Regional Quantitative Noninvasive Assessment of Cerebral Perfusion and Function with N-Isopropyl-[^{123}I]*p*-Iodoamphetamine

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Although several reports on the clinical usefulness of N-isopropyl-[^{123}I]*p*-iodoamphetamine (IMP) in the diagnosis of cerebral disease have appeared in the literature, quantitative, noninvasive measurements of regional cerebral blood flow with this method pose difficulties because cerebral IMP uptake not only depends on cerebral perfusion but also on cerebral function. Rather than trying to develop a method to measure cerebral perfusion with IMP, we have chosen to test a method to quantitatively evaluate planar and emission computed tomographic (ECT) studies by comparing the data obtained in patients with established pathology (n = 51, number of scans = 54) with the data obtained in a group of normal individuals (n = 10, number of scans = 11). Using this method, absolute cerebral IMP uptake (counts/pixel/mCi/min) and planar anterior right-left ratios were obtained. Also measured were right-left ratios obtained from 12 paired regions in three ECT slices. In the control group, we found an IMP uptake of 35.6 ± 4.3 cts/pixel/mCi/min and right-left ratios around 1.00 (s.d. <2%). The evaluation of the patients cerebral IMP uptake asymmetries relative to the normal standard values is a useful adjunct to qualitative image analysis in assessing the presence and severity of disease, as qualitative analysis is prone to false-positive and negative results. Cerebral IMP uptake as measured in cts/pixel/mCi/min is abnormal only in severe cerebral disease and therefore generally a less helpful parameter.

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Recently, N-isopropyl-[^{123}I]*p*-iodoamphetamine (IMP) has been introduced for clinical use in Europe, and is now commercially available through various suppliers. Among clinicians, this substance has generated considerable enthusiasm because it is the first compound which permits mapping of regional cerebral blood flow (rCBF) with standard nuclear medicine equipment (*1*). Since the compound passes the blood-brain barrier and is taken up and retained to a large extent by brain cells (*2,3*) by a not yet fully elucidated mechanism, its uptake is a function not only of rCBF but also of the characteristics of the perfused tissue (*4*). Thus, cerebral perfusion/function may be assessed at the tissue level distal to the "shunting" system of the circle of Willis. The pharmacokinetics of the substance seem to be such that the cerebral perfusion and uptake state at the time of injection and the first few minutes thereafter is mapped. This map changes little for 1 to 2 hr (*4,5*), even though the activity distribution progressively moves from a flow dependence to a partition coefficient distribution dependence (*3,6*). Hence, extended quasi "steady state" data taking is possible. This is needed, particularly if emission computed tomography (ECT) with a rotating camera system is to be performed.

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The usefulness of IMP has been documented in the diagnosis and follow-up of cerebral disease. In particular, early reliable infarct diagnosis is possible (*1*). Patients with TIAs may show IMP deficits on the affected side (*7*), and serial evaluation of patients undergoing cerebrovascular surgery is possible (*1*). In epilepsy, IMP studies may confirm EEG findings as areas of increased IMP uptake, and may be useful in the localization of an uncontrollable epileptic focus prior to surgery (*8*). Cerebral mass lesions are usually well visualized (*9*), but after transmission computed tomographic (TCT) studies there rarely remain diagnostic questions which can be successfully answered with an IMP study.

Although several studies have appeared in the literature concerning qualitative IMP image interpretation, detailed quantitative assessment of rCBF with IMP has only been explored by Kuhl et al. (*3*) using a four sided array detector ECT system and arterial input sampling. The aim of the present study was to explore possibilities to noninvasively quantify cerebral IMP uptake to see how much quantitative information can be obtained after i.v. injection of IMP without arterial sampling. Anterior planar as well as ECT images were acquired and the following information obtained: (a) the cerebral I-123 content at the beginning and the end of the study, (b) the I-123 uptake in the cerebral hemispheres as determined by the count rate per activity injected, and (c) the ratio of right to left hemispherical I-123 content in fixed regions of interest (ROIs) from the anterior planar images as well as from ECT slices. In the latter case, the regions were matched to the cerebral vascular perfusion territories as taken from recent morphological work (*10*).

PATIENTS, MATERIALS, AND METHODS

Patient selection

A total of 65 studies were performed in agreement with the referring hospital physicians, constituting the institution review board committee, on 61 patients and volunteers after informed consent had been obtained. The various disease states of the patients are listed in Table 1. Ten normals were studied with 11 scans. These were seven volunteers, and two young patients who had had transient unclear cerebral states half a year and 2 wk prior to scanning, respectively, and showed a normal TCT and EEG examination, and one elderly patient with carcinoma of the prostate and paralysis of the abducent nerve due to bony metastases to his skull. Thirty-two patients with cerebrovascular disease (CVD) formed the largest patient group, studied with a total of 35 scans. In this group, 24 patients with insults or bleeds except two had pathological TCT examinations either prior to or after IMP scanning. CVD patients without sustained neurological deficit were diagnosed based on the clinical presentation, and the diagnosis confirmed by angiography in five and by sonography in two cases. The epileptic patients studied all had focal symptoms and EEG signs prior or during the IMP study: two had an epilepsia partialis continua, one a myoclonic syndrome, one showed only partial seizure control after a Grand Mal seizure had been treated with phenytoin, and three had had seizures 1 to 5 days prior to the IMP scan. Multiple sclerosis patients were diagnosed based on their clinical presentation and showed pathologically evoked potential responses. Space occupying lesions were all initially diagnosed by TCT.

TABLE 1
Patients and Their Diseases

Disease	Patients	Scans
Normals	10	11
Multiple sclerosis	5	5
Epilepsy	7	7
CVD		
Fresh insults and bleeds	13	13
Old insults and bleeds	11	11
No sustained neurological deficits	8	11
Space-occupying lesions		
Tumors	3	3
Post tumor removal	3	3
Post abscess drainage	1	1
Total	61	65

Patient preparation

Injected for imaging were 4–6 mCi (148–222 MBq) N-isopropyl-[^{123}I]*p*-iodoamphetamine which had been produced by the (p,5n)-reaction and thus were free of I-124 and contained at most 2% of I-125.* Prior to injection, the patient was given ~300 mg of sodium perchlorate to block the thyroid. Injection was done in a quiet room with dimmed lights. The patient was in a supine position and had his eyes closed so that external stimuli during injection were minimized. After antecubital IMP injection, the patient rested quietly for 30 min, and was then placed on an ECT table with a special lucite head holder, which served to position the patient's head with the orbitomeatal line perpendicular to the camera surface. Fitted with a high efficiency, low-energy collimator† the camera head was adjusted so that data acquisition could take place as close to the patients brain as possible, depending on the length of the neck and the width of the shoulders (variation from 15 to 25 cm object distance reduced the count rate in a fixed ROI by about 10%).

Data acquisition and analysis

The camera system‡ was equipped with a sophisticated computer controlled inhomogeneity correction§ and set to 159 keV with a 15 or 20% window (counts at 15% window = 0.93 × counts at 20% window). Such inhomogeneity correction is very important because small

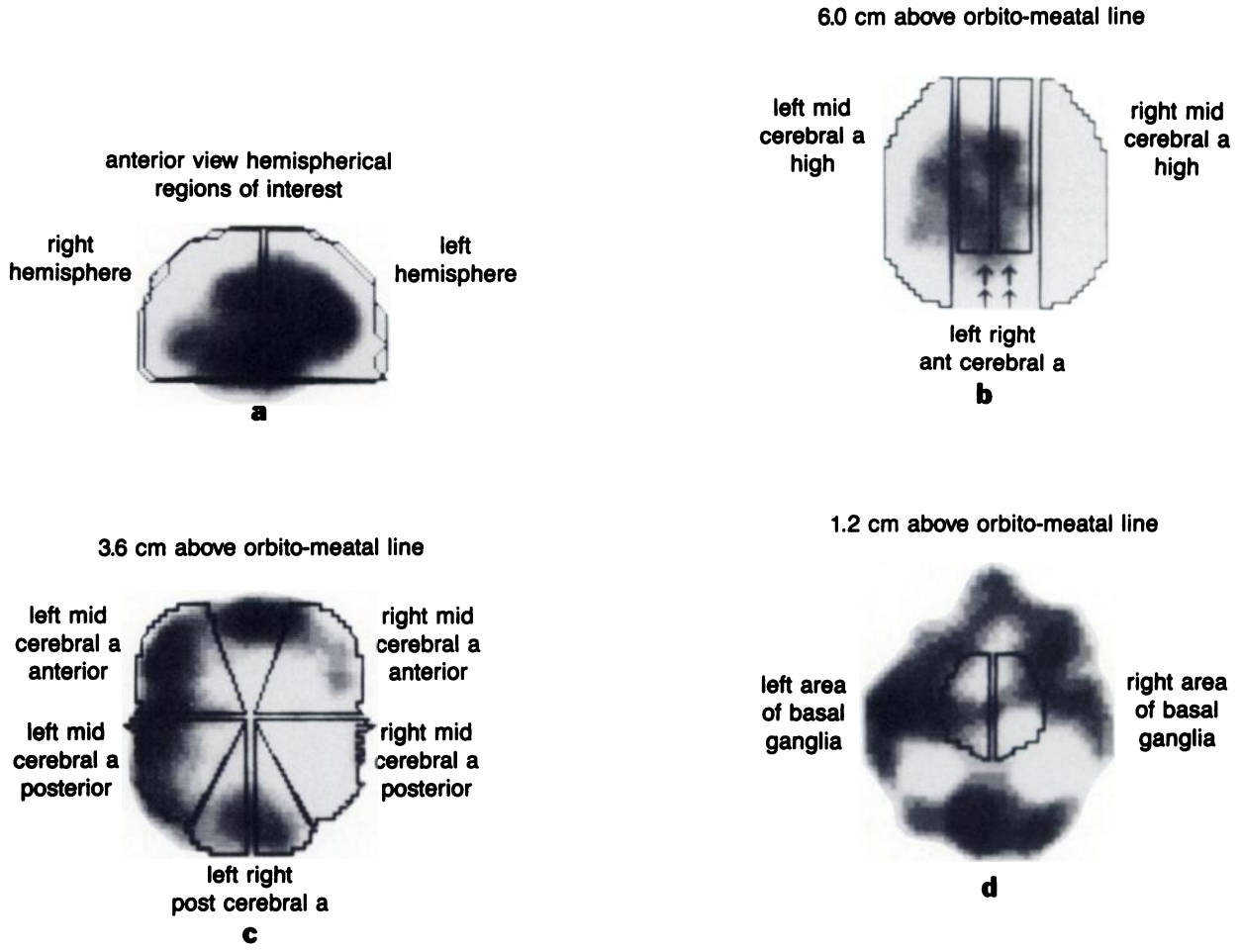

FIGURE 1
Regions of interest as used for quantitative analysis of IMP studies. In Fig. 1a, anterior scan of patient with occlusion of middle cerebral artery is shown. Figs. 1b, 1c, and 1d show regions for right-left ratio computation in three ECT slices of same patient. Note right sided activity deficit coincident with right middle cerebral artery regions

variations in cerebral IMP content may already signal pathology as discussed below. ECT data acquisition required 60 projections 6° apart into a 64 × 64 byte mode matrix.[1] Data acquisition time was 25 or 35 min. The total number of counts per projection was 40,000–50,000, thus the entire study contained 2.4–3.0 × 10^6 counts.

The raw data were reconstructed by the method of filtered backprojection, using a Shepp-Logan filter (*12*). Slice thickness was two pixels (1.2 cm). Care was taken to position the six top slices such that the lowest slice contained information from the base of the brain. This was initially accomplished by placing a point source at the level of the patients orbitomeatal line when taking an anterior planar image. As expected, this position was consistently found to coincide with the pronounced activity drop at the base of the brain so that accurate slice positioning was possible even without the use of a point source. Proper slice position was rechecked in the reconstructed images by noting the presence of activity in the region of the basal ganglia in slice 5 and 6.

For qualitative image interpretation the reconstructed ECT images were subject to a nine-point smoothing, a zooming procedure (linear magnification by a factor of 2) and a nearest neighbor interpolation to a final matrix size of 128 × 128 pixels. The spatial resolution of the reconstructed images was about 2 cm as determined from a phantom experiment with various objects filled with ~200 μCi/l of I-123 suspended in a water tank containing 400 μCi of I-123/1.

For quantitative analysis of the planar images, fixed total brain, and symmetrical right and left hemispherical ROIs were drawn (Fig. 1a). These regions as well as the ECT regions were drawn only once for the analysis of all studies and saved in a data file, as we believe that the variability in redrawing the ROIs for each patient is larger than the variability in each patient's cerebral anatomy. From the ROIs in the planar images the counts per pixel, mCi, and minute were determined. Multiplication with the patient's body surface area, as determined from weight and height measurements using standard tables, was used to correct for variations in the

fraction of the cardiac output perfusing the brain in different size people. This procedure is justified as follows. If it is assumed that the cerebral blood flow is independent of the patient's size, and the cardiac output scales with the body surface area (*13*), a larger fraction of the injected IMP is bypassing the brain in large than in small individuals, thus reducing the IMP delivered to the brain. Multiplication with the patient's body surface will correct for this. Also determined were right-left (R/L) count ratios and the ratio of counts at the end compared with the beginning of the ECT study to rule out significant cerebral I-123 content changes during a study.

For quantitative analysis of the ECT images the first six slices were added in pairs resulting in three slices of 2.4 cm thickness above the base of the brain. Each of the three slices was smoothed once (nine point). Six pairs of ROIs, matching the perfusion territories of the large cerebral vessels had been predrawn and saved in a data file. The shape of these regions had been chosen on the basis of recent morphological work (*10*). Even though our slices and the ones in Ref. *10* differ in inclination by about 15°, our ROIs still reflect the perfusion territories adequately, as they are fairly large. The six pairs of ROIs were superimposed on each patient study by moving the study on the computer screen until optimum superposition of all the ROIs with the limits and the midline of the brain in the three slices was obtained. The respective slices with their corresponding ROIs are shown in Fig. 1b, 1c, and 1d in an example of a patient with an old insult to the right middle cerebral artery (craniocaudal representation). From the count values in these regions, R/L ratios R_i (i = 1, . . . ,6) were computed for each patient. Furthermore a "Cerebral Asymmetry Index" (ASI) was defined as

$$ASI = \sum_{i=1}^{6} ((R_i - R_{i_0})^2)^{1/2}$$

where R_{i_0} is the mean normal value for the ith ratio. This index is a compound deviation of the patients R/L ratios from the normal values. It was found to be a useful quantity to obtain a summary assessment of asymmetric IMP uptake.

RESULTS

First, the cerebral IMP content was measured in a planar anterior scan before and after the ECT study to assess whether concentration changes in cerebral IMP were small enough during ECT data acquisition to permit a reconstruction free of artifacts. In the first three volunteers (not part of this study), ECT studies were begun at 10 and ended at 35 min after IMP injection. IMP content after the study was 110 ± 2% compared with the content before the study. Thus, IMP content increased significantly. It was therefore decided to start data acquisition at approximately 30 min postinjection. In a total of 60 patients the IMP content at 60 to 80 min was found to be 96 ± 3% of that at 30 to 40 min, a barely significant decrease between the beginning and the end of data acquisition (see also Ref. *7*).

Second, the mean normal value of the count rate per pixel and mCi (T) with its s.d., and this quantity multiplied by the body surface area were computed and are given in Table 2. The relative magnitude of the s.d. of the latter quantity is smaller than the former. In patients with established cerebrovascular disease, the quantity T is lower at 50.8 ± 12.2 cts/pixel/mCi/min × body surface area (n = 24) than the normal value of 63.4 ± 5.3 (n = 11) with a significance of $p < 0.01$ (Student t-test). Other patient groups show no significant difference from the normals. Figure 2 shows a plot of the absolute IMP uptake T measured on anterior planar projections together with a ± 1 s.d. confidence interval as a function of age. No statistically significant age dependence of T is found, as even in normals there is a large scatter in T. Also, only patients with severe CVD or mass lesions are found to have a decreased T value.

Third, R/L ratios of IMP uptake in the hemispherical planar and ECT regions of Fig. 1 were computed for all patients. The normal values are listed in Table 2. Ratios are given for the right compared with the left hemisphere, and the territories of the anterior cerebral artery, the middle cerebral artery in three different segments and the posterior cerebral arteries as well as the basal ganglia. Note how close the R/L ratios are to 1 with very narrow standard deviations between 1.5% and 2.0%. Further note a slight preference of IMP for the right hemisphere as reflected by the mean R/L ratios which are slightly above 1. However, this preference reaches statistical significance (to 1 s.d.) only for the anterior

TABLE 2
Normal Values: N-Isopropyl-[^{123}I]*p*-Iodoamphetamine Brain Distribution

N = 11 (5 F, 6 M)	Mean	s.d.
Age	34	15
Planar imaging		
Brain: R/L ratio	0.999	0.017
cts/pixel/mCi/min total brain (x body surface area)	35.6 (63.4)	4.3 (5.3)
cts/pixel/mCi/min right hemisphere (x body surface area)	35.4 (63.2)	4.1 (6.0)
cts/pixel/mCi/min left hemisphere (x body surface area)	35.7 (63.9)	4.4 (6.6)
ECT imaging R/L ratios		
Anterior cerebral artery	0.998	0.015
Middle cerebral artery (cranial)	1.008	0.019
Middle cerebral artery (anterior)	1.018	0.015
Middle cerebral artery (posterior)	1.009	0.012
Posterior cerebral artery	1.003	0.019
Area of basal ganglia	1.009	0.019

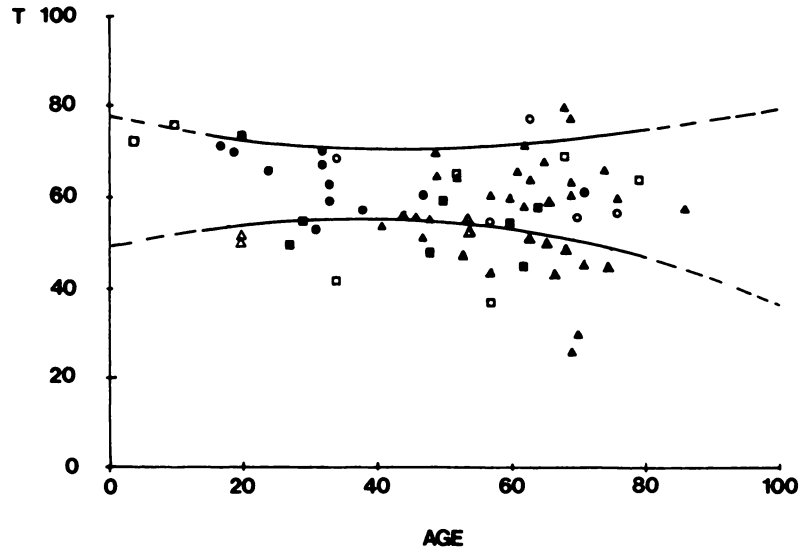

FIGURE 2
Absolute cerebral IMP uptake T measured in anterior planar view in counts/pixel/mCi/min X body surface area as function of age. Curved lines indicate ± 1 s.d. confidence interval and normal range. (●) Normals, (○) Multiple sclerosis, (□) Epilepsy, (■) Mass lesions, CVD (▲) Permanent lesion, (△) Transient neurological symptoms. There is no statistically significant age dependence in IMP uptake

perfusion territory of the middle cerebral artery. In all patients with ischemic CVD who show morphologic abnormalities pointing towards a perfusion territory (TCT or angiography), the corresponding R/L ratios appropriately reflect pathology and are only pathological in the affected area. Similar findings are obtained with mass lesions. In three of seven epileptics (without seizure activity during the IMP study), presumed but not certain, foci found by qualitative study interpretation show normal R/L ratios.

Finally, an asymmetry index (ASI), as defined in the Methods section, was computed to obtain a summary index of cerebral I-123 uptake asymmetry. In Fig. 3, the ASI of our patients is plotted against the patients T value. Normals and patients with multiple sclerosis are found mostly in the upper left hand corner of the figure, where the dashed lines delineate a box of ±1 s.d. around the normal ASI and T values. Patients with CVD and mass lesions are mostly found to the right and downwards as a result of their asymmetric cerebral perfusion and, in some cases, their reduced IMP uptake. But even some CVD patients are found to have normal ASI indices (and equivocal qualitative findings on IMP scans). Epileptics are found close to the normal zone, although the ones with seizure activity during the scan show pathological ASIs. The mean and s.d. of the ASI for the various disease groups is given in Table 3 together with the p value, comparing the respective disease group to the normals. These results confirm the impression obtained from Fig. 3, that significant uptake asymmetries occur in patients with established CVD and cerebral mass lesions. The statistical significance of the ASI for CVD patients with transient symptoms is tentative and no significance is found for the other patient groups.

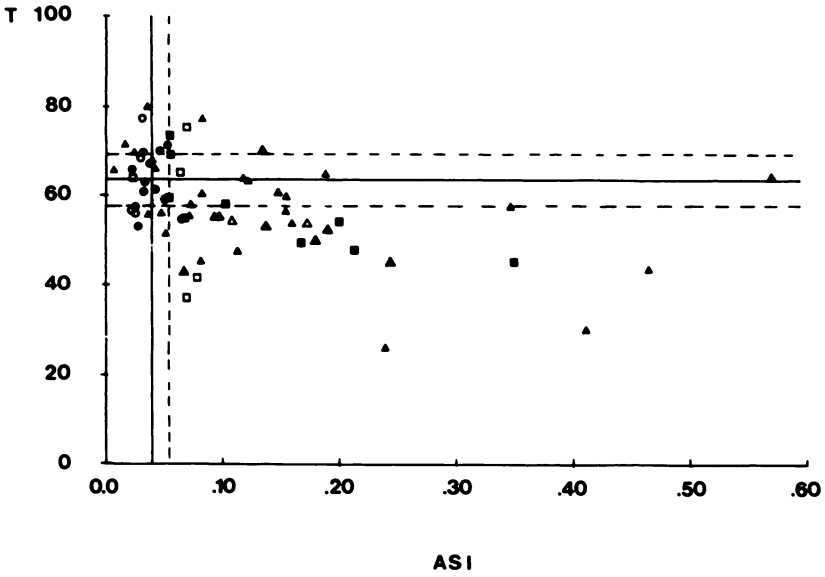

FIGURE 3
Absolute IMP uptake T compared with Asymmetry index ASI (see text). Mean and s.d. for both parameters are given. Normals fall into box limited by dashed lines in left upper area of figure. (●) Normals, (○) Multiple sclerosis, (□) Epilepsy, (■) Mass lesions, CVD (▲) Permanent lesion, (△) Transient neurological symptoms

TABLE 3
Asymmetry Index in Various Patient Groups

Disease	Number of scans	Mean	s.d.	p value
Normals	11	0.0385	0.0125	—
Multiple sclerosis	5	0.0338	0.0150	N.S.
Epilepsy	7	0.0633	0.0259	N.S.
CVD				
Established defect	24	0.169	0.150	<0.05
No sustained defect	11	0.0849	0.0365	<0.10
Space-occupying lesions	7	0.157	0.105	<0.025

DISCUSSION

The results of our kinetic studies are in agreement with other observations (*1*), where it was found that global cerebral IMP content increases rapidly at first and reaches a plateau at about 30 min after injection, lasting for at least 1 hr. However, the presence of such a plateau does not exclude IMP "redistribution" phenomena within the brain during this time, and such redistribution has in fact been observed in brain (*14*) and also in lung tissue (*7*). Nevertheless, over typical ECT acquisition times of 20 min the cerebral IMP distribution may be sufficiently stable to allow for reconstruction without kinetic artifacts.

The data in Fig. 2 show that IMP content is in itself not a good disease classifier, even though the mean IMP uptake (e.g., patients with CVD) is lower than normal. Whether the variation in IMP uptake even in normals is physiologic—other methods for measuring cerebral perfusion and function also show some variation (*15*)—or mainly due to variable IMP uptake and release by the lung in different patients, cannot be decided from our data. The reduction of this variability after multiplication with the patient's body surface suggests that part of the variability is due to a variable fraction of the cardiac output perfusing the brain in different size people. This view is supported by the finding that the two children examined had very high absolute IMP uptakes, but multiplication with the body surface area brought the uptake values into the upper end of the normal range (Fig. 2).

Quantification of right-left asymmetries in ECT slices using our approach is useful. In fact, qualitative evaluation of ECT slices also hinges mainly on a right to left comparison, but because of the very narrow s.d. of the R/L ratios (cf. Table 2), qualitative analysis may easily produce false-positive (or negative) results. Because we expect IMP studies to be of primary importance in the evaluation of CVD, the ECT ROIs in our analysis are drawn to match perfusion territories. In all cases with nonhemorrhagic CVD and clearcut evidence of disease the R/L ratios were abnormal for the affected territory. Perfusion territories of the other areas showed pathological R/L ratios only when the principal pathological R/L ratio was very abnormal, probably as a result of partial volume averaging. In patients with known CVD where the qualitative image interpretation was equivocal, the R/L ratios as well as the asymmetry index greatly helped to assess pathology, and three of these patients were pathological in the IMP study only based on abnormal quantitative evaluations, with the R/L ratios properly indicating the diseased perfusion territory. On the other hand, the scans of two normal volunteers, studied after the normal values were obtained, showed abnormal qualitative scans but this was not supported by quantitative analysis. The R/L ratio and the ASI are particularly useful when serial scans are used to monitor the patients response to therapy. In three cases with proven CVD who were scanned twice, the changes in the R/L ratio and the ASI closely matched the clinical course. One patient underwent IC-EC anastomosis. Preoperatively R/L = 1.11 and ASI = 0.142, whereas 5 wk postoperatively R/L = 1.042 (MCA anterior territory) and ASI = 0.0675.

Another patient showed similar improvement after a transient right hemisyndrome following a left MCA spasm with marked clinical improvement. A third patient showed no postoperative improvement after endarterectomy and on repeat angiography a persistent lesion was found. This was matched by a virtually unchanged IMP scan.

Even though the ASI is not a regional cerebral uptake index as the R/L ratios, but rather a compound asymmetry index, it may be somewhat more sensitive than the R/L ratios, as a subtle asymmetry in the entire perfusion territory of one MCA may leave the R/L ratios in a borderline normal range, but the ASI is pathological. Furthermore, the ASI lends itself to simple graphic representation and statistical analysis. Even though ASI (as well as R/L ratios) will miss symmetric perfusion decreases or increases, perfectly symmetric changes in CVD seem to be a rare event. Admittedly neither the magnitude of a pathological R/L ratio nor ASI will always show a positive correlation with the severity of disease. However, in our experience all of the severely ill patients had also strongly pathological R/L ratios and ASIs.

For evaluating other disease categories, the computation of R/L and ASI appears again to be useful, but the choice of perfusion territory matched ROIs offers no particular advantage for such cases. All patients with acute seizure activities during IMP injection showed pathological numbers, but as a group the ASI values were not significantly different from the normals. Patients with multiple sclerosis showed no noticeable quantitative abnormalities, a finding which is consistent with the pathophysiology of this disease.

As compared to the ECT R/L ratios, hemispherical ratios were not useful in the quantitative evaluation of the IMP studies because they are too crude an average of regionalized disease.

It is of interest to note that there may be physiological reasons for slightly more IMP uptake into parts of the right hemisphere compared to the left, which in frontal areas is of the order of 2%. There have been observations of a slightly larger right hemisphere (*16*,*17*). A recent study using TCT and PET suggests, again, that an asymmetry in hemispherical size, favoring the right exists (*18*). However, it cannot be ruled out that this finding in our IMP studies is an artifact due to either IMP redistribution during the study or due to a slightly position-dependent camera sensitivity.

CONCLUSIONS

N-isopropyl-[^{123}I]*p*-iodoamphetamine is a promising radiopharmaceutical, which is useful in assessing cerebral vascular disease and possibly epileptic disease (*1*,*4*,*8*). In our opinion, it should be used early in the diagnostic workup of patients with CVD, in particular, when cerebrovascular surgery is considered, due to the uniqueness of the information provided: the noninvasive representation of cerebral blood flow and the functional state of the brain tissues (PET provides similar information, but requires formidable logistics usually not available). It is too early to say whether this method will supplant radionuclide angiography, but in cerebrovascular disease the method appears sensitive. In epilepsy the method may be useful (*8*), but in most cases little is gained from better localizing the seizure focus. The additional information obtained from IMP studies after TCT in the diagnosis of brain tumors is at best marginal; the lack of IMP uptake even in vascular tumors is a clear demonstration that cerebral IMP uptake is not only a function of perfusion but also of IMP tissue extraction. Because of the uncertain nature of the IMP clearance mechanism by the human brain and the primary usefulness of IMP studies in patients with CVD we have limited our quantitative analysis to the computation of parameters which can be compared to normal values obtained in a group of normals.

These parameters are: (a) the IMP uptake in planar anterior scans as measured in counts/pixel/mCi/min multiplied by the body surface area, and (b) six right-left uptake ratios obtained from ECT slices with ROIs, which are perfusion territory matched. From these right-left ratios a summary index of cerebral uptake asymmetry is also obtained.

We find the IMP uptake value of limited usefulness in assessing cerebral disease as this quantity is too variable even in normals, possibly due to variable IMP uptake by the lung. Asymmetry ratios as determined from perfusion matched ROIs are useful for several reasons. First, already small variations in cerebral IMP content of the order of 2% may be pathological. Due to inhomogeneous IMP uptake even in normals, image abnormalities may be overlooked, or noise mistaken for regional decreased or luxury perfusion. Second, the choice of regions permits one to decide readily whether a single vascular territory is affected. Third, preliminary results in a few patients suggest that the magnitude of the asymmetry numbers may be used to monitor the success of therapy: the temporal changes of these numbers are found to closely match the clinical course of the patient.

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FOOTNOTES

* Product specification by the radiochemists of the Swiss Federal Institute for Reactor Research: <2% of I-125 1 day after calibration time and date, whereas our measurements were performed at least 12 hr prior to this time.

† Early in the study, the low-energy, high resolution collimator was used, but due to the low count rate [a well recognized problem in Anger camera ECT studies (*11*)] reconstructed images were too noisy. For both low-energy collimators the septal penetrance of the 159 keV I-123 photons is already considerable. Additional image degradation is due to the EC-gamma rays of I-123 with energies ranging above 600 keV (relative occurrence <2%).

‡ Picker Dyna Scan.

§ Micro-Z: inhomogeneity over camera surface <2% as specified by manufacturer.

¶ Ketronic Medax-N desktop computer equipped with an array processor.

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