Assessment of Regional Cerebral Blood Flow (rCBF) in Stroke Using SPECT and N-isopropyl-(I-123)-p-iodoamphetamine (IMP)

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SUMMARY In this study we assessed regional cerebral blood flow in patients with signs and symptoms of acute stroke using single-photon emission computed tomography (SPECT) and N-isopropyl I-123 p-iodoamphetamine (IMP). Twenty-five patients with acute cerebral infarction had both IMP brain perfusion studies and CT scans performed within one week of each other; 22 had positive and three had negative perfusion studies. Of the 22 patients who had positive perfusion studies, six had negative CT studies initially. In the 16 patients who had abnormal CT studies, eight of the studies depicted areas of edema that were smaller than the perfusion deficits noted on the IMP studies and eight had areas of edema that were approximately equal in size to the perfusion defect. Of the three patients with normal IMP studies, two had normal CT studies and one had a positive CT study showing a 3-mm lacunar infarction. Use of noninvasive techniques, mean count rates per tissue volume normalized for the injected dose was calculated. Similarly, the quantitative data from regions of interest in the stroke patients were calculated and compared to the control patients or to a normal region in the uninvolved hemisphere in the same patients. SPECT with IMP was used to assess regional brain perfusion in acute cerebral infarction. Perfusion abnormalities were seen in our patients when the CT scan was normal, and quantitative data could be used to approximate regional cerebral blood flow in these patients when compared to the normal patient population.

Stroke Vol 15, No 1, 1984

IN STROKE, the brain may appear normal by CT for several days after the acute interruption of cerebral blood flow.1,2 Positron emission computed tomography has graphically demonstrated changes in regional brain physiology in patients whose X-ray CT studies show normal anatomy.3 Although positron studies permit noninvasive measurements of regional cerebral blood flow, glucose metabolism, and oxygen utilization in man, their cost and specialized instrumentation limits their use in routine patient management. If early measurements of regional cerebral blood flow in patients are going to have an impact on the clinical management of stroke, a single-photon approach that is free of the high technology cost of positron tomography needs to be developed so that measurements of regional cerebral blood flow will not be limited to a few centers.

Single photon emission computed tomography (SPECT) can be performed with radiolabeled amines, such as N-isopropyl I-123 p-iodoamphetamine (IMP), which are highly lipophilic, have a high extraction in the brain and are flow limited. SPECT-IMP scanning in this study showed promise as a relatively inexpensive, widely available technique for the measuring of regional cerebral blood flow.

Materials and Methods

Radiopharmaceutical

The iodine-123 used for the radiolabel is cyclotron-produced by Mediphysics Laboratories (Emeryville, California) by the Te-124 (p,2n) I-123 reaction using a 23 MeV proton. A 2.1–4.6% contamination with I-124 was present at the time of injection. The half-life of I-123 is 13 hours and the half-life of I-124 is 100 hours. Amphetamines were labeled with I-123 according to the technique described by Winchell.4 Average specific activity is 1.43 mCi/mg, with an average carrier concentration of 0.14 mg/ml. The patients received about 5 mCi per study and with this dose the radiation burden to the target organ, which is the liver, was 0.5 rems/mCi.5 With 5 mCi less than ½ mg of amphetamine was injected.

Patients

Thirty-three patients were included in this study. The control group comprised eight patients with malignancy but no evidence of cerebral pathology by clinical examination or CT scan. In the experimental group were 25 patients with acute cerebral infarction who were studied by IMP scans with single-photon emission tomography and CT. The patients’ primary presenting physical findings, time of the examinations after symptoms, and results of the studies is given in table 1. Acute cerebral infarction was diagnosed on the basis of clinical history and focal neurological signs at physical examination that did not resolve over the first three days of hospitalization.

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Received May 10, 1983; revision #1 accepted July 12, 1983.
Instrumentation

Tomographic scans of all patients were obtained using the Harvard scanning multidetector brain system after intravenous injection of IMP. This scanning detector system was originally conceived by Stoddard in 1975 and manufactured by Union Carbide as Cleon 710. The hardware/software development has recently continued at Harvard University. The strengths of the system are efficient data collection, sharp resolution, and uniform geometric efficiency across the entire slice. The system sensitivity is 10,300 cts sec\(^{-1}\) mCi\(^{-1}\) cc\(^{-1}\) for energies between 135 keV - 185 keV; the resolution is 10.0 mm full width half maximum; and the slice thickness is 9.8 mm full width half maximum. Because the 1-123 used for the radiolabel was contaminated with 1-124 at the time of injection, scatter and collimator leakage from the high-energy photon of 1-124 were minimized by a subtraction mask technique previously described.

At least one tomographic image was obtained at 2 cm above the orbital mental line. Additional images were obtained depending upon the clinical situation. Four to six slices at the same level were obtained and summed for visual presentation for the total imaging time of 20-30 min at one level. Images typically consisted of 2-3 millions total counts. SPECT studies were photographed with 10% background subtraction.

Quantitative data was obtained by using an electronic cursor to outline regular areas of interest on the tomographic images depicted by the computer monitor. The computer was then able to determine the number of pixels in each region of interest, the average number of counts per pixel, and the specific number of counts in each pixel. Relative concentration of the tracer activity in each hemisphere or within the region of infarction could be calculated for comparison with the contralateral side. Counts in the regions were normalized for the injected dose and expressed as cts min\(^{-1}\) mCr\(^{-1}\) cc\(^{-1}\).

In order to determine regional cerebral blood flow, specific regions of interest were identified and cts min\(^{-1}\) mCr\(^{-1}\) cc\(^{-1}\) of brain were calculated and adjusted for such variables as number of slices obtained, dosage of I-123, and differences in the size of the region of interest. The mean slice cts min\(^{-1}\) mCr\(^{-1}\) cc\(^{-1}\) of brain tissue in 8 normal patients was calculated. Since IMP deposition has been shown to be linearly related to microsphere deposition, this factor was used to relate rCBF from regional count rates obtained from the tomographic images in the other patient studies.

Transmission computerized tomography was performed with a GE 8800 total body scanner using a 9.6-second high-resolution mode. All patients had unenhanced studies, and four also were studied after receiving intravenous contrast medium. Scans were considered abnormal if they showed areas of decreased attenuation, mass effect, hemorrhage, or abnormal gyral enhancement with contrast medium within the area of clinical concern. The abnormal CT and the SPECT IMP images were placed side by side for visual assessment of the extent of abnormality on comparable slices.

Results

The eight control patients had both normal CT and normal IMP scans (fig. 1). In these patients, the normalized count rate was 88.0 cts min\(^{-1}\) mCr\(^{-1}\) cc\(^{-1}\). Both the count rate at 20-60 min after injection and the percentage of injected dose going to the brain (7.45% ± 0.9 SD) was relatively constant.

Twenty-five patients who fit the criteria for acute cerebral infarction were studied with SPECT-IMP and CT scans. The results of the studies and comparison of the size of abnormality on CT versus IMP is given in figure 2. Patient #1 is one of 6 patients who had a
FIGURE 1. Normal control patients IMP study (left) and CT (right). High IMP uptake in cortical gray-matter related to blood flow. Interlobar fissure and Sylvian fissure well demarcated. Basal ganglia and thalamus seen centrally in this slice 2 cm above the canthal mental line. SPECT study contains 3,100,000 counts obtained in 35 min.

negative CT scan and a positive IMP study (fig. 3).

Twelve patient studies were selected for quantitative analysis using the region of interest activity concentration converted to regional cerebral blood flow measurements. In these patients, the quantitative assessment of cerebral blood flow in the abnormal region was 57.0 ± 14.5 cts min\(^{-1}\) mCi\(^{-1}\) cc\(^{-1}\) when compared to 82.3 ± 12.3 cts min\(^{-1}\) mCi\(^{-1}\) cc\(^{-1}\) in the normal region.

Three patients with large infarctions who had sequential slices at the same level for one hour after intravenous injection of IMP were examined to study the temporal distribution of activity in the infarcted regions. These studies demonstrated no evidence of redistribution of the radiopharmaceutical into the infarcted area and showed a ± 10% deviation in count rate at 20–75 min after injection (fig. 4). The grey matter/white matter ratio in a normal area was 2.03 ± 0.17 at 30–75 min.

Of the 3 infarction patients with negative IMP studies, only one patient (#25) had a positive CT scan with a small lacunar infarct. The other 2 patients also had negative CT studies. One patient (#24) whose neurologic deficit resolved, was discharged with a diagnosis of TIA. The other patient (#23) showed some recovery over the 7-day hospital stay and was discharged with a diagnosis of CVA on clinical criteria.

Discussion

Early assessment of regional cerebral perfusion in patients with stroke should be useful for objective planning of medical or surgical management. While positron tomography permits measurement of rCBF and brain metabolism, practical consideration of cost precludes widespread clinical usage in the foreseeable future. N-isopropyl 1-123 p-iodoamphetamine developed by Winchell has the potential for widespread availability. SPECT equipment is currently available from most manufacturers. Although most of these systems are rotating single head gamma cameras with less resolution and sensitivity than our multidetector system, the images of IMP appear to have good diagnostic quality.

In this study, the patients presenting with acute cerebral infarction often had dramatic tissue perfusion deficits prior to any visible change on CT. Since IMP was available only on one day per week, patients could not always be studied in the immediate period after onset of symptoms. Our earliest IMP studies were obtained 4
hours after the onset of symptoms. It is probable that patients will demonstrate perfusion deficits at the time of vascular occlusion before irreversible brain injury. Of the 6 patients who had negative CT scans and positive IMP studies, 5 were studied by CT within the first 4 days after onset of symptoms. In the group that had positive IMP studies and positive CT scans, only 9 out of 16 CT studies were obtained within this 4 day period.

As previously suggested and as demonstrated in this study, the typical low-density area seen on delayed CT scan is often much smaller than the perfusion deficit. This discrepancy in size may be due to the "penumbra" effect. Areas of infarction may be surrounded by a region of very limited blood flow which is sufficient to keep the tissues alive but is insufficient to allow normal activity. If the area of "penumbra" is large in a particular patient, the clinical picture may seem catastrophic when in fact the irreversible damage is only limited. Here, careful assessment of regional cerebral blood flow may be useful in distinguishing temporary from permanent damage.

We have not observed areas of hyperemia in any of our patients. The phenomena of luxury perfusion described by Lassen in 1966 with the Xe-133 washout approach has been observed by other investigators using different techniques. It is possible in certain pathological states such as epilepsy to image hyperemias by the I-123 IMP technique. Therefore, the failure to image that specific pathophysiologic response in stroke may be inherent in the mechanism of uptake of I-123 IMP in cerebrovascular disease. The mechanism of uptake of this radiopharmaceutical has not been fully elucidated. However, Kuhl has shown that there is a matching distribution of IMP and microspheres indicating that IMP is a good flow indicator in normal tissue. Studies comparing the distribution of IMP and microspheres in abnormal tissues need to be performed. If IMP is a "pH shift" agent, the appropriate intracellular-extracellular pHs required for a high extraction efficiency may not exist in the ischemic yet viable brain. This may explain the failure to detect luxury perfusion. Due to the small numbers of patients studied it is possible that we have not studied any patients when luxury perfusion was present.

Lassen et al have suggested that there may be gradual redistribution of activity in the area of infarction during the first hour that tends to overestimate regional cerebral blood flow. In our patients studied temporally, regional activity in the area of infarction showed only statistical variation in count rate (± 10%) with no trend toward redistribution. Therefore, redistribution did not affect the detectability of the infarction or the measurement size of the infarction during the first hour. Kuhl et al have suggested that the IMP might underestimate blood flow in the area of stroke because the degree of uptake is dependent both on blood flow and availability of binding sites. The extent to which the IMP concentration might underestimate regional cerebral blood flow in the infarcted region needs further investigation.

Previously, local cerebral blood flow was quantified by arterial sampling. Since this technique is invasive, however, it is not used in our study. An approximation of regional cerebral blood flow among our patients was estimated from regional count rates in the control patients and from normal regions in the same patients. This assumes that the uptake of IMP is linearly related to blood flow, that our system is quantitative, and that there is a constant body distribution.

Linearity of IMP activity related to blood flow has been shown both with microscopes and antipyrine in an animal model. The Harvard multidetector scanning system has been shown to be a quantitative system for fixed geometry situations. Thus the tracer is flow limited in the brain after intravenous injection and our imaging system has sufficient system linearity to take advantage of it.

While our method for the assessment of cerebral blood flow is noninvasive, it does require that the tracer concentration in the brain be constant during the time of imaging. This appears to be the case for IMP at least during the temporal window that we used (20-60 minutes after injection). It also appears to be applicable to areas of infarction as well as to normal tissue since we found no measurable redistribution of the tracer during this time. If the steady-state brain concentration of the tracer is due to a balance between washin from the lung and brain washout of IMP metabolites, as is suggested by intracarotid studies, then a steady state in cerebral blood flow will be necessary from the time of injection to the end of imaging. Recirculation of the tracer back to the brain does not appear to be a problem, however, since tracer does not appear in the contralateral hemisphere after an intracarotid injection. While we were not able to measure the variability in organ uptake from patient to patient for tissues other than the brain, the narrow range in the percentage of injected dose delivered to the brain in our control patients suggests that this may not be a serious limitation. As we have studied more patients with various diseases, however, it appears that variations in tracer clearance from the lungs as well as variations in radiopharmaceutical preparations will limit the usefulness of this noninvasive approach for comparison of regional cerebral blood flow from normals to patient studies. The relative regional count rates remain useful in individual patients since they are linearly related to CBF.

Prospective studies to study recovery in relation to the degree of tissue perfusion deficit or the ability of therapies to limit the degree of ischemic tissue should be forthcoming. Whether the patient presenting with a large perfusion deficit should be treated conservatively because of the ominous prognostic sign or treated aggressively to limit the degree of necrotic tissue is unclear and can only be determined rationally when a test becomes readily available to measure tissue perfusion in the early hours after onset of stroke. As new pharmaceuticals become widely available to medical investigators, medical therapy with infusion of thrombolytic agents and surgical intervention with endarter-
ectomy or bypass operations can be objectively evaluated. Only then will an adequate data base be available to truly evaluate the efficacy of these therapies.

SPECT imaging with IMP appears to be useful to assess brain perfusion in patients presenting with acute stroke. The technique has the potential for quantification of regional cerebral blood flow to effect management and objectively evaluate the medical and surgical therapies that may be applied to the clinical situation. Commercial development of IMP as well as other radiopharmaceuticals and further refinements in SPECT instrumentation will provide regional cerebral blood flow maps for clinicians to aid management of patients with acute stroke.

Acknowledgments
The authors express their appreciation to Paul W. Kasulis and Sheila Flynn for technical assistance, to Medi-Physics, Inc., Emeryville, California, and to Denise C. Magni for her clerical assistance in the preparation of this manuscript.

References
transaxial tomography: Union Carbide focused collimator scanner
10. Wall SD, Brant-Zawadzki M, Jeffrey RB, Barnes B. High frequency CT findings within 24 hours after cerebral infarction. AJNR 2: 553-557, 1981
Assessment of regional cerebral blood flow (rCBF) in stroke using SPECT and N-isopropyl-(I-123)-p-iodoamphetamine (IMP).

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Stroke. 1984;15:40-45
doi: 10.1161/01.STR.15.1.40

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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