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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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 reduction was observed in $\approx80\%$ 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 $\approx80\%$ 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. 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
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 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 CBV. After 15-minute inhalation of 15O-2O (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, 3.7±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.5 Briefly, large fronto-temporal craniotomy extending 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. 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 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 (0.43±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></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.
CMRO₂ improvement than those without, 40.1±9.7 age was significantly lower in the hemispheres with postoperative improvement between sexes (\(P=0.1078\); \(\chi^2\) 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 (\(P=0.2007\); \(\chi^2\) test). Similarly, the side of operated hemispheres did not predict it (\(P=0.4285\); \(\chi^2\) 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 \(^{15}\)O-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 \(^{15}\)O-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 \(\approx\)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

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**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>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±0.05</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.

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

<table>
<thead>
<tr>
<th></th>
<th>Postoperative Change of CMRO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Improved (n=13)</td>
</tr>
<tr>
<td></td>
<td>Univariate Analysis</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0</td>
</tr>
<tr>
<td>Women</td>
<td>13</td>
</tr>
<tr>
<td>Age, y</td>
<td>40.1±9.7</td>
</tr>
<tr>
<td>Onset type</td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>9</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>2</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>2</td>
</tr>
<tr>
<td>Operated side</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>8</td>
</tr>
<tr>
<td>Left</td>
<td>5</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.

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**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 (\(P=0.1078\); \(\chi^2\) 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 (\(P=0.2007\); \(\chi^2\) test). Similarly, the side of operated hemispheres did not predict it (\(P=0.4285\); \(\chi^2\) test). Only patient’s age, therefore, was included in the logistic regression analysis. As shown in Table 3, the model indicated...
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.

References
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