



# Changes in periventricular anastomosis after indirect revascularization surgery alone for adult patients with misery perfusion due to ischemic moyamoya disease

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## Abstract

Periventricular anastomosis in moyamoya disease (MMD) is an unusual angiographic finding that arises from perforating arteries such as the lenticulostriate artery (LSA), thalamic artery (THA), and anterior choroidal artery (AChA). This anastomosis is associated with increased hemorrhagic risk in MMD and can be corrected by direct revascularization surgery. The present supplementary analysis on a prospective cohort aimed to elucidate changes in periventricular anastomosis after indirect revascularization surgery alone for adult patients with misery perfusion due to ischemic MMD. Twenty-two patients with misery perfusion in the symptomatic cerebral hemisphere who underwent indirect revascularization surgery alone also underwent six-vessel cerebral angiography via arterial catheterization before and at 6 months after surgery. Before surgery, two patients (9%) had positive periventricular anastomosis from the LSA and another (5%) from the AChA; all three of these periventricular anastomoses regressed after surgery, but these changes were not statistically significant ( $p=0.0833$ ). The degree of formation of collateral vessels from the LSA significantly decreased after surgery ( $p=0.0143$ ), but the degree of collateral vessels from the THA or AChA did not differ between pre- and postoperative conditions. Eight patients with postoperative regression of the collateral vessels from any perforating artery exhibited postoperative rich collateral flow from indirect revascularization. Periventricular anastomosis tended to regress after indirect revascularization surgery alone for adult patients with misery perfusion due to ischemic MMD. Collateral vessels formed from the LSA likely regressed after indirect revascularization surgery alone for such patients, but those vessels from the THA or AChA seldom changed.

**Keywords** Adult · Moyamoya disease · Ischemia · Periventricular anastomosis · Revascularization

## Introduction

In children, moyamoya disease (MMD) manifests exclusively with cerebral ischemia, whereas in adults, it manifests with both cerebral ischemia and intracranial hemorrhage [25, 31]. The Japan Adult Moyamoya Trial demonstrated the preventive effect of superficial temporal artery (STA)-middle cerebral artery (MCA) anastomosis as direct revascularization surgery on further hemorrhagic events for adult patients with hemorrhagic-onset MMD [20]. To prevent further

events, revascularization surgery is also performed for adult patients with ischemic symptoms due to MMD [4, 11, 25]. A decreased prevalence of further ischemic and/or hemorrhagic events after direct versus indirect revascularization surgery has been reported in a number of retrospective studies [9, 15, 16]. Such revascularization surgeries for cerebral ischemia are frequently recommended for patients who have a symptomatic cerebral hemisphere exhibiting hemodynamic compromise such as misery perfusion [4, 9, 21]. In a recent prospective study involving only adult patients with MMD with ischemic presentation and misery perfusion in the affected hemisphere, we found that as indirect revascularization alone, encephalo-duro-myo-arterio-pericranial-synangiosis not only provides sufficient collateral circulation, but also improves cerebral hemodynamics and enables the recovery of cognitive function [13, 34]. The latter two effects may be more

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pronounced in such patients compared with those undergoing direct revascularization surgery [13, 33].

In MMD, an indistinct network of basal perforating arteries is often seen [25, 29, 30], and periventricular anastomosis is an atypical angiographic finding indicating the development of a connection between the collateral vessels and medullary arteries in the periventricular region, arising from the lenticulostriate artery (LSA), thalamic artery (THA), anterior choroidal artery (AChA), or other perforating arteries [5, 7, 8, 26]. These abnormal collateral anastomoses are reportedly associated with increased hemorrhagic risk in MMD [7, 8, 26, 29] and can be corrected by direct revascularization surgery [19]. This correction might be the result of the effectiveness of direct revascularization surgery in preventing further bleeding in adult patients with hemorrhagic-onset MMD [19]. By contrast, whether indirect revascularization surgery alone corrects periventricular anastomosis remains unknown.

Given this background, the aim of the present supplementary analysis of a prospective cohort [13, 34] was to elucidate changes in periventricular anastomosis after indirect revascularization surgery alone for adult patients with misery perfusion due to ischemic MMD.

## Materials and methods

### Inclusion criteria

Twenty-three consecutive Japanese patients who visited our hospital from April 2016 to March 2021 and met the following inclusion criteria were prospectively included in the original study [13, 34]: (1) presence of MMD according to the diagnostic criteria of the Research Committee on Spontaneous Occlusion of the Circle of Willis of the Ministry of Health, Labour and Welfare of Japan [25], (2) aged 30–60 years, (3) modified Rankin disability scale score 0 or 1, (4) presence of episodes of carotid territory ischemic symptoms occurring  $\leq 3$  months before presentation to our department, (5) absence of infarcts in the entire cortical area supplied by the M4 branch of the MCA on magnetic resonance imaging, and (6) presence of misery perfusion in the symptomatic cerebral hemispheres on brain  $^{15}\text{O}$  gas positron emission tomography. These 23 patients were advised to undergo indirect revascularization surgery. One patient refused this recommendation, but the remaining 22 underwent indirect revascularization surgery alone and were finally included in the original study [13, 34]. These 22 patients were analyzed in the present supplementary study. The study protocol was reviewed and approved by the institutional ethics committee at our institution, and written informed consent was obtained from all patients prior to participation.

### Assessment of collateral flow formation

All patients underwent six-vessel cerebral angiography by means of arterial catheterization both before and at 6 months after surgery [13, 34]. After revascularization surgery, the Matsushima scale was used to grade the formation of new collateral flow from the external carotid artery in the affected cerebral hemisphere [13, 17] through a comparison of pre- and postoperative angiograms, with grades A–C indicating collateral flows newly formed after surgery that fed more than two-thirds, between one- and two-thirds, and less than one-third of the MCA cortical territory, respectively, as seen on external carotid angiograms.

The degree of basal moyamoya collaterals in the affected cerebral hemisphere before and after revascularization surgery was graded as follows [27]: mild basal moyamoya collaterals, minimal net-like vessels, no “puff of smoke” appearance; moderate basal moyamoya collaterals, between mild and intense; and intense basal moyamoya collaterals, extensive net-like vessels with typical “puff of smoke” appearance.

The degree of formation of collateral vessels from each perforating artery in the affected cerebral hemisphere before and after revascularization surgery was graded as follows [3, 7, 26]: grades 0, 1, and 2 for the LSA indicated no dilatation and extension, dilation and/or extension below the level of the pericallosal artery, and dilation and extension beyond the level of the pericallosal artery, respectively; grades 0, 1, and 2 for the THA indicated no dilatation and extension, dilation and/or extension below the level of the medial posterior choroidal artery, and dilation and extension beyond the level of the medial posterior choroidal artery, respectively; and grades 0, 1, and 2 for the AChA indicated no dilatation and extension, dilation and/or extension below the level of the lateral ventricle, and dilation and extension beyond the level of the lateral ventricle, respectively. Positive periventricular anastomosis was defined as grade 2 collateral vessels for each perforating artery.

The patency of the STA in the affected cerebral hemisphere after indirect revascularization surgery was also determined based on a comparison of pre- and postoperative angiograms. When the frontal or parietal branch of the STA postoperatively exhibited the length and inner diameter sufficient for use as a donor artery for additional arterial bypass surgery, this branch was defined as patent.

Two independent neurosurgeons who were blinded to the clinical information and not involved in the surgical procedures graded the new collateral flow from the external carotid artery and collateral vessels from each perforating artery and determined the postoperative STA patency. Independent assessments to determine the interobserver

variability in grading were made separately by each investigator, and any disagreements between the two observers were resolved by consensus.

### Assessment of brain perfusion

Cerebral blood flow (CBF) changes before and after surgery were assessed using brain perfusion single-photon emission computed tomography according to previously described methods [13]. The relative change in CBF (%) in the affected MCA territory (postoperative value–preoperative value) was calculated in each patient [13].

### Pre-, intra-, and postoperative management

Patient management was conducted as previously described [13], with patients undergoing encephalo-duro-myo-arterio-pericranial-synangiosis via a large frontotemporal craniotomy between 1 and 4 months after the last ischemic event such that the synangiosis covered the areas showing misery perfusion on brain  $^{15}\text{O}$  positron emission tomography. When the scalp was incised, the frontal and parietal branches of the STA were saved for as long as possible. Two senior neurosurgeons performed the surgery in all patients.

### Statistical analysis

Data are expressed as the mean  $\pm$  standard deviation. Weighted  $\kappa$  statistics were calculated using data from the two observers to obtain the interobserver agreement of the grading of the postoperative new collateral flow from the external carotid artery, the grading of the basal moyamoya collaterals, the grading of the collateral vessels from each perforating artery, and the determination of postoperative STA patency and were interpreted according to a previous report [35]. Changes between values before and after surgery were evaluated using the Wilcoxon signed-rank test. Differences in values between two groups were evaluated using the Mann–Whitney  $U$  test. Significance was set at the  $p < 0.05$  level.

### Results

All 22 patients completed the pre- and postoperative six-vessel cerebral angiography via arterial catheterization [13, 34]. The characteristics of these 22 patients are shown in Table 1. No patients experienced episodes of bilateral carotid territory ischemic symptoms that had occurred  $\leq 3$  months before presentation to our department. The synangiosis uniformly covered most parts of the frontal and temporal cortices perfused by the MCA, except the insula cortex, in all 22 patients.

**Table 1** Patient characteristics of 22 patients analyzed in the present study

| Variables                          |            |
|------------------------------------|------------|
| Age (years, mean $\pm$ SD)         | 47 $\pm$ 6 |
| Female sex                         | 14 (64%)   |
| Familial MMD                       | 1 (5%)     |
| Hypertension                       | 8 (36%)    |
| Diabetes mellitus                  | 6 (27%)    |
| Dyslipidemia                       | 7 (32%)    |
| Thyroid disease                    | 1 (5%)     |
| TIAs alone before surgery          | 14 (64%)   |
| Suzuki angiographic stage $\geq 4$ | 10 (45%)   |

SD, standard deviation; MMD, moyamoya disease; TIAs, transient ischemic attacks

**Table 2** Results of grading of each collateral flow formation and postoperative STA patency in 22 patients

| Variables                  | Before surgery | After surgery |
|----------------------------|----------------|---------------|
| Matsushima scale           |                |               |
| A                          | NA             | 6 (27%)       |
| B                          | NA             | 13 (59%)      |
| C                          | NA             | 3 (14%)       |
| Basal moyamoya collaterals |                |               |
| Mild                       | 10 (45%)       | 15 (68%)      |
| Moderate                   | 6 (27%)        | 5 (23%)       |
| Intense                    | 6 (27%)        | 2 (9%)        |
| Postoperative STA patency  |                |               |
| Patent both branches       | NA             | 20 (91%)      |
| Patent only one branch     | NA             | 2 (9%)        |
| Occluded both branches     | NA             | 0 (0%)        |

STA, superficial temporal artery; NA, not applicable

Weighted  $\kappa$  statistics for interobserver agreement were 0.80 for grading of the postoperative new collateral flow from the external carotid artery, 0.83 for grading of the basal moyamoya collaterals, 0.83 for grading of the collateral vessels from the LSA, 0.83 for grading of the collateral vessels from the THA, 0.82 for grading of the collateral vessels from the AChA, and 1.00 for determination of postoperative STA patency. Interobserver agreements for all the grading systems and determinations were excellent [35].

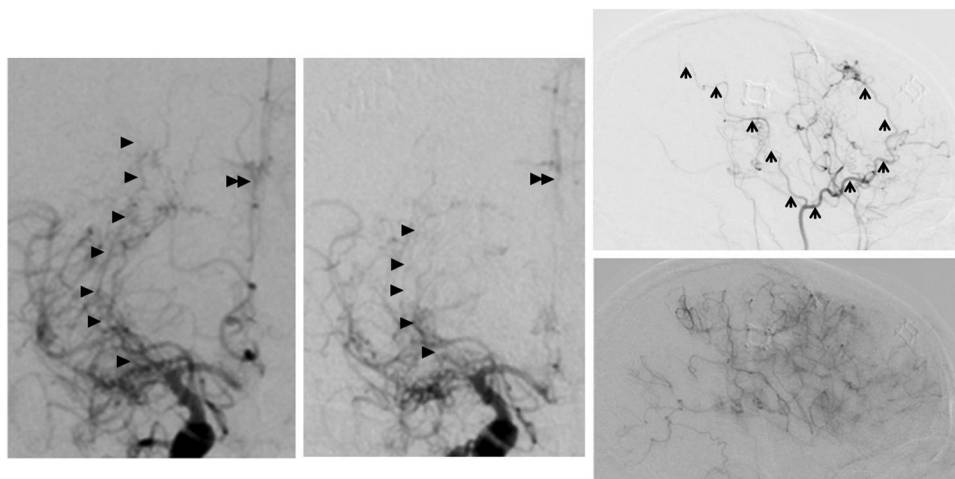
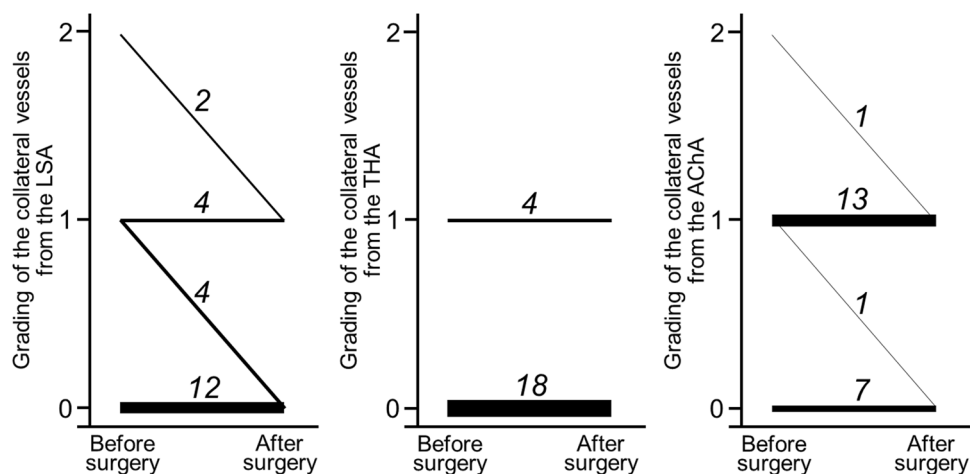
Based on the Matsushima scale regarding the postoperative new collateral flow from the external carotid artery, 19 patients (86%) were determined as showing grade A or B [13, 34] (Table 2). All 10 patients with mild basal moyamoya collaterals before surgery had unchanged collaterals after surgery; among six patients with moderate basal moyamoya collaterals before surgery, five exhibited a postoperative reduction to mild collaterals, but the other had unchanged

collaterals after surgery; and among six patients with intense basal moyamoya collaterals before surgery, four exhibited a postoperative reduction to moderate collaterals, but the other two had unchanged collaterals after surgery (Table 2).

Figure 1 shows the postoperative within-pair change in the grading of the collateral vessels from each perforating artery. For the LSA, the grade postoperatively decreased to 1 in two patients with grade 2 before surgery (Fig. 2); of eight patients with grade 1 before surgery, four exhibited a postoperative decrease to grade 0 (Fig. 3), but the other four had an unchanged grade after surgery; and the grade remained 0 postoperatively in all 12 patients with grade 0 before surgery. For the THA, four and 18 patients preoperatively exhibited grades 1 and 0, respectively; all these patients had an unchanged grade after surgery. For the AChA, the grade decreased to

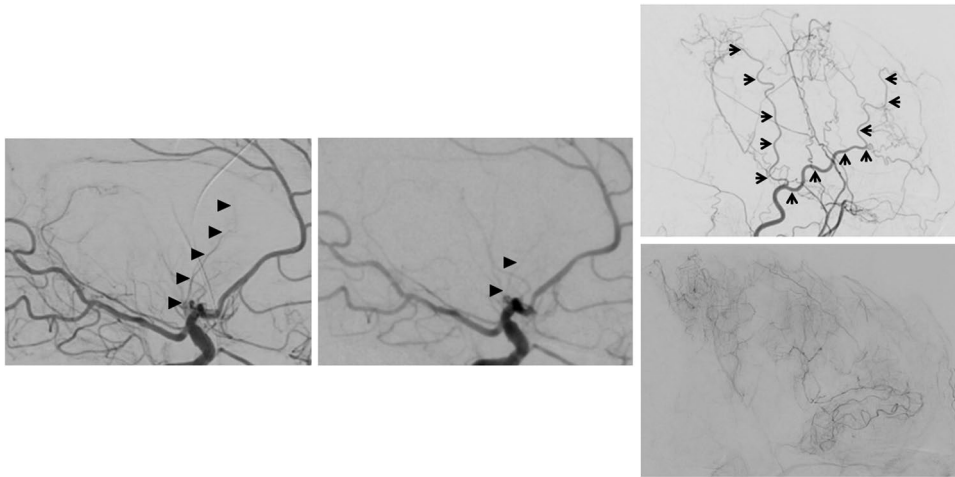
1 postoperatively in one patient with grade 2 before surgery (Fig. 4); of 14 patients with grade 1 before surgery, one exhibited a postoperative decrease to grade 0, but the other 13 had an unchanged grade after surgery; and the grade remained 0 postoperatively in all seven patients with grade 0 before surgery. Therefore, of 22 patients analyzed, before surgery, two (9%) had positive periventricular anastomosis from the LSA, and another (5%) had such anastomosis from the AChA; all three of these periventricular anastomoses regressed after surgery. No patients were preoperatively observed to have positive periventricular anastomosis from the THA. However, the change between the grade of the collateral vessels before and after surgery was not statistically significant (preoperatively  $2.0 \pm 0$  vs. postoperatively  $1.0 \pm 0$ ;  $p=0.0833$ ) in these three patients with preoperative periventricular anastomosis.

**Fig. 1** Line graphs showing within-pair change in the grading of the collateral vessels from each perforating artery in the cerebral hemisphere ipsilateral to revascularization surgery. Line widths vary with the number of cases. Diagonal lines indicate the postoperative change in the grading. Italic numerals indicate the number of cases



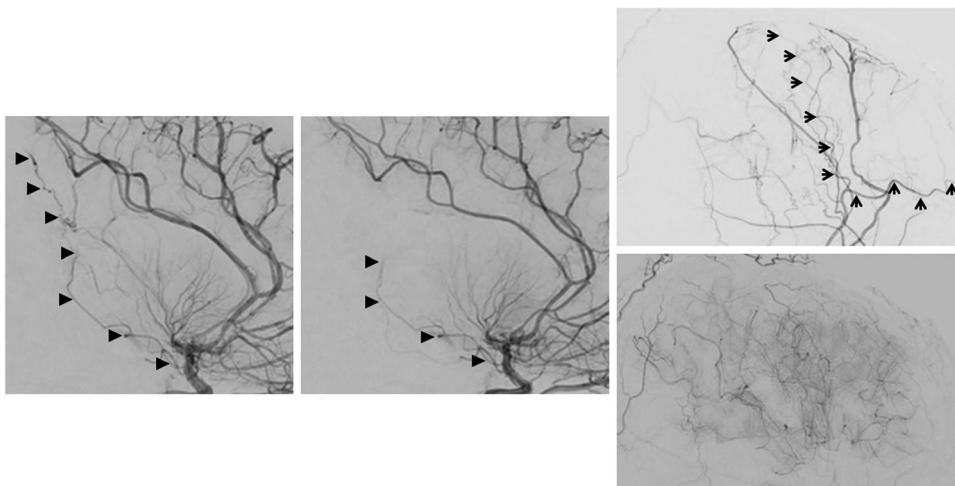
**Fig. 2** A 56-year-old man with ischemic moyamoya disease exhibiting transient attacks of left hemiparesis. Anterior–posterior view of right internal carotid angiograms shows the right lenticulostriate artery (arrow heads) dilating and extending beyond the level of the pericallosal artery (double arrow head) before surgery (left) and the same artery (arrow heads) regressing below the level of the perical-

losal artery (double arrow head) after indirect revascularization surgery (middle). Lateral view of postoperative right external carotid angiograms shows both patent branches of the right superficial temporal artery (arrows) (right upper) and collateral flows forming from indirect revascularization and feeding more than two-thirds of the right middle cerebral artery cortical territory (right lower)



**Fig. 3** A 54-year-old woman with ischemic moyamoya disease exhibiting minor stroke with right hemiparesis. Lateral view of left internal carotid angiograms shows the left lenticulostriate artery (arrow heads) dilating and extending below the level of the pericallosal artery before surgery (left) and the same artery (arrow heads) regressing after indirect revascularization surgery (middle). Lateral

view of postoperative left external carotid angiograms shows both patent branches of the left superficial temporal artery (arrows) (right upper) and collateral flows forming from indirect revascularization and feeding half of the left middle cerebral artery cortical territory (right lower)



**Fig. 4** A 42-year-old man with ischemic moyamoya disease exhibiting transient attacks of left hemiparesis. Lateral view of right internal carotid angiograms shows the anterior choroidal artery (arrow heads) dilating and extending below the level of the pericallosal artery before surgery (left) and the same artery (arrow heads) regressing after indirect revascularization surgery (middle). Lateral view

of postoperative right external carotid angiograms shows both patent branches of the right superficial temporal artery (arrows) (right upper) and collateral flows forming from indirect revascularization and feeding more than two-thirds of the right middle cerebral artery cortical territory (right lower)

The grade of the collateral vessels from the LSA significantly decreased after surgery (preoperatively  $0.5 \pm 0.7$  vs. postoperatively  $0.3 \pm 0.5$ ;  $p=0.0143$ ), but the grade from the THA (preoperatively  $0.2 \pm 0.4$  vs. postoperatively  $0.2 \pm 0.4$ ) or AChA (preoperatively  $0.7 \pm 0.6$  vs. postoperatively  $0.6 \pm 0.5$ ) did not differ between pre- and postoperative conditions. None of patients had an increase in grade. Eight patients with a postoperative decrease in the grading of the collateral vessels

from any perforating artery exhibited grade A or B on the Matsushima scale with regard to the postoperative new collateral flow from the external carotid artery. The grades of the collateral vessels from all perforating arteries remained unchanged after surgery in three patients with grade C on the Matsushima scale. Of five patients with intense or moderate basal moyamoya collaterals before surgery and a postoperative decrease in the grading of the collateral vessels from any

perforating artery, four exhibited a postoperative reduction to moderate or mild collaterals, respectively. Relative change in CBF was significantly greater in eight patients with a postoperative decrease in the grading of the collateral vessels from any perforating artery ( $19.4\% \pm 4.6\%$ ) than in 14 patients without such a condition ( $13.5\% \pm 4.5\%$ ) ( $p=0.0105$ ).

Either the frontal or parietal branch of the STA, or both, was patent after surgery in all 22 patients (Table 2, Figs. 2, 3, 4).

## Discussion

The present supplementary analysis on a prospective cohort demonstrated that periventricular anastomosis tended to regress after indirect revascularization surgery alone for adult patients with misery perfusion due to ischemic MMD. This analysis also showed that collateral vessels formed from the LSA likely regressed after indirect revascularization surgery alone for such patients, but the vessels from the THA or AChA seldom changed.

In the present study, 9%, 0%, or 5% of the patients had positive periventricular anastomosis from the LSA, THA, or AChA, respectively, before surgery. This incidence was relatively low when compared with previous findings in which the incidence was approximately 20%, 10%, or 20%, respectively [3, 26]. This discrepancy may be due to differences in patient populations, including the sample size (22 patients in the present study vs. 55 or 80 patients in those previous studies) and age (mean age of 47 years in the present study vs. 41 or 36 years in those previous studies) [3, 26]. In fact, periventricular anastomosis from the LSA or AChA is reportedly less prominent in adult patients with ischemic MMD than in pediatric patients with ischemic MMD [10, 26]. This decreased development of periventricular anastomosis from the LSA or AChA in adult patients may be due to the further involvement of the proximal MCA and the distal internal carotid artery [26]. The lower incidence of positive periventricular anastomosis in the present study may have been caused in part by the older patient population. Cerebral hemodynamic conditions in patient populations may also lead to discrepancies in the incidence of positive periventricular anastomosis among studies. Whereas in previous studies, the inclusion criterion was simply ischemic onset [3, 26], in the present study, we included only patients showing misery perfusion on positron emission tomography in addition to ischemic presentation. Therefore, the cerebral hemispheres in our patients might have exhibited more severe hemodynamic failure compared with those in previous patient populations. Considering that periventricular anastomosis serves as a main collateral pathway to compensate for the reduced cerebral perfusion in ischemic MMD [26], the decreased development of periventricular anastomosis would theoretically lead to more severe reductions in

cerebral perfusion. Furthermore, prospective observational studies involving only adult patients with ischemic MMD who received medical management alone have demonstrated that the cerebral hemisphere with misery perfusion on positron emission tomography performed within 3 months after the last ischemic event were always accompanied by angiographic disease progression [22, 23], suggesting that steno-occlusive arterial lesions might be developing at the onset of the last ischemic event in such cerebral hemispheres [22]. In the present patients, while steno-occlusive arterial lesions were developing, periventricular anastomosis developed poorly and thus might not have compensated for the reduced cerebral perfusion, resulting in the occurrence of misery perfusion in the affected cerebral hemisphere.

The main finding of the present study was that periventricular anastomosis was regressed at 6 months after indirect revascularization surgery alone in all three patients with preoperative periventricular anastomosis, but the change between the grade of the collateral vessels before and after surgery in such patients was not statistically significant, likely because of the low prevalence of periventricular anastomosis and the small sample size in the present cohort. On the other hand, in a previous report, the proportions of periventricular anastomosis from the LSA (preoperatively 28% vs. postoperatively 19%), THA (preoperatively 57% vs. postoperatively 31%), or AChA (preoperatively 60% vs. postoperatively 12%) significantly decreased between 3 and 5 months after direct revascularization surgery [19], although the patient population in that previous report was considerably younger (median age, 14 years) and included several types of initial presentations, such as cerebral ischemia and intracranial hemorrhage. In another study, a reduction in abnormal medullary arteries derived from the AChA was observed in 62% of the hemispheres undergoing indirect revascularization surgery in pediatric MMD [12]. These differences suggest a weaker effect of indirect revascularization surgery alone on the regression of collateral vessels formed from the perforating arteries. To the best of our knowledge, no previous reports have examined changes in collateral vessels from perforating arteries after revascularization surgery only for adult patients with ischemic MMD. Further studies with a larger sample size are needed to verify the effect of indirect revascularization surgery on the regression of collateral vessels in such patients.

In the present study, all patients showing postoperative regression of the collateral vessels from any perforating artery exhibited postoperative rich collateral flow from the external carotid artery. This relationship might be reasonably explained by the concepts of internal–external carotid artery conversion and periventricular anastomosis [4, 19]. In MMD, the medial end of the medullary artery connects to the perforating artery, and the direction of blood flow in the medullary artery is reversed to supply blood flow

to the cerebral cortex [5, 8]. After the completion of rich collateral flow from indirect revascularization to the cerebral cortex, this retrograde flow in the medullary artery is restored to the normal direction, resulting in regression of the pathological anastomosis and normalization of the perforating arteries. This hypothesis may be also supported by our finding that brain perfusion was more improved in patients with a postoperative decrease in the grading of the collateral vessels from any perforating artery than in those without. Furthermore, Miyakoshi et al. [18] concluded that LSA anastomosis outflow to the cortex was anterior to the central sulcus and interhemispheric fissure, THA anastomosis outflow was to the insular cortex and cortex around the central sulcus, and AChA anastomosis outflow was to the cortex posterior to the central sulcus and insular cortex. In the present study, the synangiosis sufficiently covered the cortex anterior to the central sulcus, but not the insular cortex or the cortex posterior to the central sulcus. This may explain that collateral vessels formed from the LSA likely regressed after indirect revascularization surgery alone, but the vessels from the THA or AChA seldom changed. Based on the cortical distribution of periventricular anastomotic collateral vessels proposed by Miyakoshi et al. [18] and our data, we recommend having the synangiosis cover the cortical area posterior to the central sulcus in addition to that anterior to the central sulcus via a larger fronto-temporo-parietal craniotomy.

Although direct revascularization surgery can help prevent further hemorrhagic and/or ischemic events in adult patients with ischemic MMD over the long term [14, 32], and indirect revascularization surgery alone can help prevent the same events for such patients in the midterm [1, 13], even patients with sufficient collateral flow from revascularization surgery can develop further hemorrhagic events on rare occasions [2, 24, 28]. In such cases, several investigators have proposed the tailored targeting arterial bypass strategy as a second-line surgical treatment [6, 28]. This strategy is based on the promising theory of periventricular anastomosis, which explains the mechanism of hemorrhage in MMD [6]. In this strategy, a target vessel, a cortical artery at the point at which the periventricular anastomosis of interest directly extends, is preoperatively determined in a tailored manner and anastomosed to the frontal or parietal branch of the STA [6]. Based on the cortical distribution of periventricular anastomotic collateral vessels proposed by Miyakoshi et al. [18], a recipient artery existing in the cortex near the interhemispheric fissure or further posterior to the central sulcus may be a candidate for a tailored arterial bypass strategy. However, when STA-MCA double anastomosis is routinely performed using both branches [14], or STA-MCA single anastomosis is electively performed using one branch because of another hypoplastic branch [28] in the first revascularization surgery, the STA is unavailable for the

tailored targeting arterial bypass strategy as a second-line surgical treatment. All of the present patients who underwent indirect revascularization surgery alone postoperatively had one or both branches of the STA available for additional direct revascularization surgery. This may also be a benefit of indirect revascularization surgery alone as a first-line surgical treatment for adult patients with misery perfusion due to ischemic MMD.

As described in the original study, the present study has several limitations, including the applicability of its findings to all adult MMD patients, the insufficient follow-up period, and the small sample size [13]. In particular, the regression effect of indirect revascularization surgery alone on periventricular anastomosis and the patency of the STA should be determined over the long term. The small sample size is inherent to the low prevalence of adult MMD patients with ischemic onset. Further, the present study included only patients with misery perfusion in the affected cerebral hemisphere whose prevalence was less than one-third of adult patients with ischemic MMD [13]. The synangiosis uniformly covered most parts of the frontal and temporal cortices perfused by the MCA in all our patients. Therefore, variabilities in the size and area of the synangiosis in each patient may have had a minimal effect on the present results.

## Conclusions

Periventricular anastomosis tended to regress after indirect revascularization surgery alone for adult patients with misery perfusion due to ischemic MMD. Collateral vessels formed from the LSA likely regressed after indirect revascularization surgery alone for such patients, but the vessels from the THA or AChA seldom changed.

**Author contribution** Masakazu Kobayashi: conception and design; revising the article critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Yosuke Akamatsu: conception and design, acquisition of data, analysis and interpretation of data; drafting the article critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Kohei Chida: acquisition of data; revising the article critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Shun Uchida: conception and design; revising the article critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work

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Takahiro Koji: acquisition of data; revising the article critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Yoshitaka Kubo: conception and design; revising the article critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Kuniaki Ogasawara: conception and design, acquisition of data, analysis and interpretation of data; drafting the article critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**Data availability** All data generated or analyzed during this study are not publicly available on ethical grounds. However, inquiries regarding these data can be directed to the corresponding author.

## Declarations

**Ethical approval and consent to participate** The ethics committee of the Iwate Medical University School of Medicine reviewed and approved this study protocol (No. HGH27-40). Each patient provided written informed consent prior to participation.

**Human ethics** The study protocol was established according to the ethical guidelines of the Helsinki Declaration.

**Consent for publication** Each patient provided written informed consent prior to publication.

**Competing interests** The last author (corresponding author), Kuniaki Ogasawara, has the following conflict of interest: consigned research fund from Nihon Medi-Physics Co., Ltd.

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