Regional Cerebral Blood Flow Measured With N-Isopropyl-p-[123I]Iodoamphetamine and Its Redistribution in Ischemic Cerebrovascular Disease

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Background and Purpose: The relation between the redistribution phenomenon and regional cerebral blood flow and its clinical significance were investigated in stroke patients.

Methods: Single-photon emission computed tomography studies using N-isopropyl-p-[123I]iodoamphetamine were performed on 16 patients (26 to 77 years old) with chronic infarction and 10 age-matched normal control subjects. Regional cerebral blood flow was quantitatively measured by a microsphere model, and the redistribution on delayed images was analyzed in ischemic lesions.

Results: Supratentorial mean cerebral blood flow and the ratio of gray matter to white matter in normal subjects were 52.7 ± 5.0 mL/100 g per minute and 2.34, respectively. Low-activity areas of ischemic lesions on early images were classified into two abnormal zones, an infarct area and a peri-infarct area. These regions were characterized by regional blood flow averaging 9 to 20 mL/100 g per minute and 22 to 41 mL/100 g per minute, respectively. Redistribution, which was minimally present in the infarct area, was markedly enhanced in the peri-infarct area. After bypass surgery, we observed a significant increase of blood flow (+22%) in the peri-infarct area.

Conclusions: The data indicate that the redistribution phenomenon depends on the maintenance of a minimal blood flow that would sustain cellular function and that this phenomenon is useful to evaluate bypass surgery in patients with chronic infarction. (Stroke 1993;24:1167-1172)

Key Words • cerebral blood flow • cerebrovascular disorders • tomography, emission computed

Among the most recent radiopharmaceuticals for single-photon emission computed tomography (SPECT), N-isopropyl-p-[123I]iodoamphetamine ([123I]IMP) has been particularly advantageous. It was selected as a tracer for the measurement of regional cerebral blood flow (rCBF) by Winchell et al.1,2 This agent crosses the blood-brain barrier and has high first-pass extraction and long retention in brain tissue. This retention may be related to nontropic amine-binding sites.1 The initial [123I]IMP SPECT image during the first 10 to 30 minutes (early image) represents the distribution of rCBF.3 Kuhl and coworkers4 reported the quantitative measurement of rCBF with this radiotracer using a microsphere model and a Mark IV scanner. These values of rCBF were in good agreement with those obtained by the 133Xe three-dimensional method5 and the 15O-water positron emission tomography method.6

Redistribution is related to the "filling-in" phenomenon.7,8 This concept is explained as follows: when a low-perfusion area is observed as an area of decreased activity of the radiotracer on an early image, the activity gradually increases and the low perfusion disappears on a delayed image obtained 3 to 5 hours after [123I]IMP injection. The phenomenon is assumed to reflect metabolic activity in viable cerebral tissue and to indicate a good clinical outcome in patients with cerebrovascular diseases.9 The clinical and pathophysiological significance of this phenomenon, however, has been the subject of controversy in the literature.10,11

In the present study we report the quantitative measurement of rCBF using [123I]IMP SPECT with a dual-head rotating gamma camera and the microsphere model to assess the significance of the redistribution phenomenon from the viewpoint of changes in rCBF in patients with chronic infarction.

Subjects and Methods

Patient Selection

We analyzed 16 patients with unilateral completed stroke (14 men and 2 women; age range, 26 to 77 years; mean age, 58 years) and 10 age-matched right-handed normal volunteers (age range, 24 to 69 years; mean age, 56 years). Of those patients, 6 had occlusion in the middle cerebral artery (MCA) territory, and the others had stenosis in the MCA territory or internal carotid artery. All patients were examined with [123I]IMP...
SPECT at 1 to 7 months (mean, 2.6 months) after the onset of a stroke attack. These patients were selected out of more than 60 patients with a chronic stage of infarction, according to the following criteria, which were applied on the basis of the spatial resolution of our SPECT system. The rule of selection was that the infarct lesion was simple and its size was larger than 3 x 3 cm or smaller than 1.0 cm in diameter, and it was located in the unilateral supratenorial hemisphere, which was accurately identified by x-ray computed tomography (X-CT) with contrast enhancement and carotid angiography. Since the redistribution in a lesion could be compared with activity in a normal area generally in the opposite hemisphere, we selected patients whose other hemisphere was completely normal. Nine of the patients had a large hypodense area, the size of which was larger than 3 x 3 cm. The other 7 patients had simple lacunar lesions ranging from 5 to 10 mm in diameter on X-CT. All patients had moderate to severe hemiparesis or sensory disturbance, and 4 patients complained of motor aphasia.

To prevent a reattack of stroke and to increase blood flow around the infarct area, bypass surgery between the superficial temporal artery and middle cerebral artery (STA-MCA anastomosis) was undertaken in 5 of 6 patients with occlusion. More than 6 months later, 

\[ F = R \times Cb/(N \times A) \]

where \( F \) is the cerebral blood flow in milliliters per 100 grams per minute, \( Cb \) is the brain activity concentration (in microcuries per milliliter) derived from the SPECT images, and \( R \) is the constant withdrawal rate of arterial blood in milliliters per minute, which was actually 1 ml/min. If measurement is performed sufficiently early (eg, at 5 minutes), then back diffusion is negligible. \( A \) is the total activity (from 0 to 5 minutes) in microcuries of arterial whole blood withdrawn, and \( N \) is the fraction of \( A \) that is true tracer activity. The value of \( N \) was measured by octanol extraction of the arterial blood reference sample, in which unmetabolized \([\text{I}^{231}]\text{IMP}\) was extracted from the sample.\(^4\)

\( Cb \) was obtained by the SPECT system, and \( N \) and \( A \) by a well-scintillation counter system, the actual unit of which was counts per minute per milliliter. These two systems were different, and therefore cross-calibration was needed between the systems before this study. A cross-calibration factor was obtained using a series of phantoms (21 cm in diameter x 19 cm in height) composed of water with one of 11 concentrations of \([\text{I}^{231}]\text{IMP}\). The activity of the SPECT images on the computer was linearly related to the activity concentration in the phantom measured with the well-scintillation counter. \( Cb \) was calculated by multiplying the real activity of the brain SPECT by the calibration factor.

The reproducibility of this measurement was confirmed by performing this study twice on 5 of 16 patients and 2 of 8 normal control subjects, with a 7-day interval between studies. To keep the conditions of the two studies the same, patients were laid on a bed in a dark, quiet room for 30 minutes with earplugs before the study, and \(\text{Paco}_2\) was checked at the time \([\text{I}^{231}]\text{IMP}\) was injected.

When measuring the rCBF of the normal control subjects, we selected 15 x 15-mm square regions of interest (ROIs) on the transaxial slice computer images. Three ROIs were placed in the frontal cortex of each hemisphere, two in the temporal cortex, one in the basal ganglia, and one in the occipital cortex. On the slice that included the centrum semiovale, two ROIs were placed in the parietal cortex of each hemisphere. On the slice 18 to 24 mm above the orbitomeatal line, an ROI was placed in each of the bilateral cerebellar hemispheres. Anatomical identification of each position was made by superimposing the SPECT films on the X-CT films. rCBF in each region was calculated as the mean of rCBF on the right and left sides.

In the nine patients whose hypodense areas of infarction were larger than 3 x 3 cm on X-CT, the same-sized square ROIs were placed on three different areas of the SPECT image on the computer (Fig 1). One was selected on an infarct area that was revealed as a severe filling defect of tracer activity on SPECT images and that corresponded to a hypodense area on X-CT. Since infarct areas were usually surrounded by low-perfusion areas on SPECT, another ROI was placed on the peri-infarct area, in which moderately decreased tracer activity was observed, although the density was almost normal on X-CT. The third ROI was placed in the normal hemisphere on the symmetrically opposite side of the infarct area, where both the tracer activity on SPECT and density on X-CT were completely normal.
Although a small infarct on X-CT was difficult to observe as a filling defect with SPECT, we could usually observe it as an area of moderately low perfusion around the actual infarct lesion. In the seven patients with small infarct lesions that were shown as the low-perfusion areas, 3×3-cm square ROIs were placed on two different areas on the computer. One was placed on the low-perfusion area, which was categorized as a peri-infarct area. The other was placed on the normal area, the same as above.

To assess the redistribution phenomenon more objectively, we mathematically defined a redistribution rate (RD rate) as follows:

$$\text{RD Rate} = \frac{(I - II)}{I} \times 100\%$$

where $$I = (B-A)/B$$ and $$II = (B'-A')/B'$$, $$A$$ represents the activity of the infarct area or the peri-infarct area on the early SPECT image, and $$B$$ represents the activity of the normal area located on the opposite side of area $$A$$. $$A'$$ and $$B'$$ represent the activity on the delayed SPECT image corresponding to areas $$A$$ and $$B$$, respectively (Fig 2).

### Statistical Analysis

Comparisons of group differences of mean CBF in the infarct area, peri-infarct area, and normal cortex were made by one-way analysis of variance and unpaired $$t$$ test. Statistical significance of the effects of bypass surgery was assessed using one-way analysis of variance and paired $$t$$ test. The criterion for significance was set at $$P<.01$$ and $$P<.05$$, and all data are presented as mean±SD.

### Results

rCBF (mean±SD) of the normal subjects was as follows: frontal cortex, 55.4±7.9 mL/100 g per minute; temporal cortex, 58.9±7.3 mL/100 g per minute; occipital cortex, 58.5±4.9 mL/100 g per minute; parietal cortex, 58.0±8.6 mL/100 g per minute; basal ganglia, 60.5±5.5 mL/100 g per minute; centrum semiovale, 24.6±3.5 mL/100 g per minute; and cerebellum, 67.0±9.0 mL/100 g per minute. Supratentorial mean CBF and the ratio of gray matter to white matter were 52.7±5.0 mL/100 g per minute and 2.34, respectively. The rCBF of the cerebellum was higher than that of other regions. The reproducibility of this measuring method was $$r=.99$$ (n=7 [30 regions]), indicating that the method is quite dependable.

Fig 3 presents the mean rCBF of the three regions in the patient population. rCBF of the infarct area was 13.4±4.5 mL/100 g per minute (mean±SD); the peri-infarct area, 31.9±6.5 mL/100 g per minute; and the normal area on the opposite side of the infarct, 49.2±9.7 mL/100 g per minute. Fig 4 illustrates the results of the relation between rCBF and the RD rate. When rCBF was below 20 mL/100 g per minute, the RD rate was less than 50% and redistribution was minimally present. If rCBF was between 20 and 40 mL/100 g per minute, the rate exceeded 50% and redistribution became prominent. When rCBF was more than 40 mL/100 g per minute, the RD rate tended to decrease. The patient shown in Fig 1 shows prominent redistribution with an area of rCBF in the range of 25 to 40 mL/100 g per minute around infarct lesions in the left MCA territory.

Surgical therapy consisting of STA-MCA anastomosis was performed on 5 patients with occlusion in the MCA territory (3 with infarct lesions and 2 with lacunar
lesions). The mean CBF and mean RD rate in the peri-infarct area of 5 patients were 31.0±7.8 mL/100 g per minute and 91±22%, respectively. After the bypass surgery, the rCBF in the area significantly increased by a mean of 7 mL/100 g per minute (+22%). While the mean CBF and RD rate in the infarct area of 3 patients were 10.8±4.7 mL/100 g per minute and 39±5%, respectively, there was no significant change in rCBF in the area after the operation (Fig 5). Motor aphasia and paresis in 2 patients with lacunar lesions who showed high RD rate (mean, 94%) in the peri-infarct area were improved after bypass surgery. Hemiparesis in 3 patients with infarct lesions was improved in one patient whose RD rate in the preoperative state was 37% in the infarct area and 105% in the peri-infarct area. Hemiparesis was not improved in the others, whose RD rates were 34% and 45% in the infarct area and 63% and 100% in the peri-infarct area, respectively. Therefore, high RD rate might be related to a good clinical outcome. Fig 6 shows an example of a 57-year-old man with small lacunar lesions in the subcortical white matter near the left lateral ventricle who complained of motor aphasia and moderate paresis. On the early SPECT, low-perfusion areas were observed in the left middle and inferior frontal gyri (Broca's area) and left temporal cortex, the rCBF of which was 26 to 33 mL/100 g per minute, and marked redistribution was revealed on the delayed image. After the bypass surgery, rCBF in the area increased to 31 to 40 (+19%) mL/100 g per minute.

**Discussion**

Redistribution is one of the phenomena that is judged by comparing an early image and a delayed image. Evaluation is usually done visually, and its importance in determining the patient's ultimate prognosis is still controversial. We have expanded on the qualitative method of Raynaud et al.10 and obtained absolute values for the [131]IMP RD rate with SPECT. The strength of the present study is that the RD rates were measured from exactly the same area as those used for rCBF measurement. This made it possible to precisely analyze the relation between changes in rCBF and the redistribution phenomenon in ischemic lesions.

A chronic infarct defined by a hypodense lesion on X-CT is shown as an area of low activity on early [131]IMP SPECT and can be differentiated into two abnormal zones. First, the infarct area corresponding to the hypodense area on X-CT was characterized by a severe decrease in IMP tracer uptake and rCBF ranging from 9 to 20 mL/100 g per minute in our study. The current concept regarding stroke is that the critical ischemic threshold of CBF is 10 to 20 mL/100 g per minute,11 and lethal failure with membrane damage occurs at approximately 10 mL/100 g per minute. The irreversible changes associated with this lethal failure are seen as a hypodense area on X-CT.12-14 rCBF of the infarct area in the present study may correspond to that of the ischemic threshold, and no corresponding redistribution phenomenon was observed in the delayed SPECT images. The other abnormal zone was the peri-infarct area, characterized by a moderate decrease in tracer uptake and rCBF ranging from 22 to 40 mL/100...
Fig 6. Computed tomography (two left panels) and single-photon emission computed tomography (SPECT) in a 57-year-old man with small lacunar lesions. SPECT images before (four middle panels) and after (two right panels) bypass surgery show an increase of regional cerebral blood flow in the left middle cerebral artery territory (arrows). In this area, prominent redistribution was observed on the delayed SPECT image.

Alzheimer’s disease, seizure, and herpes simplex virus encephalitis. However, in most of these reports, the quantitative measurement of rCBF was not applied. When we consider the dynamic state of the patient, SPECT images without rCBF are certainly useful, and those with absolute values of rCBF are clinically more useful, because such values accurately indicate metabolic changes in the brain. When we measured the rCBF of normal subjects by the microsphere model with a dual-head rotating gamma camera, the absolute values of mean CBF were 57.5±1.4 and 24.6±3.5 mL/100 g per minute for gray and white matter, respectively, with a ratio of gray matter to white matter of 2.34 and a global flow value of 52.7±5.0 mL/100 g per minute. The global flow value agrees well with those of 47.2±5.4 mL/100 g per minute reported by Kuhl et al., 47.0±2.9 mL/100 g per minute by Greenberg et al., and 68 mL/100 g per minute by Podreka et al.

When using the dual-head rotating gamma camera for SPECT, we encountered the problem of resolution. Hence, when the infarct areas were analyzed in our study, patients who had relatively large hypodense areas on X-CT were selected. The resolution problem, however, might not be negligible when smaller infarcts are considered. Further studies of the relation between the redistribution phenomenon, histopathological findings, and prognosis of ischemic patients using a high-resolution SPECT technique, such as a ring-type SPECT detector, are indicated to resolve these issues.

rCBF measurement with [123]IMP SPECT using the microsphere model might be a useful technique to assess patients with ischemic cerebrovascular diseases. We believe that redistribution on delayed SPECT imaging is based on the low blood flow of reversible...
ischemic lesions. Evaluation of the redistribution phenomenon may play an important role in establishing the prognosis and evaluating the efficacy of therapy in stroke patients.

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References

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