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Hemodynamic changes during neural deactivation in human brain: A positron emission tomography study of crossed cerebellar diaschisis

Hiroshi ITO, Iwao KANNO, Eku SHIMOSEGAWA, Hajime TAMURA, Kumiko OKANE and Jun HATAZAWA

Department of Radiology and Nuclear Medicine, Akita Research Institute of Brain and Blood Vessels

The mechanism of crossed cerebellar diaschisis (CCD) is considered to be secondary hypoperfusion due to neural deactivation. To elucidate the hemodynamics during neural deactivation, the hemodynamics of CCD was investigated. The cerebral blood flow (CBF), cerebral blood volume (CBV), cerebral oxygen extraction fraction (OEF), cerebral metabolic rate of oxygen ($CMRO_2$), and vascular responses to hypercapnia and acetazolamide stress for CCD were measured in 20 patients with cerebrovascular disease by positron emission tomography with $H_2{}^{15}O$, $C^{15}O$, and ${}^{15}O_2$. Vascular responses to hypercapnia and acetazolamide stress were almost the same between CCD side and unaffected side of the cerebellum, a finding that supports the idea that the mechanism of CCD is secondary hypoperfusion due to neural deactivation. The degree of decrease in CBF on the CCD side was almost the same as that in CBV, indicating that vascular blood velocity does not change during neural deactivation. The relation between CBF and CBV of the CCD and unaffected sides was $CBV = 0.29\ CBF^{0.56}$. On the CCD side, the degree of decrease in $CMRO_2$ was less than that in CBF, resulting in a significantly increased OEF. The increased OEF along with the decreased CBV on the CCD side might indicate that neural deactivation primarily causes vasoconstriction rather than a reduction of oxygen metabolism.

Key words: neural deactivation, hemodynamics, cerebellum, diaschisis, PET

INTRODUCTION

POSITRON EMISSION TOMOGRAPHY (PET) studies of the hemodynamics of crossed cerebellar diaschisis (CCD), which is caused by contralateral supratentorial lesions, have shown a reduction in cerebral blood flow (CBF) and cerebral metabolic rate of oxygen ($CMRO_2$).[1–4] No differences in vascular response to hypercapnia, hypocapnia, or acetazolamide stress were observed between the CCD side and the unaffected side of the cerebellum.[5,6] This finding implies that the mechanism of CCD is secondary hypoperfusion due to neural deactivation.

We recently used photic flicker visual stimulation to investigate changes in both regional CBF and regional cerebral blood volume (CBV) during neural activation.[7] In our observations, when the increase in CBF was large, it was caused primarily by an increase in vascular blood velocity rather than by an increase in CBV, but the relation between CBF and CBV during neural deactivation is not well understood. Since the mechanism of CCD is secondary hypoperfusion due to neural deactivation, CCD can be used to investigate the hemodynamics of neural deactivation. To the best of our knowledge, only one report showed almost the same reduction levels of CBF and CBV on the CCD side as on the unaffected side,[4] indicating no noticeable change in vascular blood velocity between the CCD and unaffected sides.

In the present study, CBF, CBV, cerebral oxygen extraction fraction (OEF), $CMRO_2$, and vascular responses to hypercapnia and acetazolamide stress for CCD were measured in each patient on the same day by the same modality. Data on vascular responses to hypercapnia and acetazolamide stress were used to confirm that the mechanism of CCD is secondary hypoperfusion due to neural deactivation. Data on CBF, CBV, OEF and $CMRO_2$

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For reprint contact: Hiroshi Ito, M.D., Ph.D., Department of Radiology and Nuclear Medicine, Akita Research Institute of Brain and Blood Vessels, 6–10 Senshu-kubota-machi, Akita 010–0874, JAPAN.

E-mail: hito@akita-noken.go.jp

were used to investigate the hemodynamics of neural deactivation.

METHODS

Subjects

We studied the case records of 20 patients (15 men and 5 women; age, 60 ± 12 yr, mean ± SD) with steno-occlusive lesions of the major cerebral artery who were affected by CCD that was sufficiently visualized on the CBF image at rest (affected/unaffected ratio < 0.93).[6] All patients were selected retrospectively from a large series of patients whose CBF, CBV, OEF, $CMRO_2$, and CBF responses to hypercapnia and acetazolamide stress had been measured by PET. All patients gave written informed consent before the PET examination. Patient information is listed in Table 1. The interval between the onset of stroke and PET examination ranged from 1 to 19 weeks. Exclusion criteria were crossed cerebellar atrophy and other morphological lesions of the cerebellum or brain stem as detected on magnetic resonance imaging (MRI), and steno-occlusive lesions in the vertebrobasilar system detected by angiography.

PET procedures

A Headtome-V PET camera (Shimadzu Corp., Kyoto, Japan) was used for all studies; it provides 47 sections with center-to-center distances of 3.125 mm.[8] The intrinsic spatial resolution was 4.0 mm in-plane and 4.3 mm full width at half maximum (FWHM) axially. Reconstruction with a Butterworth filter resulted in a final in-plane resolution of approximately 8 mm FWHM.

$C^{15}O$ study

To measure CBV, a $C^{15}O$ PET study was performed according to a previously described method.[9] Transmission scanning for attenuation correction was performed just before the $C^{15}O$ PET scanning. A head fixation system with individual molds for each subject was used to minimize head movement during the PET measurements. The static PET scan was started 3 minutes after 1 minute of continuous inhalation of $C^{15}O$ gas (approximately a total of 5 GBq supplied to the mouth). The scan time was 4 minutes. Three arterial blood samples were taken during the PET scanning.

$^{15}O_2$ study

To measure OEF and $CMRO_2$, a $^{15}O_2$ PET study was performed as previously described.[10,11] The scanning protocol consisted of a 180-second static scan following 1.5 minutes of continuous inhalation of $^{15}O_2$ gas (approximately a total of 5 GBq supplied to the mouth). The arterial input function was obtained with a beta probe for continuous measurement of arterial whole blood radioactivity. Two blood samples were taken, one at the beginning and one at the end of scanning to measure the arterial O_2 gas pressure and pH. The arterial plasma concentration of ^{15}O labeled metabolic water was calculated according to a previously reported method.[12] Correction for remaining radioactivity in cerebral blood vessels was done.[13]

Table 1 Clinical characteristics of the 20 patients with cerebral infarction

Patient	Age (y)/Sex	Lesion location	Angiography findings	Time since stroke
1	39/M	L parietal	L ICA occlusion	7 wk
2	67/F	L parietal	L MCA stenosis	6 wk
3	67/M	L basal ganglia	L MCA stenosis	10 wk
4	58/F	R frontal & parietal	R MCA stenosis	7 wk
5	29/M	R basal ganglia & insula	R MCA stenosis	5 wk
6	73/F	L parietal	L ICA stenosis	8 wk
7	61/M	R centrum semiovale	R ICA occlusion	19 wk
8	70/M	L frontal & temporal	L ICA occlusion	4 wk
9	62/M	L centrum semiovale	L ICA occlusion	3 wk
10	51/M	R basal ganglia	R MCA stenosis	4 wk
11	68/M	R basal ganglia & insula	R MCA stenosis	4 wk
12	64/M	L corona radiata	L ICA stenosis	2 wk
13	73/F	R centrum semiovale	R MCA stenosis	10 wk
14	41/M	L frontal	L ICA stenosis	1 wk
15	62/M	L centrum semiovale	L ICA stenosis	5 wk
16	72/M	L basal ganglia	L MCA stenosis	13 wk
17	56/M	L centrum semiovale	L ICA occlusion	1 wk
18	68/M	L frontal & parietal	L ICA stenosis	8 wk
19	59/M	R basal ganglia	R MCA occlusion	3 wk
20	57/F	L basal ganglia	L MCA stenosis	2 wk

M, male; F, female

R, right; L, left; ICA, internal carotid artery; MCA, middle cerebral artery

Table 2 P_aCO_2, P_aO_2, pH, blood pressure (BP) and heart rate (HR) during each $H_2{}^{15}O$ PET scan

Condition	P_aCO_2 (mm Hg)	P_aO_2 (mm Hg)	pH	BP (Systole/Diastole) (mm Hg)	HR (beats/min)
Rest	38.5 ± 2.5	85.7 ± 11.0	7.431 ± 0.017	151 ± 24/76 ± 14	67 ± 13
CO_2	43.8 ± 2.9*	104.2 ± 12.6*	7.391 ± 0.021*	158 ± 30†/79 ± 16	68 ± 15
Acetazolamide	35.9 ± 2.3*	99.5 ± 10.6*	7.443 ± 0.018*	154 ± 29/77 ± 13	67 ± 13

Values are shown as mean ± SD.
Significant difference vs. values at rest: *$p < 0.001$, †$p < 0.01$ (by paired t-test)

Table 3 CBF values at rest and during CO_2 inhalation and acetazolamide stress, and percentage changes in CBF in response to CO_2 inhalation and acetazolamide stress for contralateral and ipsilateral cerebellum

	Contralateral	Ipsilateral
CBF (ml/100 ml/min)		
Rest	41 ± 10*	51 ± 10
CO_2	56 ± 17*	72 ± 20
Acetazolamide	65 ± 21*	83 ± 23
% Change in CBF from rest		
CO_2 (%/mm Hg)	7.6 ± 6.4	8.0 ± 6.4
Acetazolamide (%)	57 ± 19	61 ± 29

Values are shown as mean ± SD.
*Significant difference between contralateral and ipsilateral cerebellum, $p < 0.001$ (by paired t-test)

Table 4 CBF at rest, CBV, OEF, $CMRO_2$, and MTT values for contralateral and ipsilateral cerebellum

	Contralateral	Ipsilateral
CBF (ml/100 ml/min)	41 ± 10*	51 ± 10
CBV (ml/100 ml)	2.1 ± 0.6†	2.8 ± 0.5
OEF	0.42 ± 0.07*	0.39 ± 0.06
$CMRO_2$ (ml/100 ml/min)	3.0 ± 0.7*	3.4 ± 0.7
MTT (sec)	3.2 ± 0.8	3.3 ± 0.8

Values are shown as mean ± SD.
*†Significant difference between contralateral and ipsilateral cerebellum, *$p < 0.001$, †$p < 0.005$ (by paired t-test)

$H_2{}^{15}O$ study

$H_2{}^{15}O$ PET studies were performed with the subjects at rest and during hypercapnia and acetazolamide stress. The interval between $H_2{}^{15}O$ PET studies was at least 15 minutes. The scanning protocol consisted of a 180-second static scan following continuous intravenous infusion of $H_2{}^{15}O$ over 2 minutes. The dose of radioactivity was 0.9 to 1.7 GBq at the start of the scan. The arterial input function was obtained with a beta probe for continuous measurement of arterial whole blood radioactivity. Dispersion and delay occurring in the beta detector system and in the internal-arterial line were corrected according to previously reported methods.[14,15] Two blood samples were taken, one at the beginning and one at the end of scanning to measure the arterial CO_2 gas pressure. The CBF images were calculated by an autoradiographic method.[16,17] Forced hypercapnia was induced by inhalation of 7% CO_2 gas, starting 1 minute before the beginning of the scan and continuing until the end of scan.[18] Acetazolamide (1 g) was administered intravenously over 2 minutes starting 10 minutes before the beginning of the scan.

Data analysis

Regions of interest (ROIs) were drawn on PET images. Elliptical ROIs were defined for the cerebellar cortex (16 mm × 32 mm) in three adjacent sections, and data were pooled to obtain the average concentration of radioactivity for the whole volume of interest.

For each whole volume of interest, vascular mean transit time (MTT) was calculated as follows[19]:

$$MTT = \frac{CBV}{CBF} \quad \text{Eq. 1}$$

For each whole volume of interest, the vascular response to hypercapnia was calculated as the percentage change in CBF per absolute change in P_aCO_2 (mmHg) as follows[18]:

$$\text{Vascular response to hypercapnia (\%/mmHg)} = 100 \times \frac{CBF_a - CBF_r}{CBF_r} \times \frac{1}{|P_aCO_{2a} - P_aCO_{2r}|} \quad \text{Eq. 2}$$

The vascular response to acetazolamide stress was calculated as the percentage change in CBF as follows:

$$\text{Vascular response to acetazolamide stress (\%)} = 100 \times \frac{CBF_a - CBF_r}{CBF_r} \quad \text{Eq. 3}$$

where the subscripts "r" and "a" denote the rest and activation conditions (hypercapnia and acetazolamide), respectively.

RESULTS

$PaCO_2$, PaO_2, pH, blood pressure and heart rate during each $H_2{}^{15}O$ PET scan are summarized for each condition in Table 2. The hemoglobin concentration and hematocrit were 13.1 ± 1.7 g/dl and 39.1% ± 4.2%, respectively (mean ± SD).

The CBF values during rest, hypercapnia, and aceta-

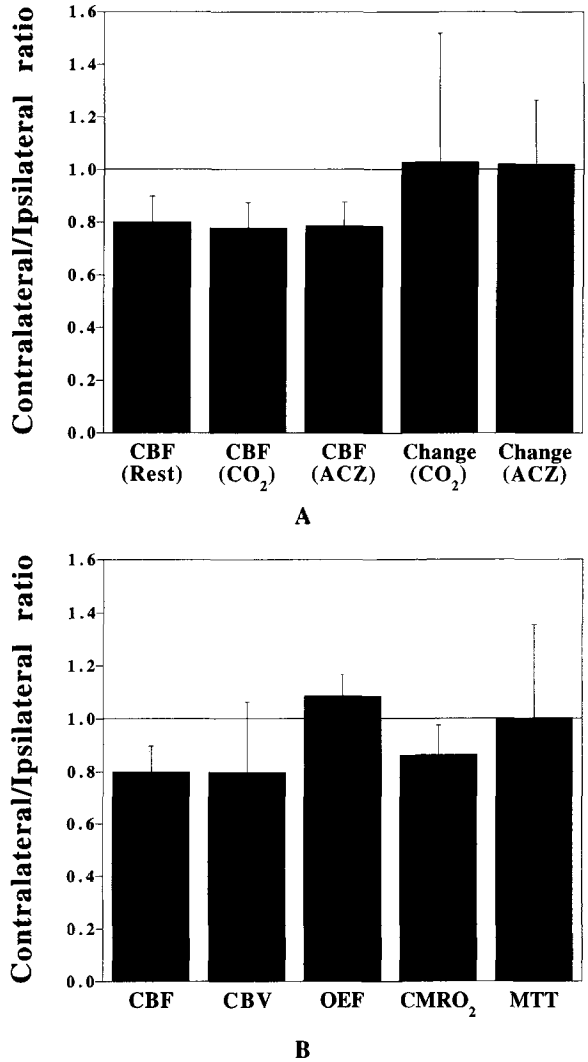

Fig. 1 A: The ratios of contralateral to ipsilateral cerebellum CBF values at rest and during hypercapnia (CO_2) and acetazolamide (ACZ) stress, and the ratios of vascular responses (Change) to hypercapnia and acetazolamide stress (mean ± SD). B: The ratios of contralateral to ipsilateral cerebellum CBF at rest, CBV, OEF, $CMRO_2$, and MTT (mean ± SD).

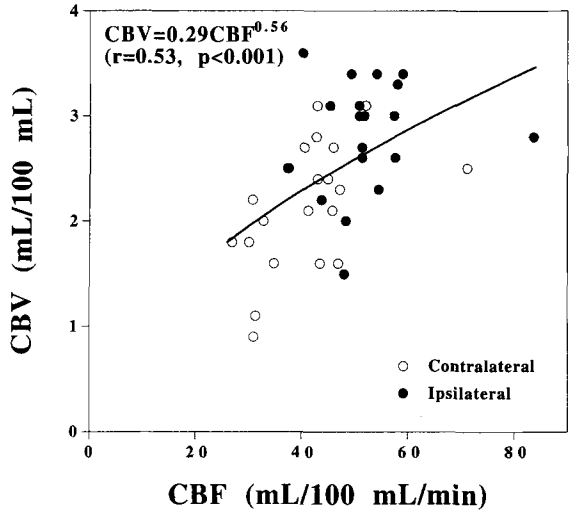

Fig. 2 Scatter plot of CBF at rest and CBV values of contralateral and ipsilateral sides of the cerebellum in all patients.

zolamide stress, and the vascular response to hypercapnia and acetazolamide stress are given in Table 3. CBF for the contralateral (affected) cerebellum was significantly lower than that for the ipsilateral (unaffected) side during all conditions. No significant differences in vascular response to hypercapnia and acetazolamide stress were observed between the contralateral and ipsilateral cerebellum.

The CBF at rest, CBV, OEF, $CMRO_2$ and MTT values are given in Table 4. CBF at rest, CBV, and $CMRO_2$ were significantly lower in the contralateral (affected) side than in the ipsilateral (unaffected) side, whereas OEF was significantly higher in the contralateral cerebellum. No significant difference in MTT was observed between the two sides.

The contralateral to ipsilateral cerebellum ratios of CBF at rest and during hypercapnia and acetazolamide stress, and the ratios of vascular responses to hypercapnia and acetazolamide stress are shown in Figure 1A. The ratio of CBF during all conditions was about 0.8. Therefore, the ratio of vascular response to hypercapnia and that of acetazolamide stress were about 1.

The contralateral to ipsilateral cerebellum ratios of CBF at rest, CBV, OEF, $CMRO_2$ and MTT are shown in Figure 1B. The ratio of CBF and that of CBV were about 0.8, so the resulting ratio for MTT was about 1.

The relations between CBF at rest and CBV values for the contralateral and ipsilateral side of the cerebellum for all patients are shown in Figure 2. The relation between CBF and CBV was determined by least squares analysis according to a previous study[20]: $CBV = 0.29\ CBF^{0.56}$.

DISCUSSION

This is the first study to retrospectively examine data on CBF, CBV, OEF, $CMRO_2$ and vascular responses to hypercapnia and acetazolamide stress for CCD in which all measurements were conducted on the same day by the same modality. As in previous reports, we found that vascular responses to hypercapnia and acetazolamide stress were almost same between the CCD side and the unaffected side of the cerebellum (Table 3, Fig. 1A). We previously reported that tissue with increased CBF due to neural activation showed the same vascular response to change in P_aCO_2 as that seen for resting CBF.[21] Inao et al. reported that despite a decreased vascular response to acetazolamide stress because of a steno-occlusive lesion of a major cerebral artery, normal CBF response to neural activation was observed.[22] These findings indicate that the mechanism of vascular response to neural activation is independent of that to either P_aCO_2 change or acetazolamide stress. No differences in vascular response to changes

in P_aCO_2 or acetazolamide stress between the CCD and unaffected sides have been reported, and this supports the concept that the mechanism of CCD is secondary hypoperfusion due to neural deactivation.[5,6] Our present data confirm that the mechanism of CCD is secondary hypoperfusion due to neural deactivation.

In our present results, the CBF at rest and CBV were significantly lower on the CCD side than the unaffected side, and the degree of difference between CBF of the two sides was almost the same as that between CBV. This resulted in no difference in MTT between the CCD and unaffected sides (Table 4, Fig. 1B).[4] This indicates that vascular blood velocity does not change during neural deactivation. In our previous report, we noted that the increase in CBF during strong neural activation (8-Hz photic flicker) was caused primarily by the increase in vascular blood velocity rather than by the increase in CBV, but the increase in CBF was slightly greater than that in CBV during weak neural activation (2-Hz photic flicker).[7] These findings indicate that the change in CBF related to neural activity might be related to a change in CBV for the low or normal range of CBF and to change in vascular blood velocity for the high range of CBF.

In our present results, the relationship between CBF at rest and CBV of the CCD and unaffected sides was $CBV = 0.29\ CBF^{0.56}$ (Fig. 2). In our previous results, the relationship between CBF and CBV for the baseline and during visual stimulation by 2-Hz and 8-Hz photic flicker was $CBV = 0.88\ CBF^{0.30}$.[7] According to Poiseuille's law, the flow of blood through a vessel is proportional to the fourth power of the vessel diameter. Blood volume is proportional to the square of the diameter. These show the relationship $CBV = c\ CBF^{0.5}$ (c: constant), which corresponds closely with our present relationship and the relationship during visual stimulation, although the CCD and the visual stimulation are different in the time scale. Both the present relationship between CBF and CBV and the relationship during visual stimulation closely corresponded with that during change in P_aCO_2,[20] suggesting that the regulation of CBF and CBV might be governed by a common microcirculatory mechanism during both change in neural activity and change in P_aCO_2.

In the present study, CBF and $CMRO_2$ were significantly lower on the CCD side than on the unaffected side, but the degree of difference between $CMRO_2$ on the two sides was less than that between CBF, resulting in a significant increase in OEF on the CCD side (Table 4, Fig. 1B). To the best of our knowledge, only one report showed a significantly higher OEF on the CCD side than on the unaffected side.[4] This increased OEF was not due to ischemia since CBV did not increase and vascular responses to hypercapnia and acetazolamide stress were intact.[18,19,23] The higher OEF with the lower CBV on the CCD side than on the unaffected side might indicate that neural deactivation primarily causes vasoconstriction rather than a reduction in oxygen metabolism.[24] Wenzel et al. has reported that the neural deactivation caused by saccades induced focal hypooxygenation, in which CBF was more reduced than oxygen delivery.[25] Although the CCD and the saccadic suppression were different in the time scale, similar phenomena were observed. In addition, no significant correlations were observed between the duration from the onset of stroke and hemodynamic parameters (CBF, CBV, OEF, and $CMRO_2$) of CCD (data not shown). Fox et al. reported that the increase in regional CBF was greater than that in regional $CMRO_2$ during neural activation, which would result in decreased regional OEF.[26] This finding is opposite to that observed during neural deactivation.

In conclusion, vascular responses to hypercapnia and acetazolamide stress were nearly equivalent between the CCD and unaffected sides of the cerebellum. This finding supports the concept that the mechanism of CCD is secondary hypoperfusion due to neural deactivation. The degree of difference between CBF values on the CCD and unaffected sides was almost the same as that between CBV values on the two sides, indicating that vascular blood velocity does not change during neural deactivation. The relationship between CBF and CBV of the CCD and unaffected sides was $CBV = 0.29\ CBF^{0.56}$. The degree of difference between $CMRO_2$ values on the two sides was less than that between the CBF values, resulting in significantly higher OEF on the CCD side. The increased OEF with the decreased CBV in the CCD side might indicate that neural deactivation primarily causes vasoconstriction rather than a reduction in oxygen metabolism.

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