Association between neoangiogenesis after first and second indirect bypass in moyamoya disease

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Abstract

Background The research on neoangiogenesis after indirect bypass for moyamoya disease (MMD) evaluated by using digital subtraction angiography (DSA) is limited. Our study objective was to investigate association between neoangiogenesis after first indirect bypass and second indirect bypass in MMD.

Methods All consecutive inpatients with MMD who received indirect bypass at Beijing Tiantan Hospital, Capital Medical University from January 2011 through December 2017 were screened. Bilateral neoangiogenesis was evaluated on lateral views and anteroposterior views by using DSA .

Results Twenty-two patients (44 hemispheres) were included in this study. After a median 7.5 months DSA follow-up, On lateral views, 9 (40.9%) hemispheres had grade A, 8 (36.4%) hemispheres had grade B, and 5 (22.7%) hemispheres had grade C after the first procedures; 11 (50.0%) hemispheres had grade A, 7 (31.8%) hemispheres had grade B, and 4 (18.2%) hemispheres had grade C after the second surgery. On anteroposterior views of ECA, 2 (9.1%) hemispheres had level 0, 3 (13.6%) had level 1, 6 (27.3%) had level 2, and 11 (50.0%) had level 3 after the first procedures; 2 (9.1%) hemispheres had level 0, 2 (9.1%) had level 1, 6 (27.3%) had level 2, and 12 (54.6%) had level 3 after second operation. Neovascularization after second operation was strongly associated with the neovascularization after first operation on lateral views (r_s =0.770; p=0.000) and the anteroposterior views (r_s =0.548; p=0.008).

Conclusion Neovascularization after second indirect bypass was strongly associated with neovascularization of first indirect bypass.

Background

Moyamoya disease (MMD) is an uncommon cerebrovascular disorder, which was characterized by progressive occlusion at the terminal portions of the bilateral internal carotid arteries and their main branches within the circle of Willis, with a compensation of the development of abnormal moyamoya vessels [1, 2]. MMD is a rare disease, but it is one of leading causes of stroke in pediatric populations and young adults [3].

The cerebrovascular supply of MMD is characterized by a dynamic transitional state of conversion of

the internal carotid system to the external carotid system (IC-EC conversion) [4]. Revascularization is performed for treatment of MMD to complement the “IC-EC conversion” and thus reduce recurrent ischemic or hemorrhagic strokes [5]. The effect of surgical revascularization is based on postoperative collateral formation from the extracranial carotid artery (ECA) into ischemic brain tissue [6, 7]. Various variables (genetic and clinical factors) may influence the postoperative collateral formation [6, 8, 9]. Because of the heterogeneity of the disease, predicting the prognosis of postoperative collateral formation exactly is complex and difficult. Interesting questions pop up in our minds. Most of patients with MMD would receive bilateral surgery, if the neoangiogenesis after first bypass could predict that after second bypass, it might be much easier to help the neurosurgeons optimizing the second surgical plan. In the present study, we attempted to explore the hypotheses by investigating the association between neoangiogenesis after first indirect bypass and second bypass using digital subtraction angiography (DSA).

Methods

Patients Data

This study is a retrospective analysis. We identified all consecutive inpatients with MMD at Beijing Tiantan Hospital, Capital Medical University from January 1, 2011, to December 31, 2017. Inclusion criteria was as follows:1) patients diagnosed based on DSA according to the guideline published by Japan in 2012 [10]; 2) patients who received bilateral indirect revascularization surgery; 3) patients who had postoperative DSA more than three months after bilateral indirect revascularization surgery. Moyamoya syndrome caused by neurofibromatosis, atherosclerosis, meningitis, Down syndrome, systemic vasculitis and leptospiral infection, was excluded [2].

Radiological Examinations

The preoperative radiologic profiles, including Suzuki stage, collateral circulation, and evaluation of neovascularization were evaluated by two independent neurosurgeons and one radiologist. Collateral circulation was evaluated based on the classification criteria by Liu et al [11]. Anterior collateral circulation was evaluated by using the Suzuki stage, and scores of 6 to 0 corresponded to Suzuki stages 0 to 6 [12]. Posterior collateral circulation was evaluated as follows, based on lateral views of

vertebrobasilar artery angiograms, the leptomeningeal collateral networks from the posterior cerebral artery territory to the anterior cerebral artery territory. The grading score was obtained based on the sum of the anterior and posterior collateral circulation and the stages of collateral circulation were made as follows: Grade I, a score of 0 to 4; Grade II, a score of 5 to 8; and Grade III, a score of 9 to12. On lateral views of ECA, neovascularization was evaluated with the Matsushima scale [13]: A, more than 2/3 of the middle cerebral artery (MCA) distribution; B, between 2/3 and 1/3 of the MCA distribution; and C, slight or none (**Fig 1**). On the anteroposterior views of ECA, neovascularization was evaluated with the Zhao level [14]: level 3, more than 2/3 of the hemispherical cortex; level 2, between 2/3 and 1/3 of the hemispherical cortex; level 1, less than 1/3 of the hemispherical cortex; level 0, minimal or none (**Fig 2**). The count of newly developed veins was recorded as previously reported [15].

Statistical Analyses

Statistical analyses were performed by using SPSS (Windows version 19.0, IBM). Unordered categorical variables were compared with chi square test, ordinal categorical variables were compared with non-parametric tests. Spearman correlation analysis was used to investigate the correlation between two values. All tests were 2-sided, and a *p* value of 0.05 was defined to indicate statistical significance.

Results

Baseline characteristics of hemispheres included in this study

A total of 44 hemispheres in 22 MMD patients who received indirect revascularization were included in our study. The median age at operation was 10 years. The male/female ratio was 24:20. Of the 44 hemispheres, 4 (9.1%) hemispheres initially presented with hemorrhagic symptoms and the others (90.9%) presented with ischemic symptoms. The majority of hemispheres presented with Suzuki stage III-IV(68.2%). And most of hemispheres had grade II collateral circulation. Posterior cerebral artery (PCA) involvement was observed in 11 (25.9%) hemispheres.

Comparison of correlation neoangiogenesis after first and second indirect bypass

The postoperative DSA after first operation was performed at a median 6.5 months, the postoperative

DSA after second indirect bypass was performed at a median 8.5 months. On lateral views of ECA, 9 (40.9%) hemispheres had grade A, 8 (36.4%) hemispheres had grade B, and 5 (22.7%) hemispheres had grade C after the first procedures; 11 (50.0%) hemispheres had grade A, 7 (31.8%) hemispheres had grade B, and 4 (18.2%) hemispheres had grade C after the second surgery. There was no difference between two hemispheres (p = 0.552). On anteroposterior views of ECA, 2 (9.1%) hemispheres had level 0, 3 (13.6%) had level 1, 6 (27.3%) had level 2, and 11 (50.0%) had level 3 after the first procedures; 2 (9.1%) hemispheres had level 0, 2 (9.1%) had level 1, 6 (27.3%) had level 2, and 12 (54.6%) had level 3 after second operation; No differences were found between the two groups (p=0.738). In addition, vein counts were not significantly different between the two groups either (p=0.573).

To assess whether neovascularization after second operation correlates with neovascularization after first operation, Spearman correlation analysis was carried out. Neovascularization after second operation was strongly associated with the neovascularization after first operation on lateral views of ECA (r_S=0.770; p=0.000), on the anteroposterior views of ECA (r_S=0.548; p=0.008), and vein counts (r_S=0.695; p=0.000).

Discussion

No known surgical bypass will reverse the MMD process, and the most important goal of surgical bypass is to reduce the frequency of TIAs, prevent the recurrent strokes, and to improve the postoperative activities of daily living and long-term prognosis of higher brain functions, by improving cerebral blood flow and restoring reserve capacity to the affected cerebral hemisphere [7,16-18]. The indirect bypass, which is relatively easier to perform than direct and combined bypass, brings blood supply to the ischemic brain tissues by the newly developed vasculature from sutured tissue [16,17,19-21].

The effect of surgical revascularization is based on postoperative collateral formation from the ECA into ischemic brain tissue. Potential predictors has been explored in previous study for neovascularization after bypass surgery. Various variables (genetic and clinical factors) may influence the postoperative collateral formation. For genetic factors, cellular experiment and animal study

showed that RNF213 had a potential role of angiogenesis and vasculogenesis in vitro and in vivo [22-24]. And recent study showed that p.R4810K variant may be correlated with the development of collateral formation and supposed that RNF213- positive patients had better postoperative collateral formation than RNF213-negative patients [25]. Our previous study showed that the patients with heterozygous p.R4810K variant in RNF213 might be related to better postoperative collateral formation [8].

For clinical factors, only few studies have investigated potential predictors for postoperative collateral formation after bypass surgery [6,9,26,27]. Our previous study showed that younger age at operation was associated with good postoperative collateral formation, while the presence of hemorrhage and dilated anterior choroidal artery was related to poor postoperative collateral formation in direct and combined bypass [9]. And anther study showed that absent moyamoya vessels and hemorrhagic onset were associated with poor neoangiogenesis after indirect bypass [6]. However, predicting the prognosis of postoperative collateral formation exactly is complex and difficult.

In present study, we found that neovascularization after second indirect bypass was strongly associated with neovascularization after first indirect bypass, which may be a easier way to help neurosurgeons optimizing the second surgical plan. Furthermore why neovascularization after second indirect bypass was strongly associated with neovascularization after first indirect bypass, we supposed that bilateral indirect bypass in one patient shared the same genetic background and similarly risk factors, which may induce the similarly neovascularization. This hypothesis may help surgeons optimizing the second surgical plan, not only indirect bypass, but also direct and combined bypass. As we know, the postoperative formation of direct and combined bypass may involve dural neoangiogenesis and STA neoangiogenesis [28], and the evaluation of the dural and STA neoangiogenesis of direct and combined bypass may help surgeons evaluating whether the indirect bypass is appropriate for the second operation, which may shorten the operation time and reduce intraoperative complications. No doubt this is just our hypothesis, and further study are needed in the future.

Limitation

The present study had a few limitations. First, it is a single neurosurgery center, non-randomized controlled study. Selection bias may exist. Second, the age at second operation was older than the age at first operation, despite there was no difference, and younger age was associated with better neoangiogenesis in previous study. Third, only a few patients were enrolled in our study, due to the invasive DSA and poor medical conditions, which might lead to biased results. Fourth, long-term follow-up DSA was not available, we could not know the long-term neoangiogenesis of indirect bypass.

Conclusions

Neovascularization of second indirect bypass was strongly associated with neovascularization of first indirect bypass.

Abbreviations

DSA: digital subtraction angiography; ECA: External carotid artery; MMA: middle meningeal artery; mRS: modified Rankin Scale; OA: occipital artery; PCA: posterior cerebral artery; STA: superficial temporal artery.

Declarations

Ethics approval and consent to participate

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

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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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

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Tables

Table 1 Baseline characteristics of hemispheres included in this study.

	Hemispheres (%)
Age at operation, median (IQR)	10 (6.25-37)
Sex(male/female)	24/20
Onset type	
Ischemic	40 (90.9)
Hemorrhagic	4 (9.1)
History of risk factors	
Hypertension	4 (9.1)
Diabetes	2 (4.5)
Hyperlipidemia	2 (4.5)
Smoking and alcohol use	2 (4.5)
mRS at admission	
0-1	30 (68.2)
≥2	14 (31.8)
Suzuki stage	
I-II	13 (29.5)
III-IV	30 (68.2)
V-VI	1 (2.3)
Collateral circulation	
Grade I	9 (20.5)
Grade II	27 (61.4)
Grade III	8 (18.2)
ECA collateral	
STA collateral	0 (0.0)
MMA collateral	14 (31.8)
OA collateral	5 (11.4)
PCA involvement	11 (25.0)
EDAS surgery	33 (75.0)
Follow-up time, median (IQR)	7.5 (6-11.75)

ECA, External carotid artery; IQR, interquartile range; MMA, middle meningeal artery; mRS, modified Rankin Scale; OA, occipital artery; PCA, posterior cerebral artery; STA, superficial temporal artery.

Table 2 Comparison of neoangiogenesis at first operation and second operation.

	First operation (%)	Second operation (%)	χ2or Z	*p* value
Age at operation, median(IQR)	9.5 (6-37.5)	10.5 (7-37.75)	-0.600	0.548
Sex(male/female)	12/10	12/10	0.000	1.000
Onset type			0.000	1.000
Ischemic	20 (90.9)	20 (90.9)		
Hemorrhagic	2 (9.1)	2 (9.1)		
History of risk factors				
Hypertension	2 (9.1)	2 (9.1)	0.000	1.000
Diabetes	1 (4.5)	1 (4.5)	0.000	1.000
Hyperlipidemia	1 (4.5)	1 (4.5)	0.000	1.000
Smoking and alcohol use	1 (4.5)	1 (4.5)	0.000	1.000
mRS at admission			0.000	1.000
0-1	16 (72.7)	16 (72.7)		
≥2	6 (27.3)	6 (27.3)		
Suzuki stage			1.463	0.481
I-II	7 (31.8)	6 (27.3)		
III-IV	15 (68.2)	15 (68.2)		
V-VI	0 (0.0)	1 (4.5)		
Collateral circulation			-0.243	0.808
Grade I	5 (22.7)	4 (18.2)		
Grade II	13 (59.1)	14 (63.6)		
Grade III	4 (18.2)	4 (18.2)		
ECA collateral				
STA collateral	0 (0.0)	0 (0.0)	0.000	1.000
MMA collateral	6 (27.3)	8 (36.4)	0.419	0517
OA collateral	1 (4.5)	4 (18.2)	0.903	0.342
PCA involvement	6 (27.3)	5 (22.7)	0.121	0.728
EDAS surgery	17 (77.3)	16 (72.7)	0.121	0.728
Follow-up time, median (IQR)	6.5 (5.75-10)	8.5 (6-13.25)	-1.181	0.238
Matsushima scale			-0.595	0.552
A	9 (40.9)	11 (50.0)		
B	8 (36.4)	7 (31.8)		
C	5 (22.7)	4 (18.2)		
Zhao level			-0.334	0.738
0	2 (9.1)	2 (9.1)		
1	3 (13.6)	2 (9.1)		
2	6 (27.3)	6 (27.3)		
3	11 (50.0)	12 (54.6)		
Vein count	4.8±2.3	5.2±2.5	-0.569	0.573

ECA, External carotid artery; IQR, interquartile range; MMA, middle meningeal artery; mRS, modified Rankin Scale; OA, occipital artery; PCA, posterior cerebral artery; STA, superficial temporal artery.

Table 3 Correlation of neoangiogenesis at first operation and second operation.

Neoangiogenesis	First operation (%)	Second operation (%)	r_s
Matsushima scale			0.770
A	9 (40.9)	11 (50.0)	
B	8 (36.4)	7 (31.8)	
C	5 (22.7)	4 (18.2)	
Zhao level			0.548
0	2 (9.1)	2 (9.1)	
1	3 (13.6)	2 (9.1)	
2	6 (27.3)	6 (27.3)	
3	11 (50.0)	12 (54.6)	
Vein count	4.8±2.3	5.2±2.5	0.695

Figures

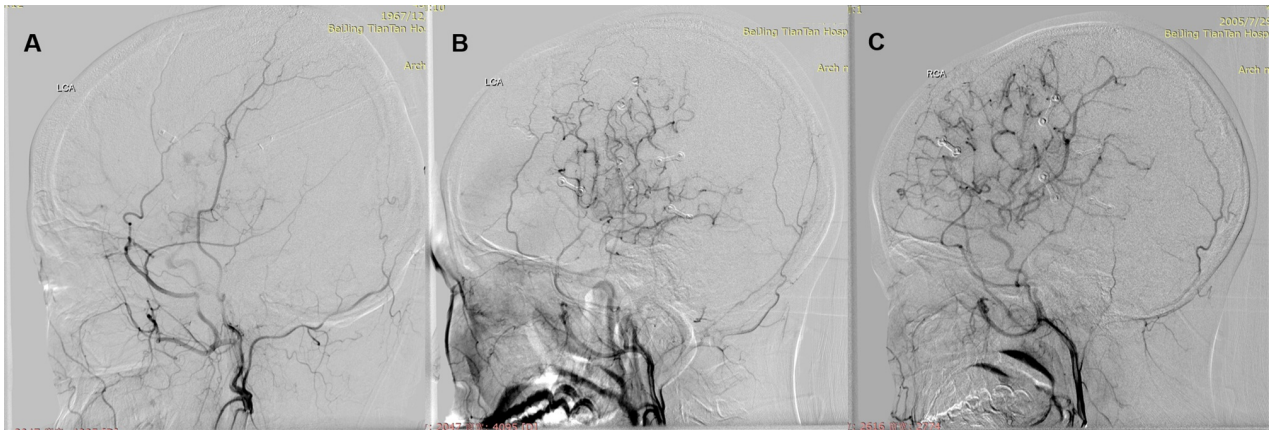

Figure 1

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

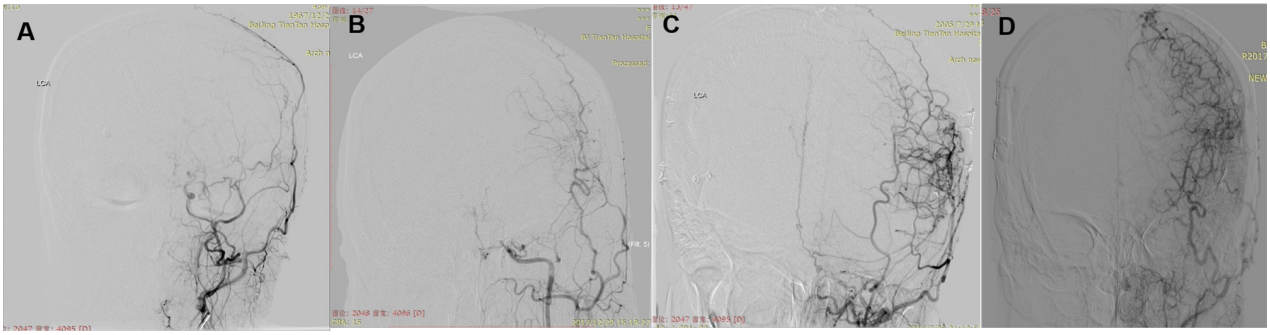

Figure 2

Neovascularization was evaluated with the Zhao level : A, level 0, minimal or none; B, level 1, less than 1/3 of the hemispherical cortex level; C, level 2, between 2/3 and 1/3 of the hemispherical cortex; D, level 3, more than 2/3 of the hemispherical cortex.

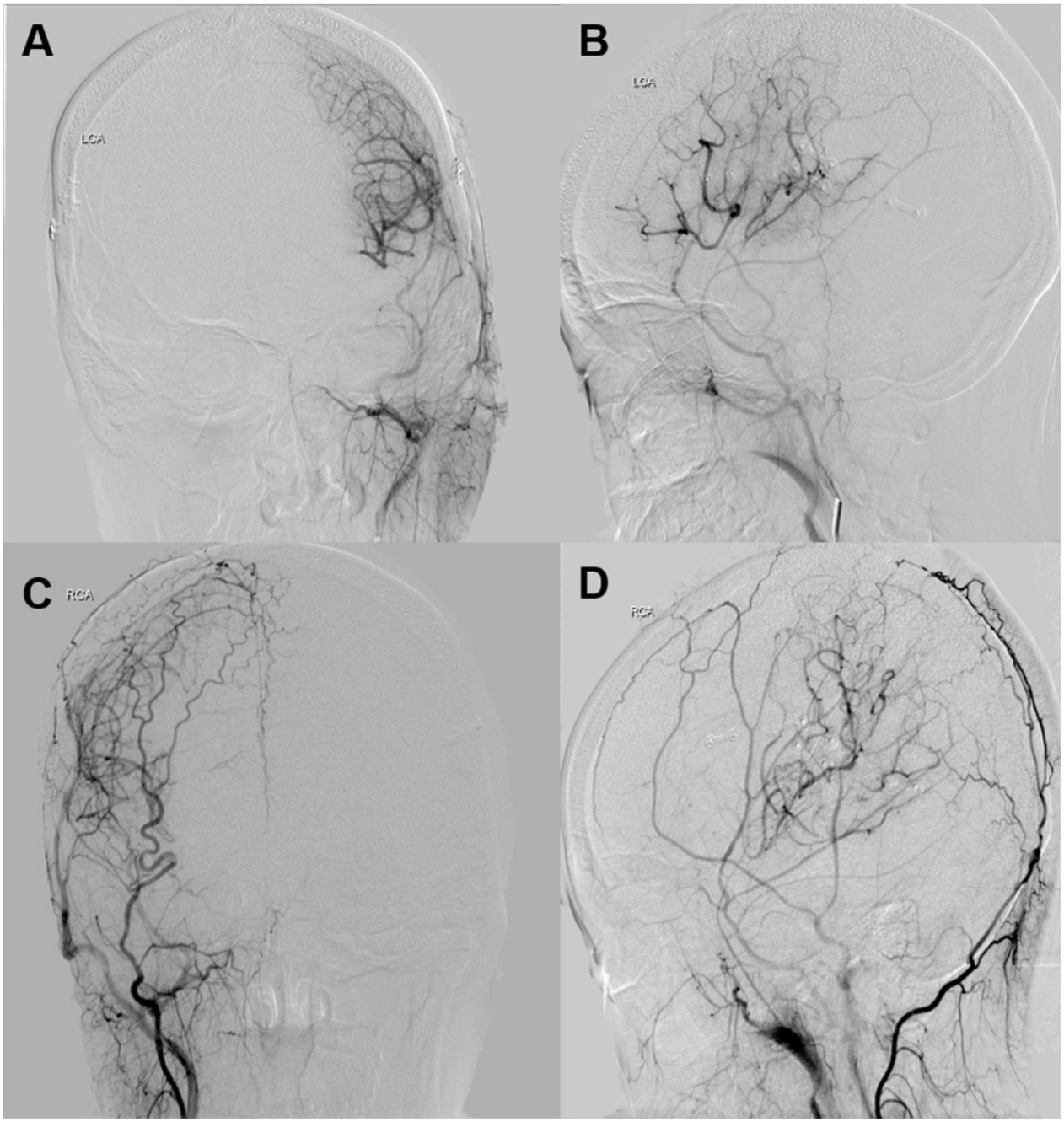

Figure 3

Neovascularization after first bypass was similar with that after second bypass: A, neovascularization after first bypass on the anteroposterior views of ECA; B, neovascularization after first bypass on lateral views of ECA; C, neovascularization after second bypass on the anteroposterior views of ECA; D, neovascularization after second bypass on lateral views of ECA.