Correlation between reduction in microvascular transit time after superficial temporal artery–middle cerebral artery bypass surgery for moyamoya disease and the development of postoperative hyperperfusion syndrome

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OBJECTIVE Hyperperfusion syndrome (HPS) is a notable complication that causes various neurological symptoms after superficial temporal artery (STA)–middle cerebral artery (MCA) bypass surgery for moyamoya disease (MMD). The authors used intraoperative indocyanine green (ICG) videoangiography to measure the change in microvascular transit time (MVTT) after bypass surgery. An analysis was then conducted to identify the correlation between change in MVTT and presence of postoperative HPS.

METHODS This study included 105 hemispheres of 81 patients with MMD who underwent STA-MCA single bypass surgery between January 2010 and January 2015. Intraoperative ICG videoangiography was performed before and after bypass surgery. The MVTT was calculated from the ICG time intensity curve recorded in the pial arterioles and venules. Multivariate logistic regression analysis was conducted to test the effect of multiple variables, including the change in MVTT after bypass surgery, on postoperative HPS.

RESULTS Postoperative HPS developed in 28 (26.7%) of the 105 hemispheres operated on. MVTT was reduced significantly after bypass surgery (prebypass 5.34 ± 2.00 sec vs postbypass 4.12 ± 1.60 sec; p < 0.001). The difference between prebypass and postbypass MVTT values, defined as ΔMVTT, was significantly greater in the HPS group than in the non-HPS group (2.55 ± 2.66 sec vs 0.75 ± 1.78 sec; p < 0.001). Receiver operating characteristic curve analysis revealed that the optimal cutoff point of ΔMVTT was 2.6 seconds (sensitivity 46.4% and specificity 85.7% as a predictor of postoperative HPS). A ΔMVTT > 2.6 seconds was an independent predictor of HPS in multivariate analysis (hazard ratio 4.88, 95% CI 1.76–13.57; p = 0.002).

CONCLUSIONS MVTT in patients with MMD was reduced significantly after bypass surgery. Patients with a ΔMVTT > 2.6 seconds tended to develop postoperative HPS. Because ΔMVTT can be easily measured during surgery, it is a useful diagnostic tool for identifying patients at high risk for HPS after STA-MCA bypass surgery for MMD.

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KEY WORDS moyamoya disease; indocyanine green videoangiography; microvascular transit time; hyperperfusion syndrome; superficial temporal artery–middle cerebral artery bypass; vascular disorders

MOYAMOYA disease (MMD) was first reported as a chronic, occlusive cerebrovascular disease of unknown etiology, characterized by bilateral steno-occlusive changes at the terminal portion of the internal carotid artery, leading to severe hemodynamic impairment in parallel with the development of collateral vessels (moyamoya vessels) at the base of the brain.23 Direct revascularization by means of superficial temporal artery (STA)–middle cerebral artery (MCA) bypass surgery is an established treatment for brain ischemia17 and preven-
tion of rebleeding in this disease.19 Despite the long-term efficacy of surgical revascularization,10,18 postoperative hyperperfusion syndrome (HPS) has drawn attention for its contribution to transient neurological deterioration14 or delayed intracerebral hemorrhage (ICH)9,20 in the perioperative period after STA-MCA bypass surgery in patients with MMD. The frequency of HPS after direct revascularization surgery for MMD has been reported to be 16.7%–38.2%, which is significantly higher than that for atherosclerotic occlusive cerebrovascular disease.8,12 To avoid the risk of a devastating ICH, the blood pressure of patients with HPS should be strictly managed.6 However, the pathophysiological mechanism and risk factors for HPS have not been elucidated.

Microscope-integrated near-infrared indocyanine green videoangiography (ICG-VA) combined with hemodynamic parameter analysis with FLOW 800 software (Carl Zeiss, Co.) has been used for intraoperative monitoring of regional cerebral blood flow (CBF) in cerebrovascular disease, including MMD.1,26 Analyzing ICG-VA findings, Czabanka et al. reported prolonged microvascular transit time (MVTT) in patients with MMD. They assumed that this represented an MMD-specific compensation mechanism for impaired CBF.3,4 However, it has not been investigated whether the MVTT changes after bypass surgery in patients with MMD and, if so, whether any change in MVTT is correlated with postoperative HPS. In the present study, we used ICG-VA and FLOW 800 software to measure MVTT before and after bypass surgery in patients with MMD who had undergone STA-MCA bypass surgery, and we examined the correlation between change in MVTT and postoperative HPS.

Methods

Patient Demographic Data and Clinical Characteristics

One hundred five hemispheres (47 right sides and 58 left sides) of 81 consecutive patients with MMD (28 males and 53 females), who had undergone STA-MCA bypass surgery between January 2010 and January 2015, were prospectively analyzed in the study. The mean patient age was 29.8 ± 18.7 years, ranging from 3 to 68 years. They included 26 children (< 16 years old) and 55 adults (≥ 16 years old). Sixty-nine patients presented with transient headache due to hemorrhagic changes; 2) apparent visual cal signs, including focal neurological deficit and severe of the anastomosis responsible for the apparent neurological deficit and severe headache due to hemorrhagic changes; 2) apparent visualization of STA-MCA bypass surgery with MRA and the absence of any ischemic changes with DWI; and 3) the absence of other pathologies, such as compression of the brain surface by the temporal muscle inserted for indirect pial synangiosis, ischemic attack, and seizure.

Surgeon Procedures and MVTT Measurement

All patients underwent STA-MCA single anastomosis while under general anesthesia. Encephalo-myo-synangiosis (EMS) was added to the direct revascularization in pediatric patients. ICG-VA was performed with the OPMI Pentero using integrated ICG technology (Carl Zeiss, Co.). Patients received an ICG (Daichi Sankyo, Co.) injection at a dose of 0.2 mg/kg as a bolus each time. Blood pressure, PaO₂ (partial pressure of oxygen in arterial blood), and PaCO₂ (partial pressure of carbon dioxide in arterial blood) were monitored during surgery. ICG images were analyzed with FLOW 800 software, an analytical color visualization tool for evaluating the fluorescence video sequences obtained by ICG-VA. From the time-transit curve of ICG intensities visualized with the FLOW 800 software, MVTT was derived as the time required for blood to flow from the arterial phase to the venous phase (Fig. 1A). One region of interest (ROI) for the arterial phase was identified on the recipient M₄ artery, just distal to the anastomosis point, and 1 ROI for the venous phase was identified on the superficial middle cerebral vein or its tributary vein, adjacent to the anastomosis site. We typically select an M₄ branch exhibiting antegrad e direction of flow as the recipient artery. Therefore, all arterial ROIs in the present study exhibited the normal antegrad e direction of flow. Analysis of the ICG time intensity curve was performed on the same ROIs before and after bypass surgery (Fig. 1B). Because the peak intensity lasts for several seconds, determining an accurate intensity peak is sometimes difficult; therefore, we used the “time to half-value of peak” (T½ peak) instead of the “time to peak” and calculated MVTT as venous T½ peak – arterial T½ peak (Fig. 1C). The difference between MVTTs before and after bypass surgery was defined as ΔMVTT.

Postoperative Management

After surgery, the patients were monitored with strict control of blood pressure. The target range for systolic blood pressure was 100–140 mm Hg. MRI, including diffusion-weighted imaging (DWI), FLAIR imaging, and MR angiography (MRA), was performed the day after surgery. Within 3 days, CBF was quantitatively determined by N-isopropyl-p-[123I]-iodoamphetamine SPECT (123I-IMP SPECT).

Definition of HPS

The diagnostic criteria for HPS are the same as those used by Fujimura et al.7 All of the following were included: 1) significant postoperative increase in CBF at the site of the anastomosis responsible for the apparent neurological signs, including focal neurological deficit and severe headache due to hemorrhagic changes; 2) apparent visualization of STA-MCA bypass surgery with MRA and the absence of any ischemic changes with DWI; and 3) the absence of other pathologies, such as compression of the brain surface by the temporal muscle inserted for indirect pial synangiosis, ischemic attack, and seizure.

Statistical Analysis

Continuous, normally distributed variables are expressed as the mean ± SD. Paired Student t-tests were used for comparisons before and after bypass surgery, and unpaired Student t-tests were used for the comparison between the HPS and non-HPS groups. Categorical variables were compared with chi-square tests. ΔMVTT cut-off values were determined on the basis of receiver operating characteristic (ROC) curve analysis using the Youden index. Multivariate analysis with the Cox proportional-hazards model tested the effect of multiple variables on the occurrence of HPS. Age, sex, hemisphere subject to surgery, and onset type were considered covariates. The
data were analyzed initially with a univariate model to determine which risk factors held significant associations (p < 0.05) with HPS. Cox regression analysis was then performed with only those covariates that significantly predicted HPS in the univariate analysis. Analyses were conducted with SPSS version 20.0 (SPSS Japan, Inc.). A p value < 0.05 was considered statistically significant.

Results
Physiological Parameters
No statistically significant differences between prebypass and postbypass status were found regarding systolic and diastolic blood pressures, PaO₂, and PaCO₂ (Table 1). Blood pressure, PaO₂, and PaCO₂ all remained within normal ranges during surgery.

Postoperative Bypass Patency and HPS
Intraoperative ICG-VA and postoperative MRA confirmed the patency of bypass in all patients. Postoperative HPS occurred in 28 (26.7%) operations. Of the 28 cases of HPS, 4 (14.3%) were in children (< 16 years old), 6 (21.4%) were in males, 9 (32.1%) were right side, and 2 (7.1%) were hemorrhage onset. The mean age of patients in the HPS group was 36.4 ± 16.6 years and that of patients in the non-HPS group was 27.4 ± 19.1 (p = 0.09; Table 2). Postoperative systolic and diastolic blood pressure did not differ between the groups (systolic 120.0 ± 9.5 mm Hg in the HPS group and 117.1 ± 10.4 mm Hg in the non-HPS group, p = 0.205; diastolic 73.4 ± 7.0 mm Hg in the HPS group and 72.4 ± 7.4 mm Hg in the non-HPS group, p = 0.534). The symptoms of all patients with HPS resolved within a few weeks and no patient developed ICH.

ΔMVTT After Bypass Surgery
MVTT was reduced significantly after bypass surgery (prebypass 5.34 ± 2.00 sec, postbypass 4.12 ± 1.60 sec; p < 0.001). MVTT was reduced after bypass surgery in both the HPS group (from 6.61 ± 2.27 sec to 4.11 ± 1.68 sec; p < 0.001) and the non-HPS group (from 4.87 ± 1.65 sec to 4.12 ± 1.55 sec; p = 0.001; Fig. 2). The ΔMVTT was significantly greater in the HPS group (2.55 ± 2.66 sec) than in the non-HPS group (0.75 ± 1.78 sec; p < 0.001; Fig. 3).

<table>
<thead>
<tr>
<th>TABLE 1. Physiological data</th>
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<tbody>
<tr>
<td>Parameter (mm Hg)</td>
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<tr>
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</tr>
<tr>
<td>Systolic blood pressure</td>
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<tr>
<td>Diastolic blood pressure</td>
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<tr>
<td>PaO₂</td>
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<tr>
<td>PaCO₂</td>
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ROC Curve Analysis for Developing HPS

Based on ROC curve analysis, the optimal ΔMVTT cutoff value for developing HPS was 2.6 seconds, and the area under the ROC curve was 0.669 (Fig. 4). At this value, the sensitivity and specificity for predicting HPS were 46.4% and 85.7%, respectively.

Risk Factors for Postoperative HPS

Univariate analysis of age, sex, operated hemisphere, onset type, and ΔMVTT > 2.6 seconds demonstrated that age ≥ 16 years and ΔMVTT > 2.6 seconds were significant predictors of all postoperative HPS (Table 2). Multivariate analysis with the Cox proportional-hazards model showed that ΔMVTT > 2.6 seconds (hazard ratio 4.88, 95% CI 1.76–13.57; p = 0.002) and adult age (≥ 16 years, hazard ratio 4.43, 95% CI 1.34–14.62; p = 0.015) were significant independent predictors of postoperative HPS (Table 3). No other risk factors were significant.

Representative Case

A 59-year-old woman suffering from cerebral infarction in the left frontal lobe and diagnosed with MMD was transferred to our institution to undergo revascularization surgery. She exhibited neither hemiparesis nor dysarthria on admission and was independent in daily life activities. She underwent STA-MCA single bypass surgery on the left side, and a cortical branch of the MCA was selected as the recipient. The prebypass MVTT was 7.7 seconds, and the MVTT after bypass surgery was markedly reduced to 4.0 seconds (Fig. 5B and E). She developed motor aphasia and dysarthria 2 days after surgery. 123I-IMP SPECT on the 2nd day after surgery showed significantly increased CBF around the site of the anastomosis compared with preoperative CBF (Fig. 5F), indicating postoperative HPS. Afterward, her blood pressure was strictly controlled and her symptoms improved on the 4th day after surgery.

Discussion

MMD is characterized by progressive steno-occlu-

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**TABLE 2. Demographic data and clinical characteristics of 81 patients (105 hemispheres) with MMD who developed postoperative HPS**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 105)</th>
<th>HPS Group (n = 28)</th>
<th>Non-HPS Group (n = 77)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in yrs, mean ± SD*</td>
<td>29.8 ± 18.7</td>
<td>36.4 ± 16.6</td>
<td>27.4 ± 19.1</td>
<td>0.090</td>
</tr>
<tr>
<td>Adult ≥ 16 yrs, no. (%)†</td>
<td>67 (63.8)</td>
<td>24 (85.7)</td>
<td>43 (55.8)</td>
<td><strong>0.005</strong></td>
</tr>
<tr>
<td>Male sex, no. (%)†</td>
<td>36 (34.3)</td>
<td>6 (21.4)</td>
<td>30 (39.0)</td>
<td>0.094</td>
</tr>
<tr>
<td>Lt side, no. (%)†</td>
<td>58 (55.2)</td>
<td>19 (67.9)</td>
<td>39 (50.6)</td>
<td>0.117</td>
</tr>
<tr>
<td>Hemorrhagic onset, no. (%)†</td>
<td>10 (9.5)</td>
<td>3 (10.7)</td>
<td>7 (9.1)</td>
<td>0.802</td>
</tr>
<tr>
<td>ΔMVTT &gt; 2.6 sec, no. (%)†</td>
<td>24 (22.9)</td>
<td>13 (46.4)</td>
<td>11 (14.3)</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Postop blood pressure in mm Hg, mean ± SD*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic*</td>
<td>117.9 ± 10.2</td>
<td>120.0 ± 9.5</td>
<td>117.1 ± 10.4</td>
<td>0.205</td>
</tr>
<tr>
<td>Diastolic*</td>
<td>72.6 ± 7.3</td>
<td>73.4 ± 7.0</td>
<td>72.4 ± 7.4</td>
<td>0.534</td>
</tr>
</tbody>
</table>

*Boldface type indicates statistical significance.
† Data were analyzed by the Student t-test.
†† Data were analyzed by the chi-square test.

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![FIG. 2. Change in MVTT after bypass surgery. MVTT was reduced significantly after bypass surgery, in both the HPS and non-HPS groups.](image-url)

![FIG. 3. Comparison between ΔMVTT of HPS and non-HPS groups. The ΔMVTT of the HPS group was significantly greater than that of the non-HPS group.](image-url)
tion of the basal cerebral arteries, leading to severe hemodynamic ischemia in parallel with the development of basal moyamoya vessels. In MMD, cerebral cortical microvessels increase in number and dilate, compensating for impaired CBF by decreasing peripheral vascular resistance. In association with this anatomical alteration, MVTT was prolonged in patients with MMD compared with that in patients with atherosclerotic cerebrovascular disease. In the present study, we demonstrated, to our knowledge for the first time, that prolonged MVTT in patients with MMD was reduced after bypass surgery. When cerebral autoregulation functions normally, arterioles constrict against the abrupt increase in blood inflow, resulting in no change in MVTT. The reduction in MVTT after bypass surgery in patients with MMD suggests that cortical microvasculature in patients with MMD becomes vasoparalytic due to long-standing vasodilation.

The reduction in MVTT was more prominent in the HPS group than in the non-HPS group. Although the pathogenesis of HPS in MMD is not fully clarified, HPS after carotid vascularization is thought to result from a loss of normal vasoconstriction caused by chronic cerebral ischemia and maladaptive autoregulatory mechanisms. Recently, we found that the cortical hyperintensity belt sign in postoperative FLAIR images correlates with postoperative neurological events after STA-MCA bypass surgery for MMD. Because the cortical hyperintensity belt sign suggests vasogenic edema, the neurological symptoms seem to be caused by disruption of the neurovascular unit caused by excessive blood flow. Moreover, the severity of the edema should correlate with the degree of impairment of autoregulation, which would accord well with the fact that patients with a greater reduction in MVTT are prone to develop postoperative HPS.

Previous studies using PET revealed that the cerebral preoperative oxygen extraction fraction and cerebral blood volume (CBV) values were higher in symptomatic hyperperfusion. Increased CBV was assumed to indicate pronounced cortical vasodilatation due to exhausted autoregulation. These findings support the notion that the prolongation of prebypass MVTT and its reduction after bypass surgery reflect microvascular vasodilation in the cortex, predisposing a patient to develop postoperative HPS.

The rate of occurrence of postoperative HPS in the present study was 26.7%, which was comparable to that in the previous report. To date, some risk factors for postoperative HPS have been identified (e.g., adult onset, hemorrhagic onset, preoperative increased oxygen extraction fraction, and preoperative increased CBV). In addition, multivariate analysis in the present study revealed that $\Delta$MVTT > 2.6 seconds was an independent predictor of postoperative HPS after STA-MCA bypass surgery in patients with MMD. Adult onset was also an independent predictor of HPS. Indeed, in the present study, pediatric patients were unlikely to develop HPS (4 of 38 hemispheres). Interestingly, only 11 of 77 non-HPS cases showed $\Delta$MVTT > 2.6 seconds, and more than one-half of them (6 cases) were children. In a child’s case, an abrupt increase in arterial inflow might be compensated via a mechanism other than increased peripheral vascular resistance caused by vasoconstriction. Given that patients tend to develop HPS a few days after surgery, excessive CBF around the anastomosis site may be adequately redistributed within a few days in the case of children. Otherwise, the low incidence of HPS in children might be attributable to the fact that indirect revascularization was performed.

![FIG. 4. ROC curve analysis for development of HPS. The ROC curve revealed that the Youden index (sensitivity + specificity–1) reached the maximum (dotted vertical line) when the cutoff point for $\Delta$MVTT was set at 2.6 seconds. At this value, the sensitivity and specificity for predicting HPS were 46.4% and 85.7%, respectively. Figure is available in color online only.](image)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td>Adult ≥16 yrs</td>
<td>4.74 (1.50–14.99)</td>
<td>0.008</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.43 (0.16–1.17)</td>
<td>0.100</td>
</tr>
<tr>
<td>Lt side</td>
<td>0.49 (0.20–1.21)</td>
<td>0.120</td>
</tr>
<tr>
<td>Hemorrhagic onset</td>
<td>1.20 (0.29–5.00)</td>
<td>0.802</td>
</tr>
<tr>
<td>$\Delta$MVTT &gt;2.6 sec</td>
<td>5.20 (1.95–13.84)</td>
<td>0.001</td>
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</tbody>
</table>

Boldface type indicates statistical significance.
Microvascular transit time change in moyamoya disease

J Neurosurg Volume 128 • May 2018

only in children. These results suggest that ΔMVTT is a good predictor of HPS, especially in adult patients. Further studies are needed to clarify this issue.

Limitations of the Study

To avoid HPS following bypass surgery, reduction of blood pressure is recommended.6 We managed patients with strict blood pressure control (systolic blood pressure 100–140 mm Hg) for at least 1 week. However, excessive reduction of blood pressure increases the risk of ischemic complication. Moreover, such strict management leads to unnecessary administration of antihypertensive drugs and prolonged bed rest for low-risk patients. MVTT measurement helps us identify high-risk patients who require strict control of blood pressure. As a predictor of postoperative HPS, the specificity of ΔMVTT (85.7%) was adequate, but its sensitivity (46.4%) was insufficient. A nonnegligible number of patients are subject to having false-negative results even if they exhibit a ΔMVTT < 2.6 seconds. On the other hand, patients with a ΔMVTT > 2.6 seconds have a high possibility of developing postoperative HPS. ICG-VA enables us to simply and safely assess intraoperative hemodynamic status during cerebrovascular surgery.22,27 In STA-MCA bypass surgery for MMD, ICG-VA has been routinely used to confirm bypass patency1 and to assess cortical perfusion after bypass surgery.12,25 Another limitation of this study is the relative subjectivity in the definition of HPS. The diagnostic criteria of CBF for HPS in patients with MMD has not been defined. This is because the change in CBF following bypass surgery in patients with MMD is localized around the anastomosis site and varies with the size of the ROI. Therefore, we used the original definition of Fujimura et al.,7 as did many previous authors, to describe HPS in patients with MMD. Despite these limitations, the measurement of MVTT by ICG-VA is a convenient diagnostic tool for identifying groups at high risk of postoperative HPS and can contribute to improved management of patients with MMD undergoing STA-MCA bypass surgery.

Conclusions

MVTT in patients with MMD was reduced significantly after bypass surgery. Patients with a ΔMVTT > 2.6 seconds tend to develop postoperative HPS. Because ΔMVTT can be easily measured intraoperatively, it is a useful diagnostic tool for identifying patients at high risk for HPS after STA-MCA bypass surgery for MMD.

References


**Disclosures**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

**Author Contributions**

Conception and design: Kataoka. Acquisition of data: Yang, Higashino, Hamano, Maruyama, Iihara, Takahashi. Analysis and interpretation of data: Kataoka, Yang, Higashino. Drafting the article: Kataoka, Yang. Critically revising the article: Iihara, Takahashi. Reviewed submitted version of manuscript: Higashino, Hamano, Maruyama, Iihara, Takahashi. Approved the final version of the manuscript on behalf of all authors: Kataoka. Administrative/technical/material support: Iihara, Takahashi. Study supervision: Iihara, Takahashi.

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