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Prediction of Cerebral Hyperperfusion after Superficial Temporal Artery-Middle Cerebral Artery Anastomosis by Three-Dimensional-Time-of-Flight Magnetic Resonance Angiography in Adult Patients with Moyamoya Disease

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Keywords
Cerebral blood flow · Cerebral hyperperfusion · Magnetic resonance angiography · Moyamoya disease · Extracranial-intracranial bypass

Abstract
Introduction: Superficial temporal artery (STA)-middle cerebral artery (MCA) anastomosis is an effective surgical procedure for adult patients with moyamoya disease (MMD) and is known to have the potential to prevent cerebral ischemia and/or hemorrhagic stroke. Cerebral hyperperfusion (CHP) syndrome is one of the serious complications of this procedure that can result in deleterious outcomes, such as delayed intracerebral hemorrhage, but the prediction of CHP before revascularization surgery remains challenging. The present study evaluated the diagnostic value of preoperative three-dimensional (3D)-time-of-flight (TOF) magnetic resonance angiography (MRA) for predicting CHP after STA-MCA anastomosis for MMD. ***Materials and Methods:*** The signal intensity of the peripheral portion of the intracranial major arteries, such as the anterior cerebral artery (ACA), MCA, and posterior cerebral artery (PCA) ipsilateral to STA-MCA anastomosis, on preoperative MRA was graded (0–2 in each vessel) according to the ability to visualize each vessel on 97 affected hemispheres in 83 adult MMD patients. Local cerebral blood flow (CBF) at the site of anastomosis was quantitatively measured by *N*-isopropyl-p-[^{123}I]-iodoamphetamine single-photon emission computed tomography 1 and 7 days after surgery, in addition to the preoperative CBF value at the corresponding area. Then, we investigated the correlation between the preoperative MRA score and the development of CHP. ***Results:*** The CHP phenomenon 1 day after STA-MCA anastomosis (local CBF increase over 150% compared with the preoperative value) was evident in 27 patients (27/97 hemispheres; 28%). Among them, 8 (8 hemispheres) developed CHP syndrome. Multivariate analysis revealed that the hemispheric MRA score (0–6), the summed ACA, MCA, and PCA scores for the affected hemisphere, was significantly associated with the development of CHP syn-

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drome ($p = 0.011$). The hemispheric MRA score was also significantly correlated with the CHP phenomenon, either symptomatic or asymptomatic ($p < 0.001$). ***Conclusion:*** The signal intensity of the intracranial major arteries, including the ACA, MCA, and PCA, on preoperative 3D-TOF MRA may identify adult MMD patients at higher risk for CHP after direct revascularization surgery.

Introduction

Superficial temporal artery (STA)-middle cerebral artery (MCA) anastomosis is an effective surgical procedure for adult patients with moyamoya disease (MMD) and is known to have the potential to prevent cerebral ischemia and/or hemorrhagic stroke [1–6]. Cerebral hyperperfusion (CHP) syndrome is one of the serious complications of this procedure that can result in deleterious outcomes, such as delayed intracerebral hemorrhage, seizure, and/or focal neurological deterioration, especially in patients with MMD [7–12]. Recent studies delineated the risk factors associated with CHP syndrome in MMD patients, such as old age, type of hemorrhage onset, and operation on the left hemisphere, but the accurate prediction of CHP before revascularization surgery remains challenging [8, 13, 14]. In the present study, we investigated the diagnostic value of preoperative three-dimensional (3D)-time-of-flight (TOF) magnetic resonance angiography (MRA), which is more available and easily performed at most clinical institutions, for predicting CHP after STA-MCA anastomosis for adult MMD.

Materials and Methods

Inclusion Criteria for Patients

Between July 2017 and September 2019, 83 consecutive adult MMD patients (97 hemispheres, aged 16–72 years, mean 44.8) who underwent STA-MCA anastomosis with indirect pial synangiosis by a single surgeon (M.F.) were assessed for eligibility. All patients satisfied the diagnostic criteria of the Research Committee on Spontaneous Occlusion of the Circle of Wills of the Ministry of Health, Labour and Welfare of Japan [6]. Surgical indications for MMD included all of the following items: the presence of ischemic symptoms (minor completed stroke and/or transient ischemic attack) and/or history of posterior hemorrhage, notable hemodynamic compromise on *N*-isopropyl-p-[^{123}I]-iodoamphetamine single-photon emission computed tomography (^{123}I-IMP-SPECT), independent activities of daily living (modified Rankin Scale scores 0–2), and the absence of major cerebral infarction exceeding the vascular territory of one major branch of the MCA [5, 6].

Surgical Procedure

All patients underwent STA-MCA (M4) anastomosis with encephalo-duro-myo-synangiosis (EDMS) under general anesthesia by a single surgeon (M.F.) at Kohnan Hospital according to the previously described procedure [2, 9]. Craniotomy was performed around the Sylvian fissure end, being approximately 8 cm in diameter, and the stump of the STA, either the frontal or parietal branch, was anastomosed to the M4 segment of the MCA, which was followed by EDMS. To avoid mechanical compression of the brain surface by the temporal muscle pedicle used for EDMS, we drilled out the inner layer of the bone flap and made a wider bone window on the side of EDMS pedicle insertion. The patency of STA-MCA anastomosis was confirmed by intraoperative indocyanine green (ICG) video angiography and Doppler ultrasonography.

Radiological Evaluation

Preoperative CBF and postoperative CBF were quantitatively measured using the autoradiographic method by ^{123}I-IMP SPECT with Infinia II (GE Healthcare, Japan), as previously described [15]. In brief, the preoperative CBF was measured within 2 months before surgery in most cases and postoperative CBF was routinely measured in the acute stage, namely on postoperative day (POD) 1 and POD 7. Magnetic resonance imaging (MRI) and MRA were routinely performed on POD 2. MRI included diffusion-weighted images (DWI), T2-weighted images, T2*-weighted images, and fluid-attenuated inversion recovery (FLAIR). We quantitatively measured the CBF, and a small region of interest (ROI) with a diameter of 1 cm was defined manually at the site of anastomosis and the ipsilateral cerebellar hemisphere according to the previously described method [15–17]. The exact sites of anastomosis were confirmed by the original axial slice on MRA. To calculate the postoperative/preoperative CBF ratio, both preoperative and postoperative CBF were adjusted to the CBF value of the ipsilateral cerebellar hemisphere on POD 1 [15–17].

Diagnosis of Cerebral Hyperperfusion Syndrome

The definition of radiological local CHP in this study included all of the following items described previously: (1) a 150% increase in CBF at the site of anastomosis, (2) visualization of STA-MCA bypass by MR angiography, and (3) the absence of other pathologies, such as compression of the brain surface by the temporal muscle inserted for indirect pial synangiosis, and ischemic changes [16, 17]. Then, we diagnosed the patients with CHP syndrome if they developed delayed symptomatic hemorrhage (intracerebral hemorrhage and/or subarachnoid hemorrhage) at the region of local CHP, seizure in the presence of local CHP, and/or neurological deterioration caused by local CHP that was able to be ameliorated by reducing the blood pressure. It is necessary for the diagnosis of CHP to exclude other pathophysiological conditions, such as cerebral ischemia or mechanical compression of the brain surface by temporal muscle pedicle, by routine computed tomography (POD 0, POD 1, and POD 7) and MRI.

MRA and Assessment of the Hemispheric MRA Score

The MRA study was performed as described previously using a 1.5T imager (Signa Excite HD; GE Healthcare, Milwaukee, WI, USA) [9]. The signal intensity of the peripheral portion of the intracranial major arteries, such as the anterior cerebral artery (ACA), MCA, and posterior cerebral artery (PCA) ipsilateral to STA-MCA anastomosis, on preoperative MRA was graded (0–2 in each vessel) according to the ability to visualize each vessel on 100

Table 1. Hemispheric MRA score, the sum of ACA, MCA, and PCA scores

ACA score	
Signal of distal ACA branches is normal	0
Signal of distal ACA branches decreases	1
Signal of distal ACA branches is difficult to identify	2
MCA score	
Signal of distal MCA branches is normal	0
Signal of distal MCA branches decreases	1
Signal of distal MCA branches is difficult to identify	2
PCA score	
Signal of distal PCA branches is normal	0
Signal of distal PCA branches decreases	1
Signal of distal PCA branches is difficult to identify	2
Hemispheric MRA score: ACA score + MCA score + PCA score	0–6

ACA, anterior cerebral artery; MCA, middle cerebral artery; MRA, magnetic resonance angiography; PCA, posterior cerebral artery.

affected hemispheres in 86 adult MMD patients, based on the previously described method with modification [18]. We defined grade 0 as the maintenance of almost normal signal intensity of peripheral arteries (A2–A4 segment, M2–M4 segment, and P2–P4 segment), grade 1 as visible but reduced signal intensity of the peripheral arteries, and grade 2 as the absence of signal intensity of the peripheral arteries. The image-determination committee, which included 4 members (T.N., M.F., S.M., and K.S.), recorded the MRA score in each hemisphere. All 4 members of the image-determination committee attended the discussion on the MRA findings, and the MRA score in each hemisphere was ultimately decided after we got unanimous in our approval of the particular score. Then, the hemispheric MRA score was calculated by summing the ACA, MCA, and PCA scores (0–6). Detailed definitions of the MRA grade in each vessel are summarized in Table 1. Representative MRA findings are shown in Figure 1a.

Postoperative Management

All patients were prospectively subjected to prophylactic intensive blood pressure reduction (systolic blood pressure of 110–130 mm Hg) in accordance with the standardized postoperative management protocol to prevent CHP using a 1–10-mg/h continuous intravenous drip infusion of nicardipine hydrochloride while awake [19]. All patients were managed by intraoperative and postoperative intravenous administration of minocycline hydrochloride (200 mg/day) until 7 days after surgery in order to avoid the deleterious effects of CHP and to reduce the risk of cerebral ischemia at remote areas [20]. We routinely administered antiplatelet agents (100 mg of aspirin/day) starting the day after surgery to all patients. If patients developed radiological CHP, we attempted further blood pressure reduction (systolic blood pressure of 100–120 mm Hg) and administered additional levetiracetam (1,000 mg/day) and edaravone (60 mg/day) until 7 days after surgery [17, 21]. Based on the temporal profile of ^{123}I-IMP-SPECT and MRI/MRA findings, we gradually allowed the return to normotensive conditions within 7–10 days after surgery [19, 20].

Statistical Analysis

To evaluate the correlation between MRA score and the development of CHP, logistic regression analysis was used for baseline characteristics: age, sex, side, onset type, Suzuki's angiographic stage, family history of moyamoya disease (%), and symptomatic CHP. All statistical analyses were performed using IBM SPSS Statistics version 24.0.0 (IBM Software Group, Chicago, IL, USA). p values <0.05 were considered significant.

Results

The clinical characteristics of adult MMD patients in this study are summarized in Table 2. Radiological CHP, either symptomatic or asymptomatic, 1 day after STA-MCA anastomosis (local CBF increase over 150% compared with the preoperative value) was evident in 27 patients (27/97 hemispheres; 28%). Among them, 8 (8 hemispheres) developed CHP syndrome. The location of CHP was completely in accordance with the site of STA-MCA anastomosis in 27 patients. The location of the symptomatic CHP was frontal lobe in 4 patients, parietal lobe in 2 patients, and temporal lobe in 2 patients. Then, we analyzed the association between CHP syndrome and clinical characteristics by logistic regression analysis. There was no significant difference in patient age, sex, or side of the operation between the groups. The hemispheric MRA score (0–6) was significantly higher in patients with CHP syndrome than in those without CHP syndrome (4.25 ± 1.58 in the CHP syndrome group vs. 2.55 ± 1.40 in the non-CHP syndrome group; $p = 0.005$). Receiver operating characteristic (ROC) revealed that the cutoff value for the preoperative total MRA score for CHP syndrome was 3.5 (sensitivity = 75.0%, specificity = 75.3%, and AUC = 0.784). Regarding each MRA score, the local MRA score of MCA (0–2) was not statistically different between both groups (1.75 ± 0.46 in the CHP syndrome group vs. 1.37 ± 0.66 in the non-CHP syndrome group; $p = 0.134$). Local MRA scores of ACA, MCA, and PCA are shown in Table 3. The CBF increase ratio, adjusted by the ipsilateral cerebellar CBF, was also significantly higher in patients with CHP syndrome than in those without CHP syndrome (257.8 ± 68.4% in the CHP syndrome group vs. 128.0 ± 35.5% in the non-CHP syndrome group; $p < 0.001$). After eliminating closely related variables in the univariate analyses, the following confounders were adopted in the logistic regression model for the multivariate analysis: age, sex, side, onset type, Suzuki's angiographic stage, and total hemispheric MRA score (0–6). The multivariate analysis revealed that the hemispheric MRA score was significantly associated with the development

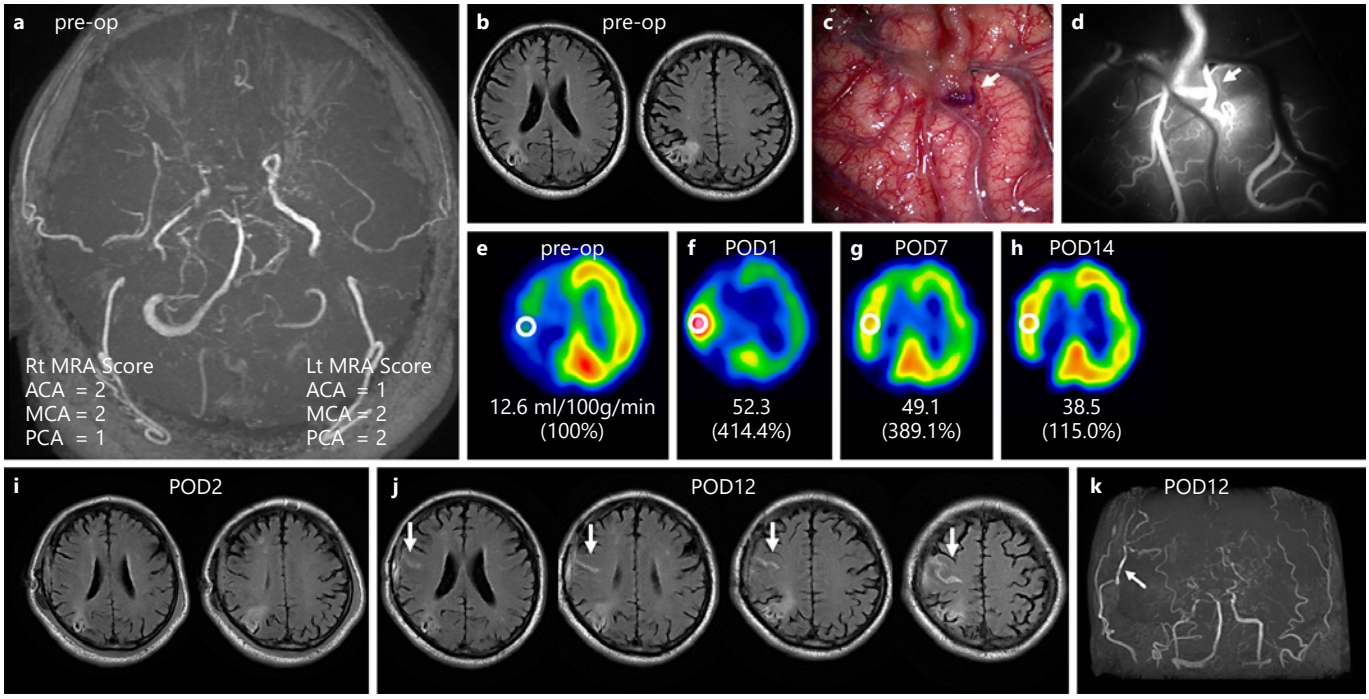

Fig. 1. a Preoperative MRA scores for each hemisphere as grade 5, bilaterally. **b** FLAIR showing cerebral infarction in the right parieto-occipital lobe. **c** Intraoperative view of right STA-MCA anastomosis (arrow). **d** Indocyanine green video-angiography confirmed the patency of the bypass artery (arrow). **e–h** ^{123}I-IMP SPECT before (**e**) and 1 day (**f**), 7 days (**g**), and 14 days (**h**) after right STA-MCA anastomosis. The shown numbers are the quantitative local CBF values of the white circle by the auto-radiographic method. Percentages in the parenthesis indicate the relative CBF ratio compared with the preoperative value. **i** FLAIR at POD 2. **j** FLAIR at POD 12 demonstrating newly developed subarachnoid hemorrhage at the vascular territory of bypass (arrows). **k** MRA 12 days after surgery indicating right STA-MCA bypass as high signal intensity (arrow). MRA, magnetic resonance angiography; STA-MCA, superficial temporal artery-middle cerebral artery; ^{123}I-IMP SPECT, *N*-isopropyl-p-[^{123}I]-iodoamphetamine single-photon emission computed tomography; CBF, cerebral blood flow; POD, postoperative day.

of postoperative CHP syndrome ($p = 0.011$). It was also significantly correlated with the CHP phenomenon, which was either symptomatic or asymptomatic (3.78 ± 1.45 in the CHP phenomenon group vs. 2.27 ± 1.28 in the non-CHP phenomenon group; $p < 0.001$). The correlation of CHP syndrome with each factor is summarized in Table 3.

Representative Case

A 58-year-old man presented with visual field deficit caused by cerebral infarction. Catheter angiography demonstrated stenosis at the terminal portion of the bilateral internal carotid arteries and abnormal vascular network formation at the base of the brain, leading to the definitive diagnosis of MMD. We evaluated the bilateral MRA score, as shown in Figure 1a, resulting in a hemispheric MRA score for the affected hemisphere of grade 5 (ACA score = 1, MCA score = 2, and PCA score = 2). FLAIR MR imaging demonstrated cerebral infarction in the right parieto-occipital lobe (Fig. 1b). ^{123}I-IMP SPECT demonstrated a significant decrease in the CBF in the entire right hemisphere (Fig. 1e). Based on the ischemic symptom of the right hemisphere, the patient underwent right STA-MCA anastomosis with EDMS. The stump of the parietal branch of the STA was anastomosed to the M4 segment of the right MCA, supplying the frontal lobe (arrow in Fig. 1c). Intraoperative indocyanine green video-angiography after anastomosis demonstrated localized early filling through the STA with slight parenchymal staining at the localized area around the site of the anastomosis (arrow in Fig. 1d). The postoperative neurological status was stable, but ^{123}I-IMP SPECT at POD 1 revealed significant CBF increase at the site of the anastomosis (414.4% compared with the preoperative value), suggesting a marked CHP phenomenon (white circle in Fig. 1f). Based on this finding, the patient was maintained under strict blood pressure control and no signal intensity change was observed on FLAIR MRI at POD 2

Table 2. Clinical characteristics of 97 affected hemispheres in 83 adult patients with moyamoya disease who underwent revascularization

	All (N = 97), described as n or mean ± SD
Age, years	44.8±13.6 (16–72)
16–20	4
21–40	28
41–60	50
60–72	15
Women:men	63:34
Left:right	46:51
Family history of moyamoya disease, %	7/97 (7%)
Onset; hemorrhage:ischemia	14:83
Hypertension	49/97 (51%)
Dyslipidemia	16/97 (17%)
Diabetes mellitus	5/97 (5%)
Suzuki's angiographic staging	3.08±0.81
MRA scoring	
MCA score (0–2)	1.40±0.66
ACA Score (0–2)	0.99±0.91
PCA score (0–2)	0.34±0.64
Total MRA score (0–6)	2.69±1.48
Symptomatic cerebral hyperperfusion	8/97 (8%)
CBF increase ratio (POD1/ preoperative value)	138.7±52.8%

ACA, anterior cerebral artery; MCA, middle cerebral artery; MRA, magnetic resonance angiography; PCA, posterior cerebral artery; CBF, cerebral blood flow; POD, postoperative day.

(Fig. 1i). The CHP phenomenon was sustained at POD 7 by ^{123}I-IMP SPECT (389.1% compared with the preoperative value; white circle in Fig. 1g); then, we gradually allowed the patient to be in a normotensive condition during the following 5 days. However, they developed seizures at POD 12, when FLAIR demonstrated subarachnoid hemorrhage at the site of anastomosis that was not evident previously (arrows in Fig. 1j). MR angiography at POD 12 confirmed the apparently patent STA-MCA bypass as thick high signal intensity (arrow in Fig. 1k). We resumed maintenance of the patient under strict blood pressure control (systolic blood pressure of 100–120 mm Hg). As the local CHP phenomenon was ameliorated by ^{123}I-IMP SPECT at POD 14 (white circle in Fig. 1h), we allowed the patient to be in a normotensive condition again. The patient was moved to the rehabilitation center with a modified Rankin Scale (mRS) score of 2. There was no cerebrovascular event during the follow-up period of 2 years (mRS 1).

Discussion

In the present study, we demonstrated that the signal intensity of the peripheral portion of the intracranial major arteries, including the ACA, MCA, and PCA, by 3D-TOF MRA has predictive value for identifying adult MMD patients at higher risk for CHP after direct revascularization surgery. This observation was based on the following results of multivariate analysis. First, the CHP phenomenon 1 day after STA-MCA anastomosis (local CBF increase over 150% compared with the preoperative value) was evident in 27 patients (27/97 hemispheres; 28%), and the hemispheric MRA score before surgery was significantly associated with the CHP phenomenon, which was either symptomatic or asymptomatic (p < 0.001). Second, 8 patients (8 hemispheres; 8%) developed CHP syndrome, and the preoperative MRA score was significantly correlated with the development of CHP syndrome such as delayed intracerebral hemorrhage, seizure, and focal neurological deterioration.

Recent evidence strongly suggests that STA-MCA anastomosis is highly effective for preventing recurrent ischemic attack in adult patients with MMD [1–4]. Moreover, the Japan Adult Moyamoya trial, a randomized controlled clinical trial to investigate the efficacy of STA-MCA anastomosis for preventing recurrent hemorrhage in adult MMD patients, strongly suggested that STA-MCA anastomosis is a powerful management choice to reduce the risk of rebleeding in hemorrhagic-onset MMD patients [5, 22]. Based on this background, the number of MMD patients undergoing revascularization surgery is increasing in neurosurgical practice. However, cerebral ischemia and CHP are known as potential complications of this procedure that can result in surgical morbidity and/or mortality. Thus, the prediction of CHP syndrome is crucial in daily clinical practice, and we have previously reported that adult MMD patients had significantly higher risk for CHP syndrome compared with pediatric patients [8]. Based on this finding, we avoid excessive blood pressure lowering in pediatric MMD patients in view of the risk of ischemic complication. Regarding the prediction of CHP syndrome among adult MMD patients, it is still difficult to make accurate prediction before surgery, even though we have reported other predictive factors related to CHP such as hemorrhagic onset [8] and smaller diameter of recipient artery by intraoperative finding [20]. The management of CHP in adult MMD patients also remains difficult, although there have been efforts to introduce intensive perioperative management protocols in multiple institutes. Therefore, we believe that

Table 3. Correlation of CHP syndrome with each factor

	Symptomatic CHP (+) (n = 8)	Symptomatic CHP (–) (n = 89)	Unadjusted		Adjusted[a]	
			OR (95% CI)	p value	OR (95% CI)	p value
Age (mean±SD)	51.3±8.7	44.2±13.8	1.041 (0.983–1.103)	0.167	1.061 (0.987–1.140)	0.106
Women:men	4:4	59:30	0.508 (0.119–2.176)	0.362		
Left:right	5:3	41:48	1.951 (0.439–8.665)	0.380	4.396 (0.706–27.378)	0.113
Family history	1:7	6:83	1.976 (0.208–18.809)	0.553		
Onset; hemorrhage:ischemia	3:5	11:78	4.255 (0.890–20.335)	0.070	5.916 (0.854–41.001)	0.072
Hypertension	5:3	44:45	1.705 (0.384–7.567)	0.483		
Dyslipidemia	2:6	14:75	1.786 (0.327–9.765)	0.504		
Diabetes mellitus	1:7	4:85	3.036 (0.297–30.980)	0.349		
Suzuki stage	3.625±0.518	3.034±0.818	2.890 (0.994–8.400)	0.051	0.639 (0.146–2.798)	0.552
MRA scoring						
MCA score	1.75±0.46	1.37±0.66	3.204 (0.698–14.712)	0.134		
ACA score	1.88±0.35	0.91±0.90	6.654 (1.144–38.688)	0.035[b]		
PCA score	0.75±0.89	0.30±0.61	2.265 (0.923–5.558)	0.074		
Total MRA score	4.25±1.58	2.55±1.40	2.174 (1.263–3.741)	0.005[b]	3.213 (1.302–7.931)	0.011[b]
CBF increase ratio						
(POD1/preoperative)	257.8±68.4%	128.0±35.5%	1.044 (1.020–1.068)	<0.001[b]		

CHP, cerebral hyperperfusion; ACA, anterior cerebral artery; MCA, middle cerebral artery; MRA, magnetic resonance angiography; PCA, posterior cerebral artery; CBF, cerebral blood flow; POD, postoperative day. [a] Multivariate analysis including age, side, onset type, Suzuki's angiographic stage, and total hemispheric MRA score (N = 97). These factors were selected according to the previous reports or $p < 0.10$ in the univariate analysis. [b] $p < 0.05$.

the predictive value of preoperative 3D-TOF MRA for the development of CHP syndrome in adult MMD patients undergoing STA-MCA anastomosis demonstrated in the present study is clinically important to counteract the complex postoperative pathophysiological condition caused by pharmacological agents such as free radical scavenger and anti-inflammatory antibiotics (minocycline hydrochloride) [19–21].

MRA has been widely applied as a diagnostic tool for MMD patients. In 1995, the first revision of the diagnostic criteria of MMD in Japan introduced MRA as the definitive diagnostic modality for MMD patients with bilateral involvement [23]. It was also reported that MRA was useful to evaluate the development of both direct bypass and indirect pial synangiosis after combined revascularization surgery for MMD [24]. Houkin and colleagues further introduced the novel MRA stage grading as an alternative for Suzuki's angiographic staging [18], but the prediction of CHP syndrome by MRA has not been attempted in MMD patients. Considering the potential role of preoperative MRA for predicting CHP syndrome after carotid endarterectomy [25], we applied MRA as a potential diagnostic modality to predict CHP in adult MMD patients in the present study. In contrast to Houkin's MRA disease stage grading of MMD [18], we focused on the peripheral signal intensity of the major intracranial arteries in this study while applying MRA signal intensity grading in CEA patients [25] and generated a hemispheric MRA score by summing ACA, MCA, and PCA scores in the affected hemisphere. Based on our study, we believe that the hemispheric MRA score by preoperative 3D-TOF MRA can be a powerful tool for identifying adult MMD patients at higher risk for CHP after direct revascularization surgery.

The reason why the total MRA score can predict CHP is undetermined, but we speculate that the decreased signal intensity of ACA and PCA, even though they are not the exact area of bypass procedure, may reflect the poor collateral blood flow to the MCA territory and could partly explain the poor distribution of the bypass flow to the wider territory after revascularization surgery. Therefore, it is conceivable that summation of ACA, MCA, and PCA scores could better reflect both hemodynamic and collateral environments in the MCA territory. Consistent with our observation, Zhang and colleagues have recently reported that anastomosis of the recipient arteries with anterograde hemodynamic sources from the MCA had a much higher risk of postoperative CHP than those from PCA or ACA [26]. Further investigation of the preoperative catheter angiography is warranted to address this important issue.

There are some limitations in this study. First, the hemispheric MRA score may be subjective compared with quantitative CBF studies such as positron emission tomography or ^{123}I-IMP SPECT. Second, our intensive perioperative management protocol with strict blood pressure control and administration of multiple agents may affect the results of symptomatology under the state of the CHP phenomenon. Finally, this was a single-center study and the number of patients included in this series was limited. Further studies with a larger number of patients will clarify these important issues.

Statement of Ethics

The present study conforms to the guidelines issued in the Declaration of Helsinki. This study was approved by the Institutional Ethics Committees (2020-0520-3).

Conflict of Interest Statement

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

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Author Contributions

Fujimura: conception and study design. Fujimura, Nishizawa, Katsuki, Tashiro, and Sato: acquisition of data. Fujimura, Mugikura, Sato, and Nishizawa: analysis and interpretation. Nishizawa: drafting. Fujimura, Tashiro, Katsuki, and Tominaga: critical revision of the article. Tominaga: study supervision.

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