Relationship Between Vasodilatation and Cerebral Blood Flow Increase in Impaired Hemodynamics: A PET Study with the Acetazolamide Test in Cerebrovascular Disease

Hidehiko Okazawa, MD, PhD[1,2]; Hiroshi Yamauchi, MD, PhD[1]; Hiroshi Toyoda, MD, PhD[1,2]; Kanji Sugimoto, MS[1]; Yasuhisa Fujibayashi, PhD[2]; and Yoshiharu Yonekura, MD, PhD[2]

[1]PET Unit, Research Institute, Shiga Medical Center, Moriyama, Japan; and [2]Biomedical Imaging Research Center, Fukui Medical University, Fukui, Japan

The changes in cerebral blood flow (CBF) and arterial-to-capillary blood volume (V_0) induced by acetazolamide (ACZ) are expected to be parallel each other in the normal circulation; however, it has not been proven that the same changes in those parameters are observed in patients with cerebrovascular disease. To investigate the relationship between changes in CBF, vasodilatory capacity, and other hemodynamic parameters, the ACZ test was performed after an ^{15}O-gas PET study. **Methods:** Twenty-two patients with unilateral major cerebral arterial occlusive disease underwent PET scans using the $H_2{}^{15}O$ bolus method with the ACZ test after the ^{15}O-gas steady-state method. CBF and V_0 for each subject were calculated using the 3-weighted integral method as well as the nonlinear least-squares fitting method. After evaluation of accuracy in V_0 values, a new parameter, the CBF/V_0 ratio, which is expected to disclose arterial perfusion pressure, was also compared between the conditions. **Results:** The regional CBF (rCBF) and V_0 increased significantly after ACZ administration in the hemisphere contralateral to the ischemic side. However, in a subgroup of patients who showed a significant reduction in the rCBF increase in the ipsilateral hemisphere (group A), the ACZ injection caused no change or a slight decrease in rCBF even though the V_0 showed a significant increase. Thus, the increases in rCBF and V_0 did not necessarily parallel each other in the ipsilateral hemispheres of patients who have impaired cerebral circulation. A parameter defined by the rCBF/V_0 ratio decreased significantly in the ipsilateral hemisphere of group A after ACZ administration, although the ratio showed no change in the contralateral hemisphere or in the other subgroup (group B). **Conclusion:** The change in the rCBF/V_0 ratio after ACZ challenge may represent an alteration in arterial perfusion pressure that is expected to indicate a critical hemodynamic status in patients with cerebrovascular disease, especially in patients who have a reduced rCBF response.

Key Words: acetazolamide; cerebrovascular disease; cerebral blood volume; vasodilatory capacity; cerebral perfusion pressure

J Nucl Med 2003; 44:1875–1883

The ability of autoregulation to maintain the cerebral blood flow (CBF), which resides in the cerebral circulation despite transient changes in systemic mean arterial blood pressure, has been shown to occur via the mechanism of arteriolar vasodilatation in the cerebral circulation (*1*). The vasodilatory change in the cerebral arteries is assumed for the compensatory hemodynamic stages in occlusive cerebrovascular disease (CVD) (*2*), which is the basis of the acetazolamide (ACZ) test for evaluating the residual vasodilatory capacity in those patients. The test assesses the cerebrovascular response to a vasodilatory stimulus by measuring changes in CBF or blood velocity (*3–5*), and it has been used for evaluation of the cerebral hemodynamic status and the risk of cerebral ischemia in patients with cerebral arterial occlusive diseases. However, it remains unknown whether the CBF increase induced by ACZ administration accurately represents the vasodilatory capacity under the varying hemodynamic conditions observed in stenoocclusive CVD. Although our previous study with healthy volunteers proved that changes in CBF were accompanied by changes in the vascular distribution volume (V_0), which represents the arterial-to-capillary blood volume (*6,7*), a vasodilatory stimulus in the affected area of patients may induce a different hemodynamic response to the stimulus because a severe occlusive change in the major cerebral arteries would affect the regional perfusion pressure. The relationship between arterial vasodilatation and an increase of regional CBF (rCBF) seems more complicated in the affected part of the brain compared with the normal cerebral

Received Mar. 10, 2003; revision accepted Aug. 14, 2003.

For correspondence or reprints contact: Hidehiko Okazawa, MD, PhD, Biomedical Imaging Research Center, Fukui Medical University, 23-3 Shimoaizuki, Matcuoka-cho, Fukui, 910-1193, Japan.

E-mail: okazawa@fmsrsa.fukui-med.ac.jp

circulation, suggesting that the measurement of rCBF changes induced by ACZ may not properly evaluate the status of hemodynamic impairment. Furthermore, a decrease in rCBF after ACZ administration, the so-called steal phenomenon, may be observed instead of an increase in patients with CVD (*8*,*9*).

The phenomenon is presumed to be caused by the redistribution of blood from the impaired regions, where autoregulatory vasodilatation is already at its maximum in response to a reduced perfusion pressure, to the relieved areas, where the ability of vasodilatation still exists. This also may be induced by the redistribution of regional arterial perfusion pressure according to the relative differences in the regional vasodilatory capacity. However, it has not yet been proven that the maximal vasodilatation with the exhaustion of vasodilatory capacity causes the steal phenomenon induced by a vasodilatory stimulus. Additional information obtained from regional changes in V_0 in the ACZ test would reveal the relationship between blood flow and vasodilatory capacity as well as provide a new index for the assessment of impaired hemodynamic status in patients with severe arterial occlusive disease. Because the cerebral perfusion pressure (C_{pp}) is considered to be correlated with the flow-to-volume ratio ($C_{pp} \propto F/V$) (*2*,*10*,*11*), the arterial perfusion pressure would be related to the CBF/V_0 that will reveal a change in arterial C_{pp}. The result that the changes in CBF and V_0 induced by ACZ were parallel in healthy subjects was consistent with this assumption under no change in the systemic blood pressure and the stable C_{pp} (*8*).

To investigate whether changes in rCBF induced by ACZ accurately reflect the vasodilatory capacity and hemodynamic stages in patients with CVD, PET scans were used for the measurement of CBF, V_0, and other hemodynamic parameters to assess the status of cerebral circulation and the vasodilatory capacity. Time–activity curves obtained from dynamic data of $H_2{}^{15}O$ PET were analyzed to evaluate whether the impaired cerebral circulation affected the timing of tracer arrival, which may cause a difference in the tracer kinetics of each hemisphere in patients. To ensure that the V_0 values were not affected by the calculation methods, V_0 was calculated using both a nonlinear least-squares (NLS) fitting and the 3-weighted integral (3-WI) method (*9*,*12*).

MATERIALS AND METHODS

Subjects

The study consisted of 22 patients (18 men, 4 women; age range, 51–77 y; mean ± SD, 66.4 ± 7.3 y) with unilateral major cerebral arterial occlusive disease. All patients studied had an occlusion or 99% stenosis in the unilateral internal carotid artery (ICA) or in a middle cerebral artery (MCA; 5 patients), which should be appropriate with the accompanying symptoms. Of the 22 patients, 5 had suffered transient ischemic attacks (TIAs), 15 had had a nonsevere, nondisabling hemispheric stroke with mild disability, and 2 had no neurologic symptoms. The interval between the latest ischemic event and the individual PET scan ranged from 2 wk to 37 mo. All 10 patients with an occlusion and 6 patients with severe stenosis in the major cerebral arteries had collateral circulations from the contralateral hemisphere via the anterior or posterior communicating arteries, the ophthalmic artery, or the leptomeningeal arteries in the same side of the occlusion. The other 6 patients with severe stenosis did not show visible collateral circulation. The study was approved by the Ethical Committee of the Research Institute of Shiga Medical Center, and written informed consent was obtained from each subject before the study.

PET Procedures

All subjects underwent PET scans with a whole-body tomography scanner (Advance; General Electric Medical Systems), which permits simultaneous acquisition of 35 image slices with an interslice spacing of 4.25 mm (*13*). Performance tests showed the intrinsic resolution of the scanner to be 4.6–5.7 mm and 4.0–5.3 mm in the transaxial direction and the axial direction, respectively. A transmission scan was performed using $^{68}Ge/^{68}Ga$ for attenuation correction in each subject before tracer administration. All emission scans were acquired in a 2-dimensional mode. The PET data were reconstructed using a Hanning filter with a resolution of 6.0-mm full width at half maximum in the transaxial direction.

The subjects were positioned on the scanner bed with their heads immobilized using a head holder. A small cannula was placed in the left brachial artery for blood sampling. The patients underwent PET scans using the bolus method with 1,110 MBq $H_2{}^{15}O$ and dynamic data acquisition, followed by the steady-state method with ^{15}O-gas inhalation as described (*14*). An additional $H_2{}^{15}O$ bolus PET scan was performed 10 min after ACZ injection. For the CBF measurement using the bolus method with $H_2{}^{15}O$ injection, a 3-min dynamic PET scan was started at the time of tracer administration from the right antecubital vein with frame durations of 5 s × 12, 10 s × 6, and 20 s × 3. The radioactivity in the arterial blood was counted continuously using an automatic coincidental radioactive counter (Pico-Count; Bioscan Inc.) during the $H_2{}^{15}O$ scans (*15*). The arterial blood was drawn using a Bio-minipump (AC-2120; Atto Co.) at a constant rate of 7 mL/min for the first 2 min, followed by manual sampling of 0.5 mL of blood every 20 s during the rest of the scan time (*16*). Radioactivity counted by the automatic radioactive counter was calibrated with that of the arterial blood sampled manually. Decay of the radioactivity from PET and blood data was corrected to the starting point of each scan, and dispersion for the external tube in the arterial curves was corrected with a double-exponential dispersion function (*16*,*17*).

In the steady-state method (*18*,*19*), the subjects inhaled $C^{15}O_2$ (400 MBq/min) and $^{15}O_2$ (800 MBq/min) continuously for approximately 10 min, followed by static data acquisition for 5 min to obtain images of the CBF, oxygen extraction fraction (OEF), and cerebral metabolic rate of oxygen ($CMRO_2$). Each subject also inhaled $C^{15}O$ as a single dose of 1,200 MBq to obtain a cerebral blood volume (CBV) image (*14*). Arterial blood was sampled during each procedure and the radioactivity in the blood was immediately measured with a scintillation counter. During the PET scanning for the steady-state method with $^{15}O_2$, the sampled blood was divided into 2 aliquots to count the radioactivity of both whole blood and plasma. The arterial tensions for CO_2 ($PaCO_2$) and O_2 (PaO_2), the pH, and the total arterial O_2 content for calculation of the $CMRO_2$ were also measured from one of the blood samples. The blood pressure of each subject was measured continuously through the arterial line and displayed on a monitor during the PET study.

ACZ (1.0 g/10 mL saline) was administered intravenously over 60 s at a constant flow rate after the ^{15}O-gas scans. The $H_2{}^{15}O$ PET scan to measure changes in CBF and V_0 was started 10 min after ACZ administration using the same procedure as for the baseline scanning.

Calculation of Parametric Images and Regional Values in Bolus Method

In the bolus method, CBF (mL/min/100 g) and V_0 (mL/100 g) images were calculated from the dynamic PET data and arterial blood curves by means of the 3-WI method based on a 2-compartment model expressed by the following equation:

$$M(t) = K_1 C_a(t) \otimes e^{-k_2 t} + V_0 C_a(t),$$

where K_1 (mL/min/g) and k_2 (/min) are rate constants for the tracers, M (Bq/g) is the radioactivity in brain tissue, and C_a (Bq/mL) is an arterial input function. The calculation procedure for the 3-WI method has been described in detail elsewhere (*7,12*). In the 3-WI method, the time delay of arterial input was corrected automatically in the program, and a time constant of $\tau = 4$ s was used for the internal dispersion correction (*7,20,21*). For the calculation of the CBV (mL/100 g) from the $C^{15}O$ scan data, a cerebral-to-large vessel hematocrit ratio of 0.85 was used (*22,23*).

V_0 values were also obtained from the dynamic data of the $H_2{}^{15}O$ bolus PET using an NLS fitting to the full operation equation for the 2-compartment model described above. The regions of interest (ROIs) were drawn on the cortical territories of the MCA in the bilateral hemispheres at the level of the centrum semiovale as shown in Figure 1, and the time–activity curves were obtained from the dynamic data of the $H_2{}^{15}O$ scans. To avoid including infarct areas in each ROI, individual MR images were referred to when drawing the ROIs. In the NLS fitting, the arterial input function with dispersion correction and the tissue time–radioactivity curve obtained from each ROI were fitted to estimate an appropriate time shift for each region in the bilateral hemisphere using the slope method (*7,21*). Using the same ROIs, the regional V_0 values for the baseline condition and after ACZ administration were obtained from the V_0 images calculated by the 3-WI method to compare them with those obtained by the NLS method. To evaluate accuracy of the model applied in this study, the NLS method was also applied to another model without V_0 (no-V_0 model) in the previous equation. The 2 models were compared for each hemisphere and for the 2 conditions using the Akaike information criteria (AIC) (*24*).

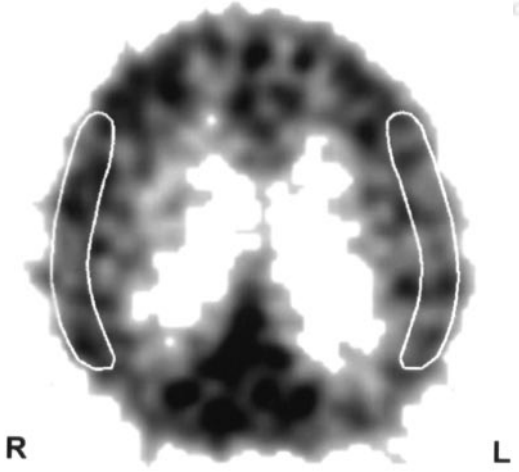

FIGURE 1. ROIs drawn on cortical territories of MCAs in bilateral hemispheres at level of centrum semiovale with reference to individual MR images. Time–activity curves for $H_2{}^{15}O$ PET scans and regional values in parametric images were obtained using the same ROIs for each subject.

Data Analysis

Regional values for each parametric image were determined using the same ROIs described above, which were applied to all parametric images for each subject. The regional values of each hemodynamic parameter thus obtained were compared statistically between the 2 hemispheres using a paired t test. Differences in rCBF and V_0 images between the 2 conditions before and after ACZ administration as well as between the bilateral hemispheres were compared statistically using repeated-measures ANOVA. Any relationship between the parameters in patients was also examined in each hemisphere using a linear regression analysis with an F test. To evaluate the changes in rCBF and V_0 before and after ACZ, the ratio of rCBF to V_0 (rCBF/V_0 ratio) was obtained for each region and compared between the bilateral hemispheres in the 2 conditions.

Patients were divided into 2 groups according to the results of the percentage change in rCBF obtained from the ACZ challenge studied previously in the healthy volunteers (*6*). The lower limit percentage in the rCBF increase was defined from the 95% reference range of the mean percentage increase in the 16 hemispheres of 8 volunteers who had the CBF measured 10 min after the ACZ challenge (*6*); the value was expected to include 95% population of healthy subjects (*25*). Group A consisted of patients who showed an rCBF increase of the ipsilateral hemisphere less than the limit of 10.5% (mean − 2 SD of the percentage increase in volunteers), and the rest of the patients were defined as group B. The differences in rCBF and V_0 between the 2 conditions and differences in each parameter of the 2 hemispheres were compared in each group using repeated-measures ANOVA.

When a difference was detected by the repeated-measures ANOVA, a post hoc comparison was performed using a paired t test. $P < 0.05$ was considered to indicate a statistically significant difference. A correction for multiple comparisons was applied to the threshold probability value of the paired t test to keep overall $\alpha = 0.05$ when testing multiple null hypotheses.

RESULTS

Of the 6 physiologic parameters measured in the 22 patients at baseline and after ACZ, only the Pa_{O_2} increased significantly from 76.6 ± 10.1 to 92.2 ± 13.0 mm Hg between the 2 conditions of baseline and after ACZ administration ($P < 0.0001$, repeated-measures ANOVA). Mean blood pressure and Pa_{CO_2}, which may affect the CBF values, and the other 3 physiologic variables did not change during the study.

The mean regional values for the cortical territories of the bilateral MCA in all patients are given in Table 1. Both hemispheres in the patients showed a significant increase in rCBF after ACZ administration, although the percentage change in rCBF in the ipsilateral hemisphere was significantly smaller than that in the contralateral hemisphere ($P < 0.001$, paired t test). The rCBF was significantly different

TABLE 1
Changes in CBF and V_0 in ACZ Test and Other Parametric Values (Mean ± SD)

Parameter	Patients with CVD (n = 22)	
	Ipsilateral	Contralateral
CBF (mL/min/100 g)		
Baseline	36.5 ± 8.1*	40.8 ± 6.8
ACZ	41.5 ± 11.2*†	54.7 ± 9.5‡
Change (%)	13.6 ± 20.2*	35.1 ± 17.6
V_0 (mL/100 g)		
Baseline	1.73 ± 0.50*	2.11 ± 0.51
ACZ	2.23 ± 0.61*‡	2.94 ± 0.73‡
Change (%)	31.8 ± 26.1§	42.6 ± 30.7
$CMRO_2$ (mL/min/100 g)	2.71 ± 0.44§	2.99 ± 0.33
OEF (%)	50.2 ± 7.4§	47.7 ± 6.2
CBV (mL/100 g)	4.21 ± 0.50§	3.90 ± 0.49

*$P < 0.001$, §$P < 0.005$ comparing between bilateral hemispheres (repeated-measures ANOVA and paired t test).
†$P < 0.005$, ‡$P < 0.001$ comparing before and after ACZ administration (repeated-measures ANOVA and paired t test).
Values are given for regions of bilateral MCAs.

between the 2 conditions ($P < 0.005$ and $P < 0.0001$) and between the bilateral hemispheres ($P < 0.001$, repeated-measures ANOVA). V_0 values obtained from the 3-WI method also showed significant differences in the 2 conditions ($P < 0.0001$) and in the 2 hemispheres ($P < 0.001$, repeated-measures ANOVA). The percentage increase in V_0 was significantly smaller in the ipsilateral hemisphere than that in the contralateral hemisphere ($P < 0.005$, paired t test). All parameters measured from the ^{15}O-gas steady-state method were significantly different between the bilateral hemispheres. In the ipsilateral hemisphere, CBV and OEF were increased, whereas the $CMRO_2$ was decreased ($P < 0.005$, paired t test). Because the CO_2 PET data were used only for calculation of OEF and $CMRO_2$ images in this study, rCBF values calculated from the steady-state method were not included in Table 1. The values were 33.7 ± 10.1 and 38.9 ± 7.5 mL/min/100 g for the ipsilateral and contralateral hemispheres, respectively, which were not different from the baseline rCBF by the $H_2{}^{15}O$ bolus method.

The V_0 values were also calculated by means of the NLS fitting method with the tissue time–activity curves obtained from the dynamic PET data using the same ROIs on the bilateral MCA territories. Figure 2 shows 2 representative tissue time–activity curves of the bilateral hemispheres and the results of the NLS fitting method. No time difference was observed in the arrival of tracer between the bilateral cortical regions of the MCA territories with a moderate rCBF difference (Fig. 2A) or a significant rCBF difference (Fig. 2B). Table 2 shows the V_0 values calculated from the 3-WI and NLS methods. The values were not different in the each hemisphere for both conditions irrespective of the calculation methods. The effect of kinetic modeling on the NLS fitting was evaluated using the AIC values. In the baseline condition, the AIC values were 234 ± 16 (ipsilateral) and 237 ± 18 (contralateral) for the V_0 model and 238 ± 15 (ipsilateral) and 243 ± 17 (contralateral) for the no-V_0 model. After the ACZ injection, the values were 240 ± 18, 247 ± 18, 248 ± 16, and 259 ± 21, respectively. The V_0 model showed significantly smaller AIC values than the no-V_0 model ($P < 0.0001$, repeated-measures ANOVA), whereas the laterality of hemispheres did not differ between the 2 models.

Patients were divided into 2 groups as defined by the normal limit of the rCBF increase in the ipsilateral hemisphere. Group A consisted of 11 patients who had a smaller increase in the ipsilateral rCBF than the limit, and group B consisted of the other 11 patients who had a greater rCBF increase than the limit. Of the 11 patients in group A, 4 had a history of TIAs (36%), 5 had suffered a stroke, and the other 2 had minor or no symptoms. On the other hand, 10 patients from group B had suffered a

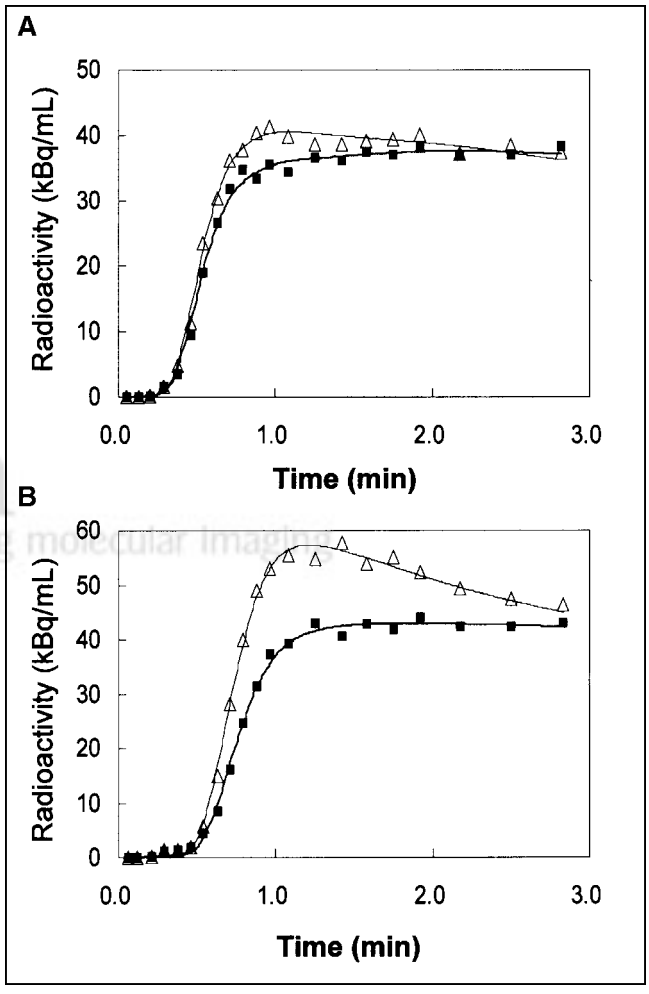

FIGURE 2. Representative tissue time–activity curves of ipsilateral (■) and contralateral (△) hemispheres as well as results of NLS fitting (solid line) with full operation equation for 2-compartment model. No difference in tracer arrival time between 2 hemispheres was observed in either case with moderate (A) or with significant (B) difference in bilateral rCBF.

TABLE 2
Comparison of V_0 Values (Mean ± SD) Calculated from 3-WI and NLS Methods

Subjects	3-WI method (mL/100 g)		NLS fitting (mL/100 g)	
	Baseline	ACZ*	Baseline	ACZ*
All patients (n = 22)				
Ipsilateral	1.73 ± 0.50	2.23 ± 0.61	1.75 ± 0.47	2.28 ± 0.60
Contralateral	2.11 ± 0.51	2.94 ± 0.73	2.16 ± 0.50	3.03 ± 0.83
Group A (n = 11)				
Ipsilateral	1.57 ± 0.51	1.95 ± 0.46	1.63 ± 0.54	2.06 ± 0.49
Contralateral	2.08 ± 0.60	2.85 ± 0.86	2.15 ± 0.52	2.97 ± 1.00
Group B (n = 11)				
Ipsilateral	1.89 ± 0.44	2.52 ± 0.63	1.86 ± 0.38	2.49 ± 0.64
Contralateral	2.14 ± 0.43	3.03 ± 0.61	2.17 ± 0.50	3.08 ± 0.68

*After ACZ administration.
Values were obtained from data of cortical territories in bilateral MCAs.

stroke (91%) and only 1 patient had a history of TIA (9%). The mean age of groups A and B was 65.2 ± 6.2 y and 67.6 ± 7.7 y, respectively, which were not significantly different. Mean values for each parameter as well as the changes in rCBF and V_0 for the 2 conditions are shown in Table 3. The absolute values of rCBF and V_0 were significantly different between the 2 hemispheres in both groups. However, the percentage change in rCBF did not differ in the 2 hemispheres of group B. The ipsilateral hemisphere of group A showed a slight decrease in rCBF after ACZ administration because 7 patients in group A showed a decrease in rCBF in the ipsilateral hemisphere. An index of the $rCBF/V_0$ ratio listed in Table 3 showed no significant differences between the bilateral hemispheres of either group, although the ipsilateral hemisphere of group A tended to show a slight increase in the ratio compared with the other side or group B. However, in the ipsilateral hemisphere of group A, the ratio decreased significantly after ACZ injection ($P < 0.05$), and the reduction was significantly greater than that of the 2 hemispheres of group B ($P < 0.05$, repeated-measures ANOVA). The change in the $rCBF/V_0$ ratio for each patient is presented in Figure 3. A decrease of the $rCBF/V_0$ was observed in the ipsilateral hemisphere of group A, whereas those of the other hemisphere and group B showed no change. Figure 4 shows the images of 2 representative patients with severe stenosis in the left MCA and right MCA, respectively. The

TABLE 3
Group Mean of CBF and V_0 Changes in ACZ Test and Other Parametric Values

Parameter	Group A (n = 11)		Group B (n = 11)	
	Ipsilateral	Contralateral	Ipsilateral	Contralateral
CBF (mL/min/100 g)				
Baseline	35.7 ± 10.7*	41.5 ± 8.1	37.3 ± 4.8†	40.1 ± 5.4
ACZ	34.8 ± 12.0*	53.9 ± 11.5‡	48.2 ± 4.9*‡	55.5 ± 7.5‡
Change (%)	−2.8 ± 11.4*	31.1 ± 21.3	29.9 ± 11.9	39.0 ± 12.7
V_0 (mL/100 g)				
Baseline	1.57 ± 0.51*	2.08 ± 0.60	1.89 ± 0.44*	2.14 ± 0.43
ACZ	1.95 ± 0.46*‡	2.85 ± 0.86‡	2.52 ± 0.63*‡	3.03 ± 0.61‡
Change (%)	29.3 ± 22.0	42.3 ± 32.3	34.4 ± 21.5	42.9 ± 19.0
CBF/V_0 (/min)				
Baseline	24.0 ± 7.6	20.9 ± 5.2	20.9 ± 4.1	19.9 ± 3.3
ACZ	18.4 ± 6.8§	20.0 ± 5.2	20.7 ± 5.0	19.4 ± 2.8
Difference	−5.5 ± 7.0†	−0.8 ± 5.6	−0.2 ± 3.0	−0.4 ± 2.5
$CMRO_2$ (mL/min/100 g)	2.62 ± 0.55	2.90 ± 0.28	2.79 ± 0.29*	3.07 ± 0.37
OEF (%)	53.4 ± 8.3*	49.1 ± 6.9	47.0 ± 4.9	46.3 ± 5.3
CBV (mL/100 g)	4.38 ± 0.60	4.06 ± 0.53	4.04 ± 0.33*	3.73 ± 0.41
CBF/CBV (/min)	8.11 ± 1.99*	10.4 ± 1.77	9.29 ± 1.30*	10.8 ± 1.72

*$P < 0.01$, †$P < 0.05$ comparing bilateral hemispheres (repeated-measures ANOVA and paired t test).
‡$P < 0.005$, §$P < 0.05$ comparing conditions of baseline and ACZ injection (repeated-measures ANOVA and paired t test).
Values (mean ± SD) are given for regions of bilateral MCAs.

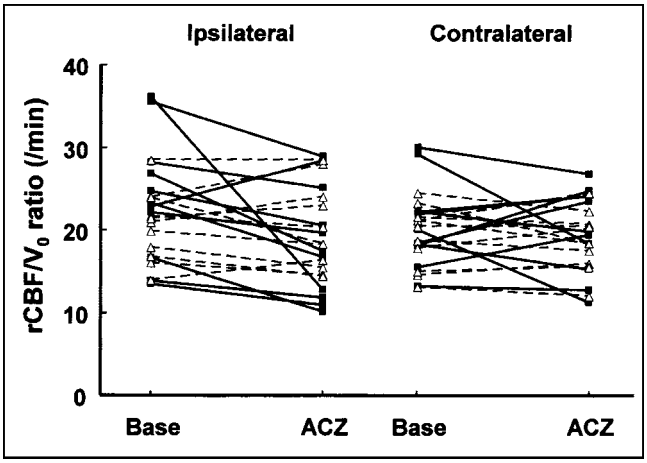

FIGURE 3. Changes in $rCBF/V_0$ ratio at cortical territories of bilateral MCA before and after ACZ administration. Decrease in $rCBF/V_0$ was observed in ipsilateral hemisphere of group A (■). Changes in patients of group A are represented by solid lines and those of group B (△) are shown as dashed lines.

interhemispheric difference in rCBF was intensified in both cases after ACZ administration, whereas the absolute rCBF in the ipsilateral side was decreased in patient A and increased in patient B, although the V_0 values in the same side were slightly increased in both cases.

The OEF in group A was significantly increased in the ipsilateral hemisphere, whereas no interhemispheric difference of OEF was seen in group B (Table 3). An asymmetric increase of OEF in the ipsilateral hemisphere was observed in 8 of 11 patients in group A (73%) and in 2 of 11 patients in group B (18%). However, only 5 of the 10 patients with an OEF increase showed a significant increase in the absolute OEF of >52.9%, which is the upper 95% limit of the reference range obtained from healthy volunteers measured at our institute. No relationship between the absolute OEF and the rCBF increase induced by ACZ administration was found in either hemisphere (ipsilateral: $F = 0.97 < F_1^{20}$ [0.95], $r = 0.22$). The CBF/CBV ratio was significantly lower in the ipsilateral hemisphere of both patient groups, although only group A showed a greater decrease in the ratio than the lower 95% limit of the reference range obtained from 7 healthy volunteers (mean, 11.9 ± 1.65 per min). Figure 5 shows the relationship between the hemodynamic parameters of the CBF/CBV ratio and OEF as well as the $rCBF/V_0$ ratio and CBV under the baseline condition for all subjects. The CBF/CBV ratio and OEF were inversely correlated in the ipsilateral hemisphere ($y = -2.1\,x + 68$; $r = 0.48$, $P < 0.05$). In addition, the $rCBF/V_0$ ratio and CBV showed a linear correlation only in the ipsilateral hemisphere of patients ($y = 0.054\,x + 3.0$; $r = 0.51$, $P < 0.05$).

DISCUSSION

The results of this study on 22 patients with unilateral major cerebral arterial occlusive disease demonstrate that the arteriolar vasodilatory capacity, which is represented by a V_0 increase, was not necessarily accompanied by rCBF change in all patients. This suggests that the changes in rCBF induced by ACZ may not represent either vasodilatory change or the residual vasodilatory capacity in the impaired hemodynamic conditions, although the previous study with 16 healthy volunteers proved that the ACZ test induces parallel increases in CBF and V_0 (*6*). A group of patients who showed a significantly smaller rCBF increase induced by ACZ in the ipsilateral hemisphere still maintained a vasodilatory capacity, although the capacity tended to be smaller compared with that of the contralateral hemisphere. This result contradicts the assumption that the steal phenomenon observed in the impaired perfusion is caused by exhaustion of the vasodilatory capacity due to the max-

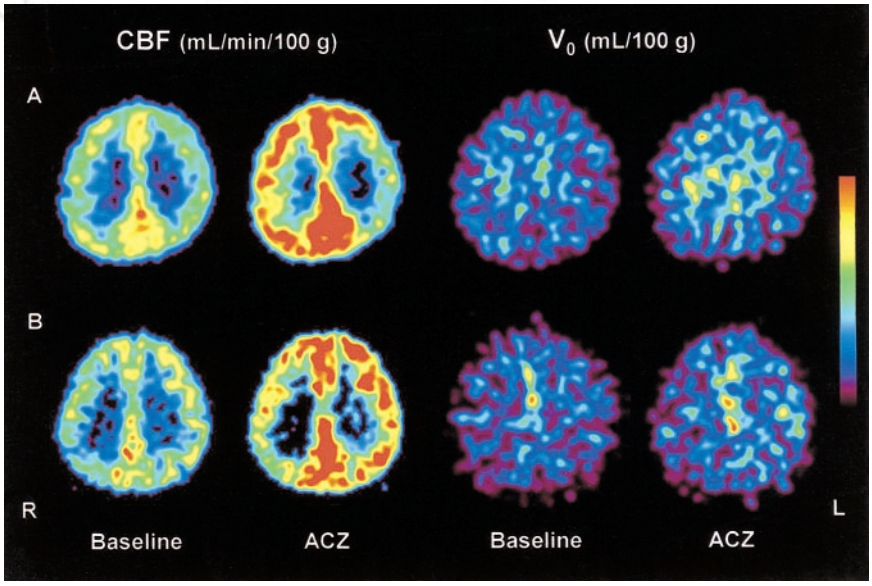

FIGURE 4. Representative images of patients with severe stenosis in left MCA from group A (top row) and in right MCA from group B (bottom row). Interhemispheric difference in rCBF was intensified after ACZ administration in both cases. rCBF in ipsilateral side decreased in patient A, whereas it increased in patient B, although V_0 values in same side slightly increased in both cases. Same color scale is used for same parametric images.

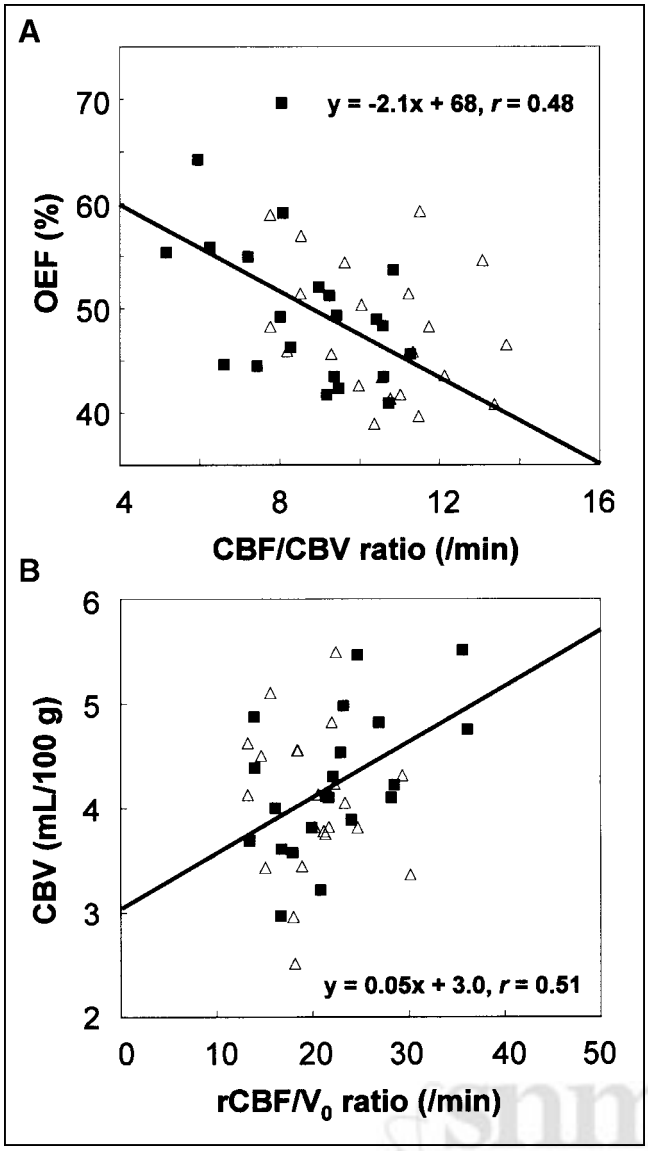

FIGURE 5. Relationship between hemodynamic parameters for CBF/CBV ratio and OEF (A) and between rCBF/V_0 ratio and CBV (B) in baseline condition for ipsilateral (■) and contralateral (△) hemispheres of all subjects. In both relationships, 2 parameters were linearly correlated only in ipsilateral hemisphere.

imal autoregulatory vasodilatation in response to a reduced C_{pp} (*3,4*). Because the cerebral hemodynamic parameters and their response to ACZ will vary in patients with CVD, the change in rCBF after ACZ administration may not appropriately represent the vasodilatory capacity or the vascular reserve if the change in rCBF is not accompanied by change in V_0. To evaluate the hemodynamic status in CVD, an assessment with multiple hemodynamic parameters would be necessary. In this study, the new parameter rCBF/V_0, which may be useful as an index of changes in the arterial perfusion pressure, was proposed to evaluate critical hemodynamic changes in major cerebral arterial occlusive disease.

To evaluate the precision of V_0 images obtained by the 3-WI method, regional values of the MCA territories were compared with those obtained by the NLS method. The hemodynamic parameter of V_0 was originally defined as the vascular distribution volume, which reflects the arterial-to-capillary blood volume when the extraction fraction of a tracer used for the rCBF measurement is sufficiently high (*7*). This parameter is usually calculated by applying the NLS method using time–activity curves for arterial input function and tissue activity obtained from ROIs on dynamic PET data. To evaluate the propriety of the kinetic model, the AIC values were obtained for the 2 models with or without V_0, and the ANOVA for AIC showed that the V_0 model is suitable for $H_2{}^{15}O$ PET data. This result is consistent with the previous similar analysis comparing the 2 models (*26*).

The 3-WI method was used to generate images on the basis of a 2-compartment model, and it was validated that the V_0 images represent the arterial-to-capillary blood volume (*7,12,14,27*). However, regional differences in the delay of tracer arrival in the impaired cerebral circulation may affect the regional values of rCBF and V_0 calculated in patients with CVD. This is because the NLS method was used to calculate V_0 values independently for each hemisphere. No difference in the time delay was observed between the tissue time–activity curves of the bilateral hemispheres, although a longer time delay for tracer arrival was expected in the ipsilateral hemisphere of patients (Fig. 2). Because the initial frame time of the dynamic PET scan was 5 s, a shorter time difference than this frame length could not be detected. No difference in the absolute values was observed between the 2 calculation methods of 3-WI and NLS, suggesting that the 3-WI method can be applied to image calculation in patients with CVD and that V_0 values obtained by this method can be used as a parameter to evaluate the hemodynamic status in patients.

A reduction in rCBF induced by ACZ (steal phenomenon) on the ipsilateral hemisphere was observed in 7 of the 11 patients from group A, and the mean rCBF of this group slightly decreased from the baseline value. However, the V_0 increased in the bilateral hemispheres of both patient groups as well as the cortices, where the steal phenomenon was observed. This divergence in the changes of rCBF and V_0 observed in the ipsilateral hemisphere of group A was not observed in the contralateral hemisphere or in the bilateral hemisphere of group B, in which the 2 parameters showed a significant parallel increase. The rCBF/V_0 ratio decreased significantly after ACZ administration only in the ipsilateral hemisphere of group A because of the divergence in the changes of rCBF and V_0. Because the rCBF/V_0 ratio is presumed to be an index reflecting cerebral arterial perfusion pressure, just as the index of the CBF/CBV ratio is expected to indicate C_{pp} (*2,10,11*), the reduction of the ratio suggested a temporal reduction of arterial perfusion pressure induced by a vasodilatory stimulus. In contrast to the impaired hemisphere of group A, the other hemisphere of group A and the bilateral hemispheres of group B showed

no change in the rCBF/V_0 ratio, suggesting that these hemispheres preserved arterial perfusion pressure under the vasodilatory stimulus. The ratio at baseline conditions tended to be greater in the ipsilateral hemisphere compared with that in the contralateral hemisphere, especially in group A. If the ratio represents the arterial perfusion pressure, this observation contradicts the evidence that the arterial pressure in the ICA was significantly lower in the occlusive side (*3*). However, the stenotic carotid artery may require an elevated arterial perfusion pressure to maintain CBF as Ruff et al. assumed that the systemic hypertension occurred in the TIA patients with major cerebral arterial stenoocclusive disease (*28*). They also presumed that a decrease in perfusion pressure in the regions of focal CBF impairment would induce TIAs when the patients suffered systemic hypotension. The significant reduction of the rCBF/V_0 ratio in our study was also consistent with a reduction of the arterial perfusion pressure that is expected to occur in the deficient collateral circulation (*8*). This observation is also consistent with the fact that the transit time was prolonged in the ipsilateral hemisphere of group A after vasodilatation because the rCBF/V_0 ratio can be defined as the reciprocal of an arterial mean transit time. Although the absolute value of the rCBF/V_0 ratio may not represent the absolute arterial perfusion pressure itself, the change in the ratio would be sensitive as a relative change in perfusion pressure and, thus, can be used as an index for evaluating the regional adaptability to vasodilatation. A change in this parameter during the ACZ test would indicate a relative redistribution of perfusion pressure and a reduced perfusion pressure in the impaired hemisphere.

The regional CBV and rCBF/V_0 ratio were mildly correlated in the impaired hemisphere. This result may indicate that a redistribution of the perfusion pressure due to the improved collateral circulation or a constriction of the arteriole had occurred in the chronic phase of autoregulation, and thus a slight increase in peripheral perfusion pressure may occur to maintain rCBF. The increase in peripheral perfusion pressure may induce an increase in the postcapillary blood volume. Indeed, the baseline V_0 in the ipsilateral hemisphere decreased significantly compared with that in the contralateral hemisphere, whereas the CBV was increased significantly. Contrary to this assumption, a passive dilatation of the postcapillary vessels could have occurred in the regions of reduced perfusion pressure. In any case, it would be probable that the increase in CBV in the ipsilateral hemisphere of CVD is mainly caused by an increase in the postcapillary venous volume in the cerebral circulation (*14*).

If the reduction of the rCBF/V_0 ratio induced by ACZ represents the reduction of arterial perfusion pressure, this parameter would be the most appropriate index for the evaluation of critical hemodynamic changes in impaired cerebral circulation. Figure 6 shows the relationship between the percentage change in V_0 and changes in the rCBF/V_0 ratio induced by ACZ injection in the ipsilateral hemisphere of all patients. The 2 parameters showed an inverse linear correlation ($y = -0.16x + 2.2$; $r = 0.72$, $P < 0.01$), indicating that the arterial blood volume increased according to the degree of reduction of perfusion pressure in the ACZ test. This is assumed to be caused not only by the vasodilatory effect of ACZ administration but also by the autoregulatory vasodilatory response to a transient change in the reduction of perfusion pressure, suggesting that these regions preserved the vasodilatory capacity despite showing the steal phenomenon.

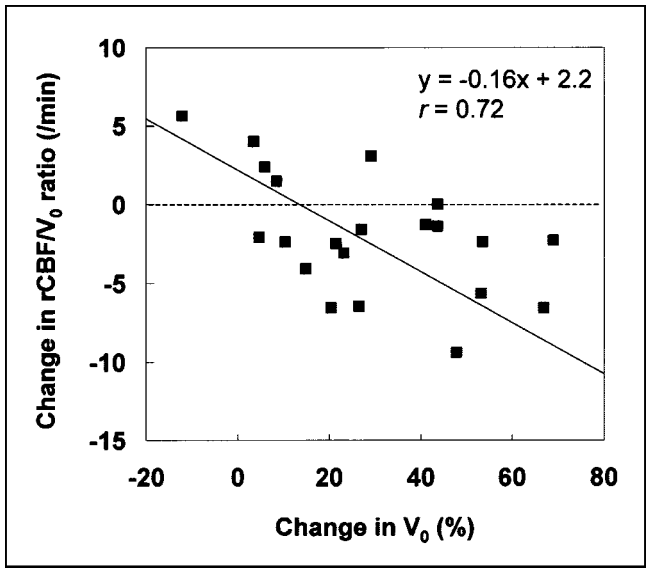

FIGURE 6. Relationship between percentage change in V_0 and changes in rCBF/V_0 ratio induced by ACZ administration in ipsilateral hemispheres of all patients. Two parameters were linearly correlated, indicating that arterial-to-capillary vasodilatation occurred in accordance with reduction of perfusion pressure in ACZ test.

A metabolic impairment in the affected hemisphere with a reduction of the vascular bed would provide insufficient vasodilatation (*25*) and responsiveness against a vasodilatory stimulus. The maximal vasodilatory change caused by autoregulation due to a decrease in perfusion pressure would not yield an increase in rCBF and V_0, resulting in no change in the rCBF/V_0 ratio. This is presumed to be caused by exhaustion of the vasodilatory capacity. However, if the cortical region showed only a reduction of the vascular density due to neuronal impairment and still preserved the vasodilatory capacity, the rCBF/V_0 ratio would be reduced by a vasodilatory stimulus. Of the 7 patients who showed the steal phenomenon, 3 showed no increase in OEF but did show a V_0 increase in the ipsilateral hemisphere, indicating a significant reduction of the rCBF/V_0 ratio. In such cases, changes in the rCBF/V_0 ratio or in V_0 might be a more sensitive parameter than OEF. Thus, the ACZ test combined with analysis of both rCBF and V_0 obtained from the bolus method using $H_2{}^{15}O$ PET is considered to be useful for evaluation of the cerebral vasodilatory capacity and critical hemodynamic status in patients with major cerebral arterial

occlusive disease to determine the indications for neurosurgical treatment and to assess the effects of treatment.

Because a large time difference in tracer arrival between the 2 hemispheres may cause a large bias in the V_0 value in the affected hemisphere, the time shift of tracer arrival should be carefully estimated individually in each hemisphere before applying the automatic calculation. In the present method with $H_2{}^{15}O$ PET, the minimal frame time of 5 s may provide small errors in time-shift estimation, although the slope method showed only a negligible difference. The rCBF/V_0 ratio might be sensitive and vulnerable to biases in V_0 that would be affected by the time shift of tracer arrival. The reciprocal of this parameter, which represents arterial mean transit time, may provide identical critical hemodynamic changes in the severe occlusive arterial disease.

CONCLUSION

This study demonstrates that the arterial vasodilatory reaction in cerebral arteries induced by ACZ was not necessarily coupled with rCBF changes in patients with unilateral cerebral arterial occlusive disease, because the decrease in rCBF was accompanied by an increase in V_0 in the region with the steal phenomenon. The ACZ test with measurements of rCBF may not accurately evaluate the vasodilatory capacity in patients with CVD, who have varied hemodynamic conditions. The discrepancy between the ACZ test and other hemodynamic parameters may be explained by the differences between the changes in rCBF and V_0 caused by ACZ. The measurement of V_0 coupled with the ACZ test would provide additional parameters for an evaluation of vasodilatory capacity and cerebral hemodynamics.

ACKNOWLEDGMENTS

The authors thank Masaaki Takahashi, Yoshihiko Kishibe, Hidekazu Matsugi, and other staff of the PET Unit in the Research Institute for technical and clinical support. The authors also appreciate the clinical assistance provided by doctors in the Departments of Neurology and Neurosurgery, Shiga Medical Center. This study was supported in part by a Grant-in-Aid for Scientific Research from Japan Society for the Promotion of Science (14207039).

REFERENCES

1. MacKenzie ET, Farrar JK, Fitch W, Graham DI, Gregory PC, Harper AM. Effects of hemorrhagic hypotension on the cerebral circulation. I. Cerebral blood flow and pial arteriolar caliber. *Stroke.* 1979;10:711–718.
2. Powers WJ. Cerebral hemodynamics in ischemic cerebrovascular disease. *Ann Neurol.* 1991;29:231–240.
3. Vorstrup S. Tomographic cerebral blood flow measurements in patients with ischemic cerebrovascular disease and evaluation of the vasodilatory capacity by the acetazolamide test. *Acta Neurol Scand.* 1988;114(suppl):1–48.
4. Yonas H, Pindzola RR. Physiological determination of cerebrovascular reserves and its use in clinical management. *Cerebrovasc Brain Metab Rev.* 1994;6:325–340.
5. Piepgras A, Schmiedek P, Leinsinger G, Haberl RL, Kirsch CM, Einhaupl KM. A simple test to assess cerebrovascular reserve capacity using transcranial Doppler sonography and acetazolamide. *Stroke.* 1990;21:1306–1311.
6. Okazawa H, Yamauchi H, Sugumoto K, Toyoda H, Kishibe Y, Takahashi M. Effects of acetazolamide on cerebral blood flow, blood volume and oxygen metabolism: a PET study with healthy volunteers. *J Cereb Blood Flow Metab.* 2001;21:1472–1479.
7. Ohta S, Meyer E, Fujita H, Reutens DC, Evans A, Gjedde A. Cerebral [^{15}O]water clearance in humans determined by PET. I. Theory and normal values. *J Cereb Blood Flow Metab.* 1996;16:765–780.
8. Vorstrup S, Brun B, Lassen NA. Evaluation of the cerebral vasodilatory capacity by the acetazolamide test before EC-IC bypass surgery in patients with occlusion of the internal carotid artery. *Stroke.* 1986;17:1291–1298.
9. Yonas H, Smith HA, Durham SR, Pentheny SL, Johnson DW. Increased stroke risk predicted by compromised cerebral blood flow reactivity. *J Neurosurg.* 1993;79:483–489.
10. Gibbs JM, Wise RJ, Leenders KL, Jones T. Evaluation of cerebral perfusion reserve in patients with carotid-artery occlusion. *Lancet.* 1984;1:310–314.
11. Schumann P, Touzani O, Young AR, Morello R, Baron JC, MacKenzie ET. Evaluation of the ratio of cerebral blood flow to cerebral blood volume as an index of local cerebral perfusion pressure. *Brain.* 1998;121:1369–1379.
12. Okazawa H, Vafaee M. Effect of vascular radioactivity on regional values of cerebral blood flow: evaluation of methods for oxygen-15-water PET to distinguish cerebral perfusion from blood volume. *J Nucl Med.* 2001;42:1032–1039.
13. DeGrado TR, Turkington TG, Williams JJ, Stearns CW, Hoffman JM, Coleman RE. Performance characteristics of a whole-body PET scanner. *J Nucl Med.* 1994;35:1398–1406.
14. Okazawa H, Yamauchi H, Sugumoto K, et al. Quantitative comparison of the bolus and steady-state methods for measurement of cerebral perfusion and oxygen metabolism: PET study using ^{15}O-gas and water. *J Cereb Blood Flow Metab.* 2001;21:793–803.
15. Votaw JR, Shulman SD. Performance evaluation of the Pico-Count flow-through detector for use in cerebral blood flow PET studies. *J Nucl Med.* 1998;39:509–515.
16. Okazawa H, Kishibe Y, Sugumoto K, Takahashi M, Yamauchi H. Delay and dispersion correction for a new coincidental radioactivity detector, Pico-Count, in quantitative PET studies. In: Senda M, Kimura Y, Herscovitch P, eds. *Brain Imaging Using PET.* San Diego, CA: Academic Press; 2002:15–21.
17. Vafaee M, Murase K, Gjedde A, Meyer E. Dispersion correction for automatic sampling of O-15-labeled H_2O and red blood cells. In: Myers R, Cunningham V, Bailey D, Jones T, eds. *Quantification of Brain Function Using PET.* San Diego, CA: Academic Press; 1996:72–75.
18. Frackowiak RSJ, Lenzi G-L, Jones T, Heather JD. Quantitative measurement of regional cerebral blood flow and oxygen metabolism in man using ^{15}O and positron emission tomography: theory, procedure and normal values. *J Comput Assist Tomogr.* 1980;4:727–736.
19. Lammertsma AA, Jones T. Correction for the presence of intravascular oxygen-15 in the steady-state technique for measuring regional oxygen extraction ratio in the brain. 1. Description of the method. *J Cereb Blood Flow Metab.* 1983;3:416–424.
20. Iida H, Kanno I, Miura S, Murakami M, Takahashi K, Uemura K. Error analysis of a quantitative cerebral blood flow measurement using $H_2{}^{15}O$ autoradiography and positron emission tomography, with respect to the dispersion of the input function. *J Cereb Blood Flow Metab.* 1986;6:536–545.
21. Meyer E. Simultaneous correction for tracer arrival delay and dispersion in CBF measurements by the $H_2{}^{15}O$ autoradiographic method and dynamic PET. *J Nucl Med.* 1989;30:1069–1078.
22. Phelps ME, Huang SC, Hoffman EJ, Kuhl DE. Validation of tomographic measurement of cerebral blood volume with C-11-labeled carboxyhemoglobin. *J Nucl Med.* 1979;20:328–334.
23. Okazawa H, Yonekura Y, Fujibayashi Y, et al. Measurement of regional cerebral plasma pool and hematocrit with copper-62-labeled HSA-DTS. *J Nucl Med.* 1996;37:1080–1085.
24. Akaike H. A new look at the statistical model identification. *IEEE Trans Automat Contr.* 1974;19:716–723.
25. Nemoto EM, Yonas H, Chang Y. Stages and thresholds of hemodynamic failure. *Stroke.* 2003;34:2–3.
26. Ito H, Kanno I, Iida H, et al. Arterial fraction of cerebral blood volume in humans measured by positron emission tomography. *Ann Nucl Med.* 2001;15:111–116.
27. Fujita H, Meyer E, Reutens DC, Kuwabara H, Evans AC, Gjedde A. Cerebral [^{15}O]water clearance in humans determined by positron emission tomography. II. Vascular responses to vibrotactile stimulation. *J Cereb Blood Flow Metab.* 1997;17:73–79.
28. Ruff RL, Talman WT, Petito F. Transient ischemic attacks associated with hypotension in hypertensive patients with carotid artery stenosis. *Stroke.* 1981; 12:353–355.