

## DIAGNOSTIC NUCLEAR MEDICINE

### Initial Experience with SPECT (Single-Photon Computerized Tomography) of the Brain Using N-isopropyl I-123 p-iodoamphetamine: Concise Communication

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**Forty-six patients were studied with N-isopropyl I-123 p-iodoamphetamine (IMP) and the Harvard Scanning Multidetector Brain System. In nine control patients, good differentiation between the gray and white matter of the cerebral cortex and the basal ganglia was evident. Regional uptake was affected by physiologic maneuvers (visual stimulation). In 24 patients studied for stroke, IMP images demonstrated areas that were involved in acute infarction in eight patients whose initial transmission computerized tomography (TCT) was normal; IMP also showed perfusion abnormalities larger than the TCT abnormality in ten patients. Perfusion abnormalities were present in 23/24 of these patients. Seven patients studied with a history of TIA had normal TCT and IMP images. In three patients studied during seizure activity, regions of hyperperfusion corresponded to the EEG seizure focus. Markedly decreased activity was present in three patients with brain tumor and corresponded to the focal abnormality on the TCT study. Our study demonstrates the feasibility of assessing regional brain perfusion using a radiopharmaceutical that is lipid soluble and has a high extraction fraction in the brain, together with single-photon ECT.**

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Regional brain perfusion can be estimated with dynamic imaging and equilibrium flow imaging using diffusible or extractable tracers (1). Investigators have used a number of positron emitters including krypton, ammonia, carbon-11 dioxide, and rubidium, along with transaxial emission computed tomography, to assess regional brain perfusion (2-6). The results obtained with these positron techniques have stimulated efforts to develop single-photon radiopharmaceuticals that are free of the high technology cost of positron tomography, estimated at \$1,700 per study, which has limited the use of regional brain perfusion imaging to a few centers (personal communication, TF Budinger).

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A single-photon emission computed tomography (SPECT) technique could have widespread clinical utility limited only by the availability of the imaging instrumentation. Regional brain perfusion in humans has been accomplished with single-photon imaging using xenon, krypton, and technetium microspheres (7-10). These studies are limited either by the special instrumentation required or by their invasiveness. The need for radiotracers that are lipid-soluble and have a high first-pass extraction fraction has led to the development of N-isopropyl I-123 p-iodoamphetamine by Winchell et al. (11).

We therefore assessed the feasibility of evaluating regional cerebral perfusion in patients with neurologic disease using single-photon emission computed tomography and N-isopropyl I-123 p-iodoamphetamine (IMP).

## MATERIALS AND METHODS

Forty-six patients with a variety of neurologic diseases were studied using the Harvard scanning multidetector brain system after intravenous injection of IMP.

The scanning detector system was originally conceived by Stoddart in 1975 (12) and the hardware and software development has continued at Harvard University. As demonstrated elsewhere (13-18), the strengths of this system are efficient data collection (large solid angle for gamma detection), sharp resolution, and uniform geometric efficiency across an entire slice. The system's sensitivity is 14,000 cps per  $\mu\text{Ci}$  per cc and resolution is 10 mm FWHM (18).

Because the I-123 used for the radiolabel is produced

by Te-124 ( $p,2n$ )  $\xrightarrow{23 \text{ MeV}}$  I-123 reaction, 2.1%-4.6%

contamination with I-124 was present at the time of injection. The effects of scatter and collimator leakage of high-energy photons from the I-124 were minimized in the images by an approximate background subtraction applied to the raw data before reconstruction. The studies were all performed in dual-channel mode with the lower-energy pulse-height window set at 135-185 keV (surrounding the I-123 peak) and the higher-energy window set at 310-360 keV.

Before scanning patients, three cylindrical phantoms were used to obtain a scatter mask. One of the cylinders was filled with 0.04 mCi of pure I-124 and placed in the gantry. The other two were filled with 0.08 mCi I-124 and placed on the patient couch in positions roughly approximating a patient's lung field and lower torso. The two-dimensional projection of intensity distributions recorded in the low-energy window provided a close approximation to the shape of the distribution from the I-124 background when a patient is scanned with I-123. This technique does not provide an exact compensation for punch-through and does not replace the requirement for very pure I-123.

For patient studies, at least one tomographic image was obtained at 2 cm above the orbito-meatal line. Additional images were obtained depending upon the clinical situation. The injected dose was 5 mCi and imaging was performed between 20-60 min after the injection. To improve the statistical quality of the images, two to six slices from the same level were summed for presentation.

The patients were divided into five groups. Nine control patients without evident cerebrovascular disease (Group I) had a known primary tumor, but normal TCT studies and normal neurological examinations. Twenty-four patients (Group II) were studied initially because of suspected cerebral vascular disease based on a history or physical finding suggesting cerebral infarction. The diagnosis of acute infarction was confirmed

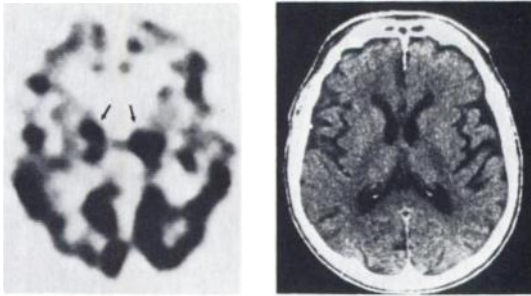
in 22 of these patients by the appearance of characteristic TCT abnormalities 4 days or more after the onset of new focal neurologic signs. There were thrombotic or embolic infarctions in the distribution of the middle cerebral (16) or posterior cerebral (3) arteries. The time from onset of symptoms to the time of the IMP tomographic study ranged from 12 hr to 7 days. Chronic cerebral infarction was confirmed in two patients by the presence of characteristic fixed abnormalities on their TCT scans and by their clinical history. Seven patients (Group III) had transient neurologic symptoms but had normal neurological examinations and normal TCT studies; they were thought to have transient ischemic attacks. Three patients with metastatic brain tumors (Group IV) had focal abnormalities on their TCT studies and focal neurologic signs on their physical examination. The primary tumors were lung, melanoma, and breast. Three patients with seizure disorders (Group V) were injected with IMP during the seizure and tomography was performed 20 min later. These three patients had normal TCT studies but showed standard electroencephalographic evidence of focal seizures.

The dictated reports were used as the interpretation for the presence or absence of disease on the TCT study. The presence of atrophy was not considered an abnormal finding. The abnormal TCT and the SPECT IMP images were placed side by side and visually assessed for the extent of abnormality in the comparable slices. In all but two patients, TCT scans were obtained within 7 days of the IMP SPECT examination.

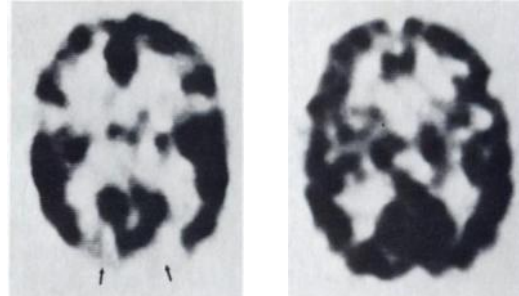
In 11 patients, multiple images of the thorax, head, and abdomen were obtained in the anterior projection using a standard large-field-of-view Anger camera and a medium-energy collimator. Imaging was performed 60 min after injection, collecting 300,000 counts per image with a 20% window centered over the 159-keV I-123 photopeak.

## RESULTS

Nine Group I patients, with primary malignancies but no suspected central nervous system disease and with normal TCT examinations, demonstrated bilaterally symmetric activity on the IMP images (Fig. 1). Activity was greatest in a strip of cortex along the convexity of the frontal, temporal, parietal, and occipital lobes corresponding anatomically to cortical gray matter. Activity was also high in the region corresponding to the basal ganglia. The region between the basal ganglia and the convexity corresponding anatomically to cortical white matter had less IMP activity. The activity in the cortical gray matter was uniform in the temporal, parietal, and occipital regions but appeared patchy in the frontal region. The contour of this activity was undulating and reflected the gyral architecture observed on the TCT image. Depressions due to the interhemispheric and



**FIG. 1.** IMP scan of normal control patient (left). Cortical uptake appears related to gray-matter blood flow, with good demarcation of interlobar fissure. In this tomographic slice at 2 cm above orbito-meatal line, basal ganglia are clearly defined (arrows), TCT scan for same patient (right). Note asymmetric atrophy of Sylvian fissure in both TCT and IMP studies.



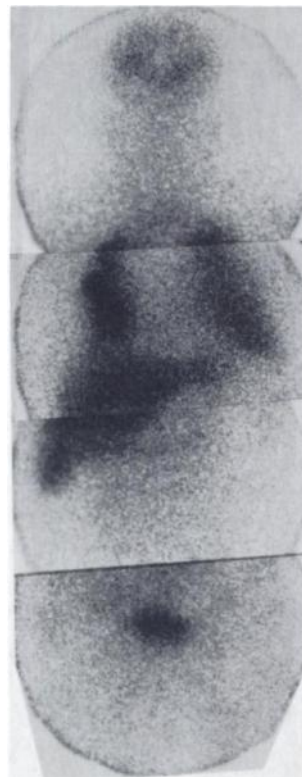
**FIG. 2.** Patient in coma with eyes closed (left). Note marked decrease of regional perfusion of associative visual cortex (arrows). Patient studied during visual stimulation with bright lights and movement in examining room (right). Note marked increased perfusion of both primary and associated visual cortical areas.

Sylvian fissures were also present. Although most patients were injected in the dim ambient light from the hallway, several patients were studied with varying visual stimulation. Activity in the visual cortex of a patient injected in a brightly lit room was greater than that in a patient studied in coma with eyes closed (Fig. 2). Decreased perfusion to the visual-associative cortex was also seen in an awake patient whose eyes were closed for 20 min after injection.

With whole-body imaging, IMP uptake was seen in lung, liver, and brain. There was no uptake evident in other soft tissues, including the eyes. Bladder activity indicated renal excretion (Fig. 3).

Twenty-one of 22 Group II patients with acute cerebral infarction showed perfusion defects in their IMP studies. Eight of these patients had normal TCT studies at the time of hospital admission (Fig. 4). Ten had IMP studies with larger perfusion defects than the abnormality demonstrated on the TCT scan. In eight patients, the perfusion abnormality on the IMP study was equal to the size of the infarct on the TCT scan. In the 19 patients with middle cerebral artery infarction, the perfusion defect involved the gray and white matter of the temporal and parietal lobes, with variable extension into the frontal and occipital lobes and the basal ganglia. In these patients there were sensory and motor deficits on the contralateral side. In the three patients with posterior cerebral infarction, there were corresponding perfusion defects involving the occipital lobe, with involvement of the visual-associative areas. In these three patients there were corresponding visual-field cuts. One patient had an abnormal TCT and normal IMP study. Two of the patients had old cerebral infarctions. In the seven Group III patients with histories consistent with transient ischemic attacks but without focal neurologic signs, both the IMP studies and the TCT scans were normal. In the three patients with metastatic brain disease (Group IV), the focal area of abnormality on the TCT scan corresponded to an area of markedly decreased IMP concentration. All three group V patients had normal TCT

scans, but by SPECT these patients demonstrated markedly increased activity involving a large portion of the temporal, parietal, and occipital lobes on the left [one patient (Fig. 5)], a focal area of increased activity limited to the posterior temporal lobe on the right (one patient), and an extensive area of increased activity involving the posterior temporal, parietal, and occipital lobes on the left (one patient). In all three cases, the areas of increased perfusion corresponded to the epicenters of seizure focus on electroencephalographic examination.



**FIG. 3.** Anterior gamma-camera composite image taken at 55 min after IMP injection, demonstrating uptake in cerebral hemispheres, lungs, liver, and bladder. Note that there is no evidence of uptake in eyes, thyroid, testicles, or renal cortex, as has been seen in various animal studies. Focal uptake in right lung is related to patient's bronchogenic carcinoma.



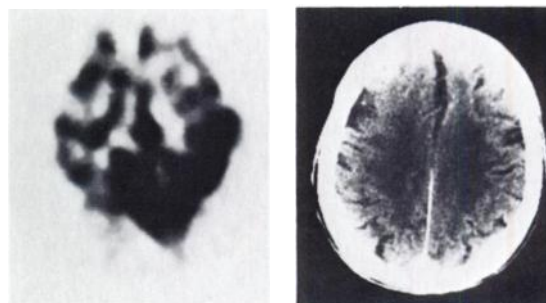
**FIG. 4.** Initial TCT, obtained on day of an acute onset of right hemiparesis and aphasia, is normal (left). IMP study shows absent perfusion in territory of left middle cerebral artery (center). Follow-up TCT study 6 days after acute event shows low-density area in left parietal lobe (right). Note that resultant infarct appears smaller than ischemic tissue demonstrated on IMP study.

#### DISCUSSION

Recent enthusiasm for single-photon emission computed tomography of the brain has been stimulated by pioneering work with positron ECT but has been hindered by slow advances in the development of practical single-photon radiopharmaceuticals. Widespread clinical utility of positron tomography is limited to a few centers because of the cost of on-site cyclotrons and the need for extensive technical support of radiochemical and radiopharmaceutical production. If the dramatic results from these centers is to be applied to clinics generally, inexpensive single-photon radiopharmaceuticals that can mimic the biodistribution of positron pharmaceuticals are required. Widespread clinical utility would then be limited only by the availability of appropriate scanning instrumentation.

N-isopropyl I-123 p-iodoamphetamine is lipid soluble and has a high extraction fraction on the first pass through the brain. Distribution and concentration remain constant during the period of tomographic imaging (11). Kuhl et al. (20) have shown good correlation between IMP deposition and local cerebral blood flow as measured by microsphere extraction in dogs. Thus the tomographic images obtained on the Harvard multidetector scanning system are maps of brain perfusion and are useful for assessing regional brain blood flow. Since activity levels obtained with our system accurately reflect the concentration of the tracer (21), quantitative measurement of cerebral regional blood flow may be possible. Preliminary reports have suggested that IMP might be useful for measuring specific receptor sites in the brain (11). Whether the redistribution image of IMP reflects specific or nonspecific binding sites is currently under investigation.

The present N-isopropyl I-123 p-iodoamphetamine is labeled with I-123 with a rather high contamination of I-124. Most of the present studies had to tolerate ~4% I-124. This I-124 contamination would probably cause more severe problems with the single-detector rotating system that is being offered by various commercial suppliers. When iodoamphetamine is labeled with a purer I-123 and the I-124 contamination problems are



**FIG. 5.** Study from a patient with hemiballism (left). During study, patient had uncontrollable flaying on entire right side of body. Tomographic image demonstrates hyperperfused seizure focus in left parietal region. TCT study is normal (right).

eliminated, the injected dose can be increased and the imaging time markedly reduced. Even at present, images of cerebral perfusion using SPECT and IMP offer sufficient quality to assess regional brain perfusion.

The information obtained from the TCT scan and the iodoamphetamine image are different in character. The perfusion studies are useful in assessing the extent of tissue involvement in patients with stroke. In eight patients with acute infarction, early TCT examinations showed normal structure, whereas functional ECT images showed lack of perfusion to areas that subsequently developed TCT changes consistent with infarction. The perfusion abnormalities were larger than the TCT changes in ten patients. These cases agree with similar observations by Lassen et al. using the xenon inhalation technique and the DCAT (7) with low-flow areas tending to be larger than low-density areas of infarction on TCT. Our results also demonstrate the expected finding of perfusion deficits occurring before structural changes of cerebral infarction as imaged on TCT scans.

Our initial experience suggests that the single-photon radiopharmaceuticals and the technique described will be valuable in assessing cerebral ischemia and regional brain perfusion in various disease states.

The potential for commercial distribution of N-isopropyl I-123 p-iodoamphetamine, the recent widespread availability of single-photon ECT imaging systems, and the biologic characteristics of these tracers suggest that the noninvasive assessment of regional cerebral perfusion with IMP may become an important addition to our diagnostic nuclear medicine capabilities.

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