# Postoperative collateral formation after indirect bypass for hemorrhagic moyamoya disease

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# Abstract

Background: The study on postoperative collateral formation for hemorrhagic moyamoya disease (MMD) evaluated by using digital subtraction angiography (DSA) is limited. Our study objective was to investigate the postoperative collateral formation after indirect bypass for hemorrhagic MMD.

Methods: All consecutive inpatients with hemorrhagic MMD received indirect bypass at Beijing Tiantan Hospital, Capital Medical University from January 2010 through December 2018 were screened. Postoperative collateral formation was evaluated on lateral views using Matsushima scale. Univariate and multivariate logistic regression analysis was carried out to determine the influence factors for postoperative collateral formation.

Results: 64 patients (64 hemispheres) were included in this study. After a median 8.5 months DSA follow-up, 14 (21.9%) hemispheres was graded as A collateral circulation, 13 (20.3%) was graded as B, and 37 (57.8%) was graded as C. Twenty-seven (43.2%) hemispheres had good postoperative collateral formation and 37 (57.8%) had poor postoperative collateral formation. Univariate logistic regression analyses showed that age at operation (OR, 0.954; 95% CI, 0.908–1.003; p=0.066), hemorrhagic site (OR, 4.694; 95% CI, 1.582–13.923; p=0.005), and PCA involvement (OR, 3.474; 95% CI, 0.922–13.086; p=0.066) may effect postoperative collateral formation. Multivariate logistic regression analyses showed that only anterior hemorrhage (OR, 5.222; 95% CI, 1.605–16.987; p=0.006) was significantly related to good postoperative collateral formation.

Conclusion: Anterior hemorrhage was significantly related to good postoperative collateral formation.


# Background

Moyamoya disease (MMD) a chronic cerebrovascular occlusive disorder, which was characterized by progressive occlusion of the internal carotid arteries or their main branches with compensatory of the basal collateral arterial network (moyamoya vessels) [1,2]. Intracranial ischemia and hemorrhage are the 2 main manifestations associated with this disease [3].

Although intracranial hemorrhage was less common than ischemic attack, it is the main cause of death in MMD patients [4]. Long-term hemodynamic stress to moyamoya vessels is considered as the reason causing vascular pathologies resulting in hemorrhage [5]. Despite it remains controversial, revascularization surgery has been identified as an effective treatment to decrease hemodynamic stress to these vessels for hemorrhagic MMD [5–7]. And direct bypass could improve cerebral blood flow immediately after successful anastomosis between donor and recipient arteries [4], while indirect bypass takes more time to improve the flow, and the effect of surgical revascularization is based on neovascularization from connective tissue [8].

The study on postoperative collateral formation evaluated by using digital subtraction angiography (DSA) is limited, because DSA not only increases the financial burden on patients, but also it is an invasive examination. Nevertheless, it critically important to know the factors of postoperative collateral formation after indirect bypass for hemorrhagic MMD, which may help the surgeons optimize the procedure. Here, we performed this retrospective study and tried to find out the factors effected postoperative collateral formation.

# Methods

*Patient Data*

The study was approved by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University. All consecutive inpatients with MMD at Beijing Tiantan Hospital, Capital Medical University from January 2010 through December 2018 were screened. Inclusion criteria included:1) patients diagnosed based on DSA according to published guidelines set by the Research Committee on MMD in Japan [9]; 2) patients who initially presented with intracranial hemorrhage confirmed by CT scan; 3) patients received indirect bypass; and 4) patients received postoperative DSA after surgical revascularization. Exclusion criteria included moyamoya syndrome caused by neurofibromatosis, Down syndrome, meningitis, and cranial irradiation [1]. Therefore, 64 patients (64 hemispheres) were included. Information on variables was collected at onset, including age at operation, sex, history of risk factors, hypertension, smoking, alcohol use, hyperlipidemia, thyroid disease diabetes, types of hemorrhage, modified Rankin Scale (mRS), and surgical modalities.

*Radiologic profiles*

The site of hemorrhage was based on the classification criteria established by Takahashi et al [10]. An anterior hemorrhage is defined as being located in the putamen, caudate head, frontal lobe, anterior half of the temporal lobe, subependymal area of the anterior part of the lateral ventricle, and anterior half of the corpus callosum. A posterior hemorrhage is defined as being located in the thalamus, posterior half of the temporal lobe, parietal lobe, occipital lobe, subependymal area of the posterior part of the lateral ventricle including the atrium, and posterior half of the corpus callosum.

Collateral circulation was evaluated based on the classification criteria by Liu et al [11]. Posterior collateral circulation was evaluated as follows: on lateral views of vertebrobasilar artery angiograms, the leptomeningeal collateral networks from the posterior cerebral artery (PCA) territory to the anterior cerebral artery (ACA) territory：1) 1 point: blood supply to the cortical border zone between the ACA and PCA territory; 2) 2 points: blood supply over the Central Sulcus via the posterior pericallosal artery. On the anteroposterior view vertebrobasilar artery angiograms, the leptomeningeal collateral networks from the PCA territory to the middle cerebral artery (MCA) territory: 1) 1 point: the anastomoses of the anterior temporal branches of PCA and MCA or the parietooccipital PCA anastomoses to MCA; 2) 1 points: the anastomoses of the anterior temporal branches of PCA and MCA or the parietooccipital PCA anastomoses to MCA; 3）2 points: blood supply extended into the Sylvian fissure；4）3 points: blood supply extended into the occlusion within the M1 or proximal M2 segments. Anterior collateral circulation was evaluated by using Suzuki stage [12], scores of 6 to 0 corresponded to Suzuki stages 0 to 6. The stages of collateral circulation were made as the following: Grade I, a score of 0 to 4; Grade II, a score of 5 to 8; Grade III, a score of 9 to12.

The stages of pre-infarction period was evaluated as the following [13]: Stage I, time to peak (TTP) was delayed, mean transit time (MTT), regional cerebral blood flow (rCBF), and regional cerebral blood volume (rCBV) were normal; Stage II, TTP and MTT were delayed, rCBF was normal, and rCBV was normal or slightly increased; Stage III, TTP and MTT were delayed, rCBF was decreased, and rCBV was normal or slightly decreased; Stage IV, TTP and MTT were delayed, rCBF and rCBV were decreased.

*Postoperative Collateral Formation*

Indirect bypass is not the preferred surgical revascularization procedure at our institution unless there were inadequate recipient or donor artery grafts [14]. And encephaloduroarteriosynangiosis (EDAS) was the prioritized technique. For patients with no available donor vessels, multiple burr hole (MBH) or encephalodurogaleo(periosteal)synangiosis (EDGS) was performed [15]. Postoperative collateral formation was evaluated by using the Matsushima scale on lateral views of external carotid angiograms [16]: A, more than 2/3 of the MCA distribution; B, between 2/3 and 1/3 of the MCA distribution; and C, slight or none (*Fig. 1)*..

*Statistical Analysis*

Statistical analyses were performed by using SPSS (Windows version 22.0, IBM). Matsushima scale A or B score was defined as good postoperative collateral formation, and Matsushima scale C score was defined as poor postoperative collateral formation. The logistic regression analysis was performed to test which variables were associated with postoperative collateral formation. Clinical variables that achieved $P < 0.10$ in the univariate analysis were included in the multivariate analysis. A probability value $< 0.05$ was defined as statistical significance.

# Results

*Baseline characteristics*

A total of 64 hemispheres of 64 patients with hemorrhagic MMD received indirect bypass were enrolled in the study. The mean ±SD age at operation was 36.2±10.7 years (range 9–61 years), and there were 42 female and 22 male patients (female/male ratio was 1.91:1.00). Of the 64 patients, 14 (21.9%) had a history of hypertension, 4 (6.3%) had a history of smoking, 3 (4.7%) had a history of alcohol use, 3 (4.7%) had thyroid disease, 2 (3.1%) had hyperlipidemia, and 1 (1.6%) had diabetes. The most common type of hemorrhage on CT was IVH (n = 33, 52.6%), followed by ICH with IVH (n = 13, 20.3%), ICH (n = 13, 20.3%), and SAH (n = 3, 4.7%). The majority of hemispheres received EDAS (n = 53, 82.8%), five (7.8%) patients received EDGS, and 6 (9.4%) patients underwent MBH (*Table 1)*..

*Radiologic profiles*

Of 64 hemispheres with hemorrhagic MMD, 34 hemispheres (53.1%) suffered anterior hemorrhage, and 30 hemispheres (46.9%) suffered posterior hemorrhage (*Table 2)*.. The majority of hemispheres presented with Suzuki stage III or IV (73.4%), and 12 hemispheres (18.8%) had posterior cerebral artery involvement. Among the 64 hemorrhagic hemispheres, 13 (20.3%) were grade I hemispheres, 48 (75.0%) were grade II hemispheres, and 3 (4.7%) were grade III hemispheres. Angiographic dilation and extension of AChA-PCoA was detected in 48 hemispheres (75%). Superficial temporal artery collateral was found in one (1.6%) hemispheres, middle meningeal artery collateral was detected in 36 (56.3%) hemispheres, and occipital artery collateral was found in 6 (9.4%) hemispheres. The distribution of the stage of pre-infarction period was as follows: Normal, n = 9 (14.1%), stage I, n = 1 (1.6%); stage II, n = 18 (28.1%); stage III, n = 18 (28.1%); stage IV, n = 18(8.1%).

*Predictors for postoperative collateral formation after indirect bypass*

After a median 8.5 months DSA follow-up, among the 64 hemispheres received indirect bypass, 14 (21.9%) hemispheres was graded as A collateral circulation, 13 (20.3%) was graded as B, and 37 (57.8%) was graded as C. Twenty-seven (43.2%) hemispheres had good postoperative collateral formation and 37 (57.8%) had poor postoperative collateral formation. Univariate logistic regression analysis showed that age at operation (OR, 0.954; 95% CI, 0.908–1.003; p = 0.066), hemorrhagic site (OR, 4.694; 95% CI, 1.582–13.923; p = 0.005), and PCA involvement (OR, 3.474; 95% CI, 0.922–13.086; p = 0.066) may effect postoperative collateral formation. Multivariate logistic regression analysis showed that only anterior hemorrhage (OR, 5.222; 95% CI, 1.605–16.987; p = 0.006) was significantly related to good postoperative collateral formation.

# Discussion

Hemorrhagic MMD was less common than ischemic MMD, but patients with hemorrhagic MMD had higher morbidity, higher mortality rates and worse prognosis than patients with ischemic MMD [17,18]. Despite it remains controversial, revascularization surgery has been identified as an effective treatment for hemorrhagic MMD [19]. The effect of indirect revascularization to improve cerebral blood flow was based on the postoperative collateral formation from ingrowth of new vessels [4,6,8]. However, because of the rarity of the disease and invasive DSA examinations, few studies focused on the postoperative collateral formation after indirect bypass in hemorrhagic MMD patients. In this study, we investigated the relationship between various factors and postoperative collateral formation, and found out that anterior hemorrhage was associated with good postoperative collateral formation.

Before evaluating the outcome of procedures in hemorrhagic MMD, it is critical important to know the natural history of MMD. Recently, natural history of patients with hemorrhagic MMD has been well-documented [18,20–23]. In Japan, Kobayashi et al conducted a study of natural history 42 hemorrhagic MMD patients, found that the annual rebleeding rate was 7.09%/person/year, and rebleeding may change hemisphere and type of hemorrhage. Morioka et al conducted long-term follow-up of 36 patients with hemorrhagic MMD [22], found that rebleeding is the most important factor in unsatisfactory outcomes, and rebleeding seems to be age-related (46–55 years). And the results of nonsurgical cohort in the Japan Adult Moyamoya (JAM) Trial showed that choroidal collaterals are a bleeding source with a high risk for hemorrhagic recurrence and a predictor of rebleeding in hemorrhagic MMD [24]. In Korea, Kim et al conducted a study of 176 adult hemorrhagic MMD patients, and found that patients presented with IVH had higher rate of recurrent hemorrhage [21]. In China, our previous study found that the annual incidence of stroke was 4.5%/person/year, and smoking was a risk factor for rebleeding, and hypertension was associated with increased mortality [18].

At present, surgical revascularization is considered to improve the cerebral blood flow and decrease the rate of stroke events, whereas the optimal treatment for patients with hemorrhagic MMD remains controversial [6,8]. In Japan, the results of JAM trial conducted by 22 institutes in Japan showed that direct bypass can decrease the incidence of hemorrhagic events, but statistically marginal [5]. In Korea, Jang et al showed that bypass surgery can reduce stroke recurrence in patients with hemorrhagic MMD [25]. In China, our previous study also showed that surgical revascularization can improve cerebral blood flow and have greater efficacy at preventing rebleeding than conservative therapy [26]. Jiang et al showed that combined bypass may be superior to conservative treatment for patients with hemorrhagic MMD [27]. However, the results of some studies were less optimistic, Ikezaki et al conducted a nationwide survey including 232 patients, which revealed that there was no significant difference in rebleeding rate between surgical and conservative treatments. Houkin et al also showed that revascularization surgery cannot always prevent rebleeding [28]. Although there is still no clear evidence that surgical revascularization significantly prevents rebleeding in adult MMD patients. but revascularization surgery is still considered the first choice for the treatment of patients with hemorrhagic MMD in our center anyhow.

There was only a few studies on indirect bypass for patients with hemorrhagic MMD [29–31]. Wang et al conducted a study of 95 adult hemorrhagic patients after EDAS, found that EDAS was beneficial for patients with hemorrhagic MMD [29]. And An et al performed 13 hemorrhagic MMD in children who received indirect bypass, revealed that revascularization surgery may have a role for prevention of rebleeding [31]. However, Aoki reported indirect bypass failed to prevent the recurrent hemorrhage in patients with hemorrhagic MMD. But our prospective cohort study showed that indirect bypass was similarly effective at preventing recurrent hemorrhagic strokes, compared with combined bypass and direct bypass [14]. And a network meta-analysis of hemorrhagic MMD revealed that indirect bypass had role in treating hemorrhagic MMD [19].

In this study, we investigated the postoperative collateral formation. Twenty-seven (43.2%) hemispheres had good postoperative collateral formation and 37 (57.8%) had poor postoperative collateral formation. And the good collateral formation was relatively low. However, recent study showed that 75% hemispheres were classified as grade A collateral circulation [29], which was much higher than our study. Two studies had diametrically opposite results, further research is needed. The results of our study revealed that anterior hemorrhage was associated with good postoperative collateral formation, and posterior hemorrhage was related to poor postoperative collateral formation. But Takahashi et al investigated the significance of the hemorrhagic site for recurrent bleeding in JAM trial [10], found that patients with posterior hemorrhage are had a higher incidence of rebleeding and got greater benefit from direct bypass. What's more, the results of 95 adult hemorrhagic study showed that the incidence rate was higher for patients with posterior hemorrhage than for anterior hemorrhage after EDAS surgery, but there was no significant difference [29].

Our study had a few limitations. First, our study was a nonrandomized retrospective, single center study, so selection bias may exist. Second, the sample size was not larger enough, there was only 64 hemispheres included in this study. Third, the median DSA follow-up was only 8.5 months, we could not investigate the long-term postoperative collateral formation. However, the general effect of indirect revascularization was very similar in the short and long term follow-up [32].

# Conclusion

Anterior hemorrhage was associated with good postoperative collateral formation.

# Abbreviations

AChA: anterior choroidal artery; DSA: digital subtraction angiography; ECA: External carotid artery; EDAS: encephaloduroarteriosynangiosis; EDGS: encephalodurogaleo(periosteal)synangiosis; ICH: intracranial hemorrhage; IVH: intraventricular hemorrhage; JAM: Japan Adult Moyamoya; MBH: multiple burr hole; MMA: middle meningeal artery; mRS: modified Rankin Scale; OA: occipital artery; PCA: posterior cerebral artery; PCF: postoperative collateral formation; PCoA: posterior communicating artery; SAH: subarachnoid hemorrhage STA: superficial temporal artery.

# Declarations


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## Availability of data and materials

The datasets supporting the conclusions of this study are available from the corresponding author on reasonable request.

### Authors’ contributions

PG, QZ and JZ: conception and design. PG, XY, XL, and XD: acquisition of data. PG, JW and QZ: analysis and interpretation of data. PG: drafting the article. RW, YZ, and DZ: technical supports and surgery. All authors critically revising the article and approved the final version of the manuscript. JZ and QZ: study supervision

### Ethics approval and consent to participate

The study was approved by Beijing Tiantan Hospital Ethics Committee, Capital medical university. Informed consent was written obtained when patients were admitted to Department of Neurosurgery.

### Consent for publication

Not applicable

### Competing interests

The authors declare that they have no competing interests.

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# Tables

**Table 1** Baseline characteristics of 64 patients

| Characteristics | Value |
|---|---|
| Sex ratio (F/M) | 42:22 |
| Age at operation, mean ±SD, y | 36.2±10.7 |
| Age | |
| □18 years | 5 (7.8%) |
| History of risk factors | |
| Hypertension | 14 (21.9%) |
| Smoking | 4 (6.3%) |
| Alcohol use | 3 (4.7%) |
| Thyroid disease | 3 (4.7%) |
| Hyperlipidemia | 2 (3.1%) |
| Diabetes | 1 (1.6%) |
| Type of hemorrhage | |
| IVH | 33 (52.6%) |
| ICH&IVH | 15 (23.4%) |
| ICH | 13 (20.3%) |
| SAH | 3 (4.7%) |
| mRS >2 at admission | 30 (46.9%) |
| Surgical modalities | |
| EDAS | 53 (82.8%) |
| EDGS | 5 (7.8%) |
| MBH | 6 (9.4%) |
| DSA follow-up, median (IQR), mons | 8.5 (6-13) |

Abbreviations: DSA, digital subtraction angiography; EDAS, encephaloduroarteriosynangiosis; EDGS, encephalodurogaleo(periosteal)synangiosis; ICH, intracranial hemorrhage; IVH, intraventricular hemorrhage;

MBH, multiple burr hole; mRS, modified Rankin Scale; SAH, subarachnoid hemorrhage

**Table 2** Radiologic profiles

| Characteristics | Value (%) |
|---|---|
| Hemorrhagic site | |
| Anterior | 34 (53.1) |
| Posterior | 30 (46.9) |
| Suzuki stage | |
| II | 7 (10.9) |
| III | 28 (43.8) |
| IV | 19 (29.7) |
| V | 1 (1.6) |
| VI | 2 (3.1) |
| PCA involvement | 12 (18.8) |
| Collateral circulation | |
| Grade I (1-4) | 13 (20.3) |
| Grade II (5-8) | 48 (75.0) |
| Grade III (9-12) | 3 (4.7) |
| Dilation of AChA-PCoA | 48 (75.0) |
| ECA collateral | |
| STA collateral | 1 (1.6) |
| MMA collateral | 36 (56.3) |
| OA collateral | 6 (9.4) |
| The stage of pre-infarction period | |
| Normal | 9 (14.1) |
| Stage I | 1 (1.6) |
| Stage II | 18 (28.1) |
| Stage III | 18 (28.1) |
| Stage IV | 18 (28.1) |

Abbreviations: AChA, anterior choroidal artery; ECA, External carotid artery; MMA, middle meningeal artery; OA, occipital artery; PCA, posterior cerebral artery; PCF, postoperative collateral formation; PCoA, posterior communicating artery.; STA, superficial temporal artery.

**Table 3** Logistic regression analysis of predictors for postoperative collateral formation

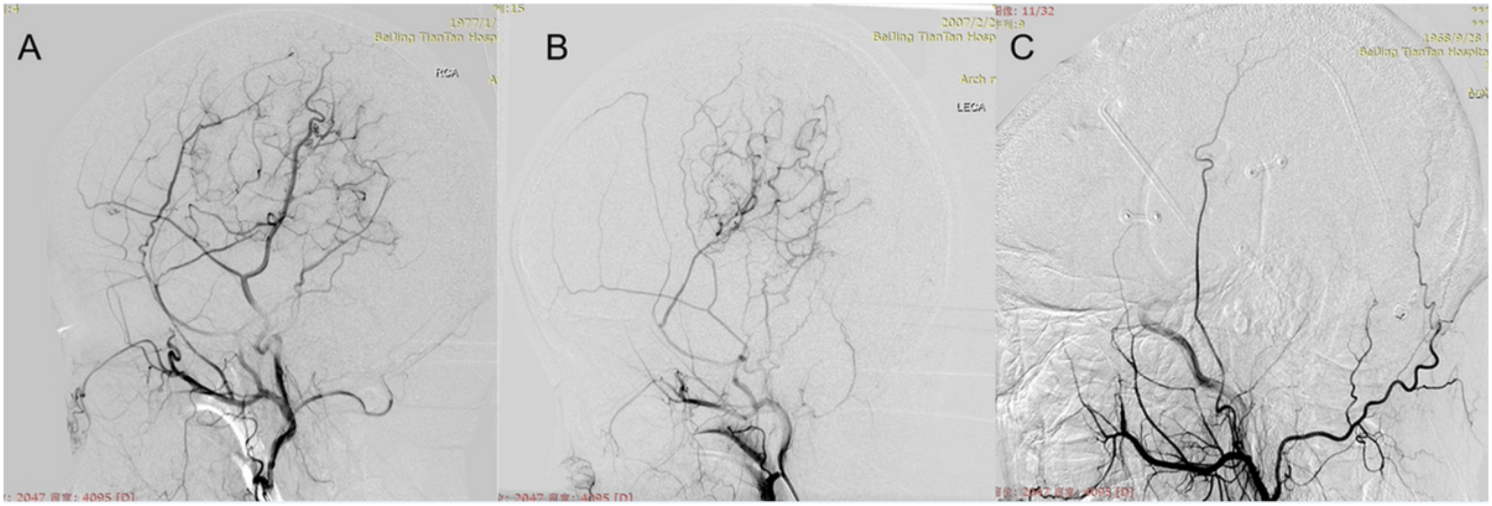
| Characteristics | PCF | | p value | | OR (95% CI) |
|---|---|---|---|---|---|
| | Good (n=27) | Poor (n=37) | Uni | Multi* | |
| Age, years | 33.3±13.0 | 38.6±8.3 | 0.066 | 0.067 | 0.948 (0.896-1.004) |
| Male sex | 8 (29.6%) | 14 (37.8%) | 0.496 | | |
| History of risk factors | | | | | |
| Hypertension | 7 (25.9%) | 7 (18.9%) | 0.504 | | |
| Smoking | 1 (3.7%) | 3 (8.1%) | 0.483 | | |
| Diabetes | 1 (3.7%) | 0 (0.0%) | 1.000 | | |
| Alcohol use | 0 (0.0%) | 3 (8.1%) | 0.999 | | |
| Hyperlipidemia | 1 (3.7%) | 1 (2.7%) | 0.821 | | |
| Thyroid disease | 1 (3.7%) | 2 (5.4%) | 0.752 | | |
| Type of hemorrhage | | | | | |
| IVH | 14 (51.9%) | 19 (51.4%) | 0.968 | | |
| ICH&IVH | 5 (18.5%) | 10 (27.0%) | 0.430 | | |
| ICH | 5 (18.5%) | 8 (21.6%) | 0.824 | | |
| SAH | 3 (11.1%) | 0 (0.0%) | 0.999 | | |
| Hemorrhagic site | | | **0.005** | **0.006** | 5.222 (1.605-16.987) |
| Anterior | 20 (74.1%) | 14 (37.8%) | | | |
| Posterior | 7 (25.9%) | 23 (63.2%) | | | |
| Suzuki stage | | | 0.823 | | |
| II | 4 (14.8%) | 3 (8.1%) | | | |
| III | 12 (44.4%) | 21 (56.8%) | | | |
| IV | 9 (33.3%) | 12 (32.4%) | | | |
| V | 1 (3.7%) | 0 (0.0%) | | | |
| VI | 1 (3.7%) | 1 (2.7%) | | | |
| PCA involvement | 8 (29.6%) | 4 (10.8%) | 0.066 | 0.067 | 4.181 (0.906-19.306) |
| Collateral circulation | | | 0.907 | | |
| Grade I (1-4) | 6 (22.2%) | 7 (18.9%) | | | |

| | | | | | |
|---|---|---|---|---|---|
| Grade II (5-8) | 19 (70.4%) | 29 (78.4%) | | | |
| Grade III (9-12) | 2 (7.4%) | 1 (2.7%) | | | |
| Dilation of AChA-PCoA | 18 (66.7%) | 30 (81.1%) | 0.193 | | |
| ECA collateral | | | | | |
| STA collateral | 0 (0.0%) | 1 (2.7%) | 1.000 | | |
| MMA collateral | 17 (63.0%) | 19 (51.4%) | 0.356 | | |
| OA collateral | 3 (11.1%) | 3 (8.1%) | 0.685 | | |
| The stage of preinfarction period | | | 0.590 | | |
| Normal | 3 (11.1%) | 6 (16.2%) | | | |
| Stage I | 0 (0.0%) | 1 (2.7%) | | | |
| Stage II | 9 (33.3%) | 9 (24.3%) | | | |
| Stage III | 12 (44.4%) | 6 (16.2%) | | | |
| Stage IV | 3 (11.1%) | 15 (40.5%) | | | |
| EDAS surgery | 23 (85.2%) | 30 (81.1%) | 0.668 | 0.998 | 0.998 (0.210-4.742) |

*Adjusted for surgical modalities.

Abbreviations: AChA, anterior choroidal artery; ECA, External carotid artery; EDAS, encephaloduroarteriosynangiosis; CI, confidence intervals; MMA, middle meningeal artery; ICH, intracranial hemorrhage; IVH, intraventricular hemorrhage; OA, occipital artery; OR, odds ratios; PCA, posterior cerebral artery; PCF, postoperative collateral formation; PCoA, posterior communicating artery; SAH, subarachnoid hemorrhage; STA, superficial temporal artery.

# Figures




### Figure 1

Postoperative collateral formation was evaluated with the Matsushima scale: A, more than 2/3 of the MCA distribution; B, between 2/3 and 1/3 of the MCA distribution. C, slight or none.