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# The preoperative focal cerebral blood flow status may be associated with slow flow in the bypass graft after combined surgery for moyamoya disease

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# ABSTRACT

**Background:** The aim of this study was to investigate the association between early postoperative slow flow in bypass grafts and preoperative focal cerebral blood flow (CBF) in patients who underwent combined surgery for moyamoya disease (MMD).

**Methods:** The subjects were 18 patients (22 surgeries) who underwent single photon emission computed tomography (SPECT) before surgery. The CBF value of the middle cerebral artery territory was extracted from the SPECT data, and the value relative to the ipsilateral cerebellar CBF (relative CBF, or RCBF) was calculated. The association between RCBF and early postoperative slow flow in the bypass graft was investigated. In addition, the correlation between the revascularization effect and preoperative RCBF was analyzed.

**Results:** In four of 22 surgeries (18.2%), slow flow in the bypass graft was identified in the early postoperative period. Preoperative RCBF in the slow flow and patent groups was  $0.86 \pm 0.15$  and  $0.87 \pm 0.15$ , respectively, with no significant difference (P = 0.72). The signal intensity of four slow-flowed bypasses was improved in all cases on magnetic resonance angiography images captured during the chronic phase (mean of 3.3 months postoperatively). The revascularization scores were  $2 \pm 0.82$  and  $2.1 \pm 0.68$  in the slow flow and patent groups, respectively, and did not differ significantly (P = 0.78). A significant correlation was not observed between preoperative RCBF and the revascularization effect.

**Conclusion:** No significant association was observed between preoperative RCBF and early postoperative slow flow in bypass grafts in patients with MMD undergoing combined surgery. Given the high rate of improved depiction of slow-flowed bypass in the chronic postoperative phase, the conceptual significance of an opportune surgical intervention is to maintain CBF by supporting the patient's own intracranial-extracranial conversion function.

Keywords: Cerebral blood flow, Combined revascularization, Moyamoya disease, Recanalization, Slow-flowed direct bypass

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## **INTRODUCTION**

Moyamoya disease (MMD) is a rare disease with slowly progressive stenosis or occlusion at the end of the bilateral internal carotid artery (ICA). It is characterized by the development of penetrating branches at the bottom of the brain as collateral circulation.<sup>[18,32]</sup> Direct, indirect, or combined extracranial (EC)-intracranial (IC) bypass surgery is a promising surgical treatment to prevent future stroke and improve neurological outcomes.<sup>[19,23]</sup> Superficial temporal artery (STA)-middle cerebral artery (MCA) bypass is the most common procedure used in direct bypass and is a promising approach for improving cerebral blood flow (CBF) with robust patency during surgery. However, bypass patency is almost guaranteed by radiological examination in the early postoperative phase, but it may not be maintained in some cases. Furthermore, the slow flow in the bypass graft may improve during the postoperative chronic phase. This event is very rare and has seldom been verified.<sup>[17,33]</sup>

The pressure gradient between the donor and the recipient and the radius of the conduit plays an important role in the patency of the bypass.<sup>[30,31]</sup> When considering the patency of direct bypass from the external carotid artery (ECA) system to the ICA system, the pressure difference with the ECA system should be considered. This difference is induced by the decrease in perfusion pressure in the ICA system caused by the progression of MMD. For the perfusion pressure of the ICA system, which cannot be measured directly, the average CBF value of the focal territory where the recipient is expected to perfuse obtained from the single photon emission computed tomography (SPECT) data imaged preoperatively might be used as a substitute. In addition, we investigated the revascularization effect obtained from magnetic resonance angiography (MRA) time-of-flight (TOF) images captured during the postoperative chronic phase to examine the role of direct bypass in combined surgery.

Studies focused on preoperative CBF have not been conducted on the slow flow in the direct bypass graft of combined surgery in the postoperative acute phase, which may help elucidate the pathophysiology of this unique phenomenon.

### MATERIALS AND METHODS

### **Study population**

Eighteen patients with MMD (22 surgeries) who underwent direct and indirect combined revascularization at our hospital from December 2019 to November 2020 were included in this study. All patient information was retrospectively collected from medical records with the approval of the Bioethics Review Board of Nagoya University Hospital. MMD was diagnosed by MRA based on the diagnostic criteria from the Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis.<sup>[9]</sup> Digital subtraction angiography (DSA) was performed as needed for the diagnosis.

Clinical information, including age at surgery, type of onset (transient ischemic attack [TIA], cerebral infarction, seizure, and others), vascular risk factors (hypertension, diabetes, hyperlipidemia, and smoking habit), and preoperative antiplatelet therapy, was investigated by performing a chart review. Neurological outcomes at postoperative discharge were investigated using the modified Rankin Scale (mRS) as an index. If the mRS score increased by 1 point or more compared with before surgery, it was judged to be deteriorated; otherwise, it was judged to be favorable. Preoperative and postoperative radiological evaluations are described below.

### Preoperative radiological findings

Preoperative magnetic resonance imaging (MRI) diffusionweighted imaging or fluid-attenuated inversion recovery images confirmed the presence of cerebral infarction. MRA images were also used to evaluate preoperative posterior cerebral artery (PCA) involvement.

### Acquisition of SPECT data

Cerebral perfusion SPECT imaging was performed using a double-headed gamma camera (Symbia T or Symbia T6, Siemens Healthcare, Erlangen, Germany). In SPECT imaging, we used the autoradiographic method with N-isopropyl-p-<sup>123</sup>I-iodoamphetamine (<sup>123</sup>I-IMP) for adult patients and the Patlak plot method with <sup>99m</sup>Tc-ethyl cysteinate dimer (<sup>99m</sup>Tc-ECD) for pediatric patients. Regional CBF was measured for each preset region of interest (ROI) using iSSP and NEURO FLEXER software (Nihon Medi-Physics, Tokyo, Japan). The anterior cerebral artery (ACA), MCA, and PCA territories were automatically defined as ROIs according to the software settings. We have previously reported on these methodologies.<sup>[1]</sup>

#### Definition of relative CBF (RCBF) before surgery

In each ROI of the ACA, MCA and PCA territories, the radioactive count was divided by that in the ipsilateral cerebellar ROI, and the quotient was defined as the RCBF.<sup>[1]</sup> In this study, of the three territories, only RCBF in the MCA territory where the bypass recipient is expected to perfuse was investigated.

### Surgical procedures

Cerebral revascularization was performed on patients with MMD according to the policies established in the

treatment guidelines.<sup>[9]</sup> According to the guidelines, surgical revascularization in MMD patients with cerebral ischemic attacks can reduce the frequency of TIA and the risk of future cerebral infarction. Furthermore, after revascularization, improvement in cerebral hemodynamics was observed on SPECT. It has also been proven to be effective in preventing rebleeding in adults with hemorrhagic-onset MMD. Therefore, at our institution, revascularization is basically indicated for ischemic onset when CBF is lower than the normal value on preoperative SPECT, and this is especially suitable for adult cases. Direct and indirect combined revascularization was performed in all subjects analyzed in this study. For direct bypass, an STA-MCA single bypass was performed. The STA graft harvested with a skin incision directly above was anastomosed to the recipient's MCA in an end-to-side manner. At our facility, vascularized temporalis muscle, periosteum, and galea were placed on the surface of the brain as an indirect revascularization procedure. The circumference of the vascularized pedicle was sutured to the inverted dura mater. These surgical designs are described in our previous studies.<sup>[2,3]</sup>

## Postoperative management protocol

All cases, in this study, were managed using a standardized postoperative protocol.<sup>[4,24,36]</sup> At our facility, a head computed tomography (CT) scan was performed on postoperative day (POD) 0 to confirm the presence or absence of complications immediately after surgery. CT/CT angiography (CTA) was performed on POD 1, and MRI and MRA images were captured on POD 2. CT and MRI scans were assessed for new postoperative ischemic or hemorrhagic strokes. Direct bypass patency was confirmed by CTA and MRA. In addition, additional CT and MRI/MRA tests were considered, depending on the incidence of new postoperative neurological symptoms.

# Relationship between preoperative RCBF and slow-flowed bypass early after surgery

Early postoperative slow flow in the bypass graft was determined by CTA performed on POD 1 or MRA performed on POD 2. Then, the association between RCBF and early postoperative slow flow in the bypass graft was statistically investigated.

## Improved bypass flow and revascularization effect evaluated using MRA in the postoperative chronic phase

At our facility, regular MRI and MRA follow-up will be performed every 2–6 months after surgery. The examination confirmed the occurrence of a new postoperative stroke and the patency of the bypass graft. If the flow of the bypass graft that was slowed in the postoperative acute phase was improved, it was confirmed by MRA performed in this postoperative chronic phase.

The cerebral revascularization effect was evaluated semiquantitatively using MRA-TOF images captured more than 6 months after the operation. Similar to the method previously proposed by our group, the degree of angiogenesis observed from the ECA system was scored on the TOF images of some slices.<sup>[5,20,38]</sup> The cerebral revascularization effect was scored on a three-point scale as follows (1–3 points): 1not visible to weakly developed, 2 moderately developed, and 3 markedly developed. This score was reviewed until a consensus was reached by three certified neurosurgeons (K.Y., K.U., and Y.A.).

# Correlation between preoperative RCBF and the effect of revascularization

The relationship between preoperative RCBF in the MCA territory where the recipient is expected to perfuse and the cerebral revascularization effect in the postoperative chronic phase was statistically investigated.

# Statistical analysis

Normally distributed data are presented as the means  $\pm$  standard deviations (SD). Non-normally distributed data are presented as the medians  $\pm$  SD. In terms of the patient baseline characteristics, the type of onset and vascular risk factors was counted on a patient basis, while the other items were described on a hemisphere basis. RCBF in the preoperative MCA territory and revascularization effect in the group with slow-flowed bypass and the group with patent was compared using the Wilcoxon rank sum test. Kendall's rank correlation coefficient ( $\tau$ ) was calculated to examine the correlation between the effect of cerebral revascularization measured on MRA images and preoperative RCBF.

JMP Pro version 15.1 (SAS Institute, Cary, NC) was used for statistical analyses. P < 0.05 indicated a significant difference.

# RESULTS

The median age at surgery was 11 years (range 2–59 years). Fourteen of the 18 patients (77.8%) were female. In terms of onset, TIA accounted for half, followed by cerebral infarction in <30%. Only one case (5.6%) of hemorrhagic onset and seizure onset was identified. Regarding vascular risk factors, two patients presented hypertension (11.1%), and diabetes and hyperlipidemia were present in one patient (5.6%) each. The preoperative radiological examination revealed cerebral infarction in 40.9% and PCA involvement in 27.3% of the hemispheres. The calculated mean preoperative RCBF was 0.86  $\pm$  0.14, which was approximately 15% lower than that of the ipsilateral cerebellum, which is considered

normal CBF. Regarding the medication status of antiplatelet drugs, 72.7% used these drugs preoperatively. Direct and indirect combined surgery was performed in all cases for cerebral revascularization. Imaging examinations performed early after surgery confirmed patency (81.8%) in 18 of the 22 bypasses. Cerebral infarction was observed in two cases (9.1%), and subarachnoid hemorrhage (SAH) was observed in one case (4.5%) as early postoperative stroke events. On the other hand, no patients presented a decrease in the mRS score at the time of discharge of 1 point or more, and all patients had a favorable course.

The results of imaging examinations performed during the postoperative chronic phase showed that the flow of all four bypass grafts that had been slowed in the early postoperative period was improved (mean of 3.3 [range 2–5] months postoperatively). The mean value of the revascularization score evaluated by MRA more than 6 months after the operation was 2.1  $\pm$  0.67, in which a moderate or higher revascularization effect had been obtained.

Comparative statistical analyses were performed between the slow flow group (four surgeries, 18.2%) and the patent group (18 surgeries, 81.8%) to investigate factors associated with slow flow in direct bypass grafts early after surgery [Table 1]. No differences in the age at surgery or sex were observed between the groups. In terms of onset, approximately 75-83% of patients in both groups had TIA or cerebral infarction. Only one patient had a hemorrhagic onset, and the early postoperative bypass was patent. As a result, no statistically significant difference was observed in the type of onset (P = 0.41). Regarding vascular risk factors, no patients with those comorbidities were identified in the slow flow group. In the patent group, two patients with hypertension, one patient with diabetes, and one patient with hyperlipidemia were identified, but a significant difference was not observed between the groups (P = 0.41). Preoperative radiological findings were one patient (25%) with existing cerebral infarction and one patient with PCA involvement in the slow flow group. In the patent group, cerebral infarction was observed in 44.4%, and PCA involvement was observed in 27.8%, but the difference between the groups was not significant. Preoperative RCBF was approximately equivalent at 0.86  $\pm$  0.15 and 0.87  $\pm$  0.15 in the slow flow group and patent group, respectively, and a significant difference was not observed (P = 0.72). The use of preoperative antiplatelet medication was not different between the two groups (P = 0.23).

Stroke events in the postoperative acute phase did not occur in the slow flow group. In the patent group, two cases of cerebral infarction (11.1%) and one case of SAH (5.6%) were observed, but the differences were not statistically significant (P = 0.68). The revascularization effects evaluated by MRA more than 6 months after the operation was  $2 \pm 0.82$  for the **Table 1:** Comparison of clinical characteristics between thegroup with slow flow and the group with patency early aftersurgery.

	Slow flow	Patent	P-value
Number of patients	3	15	
Number of surgeries	4 (18.2)	18 (81.8)	
Age at surgery	26.3±9	21.6±4.8	0.35
Female sex	4 (100)	12 (66.7)	0.18
Type of onset			0.41
Transient ischemic attack	3 (75)	8 (44.4)	
Cerebral infarction	0 (0)	7 (38.9)	
Hemorrhagic	0 (0)	1 (5.6)	
Seizure	0 (0)	1 (5.6)	
Others	1 (25)	1 (5.6)	
Vascular risk factors			
Hypertension	0 (0)	2 (11.1)	0.48
Diabetes	0 (0)	1 (5.6)	0.63
Hyperlipidemia	0 (0)	1 (5.6)	0.63
Smoking habit	0 (0)	0 (0)	NA
Preoperative radiological			
findings			
Cerebral infarction	1 (25)	8 (44.4)	0.47
PCA involvement	1 (25)	5 (27.8)	0.91
RCBF*, Mean±SD	0.86±0.15	0.87±0.15	0.72
Preoperative antiplatelet	2 (50)	14 (77.8)	0.23
medications			
Postoperative stroke at acute			0.68
phase			
Cerebral infarction	0 (0)	2 (11.1)	
Subarachnoid hemorrhage	0 (0)	1 (5.6)	
Postoperative neurological			NA
outcomes			
Favorable	4 (100)	18 (100)	
Deteriorated	0 (0)	0 (0)	
Revascularization effects**,	2±0.82	2.1±0.68	0.78
mean±SD			
PCA: Posterior cerebral artery, RCB	F: Relative cer	ebral blood fl	ow,
SD: Standard deviation, NA: Not av	ailable. *In reg	ion of interes	ts of
the middle cerebral artery territories, the radioactive count divided by			

SD: Standard deviation, NA: Not available. \*In region of interests of the middle cerebral artery territories, the radioactive count divided by that in the ipsilateral cerebellar ROI was calculated, and the value was defined as the RCBF. \*\*The cerebral revascularization effect was evaluated semiquantitatively using magnetic resonance angiography time-of-flight images captured more than 6 months after the operation

slow flow group and 2.1  $\pm$  0.68 for the patent group, showing no significant difference (*P* = 0.78).

# Correlation between preoperative RCBF and the effect of revascularization

Figure 1 shows the correlation between preoperative RCBF, which is an index of cerebral ischemia in the MCA territory, where the recipient is expected to perfuse, and the revascularization effects 6 months after surgery. As a result of the statistical examination, no significant association was found ( $\tau = -0.0124$ , P = 0.9453).



**Figure 1:** Correlation between preoperative relative cerebral blood flow and the effect of revascularization. As a result of the statistical examination, no significant association was found ( $\tau = -0.0124$ , P = 0.9453).

#### Illustrative case

An 11-year-old girl with transient motor weakness in the left upper limb was diagnosed with MMD and referred to our department for surgical treatment. Preoperative MRA showed bilateral ICA terminal stenosis, which was predominant on the right side. The development of MMVs was mild, and PCA involvement was not observed [Figure 2a]. A developed STA parietal branch was observed on MRA images [Figure 2b], white arrow). MRI did not reveal a preexisting cerebral infarction [Figure 2c]. In preoperative SPECT scans, the RCBF of the MCA territory where the recipient is expected to perfuse was 0.87 [Figure 2d]. During direct bypass, the right parietal branch of the STA was harvested and anastomosed to the recipient cortical MCA. As an indirect method, the temporalis muscle and periosteum were placed on the brain surface and sutured with the inverted dura mater. Doppler sonography and indocyanine green (ICG) video angiography confirmed that the bypass immediately after the anastomosis was patent [Figure 2e]. No neurological abnormalities were observed after the operation, and no new cerebral infarction was observed on the diffusion-weighted MRI captured on POD 2 [Figure 2f]. However, MRA showed slow flow in the bypass graft [Figure 2g, white arrow]. No signs of TIA or hyperperfusion were observed in the clinical course, and the patient was discharged at POD 12. Bypass grafts were visualized on the MRA image at 2 months after the operation, suggesting that the flow of the bypass graft was improved [Figure 2h, white arrow]. Afterward, the patient did not experience TIA, and the graft was well depicted even on MRA images captured 25 months after the operation [Figure 2i, white arrow]. In this case, the revascularization score was evaluated as two points (moderately developed). In MRA images captured from the early postoperative period to the chronic period, the depiction of the MCA donated by the ICA system decreased with the development of ECA systems such as the STA and middle meningeal artery [Figures 2g-i, yellow square dotted line].

#### DISCUSSION

This study focused on cases, in which the flow of direct bypass, which was patent during surgery, was slowed early after surgery in patients who underwent direct and indirect combined surgery for MMD. As a result, no correlation was observed between preoperative RCBF, which is a focal CBF in the MCA territory, where the recipient is expected to perfuse, and slow flow of the bypass graft in the early postoperative period. However, in the subject analyzed in this study, the flow of all four slowed bypasses improved during the postoperative chronic phase [Figure 2g-i]. This result was surprising because we speculated that slowed-flow bypass early after surgery would be affected by preoperative RCBF. In the present study, there were more cases, in which visualization of the bypass graft was evaluated by MRA on POD 2 than in cases, in which CTA was performed on POD 1. Since the signal intensity of MRA reflects the speed of blood flow, less, or no signal on MRA often implies slow flow. Therefore, we decided to examine slow flow rather than early postoperative bypass graft occlusion. Past reports on the recanalization of bypass grafts have also observed cases that are presumed to be a phenomenon of slow flow rather than occlusion. Some investigations reporting that the occluded bypass was recanalized in all cases prompted us to investigate this issue.<sup>[17,33]</sup> Regarding bypass occlusion using a vein graft in EC to IC bypass, a report from an Australian group is a powerful reference.<sup>[30]</sup> The authors proved that the flow rate specified for mean arterial pressure should not fall below a minimum of 40 ml/min to maintain blood flow for bypass based on the study by Sundt and Sundt.<sup>[31]</sup> The study used a computed flow dynamic (CFD) approach and carotid duplex ultrasound in a case series from their own institution.<sup>[30]</sup> In addition, their study indicated that the flow rate depends on the pressure gradient of blood flow through the anastomosis. Their verification might provide promising evidence when considering the results of our series. However, even with the same EC-IC bypass, graft patency in the short term was significantly better for STA-MCA arterial bypass.[13,29] At the same time, regarding the graft flow in STA-MCA bypass, the pressure gradient similar to the previous vein graft has not been calculated and analyzed probably because the graft viability and sustainability are good, and the STA graft is thinner than the vein graft, making it difficult to verify the flow rate using MRA or CFD.<sup>[26,34]</sup> Furthermore, as mentioned in a previous report, the flow on the ipsilateral side of the bypass is substantially affected by the wall shear stress that is directly related to the flow rate on the contralateral side.<sup>[30,34]</sup>



**Figure 2:** Illustrative case of moyamoya disease in an 11-year-old girl with postoperative improvement of flow in the direct bypass graft that was slowed early after combined surgery. Preoperative magnetic resonance angiography (MRA) images showed bilateral internal carotid artery terminal stenosis, which was predominant on the right side. The development of moyamoya vessels was mild, and no posterior cerebral artery involvement was observed (a). A developed superficial temporal artery (STA) parietal branch was observed on MRA images (b, white arrow). MRI did not reveal a preexisting cerebral infarction (c). In preoperative single photon emission computed tomography, the relative cerebral blood flow of the surrounding middle cerebral artery (MCA) territory perfused by the recipient candidate was 0.87. The region of interest indicates the perfusion area of the following vessels (A: anterior cerebral artery, B-D: MCA, E and G: posterior cerebral artery territory, H: perforators) (d). Doppler sonography and indocyanine green video angiography confirmed that the bypass immediately after the anastomosis was patent (e). No neurological abnormalities were observed after the operation, and no new cerebral infarction was found on the MRI diffusion weighted image captured on performed on postoperative day 2 (f). However, MRA showed that a flow of the bypass graft was not depicted (g, white arrow). Bypass grafts were visualized on the MRA images captured 2 months after the operation, suggesting that the flow was improved (h, white arrow). Afterward, the patient did not experience transient ischemic attack, and the graft was patent even on MRA images captured 25 months after the operation (i, white arrow). In MRA images from the early postoperative period to the chronic period, the depiction of the MCA donated by the internal carotid artery system decreased with the development of external carotid artery systems such as the STA and middle meningeal artery (g-i, yellow square dotted line).

This fact will complicate the estimation for patients with MMD, which is basically a bilateral disease. Similarly, the indirect revascularization effect that develops from the early postoperative period, which is peculiar to patients with MMD, makes it difficult to analyze the flow rate and pressure

gradient by simply connecting the ECA system and the ICA system with a single graft.<sup>[12,16]</sup>

Therefore, we employed SPECT, which is among the most powerful tools available to quantitatively measure cerebral perfusion, to observe preoperative focal CBF in the MCA territory, where the recipient is expected to perfuse. Furthermore, the CBF was calculated not as a focal absolute value but as RCBF relative to the ipsilateral cerebellum, which is less susceptible to being influenced by crossed cerebellar diaschisis (CCD) and exhibits normal CBF.<sup>[28]</sup> Although not a direct measure of the pressure gradient between the recipient MCA and graft STA, it is a useful alternative for patients with MMD presenting complex cerebral hemodynamics due to preoperative collateral flow development from the ECA system, posterior circulation, and contralateral circulation. Although the number of patients included in the present study was small, no significant association between the focal RCBF of the preoperative MCA territory and the slow flow bypass event was observed in the early postoperative period. Therefore, we, additionally, investigated, whether the preoperative RCBF in the MCA territory was correlated with the cerebral revascularization effect in the chronic phase 6 months after the operation. However, the correlation was not statistically significant [Figure 1]. From a rational perspective, we speculated that the lower the preoperative RCBF value, the higher the revascularization effect, which is a downward-sloping correlation. Conversely, the results might be interpreted as indicating that even when cerebral perfusion pressure is reduced, the necessary effect can be achieved in the chronic phase without relying on the rapid revascularization effect of direct bypass.

Although several studies have been conducted on early postoperative bypass occlusion with STA-MCA bypass for occlusive cerebrovascular disease due to cerebral atherosclerosis, quite few reports are available on early postoperative bypass occlusion for that procedure in patients with MMD. Takahashi and Yoshida<sup>[33]</sup> reported a case, in which a white thrombus appeared during STA-MCA bypass surgery for an Asian female patient with MMD, and the bypass was occluded but recanalized 4 months after surgery. In their case report, recanalization was obtained by removing the white thrombus that occurred during the operation by reopening the anastomosis, but bypass patency was not finally confirmed by ICG video angiography. Similar bypass occlusion was also observed at MRA 6 weeks after surgery. Similar to their case, in our series of four cases of early postoperative slow flow bypass, one case (25%) of temporary bypass occlusion was observed due to the appearance of an intraoperative white thrombus. This fact should be discussed with interest. In other words, white thrombi may have occurred immediately after surgery or early after surgery rather than intraoperatively. As discussed in a previous study, some reports of the appearance of white thrombi during surgery for STA-MCA bypass have already been reported.<sup>[14,22,33]</sup> When analyzed for the appearance of white thrombi during the operation, Mikami et al.[22] stated that higher MRA scores were significantly associated with thrombogenesis.<sup>[18]</sup> As part of a discussion based on this

finding, it is a remarkable anatomical structure indicating that the recipient artery on the brain surface is fragile and thin in patients with advanced MMD presenting with higher MRA scores. The inference is that the fragility and thinness of the arteries on the cerebral surface in patients with advanced MMD seriously interfere with the technical aspects of the anastomotic maneuver, and the errors lead to vascular endothelial damage that induces thrombogenesis. The argument is well accepted since the occurrence of an intraoperative white thrombus has been investigated in our institutional experience, and the risk was high in the absence of preoperative antiplatelet medication and in patients with advanced MMD with PCA involvement.<sup>[14]</sup> The possibility that the white thrombus does not occur during surgery and appears early after surgery should be considered.

On the other hand, in the MRA images captured in the postoperative chronic phase, improvement of flow of the bypass graft was obtained in all patients included in this series. Regarding the recanalization of a direct bypass once occluded, the study by Kim et al.<sup>[17]</sup> is guite helpful. They observed 11 (35.5%) direct bypass occlusions early after surgery in 31 adult patients with symptomatic MMD undergoing combined revascularization. Moreover, recanalization was observed within 1 week after surgery in one patient, but it was observed in the chronic phase 6 months after surgery in the other ten patients. The recanalization in the postoperative chronic phase in those ten patients was very similar to our series. This high recanalization rate rarely occurs after STA-MCA bypass for obstructive cerebrovascular diseases other than MMD, and the disease-specific nature of MMD is considered.<sup>[27]</sup> The first is the high degree of angiogenesis in patients with MMD.<sup>[6,16]</sup> Even in STA grafts where luminal blood flow is disrupted, blood flow may enter the surrounding connective tissue. The tissue is exposed to cerebrospinal fluid containing angiogenic factors through the arachnoid membrane at the brain surface, thus stimulating angiogenesis.<sup>[10,11,25]</sup> The widespread adoption of indirect revascularization as a surgical treatment for MMD may itself be the rationale for supporting this hypothesis. Based on the information provided above and the suggestion from Takahashi and Yoshida,<sup>[33]</sup> we are convinced that an occluded bypass or a bypass with a small amount of residual blood flow that is not detected by MRA may serve as a scaffold for angiogenesis in the surrounding connective tissue. In addition, the residual low-pressure blood flow in the STA graft might create a pressure gradient with the recipient artery on the brain surface, which might be the driving force for the bypass to recanalize.

Next, in combined revascularization, the effect of swelling of temporary muscle pedicles used for indirect bypass in the postoperative acute phase must be considered. Postoperative swelling of the temporalis muscle conveys potential risks of unpredictably narrowing the route through which the STA graft passes. This finding has been documented in reports from our own facility and those from other facilities where the swelling became symptomatic due to pressure on the brain.<sup>[7,15]</sup> Therefore, based on that experience, we recently split the tissue into two layers, a thin surface of the brain and a thick extraracranial side, when placing the temporalis muscle. Although we agree with the hypothesis proposed by Kim *et al.*<sup>[17]</sup> that temporalis muscle swelling is the cause of STA graft obstruction in the postoperative acute phase; this result shows that in our series, no recanalization was observed due to the release of compression on the STA graft and swelling of the temporalis muscle in the acute phase, and cases of recanalization were observed only in the postoperative chronic phase.

Numerous studies have been conducted on optimal surgical methods for MMD, but none have reached a conclusion.<sup>[6,8,16,35,37]</sup> A possible explanation is that MMD itself is a disease with a progressive pathology, and a certain treatment strategy is difficult to determine, because the natural history and rate of progression differ from patient to patient. Eventually, in this series, postoperative neurological outcomes were favorable, including cases of early postoperative slow flow in bypass grafts. Based on this result, the pathophysiology of MMD may not require direct bypass only, indirect bypass only or combined bypass for all patients. In other words, a treatment strategy of direct bypass for those cases, in which it is practically necessary, may be appropriate. The conceptual significance of the surgical intervention is to maintain CBF by supporting the patient's own IC-EC conversion function at opportune times.<sup>[1]</sup> However, for this hypothesis to be scientifically validated, studies designed to observe postoperative acute bypass occlusion/slow flow, neurological outcomes, and CBF in a larger population are needed.

## Limitations

First, since this study is a single-center retrospective study with a small number of patients, limited evidence is available to generalize the interpretation of the results to the patient population with MMD. A multicenter, prospective, and observational study is needed to obtain more convincing evidence. Second, ipsilateral cerebellar CBF, which is considered less susceptible to CCD, may not be interpreted as a normal value, depending on the target contralateral MMD stage. This conclusion is attributed to a decrease in CBF due to decreased metabolism caused by CCD, even if no significant stenosis of the vertebrobasilar artery is observed. Therefore, the MMD stage on the opposite side must be considered to improve the accuracy of CBF evaluation using RCBF. Third, if patients with severely reduced preoperative RCBF had been included, the results might have been different for the association between RCBF and early postoperative slow flow in the bypass graft and revascularization efficacy. However, the fact that most of the subjects in the present study (77.8%) had an ischemic onset reminds us that CBF is simply not directly associated with the development of neurological symptoms or stroke. A solution to this problem would be to enroll more cases and compare preoperative RCBF in cohorts matched for background factors such as onset type, age group, MMD disease stage, and imaging findings. Subsequent stratification of preoperative RCBF would ideally be used to analyze the effects on postoperative bypass patency and revascularization effects. Fourth, scoring with MRA TOF images used to assess the revascularization effect is limited by its dependence on MRA resolution and its semiquantitative aspect. Since revascularization occurs in the small arteries of the ECA system, evaluation by MRA, which visualizes blood flow velocity, may not be sufficient for analysis. Originally, it should be evaluated with fine angiographic images by DSA/ CTA. However, the method using DSA is similarly limited to semiquantitative evaluation.<sup>[21,35]</sup> Therefore, the development of a method to quantitatively measure IC-EC conversion is desired.

# CONCLUSION

No significant association was observed between preoperative focal CBF and early postoperative slow-flowed bypass in patients with MMD undergoing combined surgery. Given the highly improved depiction of slow-flowed bypass in the chronic postoperative phase, maintaining CBF by supporting the patient's own IC-EC conversion function is the conceptual significance of opportune surgical intervention.

## Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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## **Conflicts of interest**

There are no conflicts of interest

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