



Changes in cerebral blood flow in the postoperative chronic phase after combined cerebral revascularization for moyamoya disease with ischaemic onset

Yoshio Araki¹ · Takashi Mamiya¹ · Naotoshi Fujita² · Kenji Uda¹ · Kinya Yokoyama¹ · Fumiaki Kanamori¹ · Kai Takayanagi¹ · Kazuki Ishii¹ · Masahiro Nishihori¹ · Kazuhito Takeuchi¹ · Kuniaki Tanahashi¹ · Yuichi Nagata¹ · Yusuke Nishimura¹ · Takafumi Tanei¹ · Masaki Sumitomo³ · Sho Okamoto⁴ · Takashi Izumi¹ · Katsuhiko Kato⁵ · Ryuta Saito¹

Received: 2 December 2021 / Revised: 9 February 2022 / Accepted: 16 March 2022 / Published online: 23 March 2022
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2022

Abstract

The purpose of this study was to examine the effects of combined revascularization for ischaemic-onset moyamoya disease (MMD) on cerebral haemodynamics by comparing cerebral blood flow (CBF) during the postoperative chronic phase with preoperative CBF. A retrospective cohort of 24 MMD patients (representing 31 surgeries) who received single photon emission computed tomography (SPECT) before and more than 6 months after surgery was investigated. The CBF value of each vascular territory was extracted from SPECT data, and the value relative to the ipsilateral cerebellar value (relative CBF, or RCBF) was calculated. The correlation between the revascularization effect and the proportional change in RCBF before and after surgery (calculated as post-RCBF/pre-RCBF (“post/pre-RCBF”)) was analysed. Furthermore, the relationships between changes in neurological symptoms and post/pre-RCBF were investigated. Preoperative and postoperative mean RCBF values were 0.92 ± 0.15 and 0.96 ± 0.13 ($p = 0.619$) in the anterior cerebral artery territory, 0.99 ± 0.17 and 1.01 ± 0.17 ($p = 0.598$) in the middle cerebral artery territory and 1.15 ± 0.22 and 1.14 ± 0.19 ($p = 0.062$) in the posterior cerebral artery territory, respectively. No significant correlation was found between the revascularization score and post/pre-RCBF. The revascularization score and post/pre-RCBF were not significant predictors of worsening neurological symptoms postoperatively. No significant change in RCBF was observed in any vascular territory in the chronic phase after revascularization. Combined revascularization may assist in the redirection of blood flow from the internal to the external carotid system and contribute to CBF maintenance.

Keywords Cerebral blood flow · Combined revascularization surgeries · Moyamoya disease · Postoperative chronic phase · SPECT

✉ Yoshio Araki
y.araki@med.nagoya-u.ac.jp

¹ Department of Neurosurgery, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi, Japan

² Department of Radiological Technology, Nagoya University Hospital, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi, Japan

³ Department of Neurosurgery, Toyota Kosei Hospital, 500-1 Ibobara, Josui-cho, Toyota, Aichi, Japan

⁴ Aichi Rehabilitation Hospital, 1-1 Nishigara, Ehara-cho, Nishio, Aichi, Japan

⁵ Functional Medical Imaging, Biomedical Imaging Sciences, Division of Advanced Information Health Sciences, Department of Integrated Health Sciences, Nagoya University Graduate School of Medicine, 1-1-20 Daiko-Minami, Higashi-ku, Nagoya, Aichi, Japan

Introduction

In the rare condition known as moyamoya disease (MMD), the ends of the bilateral internal carotid arteries (ICAs) are narrowed or occluded, and perforating arteries called moyamoya vessels (MMVs) develop inferior to the brain [21]. In MMD, various degrees of cerebral ischaemia and intracranial haemorrhage may occur as the disease progresses. Surgical treatment via direct and indirect combined revascularization improves cerebral ischaemia and prevents haemorrhagic stroke [13, 14, 18]. However, cerebral hyperperfusion syndrome and transient neurological deficits may occur during the perioperative period [7, 8]. These phenomena have been reported to be due to rapid changes in local cerebral blood flow (CBF) as a result of direct bypass. Numerous studies have been conducted on the changes in CBF in the acute phase after cerebral revascularization, and the understanding of cerebral haemodynamics has progressed [5, 19, 23, 25]. However, few quantitative evaluations of cerebral haemodynamics in the postoperative chronic phase of cerebral revascularization for haemorrhagic MMD have been reported [12, 16]. As for ischaemic MMD, the changes in CBF during the postoperative chronic phase with respect to the onset of ischaemia have not been investigated.

The purpose of this study was to evaluate the local changes in CBF during the postoperative chronic phase compared to the preoperative values in ischaemic-onset MMD. In addition, we investigated the role of cerebral revascularization as an MMD treatment by comparing the effects of cerebral revascularization as determined from magnetic resonance imaging (MRI) time-of-flight (TOF) images with the changes in ischaemic symptoms and CBF. The results of this study clarify the significance of cerebral revascularization for ischaemic MMD.

Materials and methods

Patient population

All patient information was collected retroactively with the approval of the Bioethics Review Board of Nagoya University Hospital. MMD was diagnosed by digital subtraction angiography or magnetic resonance angiography (MRA) based on the diagnostic criteria of the Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis [20]. A retrospective cohort of 24 ischaemic-onset MMD patients (31 surgeries) who underwent cerebral revascularization and received single photon emission computed tomography (SPECT)

for the quantitative evaluation of CBF before and more than 6 months after surgery at our hospital between April 2014 and September 2020 was investigated. The preoperative and postoperative values of CBF in the ischaemic hemisphere were comprehensively analysed. Regarding clinical information, data on patient sex, concomitant diseases and habits/comorbidities (hypertension, diabetes, hyperlipidaemia, smoking) and type of onset (cerebral infarction, transient ischaemic attack (TIA)) were obtained by chart review.

Preoperative radiological findings

From the MRI data obtained prior to surgery, fluid-attenuated inversion recovery (FLAIR) images were examined for any evidence of cerebral infarction. In addition, the involvement of the posterior cerebral artery (PCA) was assessed on MRA images.

Surgical procedures

Surgical revascularizations were performed by three experienced neurosurgeons (YA, KY and SO). For the direct bypass technique, a superficial temporal artery (STA)-middle cerebral artery (MCA) single bypass was performed. The STA graft was anastomosed to the recipient's MCA in an end-to-side fashion. In our facility, the indirect revascularization technique involved the placement of the pedunculated temporalis muscle, periosteum and galea on the surface of the brain and suturing them to the inverted dura mater. Revascularization surgery was performed in patients with MMD with ischaemic symptoms according to treatment guidelines [20]. For combined revascularization, both direct and indirect methods were implemented. The surgical protocol of our facility has been described in a previous report [2]; in this study, we predominantly used the combined method regardless of the patient's age.

Postoperative evaluation

All patients were managed with a standardised postoperative protocol [3, 25]. Postoperative stroke was defined in this study as a new stroke event that occurred during the postoperative chronic phase before SPECT imaging was obtained. Postoperative cerebral infarction was confirmed by either diffusion-weighted imaging (DWI) or FLAIR MRI, and haemorrhagic stroke was diagnosed by computed tomography (CT) and MRI. Graft patency after direct bypass surgery was confirmed by postoperative CT angiography (CTA) or MRA.

The postoperative effects of cerebral revascularization were qualitatively evaluated and scored based on previously reported methods [4, 17, 26]. Several slices of MRA-TOF

images taken more than 6 months after surgery were scored using a reference standard based on the degree of angiogenesis from the external carotid artery (ECA) system. Revascularization was scored as follows: (1) not visible to weakly developed, (2) moderately developed and (3) markedly developed. These scores were evaluated by three professional neurosurgeons (K.Y., K.U. and Y.A.) and discussed until consensus was reached.

Regarding the neurological symptoms on the surgical side at the time of SPECT imaging in the postoperative chronic phase, the results of the postoperative evaluation were evaluated in comparison with the preoperative results (categorised as improvement or no change) by a certified neurosurgeon.

Acquisition of SPECT data

Brain perfusion SPECT studies were performed using a double-headed gamma camera (Symbia T or Symbia T6, Siemens Healthcare, Erlangen, Germany). In SPECT imaging, we used the autoradiographic method for N-isopropyl-p-¹²³I-iodoamphetamine (¹²³I-IMP) and the Patlak plot method for ^{99m}Tc-ethyl cysteinate dimer (^{99m}Tc-ECD). 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 (Fig. 1).

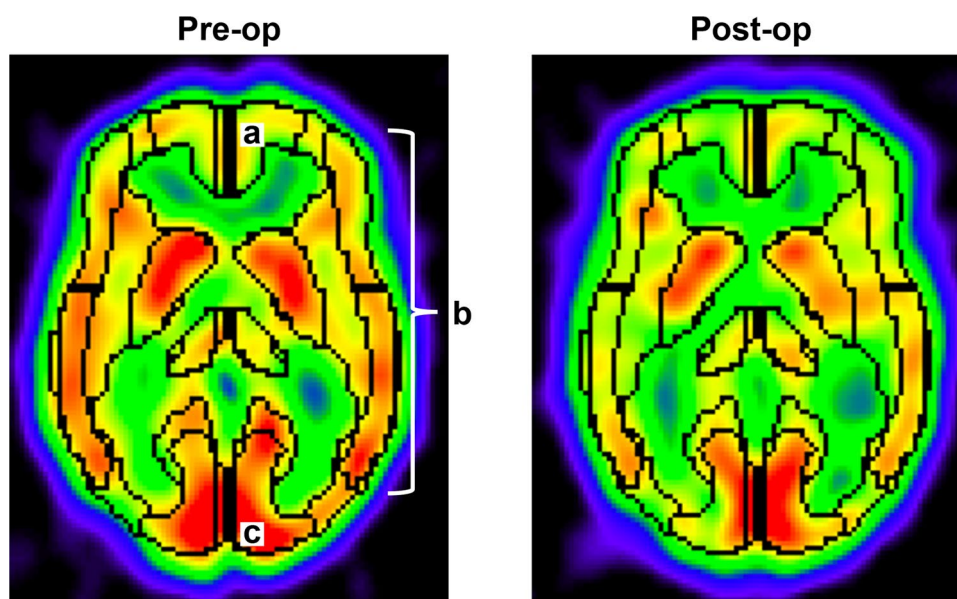


Fig. 1 SPECT images taken before cerebral revascularization (Preop) and in the postoperative chronic phase (Postop). A region of interest (ROI) for each vascular territory was set automatically by the analysis software NEURO FLEXER. **a** Anterior cerebral artery (ACA) territory; **b** middle cerebral artery (MCA) territory; **c** posterior cerebral artery (PCA) territory. The mean radioactive count in the ROI of each

Definitions of relative CBF (RCBF) and proportional change in RCBF before and after 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. The proportional change in the RCBF (denoted post/pre-RCBF) within each ROI between the preoperative phase and the postoperative chronic phase was calculated by dividing the postoperative RCBF by the preoperative RCBF.

Correlation between the effect of revascularization and post/pre-RCBF

The relationship between the grade of the effect of cerebral revascularization in the postoperative chronic phase, obtained from MRI TOF imaging data, and post/pre-RCBF in each of the ACA, MCA and PCA territories was investigated.

Relationships between neurological symptoms on the surgical side and post/pre-RCBF

Various parameters, including post/pre-RCBF, were compared between two groups of patients: a group of patients whose ischaemic symptoms improved or did not change after the operation and a group of patients whose ischaemic

of the ACA, MCA and PCA territories was divided by that of the ipsilateral cerebellar ROI, and the quotient was defined as the relative cerebral blood flow (RCBF). The rate of change in CBF (post/pre-RCBF) in each ROI before and during the postoperative chronic phase was calculated by dividing the postoperative RCBF by the preoperative RCBF

symptoms deteriorated. The changes in neurological symptoms, age at surgery, preoperative cerebral infarction/PCA involvement and revascularization score were investigated as potentially significant factors.

Age group analysis of post/pre-RCBF and changes in neurological symptoms

To examine the effect of each factor on age, the subjects of the study were divided into two groups: children (aged 17 years or younger) and adults (aged 18 years or older). Factors included preoperative cerebral infarction/PCA involvement, revascularization score, post/pre-RCBF and changes in neurological symptoms.

Statistical analysis

Normally distributed data are described as the mean \pm standard deviation (SD). Changes in RCBF before and after cerebral revascularization were evaluated using the Mann–Whitney *U*-test for the ACA, MCA and PCA territories. To examine the correlation between the cerebral revascularization score on MRA and post/pre-RCBF, Kendall's rank correlation coefficient (τ) was calculated. To perform comparisons between the groups, the Wilcoxon rank sum test was used for continuous variables, and the chi-squared test was used for categorical variables.

JMP Pro version 15.1 (SAS Institute, Cary, NC) was used for statistical analysis. $p < 0.05$ was considered to indicate a significant difference.

Results

Table 1 shows the characteristics of the patients in this study. Twenty-four MMD patients (31 surgeries) were included. The mean age of the patients at surgery was 17.3 ± 14 years (range 3–49 years). A majority of participants (87.5%) were female. Vascular risk factors were some of the less common comorbidities, with hypertension and hyperlipidaemia present in 4.2% and 8.3% of the patients, respectively. The type of onset was dominated by TIA, which accounted for 83.3% of the cohort, and cerebral infarctions accounted for the remainder. Preoperative MR examination showed cerebral infarction in approximately 1/4 of the hemispheres. PCA involvement was observed in 35.5% of the cohort. Combined surgery was performed in all patients in this study. Postoperative CTA or MRA imaging confirmed that all direct bypasses were patent. No patients developed new strokes before SPECT imaging in the chronic phase, including during the postoperative acute phase. The mean duration from surgery to SPECT imaging in the postoperative chronic phase was 13.3 ± 5 months (range 6–26).

Table 1 Characteristics of the patients in this study

Characteristic	Value (n/side, %)
Number of patients	24
Number of surgeries	31
Age at surgery, mean \pm SD	17.3 ± 14
Sex	
Male	3 (12.5)
Female	21 (87.5)
Risk factors	
Hypertension	1 (4.2)
Diabetes	0 (0)
Hyperlipidaemia	2 (8.3)
Smoking	0 (0)
Type of onset	
TIA	20 (83.3)
Cerebral infarction	4 (16.7)
Preoperative MR findings	
Cerebral infarction	8 (25.8)
PCA involvement	11 (35.5)
Type of surgery	
Combined	31 (100)
New stroke found in SPECT imaging in the postoperative chronic phase	0 (0)
Period until SPECT imaging in the postoperative chronic phase, month \pm SD	13.3 ± 5

MR, magnetic resonance; PCA, posterior cerebral artery; SD, standard deviation; SPECT, single photon emission computed tomography; TIA, transient ischaemic attack

By the revascularization scores on MRA, the mean effect of revascularization in the 31 hemispheres was 2.68 ± 0.47 (range 2–3). The percentage of cases with postoperative improvement (improvement versus no change) in neurological symptoms was 87.1% (27/31 hemispheres).

RCBF before and after cerebral revascularization in the chronic phase

The data for RCBF are shown in Table 2 and Fig. 2. The preoperative and postoperative mean values were 2.92 ± 0.15 and 0.96 ± 0.13 ($p = 0.619$) in the ACA territory, 0.99 ± 0.17 and 1.01 ± 0.17 ($p = 0.598$) in the MCA territory and 1.15 ± 0.22 and 1.14 ± 0.19 in the PCA territory, respectively ($p = 0.062$). There was no significant difference in RCBF before and after cerebral revascularization in any of the ROIs.

Relationship between the effect of revascularization and post/pre-RCBF

Figure 3 shows the correlation between the degree of effect of cerebral revascularization as observed on MRA

Table 2 Changes in cerebral blood flow relative to that in the ipsilateral cerebellum before and after surgery

RCBF ^a values	Preoperative	Postoperative	<i>p</i> value
ACA territory	0.92 ± 0.15	0.96 ± 0.13	0.619
MCA territory	0.99 ± 0.17	1.01 ± 0.17	0.598
PCA territory	1.15 ± 0.22	1.14 ± 0.19	0.062

^a In each ROI of the ACA, MCA and PCA territories, the radioactive count divided by that in the ipsilateral cerebellar ROI was calculated, and the value was defined as the relative CBF (RCBF). ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery

in the postoperative chronic phase and post/pre-RCBF in each of the ACA, MCA and PCA territories. There was no significant correlation for any of the ROIs: $\tau = 0.1166$ ($p = 0.4463$) for the ACA territory, $\tau = 0.0292$ ($p = 0.849$) for the MCA territory and $\tau = 0.1939$ ($p = 0.2044$) for the PCA territory.

Relationship between neurological symptoms on the surgical side and post/pre-RCBF

A comparative analysis of the various parameters was performed by dividing the patients into two groups: a group of patients whose neurological symptoms either improved or did not change after surgery ($n = 27$) and a group of patients whose neurological symptoms deteriorated ($n = 4$) (Table 3). Univariate analyses showed no significant differences between the groups in terms of baseline data, such as age at surgery ($p = 0.1939$) and preoperative MR findings (cerebral infarction ($p = 0.9685$), PCA involvement ($p = 0.5156$)). In addition, there was no significant difference between the groups in terms of revascularization scores, which were determined from the MRI TOF data ($p = 0.7434$). In each territory, the association of post/pre-RCBF, which is the rate of change in RCBF between the pre- and postoperative phases, with the change in symptoms was analysed, but no significant associations were found (ACA territory; $p = 0.4608$, MCA territory; $p = 0.275$, PCA territory; $p = 0.1326$). A multivariate analysis was not performed

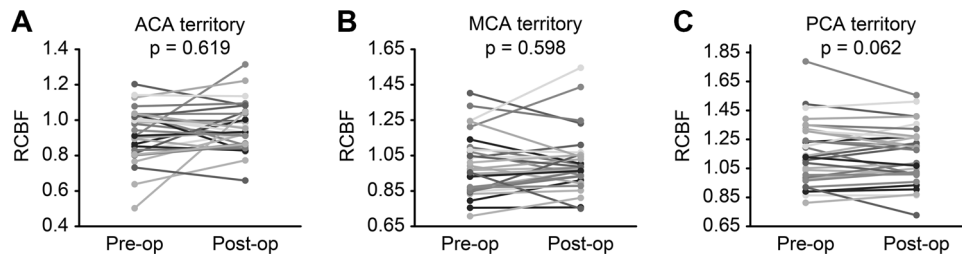


Fig. 2 Relative cerebral blood flow before and after cerebral revascularization in the chronic phase (A–C). **A** ACA territory, **B** MCA territory and **C** PCA territory. In each ROI of the ACA, MCA and

PCA territories, the radioactive count was divided by that in the ipsilateral cerebellar ROI, and the quotient was defined as the relative CBF (RCBF)

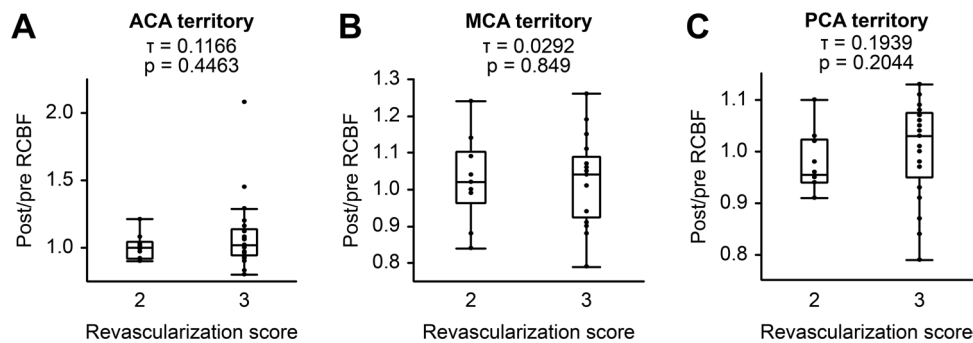


Fig. 3 Relationship between the effect of revascularization on MRA and the rate of change in cerebral blood flow before and after surgery (A–C). **A** ACA territory, **B** MCA territory and **C** PCA territory. Several slices of the MRA-TOF image taken more than 6 months after the surgery were scored against a reference value based on the degree of angiogenesis from the external carotid artery (ECA) system.

Revascularization was scored as follows: (1) not visible to weakly developed, (2) moderately developed and (3) markedly developed. The rate of change in CBF (post/pre-RCBF) in each ROI between the preoperative phase and the postoperative chronic phase was calculated by dividing the postoperative RCBF by the preoperative RCBF

Table 3 Relationship between the pre- and postoperative changes in neurological symptoms on the surgical side and cerebral blood flow

	Neurological symptom change		<i>p</i> value
	Improve-ment/no change	Deterioration	
Number of surgeries	27	4	
Age at surgery, mean ± SD	15.6 ± 13.1	28.3 ± 18.6	0.1939
Preoperative MR findings (%)			
Cerebral infarction	7 (25.9)	1 (25)	0.9685
PCA involvement	9 (33.3)	2 (50)	0.5156
Revascularization score	2.67 ± 0.48	2.75 ± 0.5	0.7434
Post/pre-RCBF ^a			
ACA territory	1.07 ± 0.25	1.04 ± 0.04	0.4608
MCA territory	1.02 ± 0.12	1.07 ± 0.1	0.275
PCA territory	0.99 ± 0.08	1.05 ± 0.05	0.1326

^a In each ROI of the ACA, MCA and PCA territories, the radioactive count divided by that in the ipsilateral cerebellar ROI was calculated, and the value was defined as the relative CBF (RCBF). The proportional change in RCBF (post/pre-RCBF) at each ROI before and during the postoperative chronic phase was calculated by dividing the postoperative RCBF by the preoperative RCBF. *ACA*, anterior cerebral artery; *CBF*, cerebral blood flow; *MCA*, middle cerebral artery; *MR*, magnetic resonance; *PCA*, posterior cerebral artery; *SD*, standard deviation

Table 4 Age group analysis of pre- and postoperative changes in cerebral blood flow and neurological symptoms

	Age groups		<i>p</i> value
	Paediatrics (≤ 17 years old)	Adults (≥ 18 years old)	
Number of surgeries	21	10	
Age at surgery, mean ± SD	9 ± 3.7	34.7 ± 11.9	
Preoperative MR findings (%)			
Cerebral infarction	5 (23.8)	3 (30)	0.136
PCA involvement	5 (23.8)	6 (60)	0.049*
Revascularization score	2.71 ± 0.46	2.6 ± 0.52	0.5313
Post/pre-RCBF ^a			
ACA territory	1.06 ± 0.28	1.06 ± 0.09	0.1896
MCA territory	1.01 ± 0.12	1.05 ± 0.11	0.2361
PCA territory	0.99 ± 0.08	1.01 ± 0.09	0.3859
Neurological symptoms (%)			0.0501
Improve/no change	20 (95.2)	7 (70)	
Deteriorated	1 (4.8)	3 (30)	

^a In each ROI of the ACA, MCA and PCA territories, the radioactive count divided by that in the ipsilateral cerebellar ROI was calculated, and the value was defined as the relative CBF (RCBF). The proportional change in RCBF (post/pre-RCBF) at each ROI between before and during the postoperative chronic phase was calculated by dividing the postoperative RCBF by the preoperative RCBF. *SD*, standard deviation; *MR*, magnetic resonance; *PCA*, posterior cerebral artery; *CBF*, cerebral blood flow; *ACA*, anterior cerebral artery; *MCA*, middle cerebral artery; *PCA*, posterior cerebral artery. * Statistical significance ($p < 0.05$)

because neurological symptoms had worsened in only a few patients ($n = 4$).

Age group analysis of post/pre-RCBF and changes in neurological symptoms

The numbers of surgeries in children up to 17 years old and adults aged 18 years and older were 21 and 10, respectively (Table 4). Amongst the preoperative MR findings, cerebral infarction was not significantly different by the age group, but PCA involvement was significantly associated with adult cases ($p = 0.049$). There was no significant difference in revascularization scores between the two groups ($p = 0.5313$). When the post/pre-RCBF in each vascular territory was compared between the two groups, no significant difference was observed between the groups in any territory (ACA territory: $p = 0.1896$, MCA territory: $p = 0.2361$, PCA territory: $p = 0.3859$). Regarding changes in neurological symptoms, the proportion of improvement/no change tended to be higher in the paediatric group than in the adult group, but no statistically significant difference was observed ($p = 0.0501$).

Discussion

This study focused on the changes in CBF during the postoperative chronic phase in patients with ischaemic MMD. SPECT comparisons of the ROI in each vascular territory

revealed no significant change in CBF in the postoperative chronic phase compared to the preoperative phase in any of the territories. Furthermore, regarding the revascularization score obtained from the MRI TOF data, the proportional change in RCBF (post/pre-RCBF) was not high even in those cases with stronger revascularization effects. In nearly 90% of the patients, the neurological symptoms on the surgical side improved or remained unchanged after surgery, but no association with post/pre-RCBF in any of the vascular territories was observed. The results of this study are surprising because it is generally believed that CBF increases revascularization during the postoperative chronic phase. Furthermore, it is believed that CBF is improved postoperatively by angiogenesis in patients with MMD with ischaemic symptoms. It has been reported that hyperperfusion syndrome due to rapid local CBF elevation can occur in the acute phase after direct bypass surgery [10]. However, to the best of our knowledge, little research has been conducted on cerebral haemodynamics beyond the acute phase [12, 16]. The results of this study provide insight into the haemodynamics during the chronic postoperative period after combined surgery for ischaemic MMD; however, this study included a small number of cases.

In this study, we chose to evaluate CBF on SPECT images more than 6 months after revascularization because, in our experience, cerebral ischaemic symptoms are not completely relieved until 6 months after cerebral revascularization and require more than 6 months to stabilise. Furthermore, the effect of direct/indirect combined revascularization changes radiologically approximately 6 months after surgery. The conversion of blood flow from the internal carotid artery (ICA) to the ECA (IC-EC conversion) as evaluated on MRA images has been found to take place over the span of several months after surgery, eventually stabilising without further MMD progression [11]. The development of the ECA system, the progression of stenotic changes in the ICA and MMV regression all occur during this period. Therefore, it is presumed that cerebral haemodynamics are unstable. The present study evaluated CBF and neurological symptoms in the postoperative chronic phase, after IC-EC conversion had stabilised. To the best of our knowledge, such assessments of the postoperative chronic phase in patients with ischaemic MMD have not been performed previously. Therefore, these results may provide valuable information regarding the role of cerebral revascularization in the pathophysiology of MMD.

A report from a single institution in China describes very interesting findings from the evaluation of cerebral haemodynamics during the postoperative chronic phase in haemorrhagic onset adult MMD [12]. The authors of that report used perfusion CT (CTP) to assess cerebral haemodynamics on the brain surface and deep within the brain both preoperatively and at a median of 6.5 months postoperatively.

In addition to CBF, they evaluated the markers cerebral blood volume (CBV), mean transit time (MTT) and time to peak (TTP). Only the relative CBV with reference to the pons showed a significant decrease from before to after the operation, regardless of whether the direct, combined or indirect surgical procedure was used and the timing of the CTP imaging. There were overall tendencies for the relative MTT and relative TTP to shorten, but there was no pattern observed regarding the surgical method or CTP imaging time. Furthermore, no significant change was observed in the relative CBF before and after surgery. Although there were differences in the type of onset between the patients with ischaemia and those with haemorrhage, there was no significant change in the relative CBF of the cortical MCA territory during the postoperative chronic phase, which is consistent with our results. On the other hand, the revascularization effect was evaluated as good, at 71.4%, which was based on CT angiography to determine the development of collaterals associated with direct or combined surgery in their facility. Similarly, in our analysis, no correlation was observed between the effects of revascularization and post/pre-RCBF. Radiologically favourable revascularization effects were consistently obtained, but no significant increase in CBF was observed. More notably, although the number of cases in the previous study was limited, the incidence of rebleeding events was low, at 1/58 hemispheres (1.7%) in the studied cohort. The relative CBV showed a significant decrease, suggesting that it may be a promising marker of good prognosis. The authors of the previous report need to verify their results by conducting larger studies. Notably, the postoperative relative TTP was significantly shortened in the patients who underwent direct or combined surgery. In our study, since we targeted the timeframe that included the onset of ischaemia and evaluated only the CBF measured by SPECT, it cannot be applied to interpret the change in TTP. However, the data in our study also included the change in local CBF during the acute phase after surgery, which was measured using the intraoperative changes in indocyanine green signal, a helpful technique [25]. As a result, the rate of change in TTP (Δ TTP) before and after anastomosis was a significant predictor of postoperative transient neurological events (TNEs). In addition, using SPECT, we investigated the changes in CBF during the postoperative acute phase, but they did not correlate with TNEs. On the other hand, TNEs have been reported to predict the occurrence of stroke events in the early postoperative period [3]. TTP shortening causes TNEs and stroke during the early postoperative period, but during the chronic postoperative period, symptoms may improve regardless of the changes in CBF. In light of these observations, CT and MR perfusion techniques may be more appropriate than semiquantitative SPECT for the evaluation of cerebral haemodynamics in the postoperative chronic phase.

On the other hand, there was no particular difference between the paediatric and adult groups in terms of the factors considered in this study (Table 4). It is widely recognised that there are age-related differences in the development of STA and other ECA systems after revascularization by direct or indirect bypass in MMD patients [6, 15]. In general, indirect bypasses do not develop as effectively in adult cases as in paediatric cases; therefore, only the direct bypass procedure tends to be applied to adult patients. However, a recent study by Uchino et al. found no age-related differences in the development of direct bypass and indirect bypass after combined surgery [22, 24]. Similarly, the age group analysis at our institution showed no significant difference in revascularization scores between the paediatric and adult cases, and the post/pre-RCBF was closely related to the revascularization effect. Therefore, combined surgery may induce revascularization enhancement different from the results of direct or indirect surgery alone. The changes in neurological symptoms were not significantly different between groups, but the paediatric cases tended to be more favourable than the adult cases. This may be because the adult group had significantly more advanced disease with greater PCA involvement than the paediatric group (paediatric: 23.8%; adult: 60%). In other words, given that there was no difference in the revascularization score or post/pre-RCBF by age group in this study, the degree of improvement in ischaemic symptoms may have been affected by the background disease stage.

In MMD, IC-EC conversion occurs as a pathological condition and affects in the development and regression of MMVs [9]. In the process of conversion, cerebral ischaemia is induced by the imbalance between the supply and demand of CBF. In other words, when ICA, MMVs or PCA stenosis progresses with the progression of disease stage, a transdural/transcranial anastomosis from the ECA needs to develop, and blood flow to the brain needs to be supplied. If IC-EC conversion is not fully achieved, cerebral infarction will occur in the watershed region away from the source of blood flow. The frequent occurrence of stroke will reduce the demand for CBF as it changes to match perfusion. However, it has been reported that higher brain functions decline accordingly [1]. Our findings suggest that an important role of cerebral revascularization in MMD is to assist IC-EC conversion by promoting blood flow from ECA systems in the pathogenesis of MMD. This logic is consistent with previous reports that EC-IC bypass fulfils the function of “reconstruction” and that indirect synangiosis fulfils the function of “consolidation” [9]. In addition, regarding CBF, the role of cerebral revascularization may not be to significantly increase CBF but to maintain it and prevent its decrease.

Limitations

The potential limitations of this study should be mentioned. First, the results of this study cannot be generalised due to the retrospective, single-centre nature of its design; therefore, the results of this study must be interpreted with caution. Second, the ROI that was set with the software was large and may not have been suitable for capturing trace or subtle CBF changes in MMD. To sensitively detect changes in CBF due to cerebral revascularization, an ROI setting that is centred on the craniotomy site should be considered. In addition, evaluation of cerebral haemodynamics by CT and MR perfusion images, which are more sensitive than semi-quantitative SPECT, should be considered. Third, although this study focused on patients with ischaemic MMD, a large proportion of patients maintained preoperative RCBF (Table 2). If the proportion of patients with severe preoperative cerebral ischaemia had been high, a significant difference may have been observed in postoperative RCBF, even with the wide ROI. Furthermore, if the preoperative RCBF had been analysed in subgroups or if the increase in the postoperative CBF rate had been calculated, different results may have been produced. Fourth, although not addressed in this study, MMD grading could have reduced the variability in the results if CBF changes were investigated.

Conclusions

In this study, no significant change in CBF from before surgery to the chronic phase after cerebral revascularization was observed in any of the vascular territories. In addition, no significant relationship was found between the changes in neurological symptoms and the MRI-evaluated revascularization effect/CBF proportional change. Cerebral revascularization may merely assist with IC-EC conversion and may contribute to the maintenance of CBF.

Author contribution Conception and design: YA and TM. Data acquisition: YA, KY, KU, FK, MK, YS, KT, KI and TM. Drafting of the article: YA, TM and NF. Statistical analysis: YA. Critical revision and advice: MN, KT, YN, YN, TT, SO and TI. Supervision: RS.

Data availability The data and materials that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability Not applicable.

Declarations

Ethics approval This study was approved by the Bioethics Review Committee of Nagoya University Hospital under the registration

name “Evaluation of bypass vessel diameter and SPECT findings before and after revascularization in patients with moyamoya disease” (2021–0043).

Consent to participate Written informed consent for participation in the study was received from all subjects.

Consent for publication Written informed consent for publication was received from all subjects.

Conflict of interest The authors declare no competing interests.

References

- Araki Y, Takagi Y, Ueda K, Ubukata S, Ishida J, Funaki T, Kikuchi T, Takahashi JC, Murai T, Miyamoto S (2014) Cognitive function of patients with adult moyamoya disease. *J Stroke Cerebrovasc Dis* 23:1789–1794. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2014.04.032>
- Araki Y, Uda K, Yokoyama K, Kanamori F, Mamiya T, Nishihori M, Izumi T, Tanahashi K, Sumitomo M, Okamoto S, Wakabayashi T, Natsume A (2020) Surgical designs of revascularization for moyamoya disease: 15 years of experience in a single center. *World Neurosurg* 139:e325–e334. <https://doi.org/10.1016/j.wneu.2020.03.217>
- Araki Y, Yokoyama K, Uda K et al (2021) Postoperative stroke and neurological outcomes in the early phase after revascularization surgeries for moyamoya disease: an age-stratified comparative analysis. *Neurosurg Rev* 44:2785–2795. <https://doi.org/10.1007/s10143-020-01459-0>
- Araki Y, Yokoyama K, Uda K, Kanamori F, Mamiya T, Nishihori M, Sumitomo M, Okamoto S, Izumi T (2021) Ipsilateral late stroke after revascularization surgery for patients with moyamoya disease. *Acta Neurochir (Wien)* 163:1493–1502. <https://doi.org/10.1007/s00701-021-04773-8>
- Cho WS, Lee HY, Kang HS, Kim JE, Bang JS, Oh CW (2013) Symptomatic cerebral hyperperfusion on SPECT after indirect revascularization surgery for moyamoya disease. *Clin Nucl Med* 38:44–46. <https://doi.org/10.1097/RLU.0b013e31827083d8>
- Czabanka M, Vajkoczy P, Schmiedek P, Horn P (2009) Age-dependent revascularization patterns in the treatment of moyamoya disease in a European patient population. *Neurosurg Focus* 26:E9. <https://doi.org/10.3171/2009.1.Focus08298>
- Fujimura M, Kaneta T, Mugikura S, Shimizu H, Tominaga T (2007) Temporary neurologic deterioration due to cerebral hyperperfusion after superficial temporal artery-middle cerebral artery anastomosis in patients with adult-onset moyamoya disease. *Surg Neurol* 67:273–282. <https://doi.org/10.1016/j.surneu.2006.07.017>
- Fujimura M, Shimizu H, Inoue T, Mugikura S, Saito A, Tominaga T (2011) 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-[¹²³I]iodoamphetamine single-photon emission computed tomography. *Neurosurgery* 68:957–964. <https://doi.org/10.1227/NEU.0b013e318208f1da>
- Fujimura M, Tominaga T (2012) Lessons learned from moyamoya disease: outcome of direct/indirect revascularization surgery for 150 affected hemispheres. *Neurol Med Chir (Tokyo)* 52:327–332. <https://doi.org/10.2176/nmc.52.327>
- Fujimura M, Tominaga T (2015) Significance of cerebral blood flow analysis in the acute stage after revascularization surgery for moyamoya disease. *Neurol Med Chir (Tokyo)* 55:775–781. <https://doi.org/10.2176/nmc.ra.2015-0063>
- Houkin K, Nakayama N, Kuroda S, Ishikawa T, Nonaka T (2004) How does angiogenesis develop in pediatric moyamoya disease after surgery? A prospective study with MR angiography. *Childs Nerv Syst* 20:734–741. <https://doi.org/10.1007/s00381-004-0971-x>
- Kang K, Ma N, Li J, Shen Y, Gu W, Ma G, Zhang D, Zhao X (2020) Cerebral hemodynamic changes after revascularization in patients with hemorrhagic moyamoya disease. *Front Neurol* 11:72. <https://doi.org/10.3389/fneur.2020.00072>
- Kuroda S, Houkin K (2008) Moyamoya disease: current concepts and future perspectives. *Lancet Neurol* 7:1056–1066. [https://doi.org/10.1016/s1474-4422\(08\)70240-0](https://doi.org/10.1016/s1474-4422(08)70240-0)
- Kuroda S, Nakayama N, Yamamoto S, Kashiwazaki D, Uchino H, Saito H, Hori E, Akioka N, Kuwayama N, Houkin K (2020) Late (5–20 years) outcomes after STA-MCA anastomosis and encephalo-duro-myo-arterio-pericranial synangiosis in patients with moyamoya disease. *J Neurosurg* 134:909–916. <https://doi.org/10.3171/2019.12.jns192938>
- Lee SB, Kim DS, Huh PW, Yoo DS, Lee TG, Cho KS (2012) Long-term follow-up results in 142 adult patients with moyamoya disease according to management modality. *Acta Neurochir (Wien)* 154:1179–1187. <https://doi.org/10.1007/s00701-012-1325-1>
- Lou J, Liu Z, Xu B, Wang YK, Liu CJ, Liu M, Liu XD (2019) Evaluation of 99mTc-ECD SPECT/CT brain imaging with NeuroGam analysis in moyamoya disease after surgical revascularization. *Medicine (Baltimore)* 98:e16525. <https://doi.org/10.1097/md.00000000000016525>
- Maruwaka M, Yoshikawa K, Okamoto S, Araki Y, Sumitomo M, Kawamura A, Yokoyama K, Wakabayashi T (2015) Biomarker research for moyamoya disease in cerebrospinal fluid using surface-enhanced laser desorption/ionization time-of-flight mass spectrometry. *J Stroke Cerebrovasc Dis* 24:104–111. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2014.07.028>
- Miyamoto S, Yoshimoto T, Hashimoto N, Okada Y, Tsuji I, Tominaga T, Nakagawara J, Takahashi JC (2014) Effects of extracranial-intracranial bypass for patients with hemorrhagic moyamoya disease: results of the Japan Adult Moyamoya Trial. *Stroke* 45:1415–1421. <https://doi.org/10.1161/strokeaha.113.004386>
- Mukerji N, Cook DJ, Steinberg GK (2015) Is local hypoperfusion the reason for transient neurological deficits after STA-MCA bypass for moyamoya disease? *J Neurosurg* 122:90–94. <https://doi.org/10.3171/2014.8.jns132413>
- Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis, Health Labour Sciences Research Grant for Research on Measures for Intractable Diseases (2012) Guidelines for diagnosis and treatment of moyamoya disease (spontaneous occlusion of the circle of Willis). *Neurol Med Chir (Tokyo)* 52:245–266. <https://doi.org/10.2176/nmc.52.245>
- Suzuki J, Takaku A (1969) Cerebrovascular “moyamoya” disease. Disease showing abnormal net-like vessels in base of brain. *Arch Neurol* 20:288–299. <https://doi.org/10.1001/archneur.1969.00480090076012>
- Uchino H, Kim JH, Fujima N, Kazumata K, Ito M, Nakayama N, Kuroda S, Houkin K (2017) Synergistic interactions between direct and indirect bypasses in combined procedures: the significance of indirect bypasses in moyamoya disease. *Neurosurgery* 80:201–209. <https://doi.org/10.1227/neu.0000000000001201>
- Uchino H, Kuroda S, Hirata K, Shiga T, Houkin K, Tamaki N (2012) Predictors and clinical features of postoperative hyperperfusion after surgical revascularization for moyamoya disease: a serial single photon emission CT/positron emission tomography study. *Stroke* 43:2610–2616. <https://doi.org/10.1161/strokeaha.112.654723>
- Uchino H, Yamamoto S, Kashiwazaki D, Akioka N, Kuwayama N, Noguuchi K, Kuroda S (2019) Using postoperative remodeling

- of donor arteries on MR angiography to predict the development of surgical collaterals in moyamoya disease. *J Neurosurg* 134:1–9. <https://doi.org/10.3171/2019.8.Jns191846>
25. Uda K, Araki Y, Muraoka S, Ota S, Wada K, Yokoyama K, Nishihori M, Izumi T, Okamoto S, Wakabayashi T (2018) Intraoperative evaluation of local cerebral hemodynamic change by indocyanine green videoangiography: prediction of incidence and duration of postoperative transient neurological events in patients with moyamoya disease. *J Neurosurg* 1:1–9. <https://doi.org/10.3171/2017.10.jns171523>
26. Yokoyama K, Maruwaka M, Yoshikawa K, Araki Y, Okamoto S, Sumitomo M, Kawamura A, Sakamoto Y, Shimizu K, Izumi T, Wakabayashi T (2018) Elevation of proenkephalin 143–183 in cerebrospinal fluid in moyamoya disease. *World Neurosurg* 109:e446–e459. <https://doi.org/10.1016/j.wneu.2017.09.204>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.