Hemodynamic and Metabolic Changes in Crossed Cerebellar Hypoperfusion

Hiroshi Yamauchi, MD; Hidenao Fukuyama, MD; and Jun Kimura, MD

Background and Purpose: The pathophysiology of crossed cerebellar diaschisis remains to be elucidated. The mechanism responsible appears to be deafferentation through the corticopontocerebellar tract, which terminates in the cerebellar gray matter. However, few studies have demonstrated the hemodynamic and metabolic changes in the cerebellar gray matter and pons in crossed cerebellar diaschisis.

Methods: Using positron emission tomography in 24 patients with unilateral supratentorial stroke, we evaluated regional blood flow, metabolic rate of oxygen, oxygen extraction fraction, and blood volume in the cerebellar cortex and pons. Sixteen patients with significant cerebellar blood flow asymmetry, defined as a percentage difference in blood flow beyond the upper 95% confidence limit defined in eight normal subjects, were selected as the group with crossed cerebellar hypoperfusion.

Results: In patients with crossed cerebellar hypoperfusion, the metabolic rate of oxygen was significantly decreased in the cerebellar cortex contralateral to the supratentorial stroke, compared with that in the ipsilateral cerebellar cortex; this decrease was less than the decrease in cerebellar blood flow. The degrees of cerebellar asymmetry in these two parameters were negatively correlated with the metabolic rate of oxygen in the pons. The oxygen extraction fraction was slightly, but significantly, increased. In contrast to the ischemic state, however, the cerebellar blood volume was decreased, with no difference in the ratio of cerebellar blood flow to blood volume.

Conclusions: These findings support interruption of the corticopontocerebellar tract as the mechanism of crossed cerebellar hypoperfusion. Our results also suggest a mild elevation in the oxygen extraction fraction in this state, with a mechanism distinct from ischemia. (Stroke 1992;23:855–860)

KEY WORDS • cerebellum • cerebrovascular disorders • diaschisis • hemodynamics • tomography, emission computed

Crossed cerebellar diaschisis was first described by Baron and coworkers in 1980. Although subsequent studies have confirmed its existence, the pathophysiology of crossed cerebellar diaschisis remains to be elucidated. The mechanism responsible appears to be deafferentation through the corticopontocerebellar tract, which terminates in the granule cells in the cerebellar gray matter. Therefore, evaluation of the changes restricted to the cerebellar cortex is mandatory to elucidate the hemodynamic and metabolic changes in crossed cerebellar diaschisis. However, few studies have shown those data.

We more closely evaluated in patients with crossed cerebellar hypoperfusion the regional hemodynamic status of the cerebellar cortex, including changes in the cerebellar blood volume. In addition, we analyzed the relation between the degree of metabolic change in the cerebellar cortex and that in the pons.

Subjects and Methods

We studied 24 patients suffering from a unilateral supratentorial stroke. All were selected retrospectively from a large series of patients in whom regional cerebral blood flow (CBF), oxygen metabolism (CMRO₂), and cerebral blood volume (CBV) had been measured using PET. Criteria for selection were 1) technically reliable measurements of CBF, CMRO₂, and CBV, 2) satisfactory visualization of the cerebellum and pons on PET images, 3) absence of clinical symptoms suggesting ischemic episodes in the vertebrobasilar artery territory, 4) absence of gross morphological alterations in the cerebellum and pons on computed tomograms or magnetic resonance imaging, and 5) normal angiographic findings in the vertebrobasilar system. There were 17 men and seven women aged 41–68 (mean±SD 57±7) years. They included eight patients with superficial middle cerebral artery territory infarcts, 10 with deep middle cerebral artery territory infarcts, four with putaminal hemorrhages, and two with thalamic hemorrhages. Cerebral angiography was performed in the patients with cerebral hemorrhages to rule out arteriovenous malformation as a cause of the hemorrhage.

The specifications of our PET scanner have been reported elsewhere. In brief, the device has four rings, each containing 192 bismuth germanate detectors, providing seven tomographic slices at one scanning process. The device offers the best spatial resolution of 7.6 mm in full-width half-maximum at the center of the scan field and axial resolution of 12 mm at the center. The scanning procedure was as follows. Before the study, a germanium-68–gallium-68 transmission scan was per-
FIGURE 1. Cerebral blood flow image corresponding to level of cerebellum in patient with crossed cerebellar hypoperfusion. Regions of interest are superimposed over cerebellar cortex and pons along with anteroposterior axis. CL, contralateral; IL, ipsilateral to supratentorial stroke.

formed during 20 minutes for attenuation correction. CBF was determined while the subject continuously inhaled 370–555 MBq C15O2 per minute through a mask. Measurement of CMRO2 and oxygen extraction fraction (OEF) required the continuous inhalation of 0.740–1.11 GBq 15O2 per minute. Data were collected for 5 minutes. A single breath of 2.96 GBq C15O was used to measure CBV. We calculated CBF, CMRO2, and OEF based on the steady-state method, and CMRO2 and OEF were corrected by the CBV. Functional images were reconstructed as constituting 64x64 pixels, each pixel representing 2.5 mmx2.5 mm. The ratio of CBF to CBV was calculated pixel by pixel as an indicator of the cerebral perfusion pressure. In all patients, PET was performed at least 1 month after the stroke event.

The scans were performed parallel to the orbitomeatal line. As shown in Figure 1, we analyzed images in the tomographic plane corresponding to the level of the cerebellum and pons. We used the scan slice that most satisfactorily visualized the cerebellar hemisphere. First, in the CBF image, we placed three circular regions of interest, each containing 11 pixels (0.6875 cm²), over the gray matter of the cerebellar hemisphere ipsilateral to the supratentorial lesion. We took care not to include the sinus in the regions of interest by comparing with the CBV image. These regions of interest were then copied over the contralateral side with respect to the anteroposterior axis, which was determined in reference to the interhemiopic line in the upper slice of the CBF image. In the same tomographic plane, we placed one circular region of interest (1.7 cm²) in the pons, with the center on the anteroposterior axis. We located the region of interest ventrally to the extent that it did not include the cavernous sinus exhibiting a high CBV on the CBV image.

From the absolute CBF value, we calculated the percentage difference between the contralateral (CL) and ipsilateral (IL) cerebellar cortices (Δ%) as Δ%= (IL-CL)/CLx100. We also studied eight normal subjects (mean age 39±14 years, younger than the patients) and calculated the asymmetry index (AI) between the right (R) and left (L) cerebellar cortices as AI = |R-L|/(R+L)x200, where |R-L| represents the absolute value of the difference. Mean±SD AI in the normal subjects was 2.29±2.30%.

We selected the 16 patients with significant cerebellar CBF asymmetry (that is, individual Δ% of >7.73%, the upper 95% confidence limit in the normal subjects) as the group with crossed cerebellar hypoperfusion. This group consisted of five patients with superficial middle cerebral artery territory infarcts, five with deep middle cerebral artery territory infarcts, four with putaminal hemorrhages, and two with thalamic hemorrhages (mean±SD age 56±6 years) (Table 1). The other eight patients exhibited no crossed cerebellar hypoperfusion (controls, mean±SD age 58±8 years). The physiological states of the patients and controls during PET, including PacO2, PacO2, hematocrit, arterial hemoglobin concentration, and mean arterial blood pressure, are given in Table 2.

Using a paired t test, we compared the results (except for CBF) in each cerebellar cortex from the patients with crossed cerebellar hypoperfusion. To test the effect of the supratentorial stroke on the bilateral cerebellum, we also compared the results (except for CBF...
from the patients with crossed cerebellar hypoperfusion (CCH) with those in the ipsilateral cerebellar cortex from the controls by using analysis of variance with Bonferroni's correction. Differences giving $p<0.05$ were considered significant. In the patients with crossed cerebellar hypoperfusion, we analyzed the metabolic relation between the cerebellum and the pons by using linear regression analysis, with a $t$ value having $p<0.05$ assumed to be significant.

**Results**

Table 3 shows the values for regional CBF, CMRO$_2$, OEF, CBV, and the CBF to CBV ratio in each patient with crossed cerebellar hypoperfusion. The contralateral cerebellar cortex had a higher OEF than the ipsilateral cortex in all patients. All but one patient showed a reduced CBV in the cerebral cortex (data not shown). This result further supports the hypothesis that pontine hypometabolism results in contralateral cerebellar hypometabolism$^{4,5,9,12,13}$ considering excitatory input from pontine nuclei to the contralateral cerebellar granule cells.$^{19}$

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>CCH</th>
<th>Lesion type</th>
<th>Lesion location</th>
<th>Time since stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58</td>
<td>M</td>
<td>+</td>
<td>Superficial infarct</td>
<td>L frontoparietal</td>
<td>2 mo</td>
</tr>
<tr>
<td>2</td>
<td>62</td>
<td>F</td>
<td>+</td>
<td>Superficial infarct</td>
<td>R frontal, parietal</td>
<td>1 mo</td>
</tr>
<tr>
<td>3</td>
<td>62</td>
<td>M</td>
<td>+</td>
<td>Superficial infarct</td>
<td>R frontal</td>
<td>6 yr</td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>M</td>
<td>+</td>
<td>Superficial infarct</td>
<td>R frontal</td>
<td>2 mo</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>F</td>
<td>+</td>
<td>Superficial infarct</td>
<td>R frontotemporal</td>
<td>1 mo</td>
</tr>
<tr>
<td>6</td>
<td>63</td>
<td>F</td>
<td>+</td>
<td>Deep infarct</td>
<td>L thalamus</td>
<td>1 yr</td>
</tr>
<tr>
<td>7</td>
<td>46</td>
<td>M</td>
<td>+</td>
<td>Deep infarct</td>
<td>R putamen, internal capsule</td>
<td>3 mo</td>
</tr>
<tr>
<td>8</td>
<td>63</td>
<td>M</td>
<td>+</td>
<td>Deep infarct</td>
<td>L corona radiata</td>
<td>1 mo</td>
</tr>
<tr>
<td>9</td>
<td>46</td>
<td>M</td>
<td>+</td>
<td>Deep infarct</td>
<td>R corona radiata</td>
<td>2 mo</td>
</tr>
<tr>
<td>10</td>
<td>63</td>
<td>F</td>
<td>+</td>
<td>Deep infarct</td>
<td>L putamen, internal capsule</td>
<td>1 mo</td>
</tr>
<tr>
<td>11</td>
<td>52</td>
<td>M</td>
<td>+</td>
<td>Hemorrhage</td>
<td>L putamen</td>
<td>2 mo</td>
</tr>
<tr>
<td>12</td>
<td>61</td>
<td>M</td>
<td>+</td>
<td>Hemorrhage</td>
<td>L putamen</td>
<td>17 yr</td>
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<tr>
<td>13</td>
<td>53</td>
<td>M</td>
<td>+</td>
<td>Hemorrhage</td>
<td>L putamen</td>
<td>1 mo</td>
</tr>
<tr>
<td>14</td>
<td>53</td>
<td>M</td>
<td>+</td>
<td>Hemorrhage</td>
<td>L putamen</td>
<td>1 mo</td>
</tr>
<tr>
<td>15</td>
<td>51</td>
<td>M</td>
<td>+</td>
<td>Hemorrhage</td>
<td>L thalamus</td>
<td>1 mo</td>
</tr>
<tr>
<td>16</td>
<td>60</td>
<td>M</td>
<td>+</td>
<td>Hemorrhage</td>
<td>L thalamus</td>
<td>1 mo</td>
</tr>
<tr>
<td>17</td>
<td>57</td>
<td>M</td>
<td>−</td>
<td>Superficial infarct</td>
<td>L frontoparietal</td>
<td>2 mo</td>
</tr>
<tr>
<td>18</td>
<td>68</td>
<td>M</td>
<td>−</td>
<td>Superficial infarct</td>
<td>L occipital</td>
<td>5 mo</td>
</tr>
<tr>
<td>19</td>
<td>60</td>
<td>M</td>
<td>−</td>
<td>Superficial infarct</td>
<td>L parietal</td>
<td>1 mo</td>
</tr>
<tr>
<td>20</td>
<td>65</td>
<td>M</td>
<td>−</td>
<td>Deep infarct</td>
<td>L internal capsule</td>
<td>2 mo</td>
</tr>
<tr>
<td>21</td>
<td>52</td>
<td>M</td>
<td>−</td>
<td>Deep infarct</td>
<td>R frontal subcortex</td>
<td>6 wk</td>
</tr>
<tr>
<td>22</td>
<td>58</td>
<td>M</td>
<td>−</td>
<td>Deep infarct</td>
<td>L centrum semiovale</td>
<td>10 wk</td>
</tr>
<tr>
<td>23</td>
<td>41</td>
<td>M</td>
<td>−</td>
<td>Deep infarct</td>
<td>L putamen, internal capsule</td>
<td>1 mo</td>
</tr>
<tr>
<td>24</td>
<td>63</td>
<td>M</td>
<td>−</td>
<td>Deep infarct</td>
<td>L parietal subcortex</td>
<td>1 mo</td>
</tr>
</tbody>
</table>

CCH, crossed cerebellar hypoperfusion; M, male; F, female; L, left; R, right.

TABLE 2. Baseline Physiological Data for Patients With Crossed Cerebellar Hypoperfusion and Controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>PacO$_2$ (mm Hg)</td>
<td>39.9±2.4</td>
<td>39.4±6.1</td>
</tr>
<tr>
<td>PacO$_2$ (mm Hg)</td>
<td>90.9±8.0</td>
<td>87.3±6.8</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>38.2±2.6</td>
<td>38.2±3.1</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>12.8±1.1</td>
<td>12.9±1.1</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>98.6±20.5</td>
<td>99.2±9.5</td>
</tr>
</tbody>
</table>

Values are mean±SD.

Lateral to the stroke. In contrast to the ischemic state, CBV was decreased, with no difference in the CBF to CBV ratio. Analysis of variance using Bonferroni's correction demonstrated the absence of a bilateral effect of the supratentorial stroke on cerebellar metabolism.

Table 4 shows the contralateral to ipsilateral ratio for CBF, CMRO$_2$, OEF, CBV, and the CBF to CBV ratio in the cerebellar cortex in each patient with crossed cerebellar hypoperfusion. The contralateral cerebellar cortex had a higher OEF than the ipsilateral cortex in all patients. All but one patient showed a reduced CBV in the contralateral cerebellar cortex.

In the patients with crossed cerebellar hypoperfusion, linear regression analysis showed that the percentage differences in CBF and CMRO$_2$ between the contralateral and ipsilateral cerebellar cortices were negatively correlated to CMRO$_2$ in the pons ($r=-0.64$, $p<0.01$ and $r=-0.60$, $p<0.02$, respectively) (Figure 2). However, they had no relation to CBF in the pons.

**Discussion**

We showed that cerebellar metabolic asymmetry is negatively correlated to pontine metabolism in patients with crossed cerebellar hypoperfusion. This relation was considered to be specific because it bore no relation to the cerebral cortical metabolic asymmetry or CMRO$_2$ in the cerebral cortex (data not shown). This result further supports the hypothesis that pontine hypometabolism results in contralateral cerebellar hypometabolism$^{4,5,9,12,13}$ considering excitatory input from pontine nuclei to the contralateral cerebellar granule cells.$^{19}$
The lack of correlation to pontine CBF indicates that a metabolic relation between the pons and the cerebellum is essential for the development of cerebellar diaschisis. Although placing bilateral regions of interest separately, not in the center of the pons, is needed for clear demonstration of the hypothesis, this would require a PET scanner with higher spatial resolution.

In contrast to previous reports,1-3,6-13 the degree of reduction in CBF was slightly greater than that in CMRO2, with a slight increase in OEF in the contralateral cerebellar cortex. We can identify three factors to explain this discrepancy. First, we selectively analyzed patients exhibiting crossed cerebellar hypoperfusion. In most previous studies,1-3,6-13 patients with unilateral supratentorial stroke were studied without regard to the presence of crossed cerebellar diaschisis. Consequently, the data as a whole are not of cerebellar blood flow and metabolism in crossed cerebellar diaschisis but those in patients with contralateral supratentorial stroke. Practically, the data in some studies show that more than a few patients with crossed cerebellar diaschisis had greater asymmetry of CBF than CMRO2 in the cerebellum.2-5,6,13 Second, we placed regions of interest over the gray matter of the cerebellar hemisphere as much as possible. The corticopontocerebellar tract, through which deafferentation of the cerebellum may occur, terminates on the granule cells in the cerebellar gray matter. To elucidate deafferentation of the cerebellar cortex from the corticopontocerebellar tract, evaluation of hemodynamic and metabolic changes restricted to the cerebellar gray matter is mandatory. In patients with cerebral malignant glioma, reduction in glucose metabolism was demonstrated in the cerebellar cortex.2-5,6,13
cortex contralateral to the tumor without metabolic change in the dentate nuclei.14 Lastly, we corrected CMRO₂ and OEF by CBV.12 It should be noted that the cerebellar CBV contralateral to the stroke was decreased compared with that in the ipsilateral cerebellar cortex. Without correction for CBV, the relative OEF increase in the contralateral cerebellar cortex would be less apparent.

The "cerebellar asymmetry present" category may include patients with borderline asymmetry on CBF data, yet with lesser CMRO₂ asymmetry for reasons of statistical noise. Thus, we also analyzed the whole patient sample without segregating the cases into two groups and likewise demonstrated increased OEF in the contralateral cerebellar cortex using a paired comparison. The correlations between pontine CMRO₂ and cerebellar CBF and CMRO₂ asymmetry were also significant.

The region of interest is centered on the cerebellar cortex on the CBF image, but for reasons of statistical noise the cerebellar cortex on the CMRO₂ image may be delineated slightly differently in the matrix coordinate, leading to artifact. Thus, we performed the same analysis again by placing the region of interest on the CMRO₂ image and obtained the same finding.

The mild increase in OEF shown in this study must be differentiated from the "misery perfusion syndrome."20 That condition involves a decreased perfusion pressure, which causes inadequate oxygen supply relative to demand, leading to a compensatory increase in OEF. Accompanied by maximal dilatation of the arterial and capillary beds, CBV increases and the CBF to CBV ratio decreases.18-21 On the contrary, the cerebellar capillary beds, CBV increases and the CBF to CBV ratio decreases, with elevation of OEF, has been reported.25 In progressive supranuclear palsy, widespread cortical CBF reduction greater than the CMRO₂ decrease, with elevation of OEF, has been reported.25 In Parkinson's disease, decreased CBF not accompanied by comparable changes in CMRO₂, implying increased OEF, was shown in the frontal and temporal cortices.29 These two studies substantiate a more prominent reduction in CBF than in CMRO₂ in the deafferented brain region.

Experimental studies30-32 suggest that the metabolism in synaptosomes is chiefly anaerobic, whereas oxidative metabolism predominates in neuronal cell bodies. In deafferented brain regions, such as through diaschisis, synaptosomal metabolism may be suppressed mainly due to decreased input. Then, oxidative metabolism would further predominate, inducing the mild elevation in OEF. Since few studies support this speculation, further investigations are needed to clarify the mechanisms underlying the mild increase in OEF in crossed cerebellar hypoperfusion and other deafferented conditions.

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