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

Ikuko Odano, MD, PhD; Toshiaki Tsuchiya, MD; Mamiko Nishihara, MD, PhD; Kunio Sakai, MD, PhD; Hiroshi Abe, MD, PhD; Ryuichi Tanaka, MD, PhD

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 nonspecific amine-binding sites. The initial [123I]IMP SPECT image during the first 10 to 30 minutes (early image) represents the distribution of rCBF. Kuhl and coworkers3 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 35Xe three-dimensional method4 and the 15O-water positron emission tomography method.5

Redistribution is related to the "filling-in" phenomenon.6,7 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 $3 \times 3$ cm or smaller than $1.0$ cm in diameter, and it was located in the unilateral supratentorial 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 $3 \times 3$ 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, $^{123}$IIMP SPECT was performed again on the same patients with the same technique to evaluate the effects of the surgical therapy.

**Data Acquisition and Analysis**

$N$-Isopropyl-$p$-$^{123}$Iiodoamphetamine was obtained from Nihon Medi-Physics (Takarazuka, Japan). The $^{123}$I was produced by the process of $^{127}\text{I}(\rho, 2n){}^{125}\text{Xe} \rightarrow ^{123}\text{I}$, a reaction of which produced less than 4.5% $^{125}$I contamination. A dose of 3.5 to 4.5 mCi of $^{123}$IIMP was injected intravenously. Fifteen minutes later, SPECT studies (early imaging) were performed with a dual-detector Siemens ZLC/75 Scintivac equipped with a Scintipac 2400 computer system. All patients and normal control subjects wore earplugs, and their eyes were closed before injection. SPECT data were acquired as follows: sampling angle of the gamma camera, $6^\circ$; sampling time, 60 seconds; slice thickness of reconstruction, 6 mm. All data were acquired in $64 \times 64$ matrices on the computer. Prefiltered raw data (Wiener and Butterworth filter) were used to construct transaxial sections according to a filtered back-projection algorithm (Shepp and Logan filter). An absorption correction was performed with Sorenson’s method ($\mu=0.12$ cm$^{-1}$), but no scatter correction was used. The camera heads were equipped with middle-energy collimators. The full width at half maximum spatial resolution was approximately 1.7 cm within the image plane and 1.7 cm in the axial direction. Each SPECT transaxial slice was obtained parallel to the orbitomeatal line. Five hours later, delayed SPECT imaging was performed with the same technique (without reinjection of $^{123}$IIMP). On the same day, X-CT with a General Electric CT/T 8800 system was obtained in the same position, the same slice thickness, and the same magnification as the SPECT study. Anatomic identification of each position was made by superimposing the SPECT films on the X-CT films.

$rCBF$ was measured by an arterial blood sampling method and the microsphere model as follows:

$$F=R \times Cb/(N \times A)$$

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 $^{123}$IIMP was extracted from the sample. $Cb$ 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 $\times$ 19 cm in height) composed of water with one of 11 concentrations of $^{123}$IIMP. 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 $^{123}$IIMP was injected.

When measuring the $rCBF$ of the normal control subjects, we selected $15 \times 15$-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. Anatomic 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 $3 \times 3$ 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, 3x3-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:

\[
RD\ Rate = \frac{|I - II|}{I} \times 100\%
\]

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 and obtained absolute values for the [123I]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 [123I]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, 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. The 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 3. Plot of regional cerebral blood flow (CBF) in infarct area, peri-infarct area, and contralateral normal cortex of the patient population. Values are mean±SD and significantly different (P<.01 and P<.05).

Fig 4. Plot shows correlation between regional cerebral blood flow (CBF) and redistribution rate in ischemic lesions. There is a significant correlation. Redistribution is noticed at 25 to 40 mL/100 g per minute of regional CBF and is marked at approximately 30 mL/100 g per minute.

Fig 5. Bar graph shows regional cerebral blood flow (CBF) changes in infarct area, peri-infarct area, and contralateral normal cortex before and after bypass surgery. Mean redistribution rate was 91±22% in the peri-infarct area before bypass surgery. After the operation, regional CBF in the area significantly increased by 22% (P<.01). There was no change in regional CBF in the infarct area and contralateral normal cortex.
g per minute, the area of which extended around the infarct core and showed normal density on X-CT. The common view is that old infarcts are surrounded with a wide zone of low blood flow and metabolism and are not seen by X-CT. In our study, the peri-infarct area corresponded with this zone, in which we found marked redistribution of the tracer on delayed SPECT images. The redistribution in the peri-infarct area became obscured when blood flow increased to the normal value. Thus, it appears that redistribution has its basis in the low blood flow in ischemic lesions.

Although the infarcts are sharply demarcated macroscopically, there are two opinions as to the histopathological findings of the peri-infarct area on X-CT. One is that there is massive neuronal loss and damage to affected fibers surrounding the infarcts, which causes functional inactivation. The other suggests that intact neurons surround the infarcts and low blood flow and metabolism result from neuronal disconnection. In our study of five patients, in which SPECT studies before and after bypass surgery were compared, rCBF was increased by 22% in the peri-infarct area after the procedure. Moreover, in two patients who showed distinct redistribution in Broca’s area, motor aphasia and hemiparesis improved after anastomosis. Although lesions that cause motor aphasia may involve areas besides Broca’s, involvement with that region plays an important role in motor aphasia. Redistribution may be closely associated with a patient’s good clinical outcome. These data suggest that redistribution might be related to neuronal disconnection or diaschisis rather than neuronal loss.

SPECT with $^{[12]}$IMP has been used for the diagnosis of not only cerebrovascular diseases but also dementia, 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. and 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 $^{[12]}$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.

Acknowledgments

The authors thank Dr. Arthur Weissman, PhD, and Dr. Toshihiro Takao, MD, PhD, Neurobiology Laboratory, Neuroscience Branch, National Institute on Drug Abuse/Addiction Research Center, for proofreading.

References

Regional cerebral blood flow measured with N-isopropyl-p-[123I]iodoamphetamine and its redistribution in ischemic cerebrovascular disease.
I Odano, T Tsuchiya, M Nishihara, K Sakai, H Abe and R Tanaka

Stroke. 1993;24:1167-1172
doi: 10.1161/01.STR.24.8.1167

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/24/8/1167

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/