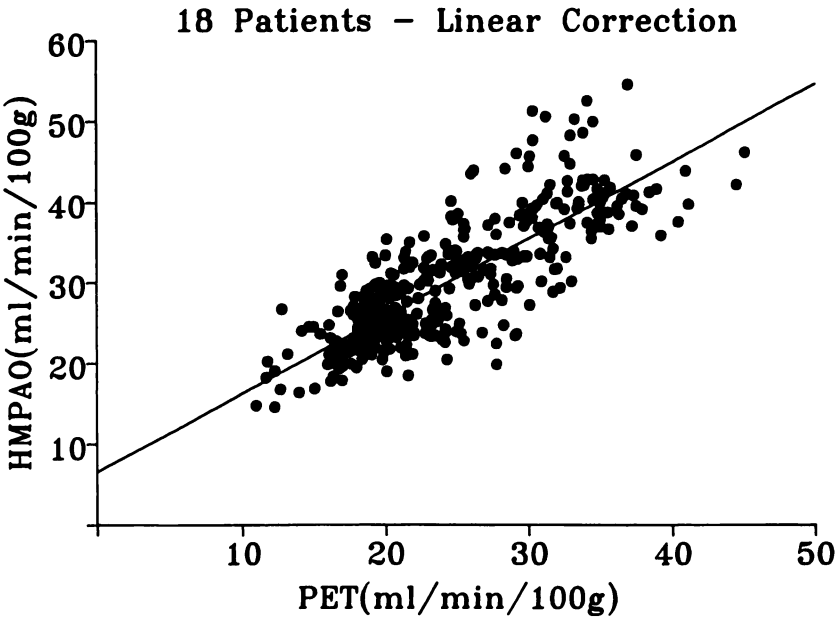

FIGURE 3
Comparison of the linearly-corrected HMPAO SPECT data with the PET rCBF data. In the linearly-corrected SPECT data, the percentages obtained for Figure 2 are multiplied by the rCBF value of the cerebellum in ml/min/100 g for the particular patient as measured by PET to convert to rCBF in ml/min/100 g. The line of best fit is shown ($p < 0.01$, $r = 0.81$).

11 normal subjects aged over 50 yr found by other workers using this method (Lammertsma, *personal communication*, 1990). It is, of course, the cerebral cortex rather than the cerebellum which is affected in the demented patient (*22*), and marked cortical atrophy was apparent in the MRI images used for positioning the patients in this investigation. This cortical atrophy is undoubtedly the main reason for the low cortical rCBF values found in this investigation. Another lesser factor is the size of the cortical ROIs used in the method of quantitation. Smaller ROIs would include a greater proportion of grey matter and this can increase the measured flow value by up to 10%.

It is widely appreciated that a number of factors influence the count density values in a SPECT section. In particular, the method of attenuation correction used is much less satisfactory than the more precise transmission method used for the PET data. It has been suggested that normalization using counts per pixel in the cerebellum would be a reasonable way of minimizing these effects and producing reproducible SPECT data (*18,23*). A comparison of images processed in this way with their PET equivalents is shown in Figure 2. These data lie on a curve which rises to a plateau above 20 ml/min/100 g, as measured by PET. Curves of this shape have been recently reported by other workers who suggested that the plateau is caused by washout from high flow regions (*24,25*). It is our view that, with pooled data from a number of patients, this feature arises, at least in part, from the variation in cerebellar

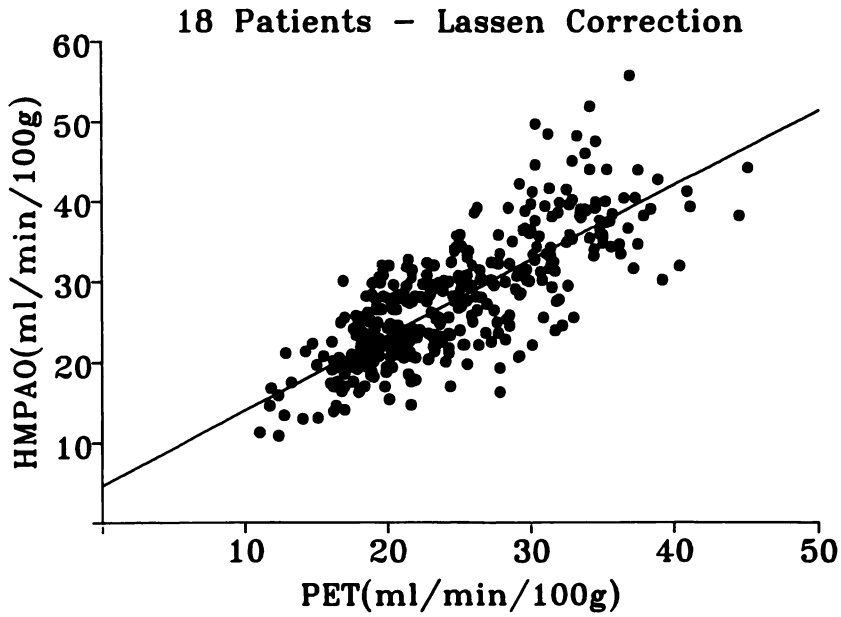

FIGURE 4
Comparison of the Lassen-corrected HMPAO SPECT data with the PET rCBF data. In the Lassen-corrected SPECT data, the rCBF cerebellar value as measured by PET is used to correct for washout from high flow regions. The line of best fit is shown ($p < 0.01$, $r = 0.79$).

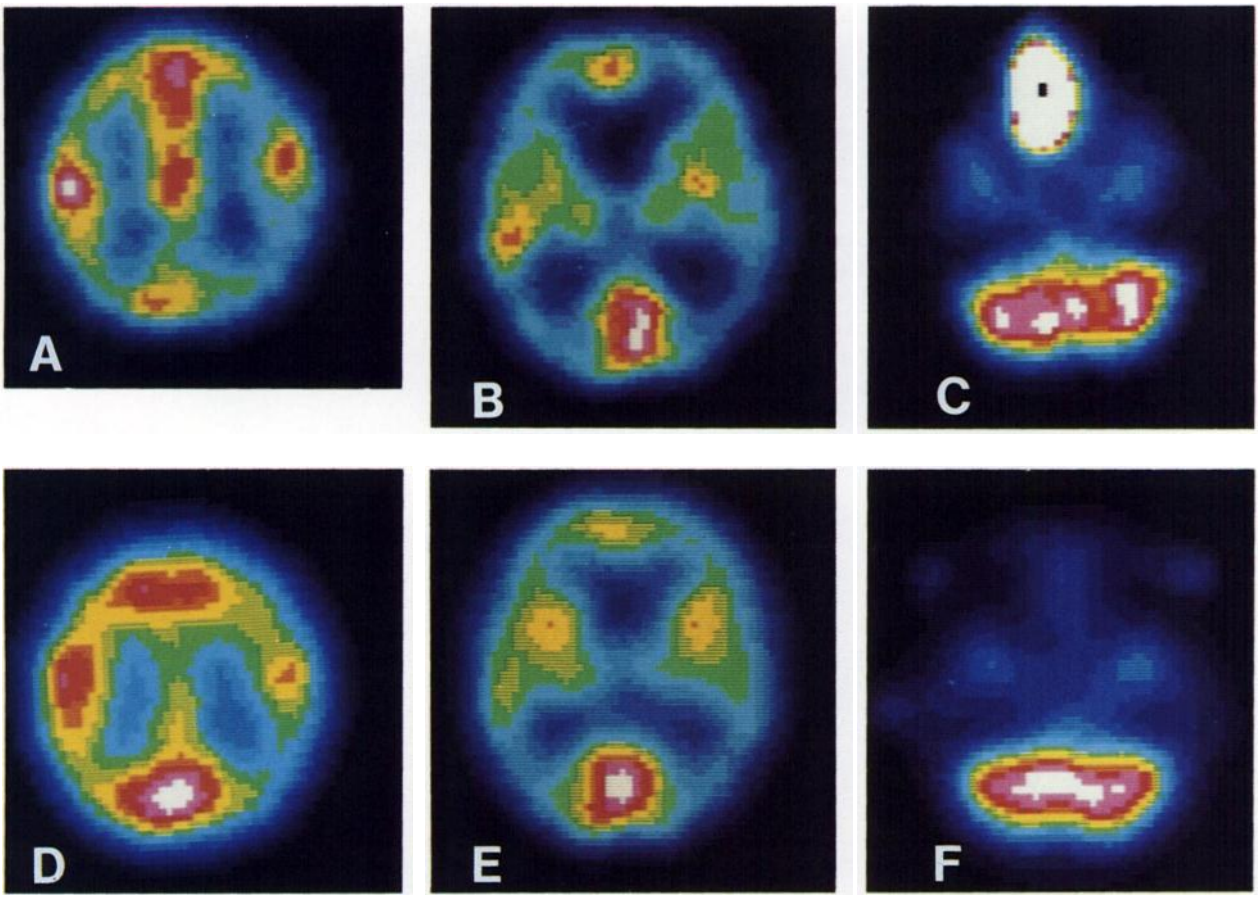

FIGURE 5
In this DAT patient, there is good agreement between the PET images (A–C) and their equivalent HMPAO SPECT images (D–F), both sets showing bilateral temporo-parieto-occipital and, to a lesser extent, fronto-parietal defects. The SPECT images are Lassen corrected.

rCBF between patients. A nonlinear relationship can be caused by expressing the cortical rCBF as a percentage of the cerebellar rCBF for each patient and then plotting all of the patients on the same graph. This method of plotting the data is equivalent to assuming a constant cerebellar rCBF for each patient, whereas we find that the cerebellar rCBF varies from patient to patient. When the HMPAO percentages are converted to ml/min/100 g using the measured cerebellar rCBF value in ml/min/100 g from the PET data, i.e., the linear correction, the relationship changes to the linear one shown in Figure 3. When the Lassen correction was applied to the data, the relationship between the HMPAO and PET rCBF values remains linear, as shown in Figure 4, with a similar gradient to Figure 3 but a slightly lower intercept on the ordinate. The effect of the Lassen correction on the pooled data is therefore not as marked as has been suggested (*24*,*25*), although this may be because the cerebellum is usually the region of highest flow in this group of patients. For regions where the flow is lower than the reference region, the cerebellum in this study, the effect of the Lassen correction is to reduce the flow values further. In fact, for this group of patients, when a lower count density threshold of around 30% is applied to the linearly-corrected images they become very similar in appearance to their Lassen-corrected equivalents. Although these findings are disappointing in terms of producing absolute rCBF values from SPECT data it seems likely that this will have little effect on the clinical use of HMPAO SPECT where the emphasis is likely to be on the detection of localized rCBF defects.

It is clear from this study that ^{99m}Tc-HMPAO images do indeed reflect rCBF, as measured by $C^{15}O_2$ PET, in the demented patient. It is not yet possible, however, to obtain rCBF values in absolute units from ^{99m}Tc-HMPAO SPECT without knowledge of the true rCBF in at least one reference region for each patient obtained using some other technique, probably PET. This situation may change, however, as more work is done on the kinetics of HMPAO uptake in the brain. Although the Lassen correction does improve the contrast in the

images, a similar subjective appearance can be obtained by applying a lower threshold to the linearly-corrected images.

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