The Effect of Deafferentation on Cerebral Blood Flow Response to Acetazolamide

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BACKGROUND AND PURPOSE: Decreased cerebral blood flow (CBF) response after acetazolamide administration may indicate increased cerebral blood volume (CBV) owing to reduced perfusion pressure from major cerebral artery steno-occlusive disease. However, decreased cerebral metabolic rate of oxygen (CMRO$_2$) caused by neuronal damage or deafferentation may also decrease the CBF response to acetazolamide, which adds complexity to the assessment of autoregulatory vasodilatation. The purpose of this study was to investigate the relationship between CBF response to acetazolamide and CBV or CMRO$_2$ in a pure form of deafferentation, crossed cerebellar diaschisis (CCD).

METHODS: We used positron emission tomography to study 17 patients with unilateral supratentorial infarct and contralateral cerebellar hypoperfusion. The CBF response to acetazolamide was assessed by measuring baseline CBF and CBF 10 minutes after an intravenous injection of acetazolamide. Multivariate analysis was used to test the independent predictive value of the CBV and CMRO$_2$ at baseline with respect to the change of CBF during acetazolamide administration.

RESULTS: Multivariate analysis revealed that in CCD CBV was significantly and independently associated with the percent change of CBF during acetazolamide administration ($P < .0001$), whereas CMRO$_2$ was not.

CONCLUSION: In deafferentation, changes in CBV may account for variations in CBF response to acetazolamide and decreased CMRO$_2$ may not affect CBF response to acetazolamide expressed as the percent change.
properly. Although it is difficult to study the region with primary minor ischemic change selectively, crossed cerebellar diaschisis (CCD) can be studied as one example of a pure form of deafferentation (11). Some supratentorial brain lesions cause a decrease in CBF and metabolism in the contralateral cerebellum without morphologic change. The main mechanism responsible for this phenomenon appears to be deafferentation through the cortico-ponto-cerebellar tract (10–12). Decreased CMRO₂ resulting from deafferentation may cause vasoconstriction, which may result in decreased CBV (12). It is not yet known how these changes in CBV and CMRO₂ affect the CBF response to acetazolamide in deafferentation. The purpose of this study was to investigate the relationship between CBF response to acetazolamide and CBV or CMRO₂ in CCD.

Methods

Patients

Seventeen patients (12 male, five female; age, 61 ± 12 years [mean ± SD]) with unilateral supratentorial infarcts were enrolled in this study. Five patients had cortical infarcts in the middle cerebral artery (MCA) territory, and 12 had purely subcortical infarcts in the MCA territory. All patients fulfilled the following criteria: 1) significant CBF asymmetry in the cerebellum as compared with normal subjects; 2) absence of clinical symptoms of ischemia in the vertebrobasilar artery territory; 3) absence of gross morphologic alterations in the cerebellum and brain stem at MR imaging; and 4) normal conventional angiographic findings in the vertebrobasilar system. The interval between ischemic event and positron emission tomography (PET) examination was 7 ± 16 months.

PET Measurements

All the subjects underwent PET with a whole-body scanner (Advance; General Electric Medical Systems, Milwaukee, WI), which permits simultaneous acquisition of 35 image sections with intersection spacing of 4.25 mm (13, 14). Written informed consent was obtained from each subject under the guidance of the Ethics Committee of the Shiga Medical Center. Performance tests showed the intrinsic resolution of the scanner to be 4.6–5.7 mm in the transaxial direction and 4.0–5.3 mm in the axial direction. As part of the scanning procedure, but before the tracer administration, the scanner was calibrated to ensure the proper setting of the scanner parameters. The PET system was then calibrated to ensure that the images were reproducible. After calibration, the PET system was used to perform the following scans:

- 18F-FDG PET: A series of 18F-FDG PET scans were performed to assess cerebral glucose metabolism. The images were obtained 1 hour after the injection of 18F-FDG. The PET data were analyzed using a statistical software package (KVPET; Koninklijke Philips Electronics N.V., Best, The Netherlands).
- 15O-H₂ PET: A series of 15O-H₂ PET scans were performed to assess cerebral blood flow (CBF). The images were obtained 15 minutes after the injection of 15O-H₂. The PET data were analyzed using a statistical software package (KVPET; Koninklijke Philips Electronics N.V., Best, The Netherlands).
- 18F-FDG PET: A series of 18F-FDG PET scans were performed to assess cerebral glucose metabolism. The images were obtained 1 hour after the injection of 18F-FDG. The PET data were analyzed using a statistical software package (KVPET; Koninklijke Philips Electronics N.V., Best, The Netherlands).

Data Analysis

We analyzed images in the tomographic plane corresponding to the level of the cerebellum. We used the scan section that most satisfactorily visualized the cerebellar hemisphere. First, in the baseline H₂¹⁵O-CBF image, we placed three circular regions of interest (ROI) in the cerebellum and brain stem at MR imaging; and normal conventional angiographic findings in the vertebrobasilar system. The interval between ischemic event and positron emission tomography (PET) examination was 7 ± 16 months.

After the baseline H₂¹⁵O study, a series of ¹⁵O-gas studies were performed. C¹⁵O₂ and ¹⁵O were inhaled continuously through a mask (14). The scan time was 5 minutes, and arterial blood was sampled manually from the brachial artery three times during each scan. Each sample was collected for 10–20 seconds to average the fluctuation due to the respiratory cycle, and the radiotracer concentrations of whole blood and plasma were measured with a well counter. Inhalation of C¹⁵O with 3-minute scanning was used to measure the CBV. Arterial samples were obtained manually twice during the scanning, and the radiotracer concentration of whole blood was measured.

After the ¹⁵O-gas study, 1 g of acetazolamide was administered intravenously (15). Ten minutes after administration, a second H₂¹⁵O study was done: an intravenous bolus injection of 555 MBq of H₂¹⁵O and a 3-minute dynamic PET scan were performed in the same way as in the baseline study.

No subject showed a significant change in PaCO₂ during PET scanning, and the changes in the physiologic data during acetazolamide administration were small in all patients.

In the ¹⁵O-gas study, we calculated CBF, CMRO₂, and oxygen extraction fraction (OEF) on the basis of the steady-state method (17). CMRO₂ and OEF were corrected for the CBV (18). In the H₂¹⁵O study, CBF was calculated by using the autoradiographic method with a partition coefficient of 0.9 (mL/g) (19, 20).

Statistical Analysis

We compared the results, except for CBF, in each cerebellar cortex by using the Wilcoxon signed-rank test. Differences were considered significant at P < .05. Spearman rank correlation was used to analyze the relationship of CBV or CMRO₂ to the change of CBF during acetazolamide administration (Δ and Δ%). A P value of <.05 was
The negative relationship between CMRO$_2$ and the percent change of CBF during acetazolamide administration, which was significant in univariate analysis, became insignificant after controlling for the effect of CBV by using multiple linear regression analysis (Table 3, model 2). The CBV was a significant independent predictor of the percent change of CBF and accounted for 62.3% of the variance.

**Discussion**

This study showed that, in deafferentation, variations in the CBF response to acetazolamide are accounted for by changes in CBV and a decrease in CMRO$_2$ does not affect the CBF response to acetazolamide expressed as the percent change. We found that both the absolute and percent changes of CBF during acetazolamide administration were significantly and negatively correlated with the baseline CBV value in CCD. In multivariate analysis, although both CBV and CMRO$_2$ were independent predictors of the absolute change of CBF, only CBV was an independent predictor of the percent change. For the absolute CBF response, CBV accounted for 20.5% of the variance and CMRO$_2$ accounted for 32.5%. As expected from the mechanism of the vasodilatory effect of acetazolamide, CMRO$_2$ was positively correlated with the CBF change. On the other hand, only CBV accounted for a significant proportion of the variance of the percent change of CBF (62.3%). The CBF response to acetazolamide expressed as the percent change can thus be used to estimate CBV in CCD because of the minor contribution of CMRO$_2$.

Several studies using various methods to measure CBF investigated the acetazolamide reactivity in CCD and showed inconsistent results (21–25). Two recent studies in which CBF response to acetazolamide was assessed by quantitative CBF by using PET showed no significant difference between the cerebellar hemispheres in the CBF response to acetazolamide expressed as the percent change (24, 25), in agreement with the findings of the present study. Because CBV was reduced in CCD, CBF response to acetazolamide should be increased if acetazolamide reactivity indicates vasodilatory capacity. In CCD, however, CMRO$_2$ is also reduced, and reduced CMRO$_2$ may cause a reduction of the CBF response to acetazolamide. The vasodilatory effect of acetazolamide probably occurs through inhibition of carbonic anhydrase in circulating red blood cells, which interferes with CO$_2$ clearance from the brain because of conversion of the CO$_2$ to circulating bicarbonate (1, 8). Consequently, increased levels of CO$_2$ around cerebral vessels cause cerebral vasodilatation. Thus, the vasodilatory effect of acetazolamide may depend on the level of the production of CO$_2$, which may be associated with baseline CMRO$_2$. In the patients studied here, CBV was positively correlated with CMRO$_2$. Therefore, the positive effect of the decreased CBV on the CBF response to acetazolamide may have been counterbalanced by the negative effect of the decrease of CMRO$_2$, resulting in the lack of

**Table 1: Baseline values of PET variables and CBF response to acetazolamide in the cerebellar hemispheres contralateral and ipsilateral to the supratentorial infarction**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Contralateral</th>
<th>Ipsilateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF (mL/100g/min)</td>
<td>43.0 ± 7.5</td>
<td>55.0 ± 8.8</td>
</tr>
<tr>
<td>CMRO$_2$ (mL/100g/min)</td>
<td>3.29 ± 0.48*</td>
<td>4.01 ± 0.34</td>
</tr>
<tr>
<td>OEF (%)</td>
<td>45.4 ± 5.5*</td>
<td>43.3 ± 5.0</td>
</tr>
<tr>
<td>CBV (mL/100g)</td>
<td>3.20 ± 0.60*</td>
<td>3.72 ± 0.56</td>
</tr>
<tr>
<td>CBF change (mL/100g/min)</td>
<td>24.9 ± 10.6t</td>
<td>28.7 ± 10.2</td>
</tr>
<tr>
<td>CBF change (%)</td>
<td>60.6 ± 23.6</td>
<td>54.4 ± 22.6</td>
</tr>
</tbody>
</table>

Note.—Values are the mean ± SD. CBF signifies cerebral blood flow; CMRO$_2$, cerebral metabolic rate of oxygen; OEF, oxygen extraction fraction; CBV, cerebral blood volume; CBF change, the change of CBF during acetazolamide administration.  
* $P < .005$ versus corresponding value in the contralateral cortex (Wilcoxon signed-rank test).  
† $P < .05$.

regarded as indicating statistical significance. We also used multiple linear regression analysis to test the independent predictive value of CBV or CMRO$_2$ with respect to the change of CBF during acetazolamide administration ($\Delta$ and $\Delta\%$). We applied this analysis by using the hemispheric values of the absolute change of CBF ($\Delta$ or $\Delta\%$) in each hemisphere (34 hemispheres) as the dependent variable and the baseline value of CBV or CMRO$_2$ as the independent variable. We adopted the two hemispheric values for each patient because of the suspected hemispheric difference of baseline hemodynamics and metabolism in each patient, although the data are not independent of each other.

**Results**

In the group as a whole, in the cerebellar cortex contralateral to the supratentorial infarction, significant decreases of CMRO$_2$ and CBV and an increase of OEF were found, as compared with the respective values in the ipsilateral cerebellar cortex. The absolute change of CBF during acetazolamide administration in the contralateral cerebellar cortex was significantly less than that in the ipsilateral cortex, whereas the percent change of CBF showed no significant difference between the two cortices (Table 1).

In univariate analysis, the absolute change of CBF during acetazolamide administration was significantly and negatively correlated with CBV, whereas the percent change of CBF was significantly and negatively correlated with both CBV and CMRO$_2$ (Fig 1). At baseline, CBV was significantly and positively correlated with CMRO$_2$ (Spearman correlation coefficient, $\rho = 0.66$; $P < .001$).

The positive relationships between CMRO$_2$ and the absolute change of CBF during acetazolamide administration became significant after controlling for the effect of CBV by using multiple linear regression analysis (model 2 in Table 2). This model, which included the values of CBV and CMRO$_2$, accounted for a significant proportion of the variance of the absolute change of CBF ($P < .0001$; $R^2 = 0.53$). CBV accounted for 20.5% of the variance of the change of CBF, whereas CMRO$_2$ accounted for 32.5% of the variance.
hemispheric difference in the CBF response expressed as the percent change. For the CBF response expressed as the absolute change, the negative effect of the decrease of CMRO2 was large, which caused a hemispheric difference in the CBF response.

Previous studies using PET showed a negative correlation between the change of CBF during acetazolamide administration and the baseline value of CBV in patients with major cerebral arterial occlusive disease, which supports the notion that evaluation of the CBF response to acetazolamide may be useful for estimating the degree of cerebral autoregulatory vasodilatation in response to reduced perfusion pressure (6, 7). This correlation, however, was shown to be weakened by the confounding effect of a decrease in CMRO2 on the CBF response to acetazolamide (7). In patients with major cerebral arterial occlusive disease and cerebral infarcts, neuronal damage or deafferentation may cause decreased CMRO2 in the normal-appearing cerebral cortex (10). In the present study, the CBF response to acetazolamide expressed as the percent change was shown to be correlated only with the CBV in CCD, which suggests that any decreases in the CMRO2 resulting from deafferentation may not affect the CBF response to acetazolamide in patients with major cerebral arterial occlusive dis-

Fig 1. Scatterplots relating the absolute (upper row) or percent (lower row) change in CBF during acetazolamide administration to the values of CBV (left panels) or CMRO2 (right panels) at baseline in the cerebellar hemispheres on both sides.

### TABLE 2: Multiple linear regression analysis of the absolute change of CBF during acetazolamide administration as the dependent variable

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>t</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBV (mL/100g)</td>
<td>-7.9</td>
<td>2.5</td>
<td>-3.0</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Model 2:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBV (mL/100g)</td>
<td>-15.6</td>
<td>2.5</td>
<td>-6.1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>CMRO2 (mL/100g/min)</td>
<td>14.0</td>
<td>2.9</td>
<td>4.8</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Note.---CBV signifies cerebral blood volume; CMRO2, cerebral metabolic rate of oxygen.

### TABLE 3: Multiple linear regression analysis of the percent change of CBF during acetazolamide administration as the dependent variable

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>t</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBV (mL/100g)</td>
<td>-28.9</td>
<td>3.8</td>
<td>-7.4</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Model 2:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBV (mL/100g)</td>
<td>-33.0</td>
<td>4.9</td>
<td>-6.7</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>CMRO2 (mL/100g/min)</td>
<td>7.5</td>
<td>5.6</td>
<td>1.3</td>
<td>.29</td>
</tr>
</tbody>
</table>

Note.---CBV signifies cerebral blood volume; CMRO2, cerebral metabolic rate of oxygen.
cases, if CMRO$_2$ reduction correlates with CBF response to acetazolamide, it is not deafferentation, but neuronal damage, that is confounding the CBF response, on the assumption that similar relationships exist in the cerebral cortical areas. Therefore, the evaluation of the neuronal integrity may be needed to interpret the results of the acetazolamide test properly. This can be done by visualizing the distribution of central-type benzodiazepine receptors (9, 26). If neuronal integrity is preserved in the cerebral cortex ipsilateral to the major cerebral arterial lesion, the CBF response to acetazolamide could be used as an index of preexisting vasodilatation. In our study, no patients showed atrophy of the cerebellar cortex contralateral to the supratentorial infarction. Neuronal damage due to transneuronal degeneration would cause a severe decrease of CMRO$_2$ that might contribute to reduced CBF response to acetazolamide.

**Conclusion**

In deafferentation, variations in the CBF response to acetazolamide may be accounted for by changes in CBV, and a reduction in CMRO$_2$ may not affect the CBF response expressed as the percent change. Evaluation of the CBF response to acetazolamide may be useful for estimating CBV in regions with secondary metabolic depression caused by deafferentation.

**References**