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CLINICAL ARTICLE

Predictors of neoangiogenesis after indirect revascularization in moyamoya disease: a multicenter retrospective study

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OBJECTIVE The effect of indirect revascularization to improve cerebral perfusion for moyamoya disease (MMD) is based on ingrowth of new vessels into the cortical brain. Preoperative indicators for neoangiogenesis would be helpful to the selection of appropriate procedures for MMD patients but have not yet been investigated. Our study aimed to identify potential predictors for neovascularization after indirect bypass surgery.

METHODS The authors reviewed consecutive cases with complete clinical and radiological documentation of patients who had undergone surgery between December 2010 and January 2018. Patients who were treated with indirect bypass surgery were included. Cerebrovascular characteristics were evaluated by catheter angiography. Neoangiogenesis after indirect bypass was determined as "good" or "poor" based on the Matsushima standard. Univariate and multivariate analyses were performed to identify predictors for neoangiogenesis after indirect bypass. Subgroup analyses by onset type and surgical type were carried out to identify specific predictors for different populations.

RESULTS In total, 231 hemispheres of 209 patients (mean ± SD age 23.06 ± 15.09 years, range 3–61 years) were retrospectively included. In 146 (63.2%) hemispheres, good neoangiogenesis was observed after indirect revascularization. Multivariate analysis showed that the status of ICA moyamoya vessels ($p < 0.001$, OR [95% CI] 3.242 [2.007–5.236]) is a predictor of favorable neoangiogenesis after indirect bypass surgery, whereas hemorrhagic onset ($p < 0.001$, OR [95% CI] 0.138 [0.054–0.353]) is a risk factor for poor neoangiogenesis. In addition, younger age was significantly associated with good neovascularization in patients with hemorrhagic onset ($p = 0.027$, OR [95% CI] 0.893 [0.808–0.987]), whereas age was not a significant predictor for neovascularization in non–hemorrhagic-onset patients ($p = 0.955$). Hemispheres with good revascularization had lower incidence of rebleeding, lower modified Rankin Scale scores, and more improvement of symptoms during long-term follow-up ($p = 0.026$, 0.006, and 0.013, respectively).

CONCLUSIONS Hemorrhagic onset predicts poor neovascularization after indirect bypass surgery for MMD patients. Abundant ICA moyamoya vessels indicate good neoangiogenesis after indirect bypass and vice versa, whereas absent ICA moyamoya vessels predict poor revascularization. Good neovascularization was associated with better long-term outcome. Future studies are needed to further address this issue and clarify the underlying pathophysiological mechanisms.

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KEYWORDS moyamoya disease; indirect revascularization; indirect bypass; predictors; risk factors; neoangiogenesis; neovascularization; vascular disorders

Indirect revascularization, or indirect bypass surgery, is an essential component of surgical treatment for moyamoya disease (MMD). This procedure improves cerebral perfusion by attaching pedicled, vascularized grafts to cortical surface and facilitating ingrowth of neoangiogenesis.[1,2,10,20] Thus far, a variety of indirect revascularization methods had been developed, including encephaloduroarteriosynangiosis (EDAS), encephalodurogaleo(periosteal) synangiosis (EDGS), and multiple burr hole (MBH) surgery.[11,12,18] Compared to direct revascularization, which

ABBREVIATIONS ACA = anterior cerebral artery; DSA = digital subtraction angiography; EC-IC = extracranial-intracranial; EDAS = encephaloduroarteriosynangiosis; EDGS = encephalodurogaleo(periosteal)synangiosis; ICA = internal carotid artery; MBH = multiple burr hole; MD = moyamoya disease; mRS = modified Rankin Scale; OphA = ophthalmic artery; PCA = posterior cerebral artery; STA = superficial temporal artery; TIA = transient ischemic attack.

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requires manual anastomosis of the extracranial donor vessel and intracranial recipient vessel, indirect revascularization is a much simpler, less strenuous technique with lower risks of postoperative complications,[15,23,27] and as demonstrated in many recently reported studies, may achieve long-term outcomes as satisfying as those for direct bypass surgery.[5,15,19] However, the timing of indirect revascularization, as well as the uncertainty of postsurgical neoangiogenesis, are the main considerations that limit the use of this method. Identification of potential predictors of good neoangiogenesis after indirect bypass, which unfortunately have not yet been investigated, would be helpful for surgeons seeking to determine which MMD patients may benefit from this procedure. Therefore, we conducted the current retrospective study with patients included from a multicenter cohort, hoping to identify potential predictors for postsurgical neoangiogenesis after indirect bypass surgery.

Methods

Patient Selection

A consecutive series of MMD patients who underwent surgical revascularization at Beijing Tiantan Hospital and Peking University International Hospital between December 2010 and January 2018 was retrospectively reviewed. Diagnosis of MMD and indications for surgery were determined according to the Japanese 2012 guidelines.[21] Patients who were diagnosed as having moyamoya syndrome secondary to other identified etiologies were ruled out from the cohort. MMD patients treated with direct or combined bypass surgery and patients with incomplete radiographic documentation were excluded. In the end, patients who were treated by indirect revascularization with preoperative and follow-up catheter angiography were included.

This study was approved by the institutional review board of Beijing Tiantan Hospital, Capital Medical University. Written informed consent was obtained from all patients.

Surgical Modalities

Direct bypass or combined bypass surgery was the favored surgical modality for most patients at our center. Indirect revascularization was performed under the following conditions: for 1) pediatric patients (≤ 18 years old), regardless of onset type, and young adult patients (18–25 years old) without history of cerebral hemorrhage; 2) adult patients with no available recipient vessel (diameter < 5 mm) found for direct bypass during surgery; and 3) adult patients under high risk of postoperative ischemic complications, including patients with disease at a late Suzuki stage (V–VI) with no reliable spontaneous collaterals and/or patients who had frequent transient ischemic attacks (TIAs) during preoperative period (more than 3 times within 3 months before surgery) and/or patients who had recent cerebral infarction (within 3 month before surgery), EDAS was the prioritized technique. For 4) patients with no available donor vessels, MBH surgery or EDGS was performed. Surgical procedures were carried out as described previously.[7,27]

Postoperative Complications and Follow-Up Protocol

Perioperative management was performed as previously described.[27] All patients underwent CT scan on postsurgical day 1. Repeat CT or MRI scans were conducted in cases of newly developed neurological symptoms during the postoperative period. Complications were recorded, including cerebral hemorrhage, cerebral ischemia, wound infection, and seizure.

Follow-up monitoring of the condition of each patient was performed by telephone or clinic interviews 3–6 months after surgery and annually thereafter. The modified Rankin Scale (mRS) was used to evaluate neurological status on admission, at discharge, and at follow-up. Recurrent cerebral hemorrhage, ischemia, and seizure were recorded. Patients with complete disappearance or self-reported decrease of symptoms were defined as "improved." Patients with no significant change of previous symptoms and no newly developed symptoms were defined as "stabilized." Patients with worsened symptoms were defined as "deteriorated."

Personal History Data

Onset type of MMD was defined as hemorrhagic (intracranial hemorrhage, subarachnoid hemorrhage, or intraventricular hemorrhage), ischemic (cerebral infarction or TIA), or atypical (seizure, headache, or asymptomatic) based on the very first presented symptoms. Prior history of surgical revascularization, burr hole drainage, or TIAs was recorded as self-reported. Personal history, including history of hypertension, diabetes, drinking, smoking, and hyperlipidemia, was defined as self-reported or by blood sample test (Supplementary Table 1).

Evaluation of Vasculature Characteristics

Preoperative vasculature characteristics of the operated hemisphere was evaluated with digital subtraction angiography (DSA) studies by two independent neurosurgeons who were blinded to surgical information. Discrepancies were discussed before a final score was graded. Moyamoya vessels generating from the internal carotid artery (ICA), ophthalmic artery, and posterior circulation were evaluated separately. Formation of ICA-end moyamoya vessels was evaluated according to a scale of 0–2 (absent, fair, abundant)[16] as shown in Fig. 1. Formation of ophthalmic and posterior circulation moyamoya vessels was evaluated simply by their existence or absence.

Formation of collaterals by major intracranial and extracranial arteries was evaluated by their existence or absence, including the anterior cerebral artery (ACA), ophthalmic artery (OphA), posterior cerebral artery (PCA), posterior choroidal artery (PchA), posterior communicating artery (PcoA), middle meningeal artery (MMA), superficial temporal artery (STA), and occipital artery (OcciA). Any existing PCA-, PchA-, or PcoA-generated collateral vessels were defined as posterior-anterior collaterals. Any MMA-, STA-, or OcciA-generated collateral vessels were defined as extracranial-intracranial (EC-IC) collaterals. In particular, spontaneous EC-IC collateral

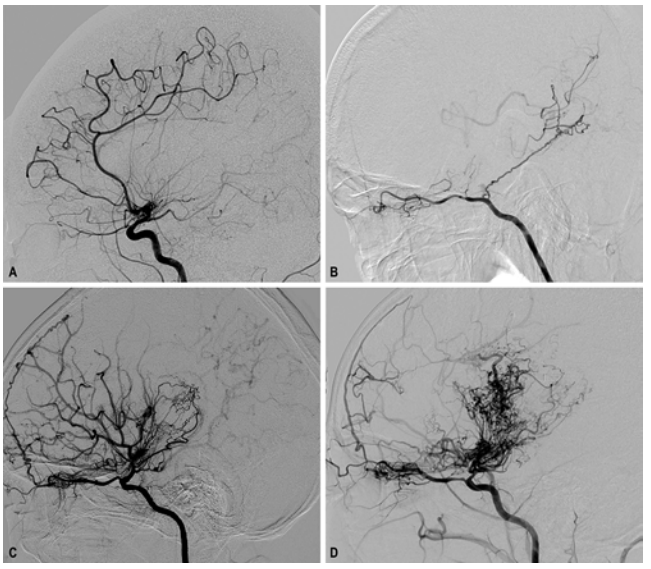

FIG. 1. Evaluation of moyamoya vessels generating from the ICA on a scale of 0–2. **A:** Absent (0): no apparent generation of ICA moyamoya vessels at early Suzuki stage. **B:** Absent (0): Disappearance of moyamoya vessels from the ICA due to occlusion of the ICA at late Suzuki stage. **C:** Fair (1): scarce and localized moyamoya vessels. **D:** Abundant (2): moyamoya vessels stretching into all directions.

formation was defined as the existence of EC-IC collaterals without prior history of any kind of surgery (burr hole drainage or surgical revascularization).

Evaluation of Postsurgical Neoangiogenesis

Follow-up DSA was scheduled at 6 to 12 months after surgery. Patency of STA at follow-up was evaluated on a scale of 0–2 (occluded, stenosed, patent) as shown in Fig. 2. The development of postsurgical collateral formation was evaluated by using the Matsushima standard[16,17] on a scale of 0–3 (null, localized, moderate, and abundant) as shown in Fig. 3. Levels 2 and 3 were determined as "good" collateral formation, and levels 0 and 1 were determined as "poor" collateral formation. Neoangiogenesis was assessed after raw data from all included patients had been collected. Evaluations were conducted by two independent neurosurgeons (Y.Z. and J.L.) who were not involved in the surgery and blinded to the baseline characteristics of patients. Discrepancies were discussed before a final score was graded.

Statistical Analysis

Statistical analysis was carried out using SPSS software (version 25.0; IBM Corp.). Continuous variables were compared using a t-test. Categorical variables were compared with the Pearson chi-square test, Fisher's exact test, or Mann-Whitney test as appropriate. In order to adjust for multiple variables, multivariate logistic regression analysis was conducted on factors achieving $p < 0.05$ in the univariate analysis and factors that were considered highly likely to be related to the outcome of indirect bypass in previous literature or according to clinical experience (i.e., age and onset). Odd ratios (ORs) and 95% confidence intervals (CIs) for good neoangiogenesis were calculated. Analysis was carried out for the entire cohort and by subgroups of surgical type, onset type. A p value < 0.05 was considered statistically significant.

Results

Demographic Data

A database of MMD patients who underwent surgical treatment during December 2010 to January 2018 at Beijing Tiantan Hospital and Peking University International Hospital was retrospectively reviewed. After excluding patients who underwent direct or combined bypass surgery, 231 hemispheres of 209 patients (mean age 23.06 ± 15.09 years, range 3–61 years) were included in this study. Their clinical characteristics are summarized in Table 1. The percentage of female patients was slightly higher than that of male patients (57.1% vs 42.9% of hemispheres). Distributions of onset types were 45 (19.5%) hemorrhagic, 173 (74.9%) ischemic, and 13 (5.6%) hemispheres were grouped as atypical onset, including 12 (5.2%) patients initially presented with seizure and one (0.4%) was completely asymptomatic. Twenty-three (10.0%) cases (hemispheres) had a history of burr hole drainage because of cerebral hemorrhage. Thirty-nine (16.9%) cases had a history of prior contralateral surgical revascularization, including 7 (3.0%) direct bypass surgery and 25 (13.9%) indirect bypass surgery.

The majority of hemispheres included in this study (198, 85.7%) underwent EDAS with the trunk or branch of the STA as the vascularized graft. Ten (4.3%) hemi-

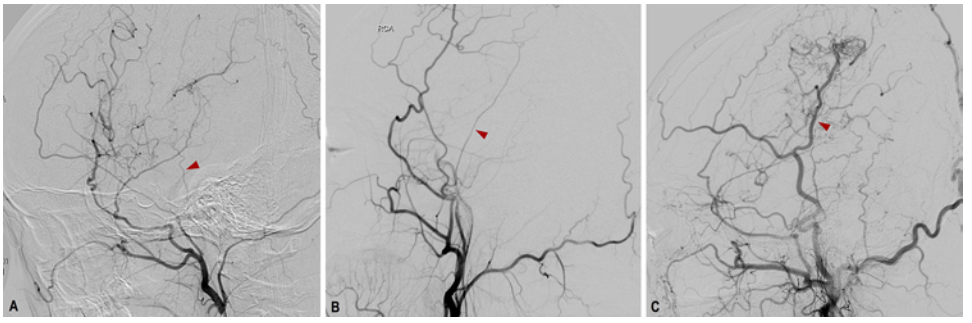

FIG. 2. Evaluation of patency of the STA at follow-up catheter angiography. **A:** Occlusion and disappearance of STA (*arrow*). **B:** Stenosis of STA (*arrow*). **C:** Dilation and patency of STA (*arrow*). Figure is available in color online only.

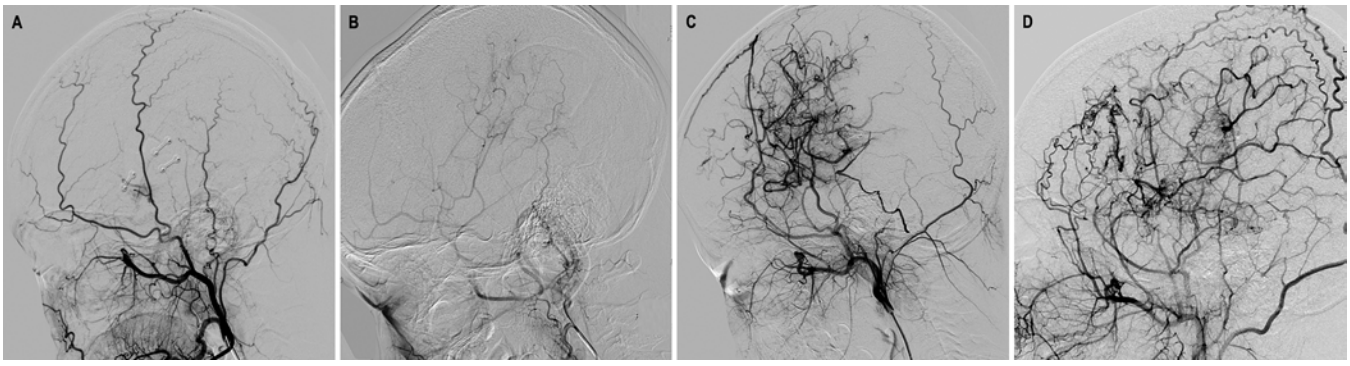

FIG. 3. Evaluation of postsurgical neoangiogenesis by using the Matsushima standard. **A:** Level 0 (null): no obvious collateral formation. **B:** Level 1 (localized): slight visualization of a few cortical branches through the bypass, covering less than one-third of MCA territory. **C:** Level 2 (moderate): two-thirds to one-third of MCA territory were filled by newly developed collaterals. **D:** Level 3 (abundant) more than two-thirds of MCA territory was filled by the external carotid artery system.

spheres underwent EDGS and 23 (10.0%) underwent MBH surgery. Mean follow-up time of DSA were 8.99 ± 5.99 months.

Analysis of Potential Predictors for Neoangiogenesis After Indirect Bypass

Among the 231 hemispheres that underwent indirect bypass, 146 (63.2%) hemispheres had good neoangiogenesis after surgery and 85 (36.8%) had poor. DSA follow-up time was not significantly different between different outcomes. Univariate analysis showed that younger age and EDAS surgery were significantly related to good neoangiogenesis ($p < 0.001$ and $p = 0.022$, respectively), whereas hemorrhagic onset and smoking were related to poor neoangiogenesis ($p < 0.001$ and $p = 0.028$, respectively; Table 2). The status of ICA moyamoya vessels was significantly correlated with the outcome of neovascularization ($p < 0.001$). Thirty-four of 44 (77.3%) patients without apparent ICA moyamoya vessels had poor neoangiogenesis ($p < 0.001$) while 87 (82.9%) of patients with abundant ICA moyamoya vessels had good neoangiogenesis ($p < 0.001$). In the meantime, the existence of ophthalmic moyamoya vessels and posterior circulation moyamoya vessels was also associated with good neoangiogenesis ($p = 0.002$ and 0.005, respectively). Concordantly, 13/18 (72.2%) hemispheres at Suzuki stage II had poor neoangiogenesis ($p = 0.002$), whereas 64/84 (76.2%) patients at Suzuki stage IV had favorable neovascularization ($p = 0.003$).[24] Collaterals, including ACA, OphA, and any kind of posterior-anterior, spontaneous, or nonspontaneous EC-IC collaterals, were not associated with postsurgical neoangiogenesis separately or collaboratively (data not shown).

To further rule out effects of various factors, multivariate analysis was conducted with the aforementioned significant factors. Hemorrhagic onset ($p < 0.001$, OR [95% CI] 0.138 [0.054–0.353]) and status of ICA moyamoya vessels ($p < 0.001$, OR [95% CI] 3.242 [2.007–5.236]) were recognized as independent predictors for neoangiogenesis after indirect bypass surgery (as seen in Table 2).

Subgroup Analysis by Type of Surgery

In order to reduce heterogeneity from the use of multiple surgical techniques and investigate procedure-specific relevant factors, we performed subgroup analysis by surgical type. Hemispheres that underwent EDAS were divided into the "EDAS subgroup" (n = 198), and those that underwent MBH (n = 23) and EDGS (n = 10) were analyzed together as the "non-EDAS subgroup" due to the limited sample size.

Among 198 hemispheres that underwent EDAS surgery, 131 (66.2%) had good postsurgical neoangiogenesis and 67 (33.8%) had poor. Multivariate analysis for this subgroup confirmed hemorrhagic onset type ($p < 0.001$, OR [95% CI] 0.117 [0.041–0.335]) and ICA moyamoya vessels ($p < 0.001$, OR [95% CI] 3.005 [1.791–5.044]) to be independent predictors for postsurgical revascularization, correlating with previous analysis of the entire group. Specially, STA patency was also independently associated with neoangiogenesis ($p = 0.003$, OR [95% CI] 2.682 [1.397–5.151]). STA patency at follow-up was significantly associated with good neoangiogenesis ($p = 0.002$), whereas occlusion and stenosis of the grafted artery were significantly related to poor neoangiogenesis ($p = 0.012$ and 0.010). Another noteworthy finding was that the area of craniotomy was not significantly associated with postsurgical neoangiogenesis ($p = 0.346$, Supplementary Table 2).

In the non-EDAS subgroup (n = 33), 15 (45.5%) hemispheres had good revascularization and 18 (54.5%) had poor revascularization (Table 3). Onset type ($p = 0.017$, OR [95% CI] 0.009 [0.000–0.433]) and ICA moyamoya vessels ($p = 0.045$, OR [95% CI] 146.501 [1.108–19362.525]) as independent predictors of neovascularization by multivariate analysis. Additionally, in MBH surgery, the number of burr holes drilled did not significantly affect postoperative neoangiogenesis ($p = 0.978$).

Subgroup Analysis by Onset Type

To further identify possible predictors for different MMD populations, we conducted subgroup analysis by onset type.

In the hemorrhagic-onset subgroup (n = 45; Table 4), good neoangiogenesis was associated with younger age (30.10 ± 10.14 years vs 39.89 ± 8.03 years, $p = 0.027$, OR [95% CI] 0.893 [0.808–0.987]). ICA moyamoya vessels

TABLE 1. Demographic data and clinical characteristics

	Value
No. of patients	209
No. of hemispheres	231
Age, yrs	
Mean	23.06 ± 15.09
<25	127 (55.0%)
25–35	41 (17.7%)
>35	63 (27.3%)
Male sex	99 (42.9%)
Onset type	
Hemorrhagic	45 (19.5%)
Ischemic	173 (74.9%)
Atypical	13 (5.6%)
Previous indirect revascularization	32 (13.9%)
Previous burr hole drainage	23 (10.0%)
mRS at admission	
Mean	1.50 ± 0.75
0–2	213 (92.2%)
≥3	18 (7.8%)
Surgical side, lt	136 (58.9%)
Surgery type	
EDAS	198 (85.7%)
EDGS	10 (4.3%)
MBH	23 (10.0%)
DSA follow-up, mos	8.99 ± 5.99

Values are number of hemispheres (%) unless otherwise indicated. Mean values are presented ± SD.

were not significantly related in multivariate analysis (p = 0.097, OR [95% CI] 2.835 [0.829–9.701]). In particular, no evidence of neoangiogenesis after burr hole drainage or spontaneous EC-IC collaterals was associated with postsurgical angiogenesis for hemorrhagic-onset patients (p = 0.800 and p = 0.464, respectively). In comparison, in the nonhemorrhagic onset subgroup (Table 5), the presence of ICA moyamoya vessels was the only predictor of good neoangiogenesis for this subgroup by multivariate analysis (p < 0.001, OR [95% CI] 3.272 [1.936–5.530]), while age was not significantly associated (p = 0.955).

Postoperative Complications and Long-Term Outcome

Among 231 hemispheres, postoperative complications occurred at an overall rate of 10.0% (23 cases), including 2 (0.9%) cases of cerebral hemorrhage, 16 (6.9%) cases of cerebral ischemia, 1 case of (0.4%) seizure, and 4 cases of (1.7%) wound infection. At discharge, none or mild neurological dysfunction (mRS 0–2) was found for 215 cases (hemispheres) (93.0%) and significant symptoms (mRS ≥ 3) for 16 (7.0%) cases (hemispheres). MRS scale at discharge was not significantly different between cases with good and those with poor neoangiogenesis (p = 0.572).

The Table 6 data demonstrate long-term outcomes of patients included in this study. Five patients were lost to long-term follow-up, and 226 hemispheres of 204 patients were followed for a mean of 20.32 ± 12.45 months. In this series, 6 (2.7%) hemispheres suffered from rebleeding. In general, hemispheres with good neoangiogenesis had fewer incidences of rebleeding compared to hemispheres with poor neoangiogenesis (0.7% vs 6.0%, p = 0.026). Notably, 5 out of 6 patients who suffered from rebleeding were hemorrhagic onset and none of them had good neovascularization (14.7% vs 0.0%, p = 0.573), including 1 patient who died. In the nonhemorrhagic onset subgroup, 1 patient with good neovascularization had an episode of cerebral hemorrhage during follow-up (0.8% vs 0.0%, p = 1.000). Multivariate logistic regression (Table 7) showed that the extent of revascularization was not an independent predictor of rebleeding (p = 0.391, OR [95% CI] 0.353 [0.033–3.810]), whereas hemorrhagic onset type was significantly associated with recurrent hemorrhage (p = 0.026, OR [95% CI] 14.490 [1.367–153.563]).

Twenty-nine (12.8%) hemispheres had recurrent ischemia (including infarction and TIAs), among which only 1 (0.4%) hemisphere had new cerebral infarction and this case was poorly revascularized. The incidence of recurrent ischemia was not significantly different between hemispheres with good versus poor revascularization, in the entire series (p = 0.274) or in subgroups (hemorrhagic: p = 0.227; nonhemorrhagic: p = 0.820).

Follow-up mRS was lower in the good neoangiogenesis group than in the poor neoangiogenesis group (0.60 ± 0.70 vs 1.06 ± 1.13, p = 0.002), and so was the percentage of patients who had long-term deterioration (0.7% vs 7.6%, p = 0.011). More hemispheres with good neoangiogenesis had long-term improvement (95.8% vs 86.7%, p = 0.013). These findings were statistically significant in the entire series, but not in the subgroups by onset type (Table 6).

Discussion

The effect of indirect revascularization to improve perfusion for moyamoya disease was based on the ingrowth of new vessels from the vascularized grafts into the cortical brain.[2] Recent studies suggested that indirect revascularization might offer as satisfying results, or even better long-term results, than direct bypass; however, the unpredictability of this simple technique is the main limitation for its use.[1,13,25] So far, few studies have investigated potential predictors for neoangiogenesis after indirect bypass surgery, which would be of great value to help bring the utmost benefit of this surgical technique to suitable MMD patients. In this study, we investigated the relationship between postsurgical neoangiogenesis and a variety of possible predictors, hoping to provide insights for this question.

We retrospectively reviewed all MMD cases from a multicenter cohort that had undergone surgical revascularization during the December 2010 to January 2018 period. After excluding patients who underwent direct or combined bypass surgery, a total of 231 hemispheres of 209 patients who were treated with indirect bypass surgery and acquired complete angiographic information were included in this study. Our findings showed that in 231 hemispheres, 146 (63.2%) achieved good neoangiogenesis after indirect bypass surgery. Onset type was significantly

TABLE 2. Logistic regression analysis of potential predictors for neoangiogenesis after indirect bypass

	Neoangiogenesis		p Value		
	Good (n = 146)	Poor (n = 85)	Univariate	Multivariate	OR (95% CI)
Age, yrs					
Mean	19.49 ± 13.74	29.20 ± 15.41	<0.001*	0.692	
0–25	97 (66.4%)	30 (35.3%)	<0.001*		
>25	49 (33.6%)	55 (64.7%)			
Male sex	62 (42.5%)	37 (43.5%)	NS		
Onset type					
Hemorrhagic	10 (6.8%)	35 (41.2%)	<0.001*	<0.001*	0.138 (0.054–0.353)
Nonhemorrhagic	136 (93.2%)	50 (58.8%)			
Personal history					
Hypertension	15 (10.3%)	10 (11.8%)	NS		
Diabetes	6 (4.1%)	0 (0%)	NS		
Drinking alcohol	3 (2.1%)	3 (3.5%)	NS		
Smoking	4 (2.7%)	8 (9.4%)	0.028*	0.285	
Hyperlipidemia	4 (2.7%)	5 (5.9%)	NS		
DSA findings					
Unilateral/bilateral MD	6 (4.1%)	9 (10.6%)	NS		
Suzuki stage			0.003*	0.112	
I	0 (0.0%)	1 (1.2%)	NS		
II	5 (3.4%)	13 (15.3%)	0.002*		
III	46 (31.5%)	29 (34.1%)	NS		
IV	64 (43.8%)	20 (23.5%)	0.003*		
V	25 (17.1%)	18 (21.2%)	NS		
VI	6 (4.1%)	4 (4.7%)	NS		
Moyamoya vessels					
ICA			<0.001*	<0.001*	3.242 (2.007–5.236)
Absent	10 (6.8%)	34 (40.0%)	<0.001*		
Fair	49 (33.6%)	33 (38.8%)	NS		
Abundant	87 (59.6%)	18 (21.2%)	<0.001*		
Ophthalmic	54 (37.0%)	15 (17.6%)	0.002*	0.407	
Posterior	61 (41.8%)	20 (23.5%)	0.005*	0.509	
Fetal PCA	23 (15.8%)	12 (14.1%)	NS		
Spontaneous EC-IC collaterals	61 (41.8%)	30 (35.3%)	NS		
EDAS surgery	131 (89.7%)	67 (78.8%)	0.022*	0.225	
Mean DSA follow-up, mos	9.24 ± 5.85	8.55 ± 6.25	NS		

NS = not significant ($p > 0.05$).
Values are number of hemispheres (%) unless otherwise indicated. Mean values are presented ± SD.
* $p < 0.05$.

related to neoangiogenesis after indirect bypass. Hemorrhagic onset was an independent risk factor for poor postsurgical neoangiogenesis (univariate: $p < 0.001$, multivariate: $p = 0.000$; OR [95% CI] 0.138 [0.054–0.353]; Table 2). This finding was in concordance with previous studies demonstrating that MMD patients presenting with hemorrhagic symptoms had poorer long-term outcome and higher rebleeding rate after indirect bypass compared to direct bypass,[3,6,14] which probably resulted from poor revascularization. In contrast, nonhemorrhagic onset could be an indicator for good neoangiogenesis.

The presence of moyamoya collaterals (puff-like collateral vessels) generating from the terminal ICA was another independent predictor for postsurgical neoangiogenesis (univariate: $p < 0.001$, multivariate: $p < 0.001$; OR [95% CI] 3.242 [2.007–5.236]; Table 2). Our results show for the first time that abundant ICA moyamoya vessels predicted abundant neoangiogenesis after bypass surgery, whereas absent or extremely scarce ICA moyamoya vessels predicted poor neoangiogenesis. Moyamoya collaterals generating from the ophthalmic artery and posterior circulation were also significantly associated with good neoangiogenesis after surgery ($p = 0.002$ and 0.005) in univariate analysis but not in multivariate analysis. As it is known that puff-like vessels are a special pathological vasculature that occurs during a certain period in moyamoya

TABLE 3. Analysis of predictors for the non-EDAS subgroup

	Neoangiogenesis		p Value		
	Good (n = 15)	Poor (n = 18)	Univariate	Multivariate	OR (95% CI)
Mean age	19.53 ± 15.58	31.17 ± 17.40	0.054	0.199	
Male sex	9 (60.0%)	7 (38.9%)	0.227		
Hemorrhagic onset	1 (6.7%)	9 (50.0%)	0.009*	0.017*	0.009 (0.000–0.433)
Suzuki stage			0.161		
I–II	1 (6.7%)	5 (27.8%)			
III–IV	12 (80.0%)	8 (44.4%)			
V–VI	2 (13.3%)	5 (27.8%)			
Moyamoya vessels					
ICA			0.003*	0.045*	146.501 (1.108–19362.525)
Absent	1 (6.7%)	7 (38.9%)	0.046*		
Fair	4 (26.7%)	9 (50.0%)	0.284		
Abundant	10 (66.7%)	2 (11.1%)	0.001*		
Ophthalmic	10 (66.7%)	3 (16.7%)	0.005*	0.054	
Posterior	7 (46.7%)	2 (11.1%)	0.047*	0.227	
Surgical type			0.240		
EDGS	12 (80.0%)	11 (61.1%)			
MBH	3 (20.0%)	7 (38.9%)			
DSA follow-up time	8.39 ± 3.46	9.40 ± 7.92	0.650		

All factors shown in Table 2 were also analyzed for this subgroup, but insignificant factors ($p > 0.05$) are not shown in this table. Values are number of hemispheres (%) unless otherwise indicated. Mean values are presented ± SD.
* $p < 0.05$.

TABLE 4. Subgroup analysis of predictors in the hemorrhagic-onset subgroup

	Neoangiogenesis		p Value		
	Good (n = 10)	Poor (n = 35)	Univariate	Multivariate	OR (95% CI)
Age	30.10 ± 10.14	39.89 ± 8.03	0.003*	0.027*	0.893 (0.808–0.987)
Male sex	8 (80.0%)	22 (62.9%)	0.310		
Neoangiogenesis after BHID	3 (75.0%)	12 (66.7%)	0.800		
Spontaneous EC-IC collaterals	5 (50.0%)	13 (37.1%)	0.464		
Suzuki stage			0.520		
I	0 (0.0%)	0 (0.0%)			
II	0 (0.0%)	1 (2.9%)			
III	3 (30.0%)	13 (37.1%)			
IV	6 (60.0%)	11 (31.4%)			
V	1 (10.0%)	9 (25.7%)			
VI	0 (0.0%)	1 (2.9%)			
Moyamoya vessels					
ICA			0.042*	0.097	2.835 (0.829–9.701)
Absent	0 (0.0%)	14 (40.0%)	0.019*		
Fair	6 (60.0%)	15 (42.9%)	0.476		
Abundant	4 (40.0%)	6 (17.1%)	0.194		
Ophthalmic	1 (10.0%)	5 (14.3%)	0.725		
Posterior	3 (30.0%)	9 (25.7%)	0.787		
EDAS surgery	9 (90.0%)	26 (74.3%)	0.292		

BHID = burr hole irrigation and drainage.
All factors shown in Table 2 were also analyzed for this subgroup, but insignificant factors ($p > 0.05$) are not shown in this table. Values are number of hemispheres (%) unless otherwise indicated. Mean values are presented ± SD.
* $p < 0.05$.

TABLE 5. Subgroup analysis of predictors in the nonhemorrhagic subgroup

	Neoangiogenesis		p Value		
	Good (n = 136)	Poor (n = 50)	Univariate	Multivariate	OR (95% CI)
Age	18.71 ± 13.67	21.72 ± 14.96	0.195	0.955	0.893 (0.808–0.987)
Male sex	76 (55.9%)	26 (52.0%)	0.637		
Spontaneous EC-IC collaterals	56 (41.2%)	17 (34.0%)	0.374		
Suzuki stage			<0.001*	0.117	
I	0 (0.0%)	1 (2.0%)	0.269		
II	5 (3.7%)	12 (24.0%)	<0.001*		
III	43 (31.6%)	16 (32.0%)	0.960		
IV	58 (42.6%)	9 (18.0%)	0.001*		
V	24 (17.6%)	9 (18.0%)	0.960		
VI	6 (4.4%)	3 (6.0%)	0.709		
Moyamoya vessels					
ICA			<0.001*	<0.001*	3.272 (1.936–5.530)
Absent	10 (7.4%)	20 (40.0%)	<0.001*		
Fair	43 (31.6%)	18 (36.0%)	0.572		
Abundant	83 (61.0%)	12 (24.0%)	<0.001*		
Ophthalmic	53 (39.0%)	10 (20.0%)	0.015*	0.304	
Posterior	58 (42.6%)	11 (22.2%)	0.010*	0.452	
EDAS surgery	122 (89.7%)	41 (82.0%)	0.157		

All factors shown in Table 2 were also analyzed for this subgroup, but insignificant factors (p > 0.05) are not shown in this table. Values are number of hemispheres (%) unless otherwise indicated. Mean values are presented ± SD.
* p < 0.05.

disease, it can be postulated that the presence of moyamoya vessels indicates potential for vascular and collateral growth in the progress of moyamoya disease. However, our study was a practical interpretation of clinical materials, and the mechanisms behind this phenomenon remain to be clarified by future studies.

Correlating with the aforementioned findings, Suzuki stage was also significantly associated with the effect of indirect bypass. Hemispheres at Suzuki stage II turned out to have poor postsurgical neoangiogenesis, whereas most hemispheres at Suzuki stage IV had good neovascularization (p = 0.002 and 0.003, respectively; Table 2). Nevertheless, this association was not significant in multivariate analysis, suggesting that ICA moyamoya vessels might be a more effective predictor. It was worth noting that compared to hemispheres at late Suzuki stages (V and

TABLE 6. Long-term outcome of all patients, hemorrhagic and nonhemorrhagic subgroups

	All Hemispheres		p	Hemorrhagic Onset		p	Nonhemorrhagic Onset		p
	Good (n = 143)	Poor (n = 83)	Value	Good (n = 10)	Poor (n = 34)	Value	Good (n = 133)	Poor (n = 49)	Value
Mean follow-up time, mos	20.0 ± 12.3	20.9 ± 12.6	0.575	25.1 ± 17.3	21.1 ± 15.4	0.484	19.1 ± 12.1	19.9 ± 10.9	0.678
Recurrent symptoms									
Cerebral hemorrhage	1 (0.7%)	5 (6.0%)	0.026*	0 (0.0%)	5 (14.7%)	0.573	1 (0.8%)	0 (0.0%)	1.000
Cerebral ischemia	21 (14.7%)	8 (9.6%)	0.274	1 (10.0%)	0 (0.0%)	0.227	20 (15.0%)	8 (16.3%)	0.820
Seizure	2 (1.4%)	1 (1.2%)	0.902	0 (0.0%)	0 (0.0%)	—	2 (1.5%)	1 (2.0%)	1.000
Follow-up mRS	0.60 ± 0.70	1.06 ± 1.13	0.002*	0.20 ± 0.42	1.38 ± 1.44	0.004*	0.63 ± 0.71	0.84 ± 0.80	0.112
0–2	141 (98.6%)	75 (90.4%)		10 (100.0%)	28 (82.4%)		180 (98.5%)	47 (95.9%)	
>3	2 (1.4%)	8 (9.6%)		0 (0.0%)	6 (17.6%)		2 (1.5%)	2 (4.1%)	
Long-term outcome			0.011*			0.339			0.311
Improvement	137 (95.8%)	72 (86.7%)	0.013*	10 (100.0%)	27 (79.4%)	0.118	127 (95.5%)	45 (91.8%)	0.338
Stabilization	5 (3.5%)	4 (4.8%)	0.624	0 (0.0%)	3 (8.8%)	1.000	5 (3.8%)	1 (2.0%)	1.000
Deterioration	1 (0.7%)	6 (7.2%)	0.011*	0 (0.0%)	3 (8.8%)	1.000	1 (0.8%)	3 (6.1%)	0.060
Death	0 (0.0%)	1 (1.2%)	0.367	0 (0.0%)	1 (11.8%)	1.000	0 (0.0%)	0 (0.0%)	—

Good and poor refer to good neoangiogenesis and poor neoangiogenesis, respectively. Values are number of hemispheres (%) unless otherwise indicated. Mean values are presented ± SD.
* p < 0.05.

TABLE 7. Multivariate analysis of factors affecting follow-up rebleeding

Factor	p Value		OR (95% CI)
	Univariate	Multivariate	
Hemorrhagic onset	<0.001*	0.026*	14.490 (1.367–153.563)
Poor revascularization	0.016*	0.391	0.353 (0.033–3.810)

* $p < 0.05$.

VI), hemispheres at early Suzuki stages (I and II) were more likely to develop poor postsurgical neoangiogenesis, although according to their definition both were characterized by fewer moyamoya vessels. This particular finding might be valuable as it could provide guidance for choosing the optimal operative timing for moyamoya patients.

Previously reported studies had demonstrated that indirect bypass surgery turns out to be more effective for younger patients than older patients in the long term.[8,9,13,22] In our series, 97 (76.4%) patients younger than 25 years had good neoangiogenesis, whereas only 49 (47.1%) patients older than 25 years had the same outcome ($p < 0.001$; Table 2). However, multivariate analysis revealed that age was not an independent predictor for neoangiogenesis after revascularization in the entire series ($p = 0.692$; Table 2), nor in the nonhemorrhagic subgroup ($p = 0.955$; Table 5), underscoring the finding that for MMD patients, especially those with nonhemorrhagic onset (ischemic or atypical), age was not the most influential factor influencing surgical effect. Therefore, there is a chance that indirect bypass might be just as beneficial to older MMD patients as to pediatric patients, provided that their disease does not have hemorrhagic onset. Having said that, the rate of good revascularization after indirect bypass surgery was still lower than direct bypass according to existing studies;[4,26] hence, the general superiority of direct bypass surgery over indirect bypass for MMD patients regardless of onset type for adult patients should not be ignored.

Specifically for hemorrhagic-onset MMD hemispheres, younger age was the only identified predictor for good neoangiogenesis ($p = 0.027$, OR [95% CI] 0.893 [0.808–0.987]; Table 4) after indirect bypass. Unlike in other subgroups, the extent of ICA moyamoya vessels was not significantly associated with good neoangiogenesis for hemorrhagic MMD patients in multivariate analysis ($p = 0.097$), though in univariate analysis the absence of ICA moyamoya vessels still predicts poor revascularization ($p = 0.019$). Additionally, though evidence of neoangiogenesis after burr hole drainage might have been considered as a sign of collateral-development potential in clinical practice, our findings showed that neoangiogenesis through burr holes was not significantly associated with good neoangiogenesis ($p = 0.800$). In general, indirect revascularization was not as effective for hemorrhagic-onset as for ischemic-onset MMD patients, and unfortunately, our sample size as well as factors investigated in this study were too limited to address more predictors specific for hemorrhagic MMD.

Multivariate analysis showed that the use of the STA as the source of grafts for indirect bypass (EDAS surgery) did not significantly affect postsurgical neoangiogenesis ($p = 0.225$; Table 2). Nonetheless, to further rule out heterogeneity and investigate procedure-related factors, we conducted subgroup analysis by surgery type. In accordance with previous findings, hemorrhagic-onset and ICA moyamoya vessels were independent predictors for neoangiogenesis regardless of surgical type (Table 3 and Supplementary Table 2). Moreover, for the EDAS subgroup, STA patency at follow-up was independently related to the outcome of neoangiogenesis ($p = 0.003$; OR [95% CI] 2.682 [1.397–5.151]), indicating the importance of intraoperative protection of grafted vessels. On the other hand, neither the area of craniotomy in the EADS group nor the number of burr holes drilled in the MBH group was associated with postsurgical neoangiogenesis, suggesting that excessive enlargement of the surgical region might be unnecessary.

In the long term, hemispheres with good neovascularization had better outcome and lower incidence of recurrent hemorrhage than those with poor neovascularization (Table 6). Six recurrent hemorrhage occurred, 5 of which were in hemispheres with hemorrhagic onset and poor revascularization ($p = 0.026$), and in 1 patient recurrent hemorrhage resulted in death. Nevertheless, multivariate analysis showed that the extent of revascularization was not significantly associated with recurrent cerebral hemorrhage (Table 7), indicating that instead of poor neovascularization, onset type was more related to future rebleeding. In comparison, the incidence of recurrent cerebral ischemia was not significantly related to the outcome of neovascularization. Even with well-revascularized hemispheres, TIAs sometimes still occurred; however, the only case of recurrent infarction was in a poorly revascularized hemisphere. Moreover, better neurological status ($p = 0.002$) and more improved outcome ($p = 0.013$) were seen in the good neoangiogenesis group, whereas deterioration was associated with poor revascularization ($p = 0.011$; Table 6), indicating that the effect of revascularization was crucial to long-term outcome for MMD patients. This finding was different from results reported by Arias et al.,[4] which probably could be attributed to the comparatively larger sample size of the current study.

Indirect bypass surgery has been widely applied in the surgical treatment of MMD and has been reported to improve cerebral perfusion.[5,15,19] However, as indirect bypass was less predictable than direct bypass surgery, the indication of this technique was comparatively restricted.[1,13] At our center, the choice of suitable patients for indirect bypass was limited to young MMD patients and those who were not eligible for direct bypass surgery. This choice was intended for the benefits of patients, but the potential selection bias cannot be ignored. However, in the current series, we found that the majority of MMD patients achieved satisfactory revascularization, again supporting the favorable effect of indirect bypass surgery. Also, we identified predictors for good neovascularization after indirect bypass. To our knowledge, this study was the first to investigate indicators for potential MMD patients who might or might not benefit from indirect bypass, providing insights into the selection of appropriate surgical procedures for suitable MMD patients.

The current study had a few limitations. First, the de-

sign was retrospective, and therefore selection bias related to different reason patients were treated with indirect bypass and possible confounding factors cannot be excluded. The timing of DSA follow-up was not rigorously controlled at 6 months sharp, which might also bias the results. Second, the sample size, though multicentered, was not big enough, especially for some subgroup analysis. Also, this cohort was Chinese population based. The possibility that the findings might not be generalized to non-Asian MMD patients cannot be excluded. Third, the current study was performed mainly to discover potential clinical and radiographic biomarkers and risk factors for good neoangiogenesis after indirect revascularization but it cannot help explain the underlying mechanics. Future studies are needed to further address this issue and elucidate the pathophysiology.

Conclusions

Hemorrhagic onset predicts poor neoangiogenesis after indirect bypass, while abundant ICA moyamoya collaterals at presentation predict good neoangiogenesis. Good neovascularization was associated with lower incidence of rebleeding and better long-term outcome. The current study offers supporting data for choosing MMD candidates and operation timing for indirect revascularization.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Yahui Zhao. Acquisition of data: Yahui Zhao, Li, Lu. Analysis and interpretation of data: Yahui Zhao, Li, Q Zhang. Drafting the article: Yahui Zhao. Critically revising the article: Yahui Zhao, Chen. Reviewed submitted version of manuscript: Yuanli Zhao, Yahui Zhao, Q Zhang, D Zhang, Wang, Chen. Approved the final version of the manuscript on behalf of all authors: Yuanli Zhao. Administrative/technical/material support: Yuanli Zhao, Q Zhang, D Zhang, Wang, Chen. Study supervision: Yuanli Zhao, Chen.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

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