Neurosci Bull October 1, 2014, 30(5): 845–856. http://www.neurosci.cn
DOI: 10.1007/s12264-013-1459-z

·Original Article·

Paradoxical reduction of cerebral blood flow after acetazolamide loading: a hemodynamic and metabolic study with ^{15}O PET

Tadashi Watabe[1,5], Eku Shimosegawa[2,5,7], Hiroki Kato[2,5], Kayako Isohashi[2,5], Mana Ishibashi[2,5], Mitsuaki Tatsumi[6], Kazuo Kitagawa[3,7], Toshiyuki Fujinaka[4,7], Toshiki Yoshimine[4,7], Jun Hatazawa[2, 5, 7]

[1]*Department of Molecular Imaging in Medicine,* [2]*Department of Nuclear Medicine and Tracer Kinetics,* [3]*Department of Neurology,* [4]*Department of Neurosurgery, Osaka University Graduate School of Medicine, Suita, Japan*

[5]*Department of Nuclear Medicine,* [6]*Department of Radiology,* [7]*Stroke Center, Osaka University Hospital, Suita, Japan*

Corresponding author: Tadashi Watabe. E-mail: twatabe@mi.med.osaka-u.ac.jp

ABSTRACT

Paradoxical reduction of cerebral blood flow (CBF) after administration of the vasodilator acetazolamide is the most severe stage of cerebrovascular reactivity failure and is often associated with an increased oxygen extraction fraction (OEF). In this study, we aimed to reveal the mechanism underlying this phenomenon by focusing on the ratio of CBF to cerebral blood volume (CBV) as a marker of regional cerebral perfusion pressure (CPP). In 37 patients with unilateral internal carotid or middle cerebral arterial (MCA) steno-occlusive disease and 8 normal controls, the baseline CBF (CBF_b), CBV, OEF, cerebral oxygen metabolic rate ($CMRO_2$), and CBF after acetazolamide loading in the anterior and posterior MCA territories were measured by ^{15}O positron emission tomography. Paradoxical CBF reduction was found in 28 of 74 regions (18 of 37 patients) in the ipsilateral hemisphere. High CBF_b (>47.6 mL/100 mL/min, n = 7) was associated with normal CBF_b/CBV, increased CBV, decreased OEF, and normal $CMRO_2$. Low CBF_b (<31.8 mL/100 mL/min, n = 9) was associated with decreased CBF_b/CBV, increased CBV, increased OEF, and decreased $CMRO_2$. These findings demonstrated that paradoxical CBF reduction is not always associated with reduction of CPP, but partly includes high-CBF_b regions with normal CPP, which has not been described in previous studies.

Keywords: acetazolamide; cerebral blood flow; paradoxical reduction; positron emission tomography; vasodilatation

INTRODUCTION

Paradoxical reduction of cerebral blood flow (CBF) after administration of vasodilators, termed the “intracerebral steal phenomenon”, was originally described in the core of an acute brain infarct after CO_2 inhalation in a cat experimental model[1,2]. The vasodilator acetazolamide (ACZ) also reduces CBF in the core of the acute ischemic region after experimental occlusion of the middle cerebral artery (MCA). Expansion of the infarct volume is higher in cats given ACZ than in controls[3]. These studies indicate that administration of vasodilators for the recovery of CBF in acute brain ischemia is harmful.

A paradoxical CBF reduction has also been documented in patients with steno-occlusive atherosclerotic carotid artery disease[4-6], and is associated with poor collateral circulation[7]. Okazawa *et al*. demonstrated that patients with paradoxical CBF reduction show a significantly increased oxygen extraction fraction (OEF), a state of misery perfusion[8,9]. These studies indicated that the paradoxical CBF reduction is a sign of severe hemodynamic failure due to a reduction of cerebral perfusion pressure (CPP) in patients with chronic ischemic disease.

Regional CPP is not measurable by non-invasive means in patients. However, the regional ratio of CBF to

cerebral blood volume (CBV) has been suggested to be an index of regional CPP[10,11]. Schumann *et al*. evaluated the CBF/CBV ratio during global CPP manipulation by varying mean arterial blood pressure (MABP) in the anesthetized baboon[12], and found that the CBF/CBV ratio is significantly correlated with MABP. As the CPP is a function of MABP and intracranial pressure, regional CBF/CBV is considered to be an index of regional CPP in the cerebral parenchyma when intracranial pressure is not pathologically altered[12].

In the present study, we tested the hypothesis that the paradoxical CBF reduction after ACZ loading is associated with a reduction of regional CPP by evaluating the CBF/CBV ratio in patients with internal carotid artery (ICA)/MCA steno-occlusive disease by means of ^{15}O positron emission tomography (PET).

PARTICIPANTS AND METHODS

Participants

This retrospective study was conducted in 37 patients (29 men, 8 women; age, 64.9 ± 10.3 years) who were examined for evaluation of hemodynamic status at Osaka University Hospital from August 2007 to January 2011. The clinical information of the patients is summarized in Table 1. All patients had severe stenosis or occlusion of the ICA or MCA on one side. Digital subtraction angiography or magnetic resonance (MR) angiography revealed ICA occlusion in 11 patients, severe stenosis of the ICA in 10, MCA occlusion in 6, and severe stenosis of the MCA in 10. The severity of the ICA stenosis was >80% by the North American Symptomatic Carotid Endarterectomy Trial criteria[13]. Ten patients had a minor stroke, 12 had a transient ischemic attack (TIA), and 15 were asymptomatic. All PET studies were performed at least one month after the last ischemic episode.

Eight healthy volunteers (4 men, 4 women; 50.5 ± 4.2 years) were included as normal controls. The criteria for the controls were (1) absence of a history of disease, (2) absence of smoking and alcohol habits, and (3) no significant brain abnormalities by MR imaging and MR angiography.

This study was approved by the Ethics Committee of Osaka University Hospital. Written informed consent was given by all participants.

PET Measurements

PET images were obtained in 3-D mode using the SET-3000 GCT/X scanner (Shimadzu Corp., Kyoto, Japan). The intrinsic spatial resolution was 3.5-mm full-width at half maximum (FWHM) in-plane and 4.2-mm FWHM axially. Transmission scanning with a ^{137}Cs point source was performed for attenuation correction. The PET images were reconstructed by a filtered-back projection method after 3D Gaussian smoothing with a 6-mm FWHM. Scattered

Table 1. Characteristics of the 37 patients enrolled in the study

		Number
Characteristics	Age (years)	64.9 ± 10.3
	Sex (male/female)	29 / 8
Angiography	ICA occlusion/stenosis	11 / 10
	MCA occlusion/stenosis	6 / 10
Symptoms	Minor stroke	10
	TIA	12
	Asymptomatic	15
	Interval between the last symptom and PET (months)	23.5 ± 34.2
Underlying disease	Hypertension	25
	Diabetes mellitus	11
	Dyslipidemia	21

ICA, internal carotid artery; MCA, middle cerebral artery; PET, positron emission tomography; TIA, transient ischemic attack.

radiation was corrected by the hybrid dual-energy window method combined with a convolution-subtraction method, and estimation of the true scatter-free component of the standard photopeak window was performed on a sonographic basis[14,15].

The baseline CBV, the baseline cerebral metabolic rate of oxygen ($CMRO_2$), the OEF at baseline, the CBF_b, and the CBF after ACZ loading (CBF_{acz}) were measured following $C^{15}O$ and $^{15}O_2$ gas inhalation, and $H_2{}^{15}O$ injection[15]. A cannula was inserted into the radial artery for arterial input. CBV measurement was performed with 4-min static scanning after 1 min of continuous inhalation of $C^{15}O$ gas (3.0 GBq/min) and a 3-min interval[16]. Arterial blood was collected 3 times during the scanning to measure the whole-blood radioactivity. OEF was measured by 3-min scanning starting simultaneously with 1.5-min $^{15}O_2$ gas bolus inhalation (1.0 GBq/min). Continuous arterial blood sampling was performed using a β-detector system to determine the whole-arterial blood radioactivity. $CMRO_2$ and OEF were calculated by an autoradiographic method[16-19]. The CBV data were used to correct for intravascular hemoglobin-bound $^{15}O_2$[20]. CBF_b was measured by 3 min of scanning started simultaneously with intravenous bolus injection of $H_2{}^{15}O$ (370 MBq)[17,21]. Continuous arterial blood sampling was also performed with a β-detector system. Delay and dispersion occurring in the β-detector system were corrected by the methods described previously[22]. Quantitation of reconstructed PET images by the 3-D mode PET scanner has been validated in a previous report[15].

At the end of the study protocol, we examined the CBF_{acz} to determine the cerebrovascular reactivity (CVR)[5]. ACZ (1 g; Diamox®, Sanwa kagaku kenkyusho Co., Ltd, Nagoya, Japan) was slowly injected intravenously for 2 min, and measurement of CBF_{acz} was started 15 min after the injection using the same protocol as for CBF_b.

Arterial O_2 and CO_2 partial pressures (PaO_2 and $PaCO_2$), pH, hematocrit (Ht), and hemoglobin concentration (Hb) were measured in arterial blood samples. Systemic blood pressure and heart rate were monitored during the PET study. MABP was calculated as [diastolic BP + (systolic BP − diastolic BP) / 3].

Data Analysis

The CBF_b images were transformed to the standard brain size and shape of a built-in PET template using SPM2 software (Wellcome Trust Centre for Neuroimaging). Parametric maps of CBV, $CMRO_2$, OEF, and CBF_{acz} were created with the same parameters as those for CBF_b normalization. The resultant images had the same anatomical format with an isotropic voxel size of 2 mm. Oval regions of interest (ROI: major axis, 45 mm) were placed on the MCA-anterior branch territory (MCA-an) and MCA-posterior branch territory (MCA-po) on 3 sequential cross-sections on both the ipsilateral and the contralateral sides of all parametric images (Fig. 1). Each ROI was confirmed to include no minor infarct region on the co-registered MRI slices. Mean values of the 3 cross-sections in each region were used to evaluate the hemodynamic status. CVR was calculated as the percentage change in the CBF after ACZ administration using the equation: $CVR = [(CBF_{acz} - CBF_b) / CBF_b] \times 100\%$. Paradoxical CBF reduction was defined as a negative value of the CVR. The CBF_b/CBV ratio was calculated as an index of the CPP[10,12]. All regions on the affected side (n = 74) were divided into a paradoxical CBF reduction group (group A: CVR <0%) and non-paradoxical CBF reduction groups (group B: CVR = 0–15% and group C: CVR >15%). The CVR threshold of 15% between groups B and C was determined based on previous studies, which set thresholds from 10% to 20%[23-25]. The CBF_b, CBV, OEF, $CMRO_2$, and CBF_b/CBV ratio were compared between the three groups and evaluated in comparison to the controls. The contralateral sides of each group were also compared.

Furthermore, ipsilateral regions showing the paradoxical CBF reduction were tentatively classified into three subgroups according to the CBF_b value (high-CBF_b: >20% of the mean value in the controls; moderate-CBF_b:

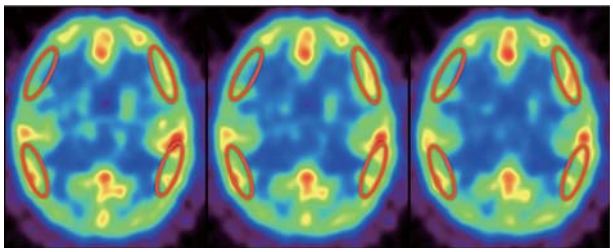

Fig. 1. Locations of regions of interest on three sequential cross-sectional images of baseline cerebral blood flow (22, 24, and 26 mm above the transaxial section with the anterior commissure to the posterior commissure line).

within ±20% of the controls; and low-CBF_b: <−20% of the controls). The CBV, OEF, $CMRO_2$, CBF_b/CBV ratio, and CVR values were compared among the ipsilateral and contralateral sides of the three subgroups, and evaluated in comparison to the controls.

Statistical Analysis

Comparisons of the arterial blood gas and MABP data among the three groups (groups A, B, and C) and controls and among the three subgroups of group A were performed using analysis of variance (ANOVA) followed by Tukey's HSD test. Comparisons of PET data among the three groups and among the three subgroups were conducted using the Steel-Dwass test. For each of the three groups or subgroups, comparisons of PET data to the controls were evaluated by the Mann-Whitney test. P <0.05 was considered to denote statistical significance.

RESULTS

The relationships between the CVR and CBF_b in the ipsilateral MCA-an and MCA-po are shown in Fig. 2. Among a total of 74 regions, 28 were classified into group A, 21 into group B, and 25 into group C. In group A, 7, 12, and 9 regions were classified into the high-, moderate-, and low-CBF_b subgroups, respectively.

Comparisons among Groups A, B, and C

The mean values of $PaCO_2$, MABP, Hb, and Ht are summarized in Table 2. No significant differences were found between each of the three groups and the controls. The MABP after ACZ in group C was increased compared to groups A and B (P = 0.018 and P = 0.012, respectively). Hb and Ht in group C were higher than those in group A (P = 0.022 and P = 0.031, respectively).

The mean values of CBF_b, CBV, OEF, $CMRO_2$, and CBF_b/CBV ratio are shown in Table 3. The bilateral CBF_b in groups B and C were lower than in controls (ipsilateral: P <0.001 and P <0.001, contralateral: P = 0.044 and P = 0.024, respectively). The ipsilateral CBV in groups A and B were higher than in the controls (P = 0.011 and P = 0.009, respectively). The bilateral $CMRO_2$ in groups A, B, and C were lower than in the controls (ipsilateral: P <0.001, P = 0.002, and P <0.001; contralateral: P = 0.006, P = 0.003, and P = 0.002, respectively). The ipsilateral CBF_b/CBV ratio in group A and the bilateral CBF_b/CBV ratio in group B were significantly lower than in controls (P <0.001, P <0.001, and P = 0.001, respectively).

Comparisons among High-, Moderate-, and Low-CBF_b Subgroups

No significant differences in the physiological parameters were found among the three subgroups (Table 4). The

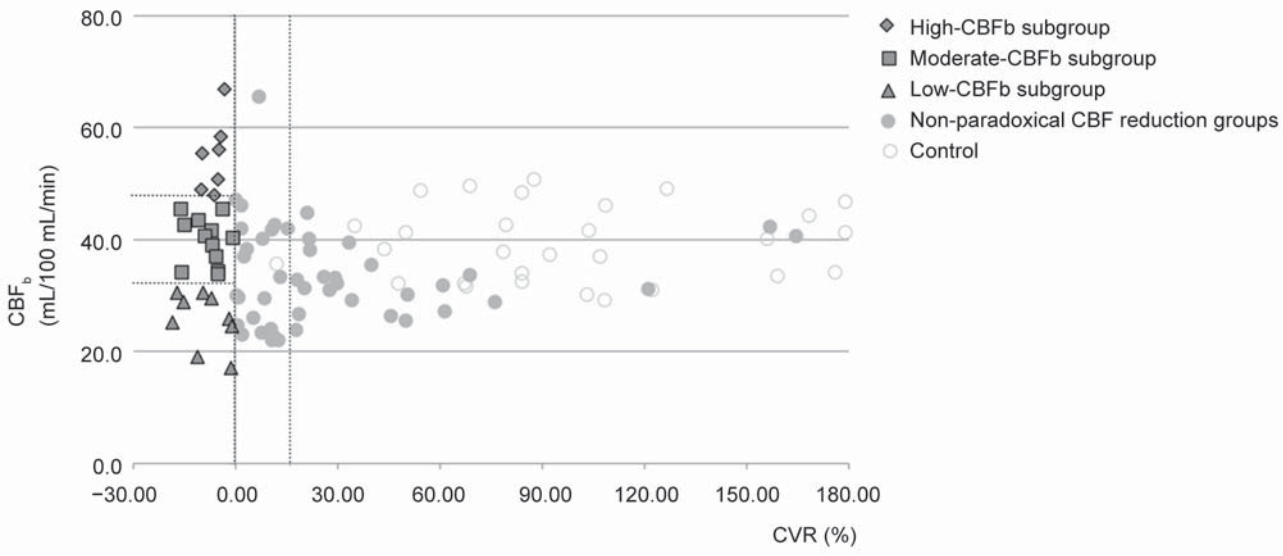

Fig. 2. Relationship between cerebrovascular reactivity (CVR) and baseline cerebral blood flow (CBF_b). The distribution of the paradoxical CBF reduction group was significantly different from the non-paradoxical CBF reduction groups (P = 0.031, Mann-Whitney U test).

Table 2. Mean ± SD values of arterial blood gas parameters and blood pressure

	Group A (CVR <0%)	Group B (CVR 0–15%)	Group C (CVR >15%)	Control	*P* value*
$PaCO_2$ at baseline (mmHg)	38.8±4.1	38.9±4.1	39.2±2.3	40.1±4.3	0.877
$PaCO_2$ after ACZ (mmHg)	36.7±4.7	37.6±4.9	37.7±3.0	39.2±4.2	0.584
MABP at baseline (mmHg)	87.6±9.6	85.9±12.4	95.0±10.2	93.6±10.6	0.072
MABP after ACZ (mmHg)	88.6±11.0[a]	87.5±12.4[A]	101.8±12.5[a,A]	97.0±15.2	0.006
Hb (g/dl)	11.9±1.5[a]	12.8±1.5	13.4±1.4[a]	12.9±1.3	0.035
Ht (%)	36.7±4.6[a]	39.4±4.5	41.0±4.0[a]	39.4±3.8	0.047

ACZ, acetazolamide; CVR, cerebrovascular reactivity; Hb, hemoglobin; Hct, hematocrit; MABP, mean arterial blood pressure; $PaCO_2$, arterial partial pressure of CO_2. *ANOVA (analysis of variance), [a]*P* <0.05 between groups A and C, [A]*P* <0.05 between groups B and C, Tukey's HSD test.

Table 3. Hemodynamic parameters in the MCA-an and MCA-po regions (mean ± SD)

		Group A (CVR <0%) (*n* = 28)		Group B (CVR 0–15%) (*n* = 21)		Group C (CVR >15%) (*n* = 25)		Control (*n* = 32)
		Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral	
Baseline	CBF_b (mL/100 mL/min)	39.0±12.2	42.3±11.6	33.9±11.2[†]	36.1±9.6[‡]	33.3±5.8[‡]	35.7±5.6[†]	39.7±6.4
	CBV (mL/100 mL)	3.62±0.79[b,‡]	2.95±0.58	3.41±0.72[‡]	3.06±0.50	2.90±0.88[b]	2.96±0.62	2.91±0.46
	OEF (%)	45.4±7.4	44.3±6.0	45.3±7.6	43.7±7.9	43.5±6.5	42.7±5.8	45.2±5.2
	$CMRO_2$ (mL/100 mL/min)	2.52±0.56[‡]	2.69±0.43[‡]	2.52±0.64[‡]	2.60±0.49[‡]	2.51±0.27[‡]	2.65±0.36[‡]	3.07±0.52
	CBF_b/CBV ratio (/min)	11.0±3.3[‡]	14.5±3.6[b]	9.9±1.9[a,‡]	11.7±1.8[b,‡]	12.3±3.5[a]	12.5±2.7	13.8±2.2
After ACZ	CVR (%)	–8.0±5.2[‡]	35.0±31.4[a,‡]	6.2±4.6[‡]	36.7±20.2[‡]	49.3±41.3[‡]	57.6±43.5[a,‡]	107.3±52.9

ACZ, acetazolamide; an, anterior branch territory; CBF_b, baseline cerebral blood flow; CBV, cerebral blood volume; $CMRO_2$, cerebral oxygen metabolic rate; CVR, cerebrovascular reactivity; MCA, middle cerebral artery; OEF, oxygen extraction fraction; po, posterior branch territory. [a]*P* <0.05, [b]*P* <0.01 by multiple comparison among groups, Steel-Dwass test; [†]*P* <0.05, [‡]*P* <0.01 *versus* control, Mann-Whitney test.

ipsilateral CBV in the high-CBF_b subgroup was higher than that in the moderate- and low-CBF_b subgroups (*P* = 0.030 and 0.034, respectively; Table 5), and the controls (*P* <0.001). The ipsilateral OEF in the high-CBF_b subgroup was lower than that in the controls (*P* = 0.007), while the ipsilateral OEF in the low-CBF_b subgroup was higher than that in the high-CBF_b subgroup (*P* = 0.002), the moderate-CBF_b subgroup (*P* = 0.034), and the controls (*P* = 0.001) (Table 5). The ipsilateral $CMRO_2$ in the low-CBF_b subgroup was lower than that in the high-CBF_b subgroup (*P* = 0.045), the moderate-CBF_b subgroup (*P* = 0.034), and the controls (*P* <0.001) (Table 5). The ipsilateral CBF_b/CBV ratio in the high-CBF_b subgroup was comparable to the controls while those in the moderate- and low-CBF_b subgroups were significantly lower than in the controls (*P* = 0.007 and *P* < 0.001) (Table 5). In addition, the contralateral CBF_b in the

Table 4. Arterial blood gas parameters and blood pressure in the three subgroups with paradoxical cerebral blood flow reduction (mean ± SD)

	High-CBF_b	Moderate-CBF_b	Low-CBF_b	P value*
$PaCO_2$ at baseline (mmHg)	40.8±3.6	38.6±4.6	36.5±4.3	0.270
$PaCO_2$ after ACZ (mmHg)	39.3±4.1	36.1±5.0	34.1±5.6	0.242
MABP at baseline (mmHg)	89.4±8.7	87.9±8.8	87.3±10.9	0.931
MABP after ACZ (mmHg)	91.1±5.1	88.7±11.7	90.4±13.2	0.909
Hb (g/dl)	11.4±1.5	12.1±1.5	12.2±1.5	0.685
Ht (%)	35.8±5.0	37.2±4.6	37.4±4.5	0.827

ACZ, acetazolamide; CBF_b, baseline cerebral blood flow; Hb, hemoglobin; Hct, hematocrit; MABP, mean arterial blood pressure; $PaCO_2$, arterial partial pressure of CO_2. Data were analyzed by ANOVA

Table 5. Hemodynamic parameters in the MCA-an and MCA-po regions of the three subgroups with paradoxical cerebral blood flow reduction (mean ± SD)

		High-CBF_b (n = 7)		Moderate-CBF_b (n = 12)		Low-CBF_b (n = 9)	
		Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral
Baseline	CBF_b (mL/100 mL/min)	$54.9±6.6^{‡}$	$55.2±11.9^{b,‡}$	39.8±4.2	$42.3±6.9^{B}$	$25.7±4.9^{‡}$	$32.3±4.8^{b,B,‡}$
	CBV (mL/100 mL)	$4.41±0.78^{a,A,‡}$	$3.36±0.46^{†}$	$3.46±0.59^{a,‡}$	2.82±0.47	$3.22±0.64^{A}$	2.79±0.67
	OEF (%)	$39.3±5.1^{b,‡}$	$40.7±5.1^{a,†}$	$44.4±6.7^{A}$	44.1±5.9	$51.7±4.8^{b,A,‡}$	$47.4±5.7^{a}$
	$CMRO_2$ (mL/100 mL/min)	$2.77±0.54^{a}$	2.83±0.51	$2.69±0.50^{A}$	2.81±0.36	$2.11±0.44^{a,A,‡}$	$2.43±0.38^{‡}$
	CBF_b/CBV ratio (/min)	$13.0±3.8^{a}$	17.0±5.6	$11.8±2.2^{A,‡}$	$15.1±1.6^{B}$	$8.4±2.6^{a,A,‡}$	$11.8±1.3^{B,†}$
After ACZ	CVR (%)	$−6.2±2.7^{‡}$	$69.2±43.8^{b,a}$	$−8.3±5.0^{‡}$	$24.0±14.2^{b,‡}$	$−9.1±6.8^{‡}$	$22.9±15.1^{a,‡}$

ACZ, acetazolamide; an, anterior branch territory; CBF_b, baseline cerebral blood flow; CBV, cerebral blood volume; $CMRO_2$, cerebral oxygen metabolic rate; CVR, cerebrovascular reactivity; MCA, middle cerebral artery; OEF, oxygen extraction fraction; po, posterior branch territory. ^{a}P <0.05, ^{b}P <0.01: comparison between high-CBF_b subgroup and moderate- or low-CBF_b subgroup in the same side; ^{A}P <0.05 and ^{B}P <0.01: comparison between low-CBF_b subgroup and high- or moderate-CBF_b subgroup in the same side, Tukey's HSD test; $^{†}P$ <0.05, $^{‡}P$ <0.01, compared with control, Mann-Whitney test.

high-CBF_b subgroup was higher than that in the controls (P = 0.002). The contralateral CBV in the high-CBF_b subgroup was also higher than that in the controls (P = 0.027).

The relationships between the ipsilateral CBF_b/CBV ratio and CBF_b, CBF_b/CBV ratio and CBV were similar among the three subgroups (Fig. 3). The low-CBF_b subgroup was located in the inferior edge of groups B and C. The moderate-CBF_b subgroup was located inside groups B, C, and controls. The high-CBF_b subgroup was

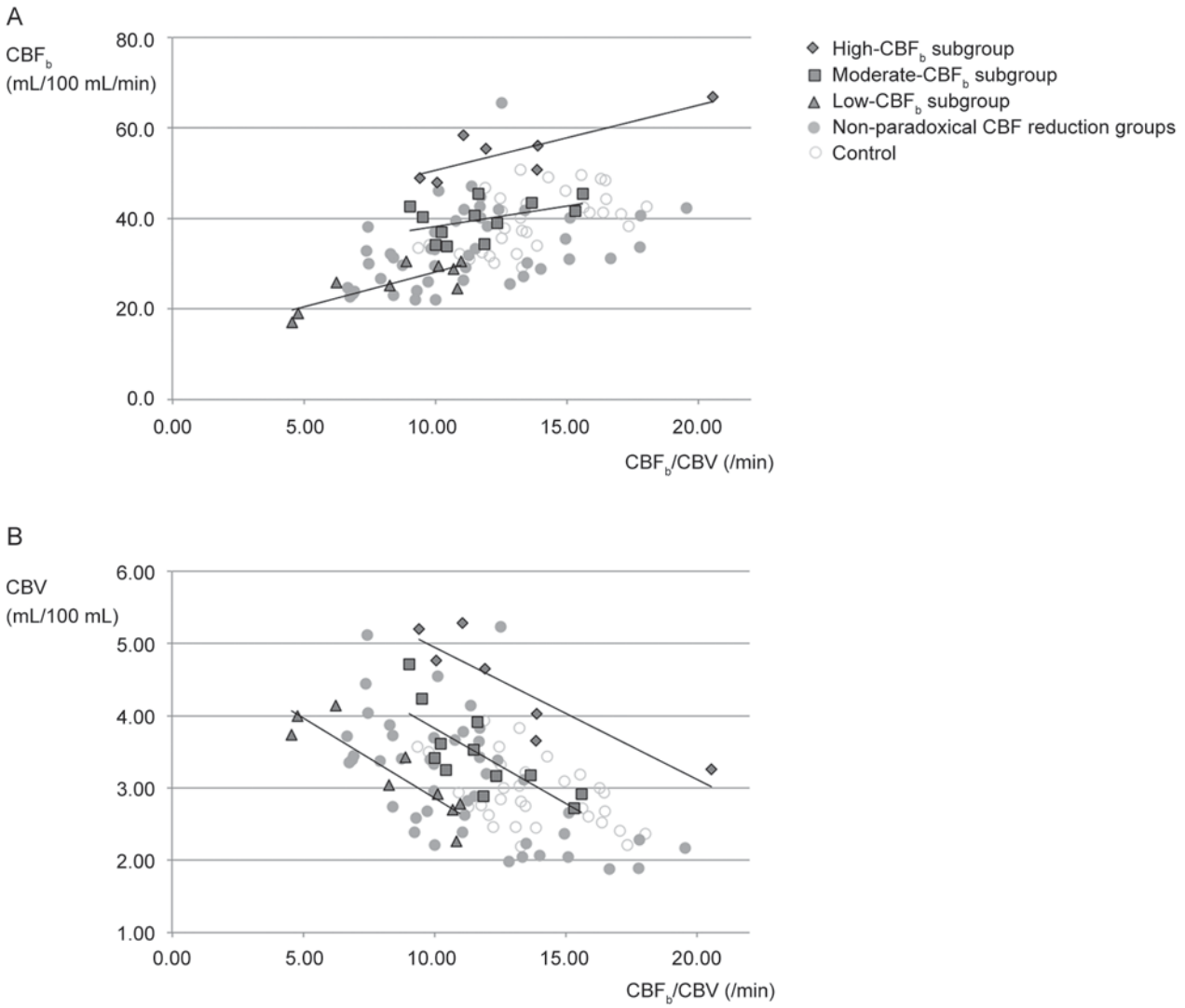

Fig. 3. Relationship between baseline cerebral blood flow to cerebral blood volume (CBF_b/CBV) ratio and CBF_b (A), and between the CBF_b/CBV ratio and CBV (B).

located adjacent to the top of the controls. Figure 4 shows a representative patient with high CBF_b in the regions with paradoxical CBF reduction.

DISCUSSION

The results of the present study demonstrated that the paradoxical CBF reduction after ACZ loading is not always associated with reduction of regional CPP but with various hemodynamic and metabolic states. On the one extreme was "misery perfusion" and stage II ischemia[26] where CBF_b was decreased, CBF_b/CBV was decreased, OEF was increased, and $CMRO_2$ was decreased. On the other was increased CBF_b, normal CBF_b/CBV, increased CBV, decreased OEF, and normal $CMRO_2$. The latter condition has not been reported in previous studies.

High Baseline CBF in Paradoxical CBF Reduction

In the high CBF_b regions with paradoxical circulation, the increases in CBF_b and CBV were proportional resulting in normal CBF_b/CBV and thus normal CPP. Low OEF in these regions suggested an excessive CBF_b increase for normal oxygen demand. Originally, increased perfusion without increased $CMRO_2$ was found after acute ischemia

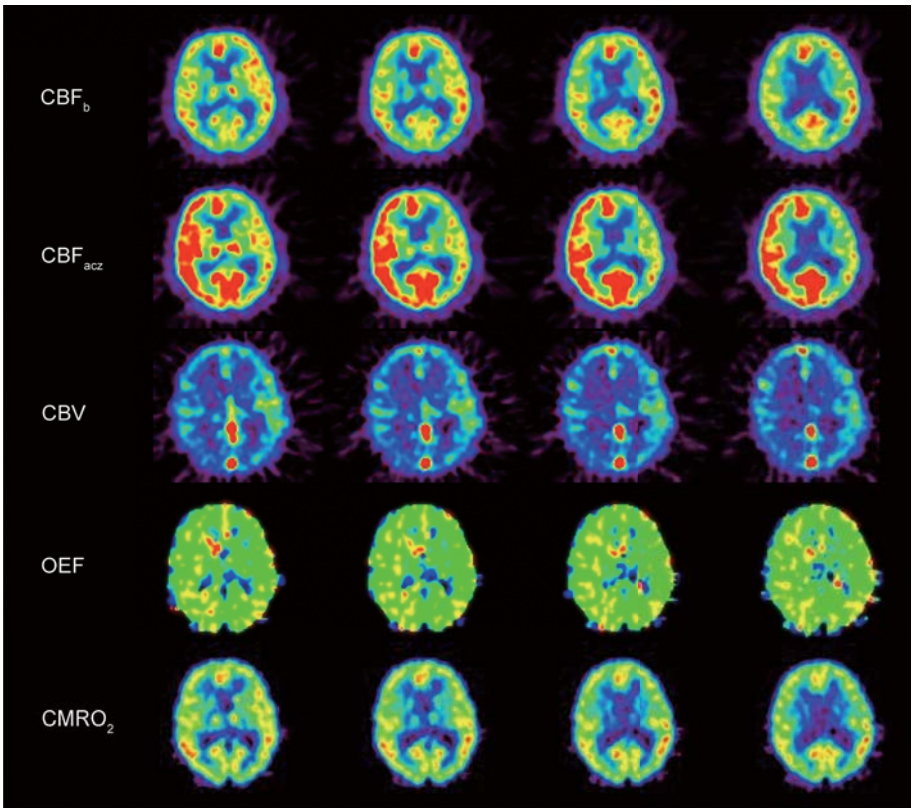

Fig. 4. Representative images from a patient (female, 71 years) with paradoxical cerebral blood flow (CBF) reduction in high-baseline CBF (CBF$_b$) regions. This patient was diagnosed with chronic severe stenosis of the left ICA. She presented with no ischemic symptoms prior to the positron emission tomography examination. Ipsilateral increase in the CBF$_b$ and cerebral blood volume (CBV), ipsilateral decrease in the CBF after acetazolamide loading (CBF$_{acz}$), ipsilateral decrease in the oxygen extraction fraction (OEF), and maintained cerebral oxygen metabolic rate (CMRO$_2$) were found in the left ICA territory.

and called the "luxury perfusion" syndrome[27]. This condition resulted in irreversible brain damage[28–30]. Our patients showed no clinical signs and MRI evidence of acute cerebral infarction. None of the patients had cerebral infarction after the examination. It is noteworthy that an excessive CBF$_b$ increase was also found in the contralateral hemisphere where the OEF was significantly decreased, the CBV was significantly increased, and the CBF$_b$/CBV did not significantly change. Therefore, we speculated that the excessive CBF$_b$ and CBV increases in our patients differ from ischemia-related luxury perfusion.

A bilateral hemispheric CBF increase during unilateral ICA occlusion was also found by Torigai *et al.* [31]. They performed balloon occlusion tests in 4 patients with intracranial aneurysm and in 6 with head and neck tumors. Each hemispheric CBF increase was proportional between the occluded and non-occluded sides. Although their study induced acute unilateral ICA occlusion, there is a physiological mechanism to increase CBF bilaterally.

Mechanism of High Baseline CBF

One possible mechanism of the bilateral increase of CBF$_b$ in the high-CBF$_b$ subgroup is dilatation of the contralateral carotid artery and/or basilar artery, as well as of the cerebral microvessels. Faraci and Heistad suggested that the large intracranial and extracranial arteries are a major site of resistance to CBF and contribute to total cerebral vascular resistance[32]. If the contralateral ICA and/or basilar artery in addition to the arterioles were dilated with sufficient collateral circulation through the circle of Willis in a patient with unilateral ICA occlusion, then the CPP may be constant and the CBF$_b$ may be increased. Furst *et al.* also

Table 6. Information on patients with regions showing paradoxical cerebral blood flow reduction

Pt	Age	Sex	Angiography	MCA-an CBFb Subgroup / Ipsi (Contra)			MCA-po CBFb Subgroup / Ipsi (Contra)			Patency of the circle of Willis	Symptom	Interval* (months)	Underlying disease
1	71	F	ICA occlusion	HC	48.0	(41.4)	HC	48.9	(40.6)	A-com, P-com	Asymptomatic		DM
2	71	F	ICA stenosis	HC	56.0	(65.4)	HC	66.9	(70.0)	A-com	TIA	2	HT, DM
3	59	M	ICA occlusion	HC	58.4	(53.1)	(-)	65.5	(60.5)	A-com, P-com	Asymptomatic		HT, DL
4	68	M	ICA stenosis	MC	40.3	(53.2)	HC	55.4	(65.0)	A-com	TIA	2	DM, HT, DL
5	46	M	ICA occlusion	MC	41.6	(45.8)	HC	50.8	(50.7)	P-com	Asymptomatic		
6	63	F	MCA stenosis	MC	43.4	(38.6)	MC	45.4	(47.8)	(-)	MS (Ipsi-BG, Ipsi-CR)	1.5	HT, DL
7	51	F	MCA stenosis	MC	39.0	(40.1)	MC	40.6	(46.0)	(-)	TIA	6	DL
8	62	F	MCA stenosis	(-)	42.7	(49.2)	MC	45.5	(51.4)	(-)	Asymptomatic		DM, DL
9	41	F	ICA stenosis	MC	42.6	(42.4)	(-)	47.2	(43.9)	(-)	MS (Ipsi-parietal, cortex)	19	HT, DL
10	71	M	ICA stenosis	MC	37.0	(42.3)	(-)	41.9	(47.9)	A-com, P-com	Asymptomatic		HT
11	73	M	ICA stenosis	MC	34.3	(33.8)	(-)	42.0	(39.3)	A-com, P-com	Asymptomatic		HT
12	63	M	MCA stenosis	LC	29.6	(31.1)	(-)	33.9	(36.9)	(-)	TIA	4	HT, DL
13	59	M	MCA stenosis	MC	34.1	(30.1)	LC	30.5	(34.3)	(-)	Asymptomatic		HT
14	74	M	ICA occlusion	LC	25.1	(34.5)	LC	30.5	(42.2)	A-com	MS (Ipsi-BG)	1	DM, HT
15	57	M	ICA stenosis	LC	19.1	(32.3)	LC	25.8	(33.2)	(-)	Asymptomatic		HT
16	78	M	ICA occlusion	LC	17.1	(26.0)	(-)	24.8	(28.1)	A-com, P-com	MS (Ipsi-BG)	1	HT, DL
17	63	M	ICA stenosis	LC	28.9	(29.7)	(-)	36.9	(35.8)	A-com	MS (Ipsi-BG, Ipsi-Th)		DM, HT
18	76	M	MCA occlusion	LC	24.5	(26.9)	(-)	23.0	(30.5)	(-)	MS (Contra-parietal, cortex)	17	HT

*Interval between the last symptom and positron emission tomography.

A-com, anterior communicating artery; an, anterior branch territory; BG, basal ganglia; CBF_b, baseline cerebral blood flow; Contra, contralateral; CR, corona radiate; DL, dyslipidemia; DM, diabetes mellitus; DWM, deep white matter; F, female; HC, high-CBF_b subgroup; HT, hypertension; ICA, internal carotid artery; Ipsi, ipsilateral; LC, low-CBF_b subgroup; M, male; MCA, middle cerebral artery; MC, moderate-CBF_b subgroup; MS, minor stroke; P-com, posterior communicating artery; Pt, patient; po, posterior branch territory; Th, thalamus; TIA, transient ischemic attack.

speculated that dilatation of the contralateral large arteries and of the microvessels in the ipsilateral hemisphere may induce bilateral elevation of the CBF_b[33]. In the present study, all patients classified into the high-CBF_b subgroup suffered from unilateral ICA occlusion or severe stenosis with a patent circle of Willis (Table 6). We speculated that compensatory dilatation of the contralateral ICA and/or basilar artery induces a bilateral increase of the CBF_b. It is known that sympathetic innervation of the carotid and cerebral vessels and their response to norepinephrine play an important role in maintaining cerebral autoregulation[34]. The contribution of large arteries to the control of cerebral circulation needs further study in patients with chronic carotid artery steno-occlusive disease.

Prognosis of Patients with High Baseline CBF

Because of the short observation period after PET examination, the prognosis of patients classified into each group and/or subgroup has not yet been precisely analyzed. Derdeyn *et al.* studied the relationship between the OEF and CBV in patients with unilateral carotid artery occlusion and found that an increase in the CBV with an increase of the OEF was associated with a higher risk of stroke[35]. However, none of the patients with increased CBV and low OEF developed stroke over a mean follow-up period of 3.1 years. We suppose that a high CBF_b in the paradoxical CBF reduction is not indicative of a high risk of ischemic stroke.

Cerebral Oxygen Metabolism in Paradoxical CBF Reduction

Cerebral oxygen metabolism was significantly and exclusively decreased in the low CBF_b regions of the paradoxical CBF reduction, even extending to the contralateral hemisphere. The reduction of $CMRO_2$ in the ipsilateral hemisphere was probably due to selective neuronal loss. In patients with unilateral cerebrovascular disease, selective neuronal necrosis, as represented by a reduction of ^{11}C-flumazenil binding, has been found in the cortical areas in the ipsilateral hemisphere with reduced CBF and reduced CVR[36,37]. In these studies, no significant reduction of ^{11}C-flumazenil binding was found in the contralateral hemisphere. In the contralateral hemisphere of the low CBF_b subgroup, metabolic reduction was considered to be attributable to trans-hemispheric functional depression. Recovery of $CMRO_2$ in the contralateral hemisphere after bypass surgery supports this view[38].

Staging of High Baseline CBF

Powers and Derdeyn *et al.* established a staging for cerebral hemodynamic crisis based on CBF_b, CBV, and OEF[26,35]. In Stage 0, CBF_b, CBV, and OEF are all normal. In Stage I, CPP is reduced and the cerebral vessels are dilated to maintain CBF_b; the CBV is increased, while the OEF remains normal. In Stage II, the capacity for compensatory vasodilation is overwhelmed and the CBF_b begins to fall. Nemoto *et al*. added Stage III chronic where OEF returns to normal levels due to impaired $CMRO_2$ and CVR is still compromised. In the present study, we showed that the abnormalities in the low-CBF_b subgroup correspond to Stage II hemodynamic failure, and those in the moderate-CBF_b subgroup correspond to Stage I. However, the abnormalities in the high-CBF_b subgroup could not be clearly categorized into any of the established stages. According to the CBF/CBV in the present study, the reduction of CPP was most severe in the low CBF_b regions of paradoxical CBF reduction (mean CBF_b/CBV = 8.4) followed by Group B (0 <CVR <15%) (mean CBF_b/CBV = 9.9), moderate CBF_b (mean CBF_b/CBV = 11.8), Group C (CVR >15%, mean CBF_b/CBV = 12.3), and high CBF_b (mean CBF_b/CBV = 12.5) in this order. An additional category for high baseline CBF we propose would be located between normal and stage I.

Limitations

There are several limitations of the present study. First, the number of patients was limited and the background characteristics of the patients were heterogeneous. Some were asymptomatic, while others suffered a minor stroke as evidenced by MR, or a TIA. The patients often had hypertension, diabetes mellitus, and dyslipidemia. Second, we determined the presence/absence of the paradoxical CBF reduction by CBF measurements conducted 15 min after ACZ injection. The ACZ effect is reported to reach a maximum at 10 to 20 min after administration[4]. According to Kuwabara *et al.*, who reported the time-dependency of the effect of ACZ on the cerebral circulation, the paradoxical CBF reduction is most prominent 5 min after injection

compared to 20 min after injection[7]. The paradoxical CBF reduction might be detectable more frequently in the early phase (at 5 to 10 min). Third, although we speculated about the role of large arteries in controlling the cerebral circulation, we did not evaluate changes in the diameter of the common carotid artery or ICA after ACZ administration. Fourth, we are still following up the patients of the present study, and the prognosis is still uncertain. The contribution of a high CBF_b to the clinical outcome and long-term changes remain unclear. However, regions with increased CBF_b and normal CPP might indicate a protective mechanism against the CBF reduction caused by the changes in circulatory dynamics. We suggest that careful follow-up, rather than revascularization treatment, is desirable in patients with such regions.

In conclusion, we have demonstrated that the paradoxical CBF reduction in patients with chronic unilateral ICA/MCA steno-occlusive disease is not always associated with a reduction of CPP and misery perfusion, but partly includes high CBF regions with normal CPP and an excessive oxygen supply. The high CBF state found in the present study has not been included in the previously-established staging of chronic brain ischemia in patients with steno-occlusive ICA/MCA disease. We consider that the high CBF in these regions might be partly due to vasodilatation of the contralateral carotid and large cerebral arteries.

ACKNOWLEDGEMENTS

This work was partly supported by the Molecular Imaging Program, a grant (21591561) from the Ministry of Education, Culture, Sports, Science, and Technology and the Japan Science and Technology Agency, Japan, by the Research Promotion Program on Health from the National Institute of Biomedical Innovation, Japan, and a Grant-in-Aid (H21-019 and H21-5) from the Ministry of Health, Welfare, and Labour, Japan.

Received date: 2013-12-04; Accepted date: 2014-01-23

REFERENCES

[1] Symon L. Experimental evidence for "intracerebral steal" following CO_2 inhalation. Scand J Clin Lab Invest Suppl 1968, 102: XIII:A.

[2] Symon L, Pasztor E, Branston NM. The distribution and density of reduced cerebral blood flow following acute middle cerebral artery occlusion: an experimental study by the technique of hydrogen clearance in baboons. Stroke 1974, 5: 355–364.

[3] Regli F, Yamaguchi T, Waltz AG. Effects of acetazolamide on cerebral ischemia and infarction after experimental occlusion of middle cerebral artery. Stroke 1971, 2: 456–460.

[4] Vorstrup S, Henriksen L, Paulson OB. Effect of acetazolamide on cerebral blood flow and cerebral metabolic rate for oxygen. J Clin Invest 1984, 74: 1634–1639.

[5] 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.

[6] 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 Suppl 1988, 114: 1–48.

[7] Kuwabara Y, Ichiya Y, Sasaki M, Yoshida T, Masuda K. Time dependency of the acetazolamide effect on cerebral hemodynamics in patients with chronic occlusive cerebral arteries. Early steal phenomenon demonstrated by $[^{15}O]H_2O$ positron emission tomography. Stroke 1995, 26: 1825–1829.

[8] Okazawa H, Yamauchi H, Toyoda H, Sugimoto K, Fujibayashi Y, Yonekura Y. Relationship between vasodilatation and cerebral blood flow increase in impaired hemodynamics: a PET study with the acetazolamide test in cerebrovascular disease. J Nucl Med 2003, 44: 1875–1883.

[9] Baron JC, Bousser MG, Rey A, Guillard A, Comar D, Castaigne P. Reversal of focal "misery-perfusion syndrome" by extra-intracranial arterial bypass in hemodynamic cerebral ischemia. A case study with ^{15}O positron emission tomography. Stroke 1981, 12: 454–459.

[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] Sette G, Baron JC, Mazoyer B, Levasseur M, Pappata S, Crouzel C. Local brain haemodynamics and oxygen metabolism in cerebrovascular disease. Positron emission tomography. Brain 1989, 112 (Pt 4): 931–951.

[12] 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 (Pt 7): 1369–1379.

[13] North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991, 325: 445–453.

[14] Matsumoto K, Kitamura K, Mizuta T, Tanaka K, Yamamoto S, Sakamoto S, *et al.* Performance characteristics of a new 3-dimensional continuous-emission and spiral-transmission

high-sensitivity and high-resolution PET camera evaluated with the NEMA NU 2-2001 standard. J Nucl Med 2006, 47: 83–90.

[15] Ibaraki M, Miura S, Shimosegawa E, Sugawara S, Mizuta T, Ishikawa A*, et al.* Quantification of cerebral blood flow and oxygen metabolism with 3-dimensional PET and ^{15}O: validation by comparison with 2-dimensional PET. J Nucl Med 2008, 49: 50–59.

[16] Mintun MA, Raichle ME, Martin WR, Herscovitch P. Brain oxygen utilization measured with O-15 radiotracers and positron emission tomography. J Nucl Med 1984, 25: 177–187.

[17] Herscovitch P, Markham J, Raichle ME. Brain blood flow measured with intravenous H2(15)O. I. Theory and error analysis. J Nucl Med 1983, 24: 782–789.

[18] Iida H, Jones T, Miura S. Modeling approach to eliminate the need to separate arterial plasma in oxygen-15 inhalation positron emission tomography. J Nucl Med 1993, 34: 1333–1340.

[19] Hatazawa J, Fujita H, Kanno I, Satoh T, Iida H, Miura S*, et al.* Regional cerebral blood flow, blood volume, oxygen extraction fraction, and oxygen utilization rate in normal volunteers measured by the autoradiographic technique and the single breath inhalation method. Ann Nucl Med 1995, 9: 15–21.

[20] 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.

[21] Kanno I, Iida H, Miura S, Murakami M, Takahashi K, Sasaki H*, et al.* A system for cerebral blood flow measurement using an H2(15)O autoradiographic method and positron emission tomography. J Cereb Blood Flow Metab 1987, 7: 143–153.

[22] Iida H, Kanno I, Miura S, Murakami M, Takahashi K, Uemura K. Error analysis of a quantitative cerebral blood flow measurement using H2(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.

[23] Kuroda S, Shiga T, Ishikawa T, Houkin K, Narita T, Katoh C*, et al.* Reduced blood flow and preserved vasoreactivity characterize oxygen hypometabolism due to incomplete infarction in occlusive carotid artery diseases. J Nucl Med 2004, 45: 943–949.

[24] Imaizumi M, Kitagawa K, Oku N, Hashikawa K, Takasawa M, Yoshikawa T*, et al.* Clinical significance of cerebrovascular reserve in acetazolamide challenge -comparison with acetazolamide challenge H_2O-PET and Gas-PET. Ann Nucl Med 2004, 18: 369–374.

[25] Isozaki M, Arai Y, Kudo T, Kiyono Y, Kobayashi M, Kubota T*, et al.* Clinical implication and prognosis of normal baseline cerebral blood flow with impaired vascular reserve in patients with major cerebral artery occlusive disease. Ann Nucl Med 2010, 24: 371–377.

[26] Powers WJ. Cerebral hemodynamics in ischemic cerebrovascular disease. Ann Neurol 1991, 29: 231–240.

[27] Lassen NA. The luxury-perfusion syndrome and its possible relation to acute metabolic acidosis localised within the brain. Lancet 1966, 2: 1113–1115.

[28] Ackerman RH, Correia JA, Alpert NM, Baron JC, Gouliamos A, Grotta JC*, et al*. Positron imaging in ischemic stroke disease using compounds labeled with oxygen 15. Initial results of clinicophysiologic correlations. Arch Neurol 1981, 38: 537–543.

[29] Wise RJ, Bernardi S, Frackowiak RS, Legg NJ, Jones T. Serial observations on the pathophysiology of acute stroke. The transition from ischaemia to infarction as reflected in regional oxygen extraction. Brain 1983, 106 (Pt 1): 197–222.

[30] Hakim AM. The cerebral ischemic penumbra. Can J Neurol Sci 1987, 14: 557–559.

[31] Torigai T, Mase M, Ohno T, Katano H, Nisikawa Y, Sakurai K*, et al.* Usefulness of dual and fully automated measurements of cerebral blood flow during balloon occlusion test of the internal carotid artery. J Stroke Cerebrovasc Dis 2011, 22(3): 197–204.

[32] Faraci FM, Heistad DD. Regulation of large cerebral arteries and cerebral microvascular pressure. Circ Res 1990, 66: 8–17.

[33] Furst H, Hartl WH, Janssen I. Patterns of cerebrovascular reactivity in patients with unilateral asymptomatic carotid artery stenosis. Stroke 1994, 25: 1193–1200.

[34] Omar NM, Marshall JM. Age-related changes in the sympathetic innervation of cerebral vessels and in carotid vascular responses to norepinephrine in the rat: *in vitro* and *in vivo* studies. J Appl Physiol 2010, 109: 314–322.

[35] Derdeyn CP, Videen TO, Yundt KD, Fritsch SM, Carpenter DA, Grubb RL*, et al.* Variability of cerebral blood volume and oxygen extraction: stages of cerebral haemodynamic impairment revisited. Brain 2002, 125: 595–607.

[36] Kuroda S, Shiga T, Houkin K, Ishikawa T, Katoh C, Tamaki N*, et al.* Cerebral oxygen metabolism and neuronal integrity in patients with impaired vasoreactivity attributable to occlusive carotid artery disease. Stroke 2006, 37: 393–398.

[37] Yamauchi H, Nishii R, Higashi T, Kagawa S, Fukuyama H. Silent cortical neuronal damage in atherosclerotic disease of the major cerebral arteries. J Cereb Blood Flow Metab 2011, 31: 953–961.

[38] Samson Y, Baron JC, Bousser MG, Rey A, Derlon JM, David P*, et al.* Effects of extra-intracranial arterial bypass on cerebral blood flow and oxygen metabolism in humans. Stroke 1985, 16: 609–616.