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 $^{15}$O-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 significantly improved in pediatric patients without parenchymal lesions ($n=8$), but not those with parenchymal lesions ($n=8$). Multivariate analysis revealed that 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 $\approx 80\%$ 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

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

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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. 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. 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. 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 (CMRO$_2$). Therefore, this prospective study was aimed to evaluate the effect of surgical revascularization on cerebral oxygen metabolism in moyamoya disease, using $^{15}$O-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. 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 ¹⁵O-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 ¹⁵O-CO (2 GBq/min) followed by 3-minute static scanning and 3-time arterial blood sampling were performed to measure CBF. After 15-minute inhalation of ¹⁵O-O₂ (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 CBF, steady-state CO₂ image was scanned and 3-time arterial blood sampling was performed for 5 minutes after 15-minute inhalation of ¹⁵O-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; CBF, 3.7±0.7 mL/100 g, and OEF, 0.40±0.05 (mean±SD).

Surgical Treatment
All patients underwent STA-MCA anastomosis combined with indirect synangiosis, encephalo-duro-myo-arterio-pericranial synangiosis.²² 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 fronto-pericranial 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. MRL, 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 ¹⁵O-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 third 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.²¹,²² 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 (0.43±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 0.43±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 ¹⁵O-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>0.43±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<0.01; 95% CI, 5.2–10.6). CBV significantly decreased from 5.3±2.0 to 3.5±1.0 mL/100 g (P<0.01; 95% CI, 0.8–2.8). However, CMRO2 did not significantly change after surgery. Thus, pre- and postoperative CMRO2 were 2.4±0.6 and 2.6±0.5 mL/min per 100 g, respectively. OEF did not show statistically significant changes after surgery, although elevated OEF normalized in all 4 hemispheres. Thus, pre- and postoperative OEFs were 0.45±0.10 and 0.40±0.05, respectively.

Clinical Factors to Determine Postoperative Improvement of CMRO2

In pediatric patients, CMRO2 was significantly lower than the control value in 16 (76%) of 21 operated hemispheres. Of these, CMRO2 significantly improved in all 8 hemispheres without ischemic or hemorrhagic lesions on MRI after surgery. However, CMRO2 did not improve in other 8 hemispheres with parenchymal lesions on MRI.

In adult patients, CMRO2 was significantly lower than the control value in 38 (79%) of 48 operated hemispheres. Of these, CMRO2 significantly improved in 13 of 22 lesion-free hemispheres after surgery. Cerebral oxygen metabolism did not change in other 9 lesion-free hemispheres. However, CMRO2 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 CMRO2 in the lesion-free hemispheres of adult patients. The effects of various factors on postoperative improvement of CMRO2 are shown in Table 3. There was no significant difference in postoperative CMRO2 improvement between sexes (P=0.1078; χ² test). Patient’s age was significantly lower in the hemispheres with postoperative CMRO2 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 CMRO2 improvement (P=0.2007; χ² test). Similarly, the side of operated hemispheres did not predict it (P=0.4285; χ² 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 CMRO2 improvement (odds ratio, 0.88; 95% CI, 0.79–0.99; P=0.0264).

Illustrative Case

An 8-year-old girl suddenly developed transient motor aphasia and was admitted to our hospital. Neurological examinations on admission revealed no definite abnormality. MRI showed no abnormality in the brain parenchyma, but cerebral angiography demonstrated severe stenosis of the left carotid forks associated with moyamoya vessels. Preoperative ¹⁵O-gas PET revealed decreased CBF and increased CBV in the territory of the left internal carotid artery. Marked reduction of CMRO2 was also observed in the left cerebral hemisphere. She underwent STA-MCA anastomosis and indirect synangiosis on the left side. Postoperative course was uneventful. Cerebral angiography performed 4 months after surgery showed good development of surgical collaterals over the operated hemispheres. Follow-up ¹⁵O-gas PET revealed that hemodynamic and metabolic parameters significantly improved after surgery. Especially, CMRO2 dramatically increased in the left cerebral hemisphere (Figure).

Discussion

This study clearly shows that cerebral oxygen metabolism is significantly depressed in ≈80% 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.6,11–19

### Table 2. Pre- and Postoperative Parameters on ¹⁵O-Gas Positron Emission Tomography in Adult Patients With Moyamoya Disease (n=48 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>5.3±2.0</td>
<td>3.5±1.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CBV, mL/100 g</td>
<td>2.4±0.6</td>
<td>2.6±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>CMRO2, mL/min per 100 g</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; CMRO2, cerebral metabolic rate for oxygen; and OEF, oxygen extraction fraction.

### Table 3. Independent Predictors of Postoperative CMRO2 Improvement Among 22 Hemispheres Without Parenchymal Lesions in Adult Patients With Moyamoya Disease

<table>
<thead>
<tr>
<th>Variable</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=0.0264</td>
<td>0.88 (0.79–0.99)</td>
<td></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; CMRO2, cerebral metabolic rate for oxygen; OR, odds ratio; and TIA, transient ischemic attack.

Kuroda et al 2017
Morimoto et al reported CBF decrease, CBV increase, cerebral metabolic rate for oxygen (CMRO₂) decrease, and oxygen extraction fraction (OEF) elevation in the left cerebral hemisphere. Note a marked reduction of CMRO₂ in the left cerebral hemisphere (arrows). Postoperative PET scans performed 4 months after surgery revealed a normalization of all of 4 PET parameters. Note a normalization of CMRO₂ in the left cerebral hemisphere (arrows).

Previously, several investigators have analyzed PET parameters, including CMRO₂, in moyamoya disease. Thus, Taki et al found CBV increase and CBF/CBV decrease in both pediatric and adult patients with moyamoya disease, but OEF was not significantly increased. Ikezaki et al reported CBF decrease, CBV increase, and OEF elevation in 13 pediatric patients without parenchymal lesions. In their study, a mean value of CMRO₂ was similar to that in the controls. Shirane et al also reported pronounced ischemia in pediatric moyamoya disease but found no differences in OEF between pediatric patients and healthy children, because of CMRO₂ reduction in the frontal and parietal cortex. Morimoto et al reported CBF decrease, CMRO₂ decrease, and OEF elevation in the MCA territory of 5 patients with moyamoya disease. Piao et al also reported similar results. Therefore, the value of CMRO₂ may largely depend on the patient’s age and their clinical conditions.

However, there are only few studies that shed light on the effects of surgical revascularization on cerebral oxygen metabolism. Thus, Morimoto et al measured PET parameters in 5 patients with moyamoya disease before and after surgery. As a result, CMRO₂ value changed from 2.8±0.6 to 3.4±0.7 mL/min per 100 g after surgery. Although there was no significant difference between them probably because of small sample size, CMRO₂ markedly improved in 2 of these 5 patients. Based on the concept of incomplete infarction, postoperative improvement of CMRO₂ in a certain subgroup of patients with moyamoya disease is peculiar. Indeed, both CBF and CBV significantly improved after surgery. OEF also normalized in all of the hemispheres that had the elevated values before surgery. These findings strongly suggest that surgical revascularization significantly improved cerebral perfusion pressure, resolving hemodynamic compromise in the operated hemispheres. Simultaneously, CMRO₂ significantly improved pediatric or younger adult patients without parenchymal lesions. These findings are different from the above-written concepts and strongly indicate that oxygen metabolism was depressed before surgery because of the reasons apart from irreversible tissue damage. Therefore, it is most likely that cerebral oxygen metabolism was reversibly depressed because of persistent ischemia before surgery and that postoperative improvement of CMRO₂ was closely related to those of cerebral hemodynamics.

It is unclear through which mechanisms cerebral oxygen metabolism is reversibly depressed in a certain subgroup of patients with moyamoya disease. Previous studies, however, have reported that cerebral oxygen metabolism significantly improved after STA-MCA anastomosis even in some patients with occlusive carotid artery diseases. Thus, Grubb et al found that CMRO₂ significantly improved after surgery in 3 of 9 patients after bypass surgery. Samson et al also reported a parallel improvement of CBF and CMRO₂ after bypass surgery and suggested that long-standing hemodynamic failure may induce a state of metabolic depression that is still potentially reversible, although the underlying mechanism is undetermined. Furthermore, some investigators have also reported that both CMRO₂ and neurological functions significantly improved after STA-MCA anastomosis in a certain subgroup of patients. Although these findings are indeed anecdotal and are not widely accepted, the present results strongly suggest the possibility that the lesion-free brains of younger humans may have potential ability to downregulate their oxygen metabolism and to protect itself against chronic hypoxia or ischemia by reducing its metabolic demand than adult’s one. Indeed, newborn mammals are much more resistant to hypoxia than adults. Child’s brain may retain its defensive mechanism to suppress metabolic demand against ischemia/hypoxia to some degree. In other words, the brain in pediatric moyamoya disease may be in the condition of reversible brain hibernation. Experimental studies would be warranted to assess the hypothesis in near future.

Ischemic or hemorrhagic stroke often causes irreversible brain damage in moyamoya disease. According to the present results, cerebral oxygen metabolism irreversibly decreases once parenchymal lesions develop. Therefore, early diagnosis and appropriate treatment would be essential to improve cerebral oxygen metabolism especially in pediatric or younger adult patients with moyamoya disease. Previous study has proven that good intellectual outcome can be expected in pediatric patients who do not have completed stroke and surgical revascularization that widely covers the frontal lobe. Therefore, postoperative reversal of depressed oxygen metabolism may contribute to improve their intellectual prognosis.

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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Disclosures
None.

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