## Introduction

Moyamoya disease is a chronic, occlusive cerebrovascular disease of unknown etiology, characterized by bilateral steno-occlusive changes at the terminal portion of the internal carotid artery and an abnormal vascular network at the base of the brain [1]. Extracranial-intracranial (EC-IC) bypass such as superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis is generally employed as the standard surgical treatment for moyamoya disease to prevent cerebral ischemic attacks [2–6]. Despite the favorable long-term outcome of STA-MCA anastomosis for moyamoya disease [4–6], increasing evidence suggests that cerebral hyperperfusion syndrome, as has been well described in patients undergoing carotid endarterectomy (CEA) [7–9], is a potential complication of EC-IC bypass, especially for moyamoya disease. Focal cerebral hyperperfusion was reported to cause transient neurological deterioration [3, 10–16] or delayed intracerebral hemorrhage (ICH) [17] during the acute stage after EC-IC bypass for moyamoya disease. Patients with moyamoya disease have a significantly higher risk for cerebral hyperperfusion syndrome than those with other occlusive cerebrovascular diseases based on routine postoperative cerebral blood flow (CBF) measurements using N-isopropyl-*p*-[$^{123}$I]-iodoamphetamine single-photon emission computed tomography ($^{123}$I-IMP-SPECT) [18].

The optimal postoperative management for avoiding the hyperperfusion syndrome has not yet been determined. Blood pressure lowering in patients with the hyperperfusion phenomenon is an effective treatment after revascularization surgery for moyamoya disease [3, 18], but aggressive blood pressure lowering to systolic blood pressure <120 mm Hg in all patients could be controversial because of the risk of perioperative ischemic complications in the contralateral hemisphere [19] and/or remote areas with hemodynamic compromise. To address this issue, we prospectively performed prophylactic blood pressure lowering applying a standardized management protocol for consecutive patients with moyamoya disease who underwent direct revascularization surgery with routine postoperative CBF measurement starting in 2008 [20]. We then compared the incidence of symptomatic cerebral hyperperfusion between this series and consecutive surgical patients operated on between 2004 and 2007 who had been treated under normotensive conditions after EC-IC bypass [3, 10], in order to establish the optimal postoperative management protocol for preventing symptomatic cerebral hyperperfusion in moyamoya disease.

## Methods

*Inclusion Criteria of Patients*

Postoperative changes in CBF and clinical course were investigated in 108 consecutive patients with moyamoya disease (male/female = 30/78; 2–69 years old, mean 33.3 years) surgically treated in 152 hemispheres by the same surgeon (M.F.) between March 2004 and December 2010. Inclusion criteria of this study, corresponding to our surgical indications for STA-MCA anastomosis, included all of the following items: the presence of ischemic symptoms (minor completed stroke and/or transient ischemic attack, TIA), apparent hemodynamic compromise on SPECT as defined below, independent activity of daily living (modified Rankin scale scores 0–2) and absence of major cerebral infarction exceeding the vascular territory of one major branch of the MCA. All hemispheres that did not match these criteria were excluded from surgery, except for 3 hemispheres from 2 patients with a history of hemorrhage who were enrolled to the Japan Adult Moyamoya trial [21] and were randomly allocated to the surgically treated group. Besides these 2 patients participating in the Japan Adult Moyamoya trial, the present study included 8 patients with a history of hemorrhage; 10 hemispheres were operated on. All 8 patients simultaneously suffered from TIAs or cerebral infarction in the affected hemispheres before surgery, which matched our surgical indication.

Preoperative CBF was quantified by the autoradiographic method in most cases, and the CBF in each subregion was automatically calculated by 3D SRT (three-dimensional stereotactic region of interest template) software (version 2) provided by Daiichi Radio-Isotope (Tokyo, Japan) using $^{123}$I-IMP-SPECT [3, 10]. The cerebral perfusion reserve capacity was quantified by the administration of acetazolamide. When the CBF at rest is <80% of normal CBF (about 42 ml/100 g/min) and/or reactivity to acetazolamide is <10%, we regard the CBF state as hemodynamic compromise. In pediatric patients with crescendo TIAs or in patients under the age of 4 we did not perform a preoperative quantitative CBF study but only qualitative $^{123}$I-IMP-SPECT without acetazolamide stress. One adult patient with progressing stroke underwent only qualitative $^{123}$I-IMP-SPECT without acetazolamide stress before surgery.

Once hemodynamic compromise was confirmed, the patients underwent revascularization surgery. All patients underwent STA-MCA (M4) anastomosis with encephaloduromyosynangiosis (EDMS) [10]. Patients were maintained under normotension, normovolemia and normocapnia during surgery, which was performed under intravenous anesthesia using propofol [22]. Craniotomy was performed around the Sylvian fissure end, approximately 8 cm in diameter, and the stump of the STA was anastomosed to the M4 segment of the MCA, which was followed by EDMS. To avoid postoperative compression of the brain surface by swollen temporal muscle used for EDMS [23], we drilled out the inner layer of the bone flap and made a relatively wide bone window at the site of EDMS graft insertion. All patients satisfied the diagnostic criteria of the Research Committee on Spontaneous Occlusion of the Circle of Willis of the Ministry of Health, Labor and Welfare, Japan [24], except for 5 patients with 'probable moyamoya disease', who showed unilateral involvement. Eight adult patients had associated cerebrovascular diseases, including 7 patients with atherosclerotic occlusive changes and 1

**Table 1.** Incidence of symptomatic cerebral hyperperfusion following EC-IC bypass in 152 hemispheres of moyamoya patients

| | Overall | Period 1 | Period 2 | p value (period 1 vs. period 2) |
|---|---|---|---|---|
| Symptomatic HP | 17.8% (27/152) | 24.7% (23/93) | 6.7% (4/59) | 0.0047* |
| Focal ND | 15.1% (23/152) | 21.5% (20/93) | 5.0% (3/59) | 0.0059* |
| Symptomatic SAH or ICH | 2.6% (4/152) | 3.2% (3/93) | 1.7% (1/59) | 0.57 |

HP = Hyperperfusion; ND = neurological deficit. * Statistically significant.

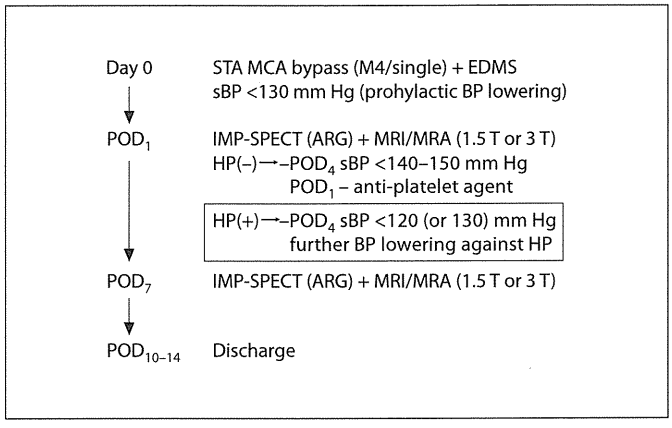


**Fig. 1.** Summary of the perioperative management protocol in period 2. Prophylactic blood pressure lowering was attempted starting immediately after revascularization surgery. sBP = Systolic blood pressure; HP = hyperperfusion; POD = postoperative day; ARG = autoradiographic.

patient with a cavernous malformation with a developmental venous anomaly. All patients were closely followed in our institutes for more than 6 months, with a mean follow-up period of 53.4 months.

*Postoperative CBF Measurement and Diagnosis of Hyperperfusion*

CBF was routinely measured by $^{123}$I-IMP-SPECT 1 and 7 days after surgery in all patients. A postoperative computed tomography (CT) scan was routinely performed immediately after surgery and 1 day after surgery in all cases. 1.5- or 3-tesla magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) were routinely performed within 2 days after surgery. MRI included diffusion-weighted images, $T_2$-weighted images, and $T_2$*-weighted images in all cases. Fluid-attenuated inversion recovery (FLAIR) was also performed in most cases. The diagnostic criteria for symptomatic cerebral hyperperfusion included all of the following items [3, 18]: (1) presence of a significant focal increase in CBF, which confined to the vascular territory of one major branch of the MCA at the site of the anastomosis that is responsible for the neurological signs, including focal neurological deficit and/or progressive/severe headache due to newly formed hemorrhagic changes; (2) apparent visualization of STA-MCA bypass by MRA and absence of any ischemic changes by diffusion-weighted images, and (3) absence of other pathologies, such as compression of the brain surface by the temporal muscle inserted for indirect pial synangiosis, ischemic attack, venous infarction, interruption of transdural collaterals and CBF increase secondary to seizure. In addition to these items, blood pressure-dependent aggravation of the symptoms and/or amelioration of the symptoms by blood pressure lowering clinically confirmed the diagnosis of symptomatic hyperperfusion in all cases. In most patients with progressive/severe headache with hemorrhagic changes, manual compression of STA at the preauricular region attenuated the symptom.

The occurrence of symptomatic cerebral hyperperfusion after revascularization surgery was evaluated by $^{123}$I-IMP-SPECT in the acute stage. Mortality and morbidity due to cerebral hyperperfusion were also evaluated 3 months after revascularization surgery. We investigated the correlation between postoperative CBF changes and clinical presentation in both periods, and compared the incidence of symptomatic cerebral hyperperfusion between the two groups.

*Postoperative Management in Two Distinct Periods*

During the initial period from March 2004 to December 2007 (period 1), 65 patients underwent STA-MCA anastomosis with EDMS in 93 hemispheres, and were maintained under normotensive conditions (<150–160 mm Hg systolic blood pressure) after surgery (table 1). If $^{123}$I-IMP-SPECT suggested cerebral hyperperfusion on the day after surgery, the patients underwent mild blood pressure lowering (<140 mm Hg systolic blood pressure) to avoid the deleterious effects of cerebral hyperperfusion while considering the risk of a contralateral ischemic complication. Only patients who developed symptomatic hyperperfusion were subjected to intensive blood pressure lowering (<130 mm Hg systolic blood pressure). During period 2, between January 2008 and December 2010, 43 patients underwent STA-MCA anastomosis with EDMS in 59 hemispheres, and were prospectively subjected to prophylactic intensive blood pressure lowering (<130 mm Hg systolic blood pressure) irrespective of patients' age, using a 1–10 mg/h continuous intravenous drip infu-

sion of nicardipine hydrochrolide, immediately after surgery in the operation room (fig. 1) [20] because most of the cases of symptomatic hyperperfusion in period 1 were resolved by blood pressure lowering <130 mm Hg systolic blood pressure irrespective of the preoperative blood pressure. To avoid unfavorable effects of intensive blood pressure lowering on the contralateral hemisphere and/or ipsilateral remote areas, we routinely administered antiplatelet agents (100 mg aspirin/day, or 200 mg cilostazol/day) starting on the day after surgery in period 2, in light of the observation that antiplatelet agents have preventive effects on ischemic stroke in moyamoya disease [25] and that abnormal thrombogenesis was found to be involved in the pathophysiology of moyamoya disease in autopsy cases [26]. Based on the temporal profile of $^{123}$I-IMP-SPECT and MRI/MRA findings, we gradually allowed a return to normotensive conditions within 7–10 days after surgery. If $^{123}$I-IMP-SPECT 7 days after surgery showed a mild increase in CBF in the entire MCA territory compared to the preoperative status, we considered that the hyperperfusion phenomenon was ameliorated, and allowed them to return to their baseline blood pressure level. If $^{123}$I-IMP-SPECT at 7 days still demonstrated a focal intense increase in CBF at the site of the anastomosis, we continued blood pressure control and repeated $^{123}$I-IMP-SPECT several days later. The details of our management protocol in period 2 are summarized in figure 1.

*Statistical Analysis*

The incidence of symptomatic cerebral hyperperfusion was compared between the two periods using the $\chi^2$ test. Systolic blood pressure 1 day after surgery was compared between the two periods using Student's t test. Patient ages were compared between the two periods using Student's t test. Since age and history of ICH are known to be related to symptomatic cerebral hyperperfusion after STA-MCA anastomosis for moyamoya disease [3], multivariate statistical analysis of the factors related to the development of symptomatic cerebral hyperperfusion, including management period (period 1 or period 2), age, sex, operated side, history of ICH, and systolic blood pressure (mm Hg) 1 day after surgery was performed using a logistic regression model.

## Results

*Overall Results during the Two Periods*

Among the 108 consecutive patients with 152 operated hemispheres, 26 patients (27 hemispheres, 17.8% of 152 operated hemispheres) demonstrated temporary neurological deterioration, including mild focal neurological signs, due to postoperative focal cerebral hyperperfusion between 2 and 14 days after surgery (table 1). Postoperative MRI did not show any ischemic changes in the 27 hemispheres. Postoperative MRA demonstrated a thick high signal intensity of STA in the operated hemisphere in all 27 hemispheres. Postoperative SPECT demonstrated significant intense increases in CBF at the sites of anastomosis in all 27 hemispheres. Twenty-two patients (23 hemispheres, 15.1%) demonstrated transient focal neurological deficits due to focal hyperperfusion, starting between 2 and 9 days after surgery and persisting for several days. In all cases, the symptoms fluctuated in a blood pressure-dependent manner, which further supported the diagnosis of symptomatic hyperperfusion. The anatomical location and temporal profile of hyperperfusion were completely in accordance with the transient neurological signs in all 22 patients. The detail of the neurological signs after 23 operations was as follows; hemiparesis and/or facial palsy in 14, aphasia in 12, and sensory disturbance on the contralateral side of the operation in 3 (some patients had multiple symptoms). Five patients demonstrated dysarthria in addition to the above-mentioned symptoms. One patient suffered from prolonged dysarthria and sensory disturbance, and ultimately developed simple partial seizures that were apparently secondary to hyperperfusion [10]. None of the other 21 patients developed seizures during the postoperative period. Four patients (4 hemispheres, 2.6%) complained of progressive/severe headache and demonstrated cerebral hyperperfusion syndrome associated with subarachnoid hemorrhage (SAH) in 3 patients (2.0%) or with ICH at the right frontal sub-cortex in 1 patient (0.66%) [17]. In all 3 patients with progressive headache due to SAH, manual compression of STA at the preauricular region ameliorated the symptoms. The distribution of newly formed SAH or ICH, demonstrated by CT scan, was in accordance with the site of the anastomosis in all 4 patients and such hemorrhagic changes were not evident immediately after surgery, thus we diagnosed them as having symptomatic hemorrhage due to cerebral hyperperfusion. None of the patients demonstrated any permanent neurological deficits due to cerebral hyperperfusion and no patients suffered from delayed neurological deterioration due to cerebral hyperperfusion during the follow-up period.

Among 108 consecutive patients with 152 operated hemispheres, there were no patients with perioperative cerebral infarction, except for the 4 patients as detailed below. Three patients in period 1 (2.0%) presented with pseudolaminar necrosis identified by MRI, probably due to the transient ischemia caused by a thrombotic event in the portion of the cerebral cortex supplied by the STA-MCA bypass in the subacute stage which did not affect their long-term neurological status [2]. One patient in period 2 (1.7%) with ipsilateral preoperative posterior cerebral artery (PCA) stenosis and an atherosclerotic background presented with cerebral infarction 3 days after surgery in the ipsilateral occipital lobe during intensive

**Table 2.** Incidence of symptomatic cerebral hyperperfusion following EC-IC bypass

| | Period 1 | Period 2 |
|---|---|---|
| Hemispheres and patients, n | 93 (65 patients) | 59 (43 patients) |
| Age, years | | |
| Range | 2–66 | 9–69 |
| Mean | 33.2 | 33.4 |
| Sex, male/female | 18/47 | 11/32 |
| Symptomatic hyperperfusion | 23 (24.7%) | 4 (6.7%)* |
| Systolic blood pressure ($POD_1$) | | |
| mm Hg | 133.9 | 120.9** |

$POD_1$ = Postoperative day 1. * p = 0.0047, ** p < 0.00001, significantly lower.

**Table 3.** Multivariate analysis of symptomatic cerebral hyperperfusion in moyamoya disease

| | Odds ratio | p value |
|---|---|---|
| Prophylactic BP lowering, period 2 | 2.158 | 0.015[1] |
| Age | 0.971 | 0.050 |
| Female sex | 0.890 | 0.661 |
| Hemisphere operated on, left | 1.174 | 0.480 |
| History of hemorrhage | 0.674 | 0.268 |
| Systolic BP, $POD_1$ | 0.996 | 0.822 |

BP = Blood pressure; $POD_1$ = postoperative day 1. [1] Significant association.

blood pressure control for symptomatic SAH due to hyperperfusion, indicating the potential risk for cerebral ischemia in the contralateral hemisphere and/or ipsilateral remote area during blood pressure lowering. However, this did not affect her long-term activity of daily living. All patients with onset of TIA showed disappearance or improvement of the ischemic attack during the follow-up period. One ischemic-onset patient (0.66%) treated during period 1 developed ICH of the ipsilateral thalamus 3 years after successful revascularization surgery. Therefore, she showed deterioration of the modified Rankin scale score from 0 to 3 after the hemorrhage. Two patients in period 1, who presented with hemorrhage as their initial presentation, developed rebleeding (1.31%), 1 from a contralateral ICH and one from SAH, but neither patient showed deterioration of their neurological status. On the postoperative MRA, the patency of the STA-MCA bypass was confirmed in all 108 patients in 152 operated hemispheres.

*Background and Incidence of Cerebral Hyperperfusion in Each Group*

As shown in tables 1 and 2, the incidence of symptomatic cerebral hyperperfusion including mild focal neurological signs was significantly lower in period 2 under prophylactic blood pressure lowering (4/59; 6.7%) than in period 1 (23/93 hemispheres, 24.7%) (p = 0.0047). As for the clinical presentation of cerebral hyperperfusion in each period, transient focal neurologic signs were seen in 19 patients in period 1 (20/93 hemispheres, 21.5%), but only in 3 period-2 patients (3/59; 5.0%, p = 0.0059) (table 1). Symptomatic hemorrhage due to cerebral hyperperfusion was found in 3 patients (3/93 hemispheres, 3.2%) in period 1, and in 1 (1/59; 1.7%) in period 2, showing no significant difference between the two periods (p = 0.57). Symptomatic cerebral hyperperfusion was relieved in all patients, and none of the patients developed permanent neurological deficits due to hyperperfusion. Systolic blood pressure on the day after surgery was significantly lower in period 2 (mean 120.9 mm Hg) than in period 1 (133.9 mm Hg) (p < 0.00001). The average patient age was 33.2 years in period 1 and 33.4 in period 2, showing no significant difference between the two periods (p = 0.949) (table 2). Of the 108 patients in both periods, patients with symptomatic hyperperfusion were significantly older (mean 39.4 years) than those without symptomatic hyperperfusion (mean 31.9 years) (p = 0.031). Multivariate analysis demonstrated that prophylactic blood pressure lowering (period 2) was significantly associated with prevention of symptomatic cerebral hyperperfusion (p = 0.006) as shown in table 3. Patient age was not found to be associated with symptomatic cerebral hyperperfusion by multivariate analysis (p = 0.050). There was no significant association between sex (p = 0.661), side of the operated hemisphere (0.480), past history of hemorrhage (0.268), and systolic blood pressure 1 day after surgery (0.822) and the occurrence of symptomatic hyperperfusion (table 3).

*Representative Case in Period 2 Suggesting a Potential Risk for Symptomatic Hyperperfusion in Asymptomatic Patients*

A 57-year-old woman presented with minor completed stroke in the left hemisphere, and was found to have moyamoya disease. She was surgically treated in period 2. Digital subtraction angiography demonstrated stenoocclusive changes at the terminal portion of the bilateral

internal carotid artery, and development of an abnormal vascular network at the base of the brain, predominantly in the left hemisphere. Preoperative $^{123}$I-IMP-SPECT 1 month after the onset of stroke showed significant hemodynamic compromise in the entire left hemisphere (fig. 2a). She underwent STA-MCA anastomosis with EDMS in the left hemisphere 2 months after the onset of stroke. The recipient artery at the M4 segment of the frontal branch of the MCA was explored and anastomosis was performed between the stump of the STA (1.0 mm in diameter) and the M4 segment (1.0 mm in diameter) that supplied the left premotor cortex. The temporary occlusion time was 20 min. The patient's systolic blood pressure was strictly maintained at <130 mm Hg starting immediately after surgery. The patient did not demonstrate any neurological signs after surgery. $^{123}$I-IMP-SPECT 1 day after surgery demonstrated a focal intense increase in CBF at the site of the anastomosis (fig. 2b). The MRI performed 1 day after surgery did not show any evidence of ischemic change, and the MRA demonstrated thick high signal intensity of the STA (fig. 3c). FLAIR imaging demonstrated asymptomatic SAH at the left Sylvian cistern extending to the left frontoparietal lobe sulcus (fig. 3a, b), which was consistent with the result of the CT scan 1 day after surgery, demonstrating faint SAH which was not evident immediately after surgery. The patient did not show any sign of infection including postoperative meningitis. Based on these findings suggesting cerebral hyperperfusion, more intensive blood pressure lowering (systolic blood pressure <120 mm Hg) was performed. She did not develop any neurological deterioration or seizure nor did she complain of headache during the postoperative period. $^{123}$I-IMP-SPECT obtained 7 days after surgery indicated amelioration of the focal hyperperfusion in the left hemisphere (fig. 2c), and FLAIR imaging showed a significant decrease in asymptomatic SAH (fig. 3d, f). She was discharged without neurological deficit 14 days after surgery, and there were no cerebrovascular events during the follow-up period.

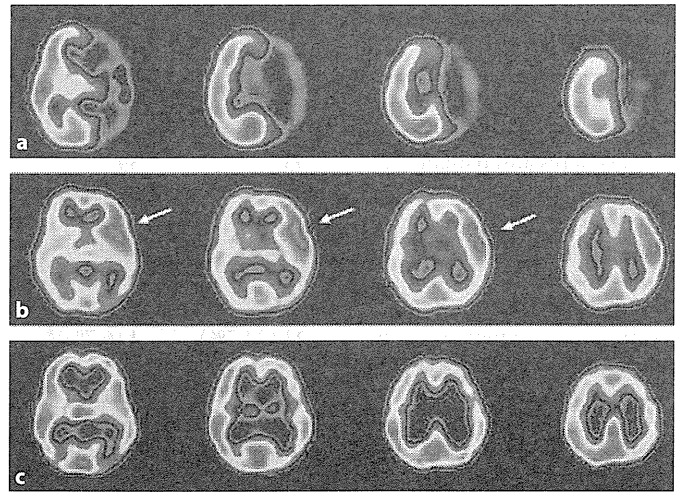


**Fig. 2.** Representative case in period 2: a 57-year-old woman with moyamoya disease presenting with minor stroke. $^{123}$I-IMP-SPECT before (**a**) and after (**b**, **c**) left STA-MCA anastomosis with pial synangiosis. Significant hemodynamic compromise in the left hemisphere was shown before surgery (**a**). Marked increase in CBF at the site of the anastomosis was evident (arrows in **b**) 1 day after surgery, and was ameliorated at 7 days after surgery (**c**). There was no difference in the CBF in the right hemisphere before (**a**) and after surgery (**b**, **c**).

## Discussion

In the present study, we prospectively introduced a standardized postoperative management protocol including prophylactic intensive blood pressure lowering (systolic blood pressure <130 mm Hg) immediately after STA-MCA anastomosis for moyamoya disease in order to prevent a postoperative hyperperfusion syndrome. We demonstrated, for the first time, that prophylactic intensive blood pressure lowering significantly ameliorates symptomatic cerebral hyperperfusion after STA-MCA anastomosis for moyamoya disease. Accurate diagnosis by flow study and further blood pressure lowering in patients with cerebral hyperperfusion is essential to prevent cerebral hyperperfusion including symptomatic hemorrhage, seizure and neurological deterioration.

### *Higher Incidence of Symptomatic Cerebral Hyperperfusion following EC-IC Bypass for Moyamoya Disease*

Symptomatic cerebral hyperperfusion following EC-IC bypass for atherosclerotic occlusive cerebrovascular disease is relatively rare and generally manifests as a mild focal neurological deficit that resolves within 2 weeks [27, 28]. Heros et al. [27] were the first to report cerebral hyperperfusion in 5 patients with atherosclerotic ischemic disease who presented with temporary neurological deterioration after STA-MCA bypass surgery among 134 patients (3.7%). The symptoms resolved in all 5 patients within 2 weeks after surgery. In a recent contribution, Yamaguchi et al. [29] reported a 6.0% (3/50) incidence of

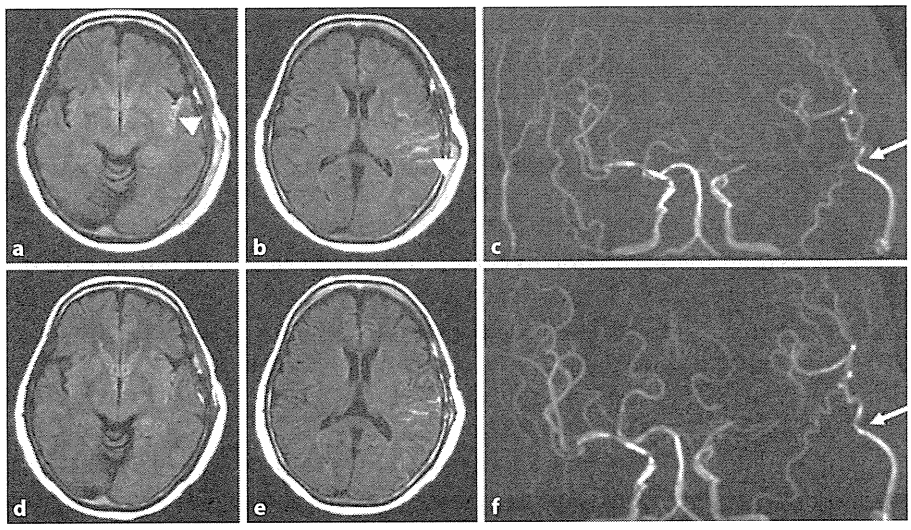

**Fig. 3.** Postoperative FLAIR by MRI 1(**a**, **b**) and 7 days (**d**, **e**) after surgery in a 57-year-old woman, demonstrating asymptomatic SAH in the left Sylvian cistern extending to the ipsilateral fronto-temporal sulcus (arrowheads in **a**, **b**). SAH was decreased 7 days after surgery (**d**, **f**). MRA 1 (**c**) and 7 days (**f**) after STA-MCA anastomosis with pial synangiosis, demonstrating STA-MCA bypass as a thick high signal sign (arrows in **c**, **f**).

symptomatic cerebral hyperperfusion under strict blood pressure control and propofol sedation. Our most recent study using routine postoperative CBF measurements by $^{123}$I-IMP-SPECT after STA-MCA (M4) anastomosis for moyamoya and non-moyamoya patients showed that none of the patients in the non-moyamoya group (0/28; 0%) versus 25 patients (26/121 hemispheres, 21.5%) in the moyamoya group developed symptomatic cerebral hyperperfusion after STA-MCA anastomosis ($p = 0.0069$) [18]. The incidence of symptomatic cerebral hyperperfusoin in patients with moyamoya disease has been suggested to be as high as 16.7–28.1% [3, 12, 16] when mild focal neurological signs are included. In the present study, the incidence of symptomatic cerebral hyperperfusion was 24.7% (23/93 hemispheres) when the patients were managed under normotensive conditions and only patients demonstrating hyperperfusion on postoperative SPECT underwent blood pressure lowering (period 1), which is almost in agreement with the previous reports [3, 12, 16].

*Management of Cerebral Hyperperfusion after EC-IC Bypass*

Since delayed ICH [17] and symptomatic SAH due to cerebral hyperperfusion after STA-MCA anastomosis [18] have been reported in patients with moyamoya disease, STA-MCA anastomosis, although it provides low flow revascularization, is considered to entail substantial risks of surgical morbidity due to hyperperfusion. Intensive blood pressure lowering in patients with evidence of hyperperfusion on flow study, while considering the risk of ischemic complication on the contralateral and/or remote areas with hemodynamic compromise, is generally accepted as the standard management of cerebral hyperperfusion after EC-IC bypassfor moyamoya disease [3, 10, 11, 18]. The intraoperative and/or postoperative use of free-radical scavengers could be an acceptable additional management to ameliorate secondary brain injury due to cerebral hyperperfusion as reported in patients undergoing CEA [30]. Regarding EC-IC bypass for atherosclerotic occlusive cerebrovascular disease, Yamaguchi et al. [29] recently recommended continuous, strict blood pressure control under continuous sedation immediately after surgery. In their study, all patients were managed in the intensive care unit under continuous propofol sedation, based on the rationale that systemic blood pressure is more easily controlled and hyperperfusion more effectively prevented under propofol sedation compared with wakefulness. But intensive blood pressure lowering for moyamoya patients has generally been controversial because of the risk of ischemic complications in the contralateral and/or remote hemodynamically compromised areas [19], especially under continuous propofol sedation that precludes monitoring of the patient's neurological status during hemodynamic changes. In the present study, we prospectively performed prophylactic blood pressure lowering in conscious patients immediately after revascularization surgery, which resulted in significant amelioration of symptomatic cerebral hyperperfusion compared to previous treatment under normotensive conditions. However, even when applying the recent protocol of prophylactic blood pressure lowering, we ob-

served symptomatic cerebral hyperperfusion in 4 patients (4/59 hemispheres, 6.7%) as well as 2 cases with asymptomatic hemorrhage including the representative case (fig. 2, 3). Furthermore, 1 adult patient sustained a minor stroke in the ipsilateral occipital lobe, in the vascular territory of the stenotic PCA revealed by the preoperative angiogram, during intensive blood pressure lowering for symptomatic cerebral hyperperfusion in period 2, pointing to the potential risk of ischemic complications under intensive blood pressure lowering. In fact, Khan et al. [19] reported 1 adult patient with moyamoya disease who died after revascularization surgery due to a massive MCA infarct on the nonoperated side.

Based on this finding, it is conceivable that patients with PCA stenosis, as observed in patients with advanced Suzuki's angiographic staging (stage IV–), which is a significant risk factor for recurrent stroke after surgery [31], could have a higher risk of ischemic complications during intensive blood pressure lowering because the PCA territory could not benefit from revascularization surgery in the acute stage. An additional strategy with more selective management that focuses on the molecular pathway underlying cerebral hyperperfusion is warranted to counteract this deleterious phenomenon.

*Mechanism of Cerebral Hyperperfusion and Feasibility of an Additional Strategy*

The mechanism underlying the occurrence of the cerebral hyperperfusion syndrome in moyamoya disease is undetermined, but could be explained as follows: firstly, in patients undergoing CEA or EC-IC bypass for atherosclerotic occlusive cerebrovascular disease, impaired cerebrovascular reactivity is reported to be a predictive factor of cerebral hyperperfusion [29, 32]. Therefore, the presence of hemodynamic compromise, including decreased cerebrovascular reactivity, could definitively be a background of the risk for cerebral hyperperfusion in moyamoya disease. Secondly, the intrinsic vulnerability of the microvascular structure in moyamoya disease, such as medial thinness, abnormality of the internal elastic lamina, and accumulation of necrotic cell components in the interstitium [33, 34] may facilitate the occurrence of hemorrhagic changes due to hyperperfusion. Thirdly, excessive production of reactive oxygen species during revascularization [35] and subsequent activation of inflammatory molecules such as vascular endothelial growth factor (VEGF) [36, 37] and matrix metalloproteinase (MMP)-9 [36, 38] may affect vascular permeability and thus result in transient neurological deterioration and/or hemorrhagic complications. In fact, VEGF [36, 37] and MMP-9 [36, 38], both of which play a potential role in increasing the permeability of the blood-brain barrier, is significantly increased in moyamoya patients compared to healthy controls. These observations suggest that the increased expression of VEGF and MMP-9 in patients with moyamoya disease [36–38] may facilitate, at least in part, the occurrence of cerebral hyperperfusion in moyamoya disease. Based on these observations, the prophylactic blockade of VEGF and/or MMP-9 in patients with moyamoya disease could be an additional therapeutic approach to counteract postoperative cerebral hyperperfusion in moyamoya disease. Finally, we used nicardipine to lower postoperative blood pressure in period 2. Since nicardipine was reported to have a protective effect against cerebral ischemia [39] and hypertension-induced brain damage [40], we do not rule out the possibility that prophylactic use of nicardipine might have contributed in part to the prevention of symptomatic hyperperfusion in our study. Elucidation of the mechanism of cerebral hyperperfusion in moyamoya disease is necessary to develop a definitive perioperative management protocol to avoid surgical complications including both cerebral hyperperfusion and cerebral ischemia.

*Limitation of the Present Study*

Previous reports including our studies have indicated that symptomatic cerebral hyperperfusion is a potential complication of EC-IC bypass for moyamoya disease. However, except for the most recent study by Kawamata et al. [41], all the previous reports [2, 3, 10–18] lacked the quantitative definition of 'hyperperfusion phenomenon' in moyamoya disease. Our present study has a similar limitation, since we could not yet define the threshold of the 'pathological increase in CBF after EC-IC bypass' for moyamoya disease. The reason why it is difficult to propose a quantitative definition of the cerebral hyperperfusion phenomenon after EC-IC bypass for moyamoya disease is as follows. Firstly, unlike the hyperperfusion syndrome after CEA [7–9], the increase in CBF is usually localized in a small area under the site of the anastomosis, thus the quantitative postoperative CBF value may totally depend on the setting of the region of interest. Secondly, susceptibility to the 'hyperperfusion phenomenon' seems to vary from one moyamoya patient to another, and various biological factors other than cerebral hemodynamics, such as intrinsic fragility of pial artery anatomy [33, 34], development of leptomeningeal anastomosis, and/or increased expression of inflammatory molecules related to blood-brain barrier impermeability [36–38],

may strongly affect the clinical response in the presence of increased CBF immediately after surgery. Therefore, we speculate that patients with moyamoya disease could be symptomatic even with a CBF increase <100% compared to the preoperative value, unlike the definition of the hyperperfusion phenomenon after CEA [7–9]. Quantitative evaluation of postoperative CBF after EC-IC bypass in consecutive cases with moyamoya disease is necessary to answer this important question. Alternatively, further evaluation of cerebral metabolism by positron emission tomography and/or evaluation of the cortex with hyperperfusion by apparent diffusion coefficient images and MRI would be of great value to address this important issue.

## Conclusion

Prophylactic blood pressure lowering ameliorates symptomatic cerebral hyperperfusion after STA-MCA anastomosis in patients with moyamoya disease. Accurate diagnosis of hyperperfusion and intensive blood pressure lowering while considering the severity of hemodynamic compromise in the contralateral and/or remote areas are essential for postoperative management of moyamoya disease.

## Disclosure Statement

None.

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# Significance of Focal Cerebral Hyperperfusion as a Cause of Transient Neurologic Deterioration After Extracranial-Intracranial Bypass for Moyamoya Disease: Comparative Study With Non-Moyamoya Patients Using *N*-Isopropyl-p-[$^{123}$I]Iodoamphetamine Single-Photon Emission Computed Tomography

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**BACKGROUND:** Superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis prevents cerebral ischemic attack by improving cerebral blood flow in patients with occlusive cerebrovascular disease and hemodynamic compromise. Recent evidence suggests that focal cerebral hyperperfusion is a potential complication of this procedure for moyamoya disease.

**OBJECTIVE:** To clarify the exact differences in the incidence and clinical manifestations of this phenomenon between patients with and without moyamoya disease.

**METHODS:** *N*-isopropyl-p-[$^{123}$I]iodoamphetamine single-photon emission computed tomography was performed 1 and 7 days after STA-MCA anastomosis on 121 hemispheres from 86 consecutive patients with moyamoya disease (2-67 years of age; mean, 34.3 years) and on 28 hemispheres from 28 non-moyamoya patients (12-67 years of age; mean, 56.5 years). The incidence of symptomatic hyperperfusion, defined as a significant focal increase in cerebral blood flow at the site of the anastomosis that is responsible for the apparent neurological signs, was compared between groups.

**RESULTS:** Symptomatic cerebral hyperperfusion including mild focal neurological signs was seen in 25 patients with moyamoya disease (26 hemispheres, 21.5%) but in none of the patients without moyamoya disease ($P = .0069$). Multivariate analysis revealed that moyamoya disease was significantly associated with the development of symptomatic cerebral hyperperfusion ($P = .0008$). All patients with symptomatic hyperperfusion were relieved by intensive blood pressure control, and no patients suffered from permanent neurological deficit caused by hyperperfusion.

**CONCLUSION:** Symptomatic cerebral hyperperfusion is a potential complication of STA-MCA anastomosis, especially in patients with moyamoya disease. Accurate diagnosis and adequate management of hyperperfusion are recommended, especially in patients with moyamoya disease.

**KEY WORDS:** Cerebral hyperperfusion, Extracranial-intracranial bypass, Moyamoya disease, Surgical complication

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**ABBREVIATIONS: EC-IC**, extracranial-intracranial; **ICH,** intracerebral hemorrhage; **$^{123}$I-IMP-SPECT,** N-isopropyl-p-[$^{123}$I]iodoamphetamine single-photon emission computed tomography; **MRA,** magnetic resonance angiography; **SAH,** subarachnoid hemorrhage; **STA-MCA,** superficial temporal artery–middle cerebral artery

Cerebrovascular reconstruction surgery including carotid endarterectomy or extracranial-intracranial (EC-IC) bypass for patients with atherosclerotic steno-occlusive cerebrovascular diseases can cause a rapid increase in cerebral blood flow (CBF) in the chronic ischemic brain, resulting in complications such as

cerebral hyperperfusion syndrome. Cerebral hyperperfusion syndrome after carotid endarterectomy is characterized by unilateral headache, face and eye pain, seizures, and focal symptoms that occur secondary to cerebral edema or intracerebral hemorrhage (ICH).[1-4] Patients with poorer cerebrovascular reactivity are known to have higher risk for hyperperfusion syndrome.[4-7] In contrast, cerebral hyperperfusion syndrome after EC-IC bypass for atherosclerotic occlusive cerebrovascular disease is rare and mostly manifests as mild focal neurological deficit,[8,9] except for 1 case of acute hyperperfusion with massive ICH after high-flow EC-IC bypass.[10]

Moyamoya disease is a chronic, occlusive cerebrovascular disease with unknown origin characterized by bilateral stenoocclusive changes at the terminal portion of the internal carotid artery and an abnormal vascular network at the base of the brain.[11] EC-IC bypass such as superficial temporal artery–middle cerebral artery (STA-MCA) anastomosis is generally the standard surgical treatment for moyamoya disease to prevent cerebral ischemic attacks.[12-15] Despite the favorable long-term outcome,[12-15] increasing evidence suggests that focal cerebral hyperperfusion may cause transient neurological deterioration[12,16-22] or delayed ICH[23] during the acute stage after EC-IC bypass for moyamoya disease. These results strongly suggest that patients with moyamoya disease are more vulnerable to cerebral hyperperfusion compared with patients with other occlusive cerebrovascular diseases. However, the differences in the incidence and clinical manifestation of cerebral hyperperfusion between patients with and without moyamoya disease have not been evaluated.

The present prospective study performed *N*-isopropyl-p-[$^{123}$I]iodoamphetamine single-photon emission computed tomography ($^{123}$I-IMP-SPECT) 1 and 7 days after STA-MCA (M4) anastomosis in 121 hemispheres of 86 consecutive patients with moyamoya disease and 28 hemispheres of 28 patients without moyamoya disease to compare the incidences of symptomatic cerebral hyperperfusion.

## PATIENTS AND METHODS

### Inclusion Criteria

The postoperative changes in CBF and clinical course were investigated in 86 consecutive patients (moyamoya group; male/female = 24/62; age, 2-67 years; mean age, 34.3 years) with moyamoya disease surgically treated in 121 hemispheres by the same surgeon (M.F.) from March 2004 to June 2009. For comparison, the postoperative changes in CBF and clinical course were also investigated in 28 patients (non-moyamoya group; male/female = 24/4; age, 12-67 years; mean age, 56.3 years), including 27 adult patients with atherosclerotic occlusive cerebrovascular disease and 1 pediatric patient with MCA occlusion probably caused by dissection, who were surgically treated in 28 affected hemispheres. Inclusion criteria of this study, corresponding to our surgical indications for STA-MCA anastomosis, included all of the following: the presence of ischemic symptoms, apparent hemodynamic compromise by SPECT, independent activity of daily living (modified Rankin scale scores, 0-2), and absence of major cerebral infarction. All hemispheres that did not match these criteria were excluded from the initial surgery. Once hemodynamic compromise was confirmed, the patients underwent revascularization surgery. All patients in the moyamoya group underwent STA-MCA (M4) anastomosis with or without encephalo-duro-myo-synangiosis.[12,16] All patients in the non-moyamoya group underwent STA-MCA (M4) anastomosis without indirect pial synangiosis. All patients in the moyamoya group satisfied the diagnostic criteria of the Research Committee on Spontaneous Occlusion of the Circle of Willis of the Ministry of Health, Labor, and Welfare, Japan, except for 4 patients with "probable moyamoya disease" with unilateral involvement. All patients were strictly followed up in our institutes for > 6 months with a mean follow-up period of 45.6 months.

### Postoperative CBF Measurement and Diagnosis of Hyperperfusion

The CBF was routinely measured by $^{123}$I-IMP-SPECT 1 and 7 days after surgery in all patients in both groups. The CBF was quantified by the autoradiographic method; the CBF in each subregion of the cerebral cortex was automatically calculated by the Three-Dimensional Stereotactic Region of Interest Template software (version 2) provided by Daiichi Radio-Isotope (Tokyo, Japan), and the diagnosis of cerebral hemodynamics was made by 2 specialized radiologists blinded to the clinical condition of the patients.[12,20] Within 2 days after surgery, 1.5- or 3-T magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) were routinely performed.[19] MRI included diffusion-weighted images, fluid-attenuated inversion recovery images, T1-/T2-weighted images, and T2*-weighted images. The diagnostic criteria for symptomatic cerebral hyperperfusion included all of the following[12,20]: the presence of a significant focal increase in CBF at the site of the anastomosis (qualitative observation of focal intense increase in CBF confined to 1 major vascular territory), which is responsible for the apparent neurological signs including focal neurological deficit and/or severe headache resulting from hemorrhagic changes; apparent visualization of STA-MCA bypass by MRA and the absence of any ischemic changes by diffusion-weighted imaging; and 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.

The occurrence of symptomatic cerebral hyperperfusion after revascularization surgery was evaluated by $^{123}$I-IMP-SPECT in the acute stage. The mortality and morbidity resulting from cerebral hyperperfusion were also evaluated 3 months after revascularization surgery. We investigated the correlation between postoperative CBF changes and clinical presentation in both groups and compared the incidence of symptomatic cerebral hyperperfusion between the moyamoya group and non-moyamoya group.

### Statistical Analysis

The incidence of symptomatic cerebral hyperperfusion was compared between the moyamoya and non-moyamoya groups by $\chi^2$ test. Because age and history of intracranial hemorrhage were known to be related to symptomatic cerebral hyperperfusion after STA-MCA anastomosis for moyamoya disease,[12] multivariate statistical analysis of the factors related to development of symptomatic cerebral hyperperfusion, including disease subtype, age, sex, operated side, and history of intracranial hemorrhage, was performed with a logistic regression model. The incidence of any cerebral hyperperfusion (both symptomatic and asymptomatic) was also compared between the moyamoya and non-

moyamoya groups. Correlation between age and development of symptomatic cerebral hyperperfusion was evaluated in the moyamoya group by the Student *t* test. Systolic blood pressure 1 day after surgery was compared between the moyamoya group and non-moyamoya group by the Student *t* test.

## RESULTS

### Moyamoya Group

Among the 86 consecutive patients with 121 operated hemispheres, 25 patients (26 hemispheres, 21.5% of 121 operated hemispheres) suffered from temporary neurological deterioration, including mild focal neurological signs, resulting from postoperative focal cerebral hyperperfusion from 2 to 14 days after surgery (Table 1). Postoperative MRI/MRA showed no ischemic changes, and the thick high signal intensity of the STA on the operated hemisphere was evident in all 26 hemispheres. Postoperative SPECT revealed significant intense increases in CBF at the sites of anastomosis on all 26 hemispheres. As Table 2 summarizes, 21 patients (22 hemispheres, 18.2%) suffered from transient focal neurological deficit caused by focal hyperperfusion that mimicked ischemic attack, which started from 2 to 9 days after surgery and was sustained for several days. The anatomic location and the temporal profile of hyperperfusion were completely in accordance with the transient neurological signs in these 21 patients. Four patients (4 hemispheres, 3.3%) complained of severe headache and suffered from cerebral hyperperfusion syndrome associated with subarachnoid hemorrhage (SAH) in 3 patients (2.5%) or with ICH at the right frontal subcortex in 1 patient (0.83%). Symptoms were relieved by intensive blood pressure control with the use of the free radical scavenger edaravone (Mitsubishi Pharma Co, Tokyo, Japan), although 1 patient with ICH required rehabilitation to relieve transient left hemiparesis for 2 months.[23] One patient with significant bilateral flow compromise manifesting as SAH required ligation of the STA-MCA bypass 2 days after the first-stage surgery to control postoperative cerebral hyperperfusion and was rescued by marked development of pial synangiosis without complication. No patient suffered from permanent neurological deficit caused by cerebral hyperperfusion. No patients suffered from delayed neurological deterioration resulting from cerebral hyperperfusion during the follow-up period. Cerebral hyperperfusion, both asymptomatic and symptomatic, was detected by SPECT in 60.3% (73 of 121 hemispheres) in the moyamoya group.

Among 86 consecutive patients with 121 operated hemispheres in the moyamoya group, no patient suffered from perioperative cerebral infarction, except for 3 patients (2.5%) presenting with pseudolaminar necrosis in the part of the cerebral cortex supplied by the STA-MCA bypass in the subacute stage, which did not affect their long-term neurological status. All patients with the onset of transient ischemic attack obtained disappearance or improvement of ischemic attack during the follow-up period. One ischemia-onset patient (0.83%) suffered from ICH on the ipsilateral thalamus 3 years after successful revascularization surgery, and she suffered deteriorated modified Rankin scale score from 0 to 3 after hemorrhage. Two hemorrhage-onset patients suffered from rebleeding (1.65%), 1 from contralateral ICH and 1 from SAH, both of which did not affect their neurological status. The patency of the STA-MCA bypass was confirmed in all 86 patients with 121 operated hemispheres by postoperative MRA.

**TABLE 1. Incidence of Symptomatic Cerebral Hyperperfusion After Extracranial-Intracranial Bypass**

| | Moyamoya | Non-Moyamoya |
|---|---|---|
| Hemispheres, n (patients, n) | 121 (86) | 28 (28) |
| Age (mean), y | 2–67 (34.3) | 12–67 (56.5) |
| Male/female, n | 24/62 | 24/4 |
| Symptomatic hyperperfusion, n (%) | 26 (21.5)[a] | 0 (0) |

[a]Significantly higher ($P$ = .0069).

### Non-Moyamoya Group

Among 28 patients with 28 operated hemispheres in the non-moyamoya group, no patient (0 of 28, 0%) suffered from symptomatic cerebral hyperperfusion. No patient suffered from perioperative cerebral infarction by postoperative MRI, and the patency of STA-MCA bypass was confirmed by MRA in all 28 patients. No patient suffered cerebral ischemic events such as transient ischemic attack and recurrent stroke during the follow-up period. One patient presented with simple partial seizure of his right upper extremity several hours after left STA-MCA anastomosis, whereas $^{123}$I-IMP-SPECT 1 day after surgery demonstrated only mild increase in CBF at the left fronto-parietal lobe. On the basis of the effect of seizure on subsequent flow study and equivocal finding of $^{123}$I-IMP-SPECT, we did not include this case as symptomatic cerebral hyperperfusion. No other patients in the non-moyamoya group suffered from seizure postoperatively. Cerebral hyperperfusion, both asymptomatic and symptomatic, was detected by SPECT in 67.9% (19 of 28 hemispheres) in the non-moyamoya group.

### Statistical Analysis

The incidence of symptomatic cerebral hyperperfusion was significantly higher in the moyamoya group (26 of 121, 21.5%) compared with the non-moyamoya group (0 of 28, 0%; $P$ = .0069). The incidence of hemorrhagic cerebral hyperperfusion was 3.3% (4 of 121) in the moyamoya group, whereas no hemorrhagic complication occurred in the non-moyamoya group (0 of 28), although there was no statistical significance between groups ($P$ = .33). There was no significant difference in the incidence of any cerebral hyperperfusion, both asymptomatic and symptomatic, between the moyamoya group (73 of 121, 60.3%) and non-moyamoya group (19 of 28, 67.9%; $P$ = .46). Multivariate analysis revealed that the disease subtype of moyamoya disease was significantly associated with the development of

**TABLE 2. Incidence of Symptomatic Cerebral Hyperperfusion After Extracranial-Intracranial Bypass in 86 Patients With Moyamoya Disease[a]**

| | Hemisphere, n (Incidence, %) | Symptomatic Period, d | Brain Damage Caused by Hyperperfusion | Permanent Neurological Deficit Caused by Hyperperfusion |
|---|---|---|---|---|
| Symptomatic hyperperfusion | 26 (21.5) | | | |
| Focal neurological deficit | 22 (18.2) | 2–14 | None | None |
| SAH | 3 (2.5) | 1–2 | None | None |
| ICH | 1 (0.8) | ≥ 4 | Minimum | None |

[a]ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage.

symptomatic cerebral hyperperfusion ($P$ = .0008), as shown in Table 3. Age was also found to be associated with symptomatic cerebral hyperperfusion by multivariate analysis ($P$ = .033), probably because of the younger age distribution in the moyamoya group compared with the non-moyamoya group. There was no significant association of sex ($P$ = .41), side of the operated hemisphere ($P$ = .49), and past history of hemorrhage ($P$ = .19) with the occurrence of symptomatic hyperperfusion (Table 3).

Because of the apparently different age distributions in the moyamoya and non-moyamoya groups (Table 1), the correlation between age and development of symptomatic cerebral hyperperfusion was examined only in the moyamoya group. Among 86 patients with moyamoya disease, patients with symptomatic hyperperfusion were relatively older (mean, 38.9 years of age) than those without symptomatic hyperperfusion (mean, 32.8 years of age), but the difference was not significant ($P$ = .12). Systolic blood pressure 1 day after surgery was 131.8 mm Hg in the moyamoya group and 126.8 mm Hg in the non-moyamoya group (no statistical difference; $P$ = .069).

## REPRESENTATIVE CASES

### Case 1: Moyamoya Disease

This 9-year-old boy, presenting with minor completed stroke in the right temporo-occipital lobe, was found to have moyamoya disease. He underwent STA-MCA anastomosis with encephalo-duro-myo-synangiosis on the left hemisphere 4 months after revascularization surgery on the right hemisphere. The recipient artery at the M4 segment of the temporal branch of the MCA was explored, and anastomosis was performed between the stump of the STA (1.0 mm in diameter) and the M4 segment (0.8 mm in diameter) that supplied the left temporal lobe. The temporary occlusion time was 19 minutes. $^{123}$I-IMP-SPECT 1 day after surgery revealed focal intense increase in CBF at the site of the anastomosis (arrows in Figure 1A). Postoperative MRI 1 day after surgery showed no evidence of ischemic change, and MRA demonstrated thick high signal intensity of the STA (arrow in Figure 1B). Two days after surgery, he suffered from fluctuating aphasia. Repeated MRI ruled out cerebral ischemia and compression of the brain surface. On the basis of the diagnosis of symptomatic cerebral hyperperfusion, his systolic blood pressure was controlled under 110 mm Hg, which improved his symptom. His aphasia resolved 5 days after surgery, and $^{123}$I-IMP-SPECT 7 days after surgery showed normalization of CBF on the left hemisphere. He was discharged without neurological deficit 16 days after surgery, and there was no cerebrovascular event during the follow-up period of 3 months.

**TABLE 3. Multivariate Analysis of Symptomatic Cerebral Hyperperfusion After Extracranial-Intracranial Bypass**

| Risk Factors | Symptomatic Cerebral Hyperperfusion: Yes | Symptomatic Cerebral Hyperperfusion: No | P |
|---|---|---|---|
| Mean age, y | 38.8 ± 14.92 | 40.52 ± 18.68 | .0330 |
| Male sex, n (%) | 6 (23.1) | 52 (42.3) | .4064 |
| Left hemisphere, n (%) | 12 (46.15) | 65 (52.84) | .4910 |
| History of hemorrhage, n (%) | 4 (15.38) | 5 (4.07) | .1876 |
| Moyamoya disease, n (%) | 26 (100) | 95 (77.2) | .0008 |

### Case 2: Atherosclerotic Right MCA (M1) Occlusion

This 66-year-old woman, presenting with minor completed stroke in the right hemisphere, was proven to have severe hemodynamic compromise of the affected hemisphere. She underwent STA-MCA anastomosis on the affected hemisphere 6 months after the onset of stroke. The recipient artery at the M4 segment of the temporal branch of the MCA was explored, and anastomosis was performed between the stump of the STA (1.0 mm in diameter) and the M4 segment (1.0 mm in diameter) that supplied the temporal lobe. The temporary occlusion time was 18 minutes. $^{123}$I-IMP-SPECT 1 day after surgery revealed focal increase in CBF at the site of the anastomosis (arrows in Figure 2A). Postoperative MRI 2 days after surgery showed no evidence of ischemic change, and MRA demonstrated the high signal intensity of ipsilateral STA (arrow in Figure 2B). Blood pressure was maintained in the normal range, and she did not present neurological sign perioperatively. There was no cerebrovascular event during the follow-up period of 4 months.

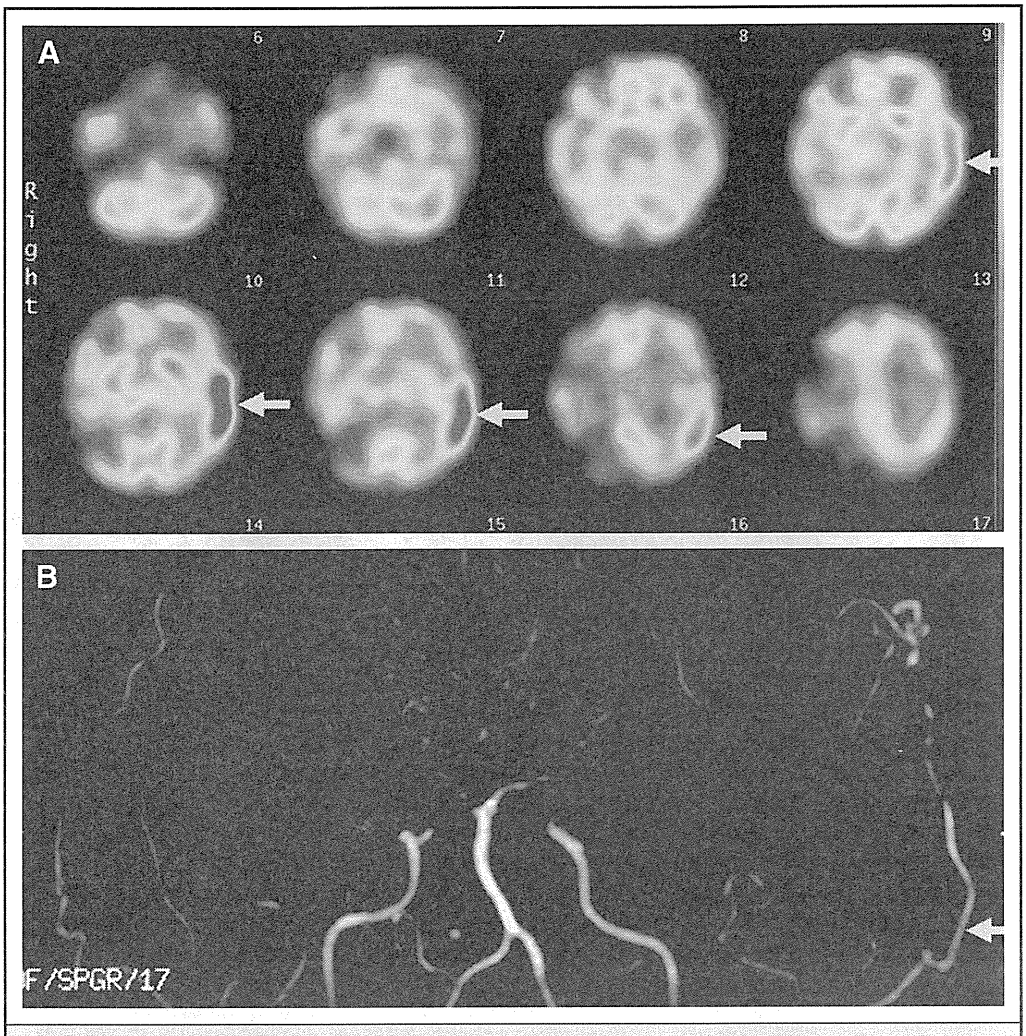


**FIGURE 1.** *Case 1: a 9-year-old boy with moyamoya disease presenting with cerebral infarction.* **A**, *N-isopropyl-p-[$^{123}$I] iodoamphetamine single-photon emission computed tomography 1 day after left superficial temporal artery–middle cerebral artery (STA-MCA) anastomosis with pial synangiosis. Marked increase in cerebral blood flow at the site of the anastomosis was evident (arrows in* **A***) in accordance with the manifestation of aphasia.* **B**, *magnetic resonance angiography 1 day after STA-MCA anastomosis with pial synangiosis demonstrating STA-MCA bypass as a thick high-signal sign (arrow in* **B***).*

Follow-up MRA 3 months after surgery showed apparently patent STA.

## DISCUSSION

In the present study, we demonstrated for the first time that patients with moyamoya disease have significantly higher risk for symptomatic hyperperfusion as a potential complication of EC-IC bypass compared with other occlusive cerebrovascular diseases treated by the same procedure. Accurate diagnosis by flow study and proper management of hyperperfusion is recommended, especially in patients with moyamoya disease, because the management of hyperperfusion is contradictory to that of cerebral ischemia.

### Incidence and Clinical Manifestation of Symptomatic Cerebral Hyperperfusion After EC-IC Bypass

Symptomatic cerebral hyperperfusion after EC-IC bypass for atherosclerotic occlusive cerebrovascular disease is rare and generally manifests as mild focal neurological deficit, which resolves within 2 weeks.[8,9] Heros et al[8] first suggested the involvement of cerebral hyperperfusion in 5 patients with atherosclerotic ischemic disease who presented with temporary neurological deterioration after STA-MCA bypass among 134 patients (3.7%). All 5 patients had resolved symptoms within 2 weeks after surgery. Kuroda and colleagues[9] also reported on a 64-year-old woman with atherosclerotic internal carotid artery occlusion who presented with transient aphasia caused by hyperperfusion from 2 to 7 days after STA-MCA anastomosis. Our results showed that

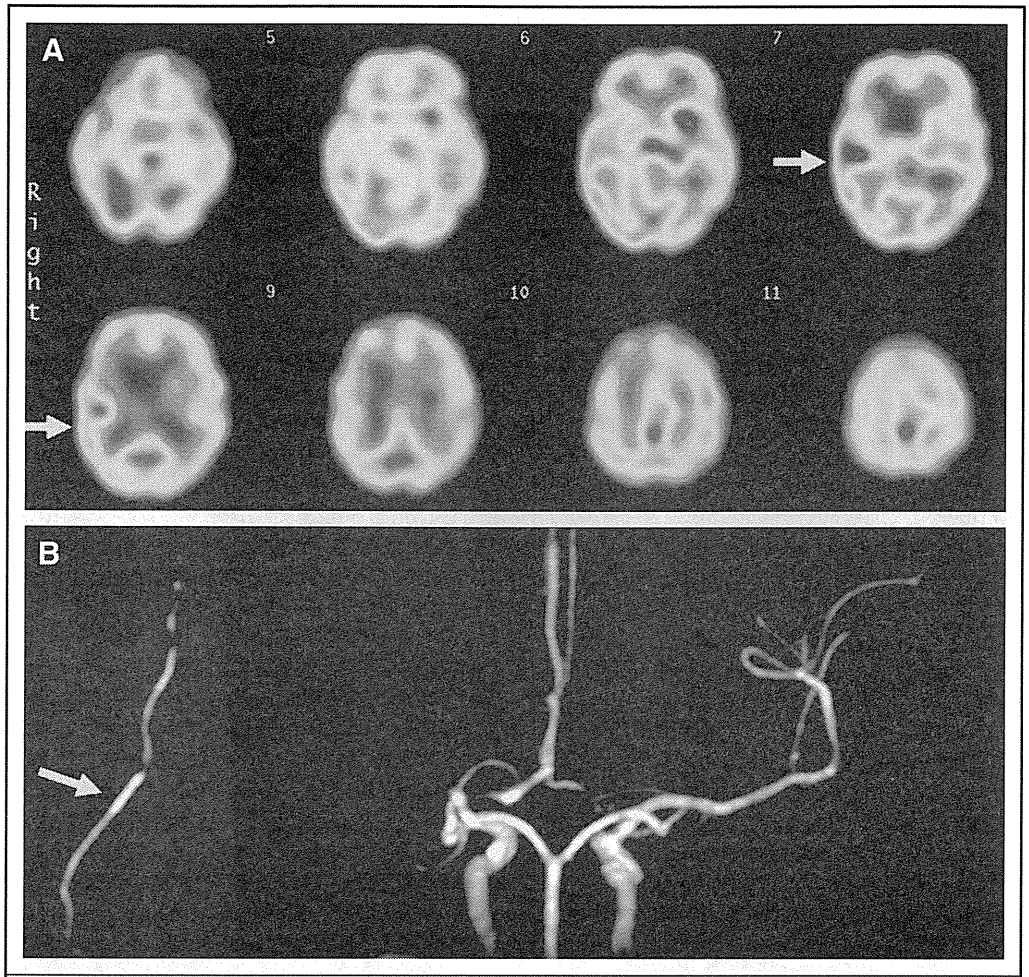


**FIGURE 2.** *Case 2: a 66-year-old woman with atherosclerotic right M1 occlusion presenting with minor completed stroke.* **A**, *N-isopropyl-p-[$^{123}$I]iodoamphetamine single-photon emission computed tomography 1 day after right superficial temporal artery–middle cerebral artery (STA-MCA) anastomosis. Focal increase in cerebral blood flow at the site of the anastomosis was evident (arrows in* **A**). **B**, *magnetic resonance angiography 1 day after STA-MCA anastomosis demonstrating STA-MCA bypass as a thick high-signal sign (arrow in* **B**). *Blood pressure was maintained in the normal range, and she did not present with neurologic sign perioperatively.*

no patients in the non-moyamoya group (0 of 28, 0%) suffered from symptomatic cerebral hyperperfusion after STA-MCA anastomosis. Regarding high-flow bypass, Stiver and Ogilvy[10] reported on a 48-year-old woman with severe right supraclinoid internal carotid artery and proximal M1 stenosis who suffered from acute hyperperfusion with massive ICH after high-flow EC-IC bypass. EC-IC bypass for atherosclerotic occlusive disease, as long as the low-flow bypass is selected, is considered to have relatively low risk for cerebral hyperperfusion, and symptoms are thought to be self-limiting in most cases.

In contrast to atherosclerotic patients, however, increasing evidence suggests that cerebral hyperperfusion is a cause of transient neurological deterioration[12,16-22] or delayed ICH[23] during the acute stage after EC-IC bypass for moyamoya disease. The incidence of temporary neurological deterioration probably caused by hyperperfusion is reported to be 16.7% to 28.1%[12,18,22] when mild focal neurological signs are included. Our most recent report, the only study in which a time sequential flow study was conducted in all cases, indicated that the incidence of symptomatic cerebral hyperperfusion was as high as 24.5% (25 of 102 consecutive surgeries),[12] although the exact difference in the incidence and clinical presentation of hyperperfusion between moyamoya patients and non-moyamoya patients was unclear.

In the present study, symptomatic cerebral hyperperfusion including mild focal neurological sign was seen in 25 patients with moyamoya disease (26 hemispheres, 21.5%) but in no

patients in the non-moyamoya group (0%; $P = .0069$). All patients with symptomatic hyperperfusion were treated with intensive blood pressure control, and no patient suffered from permanent neurological deficit resulting from cerebral hyperperfusion, although 4 patients with moyamoya disease had hemorrhagic hyperperfusion (4/121, 3.3%), including 3 patients with SAH and 1 with ICH,[23] which makes us aware of the substantial risks for surgical morbidity resulting from hyperperfusion in moyamoya patients. Regarding the time course of symptomatic cerebral hyperperfusion, focal neurological sign may manifest from postoperative day 2 and could prolong for several days, whereas SAH could occur on the day after revascularization surgery.[12,16] Intensive blood pressure control relieves symptoms caused by hyperperfusion, which may also help the diagnosis of hyperperfusion, whereas the focal neurological signs may fluctuate for a couple days before complete resolution. Thus, we recommend routine CBF measurement for patients with high risk of postoperative hyperperfusion such as moyamoya patients and patients with atherosclerotic ischemic disease associated with marked hemodynamic compromise.

We previously reported that adult-onset and/or hemorrhage-onset moyamoya patients had higher risk for symptomatic cerebral hyperperfusion.[12] In the present study, patients with symptomatic hyperperfusion were relatively older (mean, 38.9 years) than those without symptomatic hyperperfusion (mean, 32.8 years) in the moyamoya group, but we did not find a statistical difference, in contrast to our previous study. Relatively small numbers of pediatric cases in our series and our recent case with symptomatic cerebral hyperperfusion in a child (representative case 1) with marked preoperative hemodynamic compromise might have diluted the results in the present series. Nevertheless, we experienced only 2 pediatric moyamoya patients with symptomatic cerebral hyperperfusion, both presenting with mild neurological signs without hemorrhage, and we consider that accurate diagnosis of cerebral hyperperfusion is clinically important, especially for adult-onset moyamoya disease.

### Underlying Mechanism of the Occurrence of Cerebral Hyperperfusion in Patients With Moyamoya Disease

The reason why moyamoya patients had higher risk for symptomatic cerebral hyperperfusion is undetermined. Because the vulnerability of the blood-brain barrier in patients subjected to chronic ischemia is thought to be one of the important factors for cerebral hyperperfusion,[4] it is conceivable that a similar mechanism regarding blood-brain barrier maintenance, which may facilitate hemorrhage in patients with moyamoya disease, could also contribute to the occurrence of postoperative cerebral hyperperfusion. Because reactive oxygen species have been implicated in cerebral ischemia/reperfusion injury,[24] excessive production of reactive oxygen species during revascularization may also affect vascular permeability and thus result in transient neurological deterioration and/or hemorrhagic complications.[24,25] Regarding the downstream molecules related to reperfusion injury, recent studies using dura mater, arachnoid membrane, and serum obtained from the patients with moyamoya disease demonstrated that the expression of vascular endothelial growth factor[26] and matrix metalloproteinase-9,[25] both of which have a potential role to increase the permeability of the blood-brain barrier, is significantly increased in moyamoya patients compared with healthy control subjects. These observations raise the possibility that the increased expression of vascular endothelial growth factor and matrix metalloproteinase-9 in patients with moyamoya disease[25,26] may contribute, at least in part, to the vulnerability to cerebral hyperperfusion in moyamoya patients compared with the patients in the non-moyamoya group. Our results showed that there was no difference in the incidence of any cerebral hyperperfusion (symptomatic and asymptomatic) between the moyamoya and non-moyamoya groups, whereas moyamoya patients showed much higher incidence of symptomatic hyperperfusion compared with non-moyamoya patients. These findings strongly suggest a lower threshold for symptoms in the setting of hyperperfusion in moyamoya disease rather than in the hemodynamics. The issues regarding underlying mechanism of symptomatic cerebral hyperperfusion remain to be elucidated in a future study. By delineating the deleterious cascades of cerebral hyperperfusion, prophylactic blockade of these molecules in high-risk patients may be helpful in avoiding unfavorable complications, including postoperative cerebral hyperperfusion after EC-IC bypass, which could be a new therapeutic approach in combination with revascularization surgery for moyamoya disease.

Besides the intrinsic biological background of moyamoya disease, characteristic angioarchitecture of the pial artery may explain the underlying mechanism that facilitates postoperative cerebral hyperperfusion in patients with moyamoya disease. Kim and colleagues[18] speculate that poorer network formation between the pial arteries may lead to the poorer hemodynamic distribution after revascularization surgery and thus result in focal cerebral hyperperfusion after EC-IC bypass, especially in moyamoya disease. Our most recent study using a novel intraoperative infrared monitoring system on the brain surface demonstrated that the increase in the brain surface temperature around the site of the anastomosis immediately after surgical revascularization was significantly higher in patients who subsequently presented with symptomatic hyperperfusion,[20] suggesting that poorer distribution of the blood flow from STA may result in focal hyperemia and thus cause symptomatic cerebral hyperperfusion. Further study with a larger number of patients with moyamoya disease and with atherosclerotic ischemic disease may address this important issue.

## CONCLUSION

Symptomatic cerebral hyperperfusion is a potential complication of EC-IC bypass, especially in patients with moyamoya disease. Accurate diagnosis and proper management of hyperperfusion are recommended, especially in patients with moyamoya disease.

## Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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## COMMENTS

In this study, the authors report the differential risk for symptomatic cerebral hyperperfusion after revascularization for moyamoya disease compared with atherosclerotic disease. Whereas 21.5 % of the 121 moyamoya hemispheres suffered transient neurological symptoms attributable to focal hyperperfusion, none of the 28 patients with atherosclerosis demonstrated symptomatic hyperperfusion. Interestingly, imaging evidence of hyperperfusion was present in approximately two-thirds of patients in both groups, suggesting that the phenomenon is not uncommon but that the moyamoya group has a lower threshold for developing symptoms in this setting. Future studies to quantitatively assess the extent of hyperperfusion and correlation with intraoperative and postoperative bypass flow measurements will be important to provide further insights into this phenomenon.

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Fujimura et al present their large extracranial-intracranial arterial bypass experience and a comparison of the incidence of perioperative hyperperfusion syndrome, diagnosed by neurologic findings and abnormalities on *N*-isopropyl-p-[$^{123}$I]iodoamphetamine single-photon emission computed tomography, between those with moyamoya disease and those with nonmoyamoya, atherosclerotic occlusive disease. Interestingly, hyperperfusion was seen in 26 of 121 operated hemispheres for moyamoya disease and 0 of 28 hemispheres in the nonmoyamoya group. Hyperperfusion syndrome was confirmed in these patients by the presence of neurologic symptoms, absence of ischemic changes on magnetic resonance imaging, and concomitant hyperperfusion visualized in the region of the bypass on single-photon emission computed tomography imaging. In addition, subarachnoid hemorrhage and intracerebral hemorrhage were seen in a minority of patients with moyamoya disease undergoing extracranial-intracranial bypass and in none of those with atherosclerotic disease.

The authors present an elegant study that suggests a true difference in susceptibility to hyperperfusion in patients with moyamoya disease compared with those with vascular occlusive disease secondary to atherosclerotic disease. Hyperperfusion syndrome appears to be an increasingly recognized cause of neurologic deficit in the immediate postoperative period after cerebral revascularization, likely secondary to improved diagnostic imaging techniques and better understanding of this previously considered rare entity. A solid understanding of this diagnosis is particularly relevant, given that the treatment for hyperperfusion is the opposite of that for ischemia, and an unfortunate misdiagnosis may result in symptom exacerbation by inappropriate hemodynamic alterations if ischemia is wrongly suspected. Further research is essential to establish useful management guidelines for the successful prevention of cerebral hyperperfusion after revascularization; however, we commend the authors on their efforts to further illuminate the management nuances of this challenging disease.

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ORIGINAL RESEARCH

# "Brush Sign" on Susceptibility-Weighted MR Imaging Indicates the Severity of Moyamoya Disease

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**BACKGROUND AND PURPOSE:** SWI is a high spatial resolution MR imaging technique showing magnetic inhomogeneity that could demonstrate increased oxygen extraction in focal cerebral ischemia. The aim of this study was to investigate the characteristics in the signal intensity of DMVs by using SWI and to determine whether this method could indicate the severity of the hemodynamics in MMD by evaluating the correlation between SWI stage and hemodynamics on SPECT.

**MATERIALS AND METHODS:** Consecutive MMD patients were prospectively analyzed before treatment. Routine MR imaging including SWI was performed, and the number of the conspicuous DMVs draining into the subependymal veins was classified: stage 1, mild (<5); stage 2, moderate (5–10); and stage 3, severe (>10). The SWI stage was evaluated in correlation with clinical presentations, and CBF and CVR were quantified by using a SPECT iodine 123 *N*-isopropyl-p-iodoamphetamine split-dose method.

**RESULTS:** Patients were 12 males and 21 females (range, 8–66 years), consisting of 4 asymptomatic patients, 13 patients with TIA, 9 patients with infarct, and 7 patients with hemorrhage. There was a significant difference in CVR among clinical presentations, though there was no difference in age, Suzuki stage, or CBF. Conversely, SWI stage was significantly higher in patients with TIA and infarct than asymptomatic patients ($P < .01$). Higher SWI stage significantly had lower CBF and CVR in the middle cerebral artery area ($P < .05$).

**CONCLUSIONS:** SWI stage strongly correlates with ischemic presentations in MMD and also correlates with hemodynamics on SPECT, especially CVR. Increased conspicuity of DMVs, known as "brush sign", could predict the severity of MMD.

**ABBREVIATIONS:** ACA = anterior cerebral artery; ASL = arterial spin-labeling; CBF = cerebral blood flow; CBV = cerebral blood volume; CVR = cerebrovascular reserve; DMV = deep medullary vein; DSC = dynamic susceptibility contrast; $^{123}$IMP = iodine 123 *N*-isopropyl-p-iodoamphetamine; MB = microbleed; MCA = middle cerebral artery; MMD = Moyamoya disease; OEF = oxygen extraction fraction; PET = positron-emission tomography; PSI = phase shift image; ROI = region of interest; SPECT = single-photon emission CT; STA = superficial temporal artery; SWI = susceptibility-weighted image; TIA = transient ischemic attack

MMD is an uncommon cerebrovascular disease characterized by progressive stenosis of the terminal portion of the bilateral internal carotid arteries that leads to the compensatory formation of an abnormal network of perforating blood vessels, named Moyamoya vessels, that provide collateral circulation.[1,2] The clinical features of MMD substantially differ between children and adults. Most children with MMD develop TIA or cerebral infarction, whereas approximately half of adult patients develop intracranial bleeding, and half develop TIA or cerebral infarction or both.[3] The clinical presentation and outcome in MMD remain varied and are based on angiographic studies and other factors, including age, systemic factors, and the quality of the cerebral circulation and collateral networks.[4]

Therefore, imaging modalities, including SPECT, PET, xenon-CT, and dynamic perfusion CT have been applied to predict the patients with severe hemodynamic impairments. Moreover, new MR imaging-based methods such as DSC-weighted bolus tracking MR imaging and ASL are available for quantitative hemodynamic analysis.[5] In terms of MMD, measuring CVR is critical because patients with MMD are in a chronic state of cerebral vasodilation, necessary to maintain CBF. The CVR is often measured by SPECT or xenon-CT before and after administering a vasodilator, such as $CO_2$ or acetazolamide,[6] and the combination of the lower CVR and lower CBF is a reliable index for accurately detecting the existence of increased OEF, which is known as misery perfusion.[7]

Recently, the advancement of MR imaging modalities has enabled to investigators to evaluate small venous structures and iron in the brain. In particular, SWI has been accepted as a method available to evaluate deep venous flow in acute or chronic ischemia and to demonstrate increased oxygen extraction in focal cerebral ischemia.[8] Here, we first describe the

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characteristics of the signal intensity of DMVs by using SWI. We then determine whether this SWI could be used to assess the severity of the hemodynamics in MMD by evaluating the correlation between SWI stage and hemodynamics, including CBF and CVR, on SPECT.

## Materials and Methods

### *Patients*

From April 2006, 33 patients with MMD were prospectively analyzed as a preoperative assessment in this study. The patients were diagnosed with MMD according angiographic findings[9]: stenosis or occlusion is present at the terminal portions of the internal carotid artery or the proximal areas of the anterior cerebral artery and MCA, and there are abnormal vascular networks in the arterial territories near the occlusive or stenotic lesions, detected by MR angiography and intra-arterial angiography. The patients underwent preoperative MR evaluation, including SWI and hemodynamic study by using SPECT. Control SWI data were obtained from 10 healthy volunteers (mean age, 42 years; range, 33–52 years).

### *Imaging*

All patients underwent intra-arterial angiography to confirm Suzuki's staging of MMD, to evaluate collateral supplies to the affected area and development of the STA as a donor vessel for direct bypass surgery. Brain MR imaging was obtained on a 3T system (Signa Excite HDx; GE Healthcare, Milwaukee, Wisconsin) by using an 8-channel brain phased array coil. We acquired SWI contrast by using a PSI technique with a 3D gradient recalled acquisition in the steady state (TR, 44ms; TE, 30ms; flip angle, 20°; FOV, 20 cm; matrix 320 × 192; section thickness 2 mm). The PSI generates susceptibility contrast computed by multiplication of the phase and magnitude images. The PSI was postprocessed by using a high-pass filter and then converted into negative phase masks that were multiplied 4 times into the corresponding magnitude images by use of Windows-based research software (PSI Recon; GE Yokogawa Medical Systems, Tokyo, Japan). We analyzed PSI-based SWI with a minimal intensity projection to display the processed data and contiguous 6-mm-thick sections with 3-mm overlap in the transverse plane.

We also performed SPECT procedures according to the split-dose method protocol.[6] SPECT was performed by using a triple-head gamma camera (PRISM 3000; Picker, Cleveland, Ohio) equipped with a high-resolution fan-beam collimator. The data acquisition protocol was a 120° rotation with a 3° step and an acquisition time of 30 seconds per step. All images were reconstructed by filtered back-projection by using a Ramp filter, and attenuation correction by using the Chang method was applied. A 64 × 64 image matrix was used for the data acquisition and display. During the dynamic SPECT of 24 frames (1 frame took 2 minutes 30 seconds), 111 MBq of $^{123}$I-IMP (Nihon Mediphycs, Tokyo, Japan) was intravenously injected at the start of imaging, and 20 mg/kg acetazolamide (Diamox; Sanwa Kagaku Kenkyusho, Nagoya, Japan) was thereafter slowly injected intravenously over a 1-minute period at the fourth frame (9 minutes after the initial $^{123}$I-IMP injection). An additional 111 MBq of $^{123}$I-IMP was injected at the 10th frame (25 minutes after the start of imaging). Continuous arterial sampling with the octanol fraction at a constant speed of 1 mL/min for 5 minutes was started 30 seconds before the first frame and then was stopped 30 seconds after the second frame. A region of interest was set up in the cortical MCA, basal ganglia, and thalamus. The area of infarction or hemorrhage was excluded from the field of region of interest. Two perfusion images, namely, the resting and vasodilated images, were obtained with the subtraction technique. The following equation was used to estimate the percentage increase in CBF (milliliters per 100 g per minute) induced by acetazolamide challenge in the form of the CVR: CVR = values formulated (acetazolamide challenge SPECT count − resting SPECT count)/resting SPECT count (percentage).

### *Image and Statistical Analysis*

With the SWI method, we focused on the DMV, which drains into the subependymal veins. The number of the conspicuous DMVs was classified as follows: stage 1, mild (<5); stage 2, moderate (5–10); and stage 3, severe (>10). Representative images are shown in Fig 1. Two independent neuroradiology (M.M.) and cerebrovascular neurosurgery (N.H.) experts, who were blinded to the patients' clinical and radiologic information, evaluated all images. Each reader evaluated the patient images separately and independently. Statistical agreement, Cohen $\kappa$, was calculated to determine agreement between readings (IBM SPSS Statistics 15.0, SPSS Japan, Tokyo, Japan). Interpretation of the $\kappa$ statistics was based on the following scheme: 0–0.4, poor agreement; 0.4–0.7, good agreement; and >0.7, excellent agreement. Statistical analysis of the data was performed with 1-way analysis of variance and post hoc analysis by using Tukey-Kramer multiple comparison test (Instat, Version 3.05; GraphPad Software, San Diego, California). Differences were defined as significant at a probability level of $P > .05$.

## Results

Between April 2006 and August 2010, 33 patients with MMD (12 males and 21 females; mean age, 31 years; range, 8–66 years) were registered into the study. Patient characteristics are summarized in the Table. They consisted of 4 asymptomatic patients, 13 patients with TIA, 9 patients with infarction, and 7 patients with hemorrhage. Regarding Suzuki angiographic stages,[1,2] 29 patients were in stage 3 and the remaining 4 patients were in stage 4. Although a difference in CVR among the clinical presentations was detected, there was no difference in age, Suzuki stage, and CBF (Table). The DMV runs from the frontoparietal cortex down to the draining subependymal vein near the lateral ventricle, and these are normally difficult to identify radiologically. In ischemic MMD, however, DMVs are easily identified. The interrater reliability (Cohen $\kappa$) for SWI stage was calculated as 0.66, which is considered to represent substantial agreement. The SWI stage was significantly higher in patients with TIA and infarct than in controls, asymptomatic patients, and patients with hemorrhage ($P < .05$ versus control, asymptomatic, or hemorrhage; Fig 2*A*). The SWI stage in the control subjects was similar to that of the asymptomatic subjects (Fig 2*A*). In addition, CVR was significantly lower in the patients with TIA and infarct than in the asymptomatic patients ($P < .05$; Fig 2*B*, -*C* and Table), though there was no significant difference in CBF among groups. Interestingly, SWI stage and CBF were similar between asymptomatic patients and patients with hemorrhage and CVR in patients with hemorrhage was not severely impaired, which was different from that of the TIA and infarct groups.

We next assessed the correlation between SWI stage and hemodynamics (CBF and CVR) on SPECT (Fig 3*A–F*). This clearly showed that CBF was significantly higher in SWI stage