Crossed Cerebellar Hypoperfusion Indicates the Degree of Uncoupling Between Blood Flow and Metabolism in Major Cerebral Arterial Occlusion

Hiroshi Yamauchi, MD; Hidenao Fukuyama, MD; Jun Kimura, MD; Masatune Ishikawa, MD; Haruhiko Kikuchi, MD

Background and Purpose  In patients who have major cerebral arterial occlusive disease with low perfusion, a decrease in cerebral metabolism may be reflected by a reduction in contralateral cerebellar blood flow (crossed cerebellar hypoperfusion). This study was done to investigate whether comparison of the extent of cerebral blood flow asymmetry and crossed cerebellar hypoperfusion could be used to estimate the degree of uncoupling of cerebral blood flow and metabolism on the basis of a single blood flow study.

Methods  We used positron emission tomography before and after reconstructive vascular surgery to evaluate regional blood flow and oxygen metabolism in the cerebral and cerebellar cortexes of 11 patients with major cerebral arterial occlusive disease.

Results  Preoperatively these patients had cortical blood flow asymmetry in the middle cerebral artery territory. The degree of crossed cerebellar hypoperfusion had no relation to the extent of cerebral blood flow asymmetry but was significantly correlated with the extent of asymmetry in cerebral oxygen metabolism. The preoperative extent of asymmetry in the cerebral oxygen extraction fraction and the postoperative improvement of asymmetry in cerebral blood flow were correlated with the preoperative difference between the severity of cerebral blood flow asymmetry and crossed cerebellar hypoperfusion.

Conclusions  The difference between the extent of cerebral blood flow asymmetry and crossed cerebellar hypoperfusion can be used to estimate the degree of uncoupling between blood flow and metabolism, which can in turn predict the postoperative improvement of cerebral blood flow asymmetry. We suggest that this approach may be a simple means of estimating the relative uncoupling between blood flow and metabolism from a single blood flow study in patients who have major cerebral arterial occlusive disease with low perfusion.

Key Words  •  cerebellum • cerebral blood flow • diaschisis • hemodynamics • tomography, emission-computed

In patients with major cerebral arterial occlusive disease, an inadequate blood supply relative to metabolic demand may increase the risk of cerebral ischemia, suggesting that the identification of patients with this problem could help prevent stroke. In addition, only patients with this problem have an increase of cerebral blood flow (CBF) after reconstructive vascular surgery. The detection of a relative reduction in CBF is possible with single-photon emission computed tomography (SPECT). However, distinguishing a reduction caused by reduced blood supply from that caused by reduced metabolic demand is laborious and generally cannot be done with a single blood flow study.

Crossed cerebellar diaschisis was first demonstrated by Baron and coworkers with positron emission tomography (PET), and SPECT can also detect crossed cerebellar diaschisis as crossed cerebellar hypoperfusion (CCH). The mechanism responsible for CCH appears to be deafferentation due to the disruption of cerebrocerebellar functional connections. Impairment of cortical function causes hypofunction of the contralateral cerebellum that is accompanied by a decrease in blood flow. Thus, in patients with major cerebral arterial occlusive disease and low perfusion, CCH may indicate a decrease in cerebral hemispheric blood flow due to reduced metabolic demand, and the severity of CCH may be correlated with the extent of the asymmetry in cerebral metabolism. Accordingly, the difference between the extent of CBF asymmetry and CCH may indicate the degree of uncoupling between blood flow and metabolism, which could in turn predict the postoperative improvement of CBF.

To determine whether determining the relation between CBF asymmetry and CCH is useful for estimating the relative uncoupling between CBF and metabolism from a single blood flow study, we retrospectively analyzed the relation between these factors, measured by PET, in patients with major cerebral arterial occlusive disease before and after reconstructive vascular surgery.

Subjects and Methods

We studied 11 consecutive patients with PET before and after surgery for the treatment of symptomatic major cerebral arterial occlusive disease between 1984 and 1990. The subjects...
were 8 men and 3 women aged 56 to 65 years (mean±SD, 61.8±3.0 years). Their clinical and neuroradiological data are summarized in Table 1. Two patients had transient ischemic attacks and 9 had minor stroke with mild disability. Computed tomographic scanning disclosed only minor abnormalities in the middle cerebral artery (MCA) territory of the hemisphere with the major arterial disease. None of the patients had any symptoms suggesting vertebrobasilar ischemia or any cortical or brain stem abnormalities on computed tomographic scanning. Conventional angiography revealed unilateral internal carotid artery (ICA) occlusion in 3 patients, unilateral ICA stenosis in 3, unilateral MCA occlusion in 1, unilateral MCA stenosis in 1, ICA occlusion with contralateral ICA stenosis in 2, and ICA occlusion with contralateral MCA occlusion in 1. The vertebrobasilar system was angiographically normal in all patients. Of the patients with unilateral disease, 6 underwent superficial temporal artery (STA)-MCA anastomosis and 2 underwent carotid endarterectomy. Of those with bilateral disease, 2 underwent bilateral STA-MCA anastomosis and 1 underwent both STA-MCA anastomosis and carotid endarterectomy. All subjects gave informed consent to the surgery and PET studies.

The initial PET study was performed a median of 3 weeks (range, 2 days to 14 weeks) before surgery. All patients were in a stable state at the time. Postoperative bypass blood flow was assessed angiographically in 4 patients with STA-MCA anastomosis, and in all 4 patency of the bypass was good. In the other 5 patients with bypass surgery, the grafts were judged to be patent on the basis of palpable STA pulsation. In 3 patients with carotid endarterectomy, all of the operated carotid arteries were angiographically confirmed to be patent. Postoperative PET studies were performed a median of 2 months (range, 5 days to 11 months) after surgery. One patient (patient 11) achieved postoperative improvement of higher cortical function (dysphasia, dyscalculia, and finger agnosia). In the other 10 patients, the neurological status was unchanged after surgery. No patients had strokes or TIAs during the period between surgery and postoperative PET studies.

Regional CBF, the cerebral metabolic rate of oxygen (CMRO$_2$), the cerebral oxygen extraction fraction (COEF), and the cerebral blood volume (CBV) were measured with PET. The specifications of our PET scanner have been reported elsewhere.\textsuperscript{10} In brief, the device has four rings containing bismuth germinate $^{192}$Bi detectors, and it can obtain seven tomographic slices in one scanning process. The best spatial resolution is 7.6 mm at full width half maximum at the center of the scanning field, and the axial resolution is 12 mm at the center. The scanning procedure was as follows: Before the study, a $^{48}$Ge-$^{48}$Ga transmission scan was performed for 20 minutes to allow attenuation correction. CBF was determined while the subject continuously inhaled C$^{15}$O$_2$ at 370 to 555 MBq/min through a mask. Measurement of CMRO$_2$ and COEF was done with the continuous inhalation of O$_2$ at 740 MBq to 1.11 Gbq per minute. Data were collected for 5 minutes. A single breath of C$^{15}$O$_2$ (2.96 Gbq) was used to measure CBV. We calculated CBF, CMRO$_2$, and COEF by

### Table 1. Summary of the Clinical and Radiological Findings of the 11 Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Clinical Features</th>
<th>Computed Tomographic Scan</th>
<th>Angiography</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>M</td>
<td>Mild weakness of R arm for 9 months Minor L hemisphere stroke (1 month)</td>
<td>Small corticosubcortical infarct in L parietal region</td>
<td>L ICA stenosis (80%)</td>
<td>L carotid endarterectomy</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>M</td>
<td>L hemisphere TIA (6 years) Transient L visual disturbance (2 months)</td>
<td>Normal</td>
<td>L ICA stenosis (90%)</td>
<td>L carotid endarterectomy</td>
</tr>
<tr>
<td>3</td>
<td>62</td>
<td>F</td>
<td>Minor R hemisphere stroke (1 month)</td>
<td>Small infarcts in R ACA/MCA and MCA/PCA watershed areas</td>
<td>R ICA stenosis (99%)</td>
<td>R STA-MCA anastomosis</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>M</td>
<td>R visual disturbance (1 month) Minor R hemisphere stroke (6 weeks)</td>
<td>Small infarcts in R caudate head and corona radiata</td>
<td>R ICA occlusion</td>
<td>R STA-MCA anastomosis</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>F</td>
<td>L hemisphere TIA (2 years) Minor L hemisphere stroke (1 month)</td>
<td>Small infarct in L centrum semiovale</td>
<td>L ICA occlusion</td>
<td>L STA-MCA anastomosis</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>M</td>
<td>Minor R hemisphere stroke (2 months)</td>
<td>Small infarct in R putamen</td>
<td>R ICA occlusion</td>
<td>R STA-MCA anastomosis</td>
</tr>
<tr>
<td>7</td>
<td>62</td>
<td>M</td>
<td>Minor L hemisphere stroke (4 months)</td>
<td>Small infarct in L putamen</td>
<td>L MCA stenosis</td>
<td>L STA-MCA anastomosis</td>
</tr>
<tr>
<td>8</td>
<td>59</td>
<td>F</td>
<td>L hemisphere TIA (1 month, 17 days)</td>
<td>Normal</td>
<td>L MCA occlusion</td>
<td>L STA-MCA anastomosis</td>
</tr>
<tr>
<td>9</td>
<td>62</td>
<td>M</td>
<td>Minor L hemisphere stroke (5 years)</td>
<td>Small infarct in L corona radiata</td>
<td>L ICA occlusion</td>
<td>Bilateral STA-MCA anastomosis</td>
</tr>
<tr>
<td>10</td>
<td>62</td>
<td>M</td>
<td>L hemisphere TIA (3 months) Minor L hemisphere stroke (3 months)</td>
<td>Small infarcts in L corona radiata and parietal subcortex</td>
<td>L ICA occlusion</td>
<td>Bilateral STA-MCA anastomosis</td>
</tr>
<tr>
<td>11</td>
<td>65</td>
<td>M</td>
<td>Minor L hemisphere stroke (1 month)</td>
<td>L cortical atrophy</td>
<td>L ICA occlusion</td>
<td>R STA-MCA anastomosis</td>
</tr>
</tbody>
</table>

The times in brackets indicate the interval between the occurrence of each symptom and the preoperative positron emission tomographic study.

ICA indicates internal carotid artery; TIA, transient ischemic attack; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; and STA, superficial temporal artery, respectively.
the steady state method, and CMRO₂ and COEF were corrected by the CBV. Functional images were reconstructed as 64x64 pixels, with each pixel representing a 2.5 mm x 2.5 mm area. Scanning of a Renzo phantom indicated that our PET scanner was able to detect regions as small as 2.5 mm in diameter. The ratio of CBF to CBV was calculated by pixel as an indicator of cerebral perfusion reserve.

The patients in this study were scanned through tomographic planes parallel to the orbitomeatal line. Each patient's head was positioned by means of a light grid projected onto the forehead, the lines of which were aligned to markings made on the skin with a felt-tipped pen. For the follow-up studies, care was taken to ensure that, as much as possible, the patient was scanned through anatomic planes identical to those in the preoperative scan. In addition, three other lines were used to place a total of 18 to 20 circular regions of interest 10 mm in diameter over the cerebral cortex. According to the atlas of Kretschmann and Weinrich, the regions of interest in all three images were in the distribution of the anterior cerebral artery, the MCA, and the posterior cerebral artery, as well as the watershed areas between the anterior cerebral artery and MCA (anterior watershed) and the MCA and posterior cerebral artery (posterior watershed). A hemispheric value was calculated as the average of the MCA, anterior watershed, and posterior watershed regions of interest, and was weighted by region size.

From the absolute CBF values, the percent difference in blood flow (cerebral Δ%) between the cerebral cortex ipsilateral (IL) and contralateral (CL) to the diseased side was calculated as follows to determine CBF asymmetry: Cerebral Δ%=(CL-IL)/CL×100. In 3 patients with bilateral disease, the hemisphere with the more severe reduction in CBF was defined as the ipsilateral one. The change in CBF asymmetry after surgery was calculated as the difference between the preoperative and postoperative cerebral Δ% values.

We also studied cerebral Δ% in 9 normal subjects (mean age, 56±16 years) and calculated the asymmetry index (AI) between the right (R) and left (L) cerebral cortexes as follows to obtain the upper 95% confidence limit: Cerebral AI (absolute % value)=[(R-L)/(R+L)]×200, where [R-L] is the absolute value of the difference.

The cerebral AI in the normal subjects was 3.64±1.22% (mean±SD). Thus, we defined significant CBF asymmetry as a cerebral Δ% value above 6.45% (the upper 95% confidence limit for the normal subjects).

The percent difference in blood flow between the contralateral (CL) and ipsilateral (IL) cerebellar cortexes (cerebellar Δ%) was calculated from the absolute blood flow values as follows to determine the degree of cerebellar blood flow asymmetry: Cerebellar Δ%=(IL-CL)/IL×100. It was assumed that the resulting values reflected the percent changes caused by CCH (ie, indicated the severity of CCH). In the same 9 normal subjects, the asymmetry index (AI) between the right and left cerebellar cortexes was also calculated as follows to obtain the upper 95% confidence limits: Cerebellar AI (absolute % value)=[(R-L)/(R+L)]×200.

The cerebellar AI in normal subjects was 3.61±1.76% (mean±SD). Thus, we defined significant cerebellar blood

| Table 2. Physiological Data Obtained Before and After Surgery |
|-----------------------------------|-----------------|-----------------|
|                                   | Before Surgery  | After Surgery   |
| PACO₂, mm Hg                      | 39.6±4.9        | 39.3±5.3        |
| PAO₂, mm Hg                       | 87.5±7.9        | 85.3±7.7        |
| Hematocrit, %                     | 38.4±4.6        | 38.0±4.5        |
| Hemoglobin, g/dL                  | 13.0±1.5        | 12.7±1.6        |
| MABP, mm Hg                       | 100.1±9.7       | 101.6±10.2      |

MABP indicates mean arterial blood pressure. Values are mean±SD.

The cerebellar AI in normal subjects was 3.61±1.76% (mean±SD). Thus, we defined significant cerebellar blood

| Table 3. Regional CBF, CMRO₂, COEF, CBV, and CBF/CBV for the Cerebral Hemispheres Ipsilateral and Contralateral to the Site of Cerebral Arterial Disease Before and After Surgery |
|-----------------------------------|-----------------|-----------------|
|                                   | Ipsilateral     | Contralateral   |
| CBF, mL/100 g/min                 | 34.19±5.95      | 38.17±11.96     |
| CMRO₂, mL/100 g/min               | 43.39±6.34      | 46.16±12.32     |
| COEF, %                           | 2.69±0.58       | 2.66±0.68       |
|                                   | 3.30±0.51       | 3.22±0.64       |
|                                   | 4.56±5.97       | 44.79±7.67      |
|                                   | 43.85±4.07      | 44.47±7.87      |
| CBV, mL/100 g                     | 4.30±0.90       | 3.68±0.68*      |
|                                   | 3.99±0.81       | 3.58±0.46       |
| CBF/CBV, per min                  | 8.24±1.76       | 10.73±3.31*     |
|                                   | 11.41±2.74      | 13.11±3.32      |

CBF indicates cerebral blood flow; CMRO₂, cerebral metabolic rate of oxygen; COEF, cerebral oxygen extraction fraction; and CBV, cerebral blood volume.

*P<.05 compared with before surgery (paired Wilcoxon signed-rank test).
flow asymmetry as a cerebellar Δ% value above 7.67% (the upper 95% confidence limit for the normal subjects).

The absolute hemispheric values, asymmetries in CBF, CMRO₂, COEF, CBV, CBF/CBV values, and asymmetries in cerebellar blood flow and oxygen metabolism values obtained before and after surgery were compared using the paired Wilcoxon signed-rank test, and P<.05 was considered to indicate a significant difference. Spearman rank correlation was used to analyze the relation between CCH and the degrees of asymmetry in CBF, CMRO₂, and COEF as well as the relation of the degree of COEF asymmetry or the improvement in CBF asymmetry or absolute CBF to the preoperative difference between the CBF asymmetry and CCH.

**Results**

There was no significant difference between the physiological data obtained from the patients during PET scanning before and after surgery (paired Wilcoxon signed-rank test) (Table 2), and all the variables showed very little change between the preoperative and follow-up studies in the 11 patients. In the group as a whole, surgery had no marked effects on cerebral hemodynamics.

Before surgery, all patients had significant cerebral CBF asymmetry, and all but one also had significant cerebellar blood flow asymmetry. Surgery did not significantly affect any of the asymmetries in CBF, CMRO₂, COEF, CBV, and CBF/CBV values. Asymmetries in cerebellar blood flow and oxygen metabolism values also did not change.

In the analysis of absolute values, surgery significantly decreased CBV and significantly increased CBF/CBV in the hemisphere ipsilateral to the arterial disease, but the CBF, CMRO₂, and COEF showed no significant changes (Table 3). When the hemispheres were divided into operated and nonoperated ones, the results were still the same.

Analysis of individual cases showed that the effects of surgery on cerebral hemodynamics were varied and correlated with the degree of CCH. Before surgery, the degree of CCH had no significant relation to the degree of CBF asymmetry (Fig 1A), whereas the degree of CMRO₂ asymmetry was significantly correlated with the degree of CCH (Fig 1B). In addition, the degree of postoperative CBF asymmetry was significantly correlated with preoperative CCH (Fig 1C), mainly because of a decrease of CBF asymmetry in the patients with mild preoperative CCH. The same trends were seen in the three patients with bilateral cerebral arterial disease.

The preoperative extent of COEF asymmetry was weakly but significantly correlated with the preoperative CCH (Fig 2A). The only patient without significant CCH (patient 7) had the greatest COEF asymmetry. However, the preoperative extent of COEF asymmetry was more strongly correlated with the preoperative difference between the severity of CBF asymmetry and CCH (Fig 2B), which was also significantly related to the postoperative improvement of CBF asymmetry (Fig 3A). An improvement of CBF asymmetry accompanied an absolute increase of CBF in all but 2 patients (Fig 3B). The greatest improvement occurred in a patient with unilateral MCA stenosis (patient 7), the only patient with cerebral CBF asymmetry without CCH (Fig 4). Because a discrepancy between the improvement of asymmetry and the absolute increase of CBF was noted in the patients with bilateral disease, the above correlations were stronger after the exclusion of these patients.

**Discussion**

This study demonstrated that the degree of uncoupling between CBF and metabolism can be estimated from a single blood flow study in patients with major cerebral arterial occlusive disease and low perfusion. The difference between the extent of CBF asymmetry and CCH indicates the degree of uncoupling between CBF and metabolism, and can be used to predict the postoperative improvement of CBF asymmetry. Preoperatively, all our patients had significant CBF asymmetry, but measurement of CBF alone could not provide any information about the contribution of reduced blood supply and reduced metabolic demand to this. However, the degree of CCH was correlated with the degree of cerebral CMRO₂ asymmetry, suggesting that
the contribution of reduced metabolic demand could be deduced from the severity of CCH. Accordingly, the difference between the extent of CBF asymmetry and CCH could be used to predict the extent to which CBF asymmetry was uncoupled from CMRO₂ asymmetry (ie, COEF asymmetry). Our results showed that postoperative improvement of CBF asymmetry, along with an absolute increase in CBF, occurred in the patients with a large difference between the extent of CBF asymmetry and CCH. The correlation between postoperative CBF asymmetry and preoperative CCH indicates that successful surgery improved the uncoupling of CBF asymmetry from CMRO₂ asymmetry.

Many studies have demonstrated that only a small number of patients have an increase in CBF after STA-MCA anastomosis. This is probably because preoperative CBF in the majority of cases was appropriate for cerebral metabolic demands. Only patients with uncoupling of CBF from CMRO₂ show an improvement of CBF after surgery. According to the International Study, STA-MCA anastomosis may be indicated only for those patients not responding to medical therapy who may be at increased risk for hemodynamic ischemia and would benefit from this surgery. To test this hypothesis, our method of estimating the uncoupling between CBF and metabolism should be evaluated in a prospective study, because CBF can be measured by isotope techniques other than PET.

Our method is best applicable to patients with unilateral major cerebral arterial occlusive disease and no infarction in the chronic stage. In such patients, CBF asymmetry without CCH indicates "misery perfusion" and predicts an improvement of asymmetry after successful surgery. However, the correlation between cerebral metabolic asymmetry and CCH may be weak in patients with infarction, mainly because of two problems of infarct location. First, deep infarcts in the MCA territory, especially those disrupting most of the internal capsule, frequently cause marked CCH due to cerebrocerebellar tract damage. Such infarcts, especially those disrupting the thalamocortical projections, also cause ipsilateral cerebral cortical hypometabolism, possibly resulting in CCH. The degree of CCH or ipsilateral cerebral hypometabolism depends on the location and extent of the infarct. When the infarct causes more severe CCH than ipsilateral cortical hypometabolism, CCH cannot be used to indicate the extent of cerebral metabolic asymmetry. This is especially true when a pure posterior capsule infarct causes CCH without hypometabolism of the ipsilateral cerebral cortex. Thus, our method cannot be applied to patients with deep MCA territory infarcts if the severity of CCH is much greater than that of CBF asymmetry. Second, CCH may be associated mainly with frontal and parietal lesions and less with temporal lesions. Thus, patients with temporal lobe infarcts may have more

![Graph](image-url)
severe cerebral CMRO₂ asymmetry than CCH. In addition, our method is probably not so useful in patients with severe bilateral cerebral arterial disease or in patients with acute stroke in whom cerebral hemodynamics are affected bilaterally. In these patients, measurement of absolute CBF is needed to evaluate the extent of bilateral CBF changes.

Although these exceptions may decrease the sensitivity and specificity of our method, its simplicity still gives it practical value. Accordingly, the relation between our method and the acetazolamide test of vasodilatory capacity should be studied in the future with SPECT. It is necessary to clarify whether CBF asymmetry without CCH is associated with a limited vasodilatory capacity and an improvement of CBF asymmetry after surgery in patients with unilateral major cerebral arterial occlusive disease. Some patients with ICA occlusive disease who have poor collateral circulation through the circle of Willis or MCA occlusive disease may also have substantial COEF asymmetry.

In one recent SPECT study there was a close relation of CCH to cerebral vasodilatory reserve and CBF improvement after bypass surgery in unilateral major cerebral arterial occlusive diseases.

In the past decade, CBF measurement with SPECT has become increasingly available, but the evaluation of cerebral metabolism is still not feasible. In patients with major cerebral arterial occlusive disease, it is essential to estimate the degree of uncoupling between CBF and metabolism. The present study showed that the difference between CBF asymmetry and CCH could be used to estimate the relative uncoupling between CBF and metabolism, which can in turn predict the postoperative improvement of CBF asymmetry. This approach may offer a simple means of estimating the uncoupling between CBF and metabolism from a single blood flow study in patients with major cerebral arterial occlusive disease and low perfusion.

Acknowledgments

This work was supported by Scientific Research grants (C-05670556, A-04040483) from the Japanese Ministry of Education, Science and Culture and by the Japan Foundation for Aging and Health. We thank Prof Junji Konishi and his staff at the Department of Radiology and Nuclear Medicine, Faculty of Medicine, Kyoto University, and Dr Yoshiharu Yonekura, Dr Hideo Saji, and Dr Yasuhiro Magata for their support and technical help. We also thank Dr Sen Yamagata, Dr Izumi Nagata, Dr Masafumi Ogawa, Dr Yasuomi Ouchi, and Dr Yasuhiro Nagahama for their cooperation.

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Stroke. 1994;25:1945-1951
doi: 10.1161/01.STR.25.10.1945

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