Research Topics

Clinical experience of open cerebral revascularization (bypass surgery) for the management of ischemic or hemorrhagic stroke

Edited by
Long Wang, Xiang'En Shi and Amir Dehdashti

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Clinical experience of open cerebral revascularization (bypass surgery) for the management of ischemic or hemorrhagic stroke

Topic editors
Long Wang — Peking University, China
Xiang'En Shi — Capital Medical University, China
Amir Dehdashti — Northwell Health, United States

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Table of contents

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EDITED AND REVIEWED BY
Jean-Claude Baron,
University of Cambridge, United Kingdom

*CORRESPONDENCE
Alexander F. Kuffer
alexander.kueffer@icloud.com
Amir R. Dehdashti
adehdashti@northwell.edu

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Editorial: Clinical experience of open cerebral revascularization (bypass surgery) for the management of ischemic or hemorrhagic stroke

Alexander F. Kuffer*, Danielle Golub and Amir R. Dehdashti*

Northwell Health Neurosurgery, North Shore University Hospital, Manhasset, NY, United States

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Editorial on the Research Topic
Clinical experience of open cerebral revascularization (bypass surgery) for the management of ischemic or hemorrhagic stroke

The fundamental concept of cerebral revascularization involves redirecting blood flow through a conduit from a robust inflow region to an undersupplied area of the brain. Indications for this procedure encompass flow augmentation for ischemia or flow preservation in complex aneurysm or tumor surgeries.

The journey of clinical experience in cerebral bypass surgery commenced in 1967 with Yasargil's pioneering superficial temporal artery (STA) to middle cerebral artery (MCA) bypass (1). This milestone was not just a testament to surgical skill but also to advancements such as the introduction of the operative microscope, development of microinstruments, bipolar forceps for vessel coagulation, and progress in neuroanesthesiology. The late 1970s witnessed the widespread clinical application of cerebral revascularization, inspired by the success of coronary bypass surgery.

Despite these advancements, the 1985 EC/IC study (2) failed to confirm the efficacy of extracranial-intracranial bypass surgery in preventing ischemic strokes for patients with symptomatic atherosclerotic disease of the internal carotid artery. While technically successful, the clinical outcomes did not demonstrate an advantage for surgery. Criticisms were directed at the study's lack of differentiation between hemodynamic and thromboembolic causes of stroke, as well as the absence of standardized surgical procedures across study sites. The initial enthusiasm for cerebral bypass surgery waned, only to be rekindled by subsequent diagnostic technology developments.

The preoperative evaluation of the oxygen extraction fraction (OEF) using positron emission tomography (PET) emerged as a pivotal step for precise patient selection. Elevated OEF or abnormal responses to acetazolamide challenge identified patients at a higher stroke risk, making them promising candidates for cerebral revascularization. The Japanese EC-IC Bypass Trial (3) (JET) demonstrated a lower stroke recurrence in the bypass group, but the Carotid Occlusion Surgery Study (4) (COSS) was halted due to a high 30-day event rate and lack of significant outcome benefits in the surgery group.

Post-COSS, bypass surgery receded from the standard armamentarium against atherosclerotic vascular disease. It became confined to specialized high-volume centers and applied only to specific patient populations, such as those with repeated strokes or hemodynamic symptoms despite optimal medical and endovascular treatment, and acute stroke patients with small strokes and extended penumbra, harboring considerable brain tissue at risk. Several studies thereafter showed benefit for cerebral bypass in well selected patients (5).

In the context of flow augmentation for Moyamoya vasculopathy, the outcomes are favorable, revealing reductions in ischemic and hemorrhagic strokes and protection against cognitive decline (6). The Japanese Adult Moyamoya (JAM) trial (7) in 2014 showcased a significant preventive effect of bypass surgery against rebleeding. Zhang et al., in this Research Topic, present a single-center case series supported by a systematic literature review, demonstrating a substantial reduction in rebleeding, ischemic events, and mortality for patients with hemorrhagic Moyamoya disease in East Asia. Lu et al. introduce refinements in the bypass technique for Moyamoya disease, emphasizing a modified approach that separates both branches of the STA and selectively performs bypasses with M4 branches, providing improved blood flow to multiple ischemic areas while reducing hyperperfusion and maintaining scalp blood supply.

Another unequivocal indication for EC-IC bypass surgery is flow preservation in surgically or endovascularly untreatable aneurysms. Chen et al., through a systematic review, involving 21 studies and 915 patients, affirm the procedure's high safety profile. Wang et al. shed light on the management of complex intracranial aneurysms with the in situ side-to-side strategy, particularly effective when vital artery sacrifice is unavoidable. Wang and Tong propose a novel concept related to the extracranial vertebral artery, addressing the unique hemodynamic pattern of the vertebrobasilar system, and present bypasses involving the extracranial V1-3 segments of the vertebral artery. We previously reviewed our modern cohort on bypass for intracranial aneurysm and showed good clinical outcome, high safety profile and excellent aneurysm obliteration rate after aneurysm treatment (8).

History indicates that improved outcomes in cerebral bypass surgery have and will continue to be achieved through practice, innovations, and technical advancements. Developments such as scissors-attached micro-forceps, presented by Yomo et al., and intraoperative infrared thermography, described by Lin et al. as an addendum to ICG-VA for evaluating bypass patency, showcase the ongoing evolution of surgical techniques. This contrast-independent method might eventually replace ICG-VA once flow distribution and quantitative analysis become available. Meanwhile, the switch from intravenous to intraarterial injection of ICG into the STA main stem, as proposed by Ni et al., allows for detecting the clear direction of blood flow and may even predict cerebral hyperperfusion syndrome.

Looking ahead, the future of bypass surgery remains exciting, particularly in treating Moyamoya vasculopathy, complex aneurysms, some skull base tumors where vessel sacrifice is necessary and well-selected cases of intracranial steno-occlusive disease. However, its technical demands necessitate personal dedication, extensive training, a substantial minimum case volume, and an interdisciplinary team for optimal outcomes (9). Ongoing research, as highlighted in the current issue of Frontiers Research Topics, plays a pivotal role in the continuous improvement of bypass surgery, ensuring that patients will continue to benefit from this important therapeutic option in the future.

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EDITED BY
Long Wang,
Sanbo Brain Hospital,
Capital Medical University,
China

REVIEWED BY
Hui Li,
Hebei Medical University,
China
Lin Wang,
Zhejiang University,
China

*CORRESPONDENCE
Chenhui Zhou
✉ zhouchnehui1989@126.com
Bin Xu
✉ xubinww@yahoo.com
Xiang Gao
✉ qinyuecui@163.com

†These authors have contributed equally to this work

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Application of intraoperative infrared thermography in bypass surgery for adult moyamoya syndrome: A preliminary study

Jinghui Lin[1†], Yiwen Wu[1†], Xinpeng Deng[1], Shengjun Zhou[1], Yuchun Liu[1], Junjun Zhang[1], Yiyong Zeng[1], Xianru Li[1], Xiang Gao[1*], Bin Xu[2*] and Chenhui Zhou[1*]

[1]Department of Neurosurgery, Ningbo First Hospital, Ningbo University, Ningbo, Zhejiang, China,
[2]Department of Neurosurgery, Huashan Hospital, Fudan University, Shanghai, China

Background and objectives: Cerebral revascularization surgery is the mainstay of treatment for moyamoya syndrome (MMS) today, and intraoperative determination of the patency of the revascularized vessel is a critical factor in the success of the procedure. Currently, major imaging modalities include intraoperative indocyanine green (ICG) videoangiography (ICG-VA), digital subtraction angiography (DSA), and vascular ultrasound Doppler. Infrared thermography is a modern imaging modality with non-contact devices for the acquisition and analysis of thermal data. We aimed to investigate the feasibility and advantages of infrared thermography in determining anastomotic patency during MMS surgery.

Methods: Indocyanine green videoangiography and infrared thermography were performed simultaneously in 21 patients with MMS who underwent bypass surgery. The detection result of vessel patency was compared, and the feasibility and advantages of infrared thermography were assessed.

Results: The patency of the anastomosis was accurately determined in 21 patients using either ICG angiography or infrared thermography. In 20 patients, the results of infrared thermography showed that the vascular anastomosis was unobstructed, and there was an agreement with the subsequent results of ICG-VA. In one patient, we suspected inadequate patency after testing the anastomosis with infrared thermography, and the results of ICG-VA evaluation of the anastomosis confirmed that there was indeed an anastomotic obstruction.

Conclusion: Compared with ICG-VA, infrared thermography might offer an alternative non-invasive, contrast-free option in assessing anastomosis patency compared with ICG-VA, and it is likely to become more widely used in the clinic in the near future.

KEYWORDS

moyamoya syndrome, infrared thermography, indocyanine green fluorescein videoangiography, cerebral revascularization, moyamoya disease

1. Introduction

Moyamoya syndrome (MMS) is a cerebrovascular disease characterized by progressive stenosis or occlusion of the bilateral internal carotid, middle cerebral, and anterior cerebral arteries at their origins, resulting in the formation of an abnormal vascular network at the base of the skull (1). The disease earns its name as the abnormal vascular network appears as a "puff of smoke" ("*moyamoya*" in Japanese) in cerebral angiographic images, while the pathogenesis of MMS remained unclear today. MMS is highly prevalent in East Asian countries including China, Japan, and Korea. The main clinical manifestations of MMS include cerebral hemorrhage and ischemia. Surgical revascularization is now the mainstay of treatment, including direct, indirect, and combined bypass. Surgical techniques in cerebral revascularization have developed at a rapid pace to increase cerebral blood flow and reduce the risk of stroke. Nevertheless, there are increasing reports regarding the complications following revascularization surgery, leading to prolonged hospitalization stay and some of which are irreversible (2, 3). Currently, the success of bypass surgery continues to be evaluated by the degree of anastomotic patency rather than the incidence of postoperative complications. Yet, all current methods of intraoperative visualization of vascular structures have limitations and drawbacks (4).

Indocyanine green videoangiography is now widely performed (5). The patency of the anastomosis is assessed by intravenous ICG injection (6). However, contrast agents sometimes lead to allergic reactions and it requires a long time for contrast agent metabolism. Therefore, there has been a search for a way to both directly observe blood flow and assess anastomotic patency without using intravenous contrast agents. Infrared thermography involves temperature measurement of the infrared radiation received from the tissue surface and visualization of the data to compare temperature differences within the region of interest. Nowadays, infrared thermography has been widely used in clinical applications, and studies have shown good results in the prediction of flap graft survival, assessment of blood flow reconstruction in the limb, and evaluation of postoperative area infection (7, 8). We attempted to apply infrared thermography to determine anastomotic patency after cerebral blood flow reconstruction to provide a new means of intraoperative monitoring of MMS.

2. Methods

2.1. Patients

This continuously enrollment research enrolled 21 patients diagnosed as MMS qualified for surgery and admitted from October 2021 to January 2022, all of whom underwent superficial temporal arterycomputed tomography to middle cerebral artery (STA-MCA) bypass surgery. The study protocol was approved by the local institutional review board, and the experiment was conducted by the relevant institutional guidelines and in compliance with the Declaration of Helsinki as revised in 1983. The diagnosis was based on the diagnostic criteria for MMS proposed by the Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis in 2012 (9). Written informed consent was obtained from all patients.

2.2. Surgical procedure

All of the surgeries were performed by the same experienced neurosurgeon. After induction of general anesthesia, the patient was placed in the supine position with the head tilted 60° to the side. After sterilization and draping, a 15-cm arc-shaped incision on the frontotemporal scalp was made, cutting through the temporalis muscle. The temporalis muscle flap was then folded anteriorly, and care had been taken to protect the STA. A 9 cm × 8 cm craniectomy was created without damaging the middle meningeal artery. It was visible at this moment that the dura mater was in moderately high tension, with no abnormality in the color and pulsation of the brain. Next, the dura was lifted, and the STA was dissected from the surrounding tissue at the parietal branch. With the radial incision of the dura performed, the thin arteries over the surface of the brain were visible, and the recipient blood vessel in the bypass region was subjected to surgery (STA-MCA), after which the patency of the vascular anastomosis was assessed by the simultaneous application of ICG and infrared thermography. Routine computed tomography scans were performed postoperatively to seek out any secondary postoperative infarction. We did not perform routine postoperative angiography, and it was done at follow-up at 3 months.

2.3. Intraoperative infrared thermography

For our research, we used an AT1280 digital infrared camera (Electronically Modulated Online Thermometry, Iray Technology Co., Ltd., China), which was used to image local temperature gradients across the cerebral cortex by passively detecting infrared emissions. We kept the room temperature at 23°C to maintain the background temperature of the cortical surface as much as possible. After completion of the anastomosis, the high-resolution infrared camera of the infrared imaging system was set 500 mm above the brain obliquely to continuously monitor blood flow for up to 3 min, including the time to place and release the vascular blocking clips (Figure 1).

The infrared imaging system consisted of three parts: an infrared camera, the main computer, and a monitor. The thermal imaging camera was 70 mm × 63 mm × 143 mm and was set up on a collapsible tripod and connected to the main computer *via* a network cable for imaging analysis. The camera used a vanadium oxide uncooled infrared focal plane detector with a 12 μm pixel pitch, 1,280 × 1,024 pixels, a 19 mm lens, and an instantaneous field of view of 0.63 mrad. The camera can be set up at 0.5 m from the cerebral cortex to obtain an infrared field of view of 400 mm × 320 mm and can observe a minimum target diameter of 0.315 mm. The detectable wavelength band was 8–14 μm. No contrast agent or radiation was used to obtain the image. The recording speed was 15 frames per second. All images were stored on the installed computer and recorded with digital video equipment. The assessment of the patency of the vascular anastomosis can be performed directly on the monitor.

2.4. Intraoperative indocyanine green videoangiography

Indocyanine green videoangiography was performed with an operating microscope (Opmi Pentero 900, Carl Zeiss) equipped with

FIGURE 1
Photograph of the infrared imaging system in the operating room.

a fluorescent light source (wavelength 700–850 nm) and an infrared-sensitive camera. The microscope was placed perpendicular to the study area at a distance of approximately 300 mm. During the ICG-VA, the room lights are dimmed and a weight-adapted dose of 0.25 mg/kg of ICG dissolved in 10 ml of saline is injected *via* a central venous catheter. Once the ICG reaches the corresponding area, it receives excitation from near-infrared light and emits fluorescence, which is captured and recorded by the camera equipment. The operator assesses the patency of the vascular anastomosis by observing the fluorescence image microscopically. In all cases, intraoperative infrared thermography is performed before ICG-VA.

2.5. Acquisition of data

Patient data about pre-and post-operative radiological images are obtained from the department's digital patient management software. Intraoperative findings are assessed by video analysis and analysis of operative reports.

3. Results

3.1. Demographics

A total of 21 patients with MMS who underwent STA-MCA anastomoses surgery were included. Infrared thermography and ICG-VA were both applied to assess the anastomotic patency in the 21 patients. The patient's ages ranged from 27 to 59 years (median 46 years). The 17 of our patients presented with ischemic stroke symptoms, such as hemiparesis. Four patients had a history of cerebral hemorrhage (Table 1).

3.2. Assessment of anastomotic patency

Figure 2 illustrated an infrared thermographic image obtained during a right STA-MCA (M4) bypass surgery in one case. Before the release of the vascular blocking clip, the temperature of the anastomosis and the donor vessel (STA) was low and almost no blood flowed through the anastomosis, corresponding to the dark area in Figures 2A1, 2. After releasing the vascular clip from the STA, it was clear in Figures 2B1, 2 that blood with a lower temperature relative to the cerebral cortex flows from the donor's vessel through the anastomosis to the recipient's vessel, indicating good patency of the anastomosis. Furthermore, the distal branch vessels appeared for a split second in the thermal imaging as a dark image, indicating a positive flow of blood from the donor's vessels toward the cerebral cortex. Figures 2C1, 2 showed the situation at 4 s after the release of the vascular clip. All vessels became highlighted in color. These findings demonstrated the success of the revascularization and show that infrared thermography can make a correct assessment of anastomotic patency.

TABLE 1 Clinical characteristics of the study population.

Case no.	Sex	Age	Symptoms	Operated side
1	Male	54	Recurrent stroke/TIA	Right
2	Female	56	Hemiparesis	Left
3	Male	57	Recurrent stroke/TIA	Right
4	Female	47	Recurrent stroke/TIA	Right
5	Male	30	Recurrent stroke/TIA	Right
6	Female	54	Recurrent stroke/TIA	Right
7	Male	34	Hemorrhage	Left
8	Male	27	Recurrent stroke/TIA	Left
9	Female	58	Recurrent stroke/TIA	Right
10	Male	56	Recurrent stroke/TIA	Left
11	Male	37	Hemiparesis	Left
12	Male	32	Recurrent stroke/TIA	Left
13	Male	36	Hemorrhage	Right
14	Female	32	Hemorrhage	Right
15	Female	54	Recurrent stroke/TIA	Right
16	Female	54	Recurrent stroke/TIA	Right
17	Female	34	Hemorrhage	Right
18	Female	59	Recurrent stroke/TIA	Right
19	Male	39	Recurrent stroke/TIA	Left
20	Female	58	Hemiparesis	Left
21	Male	57	Recurrent stroke/TIA	Right

3.3. Infrared thermography versus ICG fluorescence imaging

We carried out infrared thermography followed by ICG-VA in each MMS patient. The validity of the infrared thermography technique was confirmed by comparing the results with the ICG assessment. Figure 3 shows that the ICG was visualized after ICG injection, unambiguously confirming the patency of the anastomotic vessels, and the same results were visualized on the infrared thermography of the same patient. In our study, a total of 21 patients were treated the same way. In 20 patients, the results of infrared thermography showed that the vascular anastomosis was unobstructed, and there was an agreement with the subsequent results of ICG-VA.

Unexpectedly, in one patient, we suspected inadequate patency after testing the anastomosis with infrared thermography, and the results of ICG-VA evaluation of the anastomosis confirmed that there was indeed an anastomotic obstruction (Figures 4A,B). After opening the anastomosis, it is obvious from Figure 4C that intravascular thrombosis was the exact cause of the anastomotic opacity in this case. This further proved the surprisingly consistent results of infrared thermography and ICG-VA in assessing anastomotic patency. The case was subsequently re-anastomosed by removing the anastomotic thrombus. Three patients developed transient neurological deterioration after surgery, including aphasia in two cases and contralateral limb asthenia in one case. Patients with these symptoms gradually resolved within 5–7 days postoperatively, and none of them experienced permanent neurological deterioration. All patients had a disappearance or improvement of transient cerebral ischemic symptoms during the follow-up period.

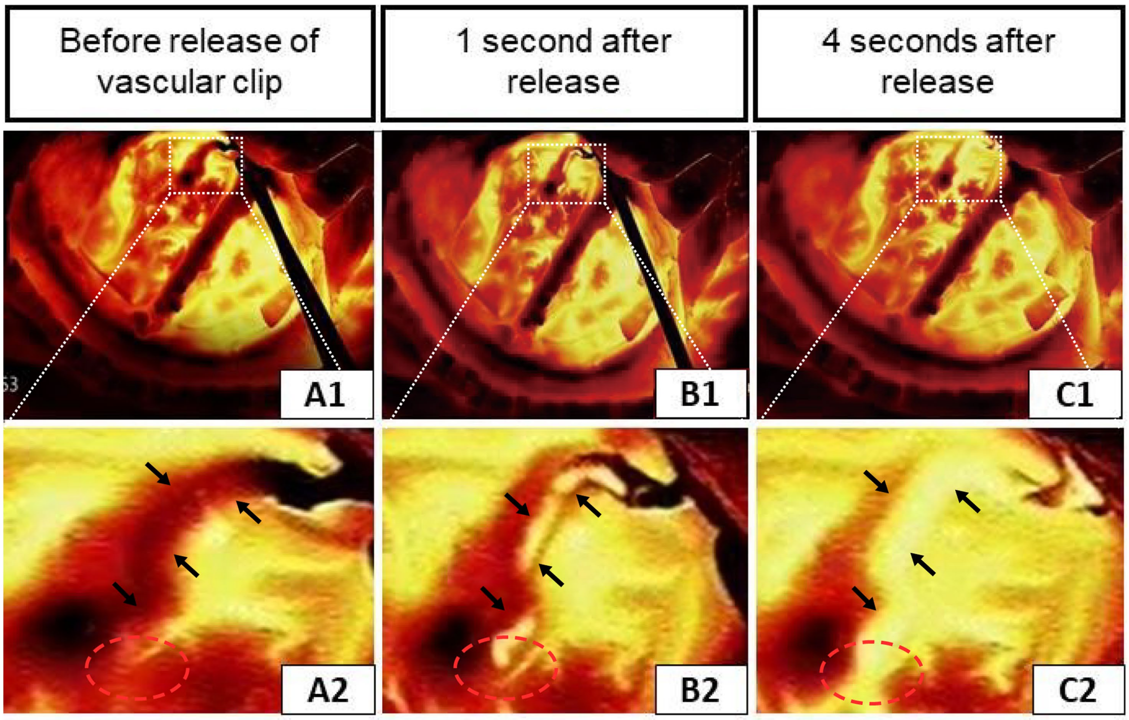

FIGURE 2
Infrared thermography of a case during right STA-middle cerebral artery (M4) bypass surgery. **(A1–C1)** Infrared thermographic images of the vessel clip before and shortly after release. **(A2–C2)** Enlarged views correspond to the upper (the black arrows indicate the STA and the red circles show the anastomosis of the donor and recipient vessels).

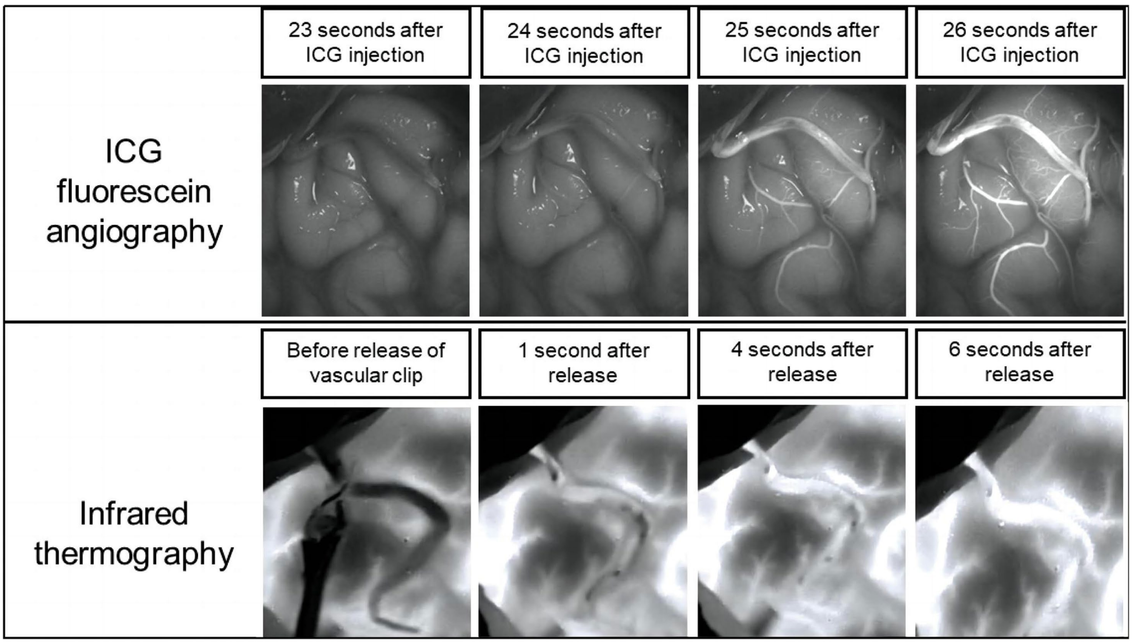

FIGURE 3
Comparison of ICG-VA and infrared thermography.

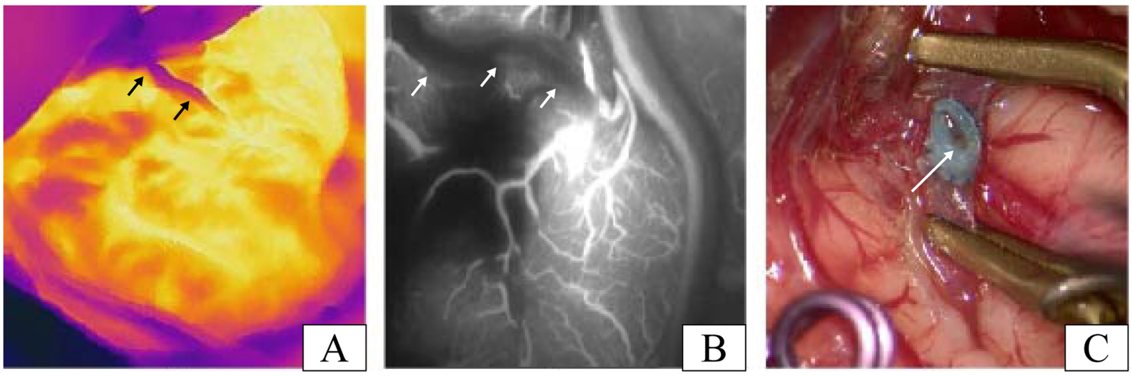

FIGURE 4
A patient with inadequate patency of vascular anastomosis in our study. **(A)** Infrared thermographic results of this patient after the release of the vascular clip (the black arrows denote the STA). **(B)** Image results of the ICG-VA after the release of the vascular clip in this patient (the white arrows indicate the STA). **(C)** Thrombosis was found after reopening the recipient artery and was the cause of the insufficient patency of the vascular anastomosis in this case (the white arrow shows the thrombosis in anastomosis).

4. Discussion

Rapid and accurate assessment of anastomotic vessel patency has been a crucial aspect of cerebrovascular surgery due to the extreme difficulty of vascular anastomosis and the lack of an objective basis for determining patency by visual inspection. In this study, we demonstrated the usefulness of infrared thermography in identifying anastomotic vessel patency during the revascularization process of patients with MMS. Surprisingly, our results demonstrated that infrared thermography is equally effective in determining anastomotic vessel patency compared to ICG-VA.

Infrared thermography in current clinical practice tends to focus on the assessment of flap blood supply for tissue defect repair (10, 11). Apart from traditional applications, we propose for the first time the application of infrared thermography to assess anastomotic vascular patency during direct revascularization procedures for the treatment of MMS. Upon completion of the vascular anastomosis, the blood flow in the clamped donor and recipient arteries is stationary, thus its temperature is almost similar to room temperature. Immediately after opening the vascular blocking clamp, the hemodynamic behavior of the donor and recipient vessels changes, so that the flowing blood rapidly returns to the same temperature as the human body. The dynamic distribution of blood flow at different temperatures resulting in significant temperature contrasts between the vessels at different sites and between the surrounding tissues. The temperature contrast results in different intensities of infrared radiation being acquired by the camera and converted into a pseudo-color thermographic video/image, highlighting areas of higher temperature with highlighting colors, along with darker areas of lower temperature. The higher the temperature, the brighter the area. The technical advantage of infrared thermography is that the pseudo-color video/images allow the surgeon to understand the patency and hemodynamic behavior of the donor and recipient vessels to make an effective and accurate intraoperative assessment of anastomotic patency.

Numerous vascular imaging techniques to date were developed. DSA is considered the standard for the diagnosis and evaluation of moyamoya disease and moyamoya syndrome (12). However, DSA is an invasive procedure with a risk of inguinal hematoma and transient neurological symptoms (13). Besides, the DSA procedure is complex and expensive to perform, requires bulky supporting instruments and specific operating rooms, and exposes both patients and operating surgeons to radiation, all of which makes it inadequate for determining the patency of anastomosed vessels. In contrast to DSA, infrared thermography is based on the blood flow to visualize changes in temperature modulation to show flow and assess patency. It is an unparalleled advantage in terms of both ease of operation and cost-effectiveness.

Microvascular ultrasound Doppler can assess anastomotic patency by quantifying vascular hemodynamic data (14). But the limitations come with it. Firstly, the ultrasound Doppler technique places too much emphasis on the probe-vessel angle, and measurements at different angles will give variable results, making the results too disparate. Secondly, microvascular ultrasound Doppler does not visualize the morphology of the vessel and is even less sensitive to tiny vessels (15, 16). Infrared thermography solves the problems of inaccurate measurement and indirect observation of blood vessels with the visualization of blood flow.

Indocyanine green videoangiography is currently the most commonly used and standard method for intraoperative assessment of anastomotic patency, with excellent temporal and spatial resolution, and is easy and simple to perform. However, it is of great importance to note that a few patients are allergic to ICG dye. Although the incidence is very rare, this is not a risk-free procedure. It is worth mentioning that the ICG-VA must be kept clean in the surgical field of view during the angiography procedure and that the viewing angle of the microscope has a major impact on the imaging results, requiring some experience of the operators in assessing anastomotic stability. If the anastomosis is suspected to be obstructed, it needs to be adjusted or re-sutured and re-imaged. Studies have shown that it takes at least 15 min for the ICG to be completely metabolized in the previous residual vessel, which undoubtedly increases the time cost (17). Compared to ICG fluorescein imaging, infrared thermography enhances the safety of the procedure without requiring contrast agents, clearly shows the blood flow into the anastomosis, and can be used at any time, repeatedly and multiple times.

5. Limitations

Admittedly, infrared thermography is far from perfect technology. One of the limitations of our study is that no corresponding software development applications have yet been seen, making infrared thermography currently only able to show the direction of blood flow and not yet able to assess the distribution of blood flow and perform the corresponding quantitative analysis. However, as technology develops, exploration and research related to infrared thermography in the cerebrovascular field would facilitate techniques to help us overcome this limitation. Furthermore, our study was a single-center and retrospective study, which resulted in limited persuasiveness and restricted generalizability. To further validate our findings, our next step is to conduct a multi-center clinical trial with a large sample-size.

6. Conclusion

Our study confirms that in vascular anastomosis procedures for MMS, infrared thermography can achieve the same assessment effect as ICG and is safe and easy to use, allowing direct, dynamic, real-time visualization of cerebral blood flow and providing neurosurgeons with new ideas for assessing anastomotic patency, and it is likely to become more widely used in the clinic in the near future.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by ethics committee of Ningbo First Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any identifiable images or data included in this article.

Author contributions

XG and BX: conceptualization and project administration. SZ and YL: methodology. XD: software and investigation. JZ and YZ: validation. XL: formal analysis. JL and YW: writing—original draft preparation. CZ: writing—review and editing and funding acquisition. XG: supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Long Wang,
Sanbo Brain Hospital, Capital Medical University, China

REVIEWED BY
Tao Xu,
Shanghai Changzheng Hospital, China
XiaoLin Chen,
Beijing Tiantan Hospital, Capital Medical University, China

*CORRESPONDENCE
Geng Guo
✉ guogeng973@163.com

†These authors have contributed equally to this work

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Extracranial-intracranial bypass surgery for intracranial aneurysm of the anterior cerebral circulation: A systematic review and meta-analysis

Yang Chen[1†], Pengyu Chen[1†], Guosheng Duan[2†], Ren Li[1], Ziao Li[1] and Geng Guo[3*]

[1]Department of Neurosurgery, The First Hospital of Shanxi Medical University, Taiyuan, Shanxi, China, [2]Shanxi Provincial People's Hospital, Shanxi Medical University, Taiyuan, China, [3]Department of Emergency, The First Hospital of Shanxi Medical University, Taiyuan, Shanxi, China

Background: The safety of extracranial–intracranial (EC–IC) bypass in the management of anterior circulation intracranial aneurysms (IAs) remains to be determined. This systematic review aims to summarize the existing evidence and provide guidance for the precise management of IAs.

Data source: We constructed search strategies and comprehensively searched Pubmed, Medline, Embase, Web of science, and Cochrane library.

Methods: This systematic review was actualized according to the PRISMA statement. We evaluated study quality using the methodological index for non-randomized study (MINORS). Effect sizes were pooled using a random-effects model. Heterogeneity between studies was assessed using the I^2 test. Publication bias was assessed using the Egger's test. The registration number for this systematic review is CRD42023396730.

Result: This systematic review included a total of 21 articles, involving 915 patients. Postoperative bypass patency rate was 99% (95% CI 0.98–1.00); short-term follow-up was 98% (95% CI 0.94–1.00); long-term follow-up was 95% (95% CI 0.93–0.97). The long-term follow-up occlusion rate of saphenous vein was higher than that of radial artery (OR 6.10 95% CI 1.04–35.59). Short-term surgery-related mortality was 0.3% (95% CI 0.000–0.012); long-term follow-up was 0.4% (95% CI 0.000–0.013); The proportion of patients with a score of 0–2 on the modified Rankin Scale (mRS) during long-term follow-up was 92% (95% CI 0.86–0.98). The incidence rates of long-term follow-up complications were: ischemic 3% (95% CI 0.01–0.06); hemorrhagic 1% (95% CI 0.00–0.03); neurological deficit 1% (95% CI 0.00–0.03); other 3% (95% CI 0.01–0.06).

Limitation: Most of the included studies were retrospective studies. Studies reporting preoperative status were not sufficient to demonstrate postoperative improvement. Lack of sufficient subgroup information such as aneurysm rupture status.

Conclusion: EC–IC therapy for anterior circulation IAs has a high safety profile. Higher level of evidence is still needed to support clinical decision.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023396730, identifier: CRD42023396730.

KEYWORDS

intracranial aneurysm, extracranial-intracranial bypass, cerebral revascularization, anterior cerebral circulation, management

1. Introduction

Regarding the optimal management of intracranial aneurysms (IA), evidence such as large randomized controlled trials is still lacking, thus controversy continues. Because most of the IAs are not symptomatic, the managements of unruptured IA are mostly prophylactic to avoid subarachnoid hemorrhage after IA rupture. However, preventive management does not always benefit patients, and some patients have significantly reduced life satisfaction (1). It is indispensable to consider the patient's wishes and make optimal management individually. The results of the International Subarachnoid Aneurysm Trial (ISAT) have made endovascular therapy the most popular management for IA, especially for small saccular aneurysms of the anterior circulation (2). Endovascular therapy is non-inferior to craniotomy but less invasive. The subsequent emergence of flow diverter (FD) such as Pipeline™ embolization device and Tubridge™ has brought new options for the management of wide-necked giant IA (3, 4). Nonetheless, treatment for giant and complex IAs is still a thorny issue. The presence of perforating arteries in the dome and neck of the giant saccular aneurysm and the irregular shape of the fusiform aneurysm result in persistent aneurysm filling after stenting and limited therapeutic benefit (5). Even Pipeline™ embolization devices weren't perfect for fusiform aneurysms treatment (6). Due to the compression symptoms caused by its mass effect or risk of complications such as thrombus and dissection, surgical relief is required, and mere endovascular treatment is no longer applicable (7). However, microsurgical clipping is unpractical to completely remodel the lumen of a dilated artery and ensure the patency of the parent artery, especially when the IA surrounds a branch artery (8). In addition, calcification and atherosclerosis of the arterial wall and intraluminal thrombosis in complex IAs increase the risk of microsurgical clipping and endovascular therapy (9). In these conditions, occlusion of the parent artery is the last option to completely isolate the aneurysm from the circulation and prevent hemorrhage. Adjunctive bypass surgery can supply the distal branch feeding areas without adequate collateral flow (10).

Since Yasargil described the first case of extracranial–intracranial (EC–IC) bypass surgery for the treatment of IA in 1969, the role of bypass surgery as an adjuvant therapy to ensure the cerebral blood supply is still irreplaceable (11, 12). Controversy persists over the choice of bypass type. In clinical practice, physicians seem to prefer intracranial–intracranial (IC–IC) bypass surgery because it is associated with higher bypass patency rates and lower complication rates (13). Compared with EC–IC bypass, IC–IC bypass has the inherent advantages of needless to harvest and process donor vessels, shorter graft, and less susceptible to neck torsion, injury, and compression obstruction (13). However, EC–IC is irreplaceable in the treatment of IAs proximal to the internal carotid bifurcation. Moreover, in view of the operating depth of IC–IC bypass and the limited range of intracranial arteries movement, EC–IC bypass is easier to master and a safer technique for most doctors (14). In recent years, more literature reports are focused on EC–IC bypass surgery, suggesting uncertainty on its safety (15).

To clarify the safety of EC–IC bypass in the management of IA of the anterior circulation, we conducted this systematic review to synthesize existing evidence and provide guidance for optimal management.

2. Materials and methods

2.1. Search strategy

This systematic review conducted according to the PRISMA statement (16). The review protocol was registered in the PROSPERO database and is available online (CRD42023396730; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023396730). The databases Pubmed, Medline, Embase, Web of science, and Cochrane library were systematically searched for all study published from 1980 to December 2022 that evaluated outcomes of EC–IC bypass therapy for anterior cerebral circulation IAs. Keywords for constructing search strategies include "intracranial aneurysm," "anterior cerebral circulation," and "cerebral revascularization." Full search queries are provided in the Supplementary material. We also checked studies in systematic reviews and literature reviews for potential sources.

2.2. Outcome definitions

Primary outcomes of the study included bypass patency rate, procedure-related mortality, and neurological function scale scores such as Glasgow Outcome Scale (GOS) and Modified Rankin Scale (mRS) at any follow-up period. Secondary outcomes were defined as the incidence of various surgical-related complications. Complications were divided into four categories including ischemic, hemorrhagic, neurological deficit and others (Deep vein thrombosis and infection et al.). Short-term follow-up is defined as within 30 days, and long-term follow-up is more than 12 months.

2.3. Inclusion and exclusion criteria

Studies included in this review had to meet the following criteria: (1) studies reported at least one primary outcome of EC–IC bypass surgery for anterior cerebral circulation IAs; (2) any type of study is qualified (prospective or retrospective); (3) if a study included aneurysms located outside the anterior cerebral circulation, or included other treatment groups, the original text should describe the results of EC–IC bypass for IAs in the anterior cerebral circulation group separately; (4) the target cohort should be not <20 patients. Studies will be excluded if they meet the following criteria: (1) type of publication is review, letter, meta-analysis, case report or comment; (2) non-English publications; (3) patients under the age of 18; (4) abstract only, original text not available; (5) The bypass technique is non-conventional, such as excimer laser-assisted non-occlusive anastomosis. (5) Studies reporting results from overlapping patient cohorts. Patients from different studies were considered overlapping patient cohorts if they were drawn from the same institution or database for the same time period.

2.4. Data extraction

Four authors (Y.C., P.Y.C., G.S.D., and G.G.) independently performed literature search and study selection. Disagreements were resolved by consensus and consultation with senior investigators. The text, tables, images, and Supplementary material of the literature were checked to ensure data integrity. Extracted data includes publication information (first author, published year, country, journal, and design type), basic demographics (number of patients, number of procedures, age, gender, aneurysm location, aneurysm size, and follow-up time), bypass type (high flow, low flow and type of graft), bypass patency rate, mortality rate, GOS or mRS score, complication rate. Since the included studies used different internal carotid artery (ICA) segmentation methods, we classified all the proximal ICA bifurcation and its branches as ICA. Most studies considered the posterior communicating artery (PcoA) as part of the anterior circulation, so we included PcoA aneurysms (17, 18). The anterior communicating artery was classified as the anterior cerebral artery (ICA). We divided postoperative complications into four categories. The ischemic complications include transient ischemic attack (TIA), vasospasm, cerebral infarction, low flow–related ischemic complications (LRICs), etc. Hemorrhagic complications include subarachnoid hemorrhage (SAH), intracranial hematoma, aneurysm rupture, etc. Neurological deficits include cranial nerve palsy, disturbance of consciousness, hemiplegia, etc. Other complications include deep vein thrombosis (DVT), infection, wound dehiscence, CSF leak, etc. If there was sample overlap between multiple studies, we included the first published study or the only study for which the primary outcome was available.

2.5. Quality assessment

Three authors (Y.C., P.Y.C., and G.S.D.) independently assessed study quality and differences were resolved by consensus. Studies were assessed according to the methodological index for non-randomized study (MINORS) scale. MINORS is a scale for evaluating non-randomized controlled studies in surgery (19). The scale contains 8 items evaluating non-comparative studies and 4 additional items evaluating comparative studies. Therefore, the maximum score for the study is 16 or 24 points respectively. Baseline characteristic data expressed as mean ± standard deviation or median (range), event rates converted to number of events (percentage).

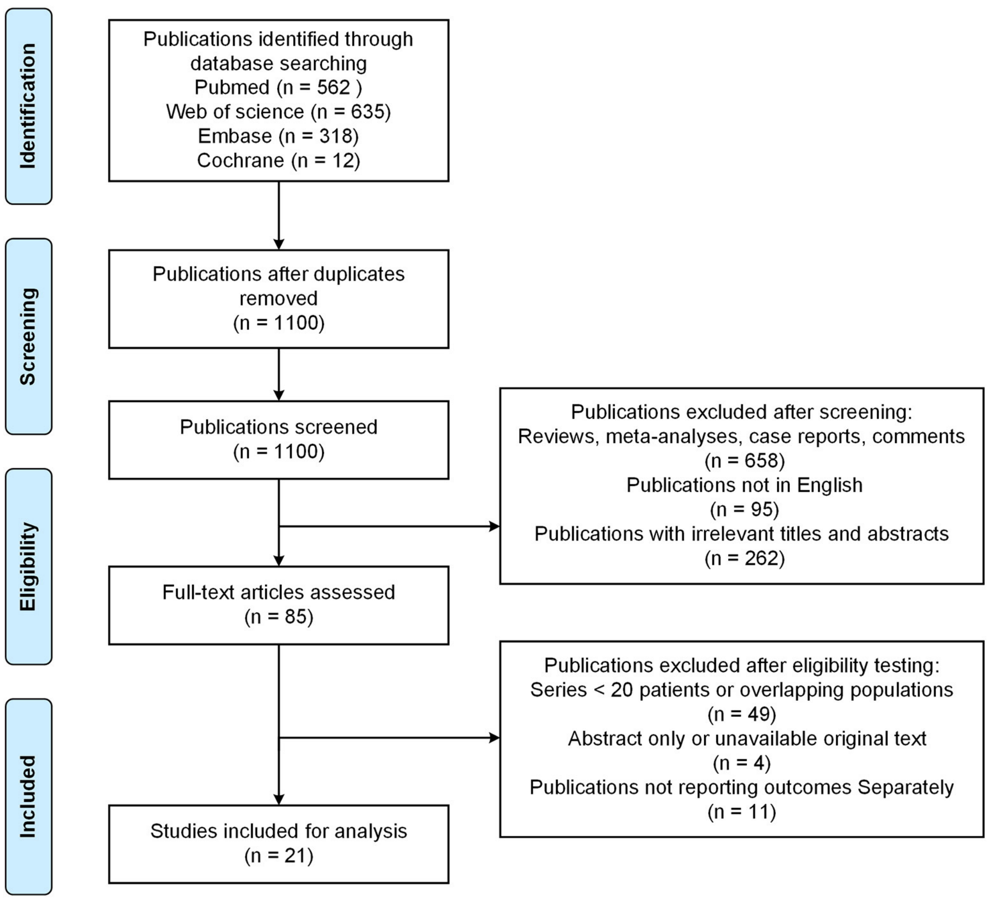

FIGURE 1
Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram of this study.

TABLE 1 Characteristics and quality of included studies.

Study	Year	Country	Journal	Design	Patient/ bypass	Age	Gender (F:M)	Aneurysm location				Aneurysm size (mm)	Follow-up (month)	MINORS
								ICA	MCA	ACA	PcoA			
Morgan et al. (20)	2002	AUS	Journal of Clinical Neuroscience	Prospective	21/21	45.61 ± 12.96	12:9	21 (100)	0	0	0	NR	Mean 41.76	14/16
Jafar et al. (21)	2002	USA	Neurosurgery	Retrospective	27/28	NR	NR	20 (71.43)	2 (7.14)	0	6 (21.43)	NR	Mean 62	10/16
Cantore et al. (22)	2008	ITA	Neurosurgery	Retrospective	40/40	NR	NR	40 (100)	0	0	0	NR	Median 102	11/16
Sanai et al. (13)	2009	USA	Neurosurgery	Retrospective	38/38	NR	NR	31 (81.58)	7 (18.42)	0	0	NR	Mean 41	20/24
Murakami et al. (23)	2009	JPN	Surgical Neurology	Retrospective	29/29	57 ± 12.16	28:1	29 (100)	0	0	0	18 (2–58)	NR	11/16
Xu et al. (24)	2011	CHN	The Canadian Journal of Neurological Sciences	Retrospective	22/22	NR	NR	19 (86.36)	3 (13.64)	0	0	NR	Mean 12	10/16
Ramanathan et al. (25)	2012	USA	Neurosurgery	Prospective	30/30	NR	NR	23 (76.67)	7 (23.33)	0	0	NR	Mean 32	22/24
Shi et al. (26)	2014	CHN	Neurosurgical Review	Retrospective	61/61	NR	NR	NR	NR	NR	NR	NR	Mean 36	10/16
Ishishita et al. (27)	2014	JPN	World Neurosurgery	Retrospective	37/37	57.57 ± 11.96	30:7	35 (94.59)	0	0	2 (5.41)	G/L: 25/12	Mean 46.7	18/24
Kalani et al. (28)	2014	USA	Neurosurgery	Retrospective	25/25	50.62 ± 14.87	18:7	17 (68)	7 (28)	1 (4)	0	NR	Mean 18.5	11/16
Rustemi et al. (29)	2015	USA	Neurosurgery	Retrospective	22/22	55.95 ± 18.47	13:9	13 (59.09)	8 (36.36)	0	1 (4.55)	22 (3–40)	Mean 44.8	12/16
White et al. (30)	2016	USA	World Neurosurgery	Retrospective	27/27	50.74 ± 15.61	18:8 NA1	18 (66.67)	8 (29.63)	1 (3.7)	0	26 (8–60)	Minimum 6	11/16
Ban et al. (14)	2017	KOR	Operative Neurosurgery	Retrospective	49/49	NR	NR	35 (71.43)	13 (26.53)	1 (2.04)	0	NR	Mean 34.2	12/16
Abdulrauf et al. (31)	2017	USA	World Neurosurgery	Prospective	30/30	50.1 ± 6.5	17:13	30 (100)	0	0	0	27.9 (20–65)	NR	18/24
				Retrospective	110/110	48.0 ± 7.3	57:53	110 (100)	0	0	0	NR		
Matsukawa et al. (32)	2017	JPN	Journal of Neurosurgery	Retrospective	80/80	59 ± 15	66:14	80 (100)	0	0	0	17 (11–17)	Median 26.1	13/16
Nussbaum et al. (33)	2018	USA	Journal of Neurosurgery	Retrospective	95/95	NR	NR	NR	NR	NR	NR	NR	Minimum 12	19/24
Ni et al. (34)	2018	CHN	World Neurosurgery	Prospective	32/32	NR	NR	0	32 (100)	0	0	NR	Mean 59.4	20/24
Nurminen et al. (35)	2019	FIN	World Neurosurgery	Retrospective	24/28	50.63 ± 16.80	13:11	24 (100)	0	0	0	30 (2–79)	Mean 51	10/16
Natarajan et al. (36)	2019	USA	World Neurosurgery	Retrospective	21/24	50.90 ± 13.93	9:12	0	22 (100)	0	0	12 (3–37)	Mean 39.3	12/16
Pescatori et al. (37)	2021	ITA	World Neurosurgery	Retrospective	55/55	NR	NR	55 (100)	0	0	0	NR	Minimum 12	12/16
Dodier et al. (38)	2022	AUT	Journal of Neurointerventional Surgery	Retrospective	41/40	57 (19–73)	30:11	41 (100)	0	0	0	24 (5–79)	Median 46.8	11/16

Data presented as mean ± standard deviation (SD), median (range), n (%) or otherwise stated. ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; PcoA, posterior communicating artery; G/L, giant/large; NR, non-reported.

TABLE 2 Types of EC–IC bypass used in the included studies.

Study	LF	HF	SVG	RAG	Double STA-MCA
Morgan et al. (20)	0	21 (100)	21 (100)	0	0
Jafar et al. (21)	0	28 (100)	28 (100)	0	0
Cantore et al. (22)	0	40 (100)	40 (100)	0	0
Sanai et al. (13)	9 (23.68)	29 (76.32)	NR	NR	0
Murakami et al. (23)	17 (58.62)	12 (41.38)	12 (41.38)	0	0
Xu et al. (24)	2 (9.09)	20 (90.91)	20 (90.91)	0	0
Ramanathan et al. (25)	7 (23.33)	23 (76.67)	NR	NR	0
Shi et al. (26)	0	61 (100)	16 (26.23)	45 (73.77)	0
Ishishita et al. (27)	0	37 (100)	20 (54.05)	17 (45.95)	0
Kalani et al. (28)	22 (88)	3 (12)	1 (4)	1 (4)	1 (4)
Rustemi et al. (29)	22 (100)	0	0	0	0
White et al. (30)	9 (33.33)	18 (66.67)	16 (59.26)	0	0
Ban et al. (14)	30 (61.22)	19 (38.78)	14 (28.57)	5 (10.2)	0
Abdulrauf et al. (31)	0	30 (100)	0	30 (100)	0
	0	110 (100)	NR	NR	0
Matsukawa et al. (32)	0	80 (100)	21 (26.25)	59 (73.75)	0
Nussbaum et al. (33)	68 (71.58)	27 (28.42)	NR	NR	0
Ni et al. (34)	0	32 (100)	0	32 (100)	0
Nurminen et al. (35)	12 (42.86)	16 (57.14)	12 (42.86)	1 (3.57)	3 (10.71)
Natarajan et al. (36)	8 (33.33)	16 (66.67)	6 (25) (include 3 Y bypasses)	13 (54.17) (include 3 Y bypasses)	0
Pescatori et al. (37)	0	55 (100)	6 (10.91)	49 (89.09)	0
Dodier et al. (38)	7 (17.5)	33 (82.5)	0	0	33 (82.5)

Data presented as n (%). LF, low flow; HF, high flow; SVG, saphenous vein graft; RAG, radial artery graft; STA, superficial temporal artery; MCA, middle cerebral artery; NR, non-reported.

2.6. Statistical analysis

We aggregated effect size using R software (V.4.2.1) and the R package "meta." We calculated pooled effect sizes and 95% confidence intervals (CI) for each outcome. Given that most of the studies we included were non-comparative and potential heterogeneity may exist, we used the random-effects model to estimate pooled values. Heterogeneity was assessed using I^2 and 95% CI. Egger's test was used to assess publication bias for pooling ≥5 studies. In addition, the graft occlusion rates of different bypass types were compared using a random-effects model. Both aggregated rates and aggregated odds ratios are presented.

3. Result

3.1. Characteristics and quality of the included studies

After identification, 21 studies were included in this review, involving a total of 22 cohorts and 915 patients (13, 14, 20–38). The study of Abdulrauf et al. (31) included a prospective cohort of 30 patients and a retrospective cohort of 110 patients. The study by Dodie et al. (38) included one patient with a failed intraoperative bypass, so a total of 40 bypasses were performed. We evaluated a total of 1,100 unique publications and 1,079 were excluded (Figure 1). Studies were published in years ranging from 2002 to 2022. The type of study design included four prospective studies and 17 retrospective studies (Table 1). Nine studies were from the United States, 3 from Japan, 3 from China, 2 from Italy, and the remaining studies were from South Korea, Austria, Australia and Finland (Table 1). Study sample sizes were ranging from 20 to 110. Patient's age and gender information was available for a total of 11 studies. Except for the patients in Natarajan et al. study, the female patients were more than male. The average age of the vast majority of study patients was older than 50 years (Table 1). Aneurysm location information was available for a total of 19 studies, with most of aneurysms located proximal to the ICA bifurcation and its branches. Aneurysm size information was available for a total of 10 cohorts, with the majority of IAs being large (≥10 mm) and giant (≥25 mm) aneurysms. Follow-up duration was described in most studies expect for two studies. A total of 6 studies were comparative and 15 studies were non-comparative. The median score of non-comparative

TABLE 3 Primary outcomes of included studies.

Study	Postoperative patency rate	Short-term follow-up patency	Long-term follow-up patency	Short-term follow-up mortality	Long-term follow-up mortality
Morgan et al. (20)	21 (100)	21 (100)	21 (100)	0	1 (4.76)
Jafar et al. (21)	NR	NR	26 (92.86)	1 (3.7)	1 (3.7)
Cantore et al. (22)	NR	NR	37 (92.5)	4 (10)	4 (10)
Sanai et al. (13)	NR	NR	NR	0	0
Murakami et al. (23)	NR	NR	NR	0	NR
Xu et al. (24)	NR	NR	NR	0	0
Ramanathan et al. (25)	NR	NR	NR	0	0
Shi et al. (26)	NR	NR	NR	0	NR
Ishishita et al. (27)	36 (97.3)	37 (100)	36 (97.3)	0	0
Kalani et al. (28)	NR	NR	22 (91.67)	0	0
Rustemi et al. (29)	22 (100)	NR	18 (81.82)	0	0
White et al. (30)	NR	NR	NR	0	NR
Ban et al. (14)	NR	NR	NR	0	0
Abdulrauf et al. (31)	30 (100)	30 (100)	NR	0	NR
	NR	99 (90)	NR	6 (5.45)	NR
Matsukawa et al. (32)	80 (100)	80 (100)	76 (95)	0	0
Nussbaum et al. (33)	NR	NR	93 (97.89)	NR	2 (2.11)
Ni et al. (34)	31 (96.88)	NR	27 (84.38)	0	0
Nurminen et al. (35)	NR	25 (89.29)	23 (82.14)	NR	NR
Natarajan et al. (36)	23 (95.83)	23 (95.83)	22 (91.67)	0	0
Pescatori et al. (37)	NR	NR	52 (94.55)	NR	5 (9.09)
Dodier et al. (38)	NR	NR	36 (92.31)	0	0

Data presented as n (%). NR, non-reported.

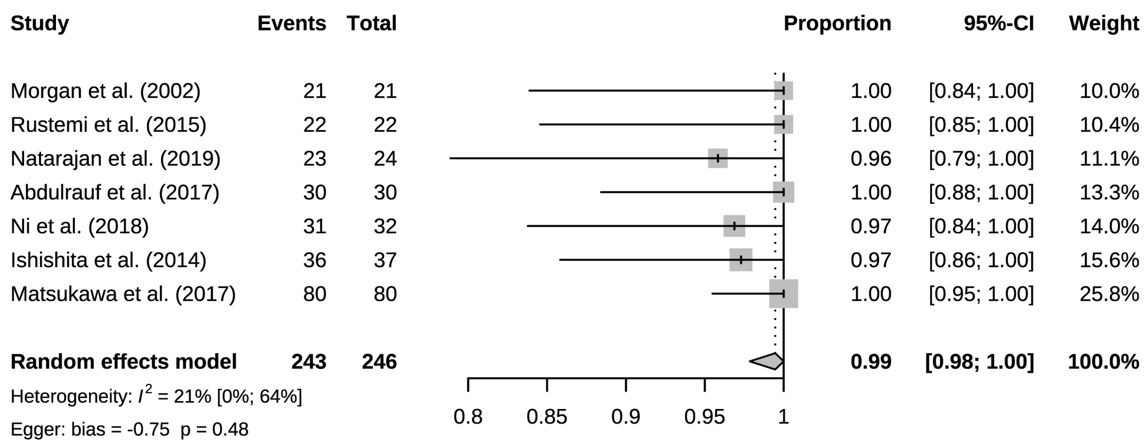

FIGURE 2
Immediate postoperative bypass patency of included studies.

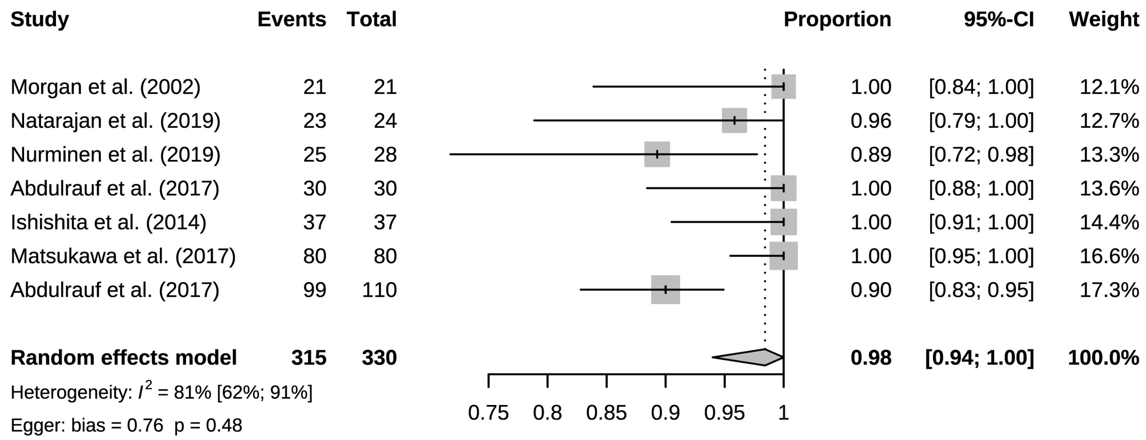

FIGURE 3
Short-term follow-up bypass patency of included studies.

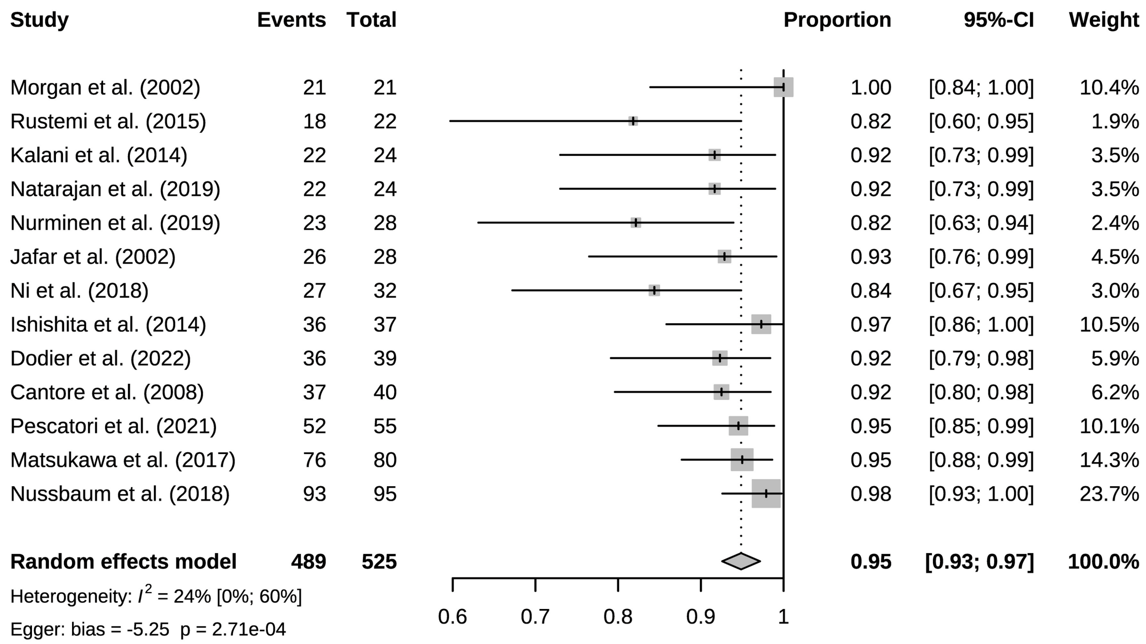

FIGURE 4
Long-term follow-up bypass patency of included studies.

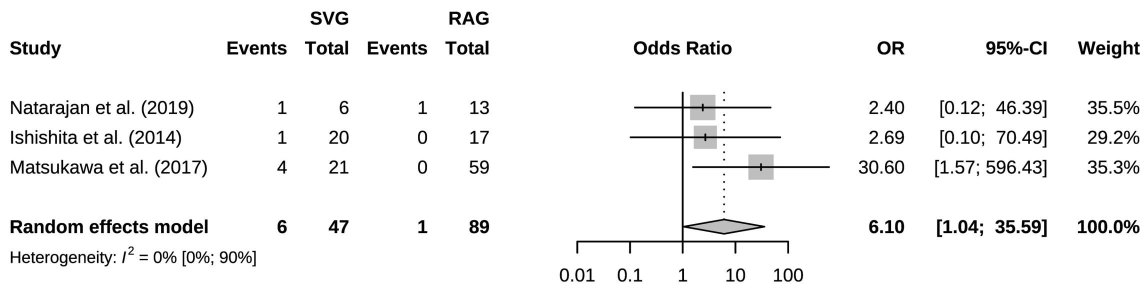

FIGURE 5
Forest plot showing occlusion rate of saphenous vein graft was higher than radial artery graft.

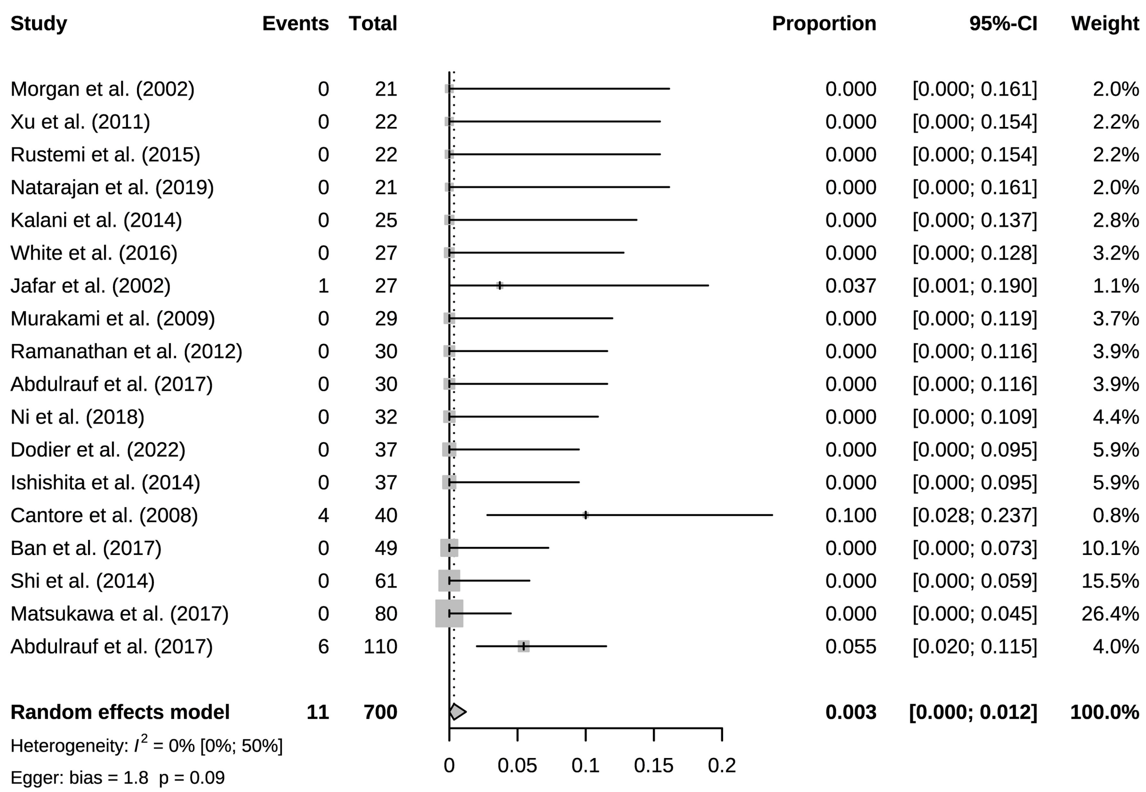

FIGURE 6
Short-term follow-up surgery-related mortality of included studies.

studies was 11 (10–14) and comparative studies was 19.5 (18–22) (Table 1).

3.2. Bypass patency and mortality

A total of 941 bypasses were performed across all studies, including 214 (23%) low flow bypasses and 727 (77%) high flow bypasses. The radial artery was used as a graft in 239 bypasses, and the saphenous vein was used as a graft in 228 bypasses. The study of Natarajan et al. included 3 Y-shaped bypasses using the radial and saphenous veins as grafts (Table 2). Both patency and mortality are reported at short-term and long-term follow-up, and patency is also reported postoperatively (Table 3). Postoperative bypass patency was available for a total of 7 studies, and the pooled patency rate was 99% (95% CI 0.98–1.00) (Figure 2). The short-term follow-up patency rate of pooled 7 studies was 98% (95% CI 0.94–1.00) (Figure 3). The heterogeneity was significant, I^2 = 81% (95% CI 62%−91%). A total of 13 studies reported long-time followed up patency, and the pooled patency rate was 95% (95% CI 0.93–0.97) (Figure 4). Four studies compared long-term patency rates for high-flow vs. low-flow bypasses and the result showed no differences between them (OR 1.89 95% CI 0.50–7.15) (Supplementary Figure S1). Saphenous vein grafts (SVG) have higher occlusion rates compared with radial artery grafts (RAG) (OR 6.10 95% CI 1.04–35.59), pooled from 3 studies (Figure 5). The long-term pooled patency rates of high-flow, low-flow, SVG and RAG were 95%, 96%, 93%, and 96% respectively (Supplementary Figures S2–S5). A total of 18 studies were pooled, and 11 people died in the short-term follow-up (n = 700), and the pooled mortality rate was 0.3% (95% CI 0.000–0.012) (Table 3, Figure 6). During the long-term follow-up, 13 people died (n = 692). The pooled mortality rate was 0.4% (95% CI 0.000–0.013), and 17 studies were pooled (Table 3, Figure 7).

3.3. Neurological function score and complication

A total of six studies reported mRS scores and two reported GOS scores (Table 4). Compared with preoperatively, the mRS scores of most studies improved significantly, and the number of 0 scorers increased. However, mRS worsening during follow-up was observed in the Nurminen's and Morgan's studies. We pooled the proportion of patients with follow-up mRS 0–2 scores from five studies, 92% (95% CI 0.86–0.98) (Figure 8). Relatively significant heterogeneity was observed, I^2 = 62% (95% CI 0%−86%). Complication rates were available for a total of nine studies (Table 5). The incidence of long-term follow-up complications: ischemic 3% (95% CI 0.01–0.06), hemorrhagic 1% (95% CI 0.00–0.03), neurological deficit 1% (95% CI 0.00–0.03), other complications 3% (95% CI 0.01–0.06) (Supplementary Figures S6–S9).

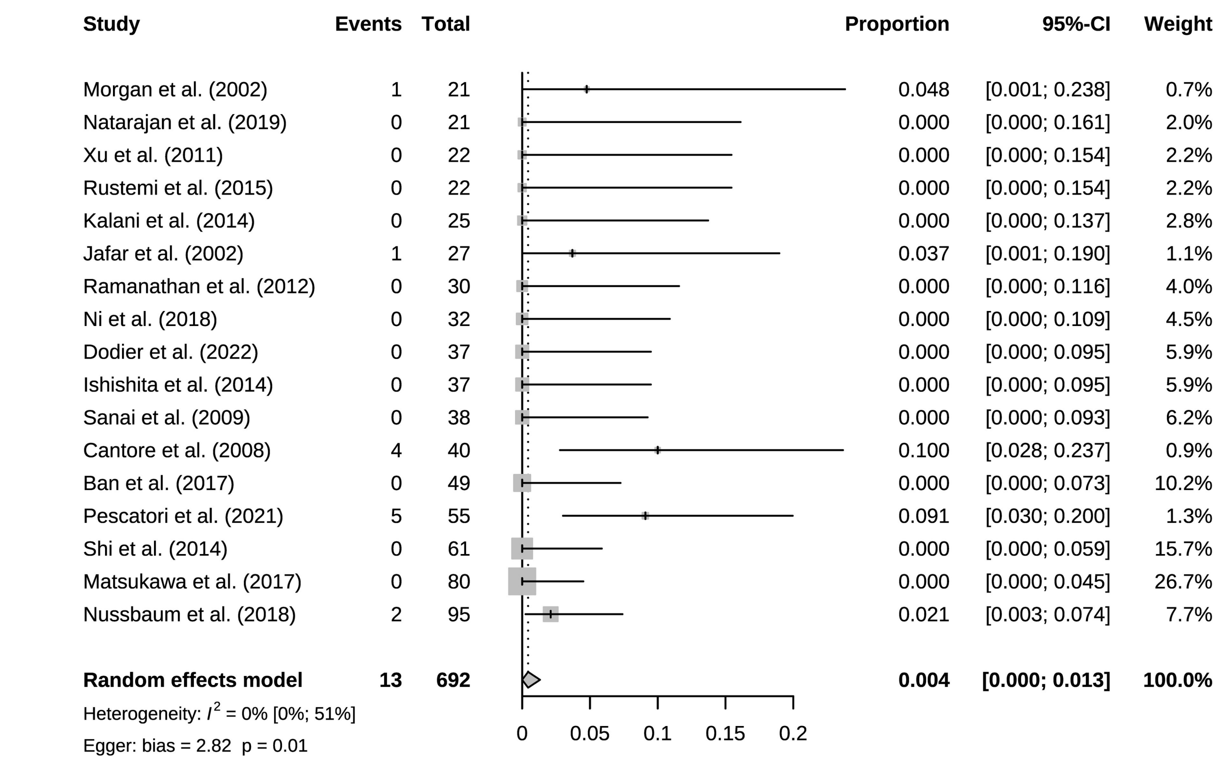

FIGURE 7
Long-term follow-up surgery-related mortality of included studies.

4. Discussion

This study included 21 eligible studies, involving a total of 915 patients. Bypass patency was high postoperatively and during follow-up. Bypass patency rate of post-operation, the short-term follow-up, and long-term follow-up were 99%, 98%, and 95%, respectively. More than three quarters of bypasses are high flow bypasses. HF bypass surgery may have lower patency rates than LF bypass, but comparison based on four studies did not show meaningful results. Our results basically consistent with a previous study of patency rates in 430 bypass surgeries (39). Its aneurysm group had an overall patency rate of 95%. Its overall patency was lower for HF bypasses than for LF bypasses, however there was no difference in long-term follow-up. With the grafts involved, it appears that the HF is prone to result in occlusion. For instance, the vasospasms of graft, vascular intimal injuries and mismatch of arteries caliber could lead to the formation of thrombus and grafts occlusion. Generally, the LF bypass is recommended due to its safety (40). Under particular circumstances, the combination of blood flow assessment is needed when applying the HF bypass to maximize the safety (12). SVG have higher occlusion rates than RAG. But only three studies were compared, and its extrapolation is limited. SVG and RAG are the most used grafts in bypass surgery. They have different characteristics, for example the radial artery has good thickness and arterial endothelium, but the saphenous vein can provide higher flow. Predominance of the radial artery in the coronary arteries has been established, however more research is needed on cerebral revascularization (41). Based on the existing evidence, we recommend that the radial artery has a greater advantage when the flow rate can be met, which is in line with the current views of most researchers (42). Mortality associated with bypass surgery in this study was extremely low, reflecting its robust safety. And the vast majority of patients showed good prognosis (mRS 0–2) after surgery. The postoperative mRS score is affected by the preoperative status. Considering some patients with poor preoperative scores, the actual improvement in prognosis should be slightly better than the current results. The risk of postoperative complications was low, and they were mostly ischemic.

The results of heterogeneity analysis showed significant heterogeneity in short-term follow-up patency rate and mRS score. This may be influenced in part by the different preoperative status of the patients, such as study by Nurminen et al. (35). The preoperative mRS 3–5 patients were 20.83%, and the postoperative mRS 3–5 patients were 25%. Its preoperative mRS score was the worst of all studies reporting mRS and may have partially influenced the results. Publication bias existed in most studies, except for bypass patency and mortality in long-term follow-up. Sources of publication bias explained by non-comparative studies and small literature numbers, which had less significance for the results.

The quantity and quality of the existing evidence for EC–IC bypass are unsatisfactory. A systematic review that included 20 studies in 2008 showed that EC–IC bypass surgery reduces ischemic stroke risk following therapeutic permanent ICA occlusion for

TABLE 4 Neurological function score of included studies.

Study reporting mRS	Evaluation timing	mRS						
		0	1	2	3	4	5	6
Matsukawa et al. (32)	Preoperative	30 (37.5)	32 (40)	15 (18.75)	0	1 (1.25)	2 (2.5)	0
	Discharge	36 (45)	21 (26.25)	17 (21.25)	3 (3.75)	3 (3.75)	0	0
	Follow-up	49 (61.25)	19 (23.75)	9 (11.25)	2 (2.5)	1 (1.25)	0	0
Nurminen et al. (35)	Preoperative	2 (8.33)	15 (62.5)	2 (8.33)	2 (8.33)	1 (4.17)	2 (8.33)	0
	Follow-up	6 (25)	6 (25)	6 (25)	3 (12.5)	2 (8.33)	1 (4.17)	0
Morgan et al. (20)	Preoperative	6 (28.57)	14 (66.67)	1 (4.76)	0	0	0	0
	Follow-up	12 (57.14)	5 (23.81)	1 (4.76)	0	0	1 (4.76)	2 (9.52)
Nussbaum et al. (33)	Follow-up	85 (89.47)			4 (4.21)	2 (2.11)	2 (2.11)	2 (2.11)
Other mRS formats								
Dodier et al. (38)	Preoperative	median 2						
	Follow-up	Improve/total 36 (97.3) mRS 0–2 36 (97.3)						
Cantore et al. (22)	Follow-up	Improve/total 35 (87.5)						
Study reporting GOS	Evaluation timing	GR			MD		SD	
Ishishita et al. (27)	Follow-up	37 (100)			0		0	
Murakami et al. (23)	Follow-up	23 (79.31)			2 (6.9)		4 (13.79)	

Data presented as n (%). mRS, modified Rankin scale; GOS, glasgow outcome scale; GR, good recovery; MD, moderately disabled; SD, severely disabled; NR, non-reported.

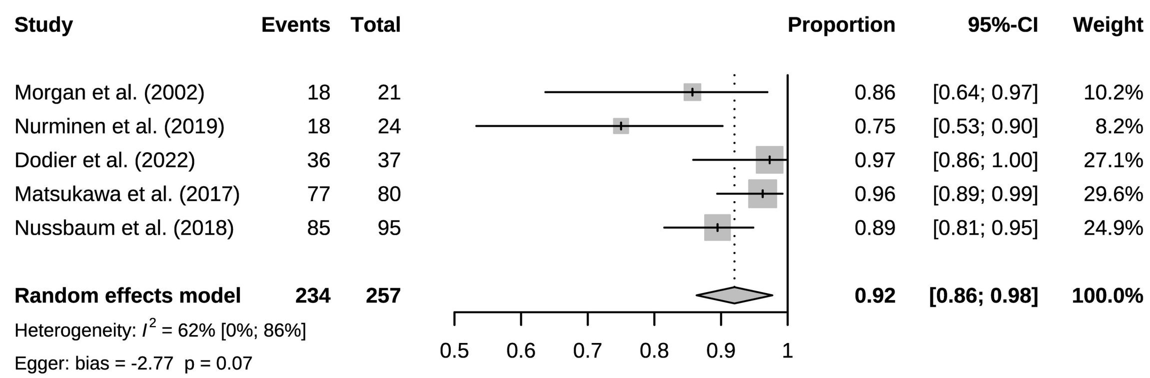

FIGURE 8
Long-term follow-up proportion of patients with 0–2 points on the modified Rankin scale.

the IAs in anterior circulation (43). This provides guidance for the selection of EC-IC bypass. But considering the sample size and quality of the included studies, the stability of the results is limited. A 2021 systematic review examined the role of EC–IC bypass in the treatment of blood-vesting aneurysms of the ICA (44). However, the sample sizes of the included studies were all <20, and there is no prospective study, precluding any reliable conclusions. The studies we included contain 4 prospective research, with all sample size more than 20, and overall quality of moderate to high. Consequently, our systematic analysis provides more solid proof of the safety in EC–IC.

Our study still has limitations. Most of the studies were retrospective, although the average quality of the studies was moderate to high. In recent years, the development of interventional therapy, especially FD, has greatly reduced the application of bypass surgery for the treatment of giant and complex IA, which poses a challenge for prospective studies of bypass surgery. There is a lack of sufficient studies reporting comparisons of preoperative status to assess postoperative improvement. In addition, subgroup information such as aneurysm rupture and balloon occlusion test (BOT) information is lacking.

In summary, current evidence suggests a high safety profile of EC–IC bypass therapy for IA in anterior circulation. But the level of evidence is low. In the era of endovascular treatment of IA, there are still complex aneurysms that are not suitable for simple endovascular treatment and microsurgical clipping. The combination of EC–IC bypass and other surgical methods such as parent artery occlusion still has an irreplaceable role. Its safety remains to be determined by evidence from large randomized controlled trials (RCT) and high-quality meta-analyses based on RCTs.

TABLE 5 Secondary outcomes of included studies.

Study	Ischemic	Hemorrhagic	Neurological deficits	Other
Morgan et al. (20)	0	0	0	0
Jafar et al. (21)	1 (3.7)	NR	1 (3.7)	NR
Xu et al. (24)	1 (4.55)	0	0	0
Ishishita et al. (27)	1 (2.7)	0	0	2 (5.41)
Kalani et al. (28)	0	1 (4)	1 (4)	1 (4)
Rustemi et al. (29)	1 (4.55)	0	0	0
Nussbaum et al. (33)	6 (6.32)	7 (7.37)	4 (4.21)	7 (7.37)
Natarajan et al. (36)	3 (14.29)	NR	NR	NR
Dodier et al. (38)	1 (2.7)	0	0	4 (10.81)

Data presented as n (%). NR, non-reported.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

YC, PC, GD, and GG performed literature search, data extraction, and statistical analysis. RL and ZL completed the visualization. YC drafted the manuscript. YC and GG revised the manuscript. GG provided funding. All authors contributed to the study design conception. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1174088/full#supplementary-material

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EDITED BY
Shinichiro Uchiyama,
Sanno Medical Center, Japan

REVIEWED BY
Hongyan Han,
Aviation General Hospital, China
Yang Wang,
Capital Medical University, China

*CORRESPONDENCE
Xiang-Hua Zhang
✉ zenzxh@126.com

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Comparison of revascularization and conservative treatment for hemorrhagic moyamoya disease in East Asian Countries: a single-center case series and a systematic review with meta-analysis

Xiang-Hua Zhang[1]*, Jun-Hua He[2], Xiang-Sheng Zhang[1], Jing Zhang[1], Cheng-jun Wang[1], Yi-Peng Dong[1] and Wu Tao[1]

[1]Department of Neurosurgery, Beijing Friendship Hospital Affiliated With Capital Medical University, Beijing, China, [2]Department of Neurosurgery, Zhejiang Provincial Tongde Hospital, Hangzhou, China

Objective: The optimal treatment approach for hemorrhagic moyamoya disease (HMMD) remains a topic of debate, particularly regarding the comparative efficacy of revascularization versus conservative treatment. Our study, which included a single-center case series and a systematic review with meta-analysis, aimed to determine whether surgical revascularization is associated with a significant reduction in postoperative rebleeding, ischemic events, and mortality compared to conservative treatment among East Asian HMMD patients.

Methods: We conducted a systematic literature review by searching PubMed, Google Scholar, Wanfang Med Online (WMO), and the China National Knowledge Infrastructure (CNKI). The outcomes of surgical revascularization and conservative treatment, including rebleeding, ischemic events and mortality, were compared. The authors' institutional series of 24 patients were also included and reviewed in the analysis.

Results: A total of 19 East Asian studies involving 1,571 patients as well as our institution's retrospective study of 24 patients were included in the study. In the adult patients-only studies, those who underwent revascularization had significantly lower rates of rebleeding, ischemic events, and mortality compared to those who received conservative treatment (13.1% (46/352) vs. 32.4% (82/253), $P < 0.00001$; 4.0% (5/124) vs. 14.9% (18/121), $P = 0.007$; and 3.3% (5/153) vs. 12.6% (12/95), $P = 0.01$, respectively). In the adult/pediatric patients' studies, similar statistical results of rebleeding, ischemic events, and mortality have been obtained (70/588 (11.9%) vs. 103/402 (25.6%), $P = 0.003$ or <0.0001 in a random or fixed-effects model, respectively; 14/296 (4.7%) vs. 26/183 (14.2%), $P = 0.001$; and 4.6% (15/328) vs. 18.7% (23/123), $P = 0.0001$, respectively).

Conclusion: The current single-center case series and systematic review with meta-analysis of studies demonstrated that surgical revascularization, including direct, indirect, and a combination of both, significantly reduces rebleeding, ischemic events, and mortality in HMMD patients in the East Asia region. More well-designed studies are warranted to further confirm these findings.

KEYWORDS

revascularization, conservative, rebleeding, ischemic, mortality, moyamoya disease, hemorrhagic

1. Introduction

Moyamoya disease (MMD) is a chronic idiopathic condition that was first described by Taceuchi and Shimizu in 1957 (1). This condition is characterized by nonatherosclerotic progressive stenosis or occlusion of the bilateral supraclinoidal internal carotid arteries and the development of an abnormal collateral vascular network at the base of the brain. This disorder is especially prevalent in East Asian populations, mainly Japan, Korea, and China, and the reported prevalence of MMD is 10.5/100,000 individuals in Japan (2), 16.1/100,000 in South Korea (3), and 3.92/100,000 in China (4), respectively. In MMD, intracranial hemorrhage occurs more frequently in adult patients than in children (5), especially in adults older than 40 years. Surgical revascularization, including direct bypass, indirect bypass, and combinations of both, has proven to be effective in improving outcomes for patients with ischemic MMD (6, 7). However, whether surgical revascularization could reduce the long-term risks of recurrent hemorrhage (8), ischemic events, and mortality in HMMD patients remains controversial. The purpose of this study was to determine whether surgical revascularization reduces the risk of recurrent hemorrhage, ischemic events, and mortality in East Asian HMMD patients.

2. Materials and methods

2.1. Literature search

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (9). A comprehensive literature search was performed on PubMed, Google Scholar, Wanfang Med Online (WMO), and the China National Knowledge Infrastructure (CNKI) for studies on HMMD published before 1 January 2023. The terms "moyamoya disease," "hemorrhagic," "conservative," and "revascularization" were used as keywords in searching the abovementioned databases. Other relevant publications were identified by examining the references included in the study.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) HMMD patients; (2) adult or pediatric patients; (3) the study including both surgical and conservative treatment groups; (4) articles written in English or Chinese.

The exclusion criteria were as follows: (1) system review articles, case reports, and editorials; (2) moyamoya syndrome; (3) other surgical treatment modalities (such as aneurysm clip or coil procedure, hematoma evacuation, and so on); and (4) without detailed outcomes for revascularization procedures and conservative treatment.

Abbreviations: MMD, Moyamoya disease; HMMD, Hemorrhagic Moyamoya disease; WMO, Wanfang Med Online; CNKI, China National Knowledge Infrastructure; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; EMS, encephalo-myo-synangiosis; EMAS, encephalo-myo-arterial-synangiosis; EDAS, encephalo-duro-arterial-synangiosis; EDMS, encephalo-duro-myo-synangiosis; EDAMS, encephalo-duro-myo-arterial-synangiosis; EDAGS, encephalo-duro-arterial-galeo-synangiosis.

2.3. Data extraction

A total of 525 studies were identified through a search of PubMed (n =52), Google Scholar (n = 84), WMO (n =104), and CNKI (n = 285), among which 110 studies were first excluded due to duplicate citations. According to the inclusion and exclusion criteria, 19 studies of the remaining 415 were finally included in the systematic review and meta-analysis (Figure 1), (Tables 1, 2).

2.4. Statistical analysis

The data available from the selected studies were imported into Review Manager, version 5.3.5 (The Cochrane Collaboration), for quantitative analysis. Odds ratios (ORs) with 95% CIs were calculated in Review Manager. The heterogeneity between the studies was considered valid with a $P < 0.05$ in Cochran's Q-test. In the Higgins inconsistency index (I^2) test, the degrees of heterogeneity were as follows: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% may represent considerable heterogeneity (29). Whether a random-effect or fixed-effect meta-analysis was performed depended on the heterogeneity among studies. The publication bias was tested by utilizing a funnel plot in our meta-analysis.

3. Results

3.1. Baseline characteristics

A total of 26 patients with HMMD were treated at our institution between May 2013 and May 2022, and two were lost to follow-up. Among the other 24 patients, 12 underwent revascularization, and the other 12 received conservative treatment. The mean follow-up time was 51 months (14–97), during which no rebleeding, ischemic event, or rebleeding-related mortality occurred in 12 patients who underwent revascularization, whereas in the conservative group, rebleeding occurred in two patients (16.7%), an ischemic event in one patient (8.3%), and death in two patients (16.7%) (Table 3).

Among the 20 studies carried out in East Asia, including our institution's consecutive case series, five studies (25%) were conducted in Japan, 13 (65%) in China, and 2 (10%) in Korea, respectively, and there were 11 (55%) studies comprising adult patients only, 6 (30%) comprising adult and pediatric patients, and 3 (15%) that did not clearly mention the study population. In total, 19 studies were retrospective cohorts, and 1 was a multicenter prospective randomized controlled trial. The follow-up duration ranged from 1 month to >10 years. Among the 20 studies reviewed, direct (STA-MCA) and indirect bypass procedures were

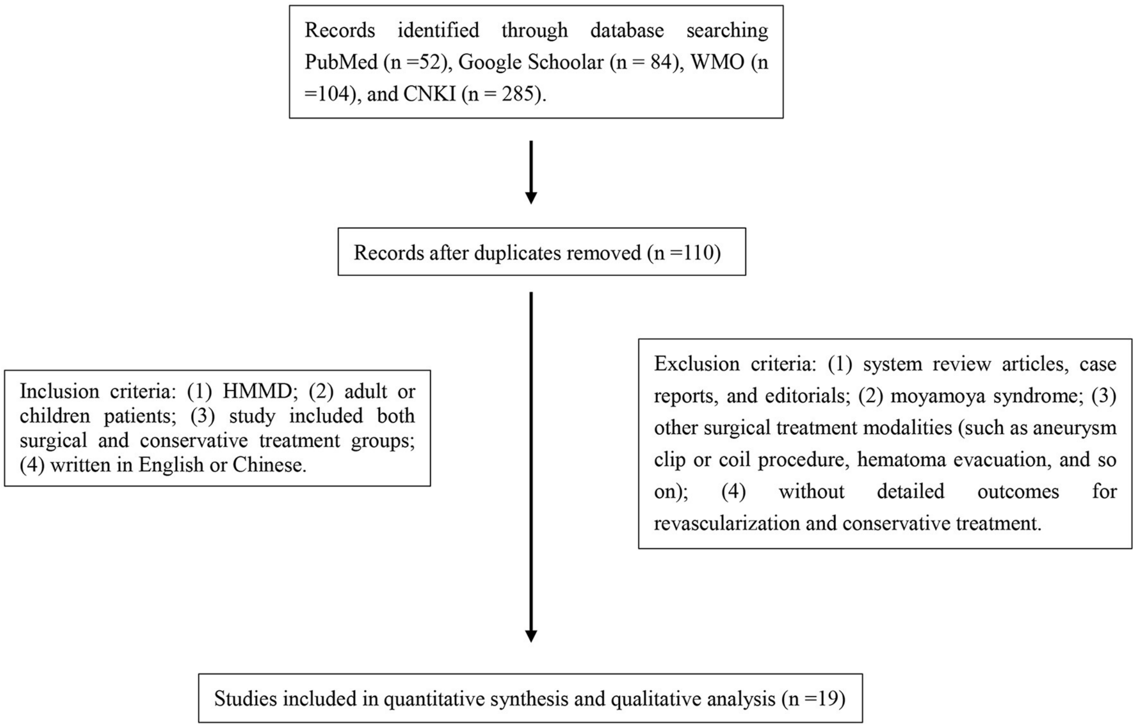

FIGURE 1
Flow diagram of the literature search strategy.

performed in 17 (85%) studies; indirect bypass alone was used in the other three studies, which included encephalic-myo-spongiosis (EMS) (12, 16, 20, 23), encephalo-duro-aterio-synangiosis (EDAS) (10, 12–14, 17, 19, 21, 27), encephalo-duro-myo-synangiosis (EDMS) (24, 26, 28), and encephalo-myo-aterio-synangiosis (EMAS) (10, 28), encephalo-duro-arterio-galeo-synangiosis (EDAGS) (16, 23), and encephalo-duro-arterio-myo-synangiosis (EDAMS) (16, 20, 23).

3.2. Rebleeding

In the 20 studies, including our institution's series, there were a total of 940 patients who underwent revascularization, among whom 116 (12.3%) patients experienced rebleeding, whereas 185 (28.2%) of the 655 patients who received conservative treatment experienced rebleeding. The rebleeding rate in the 11 adult revascularization groups was 13.1% (46 out of 352 patients), whereas, in the conservative treatment group, 82 out of 253 patients (32.4%) experienced rebleeding. The heterogeneity testing revealed no heterogeneity among these studies ($I^2 = 0\%$, $P = 0.77$). The meta-analysis showed a pooled OR of 0.23 (95% CI 0.15-0.36; $p < 0.00001$) (Figure 2) in the Mantel-Haenszel fixed-effects model. Of the nine adult/pediatric and not specifically mentioned patients, 70 (11.9%) out of the 588 patients experienced rebleeding, and 103 (25.6%) out of 402 patients were in the conservative treatment group. The patients who underwent revascularization experienced significantly less rebleeding than those who received conservative treatment (OR, 0.32; 95% CI, 0.15–0.68; $P = 0.003$, and OR, 0.46; 95% CI, 0.33–0.65; $P < 0.0001$, in a random and fixed-effects model, respectively) (Figure 3). Compared with conservative treatment, surgical revascularization significantly reduced the incidence of rebleeding in HMMD patients.

3.3. Ischemic events

Among 20 studies, there were seven studies (including our present cases) related to the post-surgical ischemic event. There were 14 cases (4.7%) of complicated postoperative ischemic events in patients who underwent revascularization and 26 cases (14.2%) were observed among 183 patients who received conservative treatment. Patients who underwent revascularization experienced fewer ischemic events compared with those who received conservative treatment (OR, 0.30; 95% CI, 0.14–0.61; $P = 0.001$, Figure 4). Among the seven studies, five studies comprised adult patients only; a total of 124 patients underwent revascularization, among whom 5 (4.0%) experienced ischemic events, whereas 18 (14.9%) of the 121 patients who received conservative treatment experienced ischemic events. There was no heterogeneity between the results of the five studies ($I = 0\%$, $P = 0.79$), and the fixed-effects model was selected for meta-analysis. A comparison of the revascularization group with the conservative treatment group in a fixed-effects meta-analysis showed a pooled OR of 0.26 (95% CI 0.10-0.70; $p = 0.007$, Figure 5). As mentioned above, in adult and pediatric HMMD patients, the revascularization procedure provided a significant advantage over conservative treatment in reducing the incidence of ischemic events.

TABLE 1 Study characteristics and rebleeding in conservative and revascularization groups.

References	Country	Study design	Sample size(n) child/adult	Age (mean ys.) male/female	NOPs (RV/RB)	NOPs (CO/RB)
Fujii et al. (10)	Japan	RC	290	NA	152/29	138/39
			NA	NA		
Ikezaki et al. (11)	Japan	RC	197	NA	80/15	117/19
			NA	NA		
Yoshida et al. (12)	Japan	RC	28 (7 lost to follow-up)	39.26 ± 15.7	8/1	13/5
			2/26	4/24		
Kawaguchi et al. (13)	Japan	RC	22	43	11/2	11/2
			0/22	7/15		
Duan et al. (14)	China	RC	61	37.6	59/0	2/2
			4/57	29/32		
Zhao et al. (15)	China	RC	23	S 46.42, NS 46.6	10/1	13/1
			0/23	12/11		
Choi et al. (16)	Korea	RC	44	44.9 (17–65)	35/6	9/4
			0/44	18/26		
Liu et al. (17)	China	RC	97	S 33, NS30	54/4	43/17
			6/91	33/64		
Miyamoto et al. (18)	Japan	MPRCT	80	S42.5, NS 41.4	42/5	38/12
			0/80	24/56		
Chen et al. (19)	China	RC	82	Child 9.6/adult 37.2	48/4	34/10
			12/70	32/50		
Li et al. (20)	China	RC	47	40.2 (18–70)	28/2	19/7
			0/47	20/27		
Wan et al. (21)	China	RC	38	39 (12–59)	35/2	3/0
			1/37	9/29		
Zheng et al. (22)	China	RC	154 (2 aneurysm obliteration)	33.95 ± 10.47 (22–61)	124/15	28/6
			10/144	52/102		
Zhang et al. (23)	China	RC	37	50.3	29/5	8/4
			0/37	23/14		
Yang et al. (24)	China	RC	89	48 (27–66)	63/12	26/18
			0/89	50/39		
Jang et al. (25)	Korea	RC	96	NA	49/3	47/7
			0/96	NA		
Jiang et al. (26)	China	RC	40	NA	16/0	24/3
			0/40	NA		
Li et al. (27)	China	RC	52	50.7	28/0	24/5
			NA	31/23		
Liu et al. (28)	China	RC	103	38.04 ± 0.52 (32–40)	57/10	46/22
			0/103	48/55		
Present casesat our institution	China	RC	24	42 ± 11.8	12/0	12/2
			0/24	11/13		

S, surgical; NS, nonsurgical; ys, years; RV, revasculation; RB, rebleeding; CO, conservative; NA, not available; RC, retrospective cohort; MPRCT, multicentered prospective randomized, controlled trial; NOPs, number of patients.

TABLE 2 Study characteristics, ischemic event, and mortality in conservative and revascularization groups.

References	Bypass approach	Follow-up	NOPs (RV/IS)	NOPs (CO/IS)	NOPs (RV/DE)	NOPs (CO/DE)
Fujii et al. (10)	STA–MCA and/or EMAS or EDAS	NA	NA	NA	NA	NA
Ikezaki et al. (11)	indirect, STA–MCA direct+indirect	47.6 ms	NA	NA	NA	NA
Yoshida et al. (12)	EDAS, EMS, STA-MCA, STA-MCA+EDAS	>10 ys	NA	NA	8/1	13/4
Kawaguchi et al. (13)	STA–MCA, EDAS	8 ys (0.8-15.1)	11/1	11/4	NA	NA
Duan et al. (14)	EDAS	27.5 ms (6–64)	NA	NA	59/0	2/2
Zhao et al. (15)	STA-MCA	S 2.52, NS 1.6 ys	10/1	13/2	NA	NA
Choi et al. (16)	STA-MCA, EDAGS EDAMS, EMS	55.4 ms (12–105)	NA	NA	35/1	9/1
Liu et al. (17)	STA-MCA, EDAS STA-MCA+EDAS	7.1 ys	NA	NA	54/2	43/4
Miyamoto et al. (18)	STA–MCA direct+indirect	5 ys	42/1	38/1	NA	NA
Chen et al. (19)	STA-MCA STA-MCA+EDAS	7.8 ys (0.6–12)	48/2	34/5	48/2	34/10
Li et al. (20)	STA-MCA EMS, EDAMS	26 ms (12–44)	NA	NA	28/0	19/4
Wan et al. (21)	EDAS	51 ms (13–125)	NA	NA	35/1	3/0
Zheng et al. (22)	STA-MCA, indirect direct+indirect	36.12 ms	124/7	28/3	124/9	28/3
Zhang et al. (23)	STA–MCA, EMS EDAMS, EDAGS direct+indirect	12–97 ms	NA	NA	29/1	8/2
Yang et al. (24)	STA-MCA+EDMS EDMS	RV 19ms (12–24) CO 10 ms (8–15)	NA	NA	NA	NA
Jang et al. (25)	STA-MCA, indirect direct+indirect	6ys	49/2	47/10	49/3	47/3
Jiang et al. (26)	STA-MCA+EDMS	1 y	NA	NA	NA	NA
Li et al. (27)	STA-MCA EDAS	5 ys	NA	NA	28/0	24/5
Liu et al. (28)	EDMS, EMAS	1–6 ms	NA	NA	NA	NA
Present cases at our institution	EMS, STA-MCA, indirect bypass, dural inversion	51 ± 30 ms (14–97)	12/0	12/1	12/0	12/2

STA–MCA, superficial temporal artery–middle cerebral artery bypass surgery; EMAS, encephalo-myo-aterio-synangiosis; EDAS, encephalo-duro-aterio-synangiosis; EMS, encephalo-myo-synangiosis; EDAGS, encephalo-duro-arterio-galeo-synangiosis; EDAMS, encephalo-duro-arterio-myo-synangiosis; EDMS, encephalo-duro-myo-synangiosis; ms, months; ys, years; RV, revasculation; CO, conservative; NA, not available; NOPs, number of patients.

3.4. Mortality

Among the six studies that included both adult and pediatric patients, there were 15 deaths (4.6%) due to rebleeding among 328 patients who underwent revascularization, whereas the mortality among patients who received conservative treatment was 18.7% (23/123). The meta-analysis showed a pooled OR of 0.24 (95% CI 0.12-0.50; $P = 0.0001$) (Figure 6) in the Mantel-Haenszel fixed-effects model, which revealed a significant reduction in mortality associated with revascularization surgery compared to conservative treatment in mixed adult/pediatric patients. Among the five studies that included only adult patients, the mortality rate was significantly lower in the revascularization group [3.3% (5/153)] than in the conservative treatment group [12.6% (12/95)]. The meta-analysis showed a pooled OR of 0.28 (95% CI 0.10-0.75; $P = 0.01$) (Figure 7) in the Mantel-Haenszel fixed-effects model. The results presented above indicate that revascularization is associated with lower mortality rates than conservative treatment.

4. Discussion

The HMMD patients experienced a significantly higher frequency of intracranial hemorrhage than ischemic events, with this difference becoming more pronounced over longer periods of follow-up (30). In Yamada et al.'s (31) study, there was no statistically significant difference in the hemorrhagic recurrence rate between the patients who underwent revascularization and those who received conservative treatment. Lee SB et al. (32) revealed that direct and combined revascularization statistically prevented ischemic stroke recurrence in adult ischemic MMD patients, whereas no statistically significant difference was found in reducing the incidence of re-hemorrhage in the HMMD adult patients who underwent revascularization surgery. To the best of our knowledge, there is still no meta-analysis study on HMMD rebleeding, ischemic events, or mortality differences between the conservative and revascularization groups in the East Asian population. The debate regarding a superior treatment option between revascularization and conservative treatment in HMMD is ongoing. An ideal treatment approach for any medical condition should prioritize strategies that result in less rebleeding, fewer ischemic events, and fewer mortalities.

TABLE 3 Baseline characteristics of our present patients.

Characteristics	Total
Age in years (mean ± SD)	42 ± 11.8
Gender (Female/Male)	13/11
Revascularization/Conservative	12/12
Revascularization procedure	2 craniectomy and EMS,10 STA-MCA, indirect bypass, and dural inversion
Rebleeding	Revascularization 0/conservative 2
Ischemic event	Revascularization 0/conservative 1
Mortality	revascularization 0/conservative 2
Follow up duration	51 ± 30 months (14–97)
MRS	0.72 ± 1.1

SD, standard deviation; mRS, modified Rankin Score.

4.1. Rebleeding

Initial and recurrent bleeding episodes in patients with moyamoya disease occur mainly in adult patients, resulting in neurological deficits and reduced quality of life. Hemorrhage is typically caused by the rupturing of fragile perforator vessels, proliferative collateral vessels, and concomitant micro-aneurysms, which are all believed to be induced by elevated autoantibodies or/and hemodynamic stress that leads to apoptosis (33, 34). In Takahashi et al.'s report on HMMD, an independent rebleeding risk factor was a hemodynamic failure, and a significant preventive effect was obtained by the direct bypass procedure in the hemodynamically disrupted hemispheres (35). Yamada S et al. found that the estimated rebleeding rate of HMMD was 9.4 ± 3.0%/3 years and 10.9 ± 3.3%/5 years, respectively (31). In the 11 adult groups of our meta-analysis, 13.1% of cases (46/352) who underwent the revascularization procedure experienced rebleeding, whereas 32.4% of cases (82/253) in conservative treatment experienced hemorrhage. In the present 20 adult/pediatric patients' groups, 12.3% (116/940) and 28.2% (185/655) rebleeding occurred in the surgical and no surgical groups, respectively, with follow-up durations ranging from 1 month to >10 years. In Kim et al.'s adult study, the estimated rebleeding rate was 16.9%/person at five years and 26.3%/person at 10 years (36), which was similar to the rate of our adult/pediatric patients' groups with

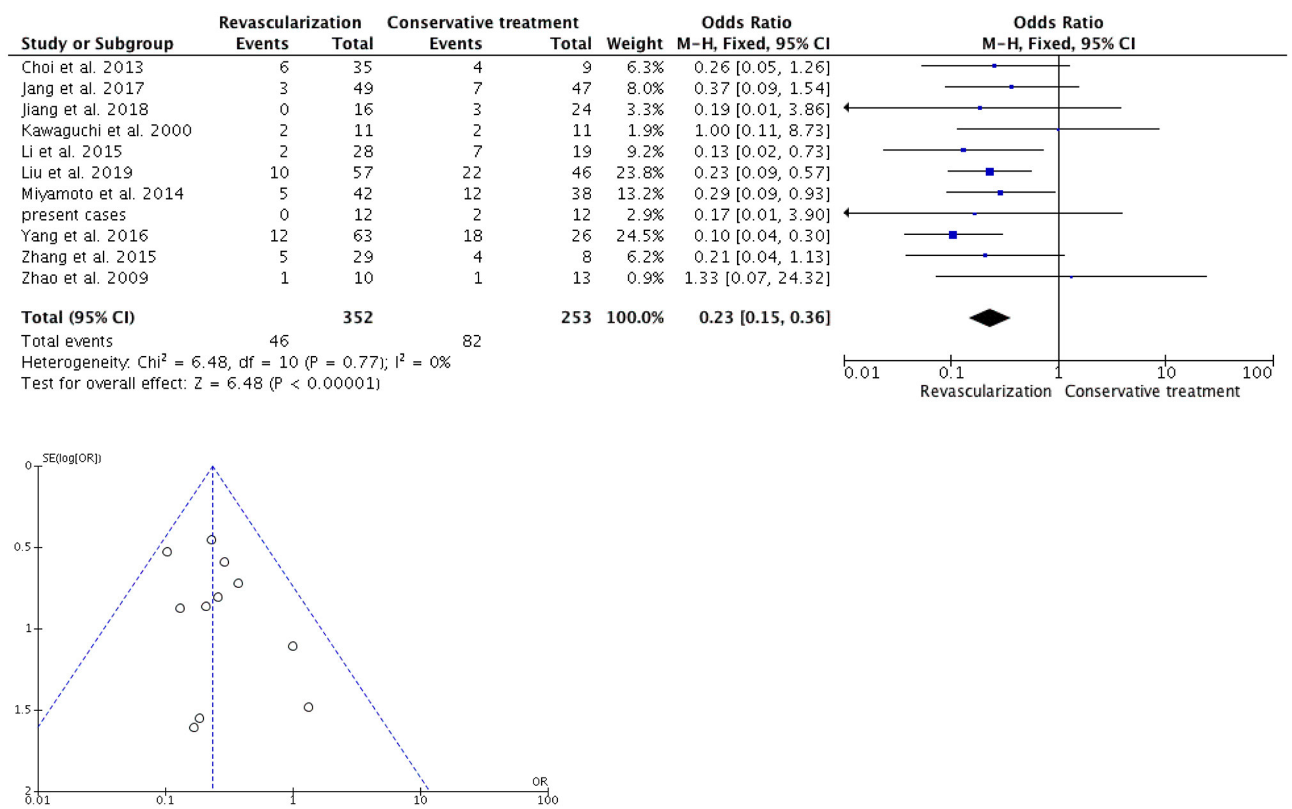

FIGURE 2
In a fixed-model, the forest plot of odd ratios for rebleeding occurred in 11 adult HMMD studies (including our present cases). Patients with revascularization had less rebleeding compared with conservative treatment (OR, 0.23; 95% CI, 0.15–0.36; $P < 0.00001$). Funnel plot for the 11 adult studies included in this meta-analysis. M-H, Mantel-Haenszel; CI, confidence interval.

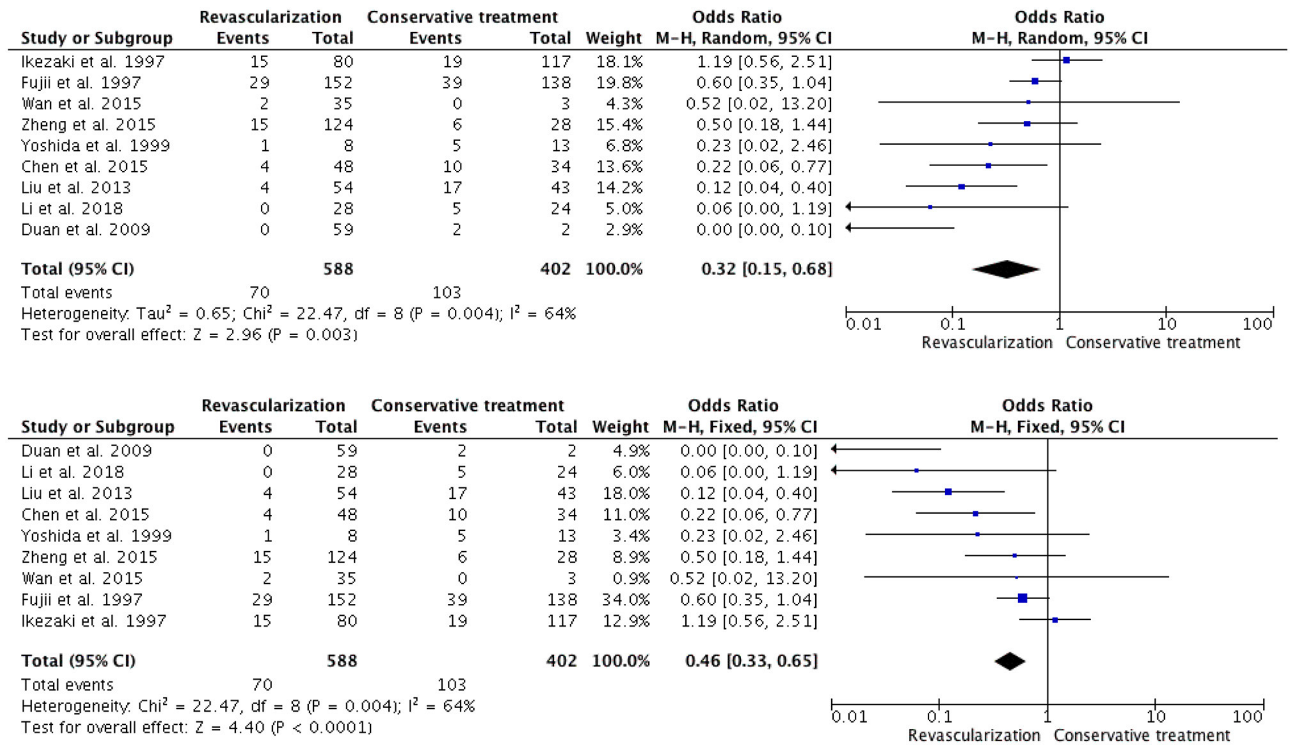

FIGURE 3
In a random and fixed-model, the forest plot of odd ratios for rebleeding occurred in nine adult/pediatric and not specifically mentioned patients HMMD studies. Patients with revascularization had less rebleeding compared with conservative treatment (OR, 0.32; 95% CI, 0.15–0.68; $P = 0.003$, and OR, 0.46; 95% CI, 0.33–0.65; $P < 0.0001$, respectively).

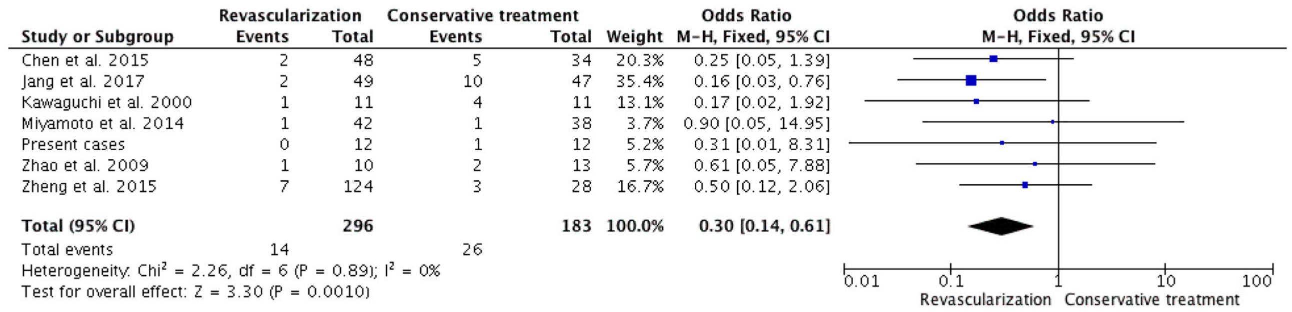

FIGURE 4
In a fixed-model, the forest plot of ORs for ischemic events in 7 adult/pediatric HMMD studies (including our present cases). Patients with revascularization had less ischemic events compared with conservative treatment (OR, 0.30; 95% CI, 0.14–0.61; $P = 0.001$).

conservative treatment. The surgical revascularization in MMD is deemed to reduce persistent hemodynamic stress on fragile collateral vessels or/and accompanying aneurysms, resulting in a significant regression of these fragile vessels. The resumed blood flow and vascular reserve capability improve hemodynamic stabilization. However, there is still no ideal revascularization modality for HMMD, and there is also no optional medicine that can stop or reverse the insidious and progressive disease course. Different kinds of implanted tissues used in indirect bypass surgery were reported: encephalo-myo-synangiosis (EMS), encephalo-myo-arterio-synangiosis (EMAS), encephalo-duro-arterio-synangiosis (EDAS), encephalo-duro-myo-synangiosis (EDMS), encephalo-duro-myo-arterio-synangiosis (EDAMS), and encephalo-duro-arterio-galeo-synangiosis (EDAGS) were performed in studies included in the present review, and the previous studies showed that about 50–80% adult patients improved after indirect bypass procedure (37, 38). Among the reviewed 20 studies, the STA-MCA bypass procedure was performed in 17 studies (85%), and in the 11 studies with adult patients only, the direct bypass surgery was performed in 10 studies (90.9%). The direct bypass results in immediate cerebral hemodynamic improvement, and the direct bypass comprises the main treatment option for the reviewed studies, especially in adult patients. At the same time, an indirect bypass was also used

Study or Subgroup	Revascularization Events	Revascularization Total	Conservative treatment Events	Conservative treatment Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Jang et al. 2017	2	49	10	47	56.1%	0.16 [0.03, 0.76]
Kawaguchi et al. 2000	1	11	4	11	20.8%	0.17 [0.02, 1.92]
Miyamoto et al. 2014	1	42	1	38	5.9%	0.90 [0.05, 14.95]
Present cases	0	12	1	12	8.3%	0.31 [0.01, 8.31]
Zhao et al. 2009	1	10	2	13	9.0%	0.61 [0.05, 7.88]
Total (95% CI)		**124**		**121**	**100.0%**	**0.26 [0.10, 0.70]**
Total events	5		18			

Heterogeneity: Chi^2 = 1.69, df = 4 (P = 0.79); I^2 = 0%
Test for overall effect: Z = 2.68 (P = 0.007)

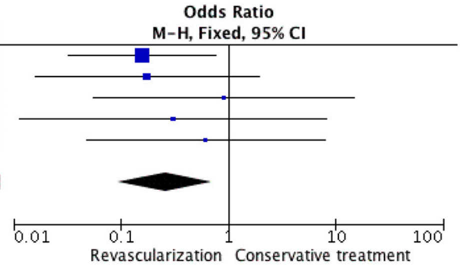

FIGURE 5
In a fixed-model, the forest plot of ORs for ischemic event occurred in five adult HMMD studies (including our present cases). Patients with revascularization had less ischemic events compared with those with conservative treatment (OR, 0.26; 95% CI, 0.10–0.70; *P* = 0.007).

Study or Subgroup	Revascularization Events	Revascularization Total	Conservative treatment Events	Conservative treatment Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chen et al. 2015	2	48	10	34	39.6%	0.10 [0.02, 0.51]
Duan et al. 2009	0	59	2	2	16.7%	0.00 [0.00, 0.10]
Liu et al. 2013	2	54	4	43	15.2%	0.38 [0.07, 2.15]
Wan et al. 2015	1	35	0	3	3.0%	0.30 [0.01, 8.98]
Yoshida et al. 1999	1	8	4	13	9.4%	0.32 [0.03, 3.56]
Zheng et al. 2015	9	124	3	28	16.0%	0.65 [0.16, 2.58]
Total (95% CI)		**328**		**123**	**100.0%**	**0.24 [0.12, 0.50]**
Total events	15		23			

Heterogeneity: Chi^2 = 8.96, df = 5 (P = 0.11); I^2 = 44%
Test for overall effect: Z = 3.84 (P = 0.0001)

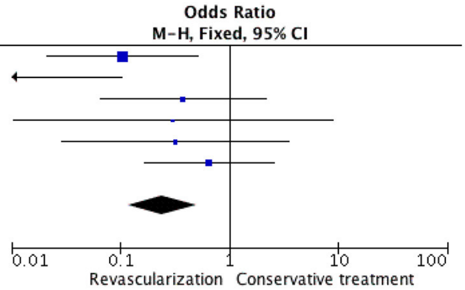

FIGURE 6
In a fixed-model, the forest plot of ORs for mortality occurred in six adult/pediatric patients HMMD studies. Patients with revascularization had less mortality compared with those with conservative treatment (OR, 0.24; 95% CI, 0.12–0.50; *P* = 0.0001).

Study or Subgroup	Revascularization Events	Revascularization Total	Conservative treatment Events	Conservative treatment Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Choi et al. 2013	1	35	1	9	10.2%	0.24 [0.01, 4.18]
Jang et al. 2017	3	49	3	47	19.1%	0.96 [0.18, 4.99]
Li et al. 2015	0	28	4	19	34.7%	0.06 [0.00, 1.20]
present cases	0	12	2	12	15.9%	0.17 [0.01, 3.90]
Zhang et al. 2015	1	29	2	8	20.1%	0.11 [0.01, 1.38]
Total (95% CI)		**153**		**95**	**100.0%**	**0.28 [0.10, 0.75]**
Total events	5		12			

Heterogeneity: Chi^2 = 3.80, df = 4 (P = 0.43); I^2 = 0%
Test for overall effect: Z = 2.51 (P = 0.01)

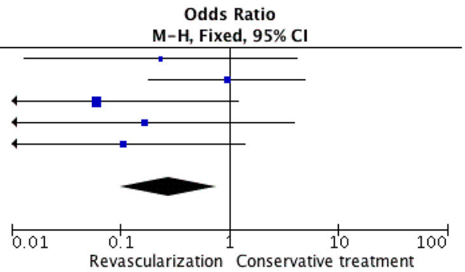

FIGURE 7
In a fixed-model, the forest plot of ORs for mortality occurred in five adult HMMD studies (including our present cases). Patients with revascularization had less mortality compared with those with conservative treatment (OR, 0.28; 95% CI, 0.10–0.75; *P* = 0.01).

as an important supplementary treatment in all 11 adult studies, of which an indirect bypass was chosen as the only treatment option in one study. The indirect bypass was accompanied by direct bypass surgery. This may be because the chronically induced angiogenesis resulting from the indirect bypass procedure will continue to contribute to further hemodynamic improvement after the immediate blood flow augmentation by direct bypass surgery. The indirect bypass is encouraging, with collateral arterial neoangiogenesis, age-dependent cerebrovascular plasticity, and low perioperative risk. Direct bypass is always challenging in pediatric or adult patients with advanced-stage MMD due to the lower bypass patency rates and caliber mismatch between donor and recipient vessels. The direct and indirect bypass procedures are reciprocal and synergistic in improving cerebral hemodynamics.

4.2. Ischemic event

Among the 20 reviewed studies, seven involved mixed adult/pediatric patients with post-surgical ischemic events, among which 14 cases (4.7%) were found to be complicated by postoperative ischemic events in 296 patients who underwent revascularization and 26 cases in 183 patients (14.2%) who received conservative treatment. Patients who underwent revascularization were significantly less likely to result in ischemic events than those with conservative treatment (OR, 0.30; 95% CI, 0.14–0.61; *P* = 0.001). Among the five adult patient-only studies, there were 5 in 124 (4.0%) revascularization patients with ischemic events, 18 in 121 (14.9%) conservatively treated patients, and adult patients who had undergone revascularization had fewer ischemic events compared with those with conservative treatment (OR, 0.26; 95% CI, 0.10–0.70; $P = 0.007$). In the study of Kim et al., 5.7% of patients (4/70, 2 with combined surgery, and 2 with indirect) experienced postoperative infarction, and the other four ischemic strokes occurred in the conservative treatment group, whose postoperative infarction rate was similar to our review (36). Kim et al. (36) also found that the ischemic events in HMMD patients were minor strokes, whereas, in our review, there were two adult patients with complete ischemic stroke and right hemiplegia, respectively (15, 18). The progressive cerebral arterieal occlusive disease and poorly developed collateral vessels always contribute to a postoperative ischemic event (39). The revascularization procedure has been shown to increase cerebral blood flow and improve cerebral vascular reserve, leading to enhanced cerebral hemodynamics and a reduction in cerebral ischemic events. On the contrary, conservative treatment with antiplatelet agents showed no potential benefit in preventing further strokes because of the mismatch between the pathophysiological changes of MMD and the pharmacological mechanism of aspirin.

Of the 20 studies included in our meta-analysis, direct bypasses (STA-MCA) were performed in 17 studies (85%), and indirect bypass was performed in only three studies (15%) (5, 12, 19). Moreover, direct bypass was the more preferable choice in adult patients due to its immediate increase in blood flow to the cerebral hemodynamic deficit area. In the acute stage after indirect bypass, there is a dangerous time window during which swelling of the temporal muscle, brain protrusion from the craniotomy site, and disruption of previous collateral circulation all potentially reduce cerebral blood flow, especially in adult patients, which can result in postoperative ischemic events (40).

4.3. Mortality

The cause of death in HMMD patients is mostly due to intracranial hemorrhage, and the previously reported mortality rate ranged from 6.8 to 28.6% (41–43). In our review, the mortality rate in six mixed adult/pediatric patient studies with revascularization (4.6%, 15/328) was significantly lower than those who received conservative treatment (18.7%, 23/123) (OR, 0.24; 95% CI, 0.12–0.50; $P = 0.0001$), and in the five studies with adult patients only, similar results were obtained (3.3% (5/153) versus 12.6% (12/95), OR, 0.28; 95% CI, 0.10–0.75; $P = 0.01$). The lower mortality rate in the adult studies, as compared with that of the mixed adult/pediatric studies, indicates that the mortality rate may be lower in adults than in pediatric patients. Sang-Hyuk et al. reported that adult HMMD patients had the worst survival outcomes, and the crude mortality for 10 years was 34.7% in hemorrhagic adult South Korean MMA patients (44), which is more than twice the mortality rate of our review. The patients with recurrent hemorrhage had an 11.04-fold risk of death compared to those without it, and the main cause of death in HMMD patients was rebleeding (45). As found in our review, the revascularization procedure significantly prevented rebleeding in HMMD patients, and the mortality rate associated with rebleeding decreased accordingly.

5. Limitations

First, different neurosurgical centers with different patient volumes have varying levels of experience, and the studies included in the review ranged over a long period of time, within which improvements were achieved in the diagnosis and treatment of MMD. Second, there are many kinds of revascularization procedures and different combinations of them in the reviewed studies, such as STA–MCA, EMS, EDAS, EDMS, EMAS, EDAGS, and EDAMS; however, the effect of each revascularization modality alone on the HMMD outcomes has not yet been fully explored or understood. Finally, despite the relatively small sample size of pediatric patients in our review, different cerebral hemodynamic responses to the revascularization procedure between adults and pediatric patients should not be ignored.

6. Conclusion

Direct revascularization, indirect bypass, and a combination of these approaches represent the mainstay treatment of HMMD, and an HMMD prognosis can be improved by surgical revascularization in terms of rebleeding, ischemic events, and mortality in East Asian Countries. Future studies may be necessary to confirm these findings, and the impact of each type of revascularization modality alone on HMMD requires future investigation and clarification.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

X-HZ: conceptualization, manuscript review, and editing. J-HH: writing the initial draft. X-SZ and JZ: application of statistical to analyze study data. C-jW: data collection. Y-PD and WT: visualization/data presentation. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer YW declared a shared affiliation with the authors X-HZ, X-SZ, C-jW, WT, Y-PD, and JZ to the handling editor at the time of review.

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EDITED BY
Long Wang,
Capital Medical University, China

REVIEWED BY
Yinian Zhang,
Southern Medical University, China
Qinghu Meng,
The Second Hospital of Shandong University, China

*CORRESPONDENCE
Xiaoguang Tong
✉ tongxg@gmail.com

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Vascular reconstruction related to the extracranial vertebral artery: the presentation of the concept and the basis for the establishment of the bypass system

Xuan Wang[1,2,3,4,5] and Xiaoguang Tong[1,2,3,4,5]*

[1]Department of Neurosurgery, Tianjin Huanhu Hospital, Tianjin, China, [2]Department of Neurosurgery, Tianjin Central Hospital for Neurosurgery and Neurology, Tianjin, China, [3]Clinical College of Neurology, Neurosurgery and Neurorehabilitation, Tianjin Medical University, Tianjin, China, [4]Laboratory of Microneurosurgery, Tianjin Neurosurgical Institute, Tianjin, China, [5]Tianjin Key Laboratory of Cerebral Vascular and Neural Degenerative Diseases, Tianjin, China

The intracranial vertebrobasilar artery system has a unique hemodynamic pattern (vessel trunk converged bilateral flow with three groups of perforators directly arising from it), is embedded within intense osseous constraints, and is located far from conventional donor vessels. Two major traditional modalities of posterior circulation revascularization encompass the superficial temporal artery to the superior cerebellar artery and the occipital artery to the posteroinferior cerebellar artery anastomosis, which are extracranial-intracranial low-flow bypass with donor arteries belonging to the anterior circulation and mainly supply focal perforators and distal vascular territories. As our understanding of flow hemodynamics has improved, the extracranial vertebral artery-related bypass has further evolved to improve the cerebral revascularization system. In this article, we propose the concept of "vascular reconstruction related to the extracranial vertebral artery" and review the design philosophy of the available innovative modalities in the respective segments. V1 transposition overcomes the issue of high rates of in-stent restenosis and provides a durable complementary alternative to endovascular treatment. V2 bypass serves as an extracranial communication pathway between the anterior and posterior circulation, providing the advantages of high-flow, short interposition grafts, orthograde flow in the vertebrobasilar system, and avoiding complex skull base manipulation. V3 bypass is characterized by profound and simultaneous vascular reconstruction of the posterior circulation, which is achieved by intracranial-intracranial or multiple bypasses in conjunction with skull base techniques. These posterior circulation vessels not only play a pivotal role in the bypass modalities designed for vertebrobasilar lesions but can also be implemented to revascularize the anterior circulation, thereby becoming a systematic methodology.

KEYWORDS
extracranial vertebral artery, cerebral revascularization, posterior circulation bypass, high-flow bypass, vascular reconstruction system

1. Introduction

There is great potential for perfection and continual improvement of the posterior circulation bypass system, which poses obvious contrasts to its anterior circulation counterpart with formulated patterns. The revascularization of the brainstem makes these procedures a formidable challenge since the intracranial vertebrobasilar artery system is confined by intense osseous constraints and is located far from conventional donor vessels. In our opinion, the underlying reason lies in the unique hemodynamic pattern of the posterior circulation, which is distinct from the simple structure of the anterior circulation with a single group of perforators located proximal to the vascular tree. The vessel trunk has converged bilateral flow with three groups of perforators directly arising from it, including the basilar apex, basilar trunk, and vertebral artery (VA) adjacent to the posteroinferior cerebellar artery (PICA). The Ausman team pioneered the use of the superior temporal artery (STA) to bypass either the superior cerebellar artery (SCA) or the posterior cerebral artery (PCA) and the occipital artery (OA) during PICA bypass procedures. They used these arteries to create tunnels that redirected blood flow to the vertebrobasilar territories through recipient transfer, which formed the foundation of the modern posterior circulation bypass system (1, 2). These two classic modalities are extracranial-intracranial low-flow bypass with donor arteries from the anterior circulation and mainly focus on their respective focal perforators. As the understanding of flow hemodynamics, skull base techniques, and cervical anatomy has improved, novel configurations for cerebral reconstruction have emerged, such as short graft medium-flow bypass supplied by the internal maxillary artery (IMA) and the extracranial vertebral artery-related bypass (3), which further revolutionized the cerebral revascularization system. However, their benefits are not yet apparent and require further investigation.

The VA is divided into four segments: the V1–V3 extracranial and the V4 intracranial. The V1 segment originates from the subclavian artery (SubCA) and extends to its point of entry into the transverse foramen of the C6 vertebra; the V2 segment courses within the transverse canal (4, 5), and the V3 segment extends from the C1 transverse foramen to the point at which the VA enters the dura (V3 can also be defined as the tortuous atlantal portion of the VA distal to the C2 transverse foramen) (6, 7). Although the anterolateral cervical approach allows the exposure of the whole length of the extracranial VA through the dissecting space between the sternocleidomastoid muscle (SCM) and the internal jugular vein (IJV) (7), yielding safe and direct visualization of the VA, previous bypass procedures were specifically applied depending on the associated pathologies of the different segments. Therefore, the title of the related chapter in Youmans' neurological surgery was still "*Extracranial vertebral artery diseases*" (4). The development of multiple bypass modalities represents an important conversion of the extracranial VA from an object to a subject of treatment. These posterior circulation vessels not only play a pivotal role in the bypass modality designed for vertebrobasilar lesions but can also be implemented to revascularize the anterior circulation, becoming a systematic methodology comprised of cervical bypass, communicating bypass, extracranial-extracranial bypass, intracranial-intracranial bypass, skull base bypass, and multiple bypasses, which differ from the specific modified procedures such as the OA-SCA and PICA-PICA bypass. Therefore, we propose the concept of "vascular reconstruction related to the extradural vertebral artery" and reviewed the design philosophy of the available innovative modalities in the respective segments (Figures 1, 2).

2. VA/V1 segment bypass

2.1. Revascularization procedures applied for the V1 segment

Proximal VA revascularization is mainly indicated for stenosis or occlusion of the VA orifice (4–8) via VA endarterectomy or transposition (9). Unlike the proximal ICA, the small caliber and deep location of the V1 orifice near the thoracic inlet make exposure challenging (4), and pure VA endarterectomy is seldom used (9). In comparison, transposition of the proximal VA onto the CCA is the most common and safe procedure (Figure 1) (10), and the V1 lacking branch vessels is more feasible to separate and mobilize than the V2 transversary segment for reimplantation into the neighboring vessel (4). Other available options for implantation sites include the SubCA or thyrocervical trunk with or without an interposition graft (4). The surgical field for the V1 region is situated between the anterior scalene muscle and the carotid sheath in close proximity to multiple complex and important structures. Manipulation of this region is associated with severe complications, including Horner's syndrome, chylothorax, and recurrent laryngeal nerve paralysis (4, 10). With the advent of endovascular techniques, balloon angioplasty, and stent implantation have become popular due to their gentle learning curve, minimally invasive nature, and shorter anesthetic duration compared to open surgery (11).

However, several recent studies have revealed the high rates of in-stent restenosis (ISR) of the VA orifice, which led to questions concerning the effectiveness of VA stenting. The possible cause remains unclear and may be associated with the well-developed muscular layer of the VA orifice (11, 12). The SSYLVIA trial revealed that the postoperative (6 months later) ISR rate of the extracranial VA stent accounted for up to 42.9% (6/14) of the cases, of which 66.7% (4/6) occurred at the VA orifice (13). Despite the small number of cases, microsurgical revascularization has recently attracted great attention (9–11). VA transposition appears to be more functional in inhibiting recurrent stenosis than VA endarterectomy (9). Rangel-Castilla et al. reported that the restenosis rate of VA-CCA transposition was 4.5% (1/22) at the average 8.8-month follow-up (10). Berguer and colleagues presented a series that enrolled 230 patients treated by microsurgical revascularization of the proximal VA. The patency rate was more than 90% at 10 years, despite the inherent risks of postoperative complications. Few patients experienced ischemic events (1.9%), and the overall remission rate of complications was 83% (10, 14).

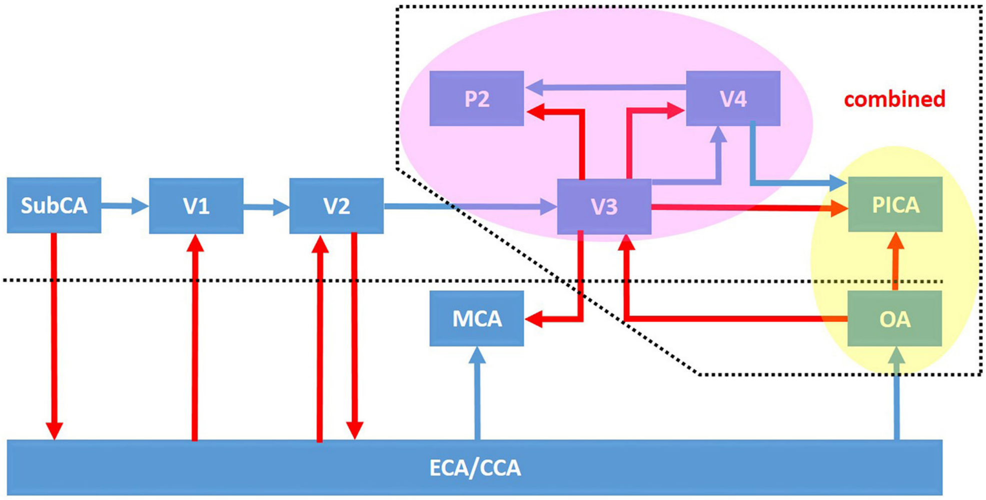

FIGURE 1
Schematic illustration of vascular reconstruction related to the extracranial vertebral artery of the respective segments. The bypass flow (red arrows) and original flow (blue arrows) are indicated in the pictures. The bypass configurations labeled in the pink and yellow areas could be established in combination for the vascular reconstruction of the overall posterior circulation. CCA, common carotid artery; ECA, external carotid artery; MCA, middle cerebral artery; OA, occipital artery; PICA, posterior inferior cerebellar artery; P2, P2 segment of the posterior cerebral artery; SubCA, subclavian artery.

2.2. Surgical approach and protection of the adjacent structures

The standard method for proximal VA exposure is the supraclavicular approach, which focuses on the VA origin in the SubCA. The supraclavicular incision parallels the clavicle, and the clavicular head of the SCM is cut and retracted upward (4, 11). In this study, the vessel was identified medially to the thyrocervical trunk as a landmark with a dissection plane between the CCA medially and the IJV laterally. This route was applied in pure VA endarterectomy to achieve extensive exposure of the SubCA for temporal occlusion of the thyrocervical trunk and internal thoracic artery and to facilitate concomitant subclavian endarterectomy for plaques extended to the SubCA (4, 9). Similarly, carrying out the bypass procedure using interposition grafts from the SubCA or the thyrocervical trunk could also be beneficial for this approach.

However, direct exposure to the supraclavicular approach requires in-depth knowledge of relevant low-lying anatomy unfamiliar to neurosurgeons. George et al. preferred primary exposure of the distal V1 segment at the C6 transverse foramen (the most caudal transverse process could be palpated) and then safely traced proximal to the VA origin through the field between the SCM and the IJV (9, 15). The skin incision extends along the medial border of the inferior part of the medial border of the SCM, which is retracted laterally without division. This approach is an optimal choice for VA-CCA transposition. It shares major steps with the anterolateral cervical approach to the V2 segment coursed in the transverse canal and does not pursue exposure with more inferior extension toward the SubCA (7, 15). The numerous adjacent important structures are mainly contained within the "VA triangle." This relationship creates a practical map to ensure prompt recognition and avoid iatrogenic injury (16). This concept was introduced by Tubbs et al. to describe the muscular bed between the retrojugular fat pad and the VA, where the longus colli and the anterior scalene muscles converge at the C6 transverse process and outline the triangle with the BA as its base. The omohyoid muscle crosses the VA triangle and can be divided for wider exposure (4, 16). The vagus nerve runs beneath the IJV (17) and does not enter the VA triangle; it is usually mobilized along with the IJV, either lateralized to expose the SubCA in the anterolateral cervical approach or medialized for a key step of the supraclavian approach to find the retrojugular fat pad that overlies the VA triangle (16). It is worth noting that vocal cord paralysis may result from excessive retraction since the right recurrent laryngeal nerve exits this nerve and winds around the SubCA (higher up than the nerve loops below the aortic arch on the left side) (4). The supraclavian and anterolateral approaches allow different routes of access through the lower or upper half of the VA triangle, respectively. During the supraclavian procedure, lateral dissection should not proceed beyond the anterior scalene muscle to avoid damage to the brachial plexus located laterally in the scalene space and the phrenic nerve lying on the surface of this muscle.

Similarly, the sympathetic chain does not run strictly along the medial muscular border of the VA triangle; it enters the VA triangle inferiorly to pass through the stellate ganglion and cross the proximal VA. Meticulous care must be taken when dissection from the C6 transverse process follows the longus colli muscle to prevent the occurrence of Horner's syndrome (15, 16). George et al. recommended the use of the aponeurosis of the longus colli muscle rolled around the sympathetic chain for protection (15). In addition to the sympathetic chain, two important structures cross the V1 segment, which is located within the lower portion of the VA triangle. The lymphatic vessel (the thoracic duct on the left side) accompanies the SubCA near the V1 origin. The inferior thyroid artery branches from the thyrocervical trunk and blocks the superior portion of the V1 segment (15, 16). Both of them could be

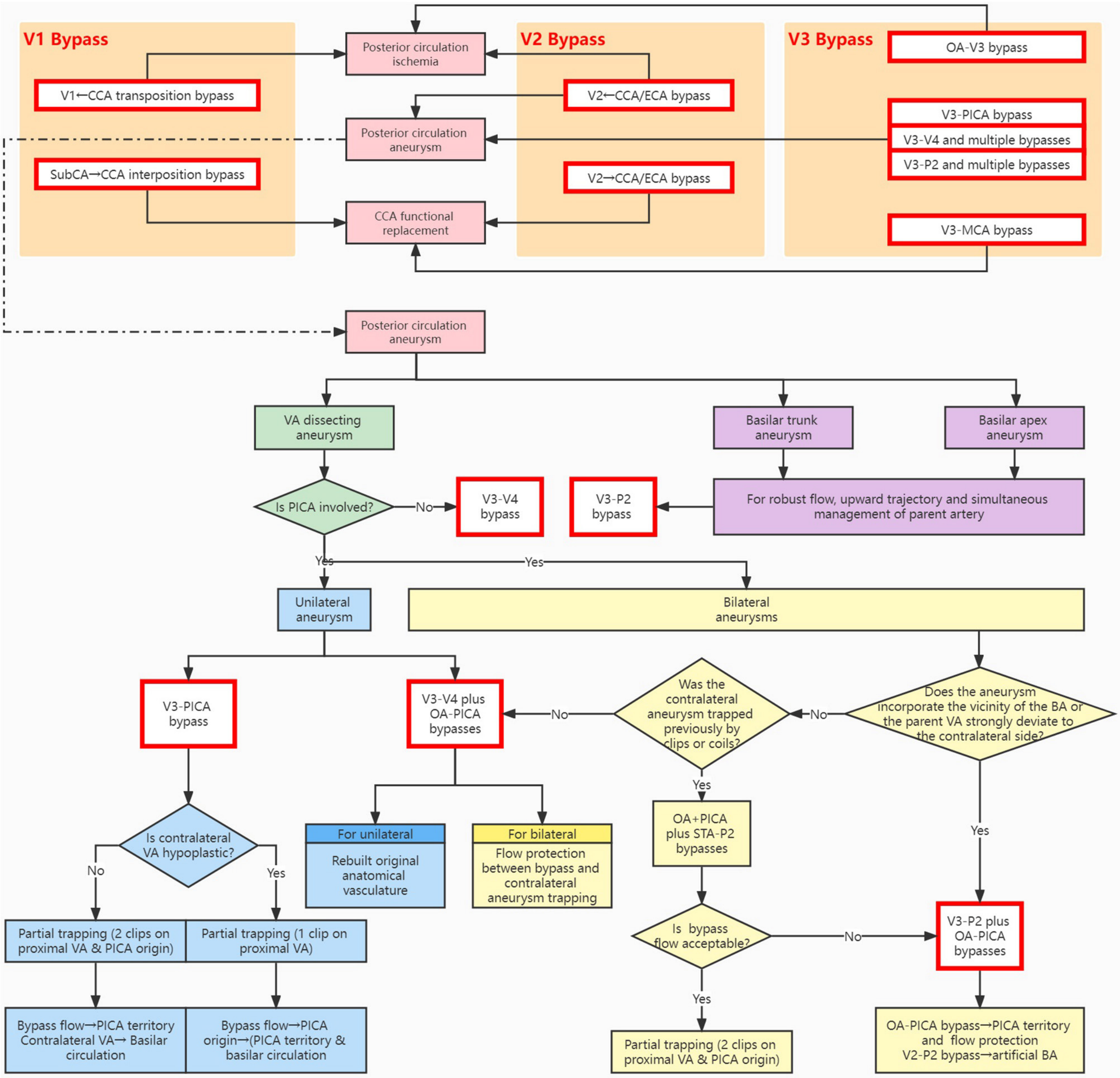

FIGURE 2
Schematic algorithm for bypass strategy of the vascular reconstruction system related to the extracranial vertebral artery. The main indications include posterior circulation ischemia, CCA functional replacement, and posterior circulation aneurysms. The methodological approach illustrates the design philosophy of the available modalities in the respective segments. BA, basilar artery; CCA, common carotid artery; ECA, external carotid artery; MCA, middle cerebral artery; OA, occipital artery; PICA, posterior inferior cerebellar artery; P2, P2 segment of the posterior cerebral artery; STA, superficial temporal artery; SubCA, subclavian artery; VA, vertebral artery; V1/V2/V3/V4, V1/V2/V3/V4 segment of the vertebral artery.

ligated and separated if necessary to avoid injury to the thoracic duct, which could result in chylothorax (9).

2.3. Extended application of the V1 region bypass

The procedure for the exposure of the V1 region involves another valuable application in supplying high flow from the SubCA for the treatment of CCA occlusion ischemia. Symptomatic occlusion of the CCA constitutes 2–4% of all cases of carotid circulation occlusion, and SubCA to carotid bypass is particularly effective for long-segment occlusion (Figures 1, 2) (18). The donor and recipient vessels are exposed through two separate incisions: the supraclavicular and pre-SCM trajectories for the SubCA and the carotid artery, respectively. The recipient site varies from the distal CCA to the proximal ICA, depending on the occlusion level, with the polytetrafluoroethylene (PTFE) conduit (not prone to kinking like the SVG) tunneled behind the IJV and ventral to the vagus nerve and phrenic nerve (18). Due to the appropriate length of the interposition graft, Illuminati et al. also employed this technique for the aggressive en bloc resection of recurrent cervical malignant tumors, and it allowed for the simultaneous replacement of the affected CCA (19). Another revascularization option involved introducing flow from the contralateral carotid artery via the retropharyngeal route; however, the short graft length does not justify this treatment in patients who cannot tolerate temporal occlusion of the remaining patent CCA. Unless the main branches of the aortic arch are unavailable, this alternative is preferred for the CCA occlusion if the surgeon is familiar with the complex anatomy of this region (see below for the V2 bypass P→ A type and V3-MCA modality) (18).

3. VA/V2 segment bypass

3.1. The posterior communicating artery Bypass

The early focus of V2 segment-related treatment for posterior circulation ischemia was limited to the decompression of osteophytic VA stenosis at the transverse foramen (20, 21). In addition, Gerke et al. reported that a V2 traumatic aneurysm occurred with distal stenosis of the parent artery, which was obliterated. The ECA was incised and directly anastomosed to the VA at the C2–C3 level (22). Along with the expansion of the application field, the V2 bypass contributed to the improvement of the posterior circulation bypass system. Since the V2 bypass connected the extracranial VA with the cervical carotid artery, which lies in close proximity, it constructed a pivotal bridge that directly communicates the anterior and posterior circulation and functions as an extracranial PCOM (Figure 1) (23).

3.2. V2 bypass conducting flow from the anterior to the posterior circulation (A→ P type)

This typical approach is primarily indicated for posterior circulation ischemia (Figure 2). Carney and Anderson initiated the V2 bypass in a symptomatic carotid occlusion patient. The parietal and occipital lobe infarcts that occurred due to the internal steal effect for flow were diverted away from the vertebrobasilar to the carotid territories through the PCOM. The large-caliber recipient VA of V2 bypassed for flow augmentation allowed for simultaneous improvement of anterior and posterior circulation perfusion and constituted a viable alternative superior to the STA-MCA bypass (24). Considering the advantages of its high flow capacity and the orthograde direction of vertebrobasilar cannulation, the V2 bypass was straightforwardly used for vertebrobasilar ischemia. The V2 bypass was introduced by Camp et al. and has already become a standard operation (22, 25–27). However, it is essential for the collateral supply from the OA muscular branch or ascending cervical artery to reconstitute a sufficient length of the distal cervical VA (28), which serves as part of the common pathway of this bypass configuration (22, 23, 26, 27).

3.3. V2 bypass conducting flow from the posterior to the anterior circulation (P→ A type)

The bypass flow is seldom oriented in this infrequent direction, and its merit lies in the revascularization of long-segment CCA lesions, but its main impediment is the lack of an appropriate high-flow donor source (Figure 2). This idea originated from the management of Takayasu's arteritis with a bypass procedure. Ziyal et al. selected the V3 segment to substitute the aortic arch as a donor, forming a key part of the overall replacement of the aortic arch and its major branches (29). Li et al. were the first to switch this novel donor site to V2 for CCA occlusion caused by Marfan syndrome to avoid the "jump bypass" between the remotely situated recipient vessel and V3 in far-lateral exposure (30), as well as its potential damage to the collateral branches from SubCA or OA, which retrogradely reperfuses the carotid artery. For the remaining available options for CCA revascularization, the "Bonnet" bypass utilized the contralateral STA or ECA as the donor source and required an interposed graft crossing the dome of the calvarium to the MCA, significantly increasing the length of the graft and posing the risk of mechanical damage (31). The V3 bypass is more applicable for directly supplying the intracranial territories when the cervical carotid luminal is infeasible as a flow pathway (see below for the V3-MCA modality).

3.4. Hybrid operation

In addition to the role of the flow modulation pathway, the V2 bypass establishes a physical trans-circulation route for endovascular therapy (Figure 2). Chwajol et al. adopted this extracranial "PCOM" for endovascular access to reach intracranial complex posterior circulation aneurysms when tortuous or proximal occluded VA prevented routine catheterization, and the true PCOM was often hypoplastic to deliver the endovascular materials in the meantime. It is a valuable method to overcome the difficulty of releasing multiple loops of kinks in which transverse foramen unroofing or reroute techniques fail to restore endovascular access. Additionally, direct surgical exposure of the cervical VA to circumvent the prohibitive vessel anatomy for endovascular catheterization requires only a single operation, whereas the V2 bypass is convenient for potential subsequent endovascular treatments (32).

4. VA/V3 segment bypass

4.1. Overview and exposure of the V3 and OA

The general trend of the V1 bypass to the V3 bypass is that the role played by the extracranial VA is shifted from the recipient to the donor. A situation in which the V1 segment received blood flow and was transformed to V2 bypass served as a communication pathway, and V3 appeared to be a notable source due to its robustness and tolerance to temporary occlusion (with contralateral VA still supplying the basilar territory) (Figure 1)

(33). Although V3 is located deep within the suboccipital triangle, it can be accessed from the intracranial surgical field of diverse recipient arteries without a second remote site and is considered a representative donor of IC-IC as well as IMA (33). The characteristic application for V3 bypass is profound and requires simultaneous vascular reconstruction of the entire posterior circulation (every component, including the PCA/SCA, BA, VA, PICA, etc.) in conjunction with advancing skull base techniques. Localizing the VA and minimizing the blood loss of the accompanying veins are the key points for exposing the V3. Tayebi Meybodi et al. (34) proposed the atlanto-mastoid line (which runs between the mastoid tip and C1 posterior tubercle) or the belly of the superior oblique capitis muscle to guide the exposure of V3. Wanibuchi et al. (35) presented a systematic method using bony landmarks to identify the "J-groove" on the posterior arch of C1, which cradles the VA. When the extracranial VA between the C1 and C2 vertebrae is used to replace V3 in the reconstructive procedure, the subatlantic triangle (formed by the levator scapulae muscle and the splenius cervicis muscle inferiorly and laterally, the longissimus capitis muscle inferiorly and medially, and the inferior oblique capitis superiorly), which is located inferolateral to the suboccipital triangle, offers a direct gateway to expose this vessel (36). Arnautović et al. named the surrounding venous compartment (not the venous plexus) of V3 the "suboccipital cavernous sinus" due to its analogy to the cavernous sinus that cushions the ICA (37). This venous compartment is covered by the posterior atlantooccipital membrane and is separated from the overlying deep suboccipital muscle. Youssef et al. (38) applied the interfascial dissection technique to dissect the natural tissue plane between the membrane and the muscle fascia in a blunt fashion to achieve bloodless exposure of the V3.

The OA is another major donor for posterior circulation and is particularly important in V3 bypass, which could be modified or combined with the traditional OA-PICA bypass. The Japanese authors advocate multiple-layer dissection of the suboccipital muscles to accomplish a far-lateral approach for harvesting the OA, which is ∼15 cm in length (prior to OA harvest, the SCM has been reflected anteriorly, the splenius capitis muscle posteroinferior, the longissimus capitis muscle inferiorly, then the semispinalis capitis muscle is reflected posteriorly, the superior oblique capitis muscle anteriorly, the rectus capitis posteriorly, and the major muscle posteriorly). This procedure helps with the exposure of V3 in the suboccipital triangle and the creation of a shallower surgical field (39, 40). Fukuda et al. (40) proposed that understanding the concept of "the transitional segment of the OA" is crucial for simplifying the harvesting procedure. The transitional segment extends from the superior edge of the splenius capitis muscle to the superior nuchal line, located where the OA pierces two anatomical planes (the tendon of the SCM and the galea aponeurotica) vertically. The corresponding reverse-C skin incision [both ends on the middle lines located on the external occipital protuberance and the spinous of C2, the apex on the mastoid process, a variant of Rhoton's inverted horseshoe incision (with a longer lateral limb) (41)] is beneficial to first expose the SCM (the lateral edge) and the splenius capitis muscle (the superior border) as landmarks to isolate the transitional segment, followed by dissecting the intramuscular segment proximally and subcutaneous segment distally within the single tissue layer (the styloid diaphragm and the epigaleal layer, respectively) (40).

4.2. OA-V3 modality

This bypass (Figures 1, 2) was initiated by the Spetzler team in a case of traumatic pseudoaneurysm of the cervical VA for flow replacement after aneurysm trapping (20, 42). Wang et al. first developed this bypass modality as a novel treatment option for bilateral vertebral steno-occlusive disease (28). OA-V3 bypass offers several major advantages over conventional OA-PICA bypass, including making the surgical field shallower and wider to avoid deep anastomosis, sparing patients invasive craniotomy and intracranial manipulation, decreasing the operative time and anesthetic duration, and broadening the application scope of posterior circulation bypass for ischemia (28). The potential limitations of the OA-V3 bypass are a caliber discrepancy between the donor and recipient vessels, rigorous criteria restrictions for selecting patients with hemodynamic compromise, and the various anastomotic techniques (e.g., double barrel bypass) employed to ensure the patency of the bypass and that lead to orthograde filling of the upper posterior circulation (28). The V2 bypass might seem attractive to surgeons who are not familiar with the dissection of the suboccipital musculature. However, this alternative bypass strategy requires an interposition graft and two anastomoses and is more suitable for VA occlusion that does not extensively involve the V2.

4.3. V3-PICA modality

This strategy is another alternative for OA-PICA bypass rather than the OA-V3 modality (Figures 1, 2), which was developed for the treatment of VA dissecting aneurysms encompassing the PICA origin with the evolution of the donor's vessel from V4 to V3. Durward initially implanted the PICA origin proximal to the vessel dissection to maintain its normal blood flow after aneurysm trapping (43). This bypass option eliminates the tedious dissection required to harvest the OA and the potential risk of hypoperfusion due to the diminutive caliber of the OA, providing an excellent substitute for OA-PICA (43, 44). However, this procedure is technically sophisticated, and the perforators of the medulla oblongata that arise from the proximal PICA may be damaged. Very few cases have enough PICA redundancy to allow for tension-free anastomosis; thus, Hamada et al. employed the STA as an interposition graft to accomplish PICA reimplantation (45). Benes et al. optimized the deep surgical space by using transcondylar and transjugular tubercle approaches, helping to simplify the direct anastomosis between the V4 and PICA without starting with the graft (46).

It should not be ignored that we cannot ensure that the reimplantation site on V4 completely avoids the pathological vessel wall. Hence, Czabanka et al. altered the proximal donor source to V3 with a radial artery graft to match the flow demand of the PICA (44). Similar to PICA reimplantation, the V3-PICA bypass revascularizes the PICA territory, while the basilar circulation is supplied by the contralateral VA (44, 47). Beyond this routine indication, in situations where the contralateral VA is hypoplastic, proximal inflow occlusion of the parent artery is performed without placing the clamp on the PICA origin, which produces a retrograde flow of the V3-PICA bypass to supply the entire basilar territory. When a conventional OA-PICA bypass is confirmed to be occluded intraoperatively, the OA could be transected proximally and mobilized to the V3 segment; here, the V3-PICA bypass was used to re-establish antegrade perfusion as a salvage maneuver (44).

4.4. V3–V4 modality and related multiple bypasses

This bypass was originally designed for local lesions as well as the OA-V3 bypass. In a case of a giant partial thrombosed VA aneurysm distal to the PICA origin where clip reconstruction failed, Evans et al. employed an SVG insert between the extracranial and intracranial VAs following aneurysm excision via a transsigmoid approach (48), similar to the creation of an interposition graft to bridge the gap in the parent artery for MCA aneurysms. Shi et al. even resected and replaced bilateral VA aneurysms located proximal to the PICA with RA grafts (49). This replacement strategy also highlights its importance in the treatment of complex skull base tumors with extensive involvement, with no requirement for deciding between radical resection of the tumor and preservation of the encased or invaded VA (50, 51). Once the VA lesion affects the PICA, the V3–V4 bypass could be advanced by integrating the OA-PICA bypass to reconstruct the entire posterior circulation (Figures 1, 2).

In retrospect, the prototype of these multiple bypasses originated from a failed endovascular angioplasty case of symptomatic stenosis at the entry segment of the VA. The surgical procedure was altered to a V3–V4 replacement bypass. To protect the PICA and BA territories during temporal occlusion due to contralateral VA occlusion, the OA was anastomosed to the contralateral PICA, which was dominant and perfused from the operative side VA (52). The characteristic configuration of multiple bypasses was established to address bilateral VA fusiform aneurysms and reconstruct the intracranial VA and ipsilateral PICA prior to aneurysm trapping. Moreover, the prolonged period of temporary flow arrest required for multiple anastomoses was compensated for with the contralateral VA, and the opposite aneurysm could be obliterated by the endovascular occlusion of the parent artery in the second stage, with the bypass flow serving as collateral circulation in turn (53) (Figure 2). Although less complicated, the V3-PICA bypass is unsuitable in cases without a favorable contralateral VA (44). Instead, V3–V4 coupled with OA-PICA bypass can restore the original anatomical vasculature and can even be used for unilateral VA aneurysms by experienced surgeons (54, 55). If the OA-PICA bypass is occluded intraoperatively because of thromboembolism, the reimplantation of the proximal OA to the interposition graft of the V3–V4 bypass can be employed for rescue adjustment (55). For large perforators emanating from the aneurysm dome, it is possible to perform OA-perforator bypass to maintain the flow to the brainstem-perforator vessels, similar to the PICA territory during VA reconstruction. However, the indications for perforator bypass are yet undefined (56).

4.5. V3-P2 modality and related multiple bypasses

The V3-P2 bypass takes advantage of the upward trajectory of the posterior petrosal approach. The ideal perpendicular course allows P2 to be directly approached without excessive retraction of the temporal lobe (57), and a similar principle is applicable for retrochiasmatic craniopharyngiomas (58), which is especially suitable for giant basilar apex aneurysms (59) and provides excellent access to high-positioned basilar quadrification that is distorted by dolichoectatic basilar trunk aneurysms (60). The reliable collateral flow established by the bypass ensures terminal BA occlusion to eliminate the flow jet effect. This flow diversion converts the basilar apex aneurysm into a "sidewall" aneurysm, facilitating aneurysm involution (59). The successful treatment of basilar trunk fusiform aneurysms (including the dolichoectatic type) lies in robust retrograde flow to alleviate the development of vascular dissection and intramural thrombus deposition (60, 61). The flow capacity of the V3-P2 bypass meets the above requirements and ensures adequate perfusion of the brainstem perforators of the basilar trunk (Figure 2).

Horie et al. (62) reported a patient with a basilar trunk giant thrombosed fusiform aneurysm who underwent STA-P2 bypass first but resorted to V3-P2 bypass when BTO failure indicated insufficient collateral reserve of the conventional donor. Although this bypass is amenable to simultaneous management of the lower BA and ipsilateral VA, such as parent artery occlusion or trapping, expertise in skull base surgery is required. Mai et al. integrated the surgical fields of the posterior transpetrosal and far lateral approaches to accommodate the interposition graft, but the sophisticated operation may be applied as a 2-day procedure (59). The bone work may be simplified to a combination of subtemporal and far-lateral craniotomies, albeit at the expense of a redundant graft length, which spans between the supratentorial and infratentorial exposure areas for the graft vessel and needs to detour around the mastoid bone (60).

V3-P2-related multiple bypasses were originally introduced as a viable alternative to their V3–V4 counterparts for bilateral VA dissecting aneurysms (Figure 2). When the sacrifice of the unilateral VA has the risk of opposite aneurysm enlargement, owing to hemodynamic stress, the V3–V4 bypass cannot depend on the contralateral parent artery to provide collateral flow during the occlusion time. For this purpose, Saito et al. adopted the STA-SCA plus OA-PICA bypass (via a combined petrosal approach) to revascularize the upper and lower halves of the posterior circulation, respectively, with the V3-P2 bypass planned as a standby, which was finally avoided due to the neurophysiological parameters and perfusion pressure indicating an acceptable bypass flow (63). In addition, if the aneurysms incorporate the vicinity of the BA or the parent VA strongly deviates to the contralateral side, the recipient site of the V4 segment is not feasible for V3–V4 bypass; thus, V3-P2-related multiple bypasses could be prepared.

This reconstruction configuration is so technically challenging among the V3 bypass options that only Ota et al. reported one case accomplished through a transcondylar fossa approach along with presigmoid exposure, where the OA-PICA bypass revascularized the affected PICA and worked in collaboration with the STA-SCA bypass to protect flow during the anastomosis. The high-flow V3-P2 bypass rebuilt an artificial BA morphologically, and the distal anastomosis between the graft and P2 was dispensed with temporary occlusion of the ipsilateral VA and achieved a shorter duration of potential ischemia, despite the filling pattern of the posterior circulation shifting to flow reversal (64). Kubota et al. proposed that the ECA be connected to V4 (or the lower BA) when the V3 segment was not available as the donor site; here, the STA-SCA coupled with the OA-AICA maintained collateral flow as well (55).

4.6. V3-MCA modality

The V3 segment also allows revascularization of the anterior circulation other than the vertebrobasilar system, which is especially suitable for CCA occlusion and presents a challenge due to the absence of conventional donor vessels such as the STA (Figure 2). Schneider et al. (65) established an anastomotic connection between the V3 and M2 segments of the MCA to restore the flow of the anterior circulation compromised by CCA occlusion, albeit without the intrinsic properties of authentic "PCOM" bypass, such as a short graft and bidirectional flow modulation. This bypass curtailed the graft length to an acceptable limit compared to the "bonnet bypass" and provided more robust blood flow than the contralateral donor STA. For both feasible options, utilizing the SubCA to reconstruct the CCA (18) or employing V2 cervical PCOM bypass (30), only selected cases met the demands that the residual lumen of the ICA be reconstituted as a recipient conduit. In contrast, the V3 segment is likely to be widely used due to its direct filling of the objective MCA territory (65) and its considerable high flow (peak flows of more than 70 ml/min, with average flows in the range of 25 ml/min) for effective flow replacement (66).

Miele et al. reported a patient with a giant supraclinoid ICA aneurysm who had undergone previous Hunterian ligation of the CCA. The initial STA-MCA bypass (ECA and ICA partially compensated by the OA muscular branch) failed to improve the perfusion. The coiled aneurysm was recanalized due to the continuous supply of the PCOM. Under the security of the second V3-MCA high-flow bypass, an endovascular sacrifice of the feeding PCOM was tolerated to achieve complete aneurysm obliteration, which is not appropriate for V2 bypass because of recipient pathway occlusion by aneurysm trapping (66). This bypass configuration has multiple applications to address cervical tumors. A replacement procedure is indicated when the malignant tumor infiltrates the carotid artery during radical tumor resection or is occluded by local radiation therapy, both of which frequently occur (33). Specifically, in a case with an infected salivary fistula followed by wide neck dissection, V3-MCA bypass helps reroute the interposition graft to circumvent the infected surgical field and avoid graft complications (67).

Author contributions

XW and XT: conception and design. XW: drafting of the article. XT: critical revision of the article and study supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Long Wang,
Capital Medical University, China

REVIEWED BY
Bin Yang,
Capital Medical University, China
Miki Fujimura,
Hokkaido University, Japan
Yabo Huang,
The First Affiliated Hospital of Soochow University, China

*CORRESPONDENCE
Jianjian Zhang
✉ zj57470@126.com
Jincao Chen
✉ yokinns@163.com

†These authors have contributed equally to this work and share first authorship

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Analyzing characteristics of collateral flow to parasylvian cortical arteries by three-dimensional digital subtraction angiography–magnetic resonance angiography fusion imaging in adult moyamoya disease

Jin Yu†, Miao Hu†, Jianjian Zhang* and Jincao Chen*

Department of Neurosurgery, Zhongnan Hospital of Wuhan University, Wuhan, China

Objective: The hemodynamic sources of recipient parasylvian cortical arteries (PSCAs) were significantly related to postoperative cerebral hyperperfusion (CHP) after bypass surgery in patients with moyamoya disease (MMD). The present study aimed to introduce a new method to investigate the characteristics of PSCAs hemodynamic sources and their relationships with clinical presentations in adult MMD and to provide preoperative evaluation for recipient vessel selection in MMD bypass surgery.

Methods: The hemodynamic sources of the PSCAs in 171 symptomatic MMD hemispheres were analyzed by three-dimensional digital subtraction angiography (3D-DSA) combined with magnetic resonance angiography (MRA) fusion imaging. The spatial and temporal characteristics of the hemodynamic sources of the PSCAs and their associations with the patient's demographics, Suzuki stage, and initial onset type were investigated.

Results: Six major types of hemodynamic sources in the PSCAs were observed. There was a significant difference between the hemodynamic sources of the PSCAs above and below the SF ($P < 0.001$). With advancing Suzuki stages, collateral flow to the PSCAs above the SF from the internal carotid arteries (ICAs) significantly decreased, while the non-ICAs increased ($P < 0.001$). Multivariate analysis revealed that hemodynamic sources of the PSCAs above the SF were significantly associated with patients' initial onset type ($P = 0.026$).

Conclusion: In MMD hemispheres, the hemodynamic sources of the PSCAs above the SF are more varied than those below the SF and present a typical conversion trend from ICAs to non-ICAs with advancing Suzuki stages. Analyzing the hemodynamic sources of the PSCAs can help in understanding the conversion pattern of compensatory vascular systems, predicting episodes in MMD, and preoperatively evaluating suitable recipient vessel selection for bypass surgery to avoid postoperative CHP.

KEYWORDS

moyamoya disease, cerebral blood flow, hemodynamics, anterior cortical circulation, bypass surgery

Introduction

During the development of moyamoya disease (MMD), numerous compensatory vascular systems are established to fight against reduced intracranial blood flow caused by chronic stenosis-occlusion at the end of the internal carotid artery (ICA) (1, 2), such as neovascularization (known as "moyamoya vessels") at the base of the brain, transdural and extracranial-intracranial collateral formation, dilation of peripheral cerebral arteries, and the development of leptomeningeal collaterals (3, 4). Besides, the conversion of the hemodynamic sources (namely, "the source of blood flow") in the parasylvian cortical arteries (PSCAs) is also an important compensatory mechanism. PSCAs mean cortical arteries around the Sylvian fissure (SF), which not only represented the cortical vessels of anterior circulation but also were commonly selected as recipient arteries in anterior revascularization. With the development of MMD, the blood flow in PSCAs from the severe stenotic middle cerebral artery (MCA) becomes less and less. Instead, the blood flow from non-MCAs [posterior cerebral artery (PCA) or anterior cerebral artery (ACA)] starts to supply PSCAs through collateral vessels to compensate for the insufficient intracranial perfusion. Indeed, in our previous study (5), we found that only 60% (45/75) of the selected PSCAs came from MCA, rather than 100% according to the current concept. Furthermore, direct anastomoses of PSCAs with anterograde hemodynamic sources from the MCA had a high risk of postoperative CHP during STA-MCA bypass in adult patients with MMD. Thus, an accurate evaluation of the collateral flow to PSCAs will help us to better understand the spatiotemporal transformation of intracranial compensation networks in MMD as well as the selection of recipient vessels in bypass surgery.

Direct evaluation of collaterals in MMD can be archived through limited angiographic methods, including computed tomographic angiography (CTA), magnetic resonance angiography (MRA), and digital subtraction angiography (DSA). However, each of these diagnostic modalities provides specific strengths as well as limitations. DSA is considered the gold standard, but objective evaluation of collaterals is rarely performed. Collateral assessment with MRA is generally limited to proximal arterial segments at the circle of Willis. MRA velocity encoding during acquisition allows for flow-sensitive images but is constrained by anatomic resolution and is therefore only useful in proximal segments as well (6). Consequently, although cortical collaterals are essential in restoring the decreased cerebral blood flow of patients with MMD, the exact associations, connections, and territory of the arterial branches that participate in the cortical vascular network have not been objectively analyzed.

In this study, we developed a new way to analyze hemodynamic sources of PSCAs by using three-dimensional (3D) DSA and MRA fusion imaging. Through this method, we further elucidated the characteristics of blood flow sources of PSCAs in adult symptomatic MMD hemispheres in relation to the patients' demographics, Suzuki stage, and initial onset type of the hemisphere.

Methods

Patients

We retrospectively collected and analyzed the data of a series of adult MMD patients admitted to the hospital between March 2019 and December 2020. Regardless of whether the diagnosis was unilateral or bilateral MMD, only the symptomatic hemispheres were included in this study. A symptomatic MMD hemisphere was defined as (1) a hemisphere with a positive history of recurrent transient ischemic attack, infarction, or hemorrhage or (2) a patient with persisting neurological symptoms, such as hemiparesis, sensory deficits, or aphasia (7, 8). Clinical characteristics of the patients were recorded, including age, sex, Suzuki stage, and initial onset type (ischemic or hemorrhagic). Each patient underwent a classical DSA with 3D videos and at least a one-time MRI scan. All patients satisfied the diagnostic criteria of spontaneous occlusion of the circle of Willis as identified by the Research Committee of the Ministry of Health, Labor, and Welfare, Japan (1, 2). This study protocol was approved by the Institutional Review Board at our hospital (Kelun-2017005) and was in accordance with the Declaration of Helsinki (revised in 1983). Written informed consent was obtained from all participants.

3D DSA-MR fusion imaging

DSA

3D DSA and 2D DSA imaging were conducted on all patients using a biplane digital angiography device (Allura Xper FD20, Philips Medical Systems, Best, The Netherlands) and a trained neuroradiologist and neurosurgeon. The 2D images of bilateral ICA, external carotid artery (ECA), common carotid artery (CCA), and vertebral artery (VA) injections were routinely obtained. 3D rotational angiography was only performed after bilateral ICA injections and one VA injection. To reconstruct the 3D DSA images, mask images were also obtained. The filling run volume was reconstructed and analyzed by using a dedicated commercially available workstation (Philips Medical Systems, Best, The Netherlands).

MRI and MRA

Each subject underwent a high-resolution time-of-flight (TOF) MRA scan using an uMR 3.0T MRI scanner (United Imaging, Shanghai, China). The TOF-MRA scanning parameters used in this study were as follows: five slabs with 20% overlap, 30 slices per slab, repetition time = 18 ms, echo time = 3.3 ms, field of view = 22 × 22 cm^2, flip angle = 16°, slice thickness = 0.5 mm, matrix = 512 × 512, and effective voxel = 0.39 × 0.39 × 0.5 mm^3. The acquisition time was about 3 min and 58 s. The other imaging sequences included three-plane scout localizers, axial 2D T2-weighted fast spin echo sequence (TR/TE = 5,385/95 ms; slice thickness = 5 mm), axial 2D T2-weighted fast spin echo sequence with fluid-attenuated inversion recovery (TR/TE = 8,000/105 ms and slice thickness = 5 mm), and 3D

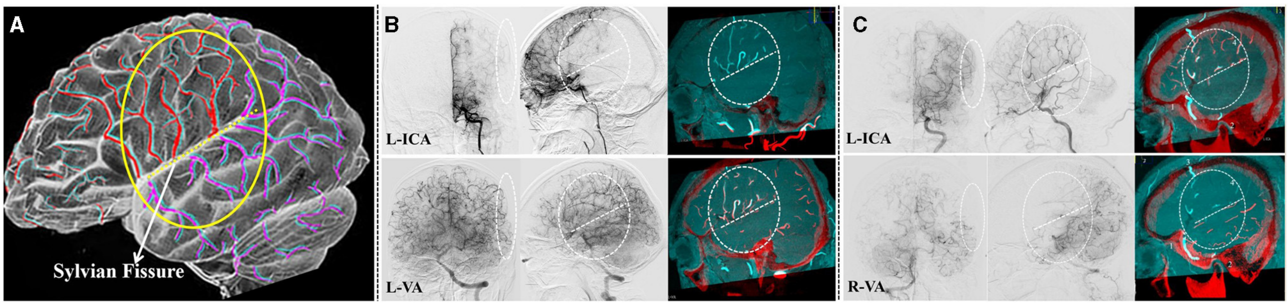

FIGURE 1
Analyzing the hemodynamic sources of the PSCAs by 3D DSA-MR fusion imaging. **(A)** The diagram of 3D DSA-MR fusion imaging used for analyzing the characteristics of collateral flow to the PSCAs. Red and purple indicate the blood on the 3D DSA images, and cyan represents the blood on the MRA images. **(B)** In this symptomatic hemisphere, all the parasylvian cortical arteries (PSCAs, in the white dashed circles and ovals) had their blood flow completely from the left posterior cerebral artery (PCA). No blood flow from the internal carotid arteries (ICAs) to the PSCAs could be found. **(C)** In this symptomatic hemisphere, the blood flow of the PSCAs below the SF clearly came from the left PCA, while that above the SF originated from the left middle cerebral artery (MCA) because the anterior cerebral artery (ACA) was occluded. From the lateral 3D DSA-MR fusion images, the collateral flow sources of the PSCAs were obviously differentiated by the Sylvian fissure (SF, white dashed line).

T1 weighted fast gradient echo sequence (TR/TE = 7.2/3.1 ms, FA = 10°, resolution = 1 mm isotropic, and acquisition matrix = 240 × 256 × 256). The FOV was 22 × 20 cm^2 on all other imaging sequences. All information regarding the images was sent to the Picture Archiving and Communication Systems (PACS, Carestream Healthcare, Rochester, NY, United States) system in the hospital.

3D DSA-MRA fusion

The obtained MRA images were imported into the DSA workstation from the PACS system. The DSA images were co-registered with the MRA images using commercially available image fusion software on the interventional tool post-processing workstation of the Philips DSA machine (Allura Xper FD20, Philips Medical Systems, Best, Netherlands). Both the MRA and DSA images were presented in different colors and displayed using volume rendering techniques (VRTs). The two 3D image volumes were overlapped to achieve fusion precision (Figure 1). The 3D DSA-MRA fusion images (axial, coronal, and sagittal views) were prepared for subsequent hemodynamic source analysis.

Procedures for analyzing the hemodynamic sources of the PSCAs

Since PSCAs above or below SF could have different hemodynamic sources, for each patient, we analyzed the hemodynamic sources of PSCAs above/below SF separately.

By using 3D DSA-MRA fusion imaging, "the hemodynamic sources of the PSCAs" (which means the source of blood flow in PSCAs) were first identified as the ICAs or non-ICAs by two senior neurosurgeons. In the present study, ICAs were defined as a combination of MCA and anterior cerebral artery (ACA), and non-ICAs included contralateral ACA (CLA), posterior cerebral artery (PCA), and external carotid artery (ECA).

When dealing with PSCAs with ICAs hemodynamic sources (whether from MCA or ACA), a built-in automatic feeding artery detection (AFD) software (Emboguide, Philips Healthcare, Best, The Netherlands) within the digital angiography unit was used (Figure 2). The AFD software procedure involved the following two simple steps: (1) manual selection of a PSCA and (2) AFD analysis, which was automatically conducted after the start position of the vessel tracking was placed on the ICA. Then, the PSCAs with ICA hemodynamic sources can be further divided into "MCA hemodynamic source" and "ACA hemodynamic source".

The PSCAs with MCA hemodynamic source can be further divided into (1) type I: anterograde blood flow that came from the ICA via the stenotic MCA or (2) type II: anterograde blood flow that came from the ICA via "moyamoya vessels" with a lack of successful compensatory collateralization.

Thus, through our procedure, the hemodynamic sources of the PSCAs could be divided into six kinds: type I MCA, type II MCA, ACA, CLA, PCA, and ECA (Figure 3).

Statistical analysis

A one-way ANOVA test was performed to check if there were any statistical differences in age and Suzuki stage between the groups. Categorical variables, such as sex and initial onset type, were analyzed in contingency tables with a chi-squared test. A multivariate statistical analysis of the factors related to the initial onset type was performed using a logistic regression model. All analyses were performed with IBM SPSS Statistics Desktop, version 24 (IBM Corp.). The results with values of P of <0.05 were considered statistically significant.

Results

Patient demographics and hemodynamic sources of the PSCAs

A total of 171 symptomatic hemispheres from 171 consecutive adult patients (patient age range: 18–77 years; mean: 47.51 years)

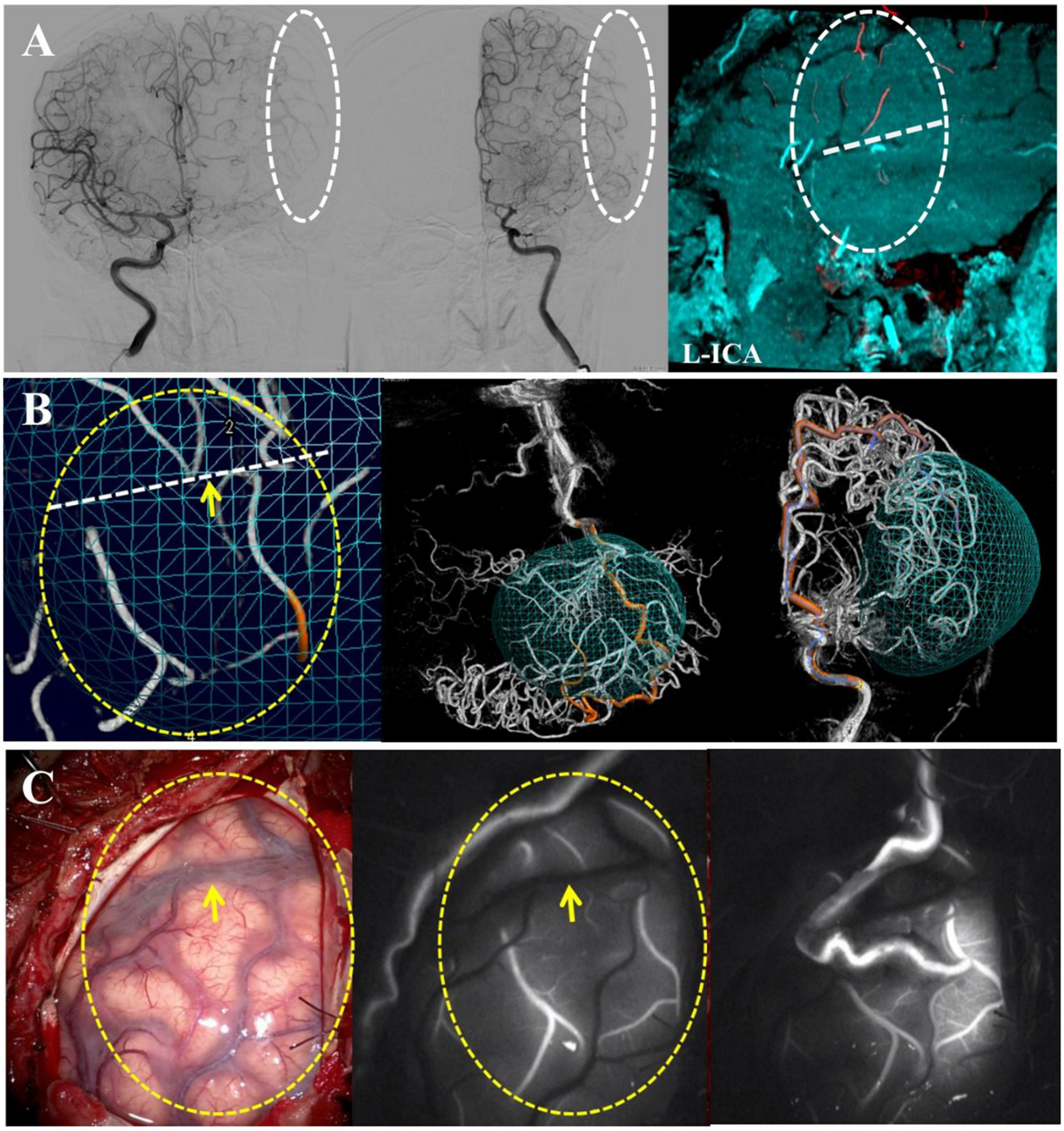

FIGURE 2
Distinguishing the hemodynamic sources of the PSCAs by an AFD analysis while difficulties encountered in the analysis procedure. **(A)** This is a unilateral MMD case with the left hemisphere involved. The 3D DSA-MR fusion images showed that the blood flow of the PSCAs above the SF might come from the ACA, CLA, or MCA. **(B)** Using automatic feeding artery detection (AFD) software, the hemodynamic source of the recipient PSCA was identified as the left ACA. If both CLA and ACA simultaneously were the flow contributions of the PSCAs, the ACA was recorded as the hemodynamic source in this study. **(C)** The intraoperative images validated our procedure for hemodynamic source analysis. In this case, the blood flow provided by the direct bypass would be widely spread into the ACA territory because of the good recipient vascular network.

with MMD were enrolled in this study. In total, 86 (50.3%) were female and 85 were male patients (49.7%). A total of 57 patients had hemorrhagic onset, and 114 patients exhibited ischemic symptoms (Table 1).

As shown in Table 1 and Figure 3, there were 62.3% of PSCAs with hemodynamic sources from the ICAs, including type I MCA (10.2%), type II MCA (40.9%), and ACA (11.1%). In comparison, 37.7% of PSCAs hemodynamically originated from non-ICAs, including the CLA (4.4%), PCA (32.2%), and ECA (1.2%).

Spatial distributional characteristics of the hemodynamic sources of the PSCAs associated with Sylvian fissures

We next evaluated the spatial distributional characteristics of the hemodynamic sources of the PSCAs around the Sylvian fissure (SF). Interestingly, we found that the hemodynamic sources of the PSCAs were obviously different above and below the SF from the 3D DSA-MRA images ($P < 0.001$) (Figures 1A, C).

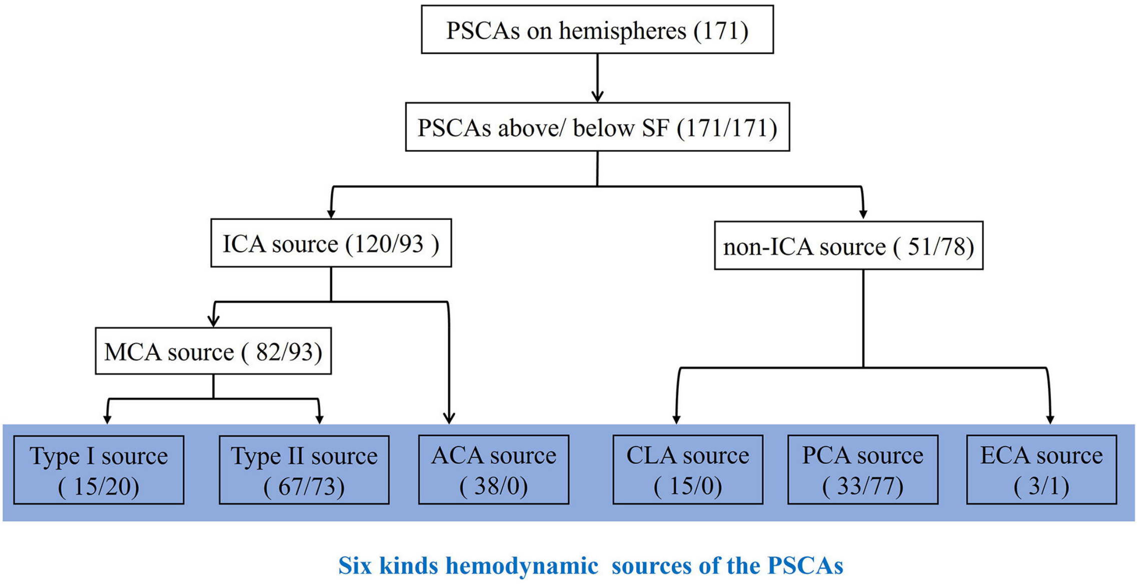

FIGURE 3
Classification and counting for hemodynamic sources of the PSCAs. For each hemisphere, the hemodynamic sources of PSCAs can be divided into two parts according to the location above or below the Sylvian fissure (SF). By using 3D DSA-MRA fusion imaging, the hemodynamic sources of the PSCAs were first identified as the ICAs or non-ICAs. ICAs were defined as a combination of the middle cerebral artery (MCA) and the anterior cerebral artery (ACA). The PSCAs with MCA hemodynamic source can be further divided into (1) type I: anterograde blood flow that came from the ICA via the stenotic MCA or (2) type II: anterograde blood flow that came from the ICA via "moyamoya vessels" with a lack of successful compensatory collateralization; non-ICAs included contralateral ACA (CLA), posterior cerebral artery (PCA), and external carotid artery (ECA). Thus, the hemodynamic sources of the PSCAs could be divided into six kinds: type I MCA, type II MCA, ACA, CLA, PCA, and ECA. The numbers in parentheses represent the number of PSCAs with corresponding hemodynamic sources. The number before the slash represents the PSCAs above the SF, and the number after the slash represents the PSCAs below the SF.

In PSCAs above the SF, we observed blood flow from all six kinds of hemodynamic sources, including type I MCA (15, 8.8%), type II MCA (67, 39.2%), ACA (38, 22.2%), CLA (15, 8.8%), PCA (33, 19.3%), and ECA (3, 1.8%) (Table 2; Figure 4A). However, only four kinds of hemodynamic sources were detected in PSCAs below the SF, including type I MCA (20, 11.7%), type II MCA (73, 42.7%), PCA (77, 45.0%), and ECA (1, 0.6%) (Table 3; Figure 4A).

This phenomenon suggests that the cerebrovascular system can establish several patterns of variant collateral flows according to the special anatomical structures/microvascular networks above and below the SF to compensate for intracranial ischemia caused by ICA stenosis in MMD.

Temporal distributional characteristics of the hemodynamic sources of the PSCAs associated with Suzuki stage

Since the patterns of variant collateral flows in PSCAs represent some kind of cerebral blood flow compensation mode in MMD, and the Suzuki stage indicates an intrinsic compensatory reorganization process, we anticipated if there was an association between the pattern of variation of collateral flow in the PSCAs and the Suzuki stage. Interestingly, we found there were significant differences between the hemodynamic sources of the PSCAs (above and below the SF) with different Suzuki stages in the ipsilateral hemisphere (*P* both <0.001).

As shown in Figure 4B, no matter whether the PSCAs were located above or below the SF, the ICAs (MCA and ACA) were the major hemodynamic sources of the PSCAs (70.2% above and 54.4% below the SF).

In terms of PSCAs above the SF, in the hemispheres with Suzuki stage 2, the type I MCA was the primary hemodynamic source (15, 78.9%), and another source was the ACA (4, 21.1%). In the hemispheres with Suzuki stage 3, the primary blood flow sources of the PSCAs were changed to the type II MCA (36, 53.2%). Moreover, increasing blood flow from the ACA (30, 44.1%) was observed in these hemispheres. Similar to hemispheres with Suzuki stage 3, the type II MCA was still the primary hemodynamic source of the PSCAs (31, 64.6%) in the hemispheres with Suzuki stage 4. However, collateral flow from the ACA (4, 8.3%) significantly decreased, and the non-ICAs, including the CLA (5, 10.4%) and PCA (7, 14.6%), started to provide blood flow to these PSCAs. Surprisingly, in the hemispheres with Suzuki stage 5, the hemodynamic sources of the PSCAs above the SF were totally changed to the non-ICAs, including the CLA (8, 22.2%), PCA (26, 72.2%), and ECA (2, 5.6%) (Table 2).

In terms of PSCAs below the SF, the type I MCA was the primary hemodynamic source providing blood flow to the PSCAs (18, 94.7%) in Suzuki stage 2 hemispheres, and another source was PCA (1, 5.3%). In Suzuki stage 3 hemispheres, the primary blood flow sources of the PSCAs were changed to the type II MCA (39, 57.4%). Meanwhile, increasing blood flow from the PCA (29, 42.6%) was observed. In Suzuki stage 4 hemispheres, the type II MCA was still the primary hemodynamic source (30, 62.5%), and

TABLE 1 Baseline characteristics of included cases.

	All patients (n = 171)
Age (years) [medians (IQR)]	47.51 (18–77)
Sex [n (%)]	
Female	86 (50.3)
Male	85 (49.7)
Original side [n (%)]	
Right	99 (58.4)
Left	72 (41.6)
Suzuki stage on original side [n (%)]	
II	15 (8.7)
III	72(42.1)
IV	63 (36.8)
V	19 (11.12)
VI	2 (1.1)
Onset on original side [n (%)]	
Hemorrhagic	57 (33.3)
Ischemic	114 (66.7)
PSCAs with ICA source [n (%)]	213 (62.3)
Type I MCAs source	35 (10.2)
Type II MCAs source	140 (40.9)
ACA source	38 (11.1)
PSCAs with non-ICA source [n (%)]	129 (37.7)
CLA source	15 (4.4)
PCA source	110 (32.2)
ECA source	4 (1.2)

PSCAs, parasylvian cortical arteries; MCA, middle cerebral artery; ACA, anterior cerebral artery; CLA, contralateral ACA; PCA, posterior cerebral artery; ECA, external carotid artery.

the PCA (16, 33.3%) flow was still the second collateral flow to the PSCAs below the SF but slightly decreased. In the hemispheres with Suzuki stage 5, similarly, most hemodynamic sources of the PSCAs below the SF also came from the non-ICAs, including the PCA (31, 86.1%) and ECA (1, 2.8%) (Table 3).

Together, with the advancing Suzuki stages, collateral flow to the PSCAs above the SF from the ICAs gradually decreased, while the non-ICAs significantly increased. However, the variation pattern of collateral flow to the PSCAs below the SF was not correlated to the Suzuki stage (Figure 4B).

Association between the hemodynamic sources of the PSCAs and the initial onset type of the hemispheres

We further investigated the relationship between the hemodynamic sources of the PSCAs and the patients' basic characteristics. We found there was a significant difference in Suzuki stages between the hemodynamic sources of the PSCAs (no matter above or below SF) (both $P < 0.001$, Tables 2, 3). In various hemodynamic sources of the PSCAs above the SF, no significant difference was observed in terms of age and sex of the patients (both $P > 0.05$). However, the groups had a significant discrepancy in initial onset type ($P = 0.014$, Table 2). The result of the Z-test showed the proportion of hemorrhagic onset in the type II MCA group (49.3%) was significantly higher than that in the type I MCA group (20%), ACA group (21.1%), and CLA group (13.3%), respectively (Table 2). However, in the hemodynamic sources of the PSCAs below the SF group, no significant difference was observed in terms of age, sex, and initial onset type (all P-values > 0.05, Table 3).

The results of the multivariate analysis revealed that the initial onset type was only significantly associated with hemodynamic sources of the PSCAs above the SF [$P = 0.026$, OR, 1.541 (1.054–2.252)], rather than other factors such as age, sex, Suzuki stage, or hemodynamic sources of the PSCAs below the SF (Table 4).

Discussion

Cortical collateral flow is critical in MMD and has been studied by radiological angiography investigations for the past decades, including DSA, CTA, and MRA alone (6, 8–10). In our previous study, we have proven that PSCAs with different hemodynamic sources from the MCA and non-MCA had a different relationship with postoperative CHP during STA-MCA bypass in MMD (5). In this study, by using the 3D DSA-MRA fusion imaging method, we further investigated the characteristics of collateral flow to cortical vessels in MMD and their relationship with patient clinical presentations. Moreover, the present study also attempts to provide useful information in the preoperative evaluation of the recipient vascular network during STA-MCA bypass procedures for adult MMD.

As a typical chronic occlusive cerebrovascular disease, MMD represents the ultimate example of excessive collateralization, recruiting a wide range of leptomeningeal and deep parenchymal vessels (6, 11). Both collaterals may provide blood flow to the PSCAs, which are representative of the anterior cortical vessels and commonly selected as the recipient arteries in STA-MCA bypass surgeries for MMD. In the present study, we demonstrated the possibility to distinguish the blood flow sources of PSCAs by using 3D DSA-MRA fusion imaging. Previous studies have proven that the 3D DSA-MRA fusion images can provide significantly more information on the vasculature and adjacent brain tissues than the MRA/MRI or 3D DSA images alone (12–14). Consequently, by using 3D DSA-MRA fusion imaging and the AFD analysis, collateral flow to all the PSCAs in this study was identified (Figures 1, 2). Interestingly, the distributional analysis demonstrated that there was a significant difference in the hemodynamic sources of the PSCAs above and below the SF ($P < 0.001$). Furthermore, the primary collateral source that compensated for decreased MCA blood flow was the ACA above the SF and the PCA below the SF (Figure 4A). These observations are in conformity with the process of intracranial collateral recruitment, which depends on the caliber and patency of primary

TABLE 2 Basic characteristic analysis between the groups according to the hemodynamic sources of the PSCAs above the SF.

	Hemodynamic sources of the PSCAs above the SF						*P*-value
	MCA (type I) ($n = 15$)	MCA (type II) ($n = 67$)	ACA ($n = 38$)	CLA ($n = 15$)	PCA ($n = 33$)	ECA ($n = 3$)	
Age, years	48.73 ± 9.52	46.12 ± 10.45	49.95 ± 12.11	48.93 ± 8.84	46.64 ± 11.23	44.00 ± 16.10	0.556
Male sex	7 (46.7%)	30 (44.8%)	25 (65.8%)	10 (66.7%)	12 (36.4%)	1 (33.3%)	0.108
Hemorrhagic onset	3 (20.0%)*	33 (49.3%)	8 (21.1%)*	2 (13.3%)*	10 (30.3%)	1 (33.3%)	0.014*
Suzuki's stage	2.00 ± 0.00	3.46 ± 0.51	3.00 ± 0.47	4.40 ± 0.74	4.79 ± 0.42	4.67 ± 0.58	<0.001*

PSCAs, parasylvian cortical arteries; SF, Sylvian fissure; MCA, middle cerebral artery; ACA, anterior cerebral artery; CLA, contralateral ACA; PCA, posterior cerebral artery; ECA, external carotid artery.
*Indicates proportion of hemorrhagic onset is significantly different from that in the MCA (type II) group.

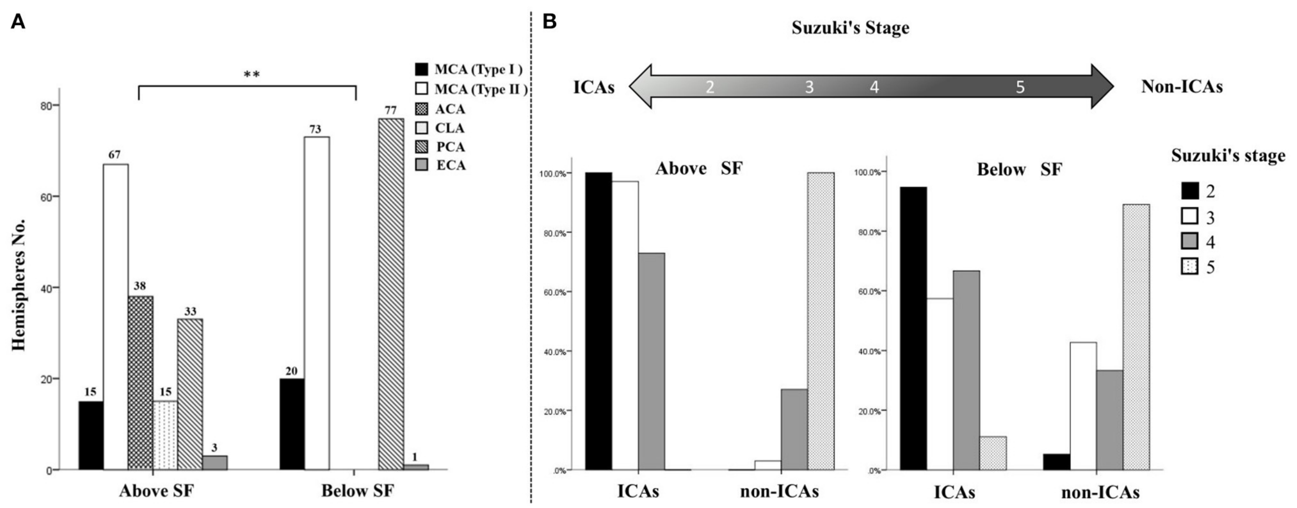

FIGURE 4
Distributional characteristics and trends of collateral flow to the PSCAs above or below the Sylvian fissure. **(A)** There was a significant difference between the hemodynamic sources of the parasylvian cortical arteries (PSCAs) above the Sylvian fissure (SF) and those of the PSCAs below the SF (**$P < 0.001$). All six types of hemodynamic sources in this study, including middle cerebral artery (MCA) type I ($n = 15$, 8.8%), MCA type II ($n = 67$, 39.2%), anterior cerebral artery (ACA) ($n = 38$, 22.2%), contralateral ACA ($n = 15$, 8.8%), posterior cerebral artery (PCA) ($n = 33$, 19.3%), and external cerebral artery (ECA) ($n = 3$, 1.8%) provided blood flow to the PSCAs above the SF. By contrast, the PSCAs below the SF had only four kinds of hemodynamic sources, including MCA type I ($n = 20$, 11.7%), MCA type II ($n = 73$, 42.7%), PCA ($n = 77$, 45.0%), and ECA ($n = 1$, 0.6%). **(B)** With advancing Suzuki stages, collateral flow to the PSCAs above the SF, but not below the SF, presented a significant conversion trend from internal carotid arteries (ICAs) to non-ICAs.

TABLE 3 Basic characteristic analysis between the groups according to the hemodynamic sources of the PSCAs below the SF.

	Hemodynamic sources of the PSCAs below the SF				*P*-value
	MCA (type I) ($n = 20$)	MCA (type II) ($n = 73$)	PCA ($n = 77$)	ECA ($n = 1$)	
Age, years	47.95 ± 9.78	46.59 ± 11.45	48.29 ± 10.67	46.00 ± 0.00	0.811
Male sex	8 (40.0%)	40 (54.8%)	37 (48.1%)	0	0.461
Hemorrhagic onset	5 (25.0%)	26 (35.6%)	26 (33.8%)	0	0.728
Suzuki's stage	2.20 ± 0.62	3.52 ± 0.60	4.00 ± 0.92	5.00 ± 0.00	<0.001*

PSCAs, parasylvian cortical arteries; SF, Sylvian fissure; MCA, middle cerebral artery; PCA, posterior cerebral artery; ECA, external carotid artery. *Significant difference.

pathways that may rapidly compensate for decreased blood flow and the adequacy of secondary collateral routes (6).

Suzuki's angiographic staging does not represent the severity of MMD but indicates an intrinsic compensatory reorganization process and represents the physiological profile of "internal carotid (IC)-external carotid (EC)" conversion in MMD (15). This point of view is strongly supported by this current study from the perspective of trends in collateral flow to the PSCAs. With the increase in Suzuki stages, the hemodynamic sources of the PSCAs above the SF had a significant trend of conversion from ICAs to non-ICAs. However, this trend could not be observed in the hemodynamic sources of the PSCAs below the SF (Figure 4B). Different configurations may exist between collateral flow to the PSCAs above and below the SF. As demonstrated by previous

TABLE 4 Multivariate analysis of factors associated with the onset type in adult symptomatic MMD hemispheres.

Factors	Hemorrhagic onset ($n = 57$)	Ischemic onset ($n = 114$)	OR (95% CI)	*P*-value
Age, years	45.70 ± 10.52	48.41 ± 10.95	1.026 (0.995–1.057)	0.105
Male sex	27 (47.4%)	58 (50.9%)	0.883(0.459–1.698)	0.708
Suzuki stage	3.60 ± 0.84	3.59 ± 0.99	0.675 (0.397–1.149)	0.148
Hemodynamic sources of the PSCAs above the SF (type I MCA/type II MCA/ACA/CLA/PCA/ECA)	3/33/8/2/10/1	12/34/30/13/23/2	1.541 (1.054–2.252)	0.026*
Hemodynamic sources of the PSCAs below the SF (type I MCA/type II MCA/PCA/ECA)	5/26/26/0	15/47/51/1	0.926 (0.737–1.163)	0.509

MMD, moyamoya disease; CI, confidence interval; OR, odds ratio; PSCAs, parasylvian cortical arteries; SF, Sylvian fissure; MCA, middle cerebral artery; ACA, anterior cerebral artery; CLA, contralateral ACA; PCA, posterior cerebral artery; ECA, external carotid artery. *Significant difference.

studies, although the specific pathophysiological factors leading to the development of collaterals were uncertain, the arterial anatomy (anatomical factor) and diminished blood pressure in downstream vessels (demand factor) were considered critical variables (6, 16). For PSCAs above the SF, the number and size of the leptomeningeal anastomoses are greatest between ACAs and MCAs, with smaller and fewer connections between MCAs and PCAs and even less prominent terminal anastomoses between PCAs and ACAs (6). In the present study, the MCA was normally the major hemodynamic source of the PSCAs above the SF in the hemispheres with Suzuki stages 2–3 but might be subsequently changed to a relative normal ACA due to progressive stenosis of the MCA and even possibly transformed to a PCA if both MCA and ACA were occluded in the hemispheres with Suzuki stages IV–V. However, for PSCAs below the SF, the leptomeningeal collaterals are less varied and mostly limited to the connections between MCAs and PCAs. The anatomical factor was antecedent to the demand factor in the development of collateral flow to the PSCAs above the SF and just opposite in the formation of collateral flow to the PSCAs below the SF. This discrepancy might be the reason why the trend of conversion from ICAs to non-ICAs was hard to observe in the hemodynamic sources of the PSCAs below the SF.

In adult MMD patients, the development of thalamic and/or choroidal collaterals is a predictor of hemorrhagic events (17–21). This finding is supported by our discovery that the hemispheres with hemodynamic sources of the PSCAs above the SF from the type II MCA had a relatively high risk of hemorrhagic stroke when compared to those from the type I MCA, ACA, and CLA, which more frequently suffered cerebral ischemia (Table 2). The multivariate analysis further revealed that only the hemodynamic sources of the PSCAs above the SF were significantly associated with the onset type ($P = 0.026$, Table 4). In this study, the type II MCA source represented anterograde blood flow that came from the ICA via the moyamoya vessels, including thalamic and/or choroidal collaterals, to the cortical arteries and a lack of successful compensatory collateralization. In such a situation, the abundant abnormal vascular anastomoses at the base of the brain may experience heavy blood flow, thus resulting in vessel dilatation, formation of microaneurysms, and vessel rupture (5). However, we observed that collateral flow to the PSCAs above the SF from the ACA or CLA was significantly correlated to the ischemic symptoms, which may be due to the blood flow pressure of the abnormal vascular anastomosis, which is significantly released by blood flowing into the relatively normal and unobstructed ACA or CLA. These findings may contribute in predicting the types of episodes in an asymptomatic MMD hemisphere.

The potential significance of the findings in STA-MCA bypass surgeries for MMD

As it has been shown in previous studies, the craniotomy planned for most STA-MCA bypass cases is most frequently centered around the SF (22, 23), and the PSCAs are usually selected as the recipient arteries for direct anastomoses. The results of this study demonstrated that, although located in an operating field, the PSCAs above and below the SF might have different hemodynamic sources. If we performed direct anastomosis on a recipient PSCA with anterograde blood flow from the type II MCA, the poor cortical vasculature of such PSCA could result in limited flow distribution after direct revascularization and a high risk of postoperative hyperperfusion (5, 24–26). Consequently, avoiding the selection of a recipient PSCA with its blood flow from the type II MCA is suggested when performing direct bypass surgeries for patients with MMD.

Limitations

This study has several limitations. First, it is a single-center study, which creates a regional bias in the sample, which could be an issue. Second, as only the symptomatic hemispheres that underwent bypass surgeries were included, data on hemispheres with Suzuki stages 1 and 6 were absent in this study. Third, visualization of cortical arteries was not better than visualization of stenosis of proximal arteries from the TOF MR angiography. Fortunately, this limitation was compromised by the use of 3D DSA imaging. Both methods worked in a mutually beneficial manner in the analysis of the hemodynamic sources of the PSCAs.

Conclusion

The hemodynamic sources of PSCAs can be accurately identified by 3D DSA-MRA fusion imaging and then help to understand the quality of the recipient vascular network before STA-MCA bypasses MMD. We demonstrated that the collateral flow sources of the PSCAs above the SF were more varied when compared to those below the SF and revealed the ICAs to non-ICAs conversion with advancing Suzuki stages. We also demonstrated that the hemispheres with hemodynamic sources of the PSCAs above the SF from the type II MCA had a relatively high risk of hemorrhagic stroke, and those from the type I MCA, ACA, and CLA more frequently presented with ischemic symptoms. This classification of the hemodynamic sources may assist with figuring out the complex parasylvian cortical collateral flow and its relationship with clinical presentations and postoperative CHP in MMD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board (IRB) at Zhongnan Hospital of Wuhan University (approval number: Kelun-2017005). Written informed consents were waived since all identifiable personal details has been hidden.

Author contributions

MH: methodology, validation, investigation, and writing—original draft preparation. JY: methodology, validation, formal analysis, investigation, writing—original draft preparation, and visualization. JZ: conceptualization, formal analysis, investigation, resources, supervision, writing—review and editing, and funding acquisition. JC: conceptualization, resources, supervision, writing—review and editing, and funding acquisition. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effect of newly developed scissors-attached micro-forceps on the recipient clamp time and occurrence of anastomotic site infarction after bypass surgery for moyamoya disease

Munetaka Yomo[1], Ryuhei Kitai[2], Hiroyuki Tada[3], Makoto Isozaki[1], Yoshifumi Higashino[1], Ken Matsuda[1], Takahiro Yamauchi[1], Ayumi Akazawa[1], Satoshi Kawajri[1], Mizuki Oiwa[1], Shintaro Yamada[1], Tadahiro Tsubota[1], Akifumi Watanabe[1], Hidehiko Okazawa[4], Yasushi Kiyono[4], Hidetaka Arishma[1] and Kenichiro Kikuta[1,5]*

[1]Division of Medicine, Department of Neurosurgery, Faculty of Medical Sciences, University of Fukui, Fukui, Japan, [2]Department of Neurosurgery, Kaga Medical Center, Kaga, Japan, [3]Technology Development Section, Charmant Co., Ltd., Sabae, Japan, [4]Biomedical Imaging Research Center, University of Fukui, Fukui, Japan, [5]Life Science Innovation Center, University of Fukui, Fukui, Japan

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EDITED BY
Long Wang,
Capital Medical University, China

REVIEWED BY
Bin Xu,
Fudan University, China
Li Ma,
Capital Medical University, China

*CORRESPONDENCE
Kenichiro Kikuta
✉ kikuta@u-fukui.ac.jp

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Introduction: This study aimed to examine the effect of newly developed scissors-attached micro-forceps in superficial temporal artery-to-middle cerebral artery (STA-MCA) anastomosis for moyamoya disease (MMD).

Materials and methods: Of 179 consecutive STA-MCA anastomoses on 95 hemispheres of 71 MMD patients at the University of Fukui Hospital between 2009 and 2023, 49 anastomoses on 26 hemispheres of 21 patients were enrolled in this retrospective cohort clinical trial intraoperative indocyanine green video-angiography did not demonstrate bypass patency in three anastomoses in two patients who were excluded. Twenty-one anastomosis in 19 hemispheres of 16 patients were performed using the conventional micro-forceps (conventional group, CG), and 25 anastomoses in 22 hemispheres of 19 patients were performed using scissors-attached micro-forceps (scissors group, SG). A small infarction near the anastomotic site detected using postoperative diffusion-weighted imaging was defined as anastomotic site infarction (ASI). Factors affecting the occurrence of ASI were examined by univariate, logistic regression, and receiver operating curve (ROC) analysis.

Results: There were no significant differences in clinical parameters such as age, sex, number of sacrificed branches, number of sacrificed large branches, and number of sutures between the CG and SG. However, the clamp time and occurrence of ASI were significantly lower in the SG than in the CG. Logistic regression analysis revealed that the clamp time was the only significant factor predicting the occurrence of ASI. A receiver operating curve analysis also revealed that the clamp time significantly predicted the occurrence of ASI (area under the curve, 0.875; cutoff value, 33.2 min).

Conclusion: The newly developed scissors-attached micro-forceps could significantly reduce the clamp time and occurrence of ASI in STA-MCA anastomosis for MMD.

KEYWORDS

moyamoya disease, STA-MCA anastomosis, clamp time, ischemia, anastomotic site, micro-forceps

1. Introduction

Superficial temporal artery-to-middle cerebral artery (STA-MCA) anastomosis was first reported by Yasargil (1). In Japan, it has been applied mainly for the treatment of moyamoya disease (MMD) (2), which is a progressive steno-occlusive disease of the terminal portion of the bilateral internal carotid arteries (ICAs) with the development of moyamoya vessels as collateral channels (3). A previous study combined direct bypass (STA-MCA anastomosis) and indirect bypass (encephalo-duro-arterio-synangiosis) for the treatment of MMD (4). A recent meta-analysis showed that combined and direct bypasses significantly benefited patients with MMD suffering from late stroke and hemorrhage compared to indirect bypass (5). Although STA-MCA anastomosis requires clamping of the MCA for some time, few reports have considered the clamp time of STA-MCA anastomosis for MMD (6).

Recent advances in magnetic resonance (MR) technology, including 3 Tesla MR imaging (3T MRI), allow the detection of asymptomatic small ischemic lesions after STA-MCA anastomosis by diffusion-weighted imaging (DWI) (7). In this study, we examined the effect of newly developed scissors-attached micro-forceps on the clamp time in STA-MCA anastomosis for MMD and examined the effect of the clamp time on the occurrence of asymptomatic small ischemic lesions after surgery.

2. Materials and methods

2.1. Enrollment of patients

We started direct bypass treatment for MMD at the University of Fukui Hospital in September 2009. Of 179 consecutive STA-MCA anastomoses on 95 hemispheres of 71 MMD patients at the University of Fukui Hospital between 2009 and 2023, 49 anastomoses on 26 hemispheres of 21 patients were enrolled in this clinical trial. Three anastomoses on two hemispheres in two patients were excluded because bypass occlusion was confirmed using intraoperative indocyanine green (ICG) video-angiography (VA). Two anastomoses on one hemisphere in one patient were performed using scissor-attached micro-forceps and were occluded probably due to the thrombus formation in the donor artery derived from the injury of STA during the harvest. Although the reconstruction of STA was performed by end-to-end anastomosis, repeated anastomosis under the administration of anti-platelet drugs could not relieve the occlusion. Another anastomosis in another patient conducted by using conventional micro-forceps was occluded probably due to the complexity of anastomosis owing to the discrepancy of diameters between the donor artery (2 mm) and the recipient artery (0.5 mm). Ultimately, 46 anastomoses on 25 hemispheres in 19 patients were included in this study. Anastomosis in the unilateral hemisphere was performed in 14 patients and on both hemispheres in 6 patients. Among 46 anastomoses on 25 hemispheres in this study, single, double, and triple anastomoses underwent 5, 19, and 1 hemispheres, respectively. While both conventional micro-forceps and newly created scissors-attached micro-forceps were used for double or triple bypass in the same operation on 17 hemispheres, only one of them was used for single anastomosis on five hemispheres in five patients and double anastomosis on three hemispheres in three patients. Accordingly, 21 anastomoses on 19 hemispheres of 16 patients were performed using the conventional micro-forceps (conventional group: CG), and 25 anastomoses on 22 hemispheres of 19 patients were performed using the scissors-attached micro-forceps (scissors group: SG; Figure 1). This study was approved by the Ethics Committee of our institute (No. 20150155), and informed consent was obtained from all patients.

2.2. The newly developed micro-forceps

The newly developed micro-forceps are 135 mm long and consist of three parts: body, head, and tip (Charmant Co., Ltd., Fukui, Japan, www.charmant.co.jp), which were made of Ti15V3Al3Cr3Sn, stainless steel (SUS304), and aged stainless steel (SUS20J-2), respectively. Each part is fixed and connected using stainless steel screws (SUS304; Figure 2A). The tip is 0.35 mm wide and 0.8 mm long. A small pair of scissors is placed at a distance of 0.8 mm from the tip for cutting ligatures (Figure 2B). This small-shaped tip design makes it possible to deal smoothly with 11-0 ligatures and needles (Figure 2C). The micro-forceps allow the surgeon to suture, tie (Figure 2C), and cut a ligature without exchanging instruments (Figures 2D–F), thus reducing the clamp time.

2.3. Operative procedures and perioperative management

A large U-shaped scalp incision was made around the ears. After reflection of the scalp and temporal muscles, a frontotemporal craniotomy was performed to expose the frontal lobe, Sylvian fissure, and temporal lobe. In most cases, we performed double anastomosis using the parietal and frontal STAs. The supra-Sylvian

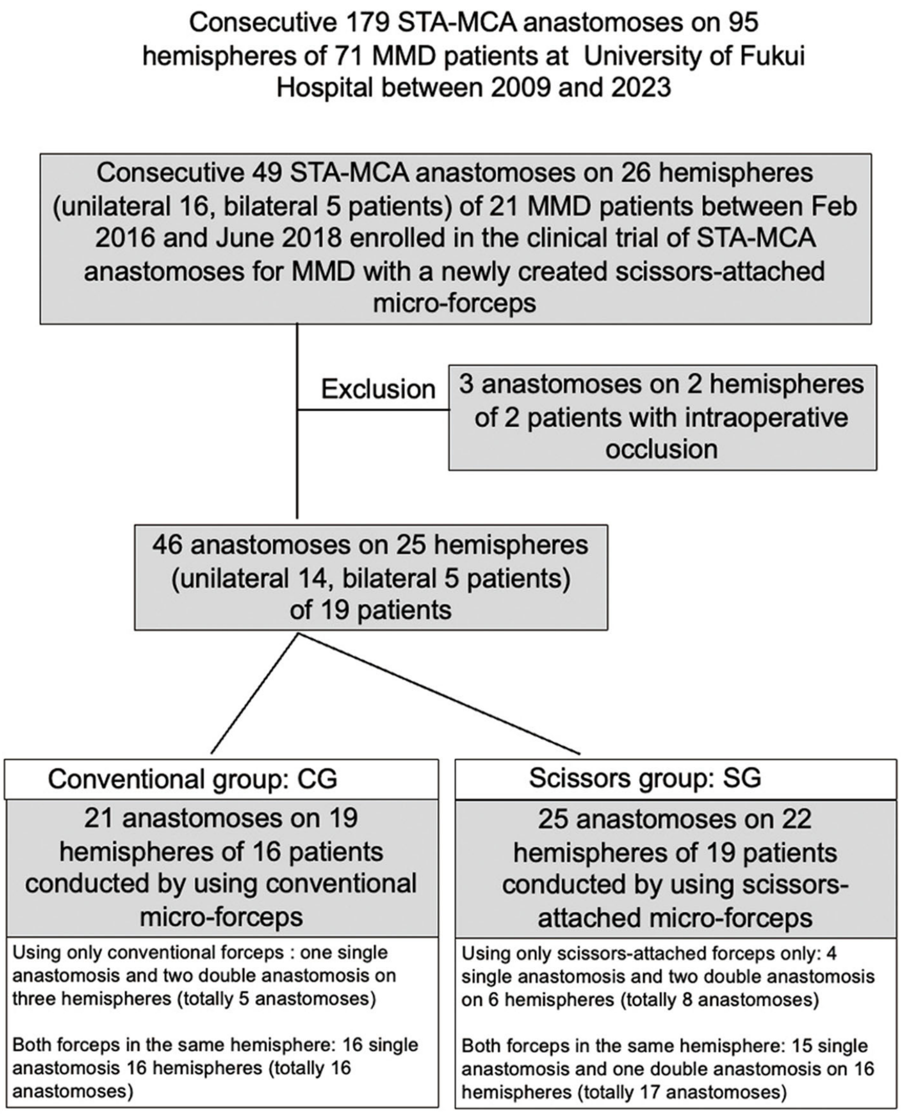

FIGURE 1
Inclusion of the patients in this clinical trial.

M4 portion of the MCA and infra-Sylvian M4 portion immediately beside the Sylvian vein were selected as the recipient arteries. Several lateral branches of the recipient artery were coagulated and sacrificed to obtain a 10 mm long branch-free recipient. After clamping the recipient artery, a circular arteriotomy was performed at its roof.

The STA-MCA anastomosis was performed using 8–10 sutures with 11-0 ligatures. One anastomosis was performed using the conventional micro-forceps, and the other was performed using the scissors-attached micro-forceps. When harvesting two branches of the STA was difficult, a single anastomosis was performed. In this case, the micro-forceps used for the anastomosis were randomly selected by the surgeon.

ICG-VA was performed in all the cases. Occlusion of three anastomoses in two patients was confirmed using ICG-VA at the final stage of the operation. After the STA-MCA anastomosis, the temporal lobe was covered with the temporal muscle using encephalo-myo-synangiosis. During the procedure, the systolic blood pressure was maintained between 100 and 140 mmHg, and the $PaCO_2$ was strictly maintained between 35 and 45 mmHg. The surgery was performed by KK and four other neurosurgeons.

2.4. 3T MRI study

MR studies were performed before surgery and within 1 week after surgery. Images were obtained using a 3T MR scanner (Signa 3-HD, General Electric, USA) with axial DWI (spin echo EPI, TR/TE = 6,300/64.4 ms, bandwidth = ±250 kHz, FOV = 240, slice thickness/gap = 5/1 mm, matrix = 128 × 256, 2NEX), axial FLAIR sequences (fast spin echo, TR/TE/TI = 10,000/120/2,450 ms, bandwidth = ±35.71 kHz, FOV = 240 mm, slice thickness/gap = 5/1 mm, matrix = 320 × 192, 1NEX),

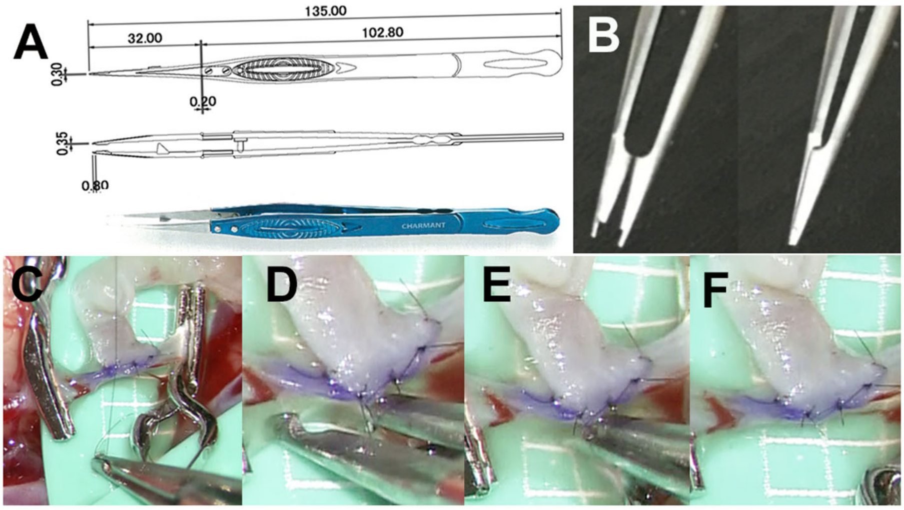

FIGURE 2
(A) Pair of micro-forceps is 135 mm long and consists of three parts: body, head, and tip (Charmant Co., Ltd., Fukui, Japan, www.charmant.co.jp), which are made of Ti15V3Al3Cr3Sn, stainless steel (SUS304), and aged stainless steel (SUS20J-2), respectively. Each part is fixed and connected by screws made of stainless steel (SUS304). **(B)** The tip is 0.35 mm wide and 0.8 mm long. There is a small pair of scissors which is 0.8 mm from the tip for cutting ligatures. **(C)** This small-shaped tip design makes it possible to work with 11-0 ligatures and needles smoothly. **(D–F)** The micro-forceps allow the surgeon suture, tie, and cut a ligature without exchanging instruments, thus reducing the clamp time.

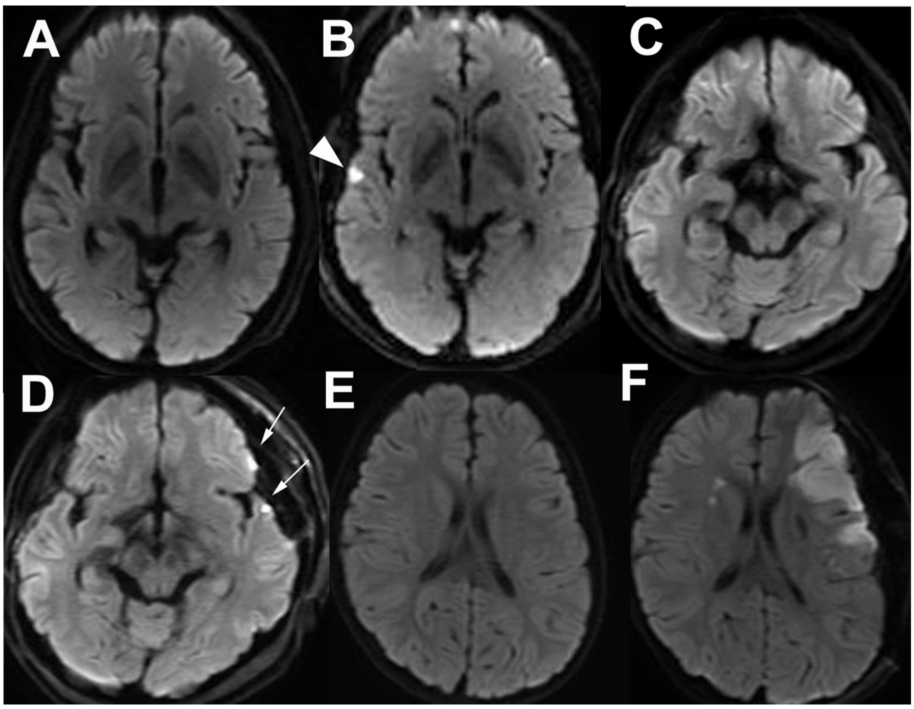

FIGURE 3
Asymptomatic small infarct lesion at the frontal and or temporal lobes adjacent to the Sylvian fissure detected by postoperative diffusion-weighted imaging (DWI) is defined as an anastomotic site infarction (ASI). Preoperative **(A)** and postoperative **(B)** DWI of a patient with temporal ASI (arrow head). Preoperative **(C)** and postoperative **(D)** DWI of a patient with frontal and temporal ASIs (arrows). Preoperative **(E)** and postoperative **(F)** DWI of a patient with major postoperative infarction at the affected side is distinguished from ASI.

and three-dimensional time-of-flight MR angiography [(3D TOF MRA) (3D SPGR, TR/TE = 22/3.5 ms, flip angle = 18°, band width = ±25 kHz, FOV = 180 mm, matrix = 320 × 192, slice thickness/gap = 1.2/−0.6 mm (ZIP2), number of slabs = 3 (location per slab = 28; overlap, five slices), 1NEX, ASSET Factor = 1.5)].

2.5. Anastomotic site infarction and symptomatic major infarction after bypass surgery

Anastomotic site infarction (ASI) was defined as an asymptomatic DWI-hyperintense lesion with a diameter <5 mm on the cortex near the Sylvian fissure detected by postoperative 3T MRI. An ASI at the temporal lobe was determined as a small ischemic lesion related to the bypass to the infra-Sylvian MCA (preoperative MRI: Figure 3A, postoperative MRI: Figure 3B). ASIs at the frontal and temporal lobes were determined as ischemic lesions related to the bypass to both the supra- and infra-Sylvian MCAs (preoperative MRI: Figure 3C, postoperative MRI: Figure 3D). Symptomatic large DWI-positive lesions or lesions in the contralateral brain were identified as major infarctions related to bypass surgery for MMD and were distinguished from ASIs (preoperative MRI: Figure 3E, postoperative MRI: Figure 3F).

2.6. Statistical analysis

A univariate analysis was performed with Pearson's chi-squared test, Fisher's exact test for categorical variables, or using the Mann–Whitney *U*-test for numeric variables. Forward and backward stepwise logistic regression analyses with the Akaike information criterion (AIC) were carried out to determine the associations of potential factors and the occurrence of ASI. The cutoff values for the receiver operating characteristic (ROC) analysis using the area under the curve (AUC) were calculated using Benis' method. All statistical analyses were performed using the JMP software (Version 10, SAS Institute Inc., Cary, NC, USA) and R (R Foundation for Statistical Computing, Vienna, Austria), with an error probability of <0.05.

3. Results

3.1. Clinical parameters of the CG and SG

There were 16 patients [(mean age, 35.4 ± 18.4 years; male-to-female ratio (M:F) = 3:13)] in the CG (21 anastomoses cases on 19 hemispheres) and 19 (mean age 33.0 ± 20.1 years, M:F = 2:17) in the SG (25 anastomoses cases on 22 hemispheres). There were 10 patients with preprocedural in the CG group and 11 in the SG group, respectively. There was one patient recent ischemic stroke in each group. There were 12, 3, and 1 patients with a preoperative modified Rankin score (preop mRS) of 0, 1, and 2, respectively in CG (mean 0.31±0.60). There were 13, 3, 2, and 1 patients with preop mRS of 0, 1, 2, and 3, respectively, in SG (mean 0.52 ± 0.90). There were 2, 13, and 1 patients with the preoperative Suzuki stage of 2, 3, and 4, respectively, in CG (mean 2.94 ± 0.44). There were 6, 11, 1, and 1 patients with the preoperative Suzuki stage of 2, 3, 4, and 5, respectively, in SG (mean 2.84 ± 0.76) (8). Regarding the outcome of bypass function, there were 7, 7, and 2 patients with Matsushima grades A, B, and C, respectively, determined by postoperative angiography at 3 months after the last surgery in CG. There were 9, 8, and 2 patients with Matsushima grades A, B, and C, respectively, in SG. The mean follow-up period of CG and SG were 67.0 ± 18.4 and 69.4 ± 15.9 months, respectively (9). There were 12 and 4 patients with mRS at the final follow-up of 0 and 1, respectively, in CG (mean 0.25 ± 0.45). There were 13, 4, and 1 patients with preop mRS of 0, 1, 2, and 3, respectively, in SG (mean 0.47 ± 0.84). There was no significant difference in the number of patients, number of anastomoses, number of males, mean age, the presence of preprocedural infarction, recent ischemic stroke, preop mRS, Suzuki stage, Matsushima grade of postoperative angiography, mean follow-up period, and mRS at the final-follow up between the two groups. In a patient-oriented comparison, the mean number of sacrificed lateral branches of the recipient artery in CG (21 anastomose) and SG (25 anastomose) were 2.4 ± 1.1 and 2.9 ± 2.2, respectively. The mean number of sacrificed lateral branches with a diameter larger than 200 mm in CG and SG were 0.14 ± 0.36 and 0.2 ± 0.58, respectively. The mean number of sutures was 10.0 ± 1.2 and 10.0 ± 1.8, respectively. There was also no significant difference in the number of sacrificed lateral branches, the number of sacrificed lateral branches with a diameter larger than 200 μm, and the number of sutures between the two groups (Table 1).

3.2. Effect of scissors-attached micro-forceps on the clamp time, clamp time per suture, and occurrence of ASIs

The clamp time of the recipient artery regarding the CG and SG was 41.0 ± 11.6 min and 24.2 ± 6.9 min, respectively. The clamp time in the SG was significantly shorter than that in the CG ($p < 0.001$; Figure 4A). Furthermore, the clamp time per suture in the CG and SG was 4.2 ± 1.4 and 2.4 ± 0.5 min, respectively. The clamp time per suture was significantly shorter in the SG than in the CG ($p < 0.001$; Figure 4B). The occurrence rates of ASI in the CG and SG were 67 and 16%, respectively. The occurrence of ASIs in CG and SG was 52.3 and 20.0%, respectively. The occurrence of ASIs was more significant in the CG than in the SG ($p = 0.0312$; Figure 4C).

3.3. Logistic regression analysis regarding the prediction of ASI occurrence

Forward and backward stepwise logistic regression analyses with AIC revealed the occurrence of ASI were predicted by the combination of the number of sacrificed lateral branches of the recipient artery, the number of sacrificed lateral branches with a diameter larger than 200 μm, and the clamp time with the minimal AIC value (AIC = 54.17). Among them, the clamp time was the only significant predictive factor [odds ratio, 1.087; 95% confidence interval (CI): 1.03–1.16, $p = 0.0080$; Table 2].

3.4. ROC analysis

The ROC analysis revealed that the clamp time was a significant predictive factor for the occurrence of ASI ($p = 0.0041$; AUC = 0.7346; cutoff value, 33.2 min; sensitivity, 68.8%; specificity, 54.6%; Figure 5A). Moreover, the clamp time per suture was a significant

TABLE 1 Characteristics of the group that underwent anastomoses using conventional forceps (Conventional group: CG) and that which underwent anastomoses using scissors-attached forceps (Scissors group: CG).

		Conventional group (CG)	Scissors group (SG)	*p*-value
No. of anastomose		21	25	1.000
No. of hemispheres		19	22	1.000
No. of patients		16	19	1.000
No. of male		3	2	0.6418
Mean age (years)		35.4 ± 18.4	33.0 ± 20.1	0.9207
Preprocedural infarction		10	11	1.000
Recent ischemic stroke		1	1	1.000
Preoperative mRS		0.31 ± 0.60	0.52 ± 0.90	0.5734
Suzuki stage	2	2	6	0.3942
	3	13	11	
	4	1	1	
	5	0	1	
	mean	2.94 ± 0.44	2.84 ± 0.76	
No. of sacrificed branches		2.4 ± 1.1	2.9 ± 2.2	0.7249
No. of sacrificed branches with the diameter larger than 200 μm		0.14 ± 0.36	0.2 ± 0.58	0.9099
No. of sutures		10.0 ± 1.2	10.0 ± 1.8	0.5306
Matsushima grade at postoperative angiography	A	7	9	0.9705
	B	7	8	
	C	2	2	
Mean follow-up period (months)		71.1 ± 12.3	69.4 ± 15.9	0.8813
mRS at final follow-up		0.25 ± 0.45	0.47 ± 0.84	0.5573

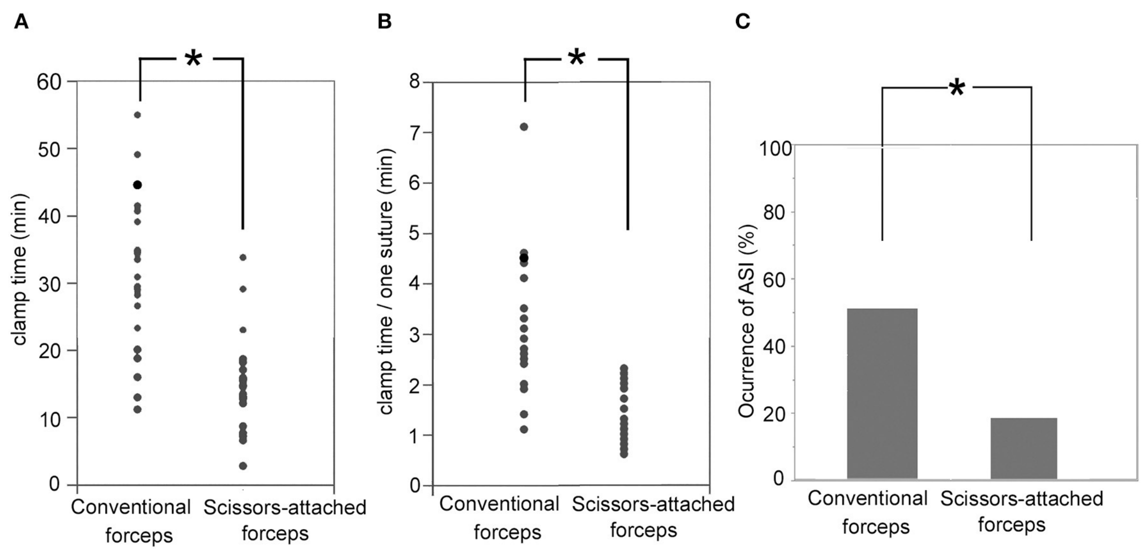

FIGURE 4
(A) Clamp time of the recipient artery regarding the SG (24.2 ± 6.9 min) was significantly shorter than CG (41.0 ± 11.6 min; $p < 0.001$). **(B)** The clamp time per suture in the SG (2.4 ± 0.5 min) was significantly shorter that in the CG (4.2 ± 1.4 min; $p < 0.001$). **(C)** Occurrence rates of ASI in the SG (16%) were significantly smaller than that in the CG (67%; $p = 0.0312$). *Indicates statistically significant.

predictive factor for the occurrence of ASI ($p = 0.0047$; AUC = 0.7271 cutoff value, 3.6 min; sensitivity, 58.3%; specificity, 57.1%; Figure 5B).

4. Discussion

The relationship between the clamp time of the major cerebral artery and the occurrence of postoperative infarction has been examined mainly during aneurysm surgery. Many researchers have investigated the duration for which major cerebral arteries in aneurysm surgery, such as the M1 portion of the MCA, ICA, dominant A1 portion of the anterior cerebral artery, and basilar artery (BA), can be occluded without ischemic complications. The mean safe occlusion times of the ICA, M1, dominant A1, and BA were 28 (range, 27–29), 31 (range, 14–93), 40, and 15.5 min (range, 13–18), respectively (10–16). Other researchers have reported that the ischemic risk in high-flow bypass with temporary occlusion of proximal cerebral arteries longer than 10 min without pharmacologic brain protection would be ∼45%. Even under brain protection, the ischemic risk remains 10–20%.

TABLE 2 Results of the logistic regression analysis for the predictive factors of the occurrence of anastomotic site infarctions (ASIs).

	OR	95%CI		*p*-value
No. of sacrificed branches	1.399	0.944	2.336	0.1293
No. of sacrificed branches with the diameter larger than 200 μm	0.184	0.008	1.136	0.1491
Clamp time (min)	1.087	1.027	1.166	0.0080*

Forward and backward stepwise logistic regression analyses with AIC reveal that the occurrence of ASIs is predicted by the combination of the number of sacrificed lateral branches of the recipient artery, number of sacrificed lateral branches with a diameter larger than 200 μm, and clamp time with the minimal AIC value (AIC = 54.17). Among them, the clamp time is the only significant predictive factor (odds ratio, 1.087; 95% CI: 1.03–1.16, p = 0.0080). AIC = 54.17. *Indicates statistically significant.

This risk would increase to 100% when the occlusion lasts longer than 30 min. Therefore, the placement of an assisted bypass to the cortical artery distal to the recipient artery is recommended for high-flow bypass (17–19).

Many studies have reported the occurrence of postoperative symptomatic major infarction after STA-MCA anastomosis for MMD. The occurrence rates ranged from 4.7 to 21.4% (20–26). Ischemic onset (20), preoperative ischemic presentation (21, 23), frequent preoperative transient ischemic attack (TIA) (23), short intervals between the last ischemic attack and the operation (20), young age (25), old age (22, 25, 26), advanced Suzuki grade (21, 24), and posterior cerebral artery involvement (20, 24–26) were reported as significant predictive factors. The lack of strict perioperative management, including intraoperative normocapnia and normotension and postoperative normotension, were also significant predictive factors (20). However, the clamp time has never been considered a predictive factor for the occurrence of major stroke after surgery. In our study, postoperative symptomatic infarction occurred in two hemispheres (three anastomoses cases) among the 25 hemispheres (46 anastomoses cases; 8% per hemisphere; 6.5% per anastomosis), which was not significantly related to the clamp time ($p = 0.9114$).

It is unclear whether the clamp time in the M4 portion is related to the occurrence of ischemic complications after STA-MCA bypass for MMD. Horn et al. (8) reported that the occurrence rates of postoperative TIA and asymptomatic stroke on DWI after STA-MCA anastomosis with a clamp time of M4 ranging from 23 to 45 min were 10 and 10%, respectively.

DWI with 3T MRI can sometimes detect asymptomatic small ischemic lesions in the cortex near the anastomotic site after STA-MCA anastomosis. We defined such lesions as ASIs. Murai et al. suggested that ASIs are derived from the coagulation and sacrifice of the lateral cortical branches of the recipient artery. In our study, the multivariate analysis revealed that the clamp time of the M4 portion was the only significant predictive factor for the occurrence of ASIs. The number of sacrificed lateral branches and that of sacrificed large lateral branches were not significantly related to the occurrence. The ROC analysis revealed that the cutoff values

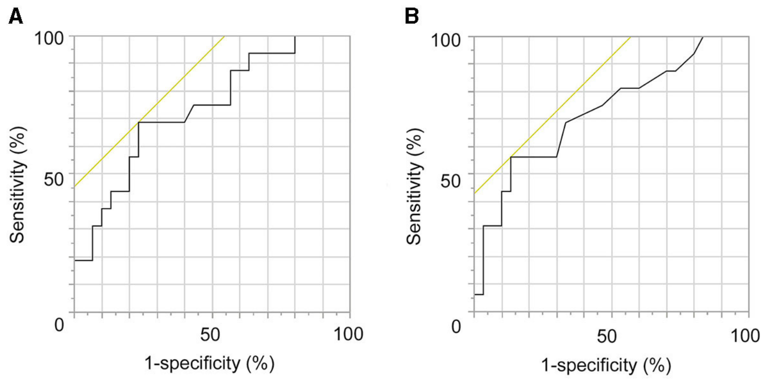

FIGURE 5
Receiver operating characteristic (ROC) analysis regarding the prediction of occurrence of anastomotic site infarctions (ASIs). **(A)** The clamp time is a significant predictive factor of the occurrence of ASIs ($p = 0.0041$; AUC = 0.7346; cutoff value, 33.2 min; sensitivity, 68.8%; specificity, 54.6%). **(B)** Clamp time per suture was a significant predictive factor of the occurrence of ASIs ($p = 0.0047$; AUC = 0.7271 cutoff value, 3.6 min; sensitivity, 58.3%; specificity, 57.1%).

regarding the clamp time and clamp time per suture were 33.2 and 3.6 min, respectively.

To reduce the clamp time, some modifications to the surgical technique and equipment have been reported. While we reported the "needle parking technique," a modification of the conventional interrupted suturing to avoid needle loss during knot tying and to reduce the clamp time (27), Krisht et al. (28) reported a similar modification in 2020. Kohno et al. (29) reported the use of the scissors-attached micro-forceps that could significantly reduce the clamp time. The micro-forceps were 150 mm long and relatively large. We designed the scissors-attached micro-forceps suitable for MMD, which could significantly reduce the clamp time, clamp time per suture, and occurrence of ASIs.

4.1. Limitations

This study had some limitations. We conducted double anastomosis by using conventional micro-forceps for one anastomosis and scissors-attached micro-forceps for another anastomosis in the same operation on 17 hemispheres of 25 hemispheres in this study. Therefore, 33 anastomose of 46 anastomose in this study were performed using both micro-forceps in the same hemisphere in the same person. Approximately 75% of the patient clinical parameters in CG and SG were the same. That is because we avoided the logistic regression analysis regarding the prediction of ASI occurrence including patient clinical parameters in this study. In addition, it was a retrospective study with a relatively small sample size. Further prospective studies with more patients are required to confirm our results.

5. Conclusion

The newly developed scissors-attached micro-forceps could significantly reduce the clamp time and occurrence of ASI in STA-MCA anastomosis for MMD. The clamp time was the only significant factor predicting the occurrence of ASIs, with a cutoff value of 33.2 min.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Faculty of Medical Sciences, University of Fukui (No. 20150155). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MY: Writing—original draft, Data curation, Formal analysis, Methodology, Project administration, Validation, Writing—review and editing. HT: Data curation, Methodology, Project administration, Writing—original draft, Conceptualization, Supervision. RK: Writing—original draft, Conceptualization, Data curation, Resources, Software, Supervision. MI: Writing—original draft, Data curation, Methodology, Supervision. YH: Data curation, Methodology, Supervision, Writing—original draft. KM: Data curation, Methodology, Supervision, Writing—original draft. TY: Investigation, Software, Data curation, Writing—original draft. AA: Supervision, Data curation, Investigation, Writing—original draft. SK: Software, Data curation, Investigation, Writing—original draft. MO: Methodology, Supervision, Data curation, Writing—original draft. SY: Data curation, Methodology, Supervision, Writing—original draft. TT: Software, Data curation, Methodology, Writing—original draft. AW: Data curation, Methodology, Software, Writing—original draft. HO: Visualization, Data curation, Methodology, Writing—original draft. YK: Supervision, Validation, Data curation, Visualization, Writing—original draft. HA: Investigation, Methodology, Project administration, Data curation, Supervision, Writing—original draft. KK: Conceptualization, Formal Analysis, Funding acquisition, Resources, Software, Validation, Visualization, Writing—review and editing, Data curation, Investigation, Methodology, Project administration, Supervision, Writing—original draft.

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Conflict of interest

HT was employed by Charmant Co., Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Long Wang,
Capital Medical University, China

REVIEWED BY
Jianjian Zhang,
Wuhan University, China
Lei Mao,
Nanjing University, China
Evgenii Belykh,
Rutgers University, Newark, United States

*CORRESPONDENCE
Jinghui Lin
✉ bpbpbbpp@126.com

†These authors have contributed equally to this work

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Application of intraarterial superselective indocyanine green angiography in bypass surgery for adult moyamoya disease

Haojin Ni[1†], Yiwen Wu[1†], Chenhui Zhou[1], Xianru Li[1], Shengjun Zhou[1], Wenting Lan[2], Zhimeng Zhang[1], Yi Huang[1], Haifeng Wang[1] and Jinghui Lin[1*]

[1]Department of Neurosurgery, The First Affiliated Hospital of Ningbo University, Ningbo, China,
[2]Department of Radiology, The First Affiliated Hospital of Ningbo University, Ningbo, China

Background: Extracranial-intracranial (EC-IC) bypass surgery is the main treatment approach to moyamoya disease, and an accurate assessment of the patency of anastomosis is critical for successful surgery. So far, the most common way to do this is the intraoperative intravenous indocyanine green (ICG) video-angiography. Intra-arterial ICG-VA has been applied to treat peripheral cerebral aneurysms, spinal arteriovenous fistulas, and dural arteriovenous fistulas, but few reports have concerned the use of arterial injection of ICG to evaluate anastomotic patency. This research aims to explore the feasibility and effects of catheter-guided superficial temporal artery injection of ICG in the evaluation of anastomotic patency after bypass surgery.

Methods: In this study, 20 patients with moyamoya disease or syndrome who underwent bypass surgery were divided into two groups, one who received intravenous ICG angiography and the other who received intra-arterial ICG angiography, to compare the two injection methods for vascular anastomosis patency. We conducted conventional intraoperative digital subtraction angiography (DSA) in a hybrid operating room during extracranial-intracranial (EC-IC) bypass surgery, including the additional step of injecting ICG into the main trunk of the superficial temporal artery (STA) through a catheter.

Results: Intra-arterial injection of indocyanine green video-angiography (ICG-VA) indicated good patency of the vascular anastomosis when compared with conventional digital subtraction angiography (DSA) and intravenous ICG-VA, confirming the feasibility of using the arterial injection of ICG for assessing anastomotic patency. And intra-arterial ICG-VA results in faster visualization than intravenous ICG-VA ($p < 0.05$). Besides, ICG-VA through arterial injection provided valuable information on the vascular blood flow direction after the bypass surgery, and allowed for visual inspection of the range of cortical brain supply from the superficial temporal artery and venous return from the cortex. Moreover, arterial injection of ICG offered a rapid dye washout effect, reducing the repeat imaging time.

Conclusion: This study indicates that intra-arterial ICG-VA has good effects in observing the direction of blood flow in blood vessels and the range of cortical brain supply from the STA, which reflects blood flow near the anastomosis and provides additional information that may allow the postoperative prediction of cerebral hyperperfusion syndrome. However, the procedure of intra-arterial ICG-VA is relatively complicated compared to intravenous ICG-VA.

KEYWORDS

moyamoya disease, cerebral revascularization, intravenous ICG video-angiography, intra-arterial ICG video-angiography, blood flow direction, cortical perfusion range

1. Introduction

Moyamoya disease is a cerebrovascular disease that mainly manifests in the distal internal carotid artery, as well as the proximal anterior and middle cerebral arteries which are progressively stenosed or occluded, leading to the formation of an abnormal vascular network at the base of the brain (1). It primarily occurs in East Asian countries like Japan, China, etc. The major complications of moyamoya disease include transient ischemic attack (TIA), ischemic and hemorrhagic strokes, cognitive impairment, headaches, and seizures, which can lead to disability or even death (2). So far, there are no definitely effective drugs for the treatment of moyamoya disease, and further investigations are needed (3). Surgical revascularization surgery includes direct, indirect, and combined bypass surgeries. Meta-analysis suggests that the first and the third have significant advantages in treating late-stage stroke and bleeding patients (4). As direct and combined bypass surgeries are the main treatments of moyamoya disease, the assessment of the patency of the anastomosed vessels during surgical bypass of moyamoya disease is therefore critical to ensuring the surgical success.

In 2003, Raabe et al. (5) introduced indocyanine green video-angiography (ICG-VA), which has since then been extensively used for the evaluation of cerebral blood flow intraoperatively in procedures such as aneurysm clipping, bypass surgery, arteriovenous malformation (AVM) and arteriovenous fistula (AVF) (6). In bypass surgery, the evaluation of patency at the anastomotic site is mainly achieved by intravenous injection of ICG (7). However, intravenous injection of ICG has several drawbacks. For instance, due to dilution by the circulation, the intracranial arteries need a large amount of ICG after peripheral venous injection of indocyanine green, and the metabolic process in cerebral vessels after imaging has to last 15 min (8) and is even unrepeatable within a short time. Since synchronization easily occurs at the anastomotic vessels when the indocyanine green flows to the cortical vessels through the carotid artery, the contrast in the imaging area is not abundantly clear, which affects the afterward assessment of results. Currently, although arterial injection of ICG has been applied to treat peripheral cerebral aneurysms, spinal arteriovenous fistulas, and dural arteriovenous fistulas (9–11), there have been few reports about the use of superselective arterial injection of ICG to estimate the patency of the anastomotic site during bypass surgery (12). Thus, this study attempts to estimate the patency of the anastomotic site after cerebral blood flow reconstruction by superselective injection of ICG into the superficial temporal artery through a catheter (select right femoral artery and apply a 5F curved catheter), and investigate the feasibility and effects of this method.

2. Methods

2.1. Patients and acquisition of data

This study involved 20 patients diagnosed with moyamoya disease or syndrome and with indications for surgery, all of whom underwent preoperative digital subtraction angiography (DSA) imaging evaluation based on the diagnostic criteria for moyamoya diseases in the 2021 Japanese moyamoya disease management guidelines (13). The inclusion criteria for patients are as follows:

i. Male or female subjects, age ranging between 18 and 70 years.
ii. Digital subtraction angiography (DSA) imaging demonstrating stenosis or occlusion in the arteries centered on the terminal portion of unilateral or bilateral ICA and abnormal vascular networks in the vicinity of the stenotic or occlusive lesions in the arterial phase.
iii. A qualifying transient ischemic attack (TIA) or ischemic stroke or hemorrhagic stroke in the stenotic or occlusive territory must have occurred within the past 12 months.
iv. No previous history of EC-IC bypass surgery.
v. Must be competent to give informed consent.

These patients were admitted to The First Affiliated Hospital of Ningbo University between December 2022 and April 2023, and underwent STA-MCA bypass surgery combined with intraoperative cerebral angiography. The research protocol has been ratified by the Medical Ethics Committee of the First Affiliated Hospital of Ningbo University (2022-085A), conducted according to relevant organizational guidelines, and complied with the Helsinki Declaration (revised in 1983). We obtained written informed consent from all the patients. Preoperative and postoperative radiographic data were obtained from the department's digital management software, and videos recorded with a KINEVO 900 microscope (Carl Zeiss) were analyzed and evaluated. Numerical data were compared within the same group using the paired *t*-test. All analyses were performed with IBM SPSS Statistics 25.0. Results with $p < 0.05$ were considered significant.

2.2. Surgical procedure

All STA-MCA bypass surgeries and intraoperative cerebral angiography were executed, respectively, by the same experienced neurosurgeon in the hybrid operating room. Following general anesthesia, the patient was in a supine position with the head tilted 60° to the opposite side. The perineum was disinfected and draped, the Seldinger technique was used to pierce the right femoral artery, a 5F sheath was inserted, and a 5F curved catheter was selected and advanced to the beginning of a parietal branch of the superficial temporal artery on the affected side. The catheter position was maintained, and heparinized saline was continuously infused through the catheter and manually flushed every 20 min to prevent thromboembolism. Next, the head was disinfected and draped, a curved incision of approximately 15 cm was made on the ipsilateral frontotemporal area, and the scalp was incised to create a flap. The temporal muscle was partially incised to create a muscle flap, and the muscle was dissected and flipped forward with adequate intraoperative protection of the superficial temporal artery. Based on the preoperative digital subtraction angiography, the bone flap of approximately 6 cm × 8 cm was removed to avoid the middle meningeal artery. Then, the dura mater was suspended, and the parietal branch of the superficial temporal artery was separated and the dura mater was radially incised. The brain surface was examined, and a suitable receptor vessel was selected for the STA-MCA anastomosis. After the anastomosis, the fluorescence microscope was turned on, and 25 mg indocyanine green (25 mg in 5 cc) was intravenously injected peripherally to determine the patency of the anastomosis. In the ICG video-angiography, the imaging is recorded under a microscope while ICG is injected. Subsequently, digital subtraction angiography (DSA) was conducted to evaluate the blood flow patency of the anastomotic site. Afterward, indocyanine green was intra-arterially injected through the catheter, and the anastomotic site was evaluated using an integrated ICG-VA microscope. The catheter sheath was removed, the vascular closure device was used to close the vessel, and local hemostatic dressings were applied. The temporal muscle was repaired, and the dural defect was closed in layers. Finally, conventional postoperative computed tomography (CT) scans were performed 2 hours after surgery to detect any secondary cerebral hemorrhage. In addition, it is necessary to monitor the patient's systemic symptoms and to check the magnetic resonance imaging (MRI) immediately if there are signs of cerebral infarction.

2.3. Intraoperative indocyanine green videoangiography

A microscope (KINEVO 900, Carl Zeiss), outfitted with a fluorescence illuminant (wavelength 700–850 nm) and an infrared camera for imaging, was used to integrate near-infrared indocyanine green fluorescence imaging. It provides an automatic zoom function and adjusts the camera gain automatically during ICG-VA to the near-infrared signal strength within the camera's dynamic range, achieving optimal visualization of the fluorescent area. The microscope was placed vertically about 300 mm away from the study area. During ICG-VA, the surgical area light was turned off, and 25 mg of indocyanine green was dissolved in 5 mL of saline and administered as a single intravenous injection through a peripheral venous catheter. When reaching the corresponding area, ICG emits fluorescence after being excited by near-infrared light, then converted to a black-white image which is displayed on the microscope monitor. The operator evaluated the patency of the anastomosis site by looking at the ICG videoangiography recording on the microscope monitor. Similarly, the graft patency of the anastomosis site was evaluated by observing the fluorescence image through the microscope after ICG was injected into the superficial temporal artery through a catheter. 25 mg of indocyanine green in 5 mL of saline was dissolved and a smaller dose (0.5 mL) was used to compare the results after peripheral venous injection. Flow control at 2 mL/min is required by micropump injection.

3. Results

3.1. Demographics

A total of 20 patients with MMD who underwent STA-MCA anastomosis surgery were included in this study, including 12 males and 8 females. The patients' ages ranged from 23 to 70 years (mean age 51 years). The patency of the anastomosis was evaluated using both intravenous and arterial injection of ICG-VA in all the patients and verified by intraoperative DSA. Among them, 19 were detected with symptoms of transient ischemic attacks, ischemic strokes, or hemorrhagic strokes, except one being asymptomatic, as shown in Table 1.

3.2. Assessment of anastomotic patency

Each patient received intravenous injection of ICG-VA, followed by intraoperative DSA and intra-arterial injection of ICG-VA. Based on the visualized demonstration of ICG after intravenous injection in Figure 1 and the evaluation results of intraoperative DSA for the same patient in Figure 2, the patency of the anastomotic vessel is clear, which is also verified by the evaluation results during intra-arterial injection of ICG-VA in the arterial phase of the same patient shown in Figures 3A–C. It should be noted that there were no adverse reactions to indocyanine green during the operation. Thus, the comparison of the results between intra-arterial injection and the intravenous injection and their intraoperative DSA evaluation all confirmed the effectiveness of intra-arterial injection of ICG-VA in evaluating anastomosis patency.

3.3. Timing of ICG signal after injection

In our current study, we recorded the timing of ICG signals after injection by both methods. As shown in Table 2, we counted the time required for two methods of ICG video-angiography to begin imaging.

TABLE 1 Study participants clinical characteristics.

Case No.	Sex	Age	Symptoms	Operated side
1	Female	53	Ischemia	Left
2	Male	43	TIA	Right
3	Female	23	Hemorrhage	Right
4	Male	42	Headache	Left
5	Male	40	Hemorrhage	Left
6	Female	37	Hemorrhage	Right
7	Female	58	Ischemia	Left
8	Male	53	Headache	Left
9	Female	57	Ischemia	Right
10	Male	56	Ischemia	Right
11	Male	55	Ischemia	Right
12	Male	59	TIA	Left
13	Male	70	TIA	Left
14	Male	47	Hemorrhage	Right
15	Female	66	Ischemia	Left
16	Male	64	TIA	Left
17	Male	31	Hemorrhage	Right
18	Male	63	Ischemia	Left
19	Female	50	TIA	Left
20	Female	47	None	Right

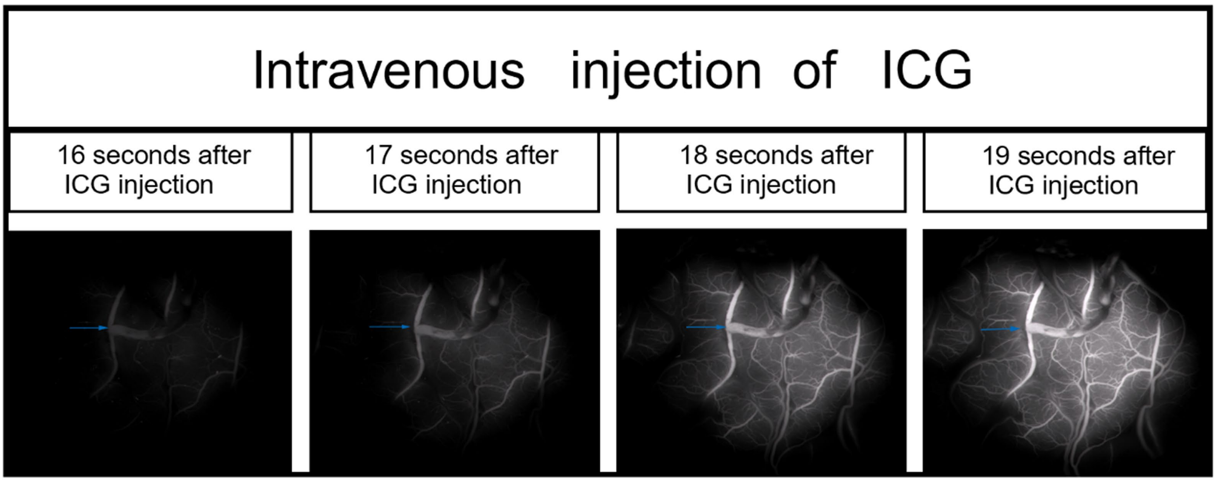

FIGURE 1
During the right middle cerebral artery (M4) bypass surgery, intravenous indocyanine green (ICG) video-angiography was performed to visualize blood vessels in one case (the anastomotic site is indicated by the blue arrow).

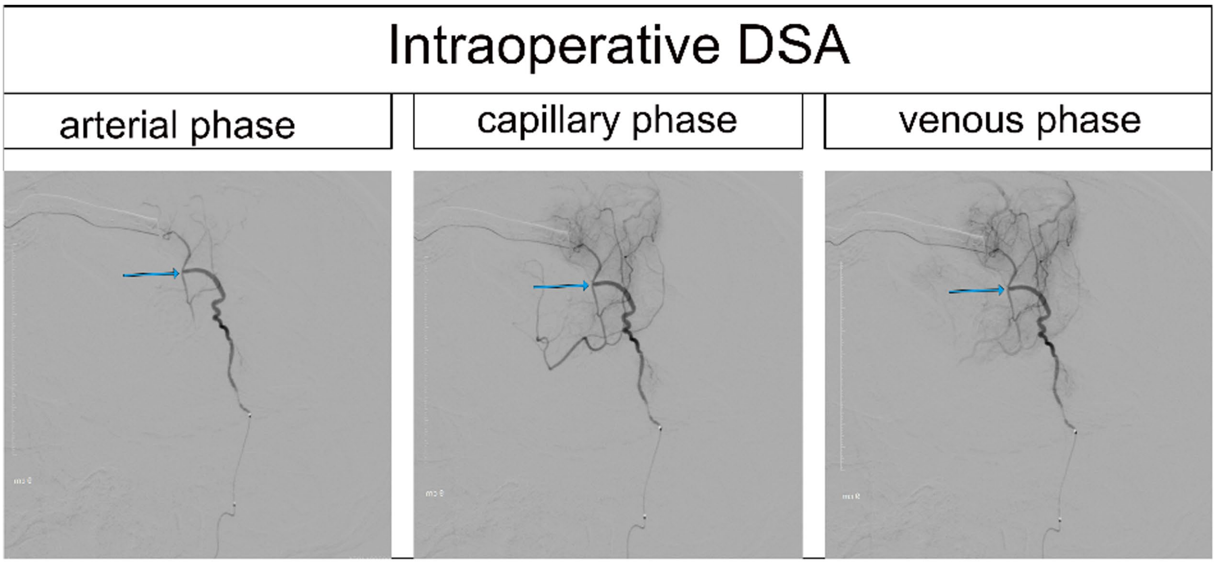

FIGURE 2
Intraoperative DSA of the same patient (the anastomotic site is indicated by the blue arrow).

The average time required for intravenous injection of ICG video-angiography was 27.3 s, while the average time required for intra-arterial injection of ICG video-angiography was only 1.08 s, there is a significant difference between the two data, it can be concluded that intra-arterial ICG-VA results in faster visualization than intravenous ICG-VA($p < 0.05$).

3.4. Blood flow observations with intravenous and intra-arterial ICGA

Although fluorescence is emitted near the anastomosis site, as shown in the imaging after intravenous injection of ICG in Figure 1, which makes it difficult to evaluate the blood flow direction after bypass grafting, the superficial temporal artery is immediately visible and subsequently flows into the recipient vessel, cerebral capillaries and refluxing vein after intra-arterial injection of ICG, as shown in Figure 3, which clearly illustrates the arterial, capillary, and venous phases of ICG entering the vessels. Furthermore, the approximate range of the cerebral cortex is supplied by the superficial temporal artery, as shown in Figure 4B, and there exists the venous reflux of the cortical area with the corresponding vein being identifiable, as shown in Figures 4C,D. However, due to the low contrast, ICG-VA intravenously injected fails to demonstrate the above positive effects, according to Figure 4A. Comparing Figure 4B and Figure 4C, we found that despite the difference of only 5 s between the two

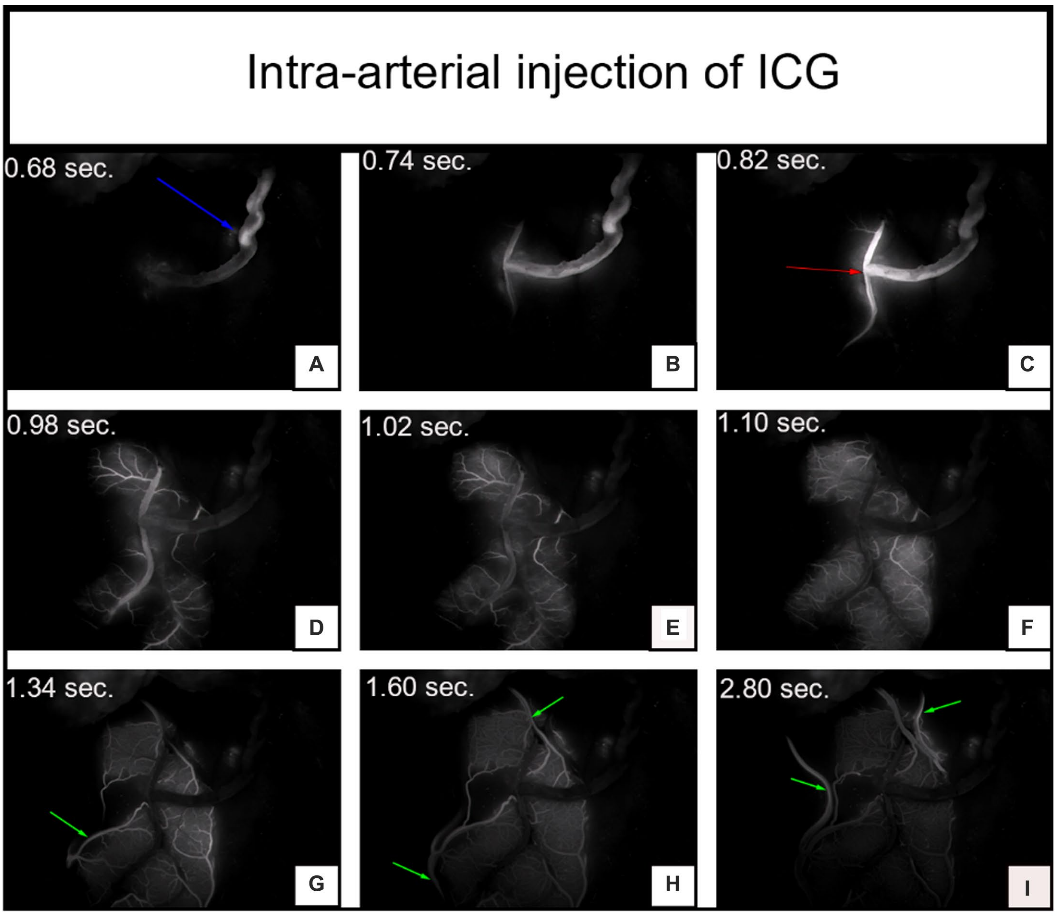

FIGURE 3
The video angiography results of the same patient after arterial injection of indocyanine green (ICG). Panels **(A–C)** depict the arterial phase of ICG injection, where the blue arrow indicates the temporal superficial artery and the red arrow indicates the anastomosis site. Panels **(D–F)** represent the capillary phase of ICG injection. Panels **(G-I)** display the venous phase, where the green arrow indicates the refluxing vein. The time of ICG signal after injection is noted in the upper left corner.

images, most of the ICG in the capillary phase was not visible after entering the venous phase, indicating that the dye washout effect of arterial injection of ICG is stronger.

4. Discussion

Direct and combined bypass are currently the main methods for treating adult moyamoya disease (4), and vascular anastomosis is the key to surgery. Due to the slender nature of the recipient and donor vessels, vascular anastomosis is extremely difficult, and intraoperative excessive damage to the intima is more likely to cause acute thrombosis (14) and occlusion of the anastomosis. Failing a timely warning and possible early detection can produce iatrogenic cerebral infarction and new-onset neurological dysfunction (7). Rapid and accurate evaluation of the patency of the anastomotic site during the bypass surgery thus becomes critical for the success of the surgery.

So far, there are various methods for intraoperative evaluation of vascular anastomosis patency, and among them, ICG video-angiography is the most common and standard technique for assessing anastomosis patency during bypass surgery, owing to its good temporal and spatial resolution and ease of use. Previously, peripheral venous injection of ICG was usually used to evaluate vascular anastomosis, while for our treatment, the images are instantly generated and visible on the screen during intra-arterial injection of ICG, while for the conventional peripheral intravenous injection, the process of imaging needs 10–30 s (15), in our study, the average time required for intravenous injection of ICG video-angiography was 27.3 s, which is consistent with the above. After imaging, our method of the intra-arterial injection allows the direct observation of blood flow direction, which makes the result more objective, reflecting the patency of the anastomotic site and visually demonstrating that the superficial temporal artery is supplying blood to the recipient vessel, representing the success of this bypass surgery. But for the conventional injection of ICG angiography, there is an uncertainty about the direction of cerebral blood flow after grafting and difficulty in detecting the blood flow direction when the cerebral blood flow velocity is high, since it requires an in-depth analysis and detection under the FLOW 800 system (16) with the ROI in a better position as setting, ultimately causing a delay and some

TABLE 2 The time from ICG injection to ICG signal appearance (seconds).

Case No.	Intravenous ICG-VA	Intra-arterial ICG-VA	*p*-value
1	19	0.1	
2	22.7	0.8	
3	23.1	2.2	
4	25.4	0.5	
5	26.2	0.2	
6	16	0.6	
7	50	3.2	
8	21.8	1.2	
9	34.4	1.2	
10	37.6	1.6	
11	20.5	1.2	
12	22.2	0.3	
13	29.2	1.2	
14	22	0.2	
15	37.2	2.2	
16	25.2	0.5	
17	26.7	1.2	
18	29.8	0.8	
19	33.6	2	
20	23.4	0.4	
Mean	27.3	1.08	2×10^{-12}

deviation. Furthermore, in our study, it becomes easily identifiable of the cortical area supplied by the superficial temporal artery and the venous reflux of the cortical area. Currently, cerebral hyperperfusion syndrome (CHS) is a not rare and thorny complication after bypass surgery, mainly manifested as epilepsy, headache, and even cerebral hemorrhage (17). A study indicates that the larger the direct perfusion range of the superficial temporal artery, the lesser the possibility of CHS occurring (18), and a case report prompts that cortical venous reddening near the anastomotic site after bypass surgery may be a sign of hyperperfusion (19). Therefore, although there are many factors that affect the occurrence of CHS, the observation of the supply area of the superficial temporal artery and cortical venous reflux can serve as additional information that may allow the prediction of cerebral hyperperfusion syndrome for subsequent prevention and treatment. Additionally, for the conventional method, the flowing of intravenous ICG into the cortical vessels through the internal carotid artery probably causes almost simultaneous imaging of the vessels in the field of surgery, which results in poorer image contrast.

The use of a relatively small dose of ICG during this arterial injection process also obtains a favorable imaging result. Although very few reports of adverse reactions to ICG but some cases exposing severe allergic reactions and cardiac arrest (20), therefore a smaller amount of ICG is conducive to the reduction of the incidence of adverse reactions (21). In addition, intra-arterial injection has a better dye washing effect than intravenous injection (22). Moreover, the reduced dosage of ICG results in less residual time in cerebral blood vessels, and in case of poor imaging effect during the operation, the next imaging can be performed more quickly, shortening the surgery time (according to our experience, usually about 1 min of the interval between two vascular imaging).

DSA is considered the gold standard for diagnosing moyamoya disease and assessing the patency of bypass surgery (23). In our study, apart from conventional cerebral angiography, catheter superselection, and indocyanine green angiography into the superficial temporal artery were also employed to obtain images so that these images were congruent with those observed under the surgical microscope, allowing for a better understanding of the anatomical structures with higher spatial resolution. Moreover, satisfactory imaging results were also achieved when injection of ICG into the branch vessel of STA using a syringe after STA-MCA anastomosis, which was specially designed for some patients who refused DSA (24).

Intraoperative microvascular Doppler ultrasound is proposed to be performed directly on the bypass vessel to assess patency using quantitative vascular flow parameters (15). A retrospective study of 51 patients with obstructive cerebrovascular disease who underwent bypass surgery suggested that a cutoff flow index (CFI) of 0.5 can be used as a threshold for evaluating graft patency, with a graft patency rate of 92% for cases with CFI >0.5 and 50% for cases with CFI <0.5 (25). However it should be noted that in view of a high requirement of Doppler technique for the angle between the probe and the vessel, measurements at different angles will yield significantly different results. Besides, it is not as perfect as needed in the spatial resolution and image quality, posing an insuperable obstacle to the evaluation of blood flow in tiny vessels (26). By contrast, intracarotid injection of indocyanine green through a catheter enables more direct observation of the patency of the anastomosis and the filling status of the cortical small vessels.

This study has some limitations. First, intra-arterial injection of ICG is not covered by the FDA permission. However, injection of a lower dose of ICG should be acceptable, compared with intravenous injection. Second, the sample capacity of this study is comparatively small. More data and cases will be better for comparative research to thoroughly evaluate the security and availability of this technology.

5. Conclusion

In vascular bypass anastomosis for moyamoya disease, intra-arterial ICG video-angiography contributes to achieving the same evaluation effect as intravenous ICG video-angiography for evaluating the patency of the anastomotic site and giving a visual display of the blood flow direction of the bypass vessel. In addition, during the imaging process, the cortical area approximately supplied by the donor vessels is observable, providing additional information that may allow the prediction of postoperative cerebral hyperperfusion syndrome. However, the procedure of intra-arterial ICG-VA is relatively complicated compared to intravenous ICG-VA.

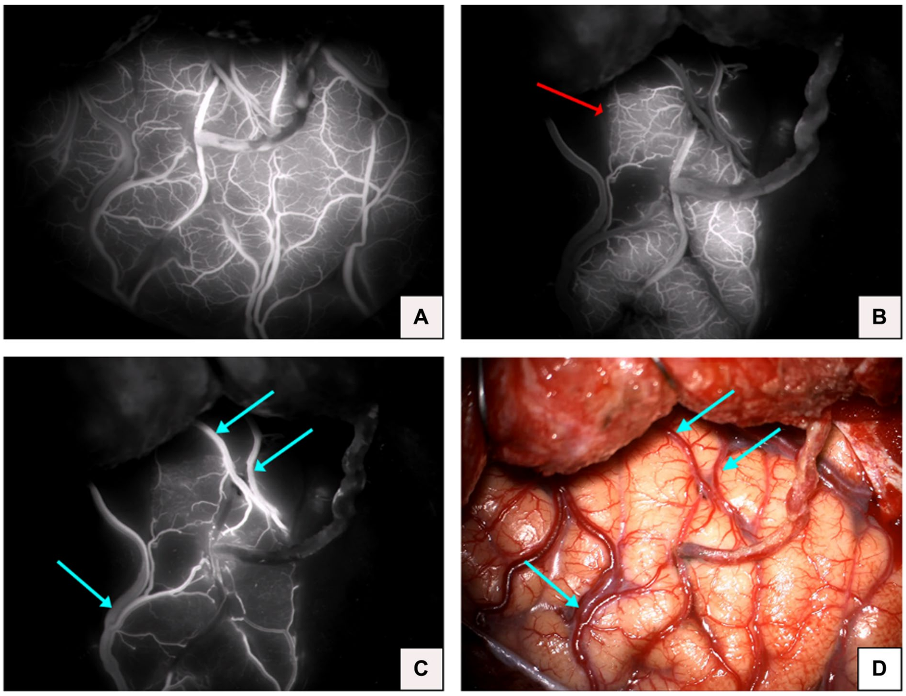

FIGURE 4
(A) Image of complete visualization after intravenous injection of ICG. **(B)** Microvascular phase after arterial injection of ICG in the same patient (red arrow indicates the cortical area of the brain supplied by the superficial temporal artery). **(C)** Venous phase after arterial injection of ICG in the same patient (blue arrow indicates the venous return). **(D)** Microscopic view of the operative field after completion of the bypass in the same patient (blue arrow indicates venous return).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Medical Ethics Committee of the First Affiliated Hospital of Ningbo University (2022-085A). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

JL: conceptualization, project administration, writing—review and editing, funding acquisition, and supervision. XL and SZ: methodology. HN and CZ: software and investigation. WL and ZZ: validation. YH and HW: formal analysis. HN and YW: writing—original draft preparation. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Long Wang,
Capital Medical University, China

REVIEWED BY
Morgan Broggi,
IRCCS Carlo Besta Neurological Institute Foundation, Italy
Elio Mazzapicchi,
IRCCS Carlo Besta Neurological Institute Foundation, Italy
Jacopo Falco,
IRCCS Carlo Besta Neurological Institute Foundation, Italy

*CORRESPONDENCE
Zheng-hui Sun
szh_301@126.com
Chen Wu
13671007509@163.com

†These authors have contributed equally to this work

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The surgical strategy and technical nuances of *in situ* side-to-side bypass for the management of complex intracranial aneurysms

Hua-wei Wang†, Zhe Xue†, Cai-hong Sun†, Dong-sheng Kong, Chen Wu* and Zheng-hui Sun*

Department of Neurosurgery, The First Medical Center of PLA General Hospital, Beijing, China

Background: Despite continuous advances in microsurgical and endovascular techniques, the treatment of complex aneurysms remains challenging. Aneurysms that are dilemmatic for conventional clipping or endovascular coiling often require bypass as part of a strategy to reduce the risk of ischemic complications. In anatomically favorable sites, the intracranial–intracranial *in situ* bypass may be an appealing choice. This article details the surgical strategies, operative nuances, and clinical outcomes of this technique with a consecutive series in our department.

Methods: A retrospective review of a prospectively maintained neurosurgical patient database was performed to identify all patients treated with side-to-side *in situ* bypass from January 2016 to June 2022. In total, 12 consecutive patients, including 12 aneurysms, were identified and included in the series. The medical records, surgical videos, neuroimaging studies, and follow-up clinic notes were reviewed for every patient.

Results: Of the 12 aneurysms, there were 5 middle cerebral artery aneurysms, 4 anterior cerebral artery aneurysms, and 3 posterior inferior cerebellar artery aneurysms. The morphology of the aneurysms was fusiform in 8 patients and saccular in the remaining 4 patients. There were 3 patients presented with subarachnoid hemorrhage. The treatment modality was simple *in situ* bypass in 8 cases and *in situ* bypass combined with other modalities in 4 cases. Bypass patency was confirmed in all cases by intraoperative micro-doppler probe and (or) infrared indocyanine green (ICG) video angiography intraoperatively and with digital subtraction angiography (DSA) or computed tomography angiography (CTA) postoperatively. None of the patients developed a clinically manifested stroke due to the procedure though a callosomarginal artery was intentionally removed in one patient. The median follow-up period was 16.2 months (6-36). All patients had achieved improved or unchanged modified Rankin scale scores at the final follow-ups.

Conclusion: Cerebral revascularization technique remains an essential skill for the treatment of complex aneurysms. The *in situ* bypass is one of the most effective techniques to revascularize efferent territory when vital artery sacrifice or occlusion is unavoidable. The configuration of *in situ* bypass should be carefully tailored to each case, with consideration of variations in anatomy and pathology of the complex aneurysms.

KEYWORDS

revascularization, intracranial-intracranial bypass, *in situ* bypass, side-to-side anastomosis, complex intracranial aneurysms

Introduction

With continuous advances in endovascular techniques, the treatment paradigm of intracranial aneurysms has shifted to intervention from microsurgery in the past 2 decades (1). However, whatever modality is selected, the management of complex aneurysms remains challenging due to their giant size, wide neck, dolichoectatic morphology, or perforator features. Overall, the reported mortality and morbidity remain relatively high (2–4). A subset of complex aneurysms that are not suitable for standard intervention or clipping may benefit from surgical revascularization, which could ensure sufficient distal blood flow and lower the risk of ischemic complication when the parent artery or distal branch was deliberately occluded as part of the treatment strategy (5).

There have been reports on the increased use of revascularization techniques for complex aneurysms management recently (6) and that equivalent results have been achieved from extracranial–intracranial (EC-IC) and intracranial-to-intracranial (IC-IC) bypasses in terms of clinical and radiological outcomes (5, 7). Both bypass techniques have been used successfully in our center (8). Nevertheless, bypass preference has changed over time with evolving microsurgical techniques and collective experience and creativity. The IC-IC bypasses (or third-generation bypass) are being more preferred recently due to the simple, elegant, and hemodynamic advantages over their EC-IC counterparts (7, 9). The *in situ* side-to-side anastomose technique epitomizes the appealing IC-IC bypasses.

The *in situ* bypass connects parallel and proximate arteries in a side-to-side fashion. In anatomically favorable sites, for example, the longitudinal fissure, Sylvian fissure, ambient cistern, and cisterna magna, it could provide cross-communication blood flow between the anterior cerebral arteries, the middle cerebral artery branches, the superior cerebellar artery and posterior cerebral artery, and the posterior inferior cerebellar arteries, respectively. However, studies reporting this technique for the management of complex intracranial aneurysms are few (10, 11). In the present study, we will summarize our experience of *in situ* bypasses and detail the surgical strategies, operative nuances, and clinical outcomes with a consecutive series in our department.

Methods

Patients and data collection

After obtaining approval from the institutional review board, a consecutive series was identified from a prospectively maintained database of bypasses for managing intracranial aneurysms from January 2016 to June 2022. Only the patients with *in situ* bypass were included in the study. Patients' demographic characteristics, radiographic images, operative videos, and medical records including procedure-related complications were reviewed. The neurological outcomes were assessed using the modified Rankin Scale (mRS) upon discharge and at subsequent follow-up visits or by telephone. A neurosurgeon who was not directly involved in the treatment performed the assessments. Bypass patency and aneurysm occlusion were evaluated using angiography at discharge, half a year, and 1 year postoperatively, and then annually. All patients provided written informed consent for database collection and research use.

Surgical steps and technical nuances

Though the surgical approaches diversify according to the locations of the aneurysms and associated vascular anatomy, the procedure of side-to-side anastomosis during each *in situ* bypass is largely identical with minor differences. In brief, with full exposure, the parallel recipient and donor arteries were circumferentially dissected. Temporary occlusion could be achieved by 2 clips crossing both vessels or four separate mini-clips clamping each vessel proximally and distally. Alternatively, three clips with one clip crossing both vessels proximally and two mini-clips occluding each artery distally were applied. Overall, the configuration of temporary clip placement should approximate the vessels while optimizing visibility.

Then, a rubber dam was placed beneath both vessels to keep them away from the blood background. A continuous suction drain was recommended in such a deep operative field as well. After methylene blue coloring, both arteries were pierced at approximately 9 o'clock and 3 o'clock positions with a fine syringe needle, and then, angled micro-scissors were used to extend the opening on the superior-medial aspect of both arteries. The length of arteriotomies was typically performed to be approximately 2.5 times the diameter of the artery. Special attention should be given to avoid damaging the vessels' posterior wall.

Two nylon threads (9-0 or 10-0) were cut to approximately 50 mm long for easy handling. Both the stay sutures were performed in an outside–inside–outside fashion at both apices of the arteriotomy. Each stay suture was tied off using a square knot, and the tail with the needle was intentionally left long. One tail was used to run the stitch through the posterior wall, and the other through the anterior wall. Some surgeons advocate small loops are created during suturing and then tightened sequentially after suturing is completed to ensure even tension along the entire suture line (12–14), but in our experience, step-by-step tightening during suturing was also practicable. Heparin irrigation was used intermittently in the surgical field during the anastomosis, and systemic heparin was not necessary. No aspirin therapy was required before and postoperatively.

After the suturing was completed, bypass patency was confirmed with an intraoperative micro-doppler probe and (or) infrared indocyanine green (ICG) video angiography. Small leaks could be stopped by covering them with a small piece of Gelfoam (Upjohn, Kalamazoo, MI) and light pressure, whereas large leaks required a stitch repair. Total intravenous anesthesia was used both to induce and maintain general anesthesia. Somatosensory and motor evoked potentials were monitored in all patients and burst suppression was maintained with propofol or barbiturates during clamp

TABLE 1 Demographic and radiological characteristics of the aneurysms.

Case no.	Age (years)	Sex	Presentation	Aneurysm location	Morphology	Size (cm)	Pre-operative mRS score
1	64	F	SAH; ICH	R A2-A3	Saccular	1.2	4
2	47	F	Headache	AcomA	Saccular	1	1
3	38	F	Dizziness	L p1-V4	Saccular	1.5	1
4	59	M	Recurrent aneurysms after clipping	R M2	Fusiform	2	0
5	11	M	Recurrent aneurysms after Coiling	L M1-M2	Fusiform, Multi-Lobular	2.5	0
6	66	M	SAH	R p2	Fusiform	0.6	3
7	65	F	SAH; Visual deficit	L A1	Fusiform	1.5	3
8	45	M	Accidental	L p1	Fusiform	1.2	0
9	51	M	Headache	R M2	Fusiform	2.2	1
10	57	M	Cerebral infarction	R M2	Fusiform	2.3	2
11	62	M	Accidental	R A1-A2	Saccular	2	0
12	17	F	Recurrent aneurysms after clipping	R M1-M2	Fusiform	2.8	0

mRS, Modified Rankin Scale; M/F, male/female; R/L, right/left; SAH, subarachnoid hemorrhage; ICH, intracranial hematoma; A, segment of anterior cerebral artery; AcomA, anterior communicating artery; M, segment of middle cerebral artery; p, segment of posterior inferior cerebellar artery; V, segment of vertebral artery.

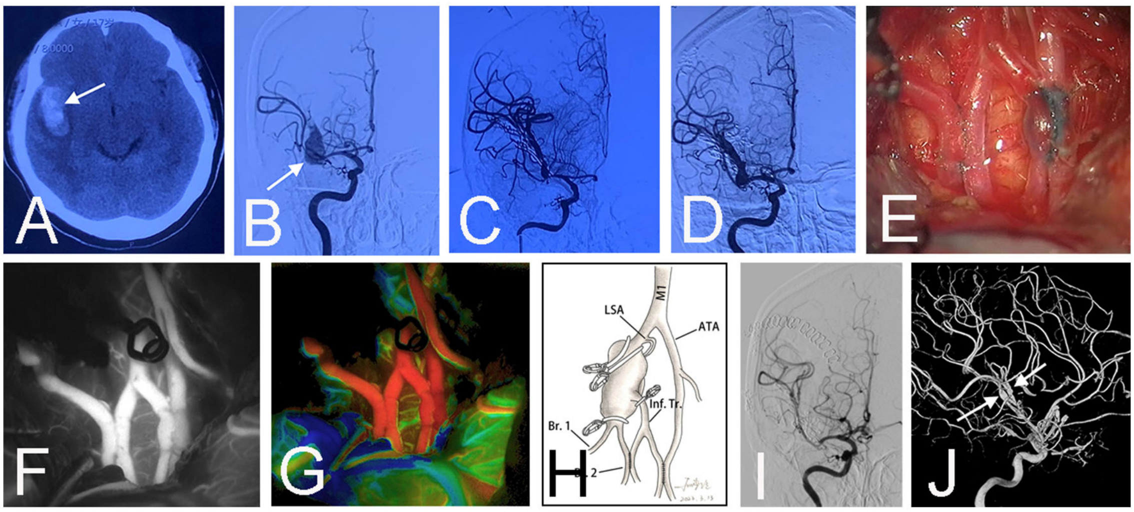

FIGURE 1
Preoperative CT scan showed a subarachnoid hemorrhage and hematoma above the corpus callosum (arrow) in a 63-year-old female (Case 1) **(A)**. Emergent CT angiography revealed a saccular aneurysm (arrow) at the location where the right anterior cerebral artery branches into the callosomarginal artery and pericallosal artery **(B)**. An emergency surgery was performed at night because the patient had a bad mental state (mRS 4). Surgical clipping was attempted, but the aneurysmal neck was brittle. Two crevasses (arrows) emerged during the aneurysm dissection **(C)**. Then a bail-out side-to-side anastomosis was performed between bilateral pericallosal arteries **(D)**. Intraoperative infrared indocyanine green angiography confirmed the patency of the anastomosis **(E)**. The aneurysm was trapped, and the right callosomarginal artery was sacrificed because it originated from the aneurysmal body and was hard to preserve. Fortunately, no infarction occurred post-surgery **(F)**. The schematic diagram illustrates the treatment in this patient **(G)**. Postoperative angiography demonstrated the obliteration of the aneurysm **(H, I)**. Three-dimensional angiography showed the patent anastomosis (arrow) and right pericallosal artery (arrowhead) **(J)**.

time. The mean blood pressure was maintained at 100 mmHg and was raised by 30% above during the clamp time. Conventional computed tomography (CT) scan and digital subtraction angiography (DSA) or computed tomography angiography (CTA) were used as a common postoperative radiological assessment.

Results

Patient and aneurysm characteristics

During a 6-year period from January 2016 to June 2022, 758 patients with intracranial aneurysms were treated by microsurgery in our department. The treatment decision was determined by a multidisciplinary team comprising neurovascular surgeons and interventional neuroradiologists. A bypass procedure was performed to re-perfuse the involved territory whenever a parent artery was to be deliberately sacrificed. After screening, there were in total of 86 patients who had undergone various types of revascularization procedures for aneurysm management in the period. Among them, twelve patients who underwent side-to-side anastomosis with or without other bypasses were identified, representing 13.9% of patients with revascularization surgery.

Of the 12 patients with *in-situ* bypasses, the average age was 48.5 years (range, 11–66), and there was a male predominance (58.3%). Three patients presented with subarachnoid hemorrhage, and two patients had recurrent aneurysms after clipping and one after coiling. The other six patients had asymptomatic aneurysms identified during the evaluation of apparently unrelated complaints. The mean mRS of all patients at presentation was 1.3 (range, 0–4). There were 12 aneurysms in total in the 12 patients, including 5 middle cerebral artery (MCA) aneurysms, 4 anterior cerebral artery (ACA) aneurysms, and 3 posterior inferior cerebellar artery (PICA) aneurysms. The mean diameter of these aneurysms was 17.3 mm, ranging from 6.0 to 28.5 mm. The morphology of the aneurysms was fusiform in eight patients and saccular in the remaining four patients. The above demographic and radiological characteristics of the aneurysms are shown in Table 1.

Clinical features and surgical results

Cranial approaches were chosen individually. Pterional craniotomy was used in all five MCA aneurysms, the far lateral approach in all three PICA aneurysms, the bifrontal craniotomy in three ACA aneurysms, and the bifrontal craniotomy combined with a pterional approach in another ACA aneurysm. The *in situ* bypass was the only revascularization procedure in eight patients and combined with others in four patients. The combined procedures included one M4-superficial temporal artery (STA)-M4 interposition bypass, one M2-M2 reimplantation, one EC-IC STA-M2+M2 double-barrel bypass, and one parallel M2-M2 *in situ* bypass. Aneurysm trapping was performed at one stage in 10 patients, and aneurysm occlusion was achieved by second-stage coiling in 2 patients. The patency of *in situ* bypasses was confirmed in all patients both intraoperatively and postoperatively. The 6-month postoperative radiological assessment demonstrated all the aneurysms were completely obliterated. No mortalities occurred and no technical- or bypass-related morbidities developed though a callosomarginal artery was intentionally removed in one patient (Case 1) (Figure 1). The median follow-up period was 16.2 months (6-36). All patients had improved or unchanged mRS scores at the final follow-up. The clinical features and surgical results of *in situ* side-to-side bypasses are listed in Table 2.

Discussion

This *in situ* side-to-side bypass technique is unique to neurovascular surgery because two neighboring and opposing arteries are seldom observed in vascular structures of other body parts. In 1986, Ikeda et al. (15) first described the microvascular side-to-side anastomosis technique in neurosurgery. After the initial case reports in the early 90s, a few case series discussed the applications of the technique and multiple new construct variations have emerged (9, 10, 14). The *in situ* bypasses are appealing because they are entirely intracranial and less vulnerable to injury, do not require harvesting an extracranial artery or graft, use donor and recipient arteries with diameters that are well matched and require just one anastomosis. Furthermore, the *in situ* bypass configuration forms a communicating artery or vascular bifurcation in a highly anatomically directed fashion, which could minimize the disruption of normal blood flow distal to the aneurysm. The favorable surgical and radiologic outcomes in our series also proved the advantages of *in situ* bypass in the management of complex cerebral aneurysms.

However, *in situ* side-to-side anastomosis is probably the most difficult bypass technique. It is commonly performed in a deep surgical corridor and requires the donor and recipient arteries to lie parallel and in proximity to each other. Fortunately, this uncommon anatomical location spared the need for tedious donor and receipt artery dissection just as required in other type of bypasses. Moreover, side-to-side anastomosis often requires more bites than others because the arteriotomy is long enough to an extent that it is two-to-three times the diameter of the arteries, whereas, with the continuous suturing technique, the amount of time spent could be kept below 45 min, as reported in others' series (14). One potential pitfall while performing the long anastomosis is suturing the two walls of the same artery together so that it gets closed. This could be avoided with an assistant from the intraluminal stent during the anastomosis though it rarely happened with a high magnification view of the microscope and methylene blue coloring of the arterial walls based on our experience.

One criticism toward the *in situ* bypass is that both the donor and recipient vessels have to be clamped to perform the side-to-side anastomosis instead of just temporarily occluding one intracranial recipient artery such as the traditional STA-MCA bypass, which had achieved very good surgical results in reported series (5). Therefore, the bypass failure would jeopardize the patency of two intracranial arteries with a subsequent risk of bilateral or wide-ranging ischemic events. However, this concern did not occur in our series. The results might be attributed to the following reasons. First, the continuous suturing technique decreased the number of knots and the amount of time spent on temporarily occluding. Second, the long arteriotomy promised a high patency rate (100%) of side-to-side anastomosis. Moreover, various methods were used to increase the tolerance of the brain to ischemia during which both arteries were temporarily occluded,

TABLE 2 Clinical features and surgical results of *in situ* side-to-side bypasses.

Case no.	Aneurysm location	Cranial approach	Bypass technique	Aneurysm occlusion	Angiography outcome	Surgical complication	Last mRS score	Follow-up (months)
1	R A2-A3	BAIH	R A3-L A3 *in situ*	Trapping	Patent bypass, complete obliteration of aneurysm	R CmaA Occlusion	1	12
2	Acom	BAIH	R A3-L A3 *in situ*	Second stage coiling	Patent bypass, complete obliteration of aneurysm	No	1	18
3	L p1-V4	Far lateral approach	R p3-L p3 *in situ*	Trapping	Patent bypass, complete obliteration of aneurysm	No	0	36
4	R M2	Pterional approach	R M2-R ATA *in situ*, R M4-STA-M4 interposition	Trapping	Patent bypass, complete obliteration of aneurysm	No	0	8
5	L M1-M2	Pterional approach	L M2-L M2 *in-Situ*, L M2-L M2 reimplantation	Trapping	Patent bypass, complete obliteration of aneurysm	No	0	12
6	R p2	Far lateral approach	R p1-R p3 *in situ*	Trapping	Patent bypass, complete obliteration of aneurysm	No	0	12
7	L A1	BAIH and Left Pterional approach	R A3-L A3 *in situ*	Trapping	Patent bypass, complete obliteration of aneurysm	No	2	18
8	L p1	Far lateral approach	R p3-L p3 *in situ*	Trapping	Patent bypass, complete obliteration of aneurysm	No	0	18
9	R M2	Pterional approach	R M2-R M2 *in situ*, R STA-M2+M2 double barrel	Trapping	Patent bypass, complete obliteration of aneurysm	No	0	24
10	R M2	Pterional approach	R M2-M2 *in situ*	Trapping	Patent bypass, complete obliteration of aneurysm	No	2	18
11	R A1-A2	BAIH	R A3-L A3 *in situ*	Second stage coiling	Patent bypass, complete obliteration of aneurysm	No	0	12
12	R M1-M2	Pterional approach	R M2-R M2+R M2-R M2	Trapping	Patent bypass, complete obliteration of aneurysm	No	0	6

mRS, Modified Rankin Scale; M/F, male/female; R/L, right/left; A, segment of anterior cerebral artery; AcomA, anterior communicating artery; M, segment of middle cerebral artery; p, segment of posterior inferior cerebellar artery; V, segment of vertebral artery; BAIH, basal anterior interhemispheric approach; ATA, anterior temporal artery; STA, superficial temporal artery; CmaA, callosomarginal artery.

including slight hypertension, barbiturates, and mild hypothermia. The electrophysiological monitoring was also very helpful during the temporary occlusive period in our series.

In terms of the management of aneurysms after the *in situ* bypass procedure, radical trapping is recommended. Proximal Hunterian ligation of the parent artery is not promising because the remaining inflow or reverse flow could contribute to aneurysm growth and rupture in spite of intraluminal thrombus formation (16, 17). Furthermore, recurrence or regrowth might occur if there are angiography-negative vessels that reverse flow into the aneurysm. Hauck and Samson (18) reported a subarachnoid hemorrhage occurring after an initial operation, and then during a second operation, they identified several angiography-negative vessels that arose from the aneurysmal dome. Thus, for recurrence-free treatment, aneurysm trapping should be performed whenever possible except for the existence of perforating arteries supplying eloquent regions near the aneurysm, in which partial trapping such as distal or proximal trapping has to be employed. Under

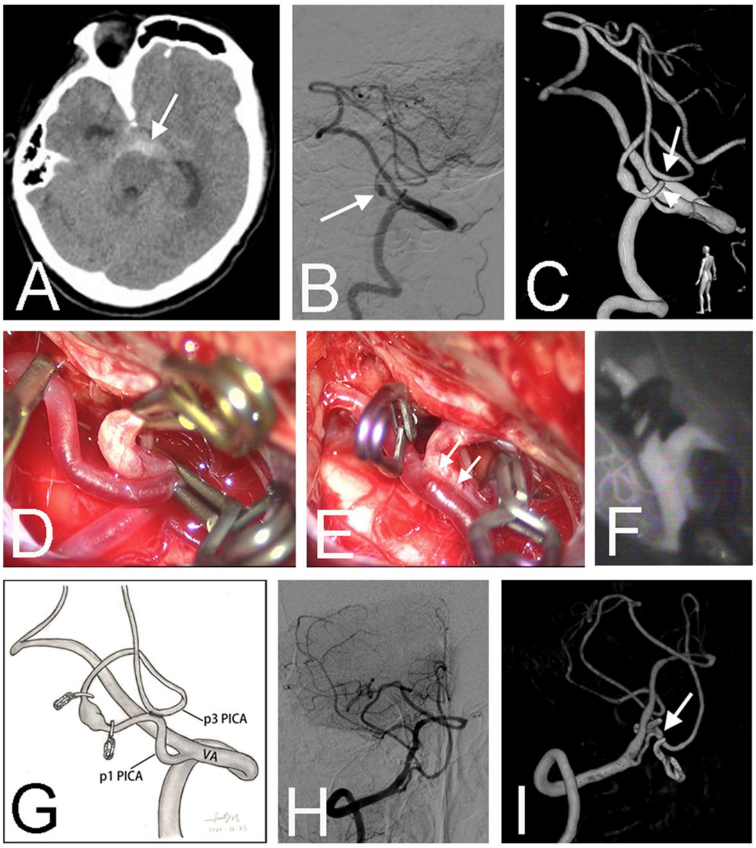

FIGURE 2
Preoperative CT scan showed a subarachnoid hemorrhage in the interpeduncular cistern (arrow) in a 66-year-old male (Case 6) **(A)**. Right vertebral angiography revealed a fusiform aneurysm (arrow) at the lateral medullary segment (p2) of the right posterior inferior cerebellar artery (PICA) **(B)**. Three-dimensional angiography confirmed the diagnosis and showed that the PICA ran in an unusual pattern, forming a loop between p1 (arrowhead) and p3 (arrow) segments **(C)**. After sufficient dissection, the proximal and distal parts of the loop were easily approximated and temporally occluded by three clips **(D)**. After the *in situ* bypass was completed, the aneurysm was trapped **(E)**. Intraoperative infrared indocyanine green angiography confirmed the patency of the anastomosis **(F)**. The schematic diagram illustrates the treatment strategy for this patient **(G)**. Postoperative angiography demonstrated the obliteration of the fusiform aneurysm **(H)**. Three-dimensional angiography showed the patent anastomosis (arrow) **(I)**.

the circumstances, the contrast-enhanced ultrasound would be beneficial to study the effect of distal clipping on the aneurysm flow and the parenchymal blood flow after the bypass as reported by Acerbi et al. (19). In certain cases, such as the A1 or anterior communicating aneurysms, simultaneous proximal and distal parent arteries occlusion is hard to achieve in a single craniotomy, and staged endovascular aneurysm occlusion is a better option to simplify the surgical exposure.

Most of the *in situ* bypasses were part of a planned surgical strategy in this series, except in one patient (case 1), in which we initially attempted to perform surgical clipping. Sometimes, the *in situ* bypass is a favorable intraoperative bailout strategy as well. It is particularly attractive in emergent situations when there is an inadvertent vascular injury during an operation or trauma or occlusion of a planned bypass (Figure 1). In this case, furthermore, a double bypass pattern as presented by Acerbi et al. would be more reasonable (20). Moreover, this technique can also be used appropriately as an adjunct to other revascularization procedures. This situation is especially common in MCA aneurysms. The uniquely complex nature of MCA aneurysms, which might not be precisely discerned even using 3-dimensional angiographic reconstructions, can necessitate feasible salvage strategies when intraoperative dissection has revealed unexpected anatomic peculiarities. The *in situ* revascularization will eliminate the added complexities of an unplanned extracranial donor artery dissection or graft harvest associated with EC-IC bypass or IC-IC revascularization.

In addition to the conventional single simple *in situ* bypass configuration, innovative bypass pattern is efficient in some situations. In our series, we performed a bypass between the proximal and distal parts of the caudal loops within the same PICA (Case 6) (Figure 2). This novel technique had also been reported by Lee and Cho (21) in a patient with a p2 dissecting aneurysm, which they called the "closing omega" technique vividly. In another patient with a MCA recurrent aneurysm after clipping, which characterized an early bifurcation of one of the trifurcated M2 branches, we conducted an ingenious parallel M2-M2 *in situ* bypasses to supply the three branches distal to the aneurysm, which spared the need for a tedious EC-IC interposition bypass or IC-IC reimplantation (Case 12) (Figure 3).

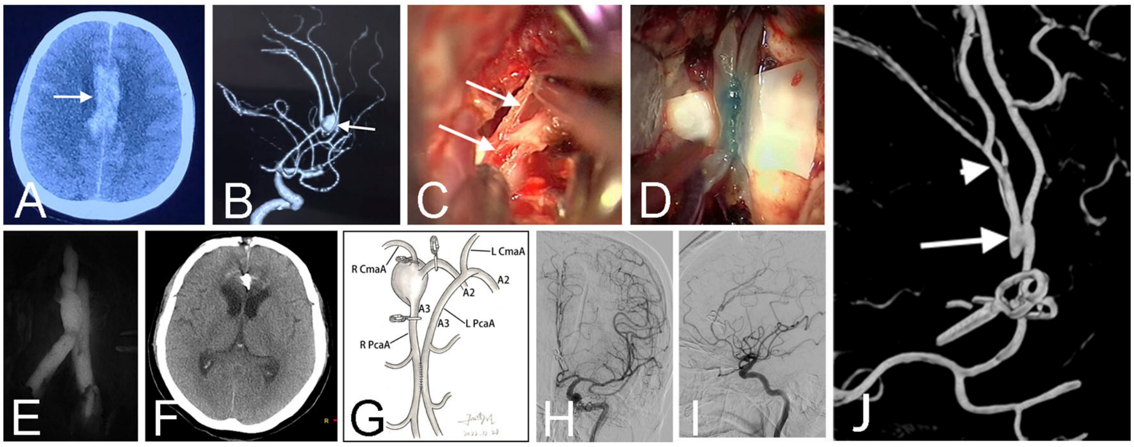

FIGURE 3
CT scan before the first surgery showed a hematoma (arrow) at the right Sylvian fissure in a 17-year-old girl (Case 12) **(A)**. Pre-operative angiography revealed a fusiform aneurysm (arrow) at the middle cerebral artery **(B)**. The early angiography after the first surgery showed the aneurysm was clamped with multiple parallel straight clips **(C)**. Follow-up angiography demonstrated the aneurysm recurred 1 year after the clipping surgery **(D)**. Intraoperative photograph at the second surgery showed the parallel *in situ* bypasses (arrows) **(E)**. Patency of the two side-to-side anastomosis was confirmed by intraoperative infrared indocyanine green angiography **(F)** and FLOW 800 analysis **(G)**. The schematic diagram illustrated the structure of bypasses and aneurysm trapping while preserving the lenticulostriate artery in this patient **(H)**. Post-operative angiography demonstrated obliteration of the fusiform aneurysm and bold blood flow of distal arteries **(I)**. Three-dimensional angiography showed the patient has two anastomoses (arrows) **(J)**.

Therefore, we firmly believe that with the expanding repertoire of microsurgical techniques and skills, more and more inspired collections of *in situ* bypass structures will be attempted by skilled cerebrovascular specialists.

It should be acknowledged that the present study has some limitations. First, the results of the present study may be biased by the retrospective study nature and the relatively small sample size. Second, this study only reflected the experience and perspective of *in situ* bypasses at a single institution that receives high volumes of patient referrals with complex clinical presentations, so the generalizability of these results is restricted. Third, we did not perform cerebral blood flow evaluation before surgery, and most of our bypass modalities were determined by a multidisciplinary team according to anatomical considerations. This policy had been adopted by most previous reports in the literature, and it also worked in our series. However, the fully preoperative assessment would benefit the surgical complications reduction. We have used CT perfusion to assist in bypass modality selection in certain cases. Last, in our series, the theoretically possible PCA-SCA *in situ* revascularization was not performed, and studies elaborating on this bypass modality and its surgical outcomes were limited. Therefore, future study is necessary to include a larger sample size with a multicenter and prospective design.

Conclusion

Despite advances in endovascular intervention, the cerebral revascularization technique remains an essential skill for the treatment of complex aneurysms. The *in situ* bypass is one of the most effective techniques to revascularize efferent territory when vital artery sacrifice or occlusion is unavoidable. The configuration of *in situ* bypasses should be carefully tailored to each case, with consideration of variations in the anatomy and pathology of the complex aneurysms.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by Chinese PLA General Hospital Review Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

CW and Z-hS: conception and design. H-wW, C-hS, and D-sK: literature search, data extraction, and statistical analysis. H-wW: drafting of the article. ZX and Z-hS: critical revision of the article and study supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Long Wang,
Capital Medical University, China

REVIEWED BY
Kenichiro Kikuta,
University of Fukui, Japan
Hang Chunhua,
Nanjing University, China

*CORRESPONDENCE
Huaqiu Zhang
✉ zhanghq@tjh.tjmu.edu.cn
Chao Gan
✉ ganchao17@outlook.com

†These authors have contributed equally to this work

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Clinical effect of a modified superficial temporal artery-middle cerebral artery bypass surgery in Moyamoya disease treatment

Liang Lu†, Yimin Huang†, Yang Han, Yu Li, Xueyan Wan, Juan Chen, Xincheng Zhang, Kai Shu, Ting Lei, Sheng Wang, Chao Gan* and Huaqiu Zhang*

Department of Neurosurgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Background: Cerebral extracranial-intracranial (EC-IC) revascularization technique (superficial temporal artery-middle cerebral artery (STA-MCA) bypass grafting) has become the preferred surgical method for the treatment of Moyamoya disease (MMD). We attempted to completely free the two branches of the superficial temporal artery without disconnection. Extracranial and intracranial blood flow reconstruction were then modified by selectively performing a direct bypass technique on one branch and a patch fusion technique on the other of the STA based on the blood flow and the vascular diameter of the intracranial surface blood vessels.

Methods: A series of modified STA-MCA bypass surgeries performed consecutively between March 2022 and March 2023 were reviewed and compared to conventional combined bypass surgeries performed during the same period. The following information was collected from all enrolled patients: demographic characteristics, clinical symptoms, and preoperative and postoperative imaging, including Suzuki stage and Matsushima grade. The modified Rankin scale (mRS) was used to assess the changes in neurological status before and after surgery.

Results: A total of 41 patients with Moyamoya disease (MMD) who underwent cerebral revascularization were included in this study, of which 30 were conventional revascularization and 11 were modified revascularization. The mean age was 49.91 years, and 18 (43.9%) of the patients were women. The modified group had a lower incidence of cerebral hyperperfusion syndrome (18.2%) than the conventional group (23.3%). After at least 3 months of follow-up, the bypass patency rate remained 100% in the modified group and 93.3% in the conventional group. All patients in the modified group achieved a better Matsushima grade (A + B), with six (54.5%) having an A and five (45.5%) having a B. In contrast, four patients (13.3%) in the conventional group had a Matsushima grade of C. In all, 72.8% of the modified group had postoperative mRS scores of 0 and 1, which was higher than that of the traditional group (63.3%).

Conclusion: The improved STA-MCA bypass could provide blood flow to multiple cerebral ischemic areas, reduce excessive blood perfusion, and ensure blood supply to the scalp, with lower complications and better clinical benefits than the traditional combined bypass.

KEYWORDS

Moyamoya disease, STA-MCA bypass, cerebral revascularization, modified surgical technique, vascular disorders

Introduction

In recent years, with the improvement of clinical diagnosis and treatment and the popularization of intracranial angiography, the incidence and diagnosis of Moyamoya disease and Moyamoya syndrome have been increasing rapidly in China (1). Currently, extracranial-intracranial blood flow reconstruction techniques (superficial temporal-middle cerebral artery bypass grafting plus Encephalo-myo-synangiosis) have become the preferred surgical option for the treatment of Moyamoya disease and have achieved good results (2, 3). However, due to the mismatch in thickness and blood flow between intracranial recipient vessels (middle cerebral artery M3 and M4) and extracranial donor vessels (superficial temporal artery frontal or parietal branches), the success rate of direct vascular anastomosis and surgical outcome are often affected (4). Especially when the superficial temporal artery branch is significantly thicker or the blood flow is too large, the direct single-vessel end-side anastomosis may lead to over-perfusion of blood flow in the recipient vessel, which may cause brain tissue edema and neurological damage, or even hemorrhage and infarction, endangering the patient's life and safety (5, 6). To address this situation, clinicians often use a variety of means to reduce donor blood flow and flow rate by narrowing the lumen of the donor vessel or increasing the degree of vessel turning (7). Some centers have also proposed the use of lateral anastomosis to reduce the donor blood flow by shunting part of the blood flow into the skull while preserving the original superficial temporal artery branch flow path (8). In recent years, our center has found that by completely freeing the superficial temporal artery and its two branches, and then selectively adopting one direct bypass and one patch fusion technique according to the branches and intracranial cerebral surface vessels, we can avoid excessive shunting from the outside to the inside of the skull, ensure the blood supply to the scalp, and add a pathway to reconstruct the intracranial and extracranial blood flow through the fusion of blood vessels, which can be said to be killing three birds with one stone. In the present study, 41 cases of patients with Moyamoya disease have been treated with extracranial-intracranial blood flow reconstruction, and the demographic characteristics, surgical methods, and clinical effects are reported in order to obtain a preliminary result about this modified bypass strategy.

Materials and methods

Study population and design

We retrospectively evaluated patients with MMD who underwent bypass surgery from March 2022 to March 2023 at Tongji Hospital and who were treated by the same group. The inclusion criteria were as follows: (1) patients with MMD confirmed by digital subtraction angiography (DSA) or magnetic resonance angiography (MRA) according to previous reports (2), (2) patients older than 18 years old, and (3) patients who underwent surgical therapy. The exclusion criteria were as follows: (1) patients who did not undergo follow-up evaluation, (2) patients who underwent only encephalo-duro-arterio-synangiosis (EDAS) or direct bypass without encephalo-myo-synangiosis (EMS), and (3) patients with secondary Moyamoya syndrome caused by other reasons, such as autoimmune diseases, Down's syndrome, and radiation exposure to the head. The following information was collected from all enrolled patients: demographic characteristics, preoperative and postoperative imaging, clinical symptoms, surgical method, complications, and follow-up. The study was approved by the Ethics Committee of Tongji Hospital. Due to the retrospective nature of the cohort study, the need for informed consent was waived.

Surgical technique

The conventional surgical techniques were described in previous research (2, 4). The modified bypass scheme of STA dissection is shown in Figure 1 and four representative surgical methods are shown in Figure 2. In conventional surgery, a single STA branch was traditionally used as a donor vessel for STA-MCA anastomosis combined with EMS. The parietal branch of the STA was usually used since the frontal branch could form a collateral formation naturally. The middle meningeal artery (MMA) was preserved as much as possible. When the recipient vessel was not found in the brain cortex, an EDAMS procedure was used with the frontal branch. When the STA could not be used, the cortex was covered with muscle alone with EMS. In modified surgery, direct anastomosis combined with indirect synangiosis is performed to use all STA vessels and tissues capable of providing future collateral formation. Both the frontal and parietal branches are utilized.

Before the scalp incision is made, the course of the STA (especially the parietal branch) is confirmed with touch pulsation or Doppler ultrasound probe. Then the scalp incision is made along the course of the parietal branch of the STA and from the midway point the incision is turned around nearly 90 degrees anteriorly to the midline. Both the frontal and parietal branches of the STA are adequately dissected and secured without cutoff. The temporal muscle is one of the sources of indirect synangiosis (EMS). As the dural opening is covered by the temporal muscle, we separate the temporal muscle as widely as possible. We usually make four burr holes for craniotomy. Of the four burr holes, one is placed just proximal to the STA, one at the distal end of the parietal branch, and one at the distal end of the frontal branch located close to the keyhole. The last one is placed at the superior temporal line where the temporal muscle is attached. In order to preserve the MMA, which is easily injured if the incision is made at the base of the temporal bone, we make the temporal bone thinner using a drill and remove the bone piece by piece during the craniotomy. A window-like incision is made in the dura mater without

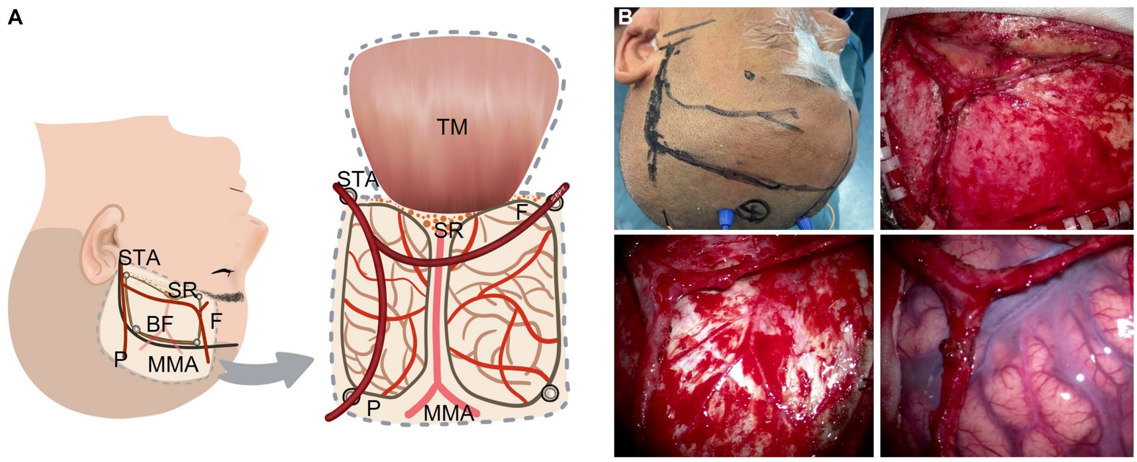

FIGURE 1
STA dissecting procedure in a modified bypass surgery with both branches of the STA intact without a cut. **(A)** Illustration (artist rendition, left hemisphere). **(B)** A representative patient. BF: bone flap; F: frontal branch of the STA; MMA: middle meningeal artery; P: parietal branch of the STA; SR: sphenoid ridge; STA: superficial temporary artery; TM: temporal muscle.

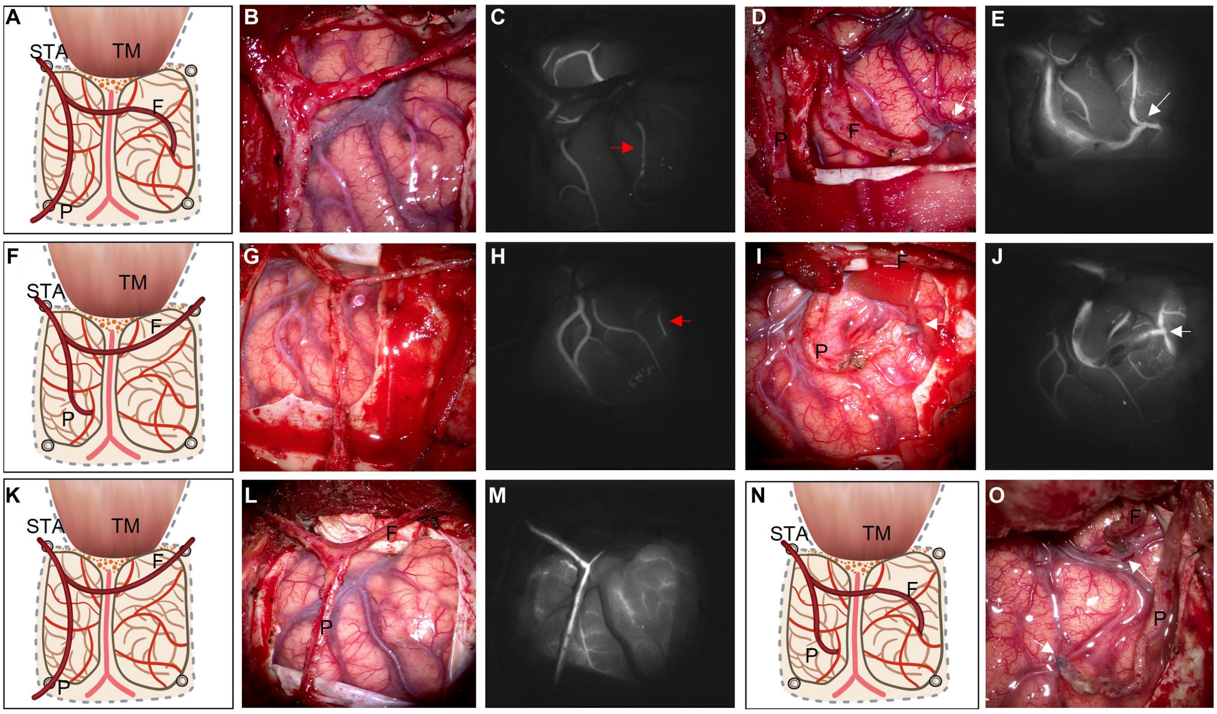

FIGURE 2
Based on ischemic area and ICG videoangiography, illustrations of four types of operative strategies are listed as follows: 1. frontal branch for STA-MCA end-to-side bypass with parietal branch EDAMS **(A)**; 2. parietal branch for STA-MCA bypass with frontal branch EDAMS **(F)**; 3. EDAMS with both branches of the STA without a cut **(K)**; 4. Double-barrel bypass with both branches of the STA **(N)**. After the STA is dissected without a cut **(B,G,L)**, ICG videoangiography is used to evaluate the relatively slow-flow recipient M4 (**C,H**, red arrow). Sometimes, recipient M4 cannot be found **(M)**. After the bypass is finished (**D,I,O**, white arrow indicate the anastomosis point), ICG videoangiography is used again to evaluate the patency of the bypass vessel (**E,J**, white arrow). F: frontal branch of the STA; P: parietal branch of the STA; STA: superficial temporary artery; TM: temporal muscle.

cutting the main branch of the MMA. The dura opening should be as wide as possible.

Before STA-MCA anastomosis was undertaken, several details needed to be cleared. Based on the results of the cerebral blood flow (CBF) study and indocyanine green (ICG) video angiography, ischemic regions and alternative recipient vessels were identified. We empirically preferred to choose the slow-flow vessel under ICG video angiography in the low-perfusion area as the recipient vessel if possible (Figures 2C,H, red arrow). The selection of a donor vessel should also consider compensation, vessel diameter, ischemic zone, and so on. When intracranial compensation exists in one branch of the STA, the other one is selected as the donor vessel. Select a vessel that matches the recipient vessel as the donor vessel. Referring to the ischemic area factor, bypass strategies are as follows: (1) When low-perfusion is mainly located in the frontal area, the frontal branch is preferred as the donor vessel for STA-MCA anastomosis, and the parietal branch is placed on the surface of the exposed cortex; (2) If a preoperative CBF study reveals a low-perfusion area mainly at the parietal area, then the parietal branch is chosen as the donor vessel; and (3) If no recipient vessel can be found, both branches of STA are performed for indirect revascularization. After STA-MCA anastomosis, the largest possible area of the exposed cortex is covered with temporal muscle and another branch of STA (EDAMS).

Radiological and clinical evaluation

All patients underwent preoperative and postoperative DSA/MRA and CT perfusion (CTP)/arterial spin labeling (ASL). MRA or vascular DSA was used preoperatively to confirm stenosis and to determine the Suzuki stage in patients with MMD (9), and postoperatively to assess bypass patency and to record Matsushima grade to assess revascularization (10). CTP or ASL was used preoperatively to identify the ischemic area in patients with MMD and to select the surgical hemisphere and the area for revascularization accordingly, and postoperatively to evaluate the alteration of perfusion. The Suzuki stage was recorded preoperatively to assess the severity of MMD patients. Specifically, in Matsushima grade, "A" represents hemodialysis in 2/3 of the middle cerebral artery (MCA) distribution, "B" represents hemodialysis in between 1/3 and 2/3 of the MCA distribution, and "C" represents poor or no hemodialysis. Patients' preoperative clinical symptoms and postoperative complications were recorded. The modified Rankin scale (mRS) was used to assess the changes in patients' neurologic functional status before and after surgery (11).

Statistical analysis

Statistical analyses were performed using R software (version 3.6.3), with categorical data being expressed as percentages and continuous variables being expressed as mean ± standard deviation (SD). The Student's t-test and Wilcoxon test were used to compare the two continuous variables and the Chi-square test, Yates' correction, or Fisher's exact tests were used for categorical variables. $p < 0.05$ was considered a statistically significant difference.

Results

Patient characteristics

A total of 41 patients with Moyamoya disease who underwent cerebral revascularization were included in this study (Table 1), of which 30 underwent conventional revascularization and 11 underwent modified revascularization. The mean age was 49.91 years, and 18 (43.9%) patients were women. There were no significant differences between the traditional and modified groups in terms of sex, age, symptoms, and comorbidities. In the traditional group, 14 cases of the right hemisphere and 16 cases of the left hemisphere underwent cerebral revascularization, and in the modified group, 4 cases of the right hemisphere and 7 cases of the left hemisphere underwent cerebral revascularization.

The starting symptoms, from most to least, were cerebral infarction (36.6%), chronic cerebral ischemia (29.3%), cerebral hemorrhage (22.0%), and TIA (12.2%). Specifically, headache, dizziness (41.5%), and limb weakness (46.3%) were more prevalent, while aphasia (14.6%), intellectual disability (7.3%), blurred vision (9.8%), and transient impairment of consciousness (12.2%) were relatively rare. As for vascular diseases, some patients had a combination of hypertension (34.1%), diabetes mellitus (17.1%), and hyperlipidemia (17.1%).

Preoperative imaging and functional analysis

All patients underwent preoperative cerebral angiography or MRA to assess and analyze the morphology of the cerebral vessels, and the Suzuki stage was used to classify patients with MMD. The vast majority of patients (Table 1) were in grade III (43.9%) or IV (34.1%), and a small number were in grade II (9.8%) or V (12.2%). The present study did not contain patients in grades I and VI. The functional status of the patients was then assessed using the mRS, with the majority of the patients located in grade 1 (39.0%) or 2 (39.0%), and a small proportion in grade 0 (2.4%), 3 (12.2%), or 4 (7.3%); the present study did not contain patients in grades 5 and 6. The majority of patients (80.5%) underwent improved single bypass combined with EMS/EDAMS. One patient underwent a double-barrel bypass due to multi-regional ischemia and permitting conditions. Five patients (12.2%) and two patients (4.9%) underwent EDAMS and EMS, respectively.

Postoperative complications

There was no significant difference in the incidence of postoperative complications between the conventional and modified groups (Table 2), which may be related to the smaller number of cases. Even so, we were able to observe that the modified group had a lower incidence of cerebral hyperperfusion syndrome (18.2%) than the conventional group (23.3%), with complications such as myasthenia gravis (3.3%) and epilepsy (3.3%) in some of the patients in the conventional group but not in those in the modified group. Similarly, in terms of scalp-related complications, some patients in the conventional group had poor scalp healing (3.3%) and subcutaneous effusion (6.7%), whereas patients in the modified group did not.

Postoperative outcome

Bypass patency during surgery was 100% in both the conventional and modified groups (Table 3). After at least 3 months of follow-up, the bypass patency rate remained 100% in the modified group and decreased to 93.3% in the conventional group, of which the two patients with bypass obstruction were patients who underwent conventional indirect bypass surgery (Supplementary Table S1).

TABLE 1 Characteristics of patients with Moyamoya disease (MMD).

Characteristic	All (*n* = 41)	Traditional (*n* = 30)	Modified (*n* = 11)	*p*	Method
Age, years	51.0 (43.5,56.0)	51.0 (43.0,56.0)	52.0 (44.0,57.0)	0.689	Wilcoxon test
Sex				1.000	Chi-square
Female	18 (43.9%)	13 (43.3%)	5 (45.5%)		
Male	23 (56.1%)	17 (56.7%)	6 (54.4%)		
Follow-up, months	3 (3, 6)	3 (3, 6)	3 (3, 5)		Wilcoxon test
Hemisphere				0.815	Yates' correction
Rt	18 (43.9%)	14 (46.7%)	4 (36.4%)		
Lt	23 (56.1%)	16 (53.3%)	7 (63.6%)		
Symptom				0.850	Yates' correction
Headache and Dizziness	17 (41.5%)	13 (43.3%)	4 (36.4%)		
Limb weakness	19 (46.3%)	14 (46.7%)	5 (45.5%)		
Aphasia	6 (14.6%)	4 (13.3%)	2 (18.2%)		
Intellectual disability	3 (7.3%)	2 (6.7%)	1 (9.1%)		
Blurred vision	4 (9.8%)	3 (10.0%)	1 (9.1%)		
Transient disorders of consciousness	5 (12.2%)	4 (13.3%)	1 (9.1%)		
Presenting symptom				0.936	Yates' correction
Hemorrhage	9 (22.0%)	7 (23.3%)	2 (18.2%)		
Infarction	15 (36.6%)	10 (33.3%)	5 (45.5%)		
TIA	5 (12.2%)	4 (13.3%)	1 (9.1%)		
Chronic cerebral ischemia	12 (29.3%)	9 (30.0%)	3 (27.3%)		
Comorbidities					
Hypertention	14 (34.1%)	10 (33.3%)	4 (36.4%)	1.000	Yates' correction
Diabetes mellitus	7 (17.1%)	6 (20.0%)	1 (9.1%)	0.723	Yates' correction
Hyperlipidemia	7 (17.1%)	5 (16.7%)	2 (18.2%)	1.000	Yates' correction
Surgical method				0.260	Yates' correction
Single-bypass+EMS/EDAMS	33 (80.5%)	25 (83.3%)	8 (72.7%)		
Double-barrel bypass	1 (2.4%)	0 (0.0%)	1 (9.1%)		
EDAMS	5 (12.2%)	3 (10.0%)	2 (18.2%)		
EMS	2 (4.9%)	2 (6.7%)	0 (0.0%)		
Suzuki stage				0.984	Yates' correction
II	4 (9.8%)	3 (10.0%)	1 (9.1%)		
III	18 (43.9%)	13 (43.3%)	5 (45.5%)		
IV	14 (34.1%)	10 (33.3%)	4 (36.4%)		
V	5 (12.2%)	4 (13.3%)	1 (9.1%)		
mRS score preop				0.947	Yates' correction
0	1 (2.4%)	1 (3.3%)	0 (0.0%)		
1	16 (39.0%)	11 (36.7%)	5 (45.5%)		
2	16 (39.0%)	12 (40.0%)	4 (36.4%)		
3	5 (12.2%)	4 (13.3%)	1 (9.1%)		
4	3 (7.3%)	2 (6.7%)	1 (9.1%)		

TIA, transient ischemic attack; EMS, encephalo-myo-synangiosis; EDAMS, encephalo-duro-arterio-myo-synangiosis; mRS, the modified Rankin scale.

All patients in the modified group achieved a better Matsushima grade (A + B) (Figure 3), with six (54.5%) having an A and five (45.5%) having a B. In contrast, 4 patients (13.3%) in the conventional group had a Matsushima grade of C, i.e., poor revascularization, and 11 patients in the conventional group had an A in their rating (36.7%). The preoperative and postoperative mRS changes reflected the impact

TABLE 2 Postoperative complications.

Characteristic	Traditional (*n* = 30)	Modified (*n* = 11)	*p*	Method
Cerebral infarction	2 (6.7%)	1 (9.1%)	1.000	Yates' correction
Cerebral hemorrhage	1 (3.3%)	0 (0.0%)	1.000	Fisher's exact test
Cerebral hyperperfusion syndrome	7 (23.3%)	2 (18.2%)	1.000	Yates' correction
Aphasia	2 (6.7%)	1 (9.1%)		
Myasthenia	1 (3.3%)	0 (0.0%)		
Epilepsy	1 (3.3%)	0 (0.0%)		
Vertigo and Vomiting	3 (10.0%)	1 (9.1%)		
Disturbance of consciousness	0 (0.0%)	0 (0.0%)		
Scalp	3 (10.0%)	0 (0.0%)	0.680	Fisher's exact test
Poor scalp healing	1 (3.3%)	0 (0.0%)		
Subcutaneous effusion	2 (6.7%)	0 (0.0%)		

TABLE 3 Postoperative outcome.

Characteristic	Traditional (*n* = 30)	Modified (*n* = 11)	*p*	Method
Bypass patency during OP	30 (100.0%)	11 (100.0%)	1.000	Fisher's exact test
Bypass patency at last FU	28 (93.3%)	11 (100.0%)	0.952	Fisher's exact test
Matsushima grade at the last FU			0.346	Yates' correction
A	11 (36.7%)	6 (54.5%)		
B	15 (50.0%)	5 (45.5%)		
C	4 (13.3%)	0 (0.0%)		
mRS score at the last FU			0.947	Yates' correction
0	9 (30.0%)	4 (36.4%)		
1	10 (33.3%)	4 (36.4%)		
2	8 (26.7%)	2 (18.2%)		
3	3 (10.0%)	1 (9.1%)		
4	0 (0.0%)	0 (0.0%)		

FU, follow-up; OP, operation.

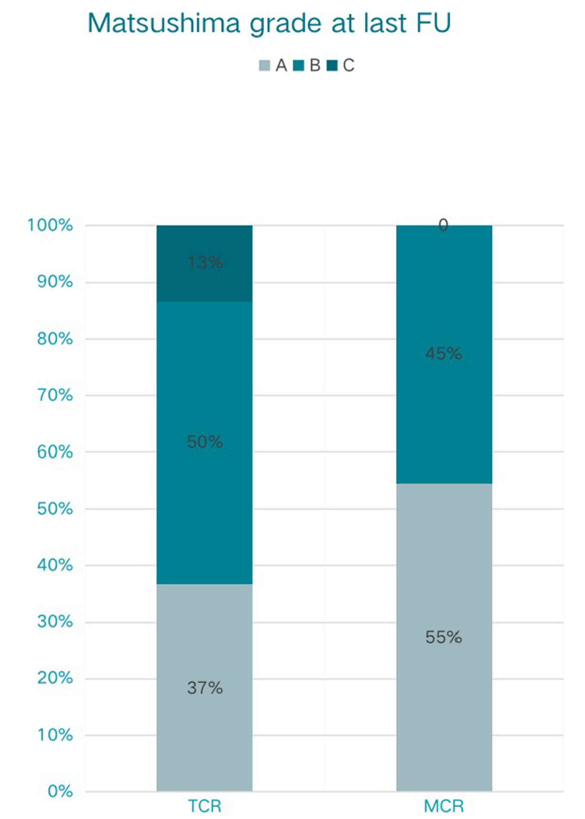

FIGURE 3
Matsushima grade at last follow-up (FU) of traditional cerebral revascularization (TCR) and modified cerebral revascularization (MCR).

of surgery on patients' neurological recovery (Figure 4), and both groups achieved a good improvement in mRS scores, with 72.8% of the modified group having postoperative mRS scores of 0 and 1, which was higher than that of the traditional group (63.3%). Among the patients who underwent indirect bypass surgery, the postoperative mRS score of the modified group was higher than that of the traditional group ($p = 0.099$) (Supplementary Table S1), but due to the small amount of data, it was necessary to further expand the sample size for verification.

Discussion

Our present study discusses a modified surgical approach to extracranial-intracranial blood flow reconstruction for the treatment of Moyamoya disease (or Moyamoya syndrome). To achieve the lowest complications and the best clinical benefit, we introduced a modified surgical method by completely separating both branches of the superficial temporal artery and selectively performing different bypasses depending on the development of the patient's middle cerebral artery (M4) branches.

Anastomosis through the superficial temporal artery branches and the cortical branches of the middle cerebral artery (direct bypass technique) combined with temporalis muscle-dural-fine-mold apposition (indirect bypass technique) has long been the preferred means for the treatment of Moyamoya disease (2, 12, 13). However, hyperperfusion or hypoperfusion of blood flow due to donor-recipient vascular mismatch and secondary cerebral edema, infarction, or hemorrhage are important factors that seriously affect the safety and efficacy of the procedure (14, 15). The present modified bypass surgical approach is performed by completely freeing the superficial temporal artery and its two branches, and then selectively choosing the bypass method based on the degree of matching between the

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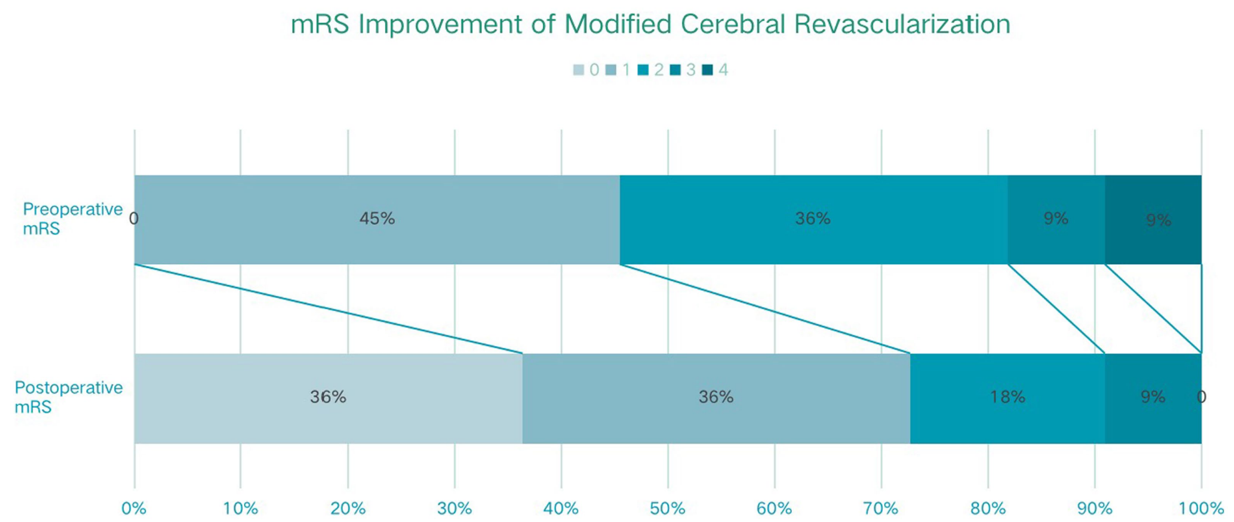

FIGURE 4
The modified Rankin scale (mRS) improvement of traditional cerebral revascularization (TCR) and modified cerebral revascularization (MCR).

recipient and donor vessels. In the case of the superficial temporal artery, which is thick and has a blood flow higher than the capacity of the middle cerebral artery in the M4 segment, a modified Y-vessel shunt is used to achieve autonomous distribution of the superficial temporal artery blood flow (16). That is, to avoid a transient large amount of blood flow from the external carotid system into the brain after anastomosis, which leads to the risk of postoperative overperfusion and edema (17). Meanwhile, the fused superficial temporal artery branch is important for the prevention of ischemic necrosis of the scalp and the promotion of vascular neovascularization (18). In patients with poor recipient vascularization, double-branch freeing and fusion of the superficial temporal artery is also significantly more effective than single-branch fusion (19).

In our newly introduced surgical approach, isolation and protection of the vessels of the superficial temporal artery and its branches (frontal and parietal) are critical to the success of the procedure. In our group, we generally used an enlarged pterional incision and designed the surgical incision along the outer edge of the vessels according to the main stem and double branch course of the superficial temporal artery. The depth of the incision was noted where the apical branch crossed the edge of the flap, and it was important to protect the vessel from being cut off. The bone window is designed in a conventional square shape. The meningeal artery with intracranial compensation is preserved and the dura is flipped and applied to the cerebral surface (20). By flipping the temporal muscle across the gap between the superficial temporal artery frontal branch and the flap, the superficial temporal artery frontal branch can be brought to the surface of the brain tissue, providing the possibility of bypass or fusion surgery (21, 22).

There are some shortcomings of the modified bypass surgical method. (1) The realization and effect of the surgery depend on the condition of the donor and recipient vessels, for example, for patients with very poor development of the superficial temporal artery or the M3-M4 segment of the brain surface vessels, it is not possible to achieve the early improvement of the blood flow through the blood vessel direct anastomotic bypass bridge, and the patients need to wait for the formation of the fused blood vessels as well as the neovascularization of the temporal muscle of the apposition to register an improvement in blood flow. For some elderly patients, the angiogenic capacity is insufficient, and the long-term effect is unsatisfactory. (2) Currently, there is no clear detection method and precise regulation of the distribution and autonomous regulation of blood flow in the two vessels of the superficial temporal artery. At present, we use electrocoagulation to control the vessels' diameter or increase the tortuosity of blood vessels to regulate the donor's blood flow. (3) The modified surgical methods have been carried out for a relatively short period of time, therefore, a long-term follow-up is necessary.

Conclusion

The improved STA-MCA bypass, which fuses two branches of the superficial temporal artery with a direct bypass and a patch, could provide blood flow to multiple cerebral ischemic areas, reduce excessive blood perfusion caused by single-vessel bypass, and ensure blood supply to the scalp, with lower complications and better clinical benefits than the traditional combined bypass.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Tongji Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

LL: Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. YiH: Data curation, Investigation, Methodology, Validation, Writing – original draft. YaH: Investigation, Methodology, Writing – review & editing. YL: Investigation, Methodology, Writing – review & editing. XW: Investigation, Methodology, Writing – original draft. JC: Investigation, Methodology, Writing – original draft. XZ: Methodology, Writing – original draft. KS: Methodology, Supervision, Writing – original draft. TL: Conceptualization, Methodology, Supervision, Writing – original draft. SW: Investigation, Methodology, Writing – review & editing. CG: Writing – original draft. HZ: Writing – original draft, Writing – review & editing.

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Conflict of interest

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1273822/full#supplementary-material

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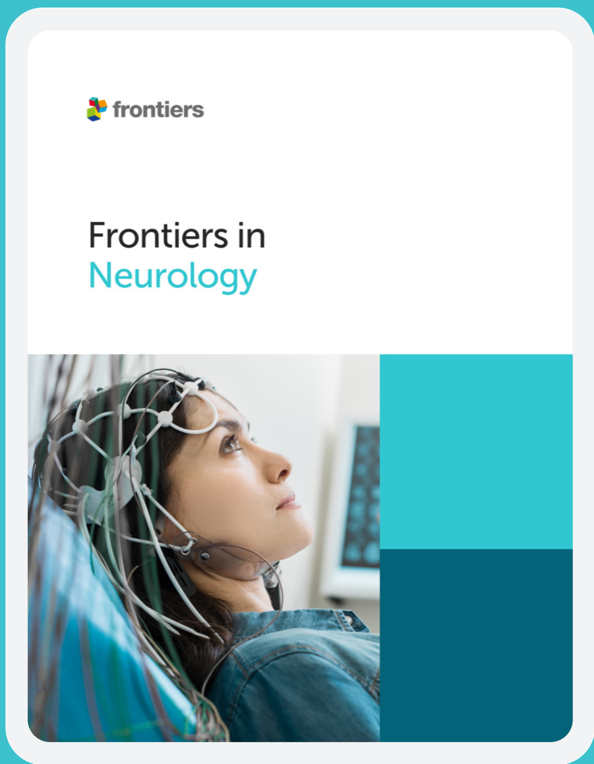

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