A Decrease in Regional Cerebral Blood Volume and Hematocrit in Crossed Cerebellar Diaschisis

Hiroshi Yamauchi, MD, PhD; Hidenao Fukuyama, MD, PhD; Yasuhiro Nagahama, MD, PhD; Hidehiko Okazawa, MD, PhD; Junji Konishi, MD, PhD

Background and Purpose—The pathophysiology of crossed cerebellar diaschisis (CCD) remains to be elucidated. In CCD, the metabolic suppression resulting from deafferentation may cause vasoconstriction, which may result in a decrease in cerebral blood volume (CBV) and may differentially affect the flows of red blood cells and of plasma. The purpose of this study was to investigate whether CCD decreases the total CBV (cerebral red blood cell volume [CRCV] plus cerebral plasma volume [CPV]) and, if so, whether CCD differentially affects the CRCV and CPV, resulting in a change in hematocrit.

Methods—We used positron emission tomography to study 7 patients with a unilateral supratentorial infarct and CCD. The distributions of CRCV and CPV were assessed by using $^{15}$O-labeled carbon monoxide and $^{62}$Cu-labeled human serum albumin–dithiosemicarbazone tracers, respectively. The CRCV, CPV, and calculated hematocrit values were compared between the cerebellar hemispheres.

Results—In the cerebellar cortex contralateral to the supratentorial infarct, the values of CRCV, CPV, and total CBV were significantly decreased compared with those in the ipsilateral cerebellar cortex. The CRCV was decreased to a greater degree than the CPV, and the value of the hematocrit was decreased in the contralateral cerebellar cortex.

Conclusions—CCD may decrease the total CBV, which may reflect vasoconstriction caused by decreased metabolism due to deafferentation. In addition, the more pronounced decrease in CRCV than in CPV may result in a decrease in hematocrit in CCD. (Stroke. 1999;30:1429-1431.)

Key Words: cerebellum ■ cerebral blood volume ■ diaschisis ■ hematocrit

In patients with cerebral infarcts, functional depression due to a decrease in neural input is prone to widely affect both cortical and subcortical structures, as a result of disconnection. In the clinical setting, hemodynamic and metabolic changes caused by deafferentation may be concomitant with those caused by reduced perfusion due to arterial occlusive diseases or ischemic neuronal loss without cavitation. Therefore, to interpret properly such complex findings on neuroimaging in patients with cerebral infarcts, it is essential to elucidate the hemodynamic and metabolic changes in deafferentation.

Deafferentation can be shown as decreases in cerebral blood flow (CBF) and metabolism in the target regions without gross morphological changes. A decrease in metabolism caused by deafferentation may result in vasoconstriction, which may be reflected by a decrease in the cerebral blood volume (CBV). However, a decrease in the CBV in the regions that have undergone deafferentation has been demonstrated by only a few studies in patients with stroke. Furthermore, in the previous studies, the total CBV (TCBV) was estimated from the cerebral red blood cell volume (CRCV) without knowledge of the changes in the cerebral plasma volume (CPV). Cerebral microcirculation may be physiologically regulated to adapt to altered neuronal function, circulating conditions, and pathological states, in which red blood cell (RBC) and plasma flow may change differently. In the conditions with vasoconstriction and low flow rate, a "tube" Fahraeus effect plus a "network" Fahraeus effect may result in a decrease in hematocrit. Therefore, vasoconstriction caused by metabolic decline due to deafferentation would cause a decrease in hematocrit as well as TCBV.

One example of a pure form of deafferentation is crossed cerebellar diaschisis (CCD), which was first demonstrated by Baron and coworkers with positron emission tomography (PET). Some supratentorial brain lesions cause a decrease in the CBF and metabolism in the contralateral cerebellum without morphological change. The main mechanism responsible for this phenomenon appears to be deafferentation through the cortico-pontocerebellar tract. A previous study showed a decrease in the CRCV in CCD. In this study, to further analyze the hemodynamic changes in CCD, we measured the CPV as well as CRCV by using PET, and we calculated hematocrit. The purpose of this study was to investigate whether CCD decreases the total CBV (CRCV plus CPV) and, if so, whether CCD differentially affects the CRCV and CPV, resulting in a change in hematocrit.
Subjects and Methods
We studied 7 patients suffering from a unilateral supratentorial infarct. The subjects were selected from 10 consecutive patients with cerebrovascular diseases in whom CBF, cerebral metabolic rate of oxygen (CMRO₂), oxygen extraction fraction (OEF), CRCV, and CPV were all measured with PET. All patients had deep middle cerebral artery (MCA) territory infarcts. These patients were 5 men and 2 women, aged 49 to 74 (mean±SD, 64±8) years. All patients fulfilled the following criteria: (1) satisfactory visualization of the cerebellum on PET images; (2) significant CBF asymmetry in the cerebellum, which lay above the upper 95% confidence limit as defined in 9 normal subjects, as described below; (3) absence of clinical symptoms of ischemia in the vertebrobasilar artery territory; (4) absence of gross morphological alterations in the cerebellum and brain stem on MRI; and (5) normal conventional angiographic findings in the vertebrobasilar system. The interval between the ischemic event and the evaluations with PET ranged from 1 to 64 (mean±SD, 24±24) months. All patients and their relatives gave informed consent to the conventional angiographic study and the PET study (under the guidance of the Ethics Committee of the Kyoto University Faculty of Medicine).

All patients were scanned with the use of a commercially available PET system (PCT-3600W, Hitachi Medical Co).9 This system simultaneously acquires 15 slices with a center-to-center distance of 7 mm. All scans were obtained at resolution of 7.5 mm full width at half maximum in the transaxial direction and of 6.5 mm in the axial direction in the wobbling mode. Patients were positioned with the orbitomeatal line parallel to the detector rings.

After a transmission scan, the CBF was determined while the subject continuously inhaled 300 MBq of CO₁⁵O per minute through a mask, and the CMRO₂ and OEF were measured during continuous inhalation of 500 MBq of CO₁⁵O per minute. Data were collected for 5 minutes. For measurement of the CRCV, 1.20 GBq of CO₁⁵O was inhaled, and the PET scanning was started ≥30 seconds after the appearance of a peak count of the brain tissue adequate for data collection and continued for 3 minutes. We calculated CBF, CMRO₂, and OEF on the basis of the steady state method.10 The CBV was calculated from the data of the CO₁⁵O scan and was incorporated in the correction of the CMRO₂ and OEF.11,12 In the calculation of the CBV, a conventional hematocrit ratio of 0.85 was used. Functional images were reconstructed with 128×128 pixels, with each pixel representing an area of 2.0×2.0 mm².

After the completion of the CO₁⁵O gas study, 296 to 740 MBq of ⁶²Cu-labeled human serum albumin–dithiosemicarbazone (⁶²Cu-HSA-DTS) was injected intravenously over 15 seconds in a total volume of 8 mL to obtain CPV images.13 PET data acquisition was started 3 minutes after administration of ⁶²Cu-HSA-DTS and continued for 8 minutes. Blood samples were obtained at 1, 5, and 7 minutes after injection of ⁶²Cu-HSA-DTS, and both whole blood radioactivity and plasma radioactivity were counted. Regional CRCV and CPV were calculated with the use of the PET images acquired in the C₁⁵O and ⁶²Cu-HSA-DTS studies according to the following equations: CRCV=Cco/(Aco/AHct) (mL/g) and CPV=CHSA/PHSA (mL/g), where Cco and CHSA are the cerebral tissue radioactivities of C₁⁵O and of ⁶²Cu-HSA-DTS, respectively, Aco is the whole blood radioactivity of C₁⁵O, PHSA is the plasma count of ⁶²Cu-HSA-DTS, and AHet is the large-vessel arterial hematocrit measured in the blood sampled from the radial artery. The regional cerebral hematocrit (CHct) was calculated from the CRCV and CPV for each patient as CHet=CRCV/TCBV, with TCBV=CRCV+CPV. We also calculated the mean transit times of blood (Tb), RBCs (Tr), and plasma (Tp), defined as follows: Tb=TCBV/CBF, Tr=Tb×(CHct/AHct), and Tp=Tb×(1−CHct/1−AHet), respectively.5

We analyzed images in the tomographic plane corresponding to the level of the cerebellum. We used the scan slice that most accurately visualized the cerebellar hemisphere. First, in the CBF image, we placed 3 circular regions of interest 16 mm in diameter over the gray matter of the cerebellar hemisphere ipsilateral to the supratentorial lesion. These regions of interest were then copied over the contralateral side with respect to the anteroposterior axis, which was determined with reference to the interhemispheric line in the upper slice of the CBF image. We took care not to include the sinus in the regions of interest by comparison with the CRCV and CPV images.3

From the absolute values of the PET variables, we calculated the percent difference between contralateral (CL) and ipsilateral (IL) cerebellar cortex (Δ%) as Δ%=\((CL−IL)/IL\)×100. We assumed that the resulting values reflected the percent changes caused by CCD. We also studied 9 normal subjects with similar ages (mean age, 56±16 years) using the CO₂ gas steady state method, and we calculated the asymmetry index (AI) between the right (R) and left (L) cerebellar cortex as AI (absolute % value)=\(|R−L|/(R+L)\)×200, where \(|R−L|\) represents the absolute value of the difference. Mean±SD AI in the normal subjects was 3.61±1.76% for CBF. The patients with significant cerebellar CBF asymmetry (ie, an individual value of the Δ% that was greater than the 7.67% that covers the upper 95% confidence limit as defined in normal subjects) were selected.

We compared the results, except for CBF, in each cerebellar cortex using the Wilcoxon signed rank test. Differences were considered significant at P<0.05. Spearman rank correlation was used to analyze the relationship between the CBF and TCBV. A P value of <0.05 was regarded as indicating statistical significance.

Results
The value of large-vessel AHct in the patients ranged from 0.26 to 0.41 (mean±SD, 0.36±0.05). No patient showed a significant change in PaO₂ or PaCO₂ during PET scanning.

In the cerebellar cortex contralateral to the supratentorial infarct, the values of CRCV, CPV, and TCBV were significantly decreased compared with those in the cerebellar cortex ipsilateral to the supratentorial infarct (Table ). In the contralateral cerebellar cortex, the value of TCBV was significantly correlated with the value of CBF (r=0.94, P<0.05).

The CRCV was decreased to a greater degree than the CPV, and the value of hematocrit was decreased in the contralateral cerebellar cortex. The calculated mean transit times of RBCs was significantly decreased, whereas the mean transit times of blood and plasma showed no significant differences.

Discussion
This study revealed that CCD decreases the TCBV (CRCV plus CPV) and that CCD differentially affects the CRCV and CPV, resulting in a change in hematocrit. We found that, in

<table>
<thead>
<tr>
<th>Variable</th>
<th>Contralateral</th>
<th>Ipsilateral</th>
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<tbody>
<tr>
<td>CBF, mL/(100 g · min)</td>
<td>40.9±8.0</td>
<td>49.4±11.1</td>
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<tr>
<td>CMRO₂, mL/(100 g · min)</td>
<td>2.85±0.29*</td>
<td>3.17±0.14</td>
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<tr>
<td>OEF, %</td>
<td>44.6±6.7*</td>
<td>40.6±7.1</td>
</tr>
<tr>
<td>CRCV, mL/100 g</td>
<td>0.92±0.25*</td>
<td>1.33±0.21</td>
</tr>
<tr>
<td>CPV, mL/100 g</td>
<td>1.99±0.44*</td>
<td>2.57±0.76</td>
</tr>
<tr>
<td>TCBV, mL/100 g</td>
<td>2.91±0.57*</td>
<td>3.90±0.79</td>
</tr>
<tr>
<td>CHct</td>
<td>0.32±0.06*</td>
<td>0.35±0.06</td>
</tr>
<tr>
<td>Tr, min</td>
<td>0.063±0.006*</td>
<td>0.077±0.009</td>
</tr>
<tr>
<td>Tp, min</td>
<td>0.076±0.007</td>
<td>0.081±0.010</td>
</tr>
<tr>
<td>Tb, min</td>
<td>0.071±0.004</td>
<td>0.079±0.008</td>
</tr>
</tbody>
</table>

 Values are mean±SD. Tr, Tp, and Tb indicate mean transit times of RBCs, plasma, and blood, respectively.

*P<0.05 vs corresponding value in the ipsilateral cortex (Wilcoxon’s signed rank test).
patients with unilateral supratentorial infarct and CCD, both the CRCV and CPV in the cerebellar cortex contralateral to the infarct were decreased compared with those in the ipsilateral cerebellar cortex and that the more pronounced decrease in CRCV than in CPV caused the decrease in hematocrit. In addition, although CBF was also decreased in this region, the calculated mean transit time of RBCs was decreased, without a change in the mean transit time of plasma. Therefore, CCD may differentially influence RBC and plasma flow.

The metabolic suppression resulting from deafferentation may cause vasoconstriction, leading to a decrease in the TCBV. One earlier PET study showed that in 4 patients with subcortical stroke, the CBV measured with C15O (CRCV) was reduced in proportion to the reduction in CBF and CMRO2 in the cerebral cortical regions with metabolic depression due to deafferentation, which was defined as having a decrease in the CMRO2 with normal OEF, supporting this hypothesis. However, in those patients, the possibility that reduced CMRO2 in the normal-appearing cortical areas may have resulted partly from neuronal loss could not be completely excluded. In this study we showed that the TCBV was decreased in CCD. CCD is one of the purest models of deafferentation because the cerebellum is anatomically distant from, and has a different arterial supply from, the area damaged by the supratentorial stroke, thus reducing potentially confounding issues. Therefore, our results confirm the decrease in the TCBV in the region with metabolic depression caused by deafferentation.

The change in CBV may be important to differentiate the reduction in CBF caused by deafferentation from that caused by ischemia in morphologically normal brain areas. The decrease in the CBV in the region that underwent deafferentation with vasoconstriction contrasts with the increase in the CBV in the ischemic region, where decreased perfusion pressure causes vasodilatation. Ischemia may induce a more pronounced increase in CPV than in CRCV, whereas deafferentation may induce a more pronounced decrease in CRCV than in CPV, as shown in this study in CCD. The different changes in CRCV and CPV may reflect physiological regulatory mechanisms for adapting to decreased neuronal function or decreased perfusion pressure.

The reason for the decrease in hematocrit in CCD is unclear. We speculate that a tube Fahraeus effect plus a network Fahraeus effect may result in a decrease in hematocrit in the region with vasoconstriction and decreased CBF. In artificial tubes with diameters of <500 μm, the hematocrit decreases with decreasing diameter (a tube Fahraeus effect). Therefore, vasoconstriction caused by metabolic decline due to deafferentation may have resulted in the decrease in hematocrit. The transit time of RBCs was decreased in CCD in this study. A greater increase in the velocity of RBCs than in that of plasma may result in concentration of RBCs in the centers of vessels with an increase in the marginal cell-free plasma layer. In addition, an irregular distribution of RBCs in arterial bifurcation may contribute to the decrease in hematocrit. Direct correlation between the blood flow rate and hematocrit in arterial branches has been demonstrated.

Gradual separation of RBCs and plasma in the arterial branching sequence may lead to a decrease of RBC concentration in the regions that underwent deafferentation with a decreased CBF (a network Fahraeus effect).

In conclusion, CCD may decrease the TCBV (CRCV plus CPV), which may reflect vasoconstriction caused by decreased metabolism. In addition, the more pronounced decrease in CRCV than in CPV may result in a decrease in hematocrit in CCD.

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References
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