



# Risk Factors for Specific Postoperative Ischemic Complications in Patients with Moyamoya Disease: A Single-Center Retrospective Study

Huan ZHU<sup>1,2</sup>, Qihang ZHANG<sup>1,2</sup>, Wenjie LI<sup>1,2</sup>, Peijiong WANG<sup>1,2</sup>, Qian ZHANG<sup>1,2</sup>, Dong ZHANG<sup>1,2</sup>, Yan ZHANG<sup>1,2</sup>

<sup>1</sup>Capital Medical University, Beijing Tiantan Hospital, Department of Neurosurgery, Beijing, China

<sup>2</sup>Capital Medical University, Beijing Neurosurgical Institute, Beijing, China

Corresponding author: Yan ZHANG ✉ yanzhang135@163.com

## ABSTRACT

**AIM:** To evaluate and compare postoperative ischemic complications to determine the risk factors for ischemic complications following revascularization surgery for Moyamoya disease (MMD).

**MATERIAL and METHODS:** This single-center retrospective study included 266 procedures between 2016 and 2021. Three types of revascularization approaches including direct bypass, indirect bypass, and combined bypass were performed. To identify risk factors for postoperative ischemic complications and contralateral cerebral infarction, preoperative clinical characteristics and radiographic features were examined using multivariate and ordinal logistic regression analyses.

**RESULTS:** Postoperative ischemic complications occurred in 103 (6.6%) procedures. Ischemic presentation ( $p=0.001$ , odds ratios [OR] 5.59, 95% confidence interval [CI] 2.05–15.23), hypertension ( $p=0.030$ , OR 2.75, 95%CI 1.11–6.83), advanced Suzuki stage ( $p=0.006$ , OR 3.19, 95%CI 1.40–7.26), and collateral circulation ( $p=0.001$  OR 0.17, 95%CI 0.06–0.47) were risk factors for postoperative ischemic complications. Ordinal regression analysis revealed that unilateral involvement ( $p=0.043$ , OR 2.70, 95%CI 0.09–5.31), hemorrhagic presentation ( $p=0.013$ , OR 3.45, 95%CI 0.72–6.18), surgical approach ( $p=0.032$ , OR –1.38, 95%CI –2.65, –0.12), and collateral circulation [ $p=0.043$ , OR –1.27, 95%CI –2.51, –0.04] were associated with the type of ischemic complications. History of hypertension ( $p=0.031$ ) and contralateral computed tomography (CT) perfusion stage ( $p=0.045$ ) were associated with contralateral infarction.

**CONCLUSION:** Inability of cerebral vessels to withstand changes in blood pressure induced by revascularization-related hemodynamic instability might be associated with postoperative complications in patients with Moyamoya disease.

**KEYWORDS:** Collateral circulation, Hypertension, Infarction, Moyamoya disease

**ABBREVIATIONS:** MMD: Moyamoya disease, CBF: Cerebral blood flow, TIA: Transient ischemic attack, RIND: Reversible ischemic neurologic deficits, ECA: External carotid artery, CTP: Computed tomography perfusion, MTT: Mean transit time, CBV: Cerebral blood volume, TTP: Time to peak, mRS: Modified Rankin score, STA: Superficial temporal artery, OR: Odds ratio, CI: Confidence interval, TNE: Transient neurologic events

Huan ZHU : 0000-0001-5313-262X  
Qihang ZHANG : 0000-0003-3217-7903  
Wenjie LI : 0000-0002-0501-2313

Peijiong WANG : 0000-0002-3364-4035  
Qian ZHANG : 0000-0001-8337-0928  
Dong ZHANG : 0000-0002-0801-4971

Yan ZHANG : 0000-0003-1634-4484

## ■ INTRODUCTION

**M**oyamoya disease (MMD), a noninflammatory cerebrovascular disease with relatively high incidence in East Asia, is characterized by the progressive stenosis or occlusion of major intracranial arteries accompanied by the formation of abnormal compensatory vessels from the base of the skull due to decreased cerebral blood flow (CBF) (33). With disease progression, patients present with symptoms of both cerebral ischemia and hemorrhage.

Revascularization surgery remains the treatment of choice despite the lack of high-quality clinical studies (1). Although complications following revascularization surgery are not uncommon, previous studies focused primarily on serious complications such as infarction and cerebral hyperperfusion syndrome, and less attention has been paid to TIA and reversible ischemic neurologic deficits (RIND), which are relatively milder. This study aimed to compare postoperative ischemic complications to determine associated risk factors in patients with MMD undergoing revascularization surgery.

## ■ MATERIAL and METHODS

### Study Design and Participants

This was a retrospective study including patients with MMD who were treated in Beijing Tiantan Hospital between 2016 and 2021. The diagnostic criteria were based on the 2012 Research Committee on Spontaneous Occlusion of the Circle of Willis guidelines (28), and the diagnosis was established by digital subtraction angiography or magnetic resonance angiography. The Ethics Committee of Beijing Tiantan Hospital, Capital Medical University approved this study [Ethics review number: KY2016-048-01, Data: 2016-11-1; This study was supported by National Natural Science Foundation of China (81870833)].

### Perioperative Variables

Patient data included sex, age at time of surgery, symptoms at onset, modified Rankin score (mRS) at admission, medical history including hypertension and diabetes, social history including history of smoking and alcohol consumption, and surgical modalities. Symptoms at onset were grouped into three main categories: nonspecific (asymptomatic, headache, and epilepsy), ischemic (TIA and infarction), hemorrhagic (intracerebral, intraventricular, and subarachnoid hemorrhage).

### Radiological Profiles

The radiological profiles of patients were evaluated using the collateral circulation grading system established by Liu et al. (19), and the computed tomography (CT) perfusion (CTP) scale established by Gao (7). In addition, the external carotid artery (ECA) collateral circulation was evaluated.

The collateral circulation grading system evaluated the blood supply of the anterior collateral circulation and the anatomical extent of pial collateral blood flow from the posterior circulation territory to the anterior circulation territory. Collateral circulation was classified into three grades: grade I (poor), score of 0–4; grade II (fair), score of 5–8; and grade III (good), score of 9–12. The ECA collateral circulation included four arteries:

middle meningeal artery, occipital artery, maxillary artery, and superficial temporal artery (STA). Compensation from the ECA was defined as the presence of one of the vessels extending into the brain.

In the study institution, evaluation of patients with MMD using CTP was conducted no more than 6 months before surgery. CTP was performed 4 sec after the injection of 50 mL iodinated contrast material (iohexol [Omnipaque]; GE Healthcare, Shanghai, China) containing 350 mg/mL iodine. The contrast material was administered through the antecubital vein at a rate of 6 mL/sec using a contrast injector (Missouri-XD2001, Ulrich, Germany), followed by 20 mL saline flush at the same injection rate. The acquisition parameters were set as follows: 80 kVp; 150 mAs; dedicated field of view, 25 cm; rotation, 1 sec; slice thickness, 5 mm; interval, 0 mm. A total of 512 slices were obtained with a total scan time of 44 sec. The CDTIvol was approximately 80 mGy.

Four perfusion parameters, including mean transit time (MTT), CBF, cerebral blood volume (CBV) and time to peak (TTP), were evaluated, and cerebellum or the normal mirrored area was set as reference. The CTP scale was categorized into four stages based on these four parameters: stage I, delayed TTP, other parameters normal; stage II, delayed TTP and MTT, normal CBF, normal or slightly increased CBV; stage III, delayed TTP and MTT, decreased CBF, normal or slightly decreased CBV; stage IV, delayed TTP and MTT, decreased CBF and CBV.

### Surgical Modalities

Three revascularization approaches were used in patients with MMD evaluated in the present study: direct bypass, indirect bypass, and combined bypass. Direct bypass involved end-to-side anastomosis of the superficial temporal artery (STA) to the M4 branch of the middle cerebral artery, and intraoperative indocyanine green video angiography and postoperative CT angiography were routinely used to ensure graft patency. Next, in cases where the graft arteries were not patent, necessary adjustment was performed. Indirect bypass included EDAS and multiple burr holes. For EDAS, the branch of the STA was dissected and sutured on the brain surface. For multiple burr holes, 5–15 burr holes were drilled over the hypoperfusion brain area, and the dura beneath was incised and separated. Combined bypass included the direct and indirect bypass approaches performed during the same surgery. In the study center, the combined bypass approach is recommended for patients with MMD. If the branches of the STA and middle cerebral artery were suitable for anastomosis, the other branch of the STA was also sutured on the brain.

### Postoperative Management and Complications

All patients received fluid replacement therapy and blood pressure monitoring after the surgery. Blood pressure was controlled not to exceed 80% of the baseline in patients who underwent direct or combined bypass and not to exceed 120% of the baseline in patients who underwent indirect bypass. Patients underwent routine CT scans after the revascularization surgery, and if necessary, repeat CT and magnetic resonance imaging scans were performed.

In the present study, postoperative ischemic complications were divided into three categories: TIA, RIND, and infarction. TIA was defined as an episode of focal neurologic deficit that resolved within 24 hours of onset, and RIND was defined as a neurologic deficit related to cerebral ischemia that persisted for more than 24 h and cleared within few weeks (15). In patients with TIA or RIND, the symptoms improved or disappeared after intensive fluid therapy, and no infarctions were observed on CT or magnetic resonance imaging both after the surgery and one month after the discharge.

### Statistical Analysis

Statistical analysis was performed using SPSS (Windows version 25.0; IBM). Continuous variables were presented as means  $\pm$  standard deviation and compared using two-tailed *t* test or one-way analysis of variance. Categorical variables were presented as numbers and percentages and compared using Pearson's chi-square or Fisher's exact test. Binary and ordinal logistic regression analyses were performed to determine variables that were associated with postoperative complications, and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

## RESULTS

### Baseline Characteristics and the Incidence of Postoperative Ischemic Complications

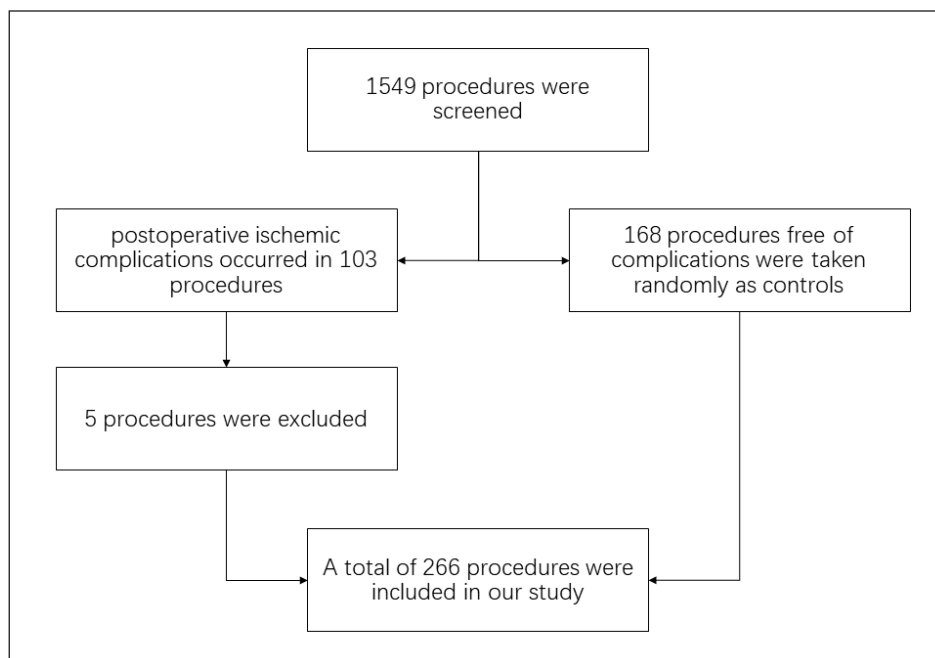
The retrospective review of the medical records identified 1,549 procedures during the study period. Postoperative ischemic complications occurred in 103 (6.6%) procedures in 103 patients. After the exclusion of 5 patients who developed postoperative infarcts but did not exhibit critical information, the remaining 98 patients with 98 procedures who developed

postoperative ischemic complications were included in the final analysis. As the comparator group, from the remaining 1,446 procedures without complications, a random sample of 168 was retrieved using the random number generator of Excel. Therefore, the final analysis group included a total of 266 procedures (Figure 1).

The mean patient age at the time of surgery was  $37.15 \pm 14.63$  years, and the clinical presentations were ischemia in 179 (67.3%) patients, hemorrhage in 62 (23.3%) patients, and nonspecific symptoms in 25 (9.4%) patients. The surgical procedure for revascularization was indirect bypass in 136 (51.1%) patients and direct or combined bypass in 130 (48.9%) patients. Most of the complications occurred within 3 days after surgery (Figure 2).

### Risk factors of Postoperative Ischemic Complications

In the current study, among a total of 98 patients who developed postoperative ischemic complications, 56 (57.1%) patients underwent indirect bypass, and 42 (42.9%) patients underwent direct or combined bypass. The univariate analysis showed that age ( $p=0.010$ ), ischemic presentation ( $p<0.001$ ), prior infarcts ( $p<0.001$ ), hypertension ( $p<0.001$ ), diabetes ( $p<0.001$ ), advanced Suzuki stage ( $p<0.001$ ), mRS ( $p=0.001$ ), collateral circulation ( $p<0.001$ ), and CTP stage ( $p<0.001$ ) were significantly associated with postoperative ischemia. After adjustment for confounding variables in the multivariate analysis, ischemic presentation ( $p=0.001$ , OR 5.59, 95%CI 2.05–15.23), hypertension ( $p=0.030$ , OR 2.75, 95%CI 1.11–6.83), advanced Suzuki stage ( $p=0.006$ , OR 3.19, 95%CI 1.40–7.26), and collateral circulation ( $p=0.001$ , OR 0.17, 95%CI 0.06–0.47) remained significantly associated with postoperative ischemia (Table I).

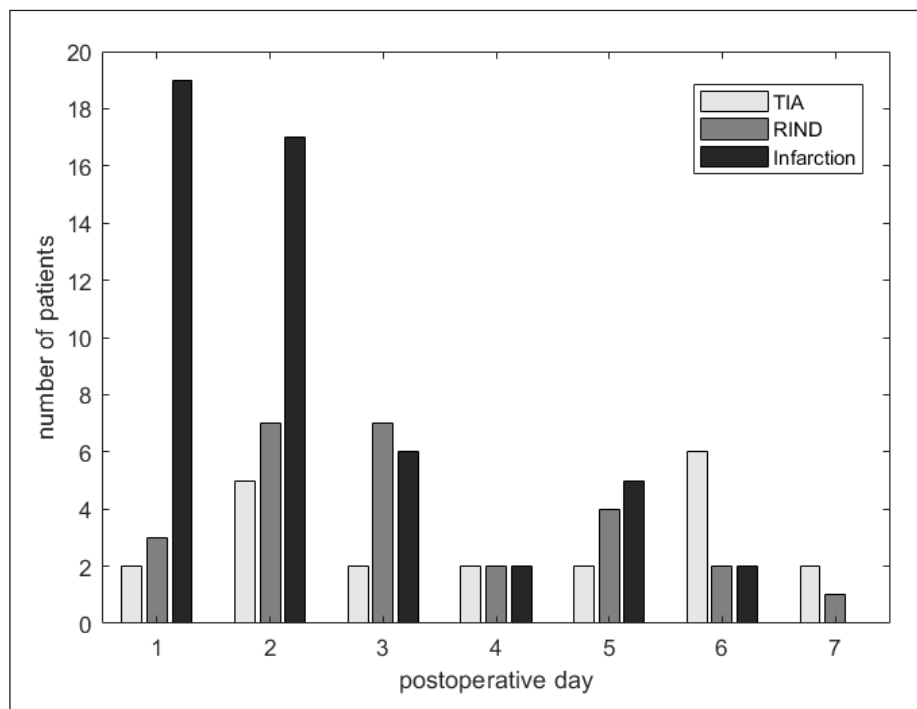


**Figure 1:** The process of sample selection.

**Table I:** Characteristics of Patients with and without Postoperative Ischemic Complications

	<b>Absent (168)</b>	<b>Present (98)</b>	<b>Uni</b>	<b>Multi</b>	<b>OR (95%CI)</b>
Age at operation	34.57 ± 15.27	41.57 ± 12.32	0.010	0.274	1.018 (0.986,1.051)
Sex					
Male	72 (42.9)	54 (55.1)	0.054	0.643	1.239 (0.501,3.063)
Female	96 (57.1)	44 (44.9)			
Unilateral involved	20 (11.9)	5 (5.1)	0.075	0.279	2.717 (0.444,16.617)
Ischemic presentation	94 (56.0)	85 (86.7)	<b>&lt;0.001</b>	<b>0.001</b>	5.587 (2.050,15.225)
Prior infarcts	90 (53.6)	82 (83.7)	<b>&lt;0.001</b>	0.066	2.541 (0.940,6.864)
Past medical history					
Smoking & alcohol consumption	24 (14.3)	18 (18.4)	0.380	0.444	1.744 (0.420,7.232)
Hypertension	37 (22.0)	49 (50.0)	<b>&lt;0.001</b>	<b>0.030</b>	2.749 (1.106,6.834)
Diabetes	12 (7.1)	20 (20.4)	<b>0.002</b>	0.955	1.037 (0.290,3.705)
Admission mRS score					
Mean	0.77 ± 0.97	1.2 ± 0.90	<b>0.001</b>	0.450	1.205 (0.743,1.955)
0	86 (51.2)	18 (18.4)			
1	49 (29.2)	54 (55.1)			
2	19 (11.3)	15 (15.3)			
3	13 (7.7)	10 (10.2)			
4	1 (0.6)	1 (1.0)			
Surgical approach (direct or combined bypass)	88 (52.4)	42 (42.9)	0.135	0.256	0.598 (0.247,1.451)
Suzuki stage*					
Mean	2.98 ± 0.65	3.57 ± 0.70	<b>&lt;0.001</b>	<b>0.006</b>	3.185 (1.398,7.255)
1	4 (3.4)	0 (0)			
2	13 (11.2)	3 (3.9)			
3	80 (69.0)	33 (42.9)			
4	19 (16.4)	35 (45.4)			
5	0 (0)	6 (7.8)			
Collateral circulation*					
Mean	8.33 ± 1.39	6.27 ± 1.89	<b>&lt;0.001</b>	<b>0.001</b>	0.172 (0.062,0.474)
Grade I(0-4)	0 (0)	17 (22.1)			
Grade II(5-8)	59 (50.9)	53 (68.8)			
Grade III(9-12)	57 (49.1)	7 (9.1)			
ECA collateral*	22 (19.0)	11 (14.3)	0.399	0.231	0.468 (0.135,1.623)
CTP stage**					
mean	2.70 ± 0.70	3.16 ± 0.66	<b>&lt;0.001</b>	0.676	1.161 (0.578,2.332)
1	9 (5.4)	1 (1.1)			
2	46 (27.4)	11 (11.5)			
3	99 (58.9)	55 (57.9)			
4	14 (8.3)	28 (29.5)			

**ECA:** External carotid artery, **CTP:** Computed tomography perfusion. \*193 patients received DSA, \*\*263 patients received CTP.



**Figure 2:** Time of occurrence of the postoperative complications.

### Differences Among Ischemic Complications and Infarction Patterns

The 98 postoperative ischemic events included 21 TIAs, 26 RIND, and 51 cerebral infarctions. The ordinal regression analysis demonstrated that unilateral involvement ( $p=0.043$ , OR 2.70, 95%CI 0.01–5.31), hemorrhagic presentation ( $p=0.013$ , OR 3.45, 95%CI 0.72–6.18), surgical approach ( $p=0.032$ , OR -1.38, 95%CI -2.65, -0.12), and collateral circulation ( $p=0.043$ , OR -1.27, 95%CI -2.51, -0.04) were associated with specific postoperative ischemic complications (Table II).

Finally, history of hypertension ( $p=0.031$ ) and contralateral CTP stage ( $p=0.045$ ) were significantly different between the patients who experienced ipsilateral ( $n=45$ ) and contralateral ( $n=6$ ) cerebral infarctions after the procedures (Table III).

## DISCUSSION

In the current study, the majority of postoperative complications occurred within the first 3 days after surgery. Ischemic presentation, prior infarcts, advanced Suzuki stage, history of hypertension, and collateral circulation were associated with postoperative ischemic complications. Patients with unilateral involvement, hemorrhagic presentation, higher collateral circulation stage, and indirect bypass were less likely to develop postoperative infarction. Furthermore, history of hypertension and contralateral CTP stage were associated with contralateral infarction after surgery.

The natural history of MMD is characterized by the transition of cerebral blood supply from the internal to the external carotid system. During this process, insufficient compensation

can lead to neurologic complications. Revascularization surgery aims to promptly improve cerebral blood supply and lower the risk of stroke in the long term. Previous studies reported hemodynamic compromise as the primary cause of postoperative ischemic complications in patients with MMD (36). Risk factors for postoperative ischemic complications include frequent preoperative TIAs (9), advanced Suzuki stage (25), posterior cerebral artery involvement (10), decrease in vascular reactivity (2), and prior infarcts (6). Other mechanisms are thrombosis near the anastomosis site (23) and compression by the swollen temporal muscle after EDAS (5). Also, hypertension is associated with unfavorable clinical outcomes owing to its adverse effects on cerebral vasculature in patients with MMD (16,22). In the current study, ischemic presentation, advanced Suzuki stage, hypertension, and prior infarcts were significant risk factors for postoperative ischemic complications, which is consistent with previous reports. One explanation for these associations might be the inability of cerebral vessels to withstand changes in blood pressure induced by revascularization-related hemodynamic instability.

Among the three main types of cerebral ischemic events in MMD, infarction is the most severe postoperative complication. In the present study, the frequency of postoperative infarction was 3.6%, which is slightly lower than that reported in a study from our center (4.9%) and is on the lower end of the reported range of 1.6%–16% (13,38). The differences among the three types of postoperative ischemic events are quantitative rather than qualitative as they share similar pathological processes and clinical characteristics (16,19,22). Therefore, we conducted ordinal logistic regression to compare these complications and found that the risk of postoperative infarction was higher in patients with lower collateral circulation stage

**Table II:** Ordinal Logistic Regression Analysis for Postoperative Ischemic Complications

	<b>TIA (21)</b>	<b>RIND (26)</b>	<b>Infarction (51)</b>	<b>p uni.</b>	<b>p ordi.</b>	<b>B (95%CI)</b>
Age at operation	40.19 ± 10.33	41.35 ± 12.41	42.25 ± 13.16	0.810	0.131	-0.037 (-0.086,0.011)
<b>Sex</b>						
Male	11 (52.4)	17 (65.4)	26 (50.9)	0.467	0.084	-0.989 (-2.110,0.133)
Female (ref.)	10 (47.6)	9 (34.6)	25 (43.1)			
Unilateral involved (ref.)	2 (9.5)	3 (11.5)	0 (0)	<b>0.027</b>	<b>0.043</b>	2.700 (0.088,5.312)
Hemorrhagic presentation (ref.)	5 (23.8)	2 (7.7)	0 (0)	<b>0.001</b>	<b>0.013</b>	3.453 (0.723,6.184)
Prior infarcts (ref.)	15 (71.4)	22 (84.6)	45 (88.2)	0.195	0.746	-0.268 (-1.896,1.359)
<b>Past medical history</b>						
Smoking & alcohol consumption (ref.)	5 (23.8)	6 (23.1)	7 (13.7)	0.427	0.984	0.016 (-1.564,1.596)
Hypertension (ref.)	8 (38.1)	12 (46.2)	29 (56.9)	0.328	0.095	-0.960 (-2.086,0.167)
Diabetes (ref.)	3 (14.3)	6 (23.1)	11 (21.6)	0.760	0.900	-0.087 (-1.450,1.276)
<b>Admission mRS score</b>						
Mean	0.95 ± 0.50	1.38 ± 1.06	1.22 ± 0.92	0.259	0.615	0.161 (-0.467,0.789)
0	3 (14.3)	4 (15.4)	11 (21.6)			
1	16 (76.2)	14 (53.8)	24 (47.1)			
2	2 (9.5)	3 (11.5)	10 (19.6)			
3	0 (0)	4 (15.4)	6 (11.7)			
4	0 (0)	1 (3.8)	0 (0)			
Surgical approach direct or combined bypass (ref.)	7 (33.3)	12 (46.2)	23 (23.5)	0.661	<b>0.032</b>	-1.384 (-2.651,-0.116)
<b>Suzuki stage*</b>						
Mean	3.56 ± 0.71	3.53 ± 0.70	3.60 ± 0.71	0.927	0.362	-0.405 (-1.278,0.467)
2	1 (5.6)	1 (5.3)	1 (2.5)			
3	7 (38.8)	8 (42.1)	18 (45.0)			
4	9 (50.0)	9 (47.3)	17 (42.5)			
5	1 (5.6)	1 (5.3)	4 (10.0)			
<b>Collateral circulation*</b>						
Mean	2.06 ± 0.54	1.95 ± 0.62	1.75 ± 0.49	0.111	0.043	-1.274 (-2.507,-0.040)
Grade I (0-4)	2 (11.1)	4 (21.1)	11 (27.5)			
Grade II (5-8)	13 (72.2)	12 (63.1)	28 (70.0)			
Grade III (9-12)	3 (16.7)	3 (15.8)	1 (2.5)			
ECA collateral (ref.)*	3 (16.7)	5 (26.3)	3 (15.0)	0.157	0.599	0.408 (-1.114,1.930)
<b>CTP stage**</b>						
Mean	3.15 ± 0.59	3.08 ± 0.86	3.20 ± 0.57	0.760	0.309	-0.420 (-1.228,0.389)
1	0 (0)	1 (4.0)	0 (0)			
2	2 (10.0)	5 (20.0)	4 (8.0)			
3	13 (65.0)	10 (50.0)	32 (64.0)			
4	5 (25.0)	9 (36.0)	14 (28.0)			

**ECA:** External carotid artery, **CTP:** Computed tomography perfusion. \*77 patients received DSA, \*\*95 patients received CTP.



**Table III:** Contralateral Infarction

	<b>ipsilateral (45)</b>	<b>contralateral (6)</b>	<b>p</b>
Age at operation	41.89 ± 1.99	45 ± 12.38	0.909
Sex (male)	23 (51.1)	3 (5.9)	1.000
Ischemic presentation	42 (93.3)	6 (11.8)	1.000
Prior infarcts	40 (88.9)	5 (9.8)	0.548
Past medical history			
Smoking & alcohol consumption	7 (15.6)	0 (0)	0.578
Hypertension	23 (51.1)	6 (11.8)	<b>0.031</b>
Diabetes	11 (24.4)	0 (0)	0.319
Surgical approach (direct or combined bypass)	20 (44.4)	3 (5.9)	1.000
Suzuki stage*			0.740
2	1 (2.9)	0 (0)	
3	16 (47.1)	2 (33.3)	
4	14 (41.2)	3 (50.0)	
5	3 (8.8)	1 (16.7)	
Collateral circulation (ipsi.)*			0.425
Grade I (0-4)	8 (23.5)	3 (50.0)	
Grade II (5-8)	25 (73.5)	3 (50.0)	
Grade III (9-12)	1 (3.0)	0 (0)	
Collateral circulation (contra.)*			0.390
Grade I (0-4)	6 (17.6)	2 (33.3)	
Grade II (5-8)	21 (61.8)	4 (66.7)	
Grade III (9-12)	7 (20.6)	0 (0)	
ECA collateral (ipsi.)*			0.394
0	32 (94.1)	5 (83.3)	
1	2 (5.9)	1 (16.7)	
ECA collateral (contra.)*			0.154
0	31 (91.2)	4 (66.7)	
1	3 (8.8)	2 (33.3)	
CTP stage (ipsi.)**			1.000
2	4 (9.1)	0 (0)	
3	28 (63.6)	4 (66.7)	
4	12 (27.3)	2 (33.3)	
CTP stage (contra.)**			0.045
1	1 (2.3)	0 (0)	
2	10 (22.7)	1 (16.6)	
3	26 (59.1)	1 (16.6)	
4	7 (15.9)	4 (66.7)	

**ECA:** External carotid artery, **CTP:** Computed tomography perfusion. \*40 patients received DSA, \*\*50 patients received CTP.

and bilateral involvement (versus unilateral involvement) and in those who underwent direct or combined bypass (12,19). Of note, insufficient compensatory blood flow is associated with severe impairment in vascular reactivity (17,29), indicating that the hemodynamic stabilization would take longer in the postoperative period in these patients. Meanwhile, compared

with indirect bypass, direct and combined bypass markedly disturb intracranial blood flow and are thus more likely to be associated with adverse events (32). Conversely, direct or combined bypass can quickly alleviate ischemia, effectively lowering the long-term risk of neurological events (3,27). Similarly, patients with unilateral MMD may demonstrate better

circulatory compensation from the unaffected hemisphere, and one study proposed that long-term prognosis might be better in patients with unilateral involvement than in those with bilateral involvement (37).

Interestingly, we also found that none of the patients with hemorrhagic presentation developed postoperative infarction. MMD-related cerebral hemorrhage can be caused by the rupture of severely dilated collateral arteries or microaneurysms (30). Furthermore, a recent study reported that patients with hemorrhagic MMD demonstrated higher serum levels of matrix metalloproteinase-9 and increased brain–blood barrier permeability than those with ischemic MMD, suggesting that the vascular structure is more fragile in these patients (20). Pathologically, fragmented elastic lamina and thinned media in the vessel wall are associated with hemorrhage, whereas collapsed and thrombosed vessels may account for ischemic presentation (18,30). Similarly, cerebral perfusion is relatively uncompromised in patients with hemorrhagic MMD (26,31), and few of the patients who receive conservative management have been reported to experience ischemic stroke during long-term follow-up (11), which might explain the lower likelihood of severe postoperative ischemic complications. In conclusion, these findings suggest that the underlying pathophysiological mechanism might differ between hemorrhagic and ischemic MMD, which warrants further investigation.

Transient neurologic events (TNE), which are sometimes considered as a specific type of postoperative complications in patients with MMD undergoing revascularization surgery, is defined as temporary neurologic deficits, such as numbness in extremities, paralysis, and aphasia, after the exclusion of infarction or intracerebral hemorrhage and resolve within 1–2 weeks. Therefore, RIND can be considered as a type of TNE. Lu et al. found that patients with poor collateral circulation were more likely to suffer from serious TNE (21), similar to the current study findings. Although the underlying mechanism remains unclear, hypoperfusion (8,24) and hyperperfusion (4), alone or together (34), have been proposed to elicit TNE. However, considering that the treatment approaches for hypoperfusion and hyperperfusion are different, identifying the primary cause is vital to prevent the progression of TNE to irreversible neurological damage such as cerebral infarction or hemorrhage.

In the current study, we also found that hypertension and higher contralateral CTP stage were associated with contralateral infarction. According to the stages of regional cerebral hypoperfusion in the preinfarction period proposed by Gao, cerebral blood supply can be maintained by the compensatory dilation of arterioles in the early stages of 1 and 2. In the presence of aggravated ischemia in stages 3 and 4, patients may exhibit symptoms due to the exhausted cerebral circulation reserve capacity and compromised neural tissue perfusion (7,35). We speculate that the severe depletion of the cerebral circulation reserve is a result of prolonged ischemia combined with the damage owing to hypertension; Furthermore, we suggest that the blood flow of the contralateral hemisphere may be further reduced in the postoperative period due to the intracerebral steal phenomenon (14). However,

due to the relatively small number of patients included in the current study, further studies are warranted to elucidate the mechanism underlying the association of hypertension and higher contralateral CTP stage with contralateral infarction.

### Limitations

The present study has several limitations. First, this was a single-center study, and selection bias cannot be denied. Second, some of the patients who underwent digital subtraction angiography in other hospitals were excluded from the multivariate analysis. Third, intraoperative variables, which might be associated with postoperative complications, were not included in the analysis. Further studies are warranted to investigate the association of additional variables, especially the genotype effect, to determine whether patients with MMD are at high risk for postoperative complications following revascularization surgery.

### CONCLUSION

Our study demonstrated that most of the postoperative complications occurred within 3 days after the procedure. Ischemic presentation, prior infarcts, advanced Suzuki stage, history of hypertension, and collateral circulation were associated with postoperative ischemic complications. Unilateral involvement, hemorrhagic presentation, advanced collateral circulation stage, and indirect bypass were associated with less likelihood of severe postoperative ischemic complications, whereas hypertension and higher contralateral CTP stage were associated with contralateral infarction.

#### AUTHORSHIP CONTRIBUTION

Study conception and design: HZ, PW

Data collection: HZ, QZ

Analysis and interpretation of results: HZ, WL

Draft manuscript preparation: HZ

Critical revision of the article: QZ, YZ

Other (study supervision, fundings, materials, etc...): DZ, YZ

All authors (HZ, QZ, WL, PW, QZ, DZ, YZ) reviewed the results and approved the final version of the manuscript.

### REFERENCES

1. Acker G, Fekonja L, Vajkoczy P: Surgical management of moyamoya disease. *Stroke* 49:476–482, 2018
2. Antonucci MU, Burns TC, Pulling TM, Rosenberg J, Marks MP, Steinberg GK, Zaharchuk G: Acute preoperative infarcts and poor cerebrovascular reserve are independent risk factors for severe ischemic complications following direct extracranial-intracranial bypass for moyamoya disease. *AJNR Am J Neuroradiol* 37:228–235, 2016
3. Deng X, Gao F, Zhang D, Zhang Y, Wang R, Wang S, Cao Y, Zhao Y, Pan Y, Liu X, Zhang Q, Zhao J: Direct versus indirect bypasses for adult ischemic-type moyamoya disease: A propensity score-matched analysis. *J Neurosurg* 128:1785–1791, 2018



4. Fujimura M, Kaneta T, Mugikura S, Shimizu H, Tominaga T: Temporary neurologic deterioration due to cerebral hyperperfusion after superficial temporal artery-middle cerebral artery anastomosis in patients with adult-onset moyamoya disease. *Surg Neurol* 67:273-282, 2007
5. Fujimura M, Kaneta T, Shimizu H, Tominaga T: Cerebral ischemia owing to compression of the brain by swollen temporal muscle used for encephalo-myo-synangiosis in moyamoya disease. *Neurosurg Rev* 32:245-249, 2009
6. Funaki T, Takahashi JC, Takagi Y, Kikuchi T, Yoshida K, Mitsuhashi T, Kataoka H, Okada T, Fushimi Y, Miyamoto S: Unstable moyamoya disease: Clinical features and impact on perioperative ischemic complications. *J Neurosurg* 122:400-407, 2015
7. Gao PY, Lin Y: CT perfusion imaging and stages of regional cerebral hypoperfusion in pre-infarction period. *Chin J Radiol* 37(10):882-886, 2003
8. Hamano E, Kataoka H, Morita N, Maruyama D, Satow T, Iihara K, Takahashi JC: Clinical implications of the cortical hyperintensity belt sign in fluid-attenuated inversion recovery images after bypass surgery for moyamoya disease. *J Neurosurg* 126:1-7, 2017
9. Hayashi T, Shirane R, Fujimura M, Tominaga T: Postoperative neurological deterioration in pediatric moyamoya disease: Watershed shift and hyperperfusion: Clinical article. *PEP* 6: 73-81, 2010
10. Jung YJ, Ahn JS, Kwon DH, Kwun BD: Ischemic complications occurring in the contralateral hemisphere after surgical treatment of adults with moyamoya disease. *J Korean Neurosurg Soc* 50:492-496, 2011
11. Kang S, Liu X, Zhang D, Wang R, Zhang Y, Zhang Q, Yang W, Zhao JZ: Natural course of moyamoya disease in patients with prior hemorrhagic stroke. *Stroke* 50:1060-1066, 2019
12. Kim JJ, Fischbein NJ, Lu Y, Pham D, Dillon WP: Regional angiographic grading system for collateral flow: Correlation with cerebral infarction in patients with middle cerebral artery occlusion. *Stroke* 35:1340-1344, 2004
13. Kim T, Oh CW, Bang JS, Kim JE, Cho WS: Moyamoya disease: Treatment and outcomes. *J Stroke* 18:21-30, 2016
14. Kim TJ, Lee JS, Hong JM, Lim YC: Intracerebral steal phenomenon: a potential mechanism for contralateral stroke after carotid artery stenting. *Neurologist* 18:128-129, 2012
15. Koudstaal PJ, van Gijn J, Frenken CW, Hijdra A, Lodder J, Vermeulen M, Bulens C, Franke CL: TIA, RIND, minor stroke: A continuum, or different subgroups? Dutch TIA study group. *J Neurol Neurosurg Psychiatry* 55:95-97, 1992
16. Kuribara T, Mikami T, Komatsu K, Suzuki H, Ohnishi H, Houkin K, Mikuni N: Prevalence of and risk factors for enlarged perivascular spaces in adult patients with moyamoya disease. *BMC Neurol* 17:149, 2017
17. Ladner TR, Donahue MJ, Arteaga DF, Faraco CC, Roach BA, Davis LT, Jordan LC, Froehler MT, Strother MK: Prior infarcts, reactivity, and angiography in moyamoya disease (PIRAMD): A scoring system for moyamoya severity based on multimodal hemodynamic imaging. *J Neurosurg* 126:495-503, 2017
18. Liu X, Zhang D, Shuo W, Zhao Y, Wang R, Zhao J: Long term outcome after conservative and surgical treatment of haemorrhagic moyamoya disease. *J Neurol Neurosurg Psychiatry* 84:258-265, 2013
19. Liu ZW, Han C, Zhao F, Qiao PG, Wang H, Bao XY, Zhang ZS, Yang WZ, Li DS, Duan L: Collateral circulation in moyamoya disease: A new grading system. *Stroke* 50:2708-2715, 2019
20. Lu J, Wang J, Lin Z, Shi G, Wang R, Zhao Y, Zhao J: MMP-9 as a biomarker for predicting hemorrhagic strokes in moyamoya disease. *Front Neurol* 12:721118, 2021
21. Lu J, Zhao Y, Ma L, Chen Y, Li M, Chen X, Wang R, Zhao Y: Predictors and clinical features of transient neurological events after combined bypass revascularization for moyamoya disease. *Clin Neurol Neurosurg* 186:105505, 2019
22. Ma Y, Zhao M, Deng X, Zhang D, Wang S, Zeng Z, Zhang Q, Zhao JZ: Comparison of clinical outcomes and characteristics between patients with and without hypertension in moyamoya disease. *J Clin Neurosci* 75:163-167, 2020
23. Mikami T, Suzuki H, Ukai R, Komatsu K, Akiyama Y, Wanibuchi M, Houkin K, Mikuni N: Predictive factors for acute thrombogenesis occurring immediately after bypass procedure for moyamoya disease. *Neurosurg Rev* 43:609-617, 2020
24. Mukerji N, Cook DJ, Steinberg GK: Is local hypoperfusion the reason for transient neurological deficits after STA-MCA bypass for moyamoya disease? *J Neurosurg* 122:90-94, 2015
25. Muraoka S, Araki Y, Kondo G, Kurimoto M, Shiba Y, Uda K, Ota S, Okamoto S, Wakabayashi T: Postoperative cerebral infarction risk factors and postoperative management of pediatric patients with moyamoya disease. *World Neurosurg* 113: e190-199, 2018
26. Nariai T, Matsushima Y, Imae S, Tanaka Y, Ishii K, Senda M, Ohno K: Severe haemodynamic stress in selected subtypes of patients with moyamoya disease: A positron emission tomography study. *J Neurol Neurosurg Psychiatry* 76:663-669, 2005
27. Pandey P, Steinberg GK: Neurosurgical advances in the treatment of moyamoya disease. *Stroke* 42:3304-3310, 2011
28. Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis, Health Labour Sciences Research Grant for Research on Measures for Intractable Diseases: Guidelines for diagnosis and treatment of moyamoya disease (spontaneous occlusion of the circle of Willis). *Neurol Med Chir (Tokyo)* 52: 245-266, 2012
29. Sam K, Poulblanc J, Sobczyk O, Han JS, Battisti-Charbonney A, Mandell DM, Tymianski M, Crawley AP, Fisher JA, Mikulis DJ: Assessing the effect of unilateral cerebral revascularisation on the vascular reactivity of the non-intervened hemisphere: A retrospective observational study. *BMJ Open* 5(2):e006014, 2015
30. Scott RM, Smith ER: Moyamoya disease and moyamoya syndrome. *N Engl J Med* 360:1226-1237, 2009
31. Shi Z, Ma G, Zhang D: Haemodynamic analysis of adult patients with moyamoya disease: CT perfusion and DSA gradings. *Stroke Vasc Neurol* 6:41-47, 2021

32. Starke RM, Komotar RJ, Connolly ES: Optimal surgical treatment for moyamoya disease in adults: Direct versus indirect bypass. *Neurosurg Focus* 26:E8, 2009
33. Suzuki J, Takaku A: Cerebrovascular “moyamoya” disease: Disease showing abnormal net-like vessels in base of brain. *Arch Neurol* 20:288-299, 1969
34. Takahashi S, Horiguchi T: Relationship between ischaemic symptoms during the early postoperative period in patients with moyamoya disease and changes in the cerebellar asymmetry index. *Clin Neurol Neurosurg* 197:106090, 2020
35. Yin H, Liu X, Zhang D, Zhang Y, Wang R, Zhao M, Zhao JZ: A novel staging system to evaluate cerebral hypoperfusion in patients with moyamoya disease. *Stroke* 49: 2837-2843, 2018
36. Yu J, Shi L, Guo Y, Xu B, Xu K: Progress on complications of direct bypass for moyamoya disease. *Int J Med Sci* 13:578-587, 2016
37. Zhang Q, Wang R, Liu Y, Zhang Y, Wang S, Cao Y, Zhao Y, Liu X, Wang J, Deng X, Gao F, Yang Z, Zhao M, Ge P, Ma Y, Zhao J, Zhang D: Clinical features and long-term outcomes of unilateral moyamoya disease. *World Neurosurg* 96:474-482, 2016
38. Zhao M, Deng X, Zhang D, Wang S, Zhang Y, Wang R, Zhao J: Risk factors for and outcomes of postoperative complications in adult patients with moyamoya disease. *J Neurosurg* 130: 531-542, 2019