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

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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 ($>47.6 \text{ mL}/100 \text{ mL}/\text{min}$, $n = 7$) was associated with normal CBF_b/CBV , increased CBV, decreased OEF, and normal CMRO_2 . Low CBF_b ($<31.8 \text{ mL}/100 \text{ mL}/\text{min}$, $n = 9$) 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 ¹⁵O 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 ¹³⁷Cs 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 $^{15}\text{O}_2$ 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 $^{15}\text{O}_2$ 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 $^{15}\text{O}_2$ ^[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 $[\text{diastolic BP} + (\text{systolic BP} - \text{diastolic BP}) / 3]$.

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: $\text{CVR} = [(\text{CBF}_{\text{acz}} - \text{CBF}_b) / \text{CBF}_b] \times 100\%$. 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: $\text{CVR} < 0\%$) and non-paradoxical CBF reduction groups (group B: $\text{CVR} = 0-15\%$ and group C: $\text{CVR} > 15\%$). 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 $\pm 20\%$ 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 $\pm$ SD values of arterial blood gas parameters and blood pressure

	Group A (CVR <0%)	Group B (CVR 0–15%)	Group C (CVR >15%)	Control	<i>P</i> value*
PaCO ₂ at baseline (mmHg)	38.8 $\pm$ 4.1	38.9 $\pm$ 4.1	39.2 $\pm$ 2.3	40.1 $\pm$ 4.3	0.877
PaCO ₂ after ACZ (mmHg)	36.7 $\pm$ 4.7	37.6 $\pm$ 4.9	37.7 $\pm$ 3.0	39.2 $\pm$ 4.2	0.584
MABP at baseline (mmHg)	87.6 $\pm$ 9.6	85.9 $\pm$ 12.4	95.0 $\pm$ 10.2	93.6 $\pm$ 10.6	0.072
MABP after ACZ (mmHg)	88.6 $\pm$ 11.0 ^a	87.5 $\pm$ 12.4 ^A	101.8 $\pm$ 12.5 ^{a,A}	97.0 $\pm$ 15.2	0.006
Hb (g/dl)	11.9 $\pm$ 1.5 ^a	12.8 $\pm$ 1.5	13.4 $\pm$ 1.4 ^a	12.9 $\pm$ 1.3	0.035
Ht (%)	36.7 $\pm$ 4.6 ^a	39.4 $\pm$ 4.5	41.0 $\pm$ 4.0 ^a	39.4 $\pm$ 3.8	0.047

ACZ, acetazolamide; CVR, cerebrovascular reactivity; Hb, hemoglobin; Hct, hematocrit; MABP, mean arterial blood pressure; PaCO₂, arterial partial pressure of CO₂. *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 $\pm$ SD)

		Group A (CVR <0%) (<i>n</i> = 28)		Group B (CVR 0–15%) (<i>n</i> = 21)		Group C (CVR >15%) (<i>n</i> = 25)		Control (<i>n</i> = 32)
		Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral	
Baseline	CBF _b (mL/100 mL/min)	39.0 $\pm$ 12.2	42.3 $\pm$ 11.6	33.9 $\pm$ 11.2 [†]	36.1 $\pm$ 9.6 [‡]	33.3 $\pm$ 5.8 [‡]	35.7 $\pm$ 5.6 [‡]	39.7 $\pm$ 6.4
	CBV (mL/100 mL)	3.62 $\pm$ 0.79 ^{b,‡}	2.95 $\pm$ 0.58	3.41 $\pm$ 0.72 [‡]	3.06 $\pm$ 0.50	2.90 $\pm$ 0.88 ^b	2.96 $\pm$ 0.62	2.91 $\pm$ 0.46
	OEF (%)	45.4 $\pm$ 7.4	44.3 $\pm$ 6.0	45.3 $\pm$ 7.6	43.7 $\pm$ 7.9	43.5 $\pm$ 6.5	42.7 $\pm$ 5.8	45.2 $\pm$ 5.2
	CMRO ₂ (mL/100 mL/min)	2.52 $\pm$ 0.56 [‡]	2.69 $\pm$ 0.43 [‡]	2.52 $\pm$ 0.64 [‡]	2.60 $\pm$ 0.49 [‡]	2.51 $\pm$ 0.27 [‡]	2.65 $\pm$ 0.36 [‡]	3.07 $\pm$ 0.52
	CBF _b /CBV ratio (/min)	11.0 $\pm$ 3.3 [‡]	14.5 $\pm$ 3.6 ^b	9.9 $\pm$ 1.9 ^{a,‡}	11.7 $\pm$ 1.8 ^{b,‡}	12.3 $\pm$ 3.5 ^a	12.5 $\pm$ 2.7	13.8 $\pm$ 2.2
After ACZ	CVR (%)	−8.0 $\pm$ 5.2 [‡]	35.0 $\pm$ 31.4 ^{a,‡}	6.2 $\pm$ 4.6 [‡]	36.7 $\pm$ 20.2 [‡]	49.3 $\pm$ 41.3 [‡]	57.6 $\pm$ 43.5 ^{a,‡}	107.3 $\pm$ 52.9

ACZ, acetazolamide; an, anterior branch territory; CBF_b, baseline cerebral blood flow; CBV, cerebral blood volume; CMRO₂, 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 CMRO₂ 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 $\pm$ SD)

	High-CBF _b	Moderate-CBF _b	Low-CBF _b	P value [*]
PaCO ₂ at baseline (mmHg)	40.8 $\pm$ 3.6	38.6 $\pm$ 4.6	36.5 $\pm$ 4.3	0.270
PaCO ₂ after ACZ (mmHg)	39.3 $\pm$ 4.1	36.1 $\pm$ 5.0	34.1 $\pm$ 5.6	0.242
MABP at baseline (mmHg)	89.4 $\pm$ 8.7	87.9 $\pm$ 8.8	87.3 $\pm$ 10.9	0.931
MABP after ACZ (mmHg)	91.1 $\pm$ 5.1	88.7 $\pm$ 11.7	90.4 $\pm$ 13.2	0.909
Hb (g/dl)	11.4 $\pm$ 1.5	12.1 $\pm$ 1.5	12.2 $\pm$ 1.5	0.685
Ht (%)	35.8 $\pm$ 5.0	37.2 $\pm$ 4.6	37.4 $\pm$ 4.5	0.827

ACZ, acetazolamide; CBF_b, baseline cerebral blood flow; Hb, hemoglobin; Hct, hematocrit; MABP, mean arterial blood pressure; PaCO₂, arterial partial pressure of CO₂. 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 $\pm$ 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 $\pm$ 6.6 [‡]	55.2 $\pm$ 11.9 ^{b,‡}	39.8 $\pm$ 4.2	42.3 $\pm$ 6.9 ^B	25.7 $\pm$ 4.9 [‡]	32.3 $\pm$ 4.8 ^{b,B,‡}
	CBV (mL/100 mL)	4.41 $\pm$ 0.78 ^{a,A,‡}	3.36 $\pm$ 0.46 [‡]	3.46 $\pm$ 0.59 ^{a,‡}	2.82 $\pm$ 0.47	3.22 $\pm$ 0.64 ^A	2.79 $\pm$ 0.67
	OEF (%)	39.3 $\pm$ 5.1 ^{b,‡}	40.7 $\pm$ 5.1 ^{a,‡}	44.4 $\pm$ 6.7 ^A	44.1 $\pm$ 5.9	51.7 $\pm$ 4.8 ^{b,A,‡}	47.4 $\pm$ 5.7 ^a
	CMRO ₂ (mL/100 mL/min)	2.77 $\pm$ 0.54 ^a	2.83 $\pm$ 0.51	2.69 $\pm$ 0.50 ^A	2.81 $\pm$ 0.36	2.11 $\pm$ 0.44 ^{a,A,‡}	2.43 $\pm$ 0.38 [‡]
	CBF _b /CBV ratio (/min)	13.0 $\pm$ 3.8 ^a	17.0 $\pm$ 5.6	11.8 $\pm$ 2.2 ^{A,‡}	15.1 $\pm$ 1.6 ^B	8.4 $\pm$ 2.6 ^{a,A,‡}	11.8 $\pm$ 1.3 ^{B,‡}
After ACZ	CVR (%)	-6.2 $\pm$ 2.7 [‡]	69.2 $\pm$ 43.8 ^{b,a}	-8.3 $\pm$ 5.0 [‡]	24.0 $\pm$ 14.2 ^{b,‡}	-9.1 $\pm$ 6.8 [‡]	22.9 $\pm$ 15.1 ^{a,‡}

ACZ, acetazolamide; an, anterior branch territory; CBF_b, baseline cerebral blood flow; CBV, cerebral blood volume; CMRO₂, cerebral oxygen metabolic rate; CVR, cerebrovascular reactivity; MCA, middle cerebral artery; OEF, oxygen extraction fraction; po, posterior branch territory.

^aP < 0.05, ^bP < 0.01: comparison between high-CBF_b subgroup and moderate- or low-CBF_b subgroup in the same side; ^AP < 0.05 and ^BP < 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 radiata; 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 $\text{CBF}_b/\text{CBV} = 8.4$) followed by Group B ($0 < \text{CVR} < 15\%$) (mean $\text{CBF}_b/\text{CBV} = 9.9$), moderate CBF_b (mean $\text{CBF}_b/\text{CBV} = 11.8$), Group C ($\text{CVR} > 15\%$, mean $\text{CBF}_b/\text{CBV} = 12.3$), and high CBF_b (mean $\text{CBF}_b/\text{CBV} = 12.5$) 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.

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