Cerebral Blood Flow Studies Using N-Isopropyl I-123 \( p \)-Iodoamphetamine

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SUMMARY Twenty patients with stroke were studied for cerebral blood perfusion abnormalities using N-isopropyl I-123 \( p \)-iodoamphetamine (IMP) and rotating dual gamma camera emission computed tomography (ECT). After a single scan, multiple transverse, coronal and sagittal section images were reconstructed with a minicomputer. In eighteen patients, we determined the values of regional cerebral blood flow (rCBF) in the region of interest using an image. Transmission computed tomography (CT) studies were also performed on the same day. ECT showed cerebral perfusion abnormalities in all cases, while CT showed abnormalities in only 10 cases. This technique seems to be useful for evaluating the rCBF in the deep brain.

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IMP has been reported to be useful for imaging relative brain perfusion because in rat brain first pass extraction efficiency was high and physical properties of IMP have been reported to be useful for imaging relative brain perfusion because in rat brain first pass extraction efficiency was high and physical properties of 1-123 (T'/2 = 13 hr., 159KeV photon) were favorable for scanning.1,2 Kuhl et al.3,4 reported that IMP is a highly lipidsoluble radiopharmaceutical and its liposolubility and pH gradient between blood (pH 7.4) and the interior of the brain cells (pH 7.0) enables it to cross the blood brain barrier and to concentrate in brain cells and that the value of whole-brain CBF of human controls was 47.2 ± 5.4 ml/100 g/min by the arterial input sampling method using IMP and single-photon emission computed tomography (ECT). We determined the value of regional cerebral blood flow (rCBF) in stroke patients with IMP and rotating dual gamma camera emission computed tomography. In this paper we describe the advantages of this method.

Clinical materials and methods

Twenty patients were studied between December 1983 and March 1984 at the University Hospital of Kanazawa. There were 9 women and 11 men, who ranged in age from 12 to 76 years of age with a mean age of 51 years. All were stroke patients diagnosed by angiography; 10 with a cerebral aneurysm with vasospasm, 2 with an occlusion of the internal carotid artery (IC), one with an IC stenosis, 3 with an occlusion of the middle cerebral artery, one with Moyamoya disease, one with RIND, one with a cerebellar AVM and one with a pontine hemorrhage (table 1). Four patients had extracranial-intracranial (EC-IC) bypass operations. In three of them, CBF studies were done before and after bypass surgery. CBF was measured by IMP and rotating dual gamma camera emission computed tomography (ECT) equipped with medium energy collimator. An arterial line was placed in the left radial artery in 18 patients and connected to a Harvard pump. IMP (1.5–3 mCi) was injected into an arm vein. At the same time an arterial blood sample was withdrawn at a constant speed of 1.2 ml/min for 5 minutes. The IMP input curve was recorded. Figure 1 shows the time course of brain and lung activity after intravenous injection of IMP. The lung activity decreases rapidly and the activity curve of the brain reaches a plateau after about 30 minutes. Scanning was started 35 minutes after IMP injection.

The equation for determining rCBF is as follows: 

\[
F = \frac{100 \text{RCb(NA)}}{N} \text{ml/100 g/min}
\]

where \( F \) is the constant withdrawal rate of arterial blood in ml/min, \( R \) is the constant withdrawal rate of arterial blood in ml/min, \( Cb \) is the brain activity concentration in \( \mu \text{Ci/g} \), \( A \) is the total activity (5 min) in the withdrawn arterial whole blood in \( \mu \text{Ci} \) and \( N \) is the fraction part of arterial whole blood activity representing unmetabolized IMP. We also used 0.75 as the value of \( N \) as determined in normal humans by Kuhl et al.4 \( Cb \) and \( A \) were determined by ECT and counting in a well counter, respectively. The full width at half maximum (FWHM) spatial resolution was 2.0 cm within the image plane. After a single scan, multiple transverse, coronal and sagittal slices were reconstructed with a Scintipac 2400S (Shimazu Co., Ltd., Kyoto, Japan). The values of rCBF were calculated in the regions of interest (ROI: 5 × 5 pixels) of each image. All patients had transmission computed tomography (CT) with a EMI-CT 1010 or GE-CT 8800 scanner on the same day. The relationship between the abnormalities of cerebral blood perfusion on ECT, low density areas on CT scans and neurological findings is reported in this paper.

Results

Twenty-three studies were performed in twenty patients. Twenty-one studies in eighteen patients were performed to quantify rCBF by analyzing the ROI activity concentration. In all the patients with stroke, ECT studies showed abnormal results with focal areas of decreased flow in 18 patients and with diffuse low perfusions in 2 patients, respectively. CT demonstrated low density areas in 8 patients on the day of ECT study. In three patients, low density areas developed one or two days later. In the remaining nine cases, there was no low density area on the CT scan (table 1).
### Table 1: Clinical, Emission Computed Tomography (ECT) and X-ray Computed Tomography (CT) Features of 20 Patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>Diagnosis</th>
<th>ECT low perfusion</th>
<th>CT low density</th>
<th>Neurological findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46 F</td>
<td>Aneurysm (Ant Com)</td>
<td>focal</td>
<td>(+)</td>
<td>disorientation</td>
</tr>
<tr>
<td>2</td>
<td>40 M</td>
<td>Aneurysm (Ant Com + MCA)</td>
<td>focal</td>
<td>(-)</td>
<td>normal</td>
</tr>
<tr>
<td>3</td>
<td>49 F</td>
<td>Aneurysm (l-Ophthamic)</td>
<td>focal</td>
<td>(+)</td>
<td>disorientation</td>
</tr>
<tr>
<td>4</td>
<td>40 M</td>
<td>r-MCA Occlusion</td>
<td>focal</td>
<td>(+)</td>
<td>l-hemiplegia</td>
</tr>
<tr>
<td>5</td>
<td>53 F</td>
<td>RIND</td>
<td>focal</td>
<td>(-)</td>
<td>normal</td>
</tr>
<tr>
<td>6</td>
<td>57 M</td>
<td>l-IC Stenosis</td>
<td>focal</td>
<td>(+)</td>
<td>r-hemiparesis</td>
</tr>
<tr>
<td>7</td>
<td>58 F</td>
<td>Aneurysm (r-Ophthamic)</td>
<td>focal</td>
<td>(-) — (+)</td>
<td>stupor, r-hemiparesis</td>
</tr>
<tr>
<td>8</td>
<td>50 M</td>
<td>l-IC Occlusion</td>
<td>focal</td>
<td>(-)</td>
<td>apasia, r-hemiparesis</td>
</tr>
<tr>
<td>9</td>
<td>76 M</td>
<td>l-MCA Occlusion</td>
<td>diffuse</td>
<td>(+)</td>
<td>stupor, l-hemiplegia</td>
</tr>
<tr>
<td>10</td>
<td>68 F</td>
<td>l-MCA Occlusion</td>
<td>focal</td>
<td>(-) — (+)</td>
<td>stupor, r-hemiparesis</td>
</tr>
<tr>
<td>11</td>
<td>41 M</td>
<td>Aneurysm (Ant Com)</td>
<td>focal</td>
<td>(-)</td>
<td>normal</td>
</tr>
<tr>
<td>12</td>
<td>61 F</td>
<td>Aneurysm (l-Ophthamic)</td>
<td>focal</td>
<td>(-)</td>
<td>normal</td>
</tr>
<tr>
<td>13</td>
<td>76 F</td>
<td>Aneurysm (r-Ophthamic)</td>
<td>focal</td>
<td>(+)</td>
<td>disorientation</td>
</tr>
<tr>
<td>14</td>
<td>12 M</td>
<td>Moyamoya disease</td>
<td>focal</td>
<td>(-) — (+)</td>
<td>l-hemiparesis</td>
</tr>
<tr>
<td>15</td>
<td>56 M</td>
<td>r-IC Occlusion</td>
<td>focal</td>
<td>(-)</td>
<td>normal</td>
</tr>
<tr>
<td>16</td>
<td>63 F</td>
<td>Aneurysm (Ant Com)</td>
<td>focal</td>
<td>(-)</td>
<td>l-hemiparesis</td>
</tr>
<tr>
<td>17</td>
<td>47 M</td>
<td>Aneurysm (Ant Com)</td>
<td>focal</td>
<td>(-)</td>
<td>disorientation</td>
</tr>
<tr>
<td>18</td>
<td>54 M</td>
<td>Aneurysm (PICA)</td>
<td>diffuse</td>
<td>(-)</td>
<td>coma</td>
</tr>
<tr>
<td>19</td>
<td>17 F</td>
<td>Cerebellar AVM</td>
<td>focal</td>
<td>(-)</td>
<td>ataxia</td>
</tr>
<tr>
<td>20 +</td>
<td>50 M</td>
<td>Pontine Hemorrhage</td>
<td>focal</td>
<td>(+)</td>
<td>stupor, quadriplegia</td>
</tr>
</tbody>
</table>

Ant Com = anterior communicating artery; MCA = middle cerebral artery; IC = internal carotid artery; PICA = posterior inferior cerebellar artery.

The abnormality demonstrated by ECT was more extensive than that demonstrated by CT scan. The CBF study by ECT was compatible with neurological deficits. The coronal slices in ECT were valuable in determining the vessels responsible for the ischemia, and the sagittal slices were also valuable in examining the motor and sensory cortex. The following three cases illustrate the capabilities of this method.

**Case 5**

The patient had hypesthesia on the left side and left homonymous hemianopsia for seven days and 2 months before ECT study. She recovered from her illness completely. There was no abnormality on the CT scan or angiography. Figure 2 shows the transverse slice 5 cm above the OM-line and the CBF values are

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**Figure 1.** Time course of brain and lung activity after intravenous injection of IMP. The lung activity decreases rapidly and the activity curve of the brain reaches a plateau after about 30 minutes.

**Figure 2.** rCBF values of the patient. ROI 4: 37, 5: 36, 6: 39, 7: 38, 8: 38, 9: 31, 10: 43, 11: 40 ml/100 g/min.
37 ml/100 g/min in ROI 4 of the left frontal lobe, 36 in ROI 5 of the right frontal lobe, 39 in ROI 6 of the left temporal lobe, 38 in ROI 7 of the right temporal lobe, 38 in ROI 8 of the left occipital lobe, 31 in ROI 9 of the right occipital lobe, 43 in ROI 10 of the left basal ganglia and 40 in ROI 11 of the right basal ganglia. The CBF value in the right occipital lobe is decreased by 18% compared to the contralateral ROI. The decrease in CBF is compatible with the history of visual field defect.

Case 8

This is a patient with an angiographically verified occlusion of the left IC. Figure 3 shows no low density area on the CT scan on the eighth day after the stroke. He had an EC-IC bypass operation a week later. Figure 4 demonstrates the slice 7 cm above the OM-line, pre- (left) and post-operation (right). The CBF values in this slice are 31 ml/100 g/min in the right frontal lobe, 23 in the left frontal, 28 in the right parietal and 23 in the left parietal lobe before the operation, and 40 in the right frontal, 30 in the left frontal, 46 in the right parietal and 29 in the left parietal lobe after the operation, respectively. The bypass operation resulted in a significant increase in the CBF of the left hemisphere as well as the right hemisphere. He recovered from the right hemiparesis and aphasia after this surgery.

Case 14

This patient is a young boy who had the sudden onset of a left hemiparesis. There was no abnormality in the CT scan on that day. It showed a low density area in the right frontal lobe next day. He was diagnosed as having "Moyamoya" disease by angiography. An ECT study was performed on the day of the stroke. Figure 5 shows low perfusion in the right frontal lobe. The CBF values in the frontal lobes were 32 ml/100 g/min on the left side and 21 (66%) on the right side, respectively. He recovered from the hemiparesis during conservative therapy.

Discussion

This study attempts to demonstrate that three dimensional maps and values for CBF can be accurately obtained by means of available technology and IMP. CT provides accurate imaging of cerebral anatomy, but there are no abnormalities on a CT scan unless
rCBF values are reduced below 34% to 26%. The brain may appear normal by CT for several days after an acute interruption of CBF. The recent development of positron-emission computed tomography (PET) provides us with three dimensional images of cerebral metabolism as well as CBF. But the enormous cost of positron camera, cyclotron and radiopharmacy greatly restricts the application of this technique. On the other hand, the ECT technique is more practical because of its low cost. Several single-photon emitting radio-pharmaceuticals have been developed to measure CBF. The rotating gamma camera system has less resolution and sensitivity than the multidetector system, but the images of IMP appear to have good diagnostic quality.

When injected intravenously, all IMP is extracted by the lungs on the first pass, it is then rapidly released into the blood according to a multiexponential function. In humans, IMP appears to reach equilibrium in the brain approximately 15 minutes after the injection and the distribution remains relatively stable for at least two hours. In our cases, time activity curves reached plateaus about 30 minutes after IMP injection.

Winchell et al suggested that IMP was bound in the brain to high-capacity, relatively non specific receptor sites for amines and that delayed distribution in the brain was related to the distribution of amine binding sites. Kuhl et al showed good correlation between IMP deposition and local CBF as measured by microsphere extraction in dogs. We obtained good CBF values in ischemic lesions as well as intact region. But it is not known how trapping and release mechanisms for IMP in ischemic lesion are affected by the changes in local metabolism, pH, permeability or receptor sites. The further research is being studied on this point.

In the case of regional or global ischemia due to spasm after a subarachnoid hemorrhage, early angiography and surgery are thought to be contraindicated. The rapid localization of IMP after intravenous injection provides a major advantage in the study of diseases such as stroke and epilepsy. This means that the distribution of CBF under certain precisely monitored conditions can be recorded for late analysis. ECT studies have also been reported to localize epileptic seizure foci more specifically than an EEG.

The flow abnormality demonstrated by ECT was usually more extensive than that seen by CT suggests that the functional abnormality is more extensive than the area of actual cell death. ECT is a promising method of identifying zones with lesser degrees of ischemia and evaluating operative results such as either EC-IC bypass or endarterectomy.

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References
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