



Restoration of periventricular vasculature after direct bypass for moyamoya disease: intra-individual comparison

Akinori Miyakoshi¹ · Takeshi Funaki¹ · Jun C Takahashi² · Yasushi Takagi³ · Takayuki Kikuchi¹ · Kazumichi Yoshida¹ · Hiroharu Kataoka¹ · Yohei Mineharu¹ · Masakazu Okawa¹ · Yukihiro Yamao¹ · Yasutaka Fushimi⁴ · Tomohisa Okada⁵ · Kaori Togashi⁴ · Susumu Miyamoto¹

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Abstract

Background While periventricular anastomosis, a unique abnormal vasculature in moyamoya disease, has been studied in relation to intracranial hemorrhage, no study has addressed its change after bypass surgery. The authors sought to test whether direct bypass surgery could restore normal periventricular vasculature.

Methods Patients who had undergone direct bypass surgery for moyamoya disease at a single institution were eligible for the study. Baseline, postoperative, and follow-up magnetic resonance angiography (MRA) scans were scheduled before surgery, after the first surgery, and 3 to 6 months after contralateral second surgery, respectively. Sliding-thin-slab maximum-intensity-projection coronal MRA images of periventricular anastomoses were scored according to the three subtypes (lenticulostriate, thalamic, and choroidal anastomosis). Baseline and postoperative MRA images were compared to obtain a matched comparison of score changes in the surgical and nonsurgical hemispheres within individuals (intra-individual comparison).

Results Of 110 patients, 42 were identified for intra-individual comparisons. The periventricular anastomosis score decreased significantly in the surgical hemispheres (median, 2 versus 1; $p < 0.001$), whereas the score remained unchanged in the nonsurgical hemispheres (median, 2 versus 2; $p = 0.57$); the score change varied significantly between the surgical and nonsurgical hemispheres ($p < 0.001$). Of the 104 periventricular-anastomosis-positive hemispheres undergoing surgery, 47 (45.2%) were assessed as negative in the follow-up MRA. Among the subtypes, choroidal anastomosis was most likely to be assessed as negative (79.7% of positive hemispheres).

Conclusions Periventricular vasculature can be restored after direct bypass. The likelihood of correction of choroidal anastomosis is a subject requiring further studies.

Keywords Moyamoya disease · Intracranial hemorrhage · Cerebral revascularization · Periventricular anastomosis

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✉ Takeshi Funaki
tfunaki@kuhp.kyoto-u.ac.jp

¹ Department of Neurosurgery, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan

² Department of Neurosurgery, National Cerebral and Cardiovascular Center, Osaka, Japan

³ Department of Neurosurgery, Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan

⁴ Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan

⁵ Department of Human Brain Research Center, Kyoto University Graduate School of Medicine, Kyoto, Japan

Abbreviations

MCA	Middle cerebral artery
MRA	Magnetic resonance angiography
PCA	Posterior cerebral artery
SPECT	Single photon emission tomography
STA	Superficial temporal artery
STS-MIP	Sliding-thin-slab maximum-intensity-projection

Introduction

Intracranial hemorrhage is a devastating symptom of moyamoya disease [9], and the effectiveness of bypass surgery in terms of preventing hemorrhage is a subject of special interest [2, 10, 12, 14, 16, 17]. This effect has been explained

in relation to the numerous abnormal collateral vessels typical of the disease, which can decrease after bypass surgery. However, the mechanism of such decrease remains unclear because these collateral vessels have rarely been defined from an anatomical perspective. Research conducted with a comparative design is also lacking in this field.

Periventricular anastomosis is a unique phenomenon defined as pathological anastomoses between the perforating or choroidal artery and the medullary artery in the periventricular area that serve as collaterals to the cortex via retrograde flow in the medullary artery (Fig. 1) [4, 8]. Periventricular anastomosis is a novel term representing fragile nature of abnormal collateral vessels in moyamoya disease and is different from a traditional idea of “basal moyamoya vessels.” After a bypass is performed to augment blood flow in the cortex, the resulting flow change in the medullary artery can restore normal periventricular vasculature, although this hypothesis has remained unproven. Testing this hypothesis is clinically relevant because the results might suggest ways of improving the effectiveness of bypass surgery to prevent hemorrhage. The objective of the present study is to test whether periventricular vasculature detected with magnetic resonance angiography (MRA) can be restored after bypass surgery.

Methods and materials

Study design

This was an intra-individual left-right hemisphere comparative study comparing the postoperative change in periventricular anastomosis in both the surgical and

nonsurgical hemispheres. The study was approved by the ethics committee of the Kyoto University Graduate School of Medicine (R1600).

Patients and setting

The present study included patients diagnosed with moyamoya disease according to the guideline [18] who had undergone direct bypass surgery of the bilateral hemispheres at Kyoto University Hospital between 2013 and 2017. Patients were excluded from the analysis if they had been diagnosed as quasi-moyamoya disease (secondary moyamoya phenomenon due to underlying disease); had not undergone imaging modalities on schedule; had undergone bypass surgery for vascular territories other than the middle cerebral artery (MCA) territory; or had undergone previous surgical treatment outside our hospital. Patients with unilateral disease involvement (unilateral moyamoya disease) were also excluded from the intra-individual comparison analysis.

Surgical treatment protocol

All patients underwent MRI, single photon emission tomography (SPECT), and angiography to determine whether bypass surgery was indicated. For those manifesting ischemic symptoms, bypass surgery was considered if hemodynamic compromise was apparent in SPECT. For those manifesting intracranial hemorrhage, bypass surgery was considered according to the inclusion criteria of the Japan Adult Moyamoya Trial [17]. Either direct bypass, single superficial temporal artery (STA)–MCA anastomosis, or combined bypass comprising STA–MCA anastomosis and encephalo-my-

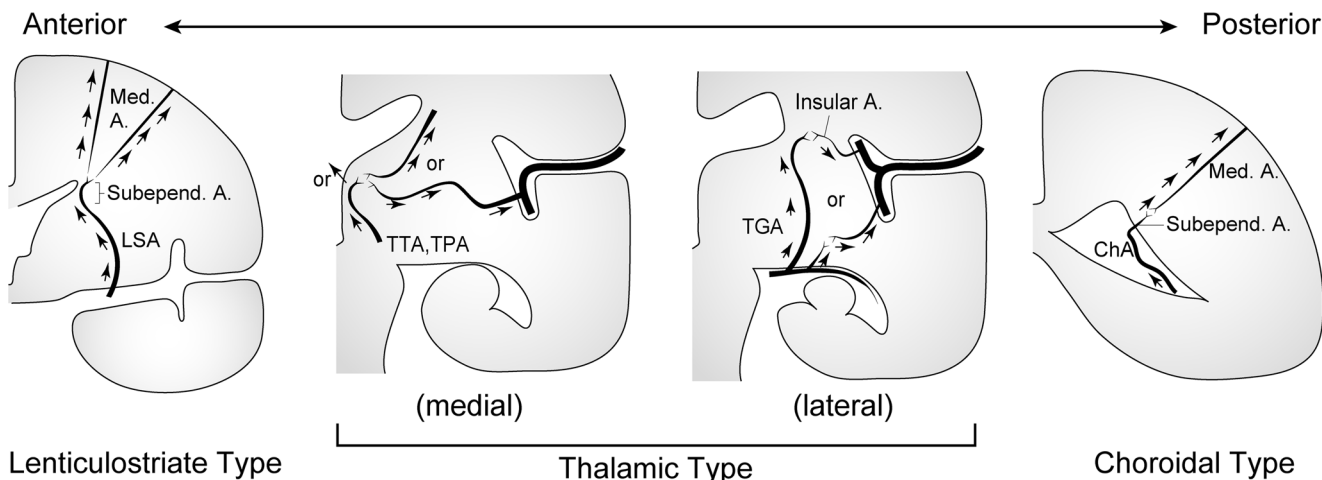


Fig. 1 Schematic illustration showing a coronal plane of the left cerebral hemisphere and three subtypes of periventricular anastomoses: lenticulostriate, thalamic, and choroidal anastomoses. Each subtype is scored 1 for positive and 0 for negative, and the sum of these subscale scores for each hemisphere represents the periventricular anastomosis score; the scores thus range from 0 to 3. A. indicates artery; ChA,

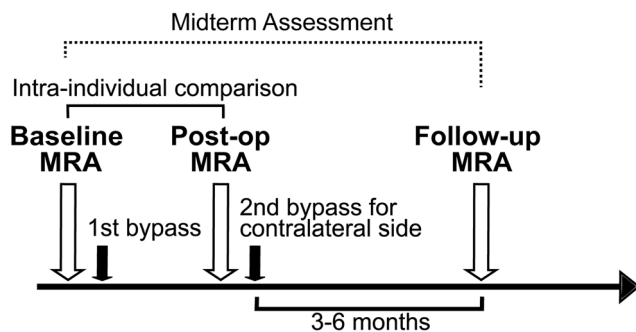
choroidal artery; LSA, lenticulostriate artery; Med, medullary; Subepend, subependymal; TGA, thalamogeniculate artery; TPA, thalamoperforating artery; TTA, thalamotuberal artery. Reprinted with permission from Funaki et al.: *Neurol Med Chir (Tokyo)* 55:204–209, 2015

synangiosis was adopted as a first-line surgical treatment. The surgical procedure in our institution is described in detail elsewhere [15]. Surgeons used a large horseshoe-shaped scalp incision surrounding the branch of the STA. In children, encephalo-myo-synangiosis was combined with direct bypass. For patients with bilateral involvement of the carotid arteries, a second bypass surgery of the contralateral MCA territory was performed at least 1 month after the first surgery. In all cases, the patency of the bypass was assessed with angiography performed 3 to 6 months after the second surgery.

Imaging schedule

All patients underwent prescheduled 3 MRA scans (Fig. 2): baseline MRA performed a few days before the first bypass surgery, postoperative MRA performed after the first surgery and a few days before the second surgery on the contralateral side, and follow-up MRA performed 3 to 6 months after the second surgery. The time interval between any two consecutive scans was not to exceed 12 months, and postoperative MRA was optionally performed several months before the second surgery in cases with a long time interval between the first and second surgeries. The method used for processing MRA images is described in detail elsewhere [8]. In brief, time-of-flight MRA source images were scanned with a 3-T MR scanner (MAGNETOM Trio, Skyra, Prisma, Siemens Healthineer AG, Erlangen, Germany) by using 32-channel head coil; these were converted into sliding-thin-slab

Cases with bilateral involvement



Cases with unilateral involvement

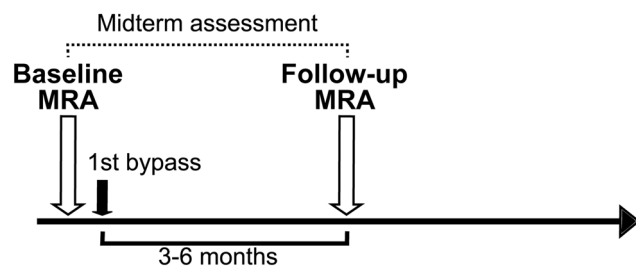


Fig. 2 Imaging schedule for this study. MRA indicates magnetic resonance angiography

maximum-intensity-projection (STS-MIP) images with 5- to 15-mm-thick slabs in a coronal plane perpendicular to the lateral ventricle (Fig. 3).

Measurement of periventricular anastomosis

Two raters (A.M. and T.F.), blinded to other clinical information to avoid biases, retrospectively viewed the STS-MIP MRA images to grade the development of periventricular anastomosis by hemisphere. The methods used for classification and grading of the periventricular anastomoses followed those of our previous study [4, 8]. In brief, anastomoses were classified into three subtypes: (1) lenticulostriate, beginning at the lenticulostriate artery and connecting to the medullary artery; (2) thalamic, beginning at the thalamotuberal, thalamoperforating, or thalamogeniculate arteries and connecting to the medullary or insular arteries; and (3) choroidal, beginning at the plexal segment of the anterior or posterior choroidal arteries and connecting to the medullary artery (Fig. 1). Detection of at least the proximal part of the medullary or insular arteries was considered a positive indicator for the presence of periventricular anastomosis. For the thalamic type, a vessel signal extending outside the thalamus or inside the third ventricle was judged as a positive indicator. Each subtype was scored 1 for positive and 0 for negative, and the sum of these subscale scores for each hemisphere represented the periventricular anastomosis score; the scores thus ranged from 0 to 3.

The presence of anastomosis was determined by a consensus of two raters. Inter-rater agreement was not assessed in the present study because good agreement has already been reported [8].

Suzuki stage [19] and involvement of the posterior cerebral artery (PCA) were recorded with conventional angiography for each hemisphere. PCA involvement was defined as the presence of occlusion or stenosis greater than 50% in the P1 to P3 segments of either PCA [7].

Statistical analysis

The outcome measure was the change in the periventricular anastomosis score after surgery, regarded as an ordinal variable. For intra-individual comparison, the score change was calculated using baseline and postoperative MRA images (Figs. 2 and 3) and a comparison was made between the surgical hemisphere (the hemisphere first receiving surgery) and the nonsurgical hemisphere (the hemisphere receiving surgery thereafter). As this was a matched comparison between the right and left hemispheres within individuals, the Wilcoxon matched pairs signed rank sum test was used for the comparison and no statistical adjustment was required. p values of < 0.05 were considered significant.

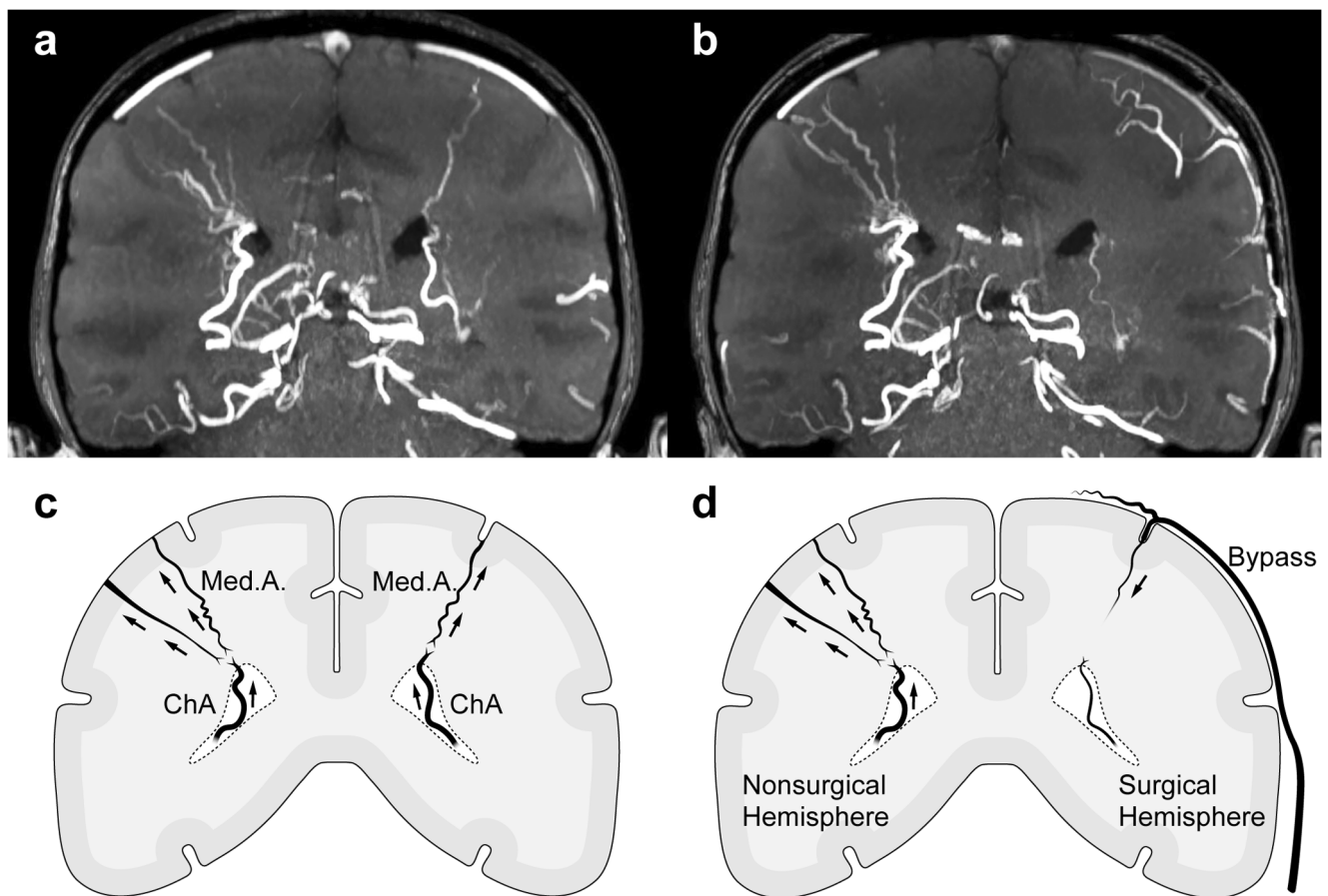


Fig. 3 Baseline (a) and postoperative (b) coronal, thin-slab maximum-intensity-projection magnetic resonance angiography and corresponding schematic illustrations (c and d, respectively) representing intra-individual comparison. Note that choroidal anastomosis is assessed as negative after surgery in the left hemisphere receiving bypass surgery

(the surgical hemisphere), whereas it remains positive in the right hemisphere not receiving bypass surgery (the nonsurgical hemisphere). Blood flow in the medullary artery should return to normal after surgery because it is no longer detectable in magnetic resonance angiography. ChA indicates choroidal artery; Med.A., medullary artery

We also assessed midterm change in each subtype of periventricular anastomosis in the surgical hemispheres using baseline and follow-up MRA images (Fig. 2). This analysis included cases with unilateral disease involvement. Each subtype of periventricular anastomosis was assessed as a dichotomous variable (positive/negative), and McNemar's test was used to assess the change. All analyses were performed with JMP software (Version 13, SAS Institute Inc., USA).

Results

A total of 110 patients underwent 170 bypass surgeries at our hospital between 2013 and 2017. Of these patients, 68 were excluded from the intra-individual comparison because they had either undergone only unilateral bypass (45 patients), fulfilled the exclusion criteria (22 patients), or had undergone bilateral bypass surgery at an interval exceeding 12 months (1 patient), as shown in the flow chart (Fig. 4). The remaining

42 patients, accounting for 42 surgical and 42 nonsurgical hemispheres, were analyzed for intra-individual comparison.

Intra-individual comparison

The median age was 10 years (range, 1–65), and the female-to-male ratio was 1.8. At onset, 28 patients (66.7%) presented with ischemic symptoms, 11 (26.2%) with hemorrhagic symptoms, and 3 (7.1%) with other symptoms. The surgical hemispheres—the hemispheres receiving surgery first—comprised 27 (64.3%) left and 15 (35.7%) right hemispheres. The surgical and nonsurgical hemispheres exhibited no significant difference in baseline periventricular anastomosis score ($p = 0.12$). The median baseline score for the surgical hemispheres was 2, with 9 hemispheres scored as 0, 11 scored as 1, 14 scored as 2, and 8 scored as 3 (Fig. 5). The median baseline score for in the nonsurgical hemispheres was also 2, with 5 scored as 0, 12 scored as 1, 15 scored as 2, and 10 scored as 3 (Fig. 5). The surgical and nonsurgical hemispheres also exhibited no significant difference in baseline Suzuki stage

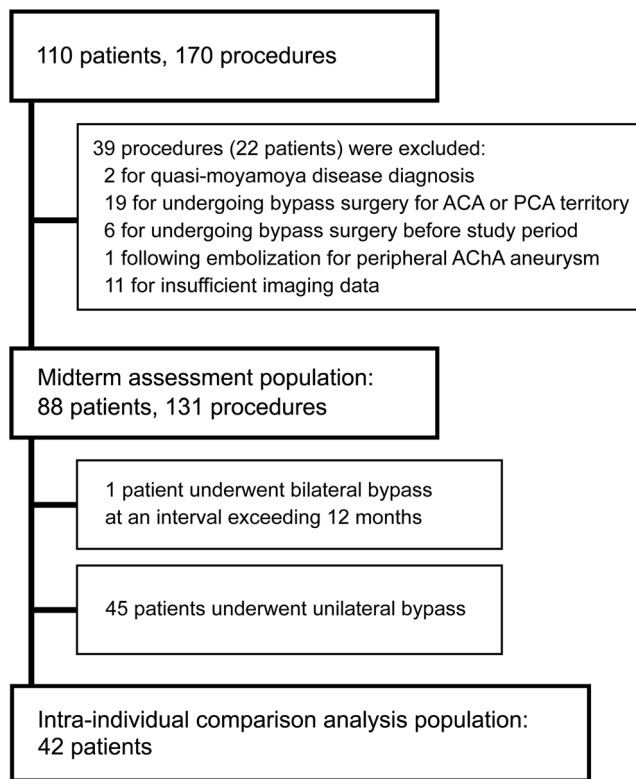


Fig. 4 Flowchart for inclusion. ACA indicates anterior cerebral artery; AChA, anterior choroidal artery; PCA, posterior cerebral artery

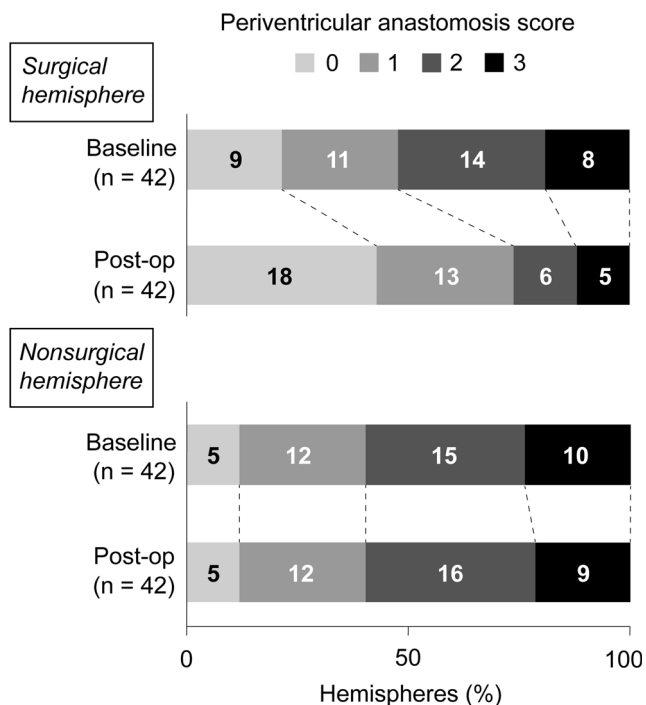


Fig. 5 Change in periventricular anastomosis score in the surgical and nonsurgical hemispheres in intra-individual comparison analysis. $p < 0.001$ in the comparison between surgical and nonsurgical hemispheres

(median, 2 versus 2; $p = 0.79$). Although the prevalence of PCA involvement was higher in the surgical hemispheres than in the nonsurgical hemispheres, the difference was not significant (21.4% versus 9.5%, $p = 0.06$ in McNemar’s test). The median time interval between the first surgery and postoperative MRA was 50 days (interquartile range, 40–81).

As shown in Figs. 5 and 6, a significant decrease in the periventricular anastomosis score was observed in the surgical hemisphere after surgery as compared with the baseline (median, 2 versus 1; $p < 0.001$), whereas no significant difference was observed in the nonsurgical hemisphere (median, 2 versus 2; $p = 0.57$). A comparison of the surgical and nonsurgical hemispheres revealed a significant difference in score change ($p < 0.001$).

Midterm assessment

This analysis included 88 patients with 131 hemispheres receiving bypass surgery (Fig. 4) and assessed midterm changes in periventricular anastomosis after surgery. The median age of the 88 patients was 14.5 years (range, 1–67), and the female-to-male ratio was 1.6. At onset, 63 patients (71.6%) presented with ischemic symptoms, 19 (21.6%) with hemorrhagic symptoms, and 6 (6.8%) with other symptoms. Median baseline Suzuki stage in the 131 hemispheres was 3. The median period from surgery to follow-up MRA was 112 days (interquartile range, 95–152).

Of the 104 hemispheres positive for at least one periventricular anastomosis at baseline, 47 (45.2%) were assessed as negative at follow-up. In contrast, of the 27 hemispheres negative for any periventricular anastomosis at baseline, only 2 (7.4%) were assessed as positive at follow-up. The proportion of hemispheres positive for at least one

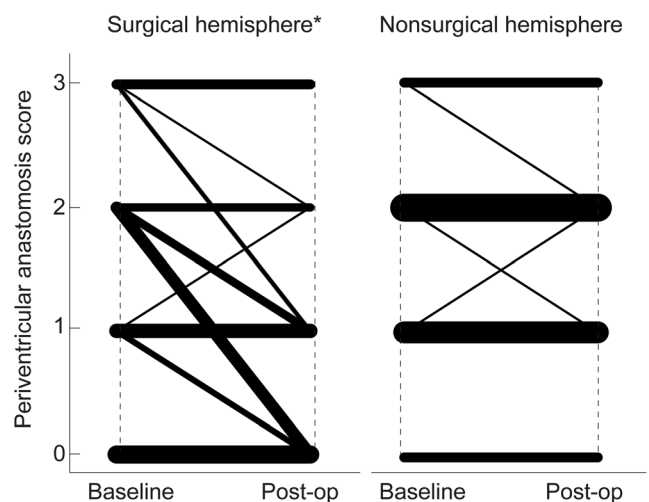


Fig. 6 Line graph showing within-pair change in periventricular anastomosis score in the surgical and nonsurgical hemispheres. Line widths vary with the number of cases. Diagonal lines indicate the change from the baseline. * $p < 0.001$

periventricular anastomosis significantly decreased after surgery compared with the baseline (104/131 or 79.4% versus 59/131 or 45.0%, $p < 0.001$, Fig. 7).

As shown in Fig. 7, the proportion of hemispheres positive for lenticulostriate, thalamic, and choroidal subtypes also significantly decreased (27.5% versus 19.1%, $p < 0.01$; 56.5% versus 30.5%, $p < 0.001$; 60.3% versus 12.2%, $p < 0.001$; respectively). Anastomoses were assessed as negative at follow-up in 11 of 36 (30.5%) lenticulostriate-anastomosis-positive hemispheres, 34 of 74 (45.9%) thalamic-anastomosis-positive hemispheres, and 63 of 79 (79.7%) choroidal-anastomosis-positive hemispheres.

Discussion

The results of the intra-individual comparison suggest that the periventricular anastomosis score decreases after bypass surgery. The results of the midterm assessment suggest that, among the subtypes of periventricular anastomosis, choroidal anastomosis is most likely to decrease.

Our results accord with those in pioneering studies addressing postoperative changes in “basal moyamoya vessels.” Houkin et al. revealed that moyamoya vessels detected with conventional angiography decreased in 25% of adult patients after bypass surgery [10]. A study by Liu X et al. observed a reduction in moyamoya vessels in 13 of 17 hemispheres after bypass surgery for hemorrhagic moyamoya disease [16].

Our results are also consistent with several studies addressing postoperative changes in the choroidal artery. In a study using conventional angiography, Irikura et al. reported that a

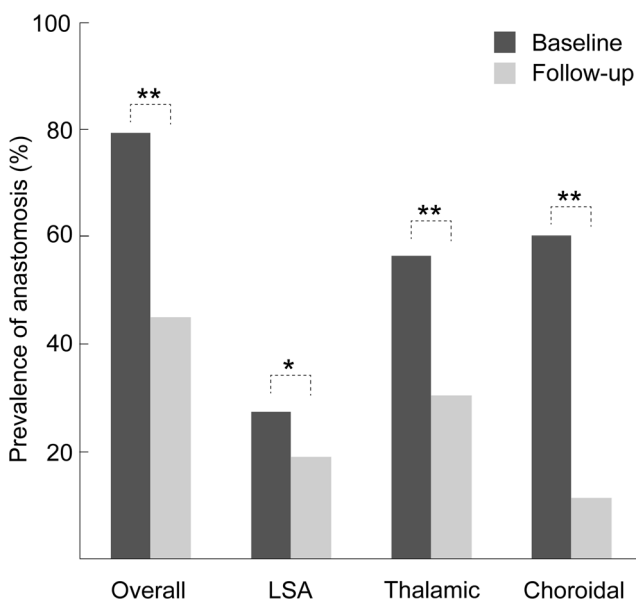


Fig. 7 Graph showing change in proportion positive for each subtype of anastomosis in the midterm assessment. Overall indicates hemispheres positive for at least one periventricular anastomosis. LSA indicates lenticulostriate artery. * $p < 0.01$, ** $p < 0.001$

reduction in abnormal medullary arteries derived from the anterior choroidal artery was observed in 62% of the hemispheres undergoing indirect bypass [11]. Jiang et al. similarly reported that an improvement in the abnormal extension of the anterior choroidal and posterior communicating arteries was observed in 75 of 107 hemispheres receiving surgery (70.1%) [14]. Our results showing that 79.7% of choroidal anastomoses were assessed as negative after surgery are comparable to theirs. Our study, through its unique comparative design using noninvasive MRA, might serve to highlight the importance of the preceding studies.

The reduction in abnormal vessels after surgery might reasonably be explained by the concept of periventricular anastomosis. In normal anatomy, the medullary arteries, emerging from the pial arteries to penetrate the parenchyma and supply the deeper white matter, do not form functional anastomoses until they become capillaries [1]. In moyamoya disease, the medial end of the medullary artery connects to the perforating or choroidal artery and the direction of blood flow in the medullary artery is reversed to supply blood flow to the cortex [4, 8]. After successful bypass to the cortical artery, this retrograde flow in the medullary artery can be restored to normal, resulting in elimination of the pathological anastomosis and normalization of the perforating or choroidal arteries, as schematized in Fig. 3. This change might accordingly be observed as shrinkage of the abnormal vessels because normograde flow in the medullary artery is almost invisible.

Correction of abnormal periventricular vasculature might be considered a key mechanism in the preventive effect of bypass surgery against rebleeding, as suggested in recent studies, including a randomized controlled trial and meta-analysis [2, 12, 13, 16, 17]. Our results on choroidal anastomosis also correspond well with recent sub-analysis results of a randomized controlled trial suggesting that patients with hemorrhage located at the posterior half of the brain accrued greater benefit from bypass surgery [20]. Such a surgical benefit for the posterior hemorrhage group might be explained by the likelihood of correction of choroidal anastomosis as suggested in the present study because choroidal anastomosis is considered a typical bleeding source in posterior hemorrhage [5]. Recent studies have revealed that choroidal anastomosis is a strong predictor of rebleeding in hemorrhagic moyamoya disease [3, 6] and correcting choroidal anastomosis after bypass surgery could become an important subject requiring verification in additional studies. The present results might also promote further studies elucidating why choroidal anastomosis is more likely to be corrected after surgery. Addressing this question might improve the effect of bypass surgery at preventing hemorrhage.

The present study has several limitations. First, the results were derived only from cases treated with a specific bypass procedure at a single center and generalizing from the present results is a questionable assumption. Second, although

interrater agreement for diagnosing the periventricular anastomosis score is good [8], the results could have been contaminated by misclassification of periventricular anastomoses. Third, despite the matched intra-individual comparison, the prevalence of PCA involvement was slightly higher in the surgical hemisphere, reflecting the practical trend toward treating the more severely affected hemisphere first. This potential difference, however, could have only a minimal effect on the present results because the periventricular anastomosis scores of the surgical and nonsurgical hemispheres did not differ at baseline; rather, they were slightly higher in the nonsurgical hemisphere, as shown in Fig. 5.

Conclusion

Periventricular anastomosis, a fragile periventricular vasculature present in moyamoya disease, can be corrected with direct bypass surgery. The correction might result from the effectiveness of direct bypass at preventing bleeding. Among the subtypes of anastomosis, correction of choroidal anastomosis appears the most likely to occur and this should be validated in further studies.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Informed consent All subjects gave opt-out consent.

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Comments

In this study, the authors used MRA to evaluate the periventricular anastomosis in patients with moyamoya disease and score the changes after direct bypass surgery including intra-individual comparison. The study nicely demonstrated the beneficial effect of direct EC-IC bypass on periventricular anastomosis in patients with moyamoya disease. This effect has long been purported to occur and described anecdotally, but this is the first study to demonstrate this effect as related to direct bypass surgery. Further work aiming to elucidate the factors influencing the degree of improvement would be welcome. For example, measuring flow in the bypass during surgery and afterwards and determining whether a robust bypass with greater flow augmentation, might be a factor, would be of great value. Also, longer term correlation of the changes in anastomosis patterns with the risk of bleeding and outcomes would be most welcome. But for the time being, the authors are to be congratulated on this novel work which nicely adds to our understanding of this elusive disease.

Fady Charbel
Illinois, USA