Effects of Surgical Revascularization on Cerebral Oxygen Metabolism in Patients With Moyamoya Disease
An 15O-Gas Positron Emission Tomographic Study

Satoshi Kuroda, MD, PhD; Daina Kashiwazaki, MD; Kenji Hirata, MD, PhD; Tohru Shiga, MD, PhD; Kiyohiro Houkin, MD, PhD; Nagara Tamaki, MD, PhD

Background and Purpose—This prospective study was aimed to evaluate the effects of surgical revascularization on cerebral oxygen metabolism in moyamoya disease.

Methods—This study included totally 69 hemispheres of 42 patients who underwent superficial temporal artery to middle cerebral artery anastomosis and indirect bypass for moyamoya disease between 2000 and 2011. There were 12 children and 30 adults. MRI and 15O-gas positron emission tomography were performed before and 3 to 4 months after surgery. Hemodynamic and metabolic parameters were precisely quantified and statistically analyzed.

Results—Preoperative positron emission tomographic scans revealed that cerebral blood flow was decreased, cerebral blood volume was increased, and cerebral metabolic rate for oxygen was decreased in both pediatric and adult patients. Cerebral metabolic rate for oxygen reduction was observed in ≈80% of pediatric (16/21; 76%) and adult hemispheres (38/48; 79%). Surgical revascularization resolved hemodynamic compromise in all operated hemispheres. Cerebral metabolic rate for oxygen significantly improved in younger adult patients without parenchymal lesions (P=0.0264; odds ratio, 0.88; 95% confidence interval, 0.79–0.99).

Conclusions—Cerebral oxygen metabolism is significantly depressed in ≈80% of the involved hemispheres of moyamoya disease and improves in pediatric and younger adult patients without parenchymal lesions after bypass surgery. Cerebral oxygen metabolism may be reversibly depressed in response to cerebral ischemia in them although the underlying mechanisms are still unclear. (Stroke. 2014;45:2717-2721.)

Key Words: brain ischemia ■ bypass surgery ■ moyamoya disease ■ positron emission tomography

Moyamoya disease is a unique cerebrovascular disorder characterized by progressive stenosis of the terminal portion of the internal carotid artery. The perforating arteries in the basal ganglia and thalamus markedly dilate and function as an important collateral circulation, called as moyamoya vessels.1,2 The posterior cerebral arteries are also involved in a certain subgroup of patients. Therefore, cerebral hemodynamics is often impaired especially in the frontal lobe, leading to transient ischemic attack and cerebral infarction. Furthermore, the dilated, fragile moyamoya vessels often rupture and cause intracranial hemorrhage. Superficial temporal artery to middle cerebral artery (STA-MCA) anastomosis and indirect synangiosis are known to improve cerebral hemodynamics and are used to reduce the risk of subsequent cerebrovascular events and contribute to improve long-term outcome in patients with moyamoya disease, although the value of this approach has only been shown by clinical trial in adults to prevent intracerebral hemorrhage.3-10

Using single photon emission computed tomography and positron emission tomography (PET), many previous studies have shown that surgical revascularization improves the parameters of cerebral hemodynamics, including cerebral blood flow (CBF), cerebral blood volume (CBV), cerebrovascular reactivity to acetazolamide, and elevated oxygen extraction fraction (OEF) in moyamoya disease. These beneficial effects are prominent especially in the frontal lobe.6,11-19 However, there are no studies that focused on surgical effects on cerebral oxygen metabolism in moyamoya disease, although some of previous studies just presented the data of cerebral metabolic rate for oxygen (CMRO2). Therefore, this prospective study was aimed to evaluate the effect of surgical revascularization on cerebral oxygen metabolism in moyamoya disease, using 15O-gas PET.

Patients and Methods

This prospective study included totally 42 patients who were admitted to our hospital between 2000 and 2011. All of them were diagnosed as...
moyamoya disease based on the guideline for the diagnosis of moyamoya disease set by the Research Committee on Moyamoya Disease (Spontaneous Occlusion of the Circle of Willis) of the Ministry of Health, Welfare, and Labor of Japan.20 There were 12 children and 30 adults. There were 10 men and 32 women. Mean age was 11.7±3.9 and 45.8±11.7 years in pediatric and adult patients, respectively. In pediatric patients, clinical diagnosis included transient ischemic attack in 7, ischemic stroke in 2, headache in 2, and asymptomatic in 1. In adult patients, clinical diagnosis included transient ischemic attack in 15, ischemic stroke in 7, hemorrhagic stroke in 4, and asymptomatic in 4.

Radiological Examinations
MRL cerebral angiography, and 18O-gas PET were performed before and 3 to 4 months after surgery in all patients. T1-weighted images, T2-weighted images, and fluid attenuated inversion recovery images were obtained to locate ischemic and hemorrhagic lesions in the brain parenchyma. All patients were scanned with ECAT EXACT HR+ (Siemens) before and 3 to 4 months after surgery, as described previously.21,22 Briefly, 1-minute inhalation of 18O-CO2 (2 Gbq/min) followed by 3-minute static scanning and 3-time arterial blood sampling were performed to measure CBV. After 15-minute inhalation of 18O2 (0.5 Gbq/min), a steady-state O2 image was scanned and 3-time arterial blood sampling was performed for 5 minutes to measure OEF and CMRO2. Finally, to determine CBV, steady-state CO2 image was scanned and 3-time arterial blood sampling was performed for 5 minutes after 15-minute inhalation of 18O-CO2 (0.5 Gbq/min). Each PET parameter was obtained using 10-mm diameter circular regions of interest, which were placed on the frontal or temporal cortex without cerebral infarction.

Normal PET values were obtained from 10 adult volunteers: CBF, 44±4 mL/min per 100 g; CMRO2, 3.3±0.6 mL/min per 100 g; CBV, 3.7±0.7 mL/100 g, and OEF, 0.4±0.05 (mean±SD).

Surgical Treatment
All patients underwent STA-MCA anastomosis combined with indirect synangiosis, encephalo-duro-Myo-arterio-pericranial synangiosis.6 Briefly, large fronto-temporal craniotomy extending to the frontal area was made. The 1 or 2 branches of STA were anastomosed to the cortical branches of MCA. The pedicles of dura mater, temporal muscle, and frontal pericranium were used to cover the brain surface as the donor tissues of indirect bypass. Surgical revascularization was performed on 21 hemispheres in 12 pediatric patients and on 48 hemispheres in 30 adult patients. Therefore, totally 69 hemispheres were analyzed in this study. MRI, cerebral angiography, and PET were repeated 3 to 4 months after surgery to assess its effects on cerebral hemodynamics and metabolism in all patients.

Statistical Analysis
Data were expressed as percentages or mean±SD. Categorical variables were compared using a χ2 test. Continuous variables were compared using paired t test and unpaired t test as appropriate. Differences were considered to be statistically significant if the P value was <0.05. Differences between pre- and postoperative values that were higher and lower than the 95% confidence interval (CI) were judged as increased and decreased, respectively. The differences within 95% CI were judged as unchanged. A multivariate logistic regression model was conducted to test the effects of surgical revascularization on hemodynamic and metabolic parameters on 18O-gas PET. A forward stepwise model-building procedure was performed for the parameters, using P<0.10 achieved in univariate analysis. In the final multivariate analysis, the statistical level of significance was set at P<0.05.

Results
Clinical Results
There was no surgical mortality. Ischemic stroke developed in 3 (4.3%) of 69 operated hemispheres. None of operated patients experienced ischemic or hemorrhagic stroke after surgery during follow-up periods of mean 9.3 years.

On postoperative angiography, STA-MCA anastomosis and indirect synangiosis widely covered the operated hemispheres in all 69 hemispheres. Thus, postoperative external carotid angiography revealed that surgical collaterals opacified more than two thirds of the MCA territory in 50 hemispheres and between one thirds and two thirds of the MCA territory in 19. Basal moyamoya vessels disappeared or markedly diminished in all operated hemispheres.

PET Parameters in Pediatric Patients
Totally 21 hemispheres of 12 pediatric patients underwent surgical revascularization. Table 1 shows pre- and postoperative PET parameters in these 22 hemispheres. Before surgery, CBF was 36.5±8.2 mL/min per 100 g and CMRO2 was 2.9±0.7 mL/min per 100 g, being significantly lower than the control values obtained from adult volunteers (P<0.01). The differences would be much larger between pediatric patients and healthy children because it is well known that CBF and CMRO2 are much higher in children than in adults.12,17 CMRO2 was decreased in 16 of 21 hemispheres (76%). Mean CBV value was 5.9±2.3 mL/100 g, being significantly higher than the control value (P<0.01). Although OEF was significantly elevated in 5 (22.7%) of 22 hemispheres, mean OEF value (0.4±0.10) did not differ from the control value.

As shown in Table 1, surgical revascularization significantly improved CBF, CBV, and CMRO2 in the operated hemispheres. Thus, CBF significantly increased from 36.5±8.2 to 42.4±5.5 mL/min per 100 g after surgery (P<0.01; 95% CI, 3.0–8.7). CBV significantly decreased from 5.9±2.3 to 3.7±0.8 mL per 100 g (P<0.01; 95% CI, 0.7–3.8). Furthermore, CMRO2 significantly increased from 2.9±0.7 to 3.5±0.5 mL/min per 100 g after surgery (P<0.01; 95% CI, 0.3–0.9). However, OEF did not show statistically significant change after surgery although significantly elevated OEF normalized in all 5 hemispheres. Thus, pre- and postoperative OEFs were 0.4±0.10 and 0.46±0.04, respectively.

PET Parameters in Adult Patients
Totally 48 hemispheres of 30 adult patients underwent surgical revascularization. Table 2 shows pre- and postoperative PET parameters in these 48 hemispheres. Before surgery, mean CBF value was 29.7±7.3 mL/min per 100 g and CMRO2 was 2.4±0.6 mL/min per 100 g, being significantly lower than the control value (P<0.01). CMRO2 was decreased in 38 of 48 hemispheres (79%). Mean CBV value was 5.3±2.0 mL/100 g.

Table 1. Pre- and Postoperative Parameters on 18O-Gas Positron Emission Tomography in Pediatric Patients With Moyamoya Disease (n=21 Hemispheres)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preop.</th>
<th>Postop.</th>
<th>Significance, P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF, mL/min per 100 g</td>
<td>36.5±8.2</td>
<td>42.4±5.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CBV, mL/100 g</td>
<td>5.9±2.3</td>
<td>3.7±0.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CMRO2, mL/min per 100 g</td>
<td>2.9±0.7</td>
<td>3.5±0.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>OEF</td>
<td>0.4±0.1</td>
<td>0.46±0.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

CBF indicates cerebral blood flow; CBV, cerebral blood volume; CMRO2, cerebral metabolic rate for oxygen; and OEF, oxygen extraction fraction.
being significantly higher than the control value ($P<0.05$). Although OEF was significantly elevated in 7 (14.6%) of 48 hemispheres, mean OEF value (0.45±0.10) did not differ from the control value.

As shown in Table 2, surgical revascularization significantly improved CBF and CBV in adult patients. Thus, CBF significantly increased from 29.7±7.3 to 37.6±6.9 mL/min per 100 g after surgery ($P=0.0126$; unpaired $t$ test). Patient’s age was significantly lower in the hemispheres with postoperative improvement ($P=0.0264$; $t$ test). Similarly, the side of operated hemispheres did not predict it ($P=0.4285$; $t$ test). Only patient’s age, therefore, was included in the logistic regression analysis. As shown in Table 3, the model indicated that patient’s age is an independent factor as predictor of postoperative CMRO$_2$ improvement (odds ratio, 0.88; 95% CI, 0.79–0.99; $P=0.0264$).

### Table 2. Pre- and Postoperative Parameters on $^{15}$O-Gas Positron Emission Tomography in Adult Patients With Moyamoya Disease (n=48 Hemispheres)

<table>
<thead>
<tr>
<th></th>
<th>Preop.</th>
<th>Postop.</th>
<th>Significance, $P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF, mL/min per 100 g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBV, mL/100 g</td>
<td>5.3±2.0</td>
<td>3.5±1.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CMRO$_2$, mL/min per 100 g</td>
<td>2.4±0.6</td>
<td>2.6±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>OEF</td>
<td>0.45±0.1</td>
<td>0.40±0.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

CBF indicates cerebral blood flow; CBV, cerebral blood volume; CMRO$_2$, cerebral metabolic rate for oxygen; and OEF, oxygen extraction fraction.

### Clinical Factors to Determine Postoperative Improvement of CMRO$_2$

In pediatric patients, CMRO$_2$ was significantly lower than the control value in 16 (76%) of 21 operated hemispheres. Of these, CMRO$_2$ significantly improved in all 8 hemispheres without ischemic or hemorrhagic lesions on MRI after surgery. However, CMRO$_2$ did not improve in other 8 hemispheres with parenchymal lesions on MRI.

In adult patients, CMRO$_2$ was significantly lower than the control value in 38 (79%) of 48 operated hemispheres. Of these, CMRO$_2$ significantly improved in 13 of 22 lesion-free hemispheres after surgery. Cerebral oxygen metabolism did not change in other 9 lesion-free hemispheres. However, CMRO$_2$ did not improve in the remaining 25 hemispheres with parenchymal lesions on MRI.

As the next step, therefore, statistical analysis was performed to determine clinical factors that were closely related to postoperative improvement of CMRO$_2$, in the lesion-free hemispheres of adult patients. The effects of various factors on postoperative improvement of CMRO$_2$ are shown in Table 3. There was no significant difference in postoperative CMRO$_2$ improvement between sexes ($P=0.1078$; $\chi^2$ test). Patient’s age was significantly lower in the hemispheres with postoperative CMRO$_2$ improvement than those without, 40.1±9.7 and 51.4±9.4 years, respectively ($P=0.0126$; unpaired $t$ test). Onset type was not a significant predictor for postoperative CMRO$_2$ improvement ($P=0.2007$; $\chi^2$ test). Similarly, the side of operated hemispheres did not predict it ($P=0.4285$; $\chi^2$ test).

### Discussion

This study clearly shows that cerebral oxygen metabolism is significantly depressed in $\approx80\%$ of involved hemispheres in both pediatric (16/21; 76%) and adult moyamoya disease (38/48; 79%). Furthermore, effective surgical revascularization significantly improves it in a certain subgroup of patients, including pediatric or younger adult patients without parenchymal lesions. This is the first report that focuses on the effects of surgical revascularization on cerebral oxygen metabolism in moyamoya disease.

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**Table 3. Independent Predictors of Postoperative CMRO$_2$ Improvement Among 22 Hemispheres Without Parenchymal Lesions in Adult Patients With Moyamoya Disease**

<table>
<thead>
<tr>
<th></th>
<th>Improved (n=13)</th>
<th>Unchanged (n=9)</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0</td>
<td>3</td>
<td>$P=0.1078$</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Women</td>
<td>13</td>
<td>6</td>
<td>$P=0.2007$</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Age, y</td>
<td>40.1±9.7</td>
<td>51.4±9.4</td>
<td>$P=0.0126$</td>
<td>$P=0.0264$</td>
<td>0.88 (0.79–0.99)</td>
</tr>
<tr>
<td>Onset type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>9</td>
<td>8</td>
<td>$P=0.2007$</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0</td>
<td>1</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>2</td>
<td>0</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>2</td>
<td>0</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Operated side</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>8</td>
<td>4</td>
<td>$P=0.4285$</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Left</td>
<td>5</td>
<td>5</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Continuous data are expressed as mean±SD. CI indicates confidence interval; CMRO$_2$, cerebral metabolic rate for oxygen; OR, odds ratio; and TIA, transient ischemic attack.
Cerebral oxygen metabolism is significantly depressed in ≈80% of the involved hemispheres of moyamoya disease and improves in pediatric and younger adult patients without parenchymal lesions after STA-MCA anastomosis and indirect synangiosis. Pre- and postoperative PET measurements strongly suggest that their cerebral oxygen metabolism was reversibly depressed in response to cerebral ischemia, although the underlying mechanisms are still unclear.

Conclusions

Cerebral oxygen metabolism is significantly depressed in ≈80% of the involved hemispheres of moyamoya disease and improves in pediatric and younger adult patients without parenchymal lesions after STA-MCA anastomosis and indirect synangiosis. Pre- and postoperative PET measurements strongly suggest that their cerebral oxygen metabolism was reversibly depressed in response to cerebral ischemia, although the underlying mechanisms are still unclear.

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Sources of Funding

This study was partly supported by a grant from the Research Committee on Moyamoya Disease, sponsored by the Ministry of Health, Labor, and Welfare of Japan.

Disclosures

None.

References

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Stroke. 2014;45:2717-2721; originally published online August 12, 2014;
doi: 10.1161/STROKEAHA.114.006009
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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