De Novo Ivy Sign Indicates Postoperative Hyperperfusion in Moyamoya Disease

Nobutaka Horie, MD, PhD; Minoru Morikawa, MD, PhD; Youichi Morofuji, MD, PhD; Takeshi Hiu, MD, PhD; Tsuyoshi Izumo, MD, PhD; Kentaro Hayashi, MD, PhD; Izumi Nagata, MD, PhD

Background and Purpose—The ivy sign on fluid-attenuated inversion recovery MRI is a specific finding in moyamoya disease (MMD). This sign indicates decreased cerebral perfusion, dilated pial vasculature, and slow leptomeningeal collateral flow. This study aimed to clarify the characteristics of perioperative changes in the ivy sign in relation to cerebral hyperperfusion, which frequently occurs in MMD of unknown pathogenesis.

Methods—This prospective study included patients with MMD who underwent superior temporal artery–middle cerebral artery single bypass. Fluid-attenuated inversion recovery MRI was performed to evaluate the appearance of the ivy sign in the ipsilateral hemisphere preoperatively and on postoperative days 2 and 30. The ivy sign was assessed in combination with perioperative symptoms and cerebral hemodynamics using single-photon emission computed tomography.

Results—Of 42 consecutive patients (55 sides) who underwent bypass surgery, 32 (58.2%) showed an increase in the ivy sign (de novo ivy sign) on postoperative day 2; this had disappeared by day 30. Interestingly, these 32 patients had a significantly higher incidence of hyperperfusion on single-photon emission computed tomography and hyperperfusion syndrome, and there was no correlation between the de novo ivy sign and a preoperative ivy sign or the preoperative cerebral hemodynamics. In multivariate analysis, a de novo ivy sign was significantly correlated with postoperative hyperperfusion.

Conclusions—In MMD, a de novo ivy sign could indicate postoperative hyperperfusion after bypass, which is not always correlated with preoperative hemodynamic impairment. Additional factors other than preoperative cerebral hemodynamics might be involved in postoperative hyperperfusion in MMD. (Stroke. 2014;45:00-00.)

Key Word: moyamoya disease

Moyamoya disease (MMD) is an uncommon cerebrovascular disease characterized by progressive stenosis of the terminal portion of the bilateral internal carotid arteries. This stenosis leads to the compensatory formation of an abnormal network of perforating blood vessels, termed moyamoya vessels, that provide collateral circulation. For patients with symptomatic MMD and asymptomatic MMD with impaired hemodynamics, revascularization surgery involves direct bypass (superior temporal artery [STA]→middle cerebral artery [MCA] anastomosis) and, in patients in whom the STA is not developed, indirect bypass (encephalomyosynangiosis or encephaloduroarteriosynangiosis).

Hyperperfusion after STA–MCA bypass has been a recent focus in MMD. Hyperperfusion occurs more frequently in adult MMD than in pediatric MMD or atherosclerosis of unknown pathogenesis. Therefore, prediction or immediate detection of postoperative hyperperfusion is mandatory to avoid symptomatic hyperperfusion and hemorrhagic complications in MMD. The ivy sign is an MMD-specific finding on fluid-attenuated inversion recovery (FLAIR) MRI and is reportedly correlated with poor cerebrovascular reserve (CVR). Impaired CVR is a risk factor for postoperative hyperperfusion after carotid revascularization; therefore, the ivy sign could be related to postoperative hyperperfusion in MMD as well, but this has not been clarified.

This study aimed to clarify the characteristics of the perioperative ivy sign on FLAIR images and determine whether the presence of a perioperative ivy sign correlates with postoperative hyperperfusion in MMD.

Methods

Beginning January 2010, consecutive patients with MMD who underwent STA–MCA anastomosis were prospectively analyzed. The indication for surgical revascularization was symptomatic or hemodynamic compromise on single-photon emission computed tomography. All patients were diagnosed with MMD according to angiographic
findings (Methods in the online-only Data Supplement). STA–MCA single anastomosis with encephalomyosynangiosis was performed by the same operator (I.N.) under general anesthesia. MRI, including FLAIR imaging and single-photon emission computed tomography evaluation, was performed within 2 weeks before and at 2 and 30 days after surgery.

The diagnostic criteria for symptomatic hyperperfusion are described in the Methods in the online-only Data Supplement. When hyperperfusion developed, the patients were treated with strict blood pressure control using calcium channel antagonists, free radical scavengers, and sedative agents. Blood pressure–dependent aggravation and amelioration of clinical symptoms confirmed the diagnosis of symptomatic hyperperfusion.

A perioperative ivy sign on FLAIR images was defined as a linear high-signal intensity lesion along the cortical sulci or brain surface in the cerebral hemisphere. The cortico-subcortical region of the cerebral hemisphere at 2 levels (level of basal ganglia and level of lateral ventricle body) was divided into the following 2 regions modified from a previous report (Figure 1A).1 and the degree of the ivy sign (ivy sign score, 0–2) was evaluated in the anterior and posterior halves of the MCA region (ant-MCA and post-MCA, respectively) separately (total ivy sign score 0–8) at 3 time points (preoperatively and days 2 and 30 postoperatively). Details of the imaging protocol/analysis and statistical analysis procedures are described in the Methods in the online-only Data Supplement.

Results

Patient Characteristics

The characteristics of the study population are listed in Table I in the online-only Data Supplement. Forty-two consecutive patients (55 sides) who underwent bypass surgery were analyzed. Among the 55 sides, 32 (58.2%) showed an ivy sign increase (de novo ivy sign) at postoperative day 2, which had improved at day 30. There were no significant differences in clinical presentations, preoperative cerebral blood flow (CBF) and CVR in MCA, or preoperative ivy sign scores between patients with and without de novo ivy signs. However, patients showing de novo ivy signs developed postoperative hyperperfusion (P=0.002) and symptomatic hyperperfusion (P=0.017) significantly more often than did patients without de novo ivy signs (Table I in the online-only Data Supplement; Figure 1B).

No patients in this study presented perioperative focal seizures regardless of the presence of hyperperfusion. Interestingly, de novo ivy signs showed a weak correlation with preoperative CBF or CVR in MCA, indicating that the preoperative hemodynamic status did not always affect the de novo ivy sign (Table II and Figure I in the online-only Data Supplement). Nevertheless, the de novo ivy sign preferably occurred in the territory of anastomosis (Figure II in the online-only Data Supplement), which confirms that hemodynamic changes after bypass surgery contributed to the de novo ivy sign. A representative case is shown in Figure 2.

Finally, we assessed factors related to postoperative hyperperfusion after bypass surgery in MMD. Multivariate logistic regression analysis showed that a de novo ivy sign was an independent factor related to postoperative hyperperfusion (odds ratio, 7.75; 95% confidence interval, 1.08–55.75; P=0.04; Table).

Discussion

Recently, leptomeningeal high-signal intensity on unenhanced FLAIR imaging was reported as an ivy sign and is assumed to indicate decreased cerebral perfusion, dilated pial vasculature, and slow flow of developed leptomeningeal collaterals. The ivy sign is an MMD-specific finding, and its specific hemodynamic impairment might involve the cortical surface of the brain in MMD. Interestingly, increasing evidence has suggested recently that symptomatic hyperperfusion may occur after revascularization surgery in 15.0% to 31.5% of patients with MMD, which is different from that occurring after revascularization surgery for atherosclerotic disease despite performance of the same STA–MCA bypass surgery. This hyperperfusion leads to transient neurological deterioration, seizures, or delayed intracerebral hemorrhage; therefore, early detection and careful management of hyperperfusion is mandatory after bypass for MMD. However, the mechanism of postoperative hyperperfusion in MMD remains undetermined, and no evidence has been established to explain the difference in the frequency of postoperative hyperperfusion between MMD and atherosclerotic disease. In this study, we assessed the relationship between an ivy sign increase (de novo ivy sign) and postoperative hyperperfusion. We have provided evidence that a de novo ivy sign indicates hyperperfusion, which is not always related to preoperative hemodynamic factors. Recent studies have also reported that preoperative CBF and CVR do not predict postoperative hyperperfusion in MMD, which strongly supports our results.

Therefore, perioperative hemodynamic changes in...
MMD could be specific and different from those in atherosclerotic disease.

The pathological mechanism of the de novo ivy sign is uncertain but is MMD specific and cannot be seen in patients with hyperperfusion after carotid revascularization (Table III in the online-only Data Supplement). We speculate that the sign could indicate a focal increase in CBF in pial vessels in MMD because bypass flow through the anastomosed STA is reportedly larger in MMD than in atherosclerosis owing to a larger gradient pressure. Therefore, this differs from the preoperative ivy sign showing chronically engorged pial vasculature because of ischemia. Our results also showed that the postoperative de novo ivy sign diminished in the follow-up, indicating that the de novo ivy sign is a transient hemodynamic change after bypass surgery. Therefore, one should note that bypass surgery causes dynamic changes in postoperative cortical hemodynamics in MMD, and careful postoperative monitoring and management is mandatory for patients with MMD.

In conclusion, the postoperative de novo ivy sign could be a marker of hyperperfusion after bypass surgery in MMD. Therefore, FLAIR imaging might be helpful to detect hyperperfusion without assessment by single-photon emission computed tomography or positron emission tomography, which are not always immediately available.

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### Disclosures

None.
References
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Supplemental Materials

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Supplemental Methods

Diagnostic criteria for Moyamoya Disease (MMD) and symptomatic hyperperfusion (HP)

All patients were diagnosed with MMD according to angiographic findings¹: (1) stenosis or occlusion at the terminal portion of the internal carotid artery or proximal areas of the anterior cerebral artery and middle cerebral artery (MCA) and (2) abnormal vascular networks in the arterial territories near the occlusive or stenotic lesions as detected by MR angiography and intra-arterial angiography.

The diagnostic criteria for symptomatic HP were (1) the presence of neurologic signs, including focal neurologic deficits and/or severe headache; (2) confirmed patency of the bypass by MR angiography and the absence of any ischemic changes by diffusion-weighted imaging; (3) marked postoperative increase in cerebral blood flow (CBF) in the ipsilateral hemisphere exceeding that in the contralateral hemisphere; and (4) the absence of other pathologies such as compression of the brain surface by swelling of the temporal muscle graft, ischemic attack, or seizure.²,³

Imaging protocol and analysis

Magnetic resonance imaging was conducted on a 3.0 Tesla system (Signa HDx; GE Healthcare, Milwaukee, WI, USA) using an eight-channel head coil. The sequence protocol included transversal
fluid-attenuated inversion recovery with TR = 8000 ms, TE = 110 ms, TI = 2250 ms, NEX = 1, slice thickness = 5 mm, interslice gap = 1 mm, FOV = 220 mm, and image matrix = 384 × 192.

Cerebral blood flow was evaluated with $^{123}$I-iodoamphetamine single-photon emission computed tomography (SPECT) with or without acetazolamide administration for assessment of cerebrovascular reserve. Cerebrovascular reserve was calculated using the following formula:

$\frac{(\text{acetazolamide challenging SPECT count} - \text{resting SPECT count})}{\text{resting SPECT count}} \times 100\%$.

A perioperative ivy sign on FLAIR images was defined as a linear high-signal-intensity lesion along the cortical sulci or brain surface in the cerebral hemisphere.$^4$ We confirmed that this was not due to postoperative cortical surface hemorrhage on other MR sequences. The cortico-subcortical region of the cerebral hemisphere at two levels (level of basal ganglia and level of lateral ventricle body) was divided into the following two regions modified from a previous report (Figure 1A).$^4$ The anterior and posterior halves of the MCA region (ant-MCA and post-MCA, respectively) were separated by the central sulcus. The temporal lobe belonged to the post-MCA. Each region was separately evaluated. The degree of the ivy sign (ivy sign score) in each region was classified into one of three grades (0–2), where grade 0 indicated an absence of the ivy sign, grade 1 indicated that the ivy sign was seen on less than half of the cortical surface in each region, and grade 2 indicated that the ivy sign was seen on more than half of the cortical surface.$^5$ The score was evaluated at three time points (preoperatively and days 2 and 30 postoperatively).

A neurosurgeon and neuroradiologist (N.H. and M.M., >15 years of experience) reviewed ivy signs independently without knowledge of the clinical information or SPECT findings. When the initial interpretation differed between the two raters, the final interpretation was reached by consensus. Cohen’s kappa was determined by the ivy sign score by each rater (N.H. and M.M.) and by one rater (N.H.) at an interval of >7 days. Cohen’s kappa was evaluated with established grading of agreement: 0.00 (no agreement), 0.00–0.20 (poor), 0.21–0.40 (fair), 0.41–0.60 (moderate),
0.61–0.80 (substantial), and 0.81–1.00 (nearly perfect). Overall, interobserver and intraobserver reproducibility were substantial to nearly perfect for ivy sign score grades preoperatively (kappa coefficient = 0.69 and 0.80, respectively) and 2 days postoperatively (kappa coefficient = 0.62 and 0.82, respectively).

**Statistical analysis**

Data are presented as mean ± standard error of the mean. Statistical analysis was performed with GraphPad Instat, version 3.05 (GraphPad Software, Inc., La Jolla, CA, USA) and SPSS, version 15.0 (SPSS Japan, Inc., Tokyo, Japan). The independent-samples t-test and Fisher’s exact test were used to compare continuous and categorical characteristics, respectively. Multivariate logistic regression analysis was performed to identify factors associated with postoperative HP. Differences were defined as significant at a probability level of <0.05.
### Supplemental Table I. Characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Ivy sign increase (+)</th>
<th>Ivy sign increase (-)</th>
<th><em>P</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n=32</strong></td>
<td><strong>n=23</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ± SEM</td>
<td>28.3 ± 3.1</td>
<td>22.9 ± 3.5</td>
<td>0.258</td>
</tr>
<tr>
<td>Ischemic Presentation (%)</td>
<td>24 (75.0)</td>
<td>12 (52.2)</td>
<td>0.094</td>
</tr>
<tr>
<td>Hemorrhagic Presentation (%)</td>
<td>3 (9.4)</td>
<td>2 (8.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Preoperative CBF ± SEM (ml/100g/min)</td>
<td>33.8 ± 2.2</td>
<td>33.1 ± 1.7</td>
<td>0.829</td>
</tr>
<tr>
<td>Preoperative CVR ± SEM (%)</td>
<td>5.9 ± 5.0</td>
<td>14.2 ± 6.6</td>
<td>0.321</td>
</tr>
<tr>
<td>Preoperative Ivy Sign Score</td>
<td>1.0 ± 0.2</td>
<td>1.0 ± 0.3</td>
<td>0.931</td>
</tr>
<tr>
<td>Hyperperfusion on SPECT (%)</td>
<td>14 (43.8)</td>
<td>1 (4.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Symptomatic Hyperperfusion (%)</td>
<td>10 (31.2)</td>
<td>1 (4.3)</td>
<td>0.017</td>
</tr>
</tbody>
</table>

SEM: standard error of the mean, CBF: cerebral blood flow, CVR: cerebrovascular reserve, SPECT: single-photon emission computed tomography

### Supplemental Table II: Preoperative CBF and CVR in the selected area showing *de novo* ivy sign in 32 patients

<table>
<thead>
<tr>
<th></th>
<th>The area of <em>de novo</em> ivy sign</th>
<th>Outside the area of <em>de novo</em> ivy sign</th>
<th><em>P</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative CBF ± SEM (ml/100g/min)</td>
<td>33.7 ± 1.6</td>
<td>32.3 ± 2.8</td>
<td>0.67</td>
</tr>
<tr>
<td>Preoperative CVR ± SEM (%)</td>
<td>10.4 ± 4.2</td>
<td>5.5 ± 5.4</td>
<td>0.49</td>
</tr>
</tbody>
</table>

SEM: standard error of the mean, CBF: cerebral blood flow, CVR: cerebrovascular reserve
<table>
<thead>
<tr>
<th></th>
<th>Hyperperfusion (+)</th>
<th>Hyperperfusion (-)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ± SEM</td>
<td>74.6 ± 1.0</td>
<td>73.0 ± 1.6</td>
<td>n.s</td>
</tr>
<tr>
<td>CEA : CAS</td>
<td>6 : 7</td>
<td>116 : 81</td>
<td>n.s</td>
</tr>
<tr>
<td>Preoperative CBF ± SEM (ml/100g/min)</td>
<td>28.6 ± 2.1</td>
<td>33.0 ± 1.3</td>
<td>0.04</td>
</tr>
<tr>
<td>Preoperative CVR ± SEM (%)</td>
<td>3.1 ± 5.2</td>
<td>16.4 ± 4.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Preoperative ivy sign score</td>
<td>0</td>
<td>0</td>
<td>n.s</td>
</tr>
<tr>
<td>Postoperative ivy sign score</td>
<td>0</td>
<td>0</td>
<td>n.s</td>
</tr>
<tr>
<td>Hyperperfusion Syndrome (%)</td>
<td>2 (15.4)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

SEM: standard error of the mean, CEA: carotid endarterectomy, CAS: carotid arterial stenting, CBF: cerebral blood flow, CVR: cerebrovascular reserve, n=number
Supplemental Figure I

The graphs show that the ivy score increase (de novo ivy sign) had a very weak correlation with preoperative cerebral blood flow (CBF: $r=0.17$, $P=0.25$) or cerebrovascular reserve (CVR: $r=0.06$, $P=0.71$) in the middle cerebral artery.

Correlations were analyzed by Pearson’s rank correlation test, which measures the linear relationship between two variables, because we expected a linear relationship. Very weak, weak, moderate, strong, and very strong correlations were defined as 0.00–0.19, 0.20–0.39, 0.40–0.59, 0.60–0.79, and 0.80–1.00, respectively.

Supplemental Figure II

The graph shows the relationship between the anastomosis site (suprasylvian or infrasylvian) and location of the de novo ivy sign in 32 patients. Suprasylvian anastomosis was performed in 27 patients, and infrasylvian anastomosis was performed in 5 patients. Interestingly, 20 patients (62.5%; 17 suprasylvian and 3 infrasylvian anastomoses) showed the de novo ivy sign in the same territory, and 11 patients (34.4%; 9 suprasylvian and 2 infrasylvian anastomoses) showed the de novo ivy sign in both territories. N=number.
Supplemental References


