Predictors and Clinical Features of Postoperative Hyperperfusion after Surgical Revascularization for Moyamoya Disease

A Serial Single Photon Emission CT/Positron Emission Tomography Study

Haruto Uchino, MD; Satoshi Kuroda, MD, PhD; Kenji Hirata, MD, PhD; Tohru Shiga, MD, PhD; Kiyohiro Houkin, MD, PhD; Nagara Tamaki, MD, PhD

Background and Purpose—Clinical features and pathophysiology of postoperative hyperperfusion in moyamoya disease are still unclear. This study was aimed to clarify the incidence and time course of postoperative hyperperfusion and to determine the independent predictors of postoperative hyperperfusion in moyamoya disease.

Methods—This prospective study included 41 patients who underwent surgical revascularization for moyamoya disease. Using 15O-gas positron emission tomography, hemodynamic and metabolic parameters were quantified before surgery. Using single photon emission CT, cerebral blood flow was serially measured just after surgery and on 2 and 7 days postsurgery. A multivariate logistic regression analysis was conducted to test the effect of multiple variables on postoperative hyperperfusion.

Results—Postoperative hyperperfusion was observed in 29 (50.0%) of 58 operated hemispheres. The incidence of both radiological and symptomatic hyperperfusion was significantly higher in adult patients than in pediatric ones (P=0.026 and P=0.0037, respectively). Hyperperfusion just after surgery more often led to subsequent neurological deficits (P=0.033). A multivariate analysis revealed that preoperative cerebral blood volume increase was an independent predictor of both radiological and symptomatic hyperperfusion after surgery in adult moyamoya disease (OR, 6.6 and 12.3, respectively).

Conclusions—Postoperative hyperperfusion after surgical revascularization is not rare in moyamoya disease. Adult patients with a cerebral blood volume increase may be at high risk for radiological and symptomatic hyperperfusion after surgery. Careful perioperative management would reduce surgical complications and improve long-term outcome in moyamoya disease. (Stroke. 2012;43:00-00.)

Key Words: bypass surgery ■ hyperperfusion ■ moyamoya disease ■ PET ■ SPECT

Moyamoya disease is an uncommon cerebrovascular disorder characterized by progressive occlusion of the supraclinoid internal carotid artery and its main branches, resulting in the formation of a fine vascular network (the “moyamoya” vessels) at the base of the brain.1–3 Surgical revascularization is the most successful therapy to improve cerebral hemodynamics and reduce the risk of subsequent ischemic stroke.4–7 Direct bypass procedures such as superficial temporal artery to middle cerebral artery (STA-MCA) anastomosis are quite useful to improve cerebral hemodynamics immediately after surgery.4–8 The procedures also have the advantage to reduce the incidence of ischemic complications in the perioperative period.4

However, it should be reminded that direct bypass procedures possibly carry the risk of their specific complications.9–12 Of these, postoperative hyperperfusion is recently recognized to occur after direct bypass surgery for moyamoya disease.9,10,11 Postoperative hyperperfusion may lead to transient or permanent neurological deficits. Recent studies have shown that symptomatic hyperperfusion develops in 15% to 27.5% of patients who underwent direct bypass surgery for moyamoya disease.15–17 Neurological deficits usually resolve within 7 days but may persist in some patients.10,18 Regardless of symptomatic or silent, however, the incidence of postoperative hyperperfusion is still unclear, and the risk factors also remain obscure. Furthermore, there are few studies that denote its chronological feature.

Therefore, this study was aimed to clarify its incidence and clinical features in pediatric and adult patients with moyamoya disease by serially measuring blood flow for 1 week.
after surgery. Furthermore, this study aimed to determine the predictors of postoperative hyperperfusion in moyamoya disease using $^{15}$O-gas positron emission tomography.

**Methods**

**Patients**
This prospective study included 41 patients who underwent surgical revascularization for moyamoya disease at our hospital between April 2006 and February 2011. All of them met the guideline for the diagnosis set by the Research Committee on Moyamoya Disease of the Ministry of Health, Labor and Welfare of Japan. There were 12 males and 29 females. Their mean age was 33.7 ± 19.6 years, ranging from 3 to 71 years. There were 13 children (<20 years) and 28 adults. Their clinical diagnosis included transient ischemic attack in 26 patients, ischemic stroke in 6, intracranial bleeding in 3, and asymptomatic in 6. This study was approved by an Institutional Review Board at Hokkaido University Hospital.

**Preoperative Radiological Examinations**
All patients underwent MRI, MR angiography, and cerebral angiography before surgery. MRI and MR angiography were performed using a 1.5- or 3.0-T apparatus. Disease stage was classified into 6 stages according to Suzuki’s angiographic stage. Using $^{123}$I-N-isopropyl-p-iodoamphetamine single photon emission CT (SPECT), cerebral blood flow (CBF) before and after intravenous injection of 10 mg/kg acetazolamide was quantitatively measured in all patients. Cerebrovascular reactivity (CVR) to acetazolamide was determined as follows: CVR (%) = 100 × (CBFACZ - CBFbase)/CBFbase, where CBFbase and CBFACZ represent CBF before and after intravenous injection of acetazolamide, respectively. CVR and CBF were rated as reduced when they were <27 mL/min per 100 g and <14%, respectively. In this study, the involved hemisphere was considered as the candidate for surgical revascularization when having impaired reactivity to acetazolamide.

In 33 of 41 patients, $^{15}$O-gas positron emission tomography was also performed to determine CBF, cerebral blood volume (CBV), cerebral metabolic rate of oxygen, and oxygen extraction fraction (OEF). Normal positron emission tomography values were obtained from 10 normal volunteers: CBF, 45–74 mL/min/100 g; CBV, 3.7 ± 0.7 mL/100 g; cerebral metabolic rate of oxygen, 3.3 ± 0.6 mL/min/100 g, and OEF, 0.43 ± 0.05 (mean ± SD). The values were rated as decreased when any of them were less than mean–2 SD and rated as increased when any of them were more than mean+2 SD.

**Surgical Procedures**
Totally 58 hemispheres of 41 patients underwent STA-MCA anastomosis and encephalo-duro-myo-arterio-pericranial synangiosis.

**Postoperative Management**
All patients were strictly managed to avoid hypovolemia and anemia. Systolic blood pressure was maintained between 100 and 140 mm Hg. Using $^{15}$O-gas SPECT, cerebral blood flow (CBF) was qualitatively determined 3 times within 1 week post-surgery. The first CBF measurement was performed immediately after surgery. Subsequent measurements were repeated 2 and 7 days post-surgery. MRI and MR angiography were also performed within 7 days after surgery.

**Definition of Hyperperfusion**
Postoperative hyperperfusion was defined as focal and intense increase of CBF followed by its normalization on subsequent SPECT studies (Figure 1). On qualitative SPECT studies during 1 week after surgery, the ipsilateral cerebellum was referred to as the inner normal control. Recent study has shown that CBF in the cerebral cortex ranges from 70% to 114% of that in the cerebellum in 11 normal volunteers (mean, 42.5 ± 18.2 years). In this study, therefore, CBF was rated as increased when CBF in the operated middle cerebral artery territory was >150% of the ipsilateral cerebellum. The patients were judged as developing radiological hyperperfusion when they did not develop any neurological deficits regardless of neurological hyperperfusion on postoperative SPECT. On the other hand, they were judged as developing symptomatic hyperperfusion when they developed severe headache and/or focal neurological deficits corresponding to the area where hyperperfusion occurred after surgery.

**Statistical Analysis**
All continuous data were expressed as mean ± SD. The data between 2 groups were compared by use of χ² test or unpaired t test as appropriate. A multivariate logistic regression analysis was conducted to test the effects of various clinical parameters on the occurrence of symptomatic hyperperfusion. A forward stepwise model-building procedure was performed for the parameters using P < 0.15 achieved in univariate analysis. The level of significance was set at P < 0.05.

**Results**

**Incidence of Postoperative Hyperperfusion**
Postoperative MR angiography, STA-MCA anastomosis was patent in all operated hemispheres. Repeated SPECT studies identified radiological hyperperfusion in 29 (50%) of 58 operated hemispheres. Of these, 13 hemispheres (44.8%) were symptomatic.

In pediatric cases, hyperperfusion was detected in 4 (20%) of 20 operated hemispheres. Of these, only one (5%) developed temporary neurological deficits. In adult cases, however, hyperperfusion was detected in 25 (65.7%) of 38 operated hemispheres (Figure 2). Of these, 12 hemispheres (31.5%) were symptomatic (Table 1). The incidence of both symptomatic and radiological hyperperfusion was significantly higher in adult patients than in pediatric ones (P = 0.0037 and P = 0.026, respectively).

**Clinical Features of Symptomatic Hyperperfusion**
Clinical features of 13 patients who developed symptomatic hyperperfusion after surgery widely varied (Table 2). In 8 (61.5%) of 13 patients, hyperperfusion was observed just after surgery. In 4 (30.8%) of 13 patients, hyperperfusion persisted for at least 1 week after surgery. No neurological deficits developed in other 28 patients in this study.

Neurological symptoms included motor weakness in 2 patients, motor aphasia in 7, dysarthria in 3, and seizure in 2
Early Onset of Hyperperfusion May Cause Neurological Signs

SPECT studies just after surgery identified radiological hyperperfusion in 9 adult patients. Of these, 7 patients (77.7%) developed hyperperfusion-related deficits. As shown in Table 2, the onset of their neurological deficits varied from immediate to 11 days postsurgery. However, hyperperfusion-related neurological deterioration developed in only 5 (31.3%) of 16 patients in whom radiological hyperperfusion occurred thereafter. Therefore, the adult patients with hyperperfusion just after surgery are at significantly higher risk for subsequent neurological deterioration ($P=0.033$, $\chi^2$ test). There was no significant difference in clinical features between the patients with immediate hyperperfusion and those with delayed hyperperfusion.

Independent Predictors of Hyperperfusion in Adults

The effects of various factors on postoperative hyperperfusion in adult patients are shown in Table 3. The logistic regression analysis indicated CBV increase as the independent predictor of postoperative hyperperfusion in adult moyamoya disease (OR, 6.6; 95% CI, 1.1–39.0; $P=0.0349$).

Likewise, the effects of various factors on postoperative symptomatic hyperperfusion are shown in Table 4. The logistic regression analysis also revealed that CBV increase could predict symptomatic hyperperfusion in adult moyamoya disease (OR, 12.3; 95% CI, 1.1–131.6; $P=0.0368$).

Discussion

This study demonstrates that radiological hyperperfusion occurs in 50% of patients with moyamoya disease after surgery. The incidence of both radiological and symptomatic hyperperfusion is much higher in adult patients than in pediatric ones. Majority of hyperperfusion-related symptoms disappeared within 24 hours but persisted for 2 to 14 days in approximately 25% of patients. Serial SPECT studies demonstrate that hyperperfusion just after surgery may easily lead to subsequent neurological deficits. Finally, multivariate analysis reveals that CBV increase may be an independent predictor of both radiological and symptomatic hyperperfusion after surgery in adult moyamoya disease.

Historically, postoperative hyperperfusion is known as one of the serious complications after carotid endarterectomy (CEA), leading to temporary or permanent neurological deteriorations. Of these, intracerebral hemorrhage is often fatal.26,27 Cognitive impairment is also accepted as one of prolonged complications.28 Excessive proliferation and edema of endothelial and smooth cells are found in the arteriolar walls of patients who develop cerebral edema and hemorrhage after CEA.29 Previous studies strongly suggest that long-lasting and dense cerebral ischemia may play a key role to induce postoperative hyperperfusion. Thus, critical reduction of cerebral perfusion pressure may induce a persistent maximal dilatation of the arterioles, leading to postoperative hyperperfusion in response to a rapid recovery of cerebral perfusion pressure after CEA. Experimental studies show medial hypertrophy, loss of contractile strength,
and decreased resistance in the arterioles of chronically hypoperfused vascular beds.30,31 Recent studies reveal that impaired acetazolamide reactivity can highly predict the occurrence of post-CEA hyperperfusion.32–34 A similar phenomenon can be observed after STA-MCA anastomosis for patients with severely disturbed cerebral hemodynamics.35,36 Interestingly, the reduction of both CBF and CVR can also anticipate the occurrence of hyperperfusion after STA-MCA anastomosis.32,37

However, clinical significance of postoperative hyperperfusion has not been recognized in moyamoya disease until recently. Thus, Uno et al11 reported an adult case that developed symptomatic hyperperfusion after surgery for moyamoya disease. Subsequently, several studies have evaluated its clinical features in moyamoya disease. Thus, the incidence of symptomatic hyperperfusion ranges from 15% to 28% in adult patients with moyamoya disease but was very low (5.9%) in pediatric patients, correlating very well with the present results.14–17,38 Therefore, adult patients with moyamoya disease are at high risk for symptomatic hyperperfusion after surgery. More importantly, this study first demonstrates that the incidence of radiological hyperperfusion is much higher, 20% and 67.5% in pediatric and adult patients, respectively. Therefore, the potential risk for postoperative hyperperfusion syndrome is much higher than considered before. In addition, this study reveals that 7 of 13 patients develop motor aphasia due to postoperative hyperperfusion, although previous reports have not pointed out this fact. There are several explanations for this finding. First,

<p>| Table 2. Clinical Data in Patients With Symptomatic Hyperperfusion After Surgery |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, y/Sex</th>
<th>Clinical Diagnosis</th>
<th>Side</th>
<th>Hyperperfusion on SPECT</th>
<th>Symptoms</th>
<th>Onset and Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34/F</td>
<td>TIA</td>
<td>L</td>
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<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>52/F</td>
<td>TIA</td>
<td>L</td>
<td>No</td>
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<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>41/F</td>
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<td>R</td>
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<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>58/F</td>
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<td>No</td>
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<td>No</td>
</tr>
<tr>
<td>5</td>
<td>35 M</td>
<td>TIA</td>
<td>L</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td>6</td>
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<td>L</td>
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<td>Yes</td>
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<tr>
<td>7</td>
<td>43/M</td>
<td>Ischemic stroke</td>
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<td>No</td>
</tr>
<tr>
<td>8</td>
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<td>No</td>
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<td>Yes</td>
</tr>
<tr>
<td>9</td>
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<tr>
<td>10</td>
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<tr>
<td>11</td>
<td>16/F</td>
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<td>R</td>
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<tr>
<td>12</td>
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<td>No</td>
</tr>
<tr>
<td>13</td>
<td>55/M</td>
<td>Asymptomatic</td>
<td>L</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

SPECT indicates single photon emission CT; POD, postoperative day; F, female; M, male; L, left; R, right.

| Table 3. Predictors for Postoperative Hyperperfusion in Adult Moyamoya Disease |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Hyperperfusion | Univariate Analysis | Multivariate Analysis | OR (95% CI) |
| No. | Yes | No | P | OR | P |
| 25 | 13 | | | | |
| Age, y | 44.9±11.0 | 48.7±10.9 | 0.1586 | | |
| Male sex | 7 | 3 | 0.5323 | | |
| Clinical diagnosis (hemisphere, no.) | | | 0.6397 | | |
| TIA | 14 | 5 | | | |
| Ischemic stroke | 2 | 3 | | | |
| Intracranial bleeding | 3 | 1 | | | |
| Asymptomatic | 6 | 4 | | | |
| Suzuki’s stage (≥4) | 19 | 8 | 0.1244 | 0.1244 | |
| PET parameters | | | | | |
| CBF decrease | 22 | 12 | 0.5764 | | |
| CBV increase | 21 | 7 | 0.0165 | 0.0349 | 6.6 (1.1–39.0) |
| CMRO2 decrease | 12 | 10 | 0.4949 | | |
| OEF elevation | 16 | 9 | 0.5200 | | |
| CVR decrease | 20 | 10 | 0.9999 | | |

TIA indicates transient ischemic attack; PET, positron emission tomography; CBF, cerebral blood flow; CBV, cerebral blood volume; CMRO2, cerebral metabolic rate of oxygen; OEF, oxygen extraction fraction; CVR, cerebrovascular reactivity.
cerebral hemodynamics are severely impaired in the frontal lobe in the majority of patients with moyamoya disease.\textsuperscript{39} Second, language function may be exclusively sensitive to hyperperfusion relative to other area of the brain.

Serial SPECT studies reveal that adult patients with radiological hyperperfusion just after surgery more often develop neurological signs than those with delayed onset. This is the first study that systematically analyzes chronological course of hyperperfusion after surgery in moyamoya disease. However, all neurological symptoms are transient and resolve within several days by strictly controlling blood pressure within normal limits. Therefore, serial SPECT studies are quite useful to predict symptomatic hyperperfusion and avoid permanent neurological sequelae.

In this study, multivariate analysis is used to explore the predictors of postoperative hyperperfusion in adult patients. Pediatric patients were not included because of their low incidence. As the results show, clinical diagnosis at onset was not related to the occurrence of postoperative hyperperfusion. Previously, Ohue et al\textsuperscript{14} stated that symptomatic hyperperfusion more often occurs in ischemic-onset patients than in hemorrhagic-onset patients. In contrast, Fujimura et al\textsuperscript{17} concluded that adult-onset and hemorrhagic-onset patients are at higher risk for symptomatic hyperperfusion. Therefore, there is a distinct discrepancy among these studies. Larger studies would be necessary to decide whether the onset type is closely related to its occurrence.

As aforementioned, CVR is accepted as a useful parameter to predict the occurrence of post-CEA hyperperfusion. However, the hemispheres with reduced CVR per se are the candidates for surgical revascularization in moyamoya disease.\textsuperscript{8} This study clearly shows that preoperative CBV increase can be an independent predictor of both radiological and symptomatic hyperperfusion after surgery in adult moyamoya patients (OR, 6.6 and 12.3, respectively). Theoretically, an increased CBV strongly suggests an autoregulatory vasodilatation in response to the cerebral perfusion pressure reduction.\textsuperscript{48} On the other hand, OEF elevation cannot predict the occurrence of both radiological and symptomatic hyperperfusion after bypass surgery. Derdeyn et al\textsuperscript{41} precisely evaluated clinical significance of CBV increase in hemodynamic impairment due to occlusive cerebrovascular disease. They found that an OEF increase in the territory of an occluded carotid artery often occurs in the absence of a CBV elevation and that patients with both increased OEF and increased CBV are at much higher risk for subsequent stroke than those with increased OEF and normal CBV. Based on these observations, they have concluded that increased CBV may indicate pronounced vasodilatation due to exhausted autoregulatory vasodilatation in patients with chronic carotid occlusion and increased OEF.\textsuperscript{43} Recently, Hokari et al\textsuperscript{21} also reported the importance of CBV measurement to predict an increased OEF in patients with both decreased CBF and decreased CVR due to occlusive carotid artery disease using SPECT. Furthermore, Fukuda et al\textsuperscript{42} demonstrated that an increased CBV was the only significant predictor of post-CEA hyperperfusion. Therefore, preoperative measurement of CBV may be useful to predict the occurrence of postoperative hyperperfusion in adult moyamoya disease.

As aforementioned, pediatric patients with moyamoya disease were not included in multivariate analysis. As previously reported, however, CBV is known to be often elevated in most of them.\textsuperscript{33,44} Indeed, all pediatric patients had a CBV increase on positron emission tomography scans, although most of them did not show hyperperfusion after surgery. This finding strongly suggests pathophysiological differences in a CBV increase in response to cerebral perfusion pressure reduction between pediatric and adult patients with moyamoya dis-
ease. Thus, autoregulatory vasodilatation may quickly recover after STA-MCA anastomosis starts to supply blood flow in pediatric patients. However, such vasodilatation may require longer time to recover in adult patients probably because of long-lasting cerebral ischemia. The difference in the caliber of STA may be another explanation for the discrepancy between them. Thus, the caliber of STA largely determines blood flow just after STA-MCA anastomosis.45

In conclusion, radiological hyperperfusion occurs in 50% of patients with moyamoya disease after surgery, being higher than considered before. Adult patients are at much higher risk for postoperative hyperperfusion than pediatric patients. Preoperative CBV increase may be an independent predictor of both radiological and symptomatic hyperperfusion after surgery in adult patients.

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Disclosures
None.

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