Validation Studies of Iodine-123-Iodoamphetamine as a Cerebral Blood Flow Tracer Using Emission Tomography

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We studied the radioisotope iodine-123-iodoamphetamine ([^{123}I]IMP) and its performance in single-photon emission computed tomographic (SPECT) studies of cerebral blood flow (CBF). In seven normal volunteers, IMP/SPECT CBF measurements were calculated using a two-compartment model and were compared with the results of CBF measurements utilizing (O^{15})-H$_2$O and positron emission tomography (PET). Calculated mean PET CBF was 57.6 ml/100 g/min while the SPECT CBF value was 47.3 ml/100 g/min. The response of IMP/SPECT CBF to alterations in arterial PaCO$_2$ was studied in hypo-, eu- and hypercarbic subjects. SPECT CBF values showed a reactivity of 1.03 ml/100 g/min per mmHg P$_a$CO$_2$ change. These results show that the IMP/SPECT CBF technique may be used for quantitative imaging of CBF in man. They provide further support for IMP as a CBF tracer.

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Single-photon emission computed tomography (SPECT) is being applied increasingly to the study of normal and pathologic states. Like its counterpart, positron emission tomography (PET), this technique offers promise as a tool with which to image functional brain activity. To date, SPECT has been limited to cerebral perfusion studies, blood volume imaging, and pilot neuroreceptor imaging. While PET studies have been able to quantitate hemodynamic and metabolic functions, quantitative studies with SPECT have been limited. Several single-photon ligands have been reputed to function as perfusion tracers following parenteral administration in man. These include N-isopropyl-p-iodoamphetamine (IMP), and N,N,N trimethyl-N-[2-hydroxy-3-methyl-5 iodobenzyl] (HIPDM) both labeled with iodine-123 (^{123}I), as well as hexamethyl-propyl-eneamine oxime (HM-PAO) and L,L-ethyl cysteinate

dimer (ECD) both labeled with technetium-99m (^{99m}Tc). Earlier work by Kuhl et al. (1) and Matsuda et al. (2) sought to quantify cerebral blood flow (CBF) using IMP/SPECT by applying the uptake approach to CBF modeling. Using a camera with fixed crystals, Kuhl et al. (1) modeled the uptake of tracer over the first 5 min following injection, concluding from his data that the IMP is nearly completely removed by the brain after a single pass. Matsuda et al. (2) also modeled the tracer uptake during the early part of the time curve following injection. The limitations to these modeling approaches include the limits of current SPECT cameras and the pharmacology of IMP in particular. Rotating head SPECT cameras acquire data over relatively long periods, generally from 30–60 min, and rotating camera heads require that the profile of brain isotope activity remain fairly constant over this period if image reconstruction is to be accurate. The uptake of isotope may require longer than 5 min to stabilize following injection, and in the case of IMP, brain uptake increases over a 15–20 min equilibration phase before a relatively stable level of brain activity is achieved (1). Therefore, models enabling the calculation of CBF must take into consideration these latter alterations of cerebral activity.

We now report the results of studies in normal man designed to establish an efficacious model for CBF using IMP. The results of IMP/SPECT CBF results were compared to the more established three-dimensional technique of PET using the H$_2$^{15}O continuous infusion technique. We also report the results of studies designed to assess the response of IMP/SPECT to known modifiers of cerebral vasoreactivity.

MATERIALS AND METHODS

All procedures were approved by the Institutional Review Board of the University of Pennsylvania. Informed consent was obtained from each subject. Normal right-handed men between the ages of 18 and 35 yr were eligible for inclusion in this study. SPECT and PET local cerebral blood flow (LCBF) measurements were performed under baseline resting conditions and measurements of SPECT LCBF were also made under conditions of altered arterial pCO$_2$. Comparison of

baseline LCBF values for SPECT and PET were performed by doing both procedures in the same subject on the same day. An early morning PET study was followed within 1 hr by the SPECT study. This order of studies was necessitated by the very short half-life of ^{15}O (2 min) as compared to ^{123}I (13.1 hr).

Measurement of LCBF with PET

Measurement of cerebral blood flow with PET was performed using the equilibrium technique of Jones et al. (3) as modified in our laboratory for the continuous infusion of $H_2^{15}O$ (4). A catheter was inserted into the radial artery following local anesthesia (2% xylocaine infiltration) for the purpose of obtaining blood samples, and a second catheter was inserted into an antecubital vein for the administration of the radiolabeled tracers. The subject was placed into the PETT V tomographic scanner (5) at an angle 20° hyperextension to the orbital-meatal plane. Radiolabeled $H_2^{15}O$ (2–3 mCi/min) was infused into the venous catheter for 20–24 min. Eight minutes after the start of the infusion (when the brain activity had reached equilibrium), scanning began and continued to the end of the infusion. Arterial blood samples were obtained every 2.5 min throughout the infusion for the determination of the ^{15}O concentration in the whole blood. An arterial blood sample was also drawn and analyzed for blood gases and pH.

Calculation of CBF with $H_2^{15}O$ was made using the operational equation of Subramanyan et al. (6). For each slice, a large region of interest (ROI) was placed to obtain the total counts in the slice and a ROI around the 50% intensity level of the slice was placed to obtain the area of the slice (4). The count density was calculated as the total counts in the large ROI divided by the area determined by the 50% threshold and this count density was used to calculate whole-brain CBF. We have shown previously that with this scanner and a normal distribution of activity that the 50% threshold level corresponds well with the area of the brain as measured with nuclear magnetic resonance (4).

Measurement of CBF with SPECT

SPECT images of CBF were obtained using [^{123}I]IMP (Spectamine-Medi+Physics, Richmond, CA). IMP was injected as a bolus into an antecubital vein in a dose of 3.0 mCi. Prior to IMP injection, each subject drank a bolus of dilute Lugol's solution to block thyroid uptake of circulating free iodine. Blood samples were obtained throughout the study from the indwelling radial arterial catheter. Image acquisition was commenced 20 min after IMP injection. During this time the subject lay supine with eyes and ears unencumbered. Ambient noise and personnel activity was kept to a minimum and the laboratory was dimly illuminated via filtered daylight.

A Siemens Dual-Head Rota-Spect camera was used in this study. IMP imaging employed medium-energy parallel collimators because of trace ^{124}I impurity in the IMP dose. The IMP now commercially available is ^{124}I free, permitting the use of a low-energy collimator with a concomitant increase in count rate. Phantom studies using ^{99m}Tc-labeled tracers have demonstrated that this system has an effective image resolution of 12 mm using high-energy collimators. For ^{123}I, the system has a resolution of 19 mm using medium-energy collimators.

Quality control for image acquisition was performed prior to each study as follows. Orientation of the x and y axes of each camera head relative to the computer matrix (center of rotation study) was performed by scanning four point sources consisting of [^{99m}Tc]pertechnetate. This value was within ±0.5 pixels for each study. Flood correction for each camera head was performed by scanning a sheet source of uniform thickness filled with a saline solution containing 10.0 mCi of ^{99m}Tc for a total of 30 × 10^6 counts. Following the quality control data acquisition, the system was then peaked for ^{123}I automatically using the aliquot of IMP comprising the patient dose as a point source.

Arterial blood samples were analyzed as follows. Total isotope activity was measured in 0.5 ml aliquots of whole blood using a scintillation well-counter. A total of 17 samples, along with a 0.5 ml aliquot from the source, were counted in duplicate for each study. Seven arterial blood samples were obtained during the first two minutes postinjection in order to fit the peak of arterial blood activity. The concentration of unmetabolized IMP was determined in six blood samples by double extractions with octanol. The first wash mixed 2.0 ml of octanol saturated with normal saline with each 0.5 ml whole-blood aliquot. The second wash mixed 1.0 ml of supernatant with 6.0 ml of the octanol solution. The final 1.0 ml of supernatant was counted in the same well-counter as that used for the whole-blood samples.

The head curve of IMP uptake was monitored throughout the study by time sampling from one camera head aligned parallel to the sagittal plane of the brain during the 20-min uptake period. During scanning, changes in absolute counts due to camera head rotation occurred due to differential attenuation as the head is viewed from different directions. This angle dependency was removed by determining the counts versus angle plot at 30-degree increments after completion of the scan.

Tomographic scanning was performed so that each head rotated through 360° in 3-degree increments and was started 20 min after the IMP administration. Acquisition was for 30 sec per frame, with 120 frames total (~60 min) in a 64 × 64 matrix. A 12.0 by 1.4 cm single slice head source phantom filled uniformly with a saline solution containing 100 μCi of [^{123}I]IMP (to approximate brain tissue activity) was aligned parallel to the transverse plane. This phantom was scanned along with the brain and was displaced by 10–12 cm from the head. At the end of the study, two 0.5-ml aliquots from this source were measured along with the blood samples in the same well-counter. This procedure permitted calibration of the imaged tissue counts so that absolute tissue count densities could be generated for the quantitative analysis. Counting was done immediately following completion of the study and was decay corrected for the half-life of ^{123}I (13.1 hr).

Reconstruction of the tomographic images was performed in a 64 × 64 matrix. Quantitative analysis of the SPECT data was performed on one-pixel thick image slices (6 mm), reconstructed using a Butterworth filter with a cutoff frequency of 0.04 cycles/mm, and an attenuation coefficient of 0.12 cm^{-1} fitted to the 40% edge of cerebral activity in the x, y and z planes. On average 2 × 10^6 counts were acquired for each study.

Modeling of LCBF with IMP and SPECT was based upon a two-compartment model (2). The tracer IMP was assumed

to be freely diffusible from blood to brain with a constant rate of backflux. The following expression was used:

$$\text{Flow} = \frac{\int_{20}^{T} C_b(t)dt}{e^{-kT} \int_{0}^{T} C_a(t)E(t)e^{kt}dt},$$

where:

$C_b(t)$ = brain ^{123}I concentration at time t
$C_a(t)$ = arterial blood ^{123}I concentration at time t
$E(t)$ = extraction fraction at time t
k = rate constant for backflux diffusion
T = time at the end of SPECT scanning.

The extraction fraction $E(t)$ was determined as described above. It was assumed that CBF remained constant throughout the entire measurement period and that the head counts obtained from a single camera head after correcting for camera head rotation were representative of brain activity. With these assumptions, the equation above was used to obtain the best value for the back diffusion constant, k and CBF by a least-squares procedure.

Experimental Protocols

Cerebral blood flow was measured in seven normal male volunteers (19–34 yr of age) with both PET and SPECT. In order to examine the ability of [^{123}I]IMP SPECT to measure changes in CBF under conditions of altered arterial $PaCO_2$, additional subjects were studied. Hypocapnia was induced by having the subject hyperventilate to a fixed end-expiratory CO_2 with the hyperventilation controlled by continuous monitoring of the end-expiratory CO_2. Hypercapnia was induced by ventilation with a 7% CO_2 in air mixture administered through a non-rebreathing system. This vasoreactivity study included two of the subjects of the PET-SPECT comparison study that had a second blood flow measurement made with [^{123}I]IMP SPECT at an altered arterial $PaCO_2$, and seven additional subjects that had either a single SPECT measurement or two SPECT measurements. Four CBF studies were undertaken during hyperventilation, four during hypercapnia, and 12 at a normal $PaCO_2$.

The IMP was injected 8–10 min following stabilization of the end-expiratory CO_2 readings. Arterial blood gases were obtained at the time of [^{123}I]IMP injection and 2.0 min postinjection. The average of these two $PaCO_2$ values was used in calculating cerebral vasoreactivity.

RESULTS

Seven normal volunteers underwent PET measurements of CBF while SPECT was performed on sixteen. Data representative of the time course of the arterial concentration of [^{123}I]IMP and head curve of ^{123}I activity from one subject are shown in Figures 1A and 2, respectively. As can be seen, the arterial ^{123}I concentration peaks and then falls very quickly following the administration of the [^{123}I]IMP. Figure 1B shows the mean extraction fraction data for all subjects. One minute following injection the extraction was 0.87 ± 0.06 and by 30 min it had fallen to 0.63 ± 0.056. The head curve increases rapidly after IMP injection and
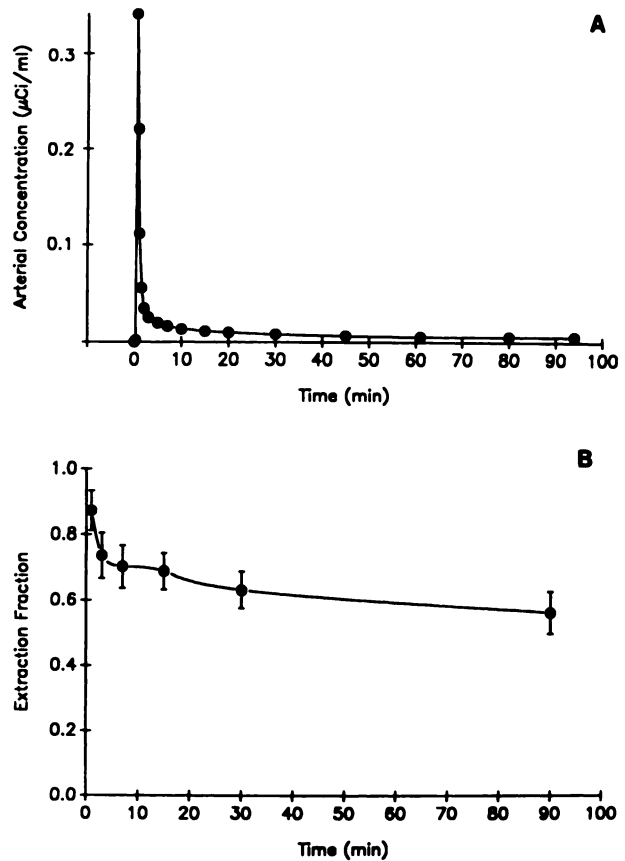
FIGURE 1
(A) A typical arterial concentration curve following a bolus i.v. injection of 3 mCi [^{123}I]IMP. This curve has been corrected for the nonlipophylic fraction that cannot cross the blood-brain barrier. (B) The extraction fraction data of ^{123}I in the blood for all subjects studied. Data shown are mean ± s.d.

then continues to rise very slowly. By 30 min, it has reached a plateau and begins to decrease very slowly.

The results of the SPECT-PET comparison are presented in Table 1 and Figure 3. CBF (mean ± s.d.) for PET was 57.6 ± 12.3 ml/100 g/min compared with
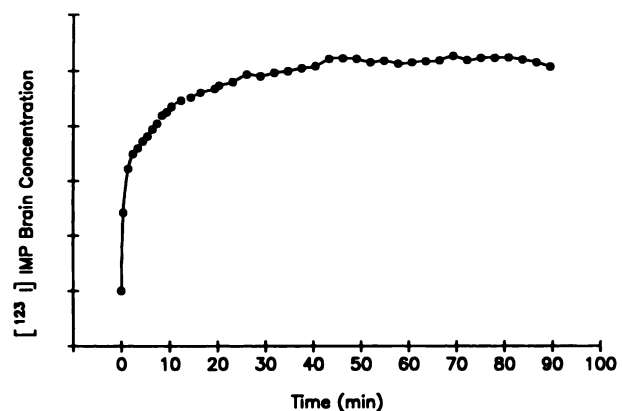
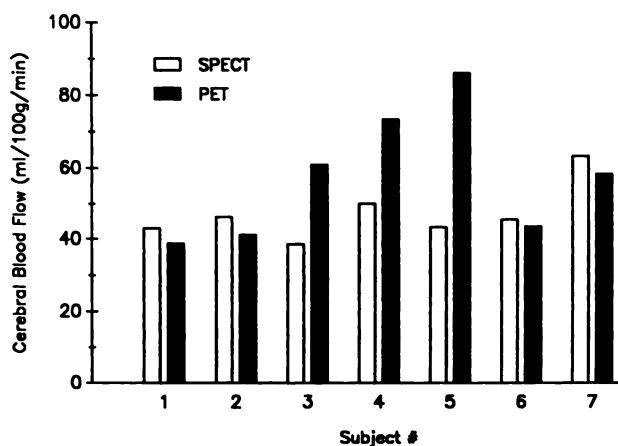**FIGURE 2**
The time course of ^{123}I concentration in the head following an i.v. bolus administration of [^{123}I]IMP. The head activity is relatively stable by 20 min after tracer administration.

TABLE 1
Comparison Between Whole-Brain Blood Flow Obtained with SPECT and with PET

Subject	Whole-Brain blood flow ml/100 g/min		P_aCO_2 mmHg	
	SPECT	PET	SPECT	PET
1	43.0	38.7	41.0	40.6
2	46.3	41.2	40.7	42.0
3	38.6	61.0	45.2	45.9
4	50.2	73.6	44.5	44.5
5	43.5	86.4	40.7	39.3
6	45.7	43.7	40.1	39.6
7	63.6	58.6	43.7	45.2
Mean	47.3	57.6	42.3	42.4
s.d.	7.4	16.5	2.0	2.5

47.3 ± 7.4 for SPECT. These mean CBF values are not significantly different (Student's t-test) although the PET and SPECT CBF values were not correlated with one another. Mean $PaCO_2$ during the PET study was identical to that during the SPECT study.

The results of the IMP/SPECT studies during hyperventilation and during CO_2 inhalation are presented in Figure 4. Four additional subjects were studied under resting baseline conditions while four subjects were studied under hypercarbic, and four under hypocarbic conditions. In the total group of eleven normal subjects studied under eucarbic conditions, mean CBF was 51.0 ± 5.7 ml/100 g/min. In the four hypocarbic subjects, mean CBF was 39.6 ± 3.5 ml/100 g/min while in the four hypercarbic subjects mean CBF was 70.3 ± 5.3 ml/100 g/min. Over the range of hypo-, eu-, and hypercarbia (~31 torr $PaCO_2$, see Fig. 4), IMP/SPECT CBF measurements exhibited a reactivity of 1.03 ml/100 g/min per mmHg P_aCO_2.
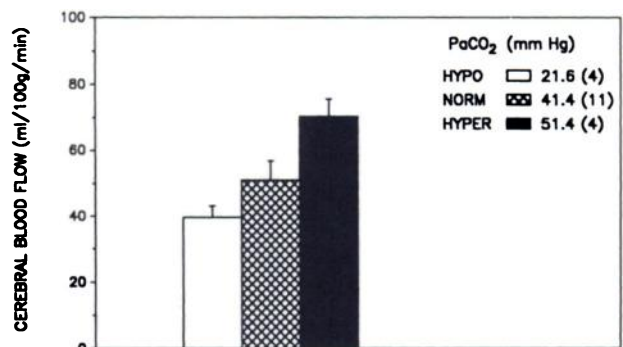
The backflux rate constant was 0.011 min^{-1} (range 0.008–0.015 min^{-1}).

DISCUSSION

The values for CBF obtained in this study agree well with other values in the literature as obtained with a number of techniques. The original studies of Kety and Schmidt (7) using the N_2O technique yielded a mean CBF of 54 ± 12 ml/100 g/min (s.d.) in young male volunteers, while using the same technique, but with [85]Kr as the tracer, Lassen and Munck (8) obtained a value of 52 ml/100 g/min. The value of CBF as obtained with the clearance of ^{133}Xe following an intracarotid bolus injection is 50–53 ml/100 g/min (9,10). Cerebral blood flow has been measured with PET using equilibrium breathing of CO_2 labeled with [15]O (6,11) as well as with continuous infusion of H_2[15]O (4). A mean whole-brain CBF of 49.8 ml/100 g/min was obtained in the study of Frackowiak et al. (11), while Jones et al. (4) obtained a value of 62 ml/100 g/min. Using a bolus administration of either C[15]O_2 as a single breath, or H_2[15]O as an intravenous injection, and a series of PET scans over the next 10 min, Huang et al. (12) measured whole-brain blood flow of 42 ml/100 g/min. These values agree quite well with the value of 57.6 ± 16.5 ml/100 g/min obtained in the present study.

Much less data exists on the quantitative aspects of ^{123}I-isopropyliodo-amphetamine as a tracer for cerebral blood flow in SPECT. Shortly after Winchell et al. (13, 14) suggested that ^{123}I-amines may be useful as cerebral perfusion agents, Kuhl et al. (1) examined [^{123}I]IMP as a quantitative blood flow tracer. They found an excellent correlation in a series of dogs between blood flow as determined with [^{123}I]IMP and that measured with radiolabeled microspheres. Using the Mark IV scanner, they obtained a mean whole-brain blood flow of 47.2 ± 5.4 ml/100 g/min in a series of five normal

FIGURE 3
A comparison, subject by subject, of the CBF data with [^{123}I] IMP and SPECT (open bars) and with H_2[15]O and PET (closed bars). The agreement is quite good except in three subjects where the blood flow determined with PET is higher than that determined with SPECT.

FIGURE 4
The effect of alterations in arterial carbon dioxide tension (P_aCO_2) on whole-brain blood flow as measured with [^{123}I]IMP. The sensitivity to CO_2 is 1.03 ml/100 g/min per mmHg. Data shown as mean ± s.d. The numbers in parentheses are the numbers of animals in each group.

human volunteers. In these studies, brain tissue activity was obtained by scanning the head over the first 8.3 min following the bolus injection of [123I]IMP and a microsphere model (i.e., a model assuming that none of the extracted activity is lost during the period of scanning) was used to calculate CBF. Matsuda et al. (2) used a dual-head rotating gamma camera system and in four normal volunteers obtained a mean whole-brain blood flow of 58 ± 2 ml/100 g/min (mean ± s.e.m.). In these studies, scanning started immediately after injection of the [123I]IMP and continued for only 5 min. The input was determined by counting the blood sample obtained from a continuous arterial blood withdrawal over the duration of the scan.

The majority of other studies in which [123I]IMP was used as a CBF tracer, including studies in stroke (15–20), tumors (15,21–22), epilepsy (23), and dementia (24–26) did not involve quantification of blood flow and so cannot be directly compared to our data.

In this study, the calculated blood flow increased from 39.6 ml/100 g/min to 70.3 ml/100 g/min as arterial carbon dioxide tension increased from 21.6 mmHg to 51.4 mmHg. This represents an increase in blood flow of 1.03 ml/100 g/min per mmHg, which compares favorably with that obtained in previous studies over a similar carbon dioxide tension range (1.4 ml/100 g/min per mmHg) (27), (0.95 ml/100 g/min per mmHg) (28), (1.11 ml/100 g/min per mmHg) (29), and (1.34 ml/100 g/min per mmHg) (30). The ability of IMP to quantitatively measure changes in CBF induced by alterations in arterial blood carbon dioxide tension is evidence that IMP is a quantitative CBF agent at least under physiologic conditions. This confirms data obtained in animals (31–33), which has also demonstrated the validity of IMP as a quantitative blood flow tracer.

Although whole-brain blood flow obtained with [123I] IMP and SPECT was not significantly different than that obtained with H2 15O and PET, the blood flow using IMP (47.3 ml/100 g/min) was almost 20% less than that obtained with PET (57.6 ml/100 g/min). This may be due to less than perfect extraction of IMP by the brain. It has been shown in the monkey that only ~92% of the injected dose is extracted in the first pass (1). If this is also true in man, then the mean blood flow obtained with IMP in the seven subjects in which CBF was measured with both H2 15O and IMP would be 51.4 ml/100 g/min which is within 10% of that obtained with H2 15O and PET. In the 11 normocapnic subjects in which CBF was measured with IMP, the whole-brain CBF would be 55.4 ml/100 g/min.

These studies demonstrate that quantitative CBF can be measured with SPECT using 123I-isopropylamphetamine as a tracer. It is necessary, however, to use an appropriate model that corrects for the loss of tracer from the tissue, and to correct the arterial blood sample concentrations for the fraction that cannot be extracted from the blood.

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