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Understanding external carotid artery collateralisation after cerebral revascularisation in moyamoya disease: insights from quantitative analysis

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ABSTRACT

Background This study aims to quantitatively evaluate collateralisation angiogenesis ratio (CAR) of external carotid artery and intracranial arterial residual volumes (ARV) postcerebral revascularisation in moyamoya disease (MMD) and elucidate the factors influencing external carotid artery collateralisation.

Methods The study retrospectively analysed 297 patients diagnosed with MMD who underwent cerebral revascularisation at our University's Hospital, between January 2015 and May 2023. The clinical data, imaging results and surgical specifics for the patients were collected. Using a newly proposed digital subtraction angiography-based evaluation system, the CAR of external carotid artery and the intracranial ARV were evaluated quantitatively following standardised protocols.

Results The study included 136 male and 161 female patients. The severity of ischaemic (r=−0.297) and haemorrhagic (r=−0.270) MMD, as assessed by the Suzuki stage, demonstrated a significant negative correlation with intracranial ARV (p<0.001). However, no significant correlation was observed between the intracranial ARV and the modified Rankin Scale scores. Patients with fetal-type posterior cerebral arteries exhibited greater intracranial ARV compared with those without (p=0.003). Additionally, a positive correlation was observed between external carotid artery collateralisation and intracranial ARV post-revascularisation (r=0.340, p<0.001). The CAR of external carotid artery following cerebral revascularisation in patients with MMD remained independent correlation of the intracranial ARV (β=0.385, 95% CI (0.921 to 1.669), p<0.001) and Suzuki stage (β=0.211, 95% CI (0.009 to 0.030), p<0.001).

Conclusions This study showed a complex association between ARV, the Suzuki stage and the collateralisation of the external carotid artery in patients with MMD who are undergoing revascularisation. These findings provide insights into MMD progression and revascularisation outcomes and may guide clinical decision-making to improve patient care.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The cause of moyamoya disease (MMD)—a rare cerebrovascular disorder characterised by gradual narrowing or obstruction of the internal carotid arteries—remains unknown despite collaborative investigations.

WHAT THIS STUDY ADDS

⇒ This study revealed a complex association among MMD severity, the intracranial arterial residual volumes, and external carotid artery compensation development in patients with MMD undergoing revascularisation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings provide insights into MMD progression and revascularisation outcomes and may guide clinical decision-making to improve patient care.

INTRODUCTION

Moyamoya disease (MMD) is a rare cerebrovascular disorder characterised by gradual narrowing or obstruction of the internal carotid arteries (ICA).[1] This pathophysiological process gives rise to the formation of fragile collateral vessels at the base of the brain, consequently elevating susceptibility to ischaemic and haemorrhagic events, which are the cardinal clinical manifestations of this condition.[2 3] The cause of MMD remains unknown despite collaborative investigations. Nevertheless, the nature of revascularisation interventions to improve cerebral blood flow dynamics and prevent cerebrovascular events is crucial. Revascularisation, which comprises direct and indirect modalities, has become the mainstay therapeutic intervention for MMD. Its objective is to restore adequate cerebral perfusion and mitigate the risk of a subsequent stroke.[4 5]

Nonetheless, the judicious timing of surgical intervention remains a challenge in managing MMD.[6] This challenge arises from the complex equilibrium among the natural progression of the disease, evolution of collateral vascular pathways and optimal window

for surgical intervention.[7] Determining the precise junction at which revascularisation confers optimal outcomes is challenging. Studies show that delayed surgical intervention may escalate vulnerability to cerebral infarction, whereas early initiation may prevent the maturation of collateral vessels, potentially compromising the efficacy of revascularisation.[8]

The magnitude and efficacy of collateralisation for revascularisation in MMD have been subjects of intensive investigation. The complex interplay among the ICAs, their associated collateral networks and the external carotid artery (ECA) system contributes to the complex and multifaceted nature of revascularisation outcomes.[9 10] Previous studies primarily relied on qualitative assessments of angiographic imagery, restricting comprehensive and quantitative evaluations of postoperative collateralisation.[11 12]

This investigation quantitatively evaluated the collateralisation of the ECA and the intracranial arterial residual volumes (ARV) after cerebral revascularisation in patients with MMD. Our research aimed to introduce a novel perspective on this subject. We further aimed to explain the determinants influencing the collateralisation of the ECA in patients with MMD after cerebral revascularisation. This integrated approach can help bridge the gap between disease progression, the collateralisation of the ECA and optimal timing for surgical intervention. Thus, it provides valuable insights that can effectively guide clinical practices, improving patient outcomes.

METHODS

Study design and population

This retrospective study encompassed patients who were diagnosed with MMD at our University Hospital from January 2015 to May 2023. Patient inclusion was based on the established diagnostic criteria for MMD.[13] The exclusion criteria included patients with MMD attributed to identifiable causes and those subjected to postoperative haematoma evacuation or decompressive craniotomy. Patients meeting the inclusion criteria underwent either direct or indirect revascularisation surgery, depending on the quality of the recipient artery. Digital subtraction angiography (DSA) evaluations were performed during the follow-up period.

Data collection

Clinical data were collected from the electronic medical records at the hospital. These data encompassed demographic variables such as age, sex, the modified Rankin Scale (mRS) score at admission and the duration of follow-up. Relevant operation details, such as neurological symptoms and imaging results, were also gathered. The specifics of the surgical procedures, including the type of cerebral revascularisation conducted, were meticulously recorded.

Diagnostic criteria and imaging

The diagnosis of MMD adheres to the guidelines established by the Research Committee on Spontaneous Occlusion of the Circle of Willis.[13] Definitive diagnosis and evaluation of ICA stenosis and occlusion are conducted through DSA. Image assessments are independently carried out by two seasoned radiologists using the Suzuki stage,[14] which helps determine the posterior cerebral artery type. In this research, the term ‘fetal posterior cerebral artery’ denotes the complete fetal-type posterior cerebral artery.[15]

Intracranial ARVs

The progression of MMD causes the ICA and its branches to gradually disappear, to be replaced by collateralisation vessels. Due to the inconsistent number or amount of arteries involved in intracranial blood supply in patients with MMD at different stages, this study uses intracranial ARV as a measure of the number or amount of arteries involved in intracranial blood supply. Any blood flow that supplies the brain through the ICA, including the collateral circulation from the ophthalmic artery and other arteries, is included in the intracranial ARV.

Collateralisation angiogenesis ratio

Following cerebral revascularisation in patients with MMD, a new pathway is established for the ECA to supply blood to the brain. The collateralisation angiogenesis ratio (CAR) is used to evaluate collateralisation of the ECA after cerebral revascularisation in MMD. This ratio is calculated by analysing angiographic data obtained via DSA.

Surgical procedures

Patients with MMD who have suffered haemorrhagic or ischaemic strokes often undergo cerebral revascularisation surgery. Direct revascularisation (superficial temporal artery to middle cerebral artery (STA-MCA) bypass) entails anastomosing the STA to the MCA, which quickly restores blood supply to the brain. Indirect revascularisation (encephaloduroarteriosynangiosis) improves blood flow by attaching the STA to the brain’s surface, thereby promoting the angiogenesis of new vessels.

Follow-up and imaging review

During the patient’s postoperative follow-up, a DSA examination was conducted. A quantitative evaluation system assessed the collateralisation of the ECA and the intracranial ARV. The patients were followed up for an average duration of 11.9 months.

Image data selection and criteria

Angiographic data underwent meticulous review, and patients lacking separate angiograms of the ICA and ECAs or those with incomplete angiographic cycles were excluded.

Converting dynamic DSA

Dynamic DSA was standardised by converting it into 1024×1024 pixels JPEG images at a 1:1 ratio (figure 1A).

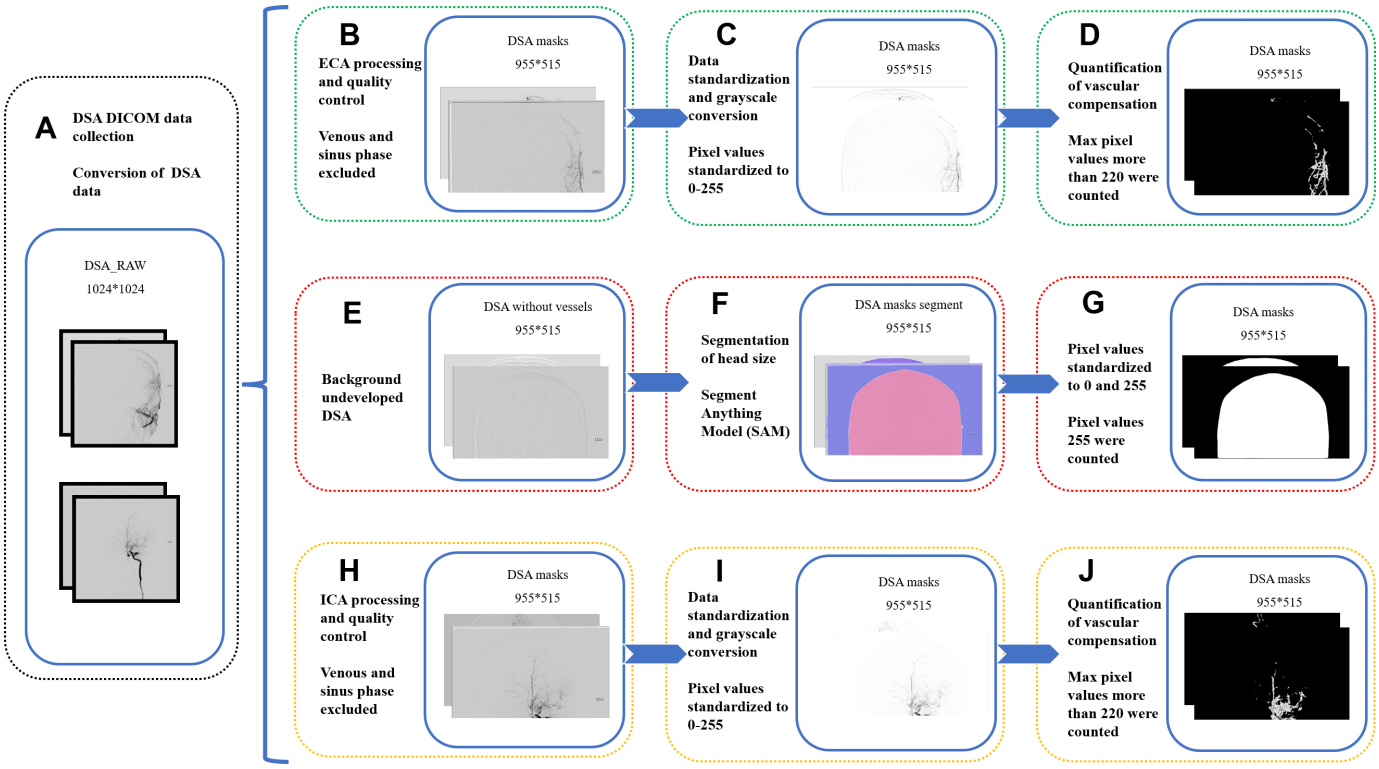

Figure 1 Data processing flow for the ARV and CAR in MMD. (A) Original DSA image. Each frame of the original DSA image was converted into JPEG images of 1024×1024 pixels. (B, H) Analysis area. Quality control of the JPEG images, excluding patients who did not undergo ECA and ICA angiography alone or had incomplete angiography cycles. The area above the starting point of the STA and ICA is selectively intercepted to generate 955×515 pixels JPEG images. (C, I) Standardised image. A standardised image with a consistent background is obtained by subtracting the image in panel E image from the image in panel B, H. (D, J) Calculation image. Greyscale conversion is performed on the image, and the number of pixels with a pixel value greater than 220 is calculated. (E) Background image. The contrast agent has not started to develop (955×515 pixels). (F) Segmented image. The image in panel E automatically segmented through the segment anything model. The purple area represents the segmented head size. (G) Head size calculation. The number of pixels with a value of 255 was calculated. ARV, arterial residual volume; CAR, collateralisation angiogenesis ratio; DSA, digital subtraction angiography; ECA, external carotid artery; MMD, moyamoya disease; STA, superficial temporal artery; ICA, internal carotid artery.

This process enabled uniform image analysis and facilitated comparison across patients.

Data processing and quality control

In image processing and quality control, we selectively captured the region above the origin of the skull base to concentrate on the collateral area of the STA following cerebral revascularisation (see figure 1B,H). This method ensures the inclusion of only pertinent areas of interest in the analysis. The angiographic images underwent quality assurance by an experienced clinician with 5 years of practical experience. We preserved only the imaging data that excluded venous and sinus phases to ensure the inclusion of high-quality, relevant images.

Data normalisation and greyscale conversion

Normalisation adjusts for the varying contrast backgrounds from different imaging devices by subtracting the initial background image from all subsequent patient images (figure 1C,I). This method produces a uniform white background with black vessels, and the pixel values are normalised to fall within the 0–255 range.

Quantification of vascular collateralisation

After numerous experiments, the pixel threshold was established at 220 to capture an optimal vascular image. The pixel count exceeding this threshold was determined independently for both the anterior and lateral position images. To minimise errors from pixel overlap and to provide a thorough evaluation of the target area, the mean of the pixel counts from the anterior–posterior and lateral views was taken as the definitive measure for vascular quantification (figure 1D,G).

Standardisation of head size

The segment anything model (figure 1F) was used to segment the anterior and lateral positions image data (figure 1E), with the skull pixel value set to 255 and the background pixel value set to 0 (figure 1G). Calculate the relative ratio between the number of blood vessels and the size of the head to achieve standardisation of head size.[16]

Vascular quantitative calculation

To minimise the effects of vascular overlap on the outcomes, both anterior and lateral position images were

Table 1 Basic information and radiological data of the patients

Characteristic	Total (n, %)
Age, years	30.2±15.5
Age group	
Children	88 (29.6)
Adult	209 (70.4)
Sex	
Male	136 (45.8)
Female	161 (54.2)
Suzuki stage	
I	0
II	2 (0.7)
III	29 (9.8)
IV	126 (42.4)
V	109 (36.7)
VI	31 (10.4)
Symptom types	
Ischaemic	201 (67.7)
Haemorrhagic	96 (32.3)
Surgery side	
Right	108 (36.4)
Left	189 (63.6)
Surgery type	
Direct	131 (44.1)
Indirect	166 (55.9)
mRS score on admission	
0	18 (6.1)
1	219 (73.7)
2	44 (14.8)
3	14 (4.7)
4	2 (0.7)
5	0
6	0
Follow-up (months)	11.9±11.2

Values are represented as mean±SD, or n (%).
mRS, modified Rankin Scale.

processed and analysed. The average of pixel counts was taken as the definitive count of blood vessels. This final count was denoted as CAR and ARV, representing the quantity of extracervical and intracranial vessels, respectively. Figure 1 illustrates all the procedures involved.[17] The data processing flow is illustrated in figure 1.

Calculation formula:

$$CAR = \frac{LEp+AEp}{2Hp} \times 100\%$$

$$ARV = \frac{LIp+AIp}{2Hp} \times 100\%$$

Table 2 Correlation coefficients of the intracranial ARV and the CAR of external carotid artery with basic information parameters in all participants (n=297)

Variables	Suzuki stage	mRS score	ARV
ARV			
Ischaemic	−0.297**	−0.004	
Haemorrhagic	−0.270**	−0.050	
Total	−0.315**	−0.060	
CAR			
Ischaemic	0.117	−0.005	0.314**
Haemorrhagic	−0.038	−0.077	0.391**
Total	0.064	−0.084	0.340**

**p < 0.001.
ARV, arterial residual volumes; CAR, collateralisation angiogenesis ratio; mRS, modified Rankin Scale.

All processes were performed using the Python V.3.8.12 programming environment on a computer equipped with a 3.6 GHz Intel Core i7-9700K CPU and an NVIDIA GeForce RTX 2080 Ti GPU.

Patient and public involvement

No patients were involved.

Statistical analyses

IBM SPSS Statistics V.20.0 for Windows (IBM) was used for data analysis. Bivariate correlation analysis involved using Pearson's correlation coefficient to determine the strength and direction of linear relationships among continuous variables. Conversely, Spearman's rank correlation coefficient was used to assess the associations between ordinal variables or continuous variables that are not normally distributed. To detect significant differences between groups for categorical variables, we used the χ^2 test; for comparisons of ordinal variables, the Mann-Whitney U test was used. The normality of data was assessed using the Shapiro-Wilk test. A multiple linear regression analysis was conducted to evaluate the relationship between the dependent variables and the independent variables. Standardised β coefficients were calculated to determine the relative strength and direction of the associations between the predictors and the outcomes. 95% CIs were also calculated to provide an estimated range for each β coefficient. Results were considered statistically significant if the p value was less than 0.05.

RESULTS

The retrospective study analysed 553 patients with MMD who underwent cerebral revascularisation in our hospital between January 2015 and May 2023. Patients were followed up with DSA during the follow-up period. 42 patients with MMD were excluded due to a lack of complete imaging data. Another 138 patients were excluded due to poor quality of angiography of the ICA and ECA. During the standardisation of head size, 76

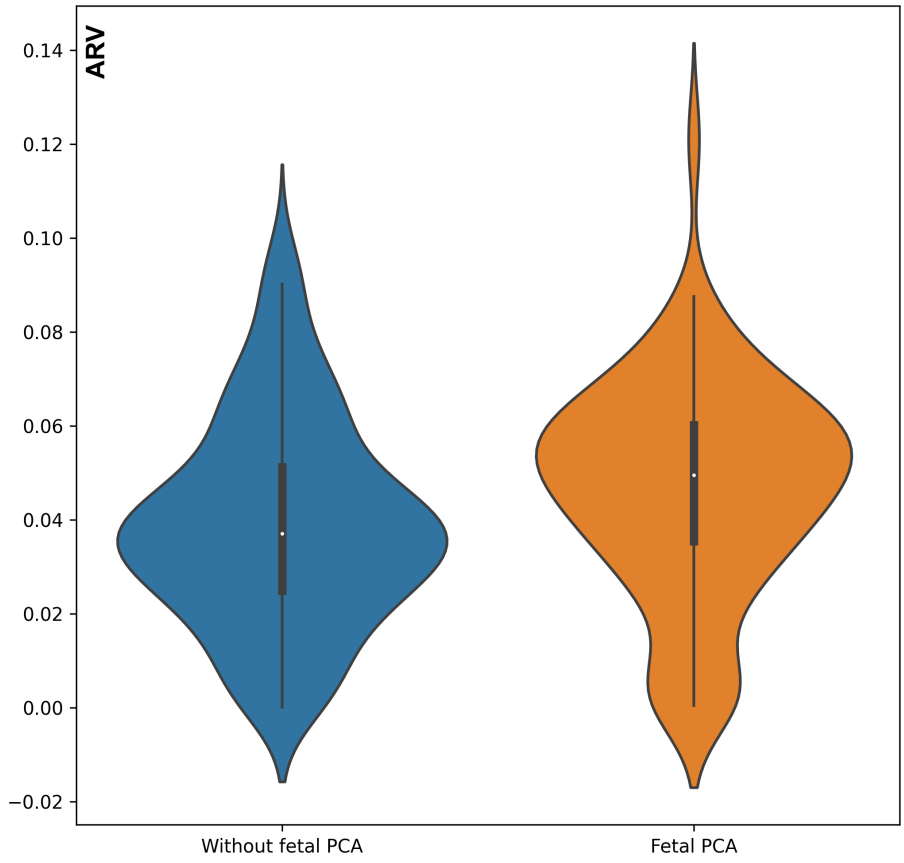

Figure 2 Violin plot showing the distribution of the intracranial arterial residual volumes (ARV) in MMD patients without fetal type posterior cerebral artery (PCA) (n=163, shown in green) and with fetal type PCA (n=134, shown in yellow) MMD, with the horizontal line representing the median and the box indicating the IQR. The between-group difference was statistically significant (p<0.001). MMD, moyamoya disease.

patients with MMD were excluded due to mask generation failure. Therefore, the final analysis included 297 patients with MMD.

The study included 136 and 161 male and female patients, respectively. They included 88 children and 209 adult patients. The Suzuki stage and mRS score on admission of the study patients are shown in table 1. Among them, 90 patients developed haemorrhagic MMD and 207 patients developed ischaemic MMD. The treatment methods include direct and indirect cerebral revascularisation, with 131 cases and 166 cases, respectively. 189 patients underwent left-side cerebral revascularisation surgery and 108 patients underwent right-side surgery. The average follow-up duration for all patients undergoing DSA was 11.9 months (table 1).

Quantitative evaluation of the ICA revealed a substantial negative correlation between the intracranial ARV and the Suzuki stage (table 2; Figure S5). However, no significant correlation was observed between the intracranial ARV and the mRS scores. Further stratified analysis of ischaemic and haemorrhagic MMD revealed a significant negative correlation between intracranial ARV and Suzuki stage, irrespective of haemorrhagic (r=−0.270) or ischaemic (r=−0.297) MMD (online supplemental figures S3 and S4; table 2; p<0.001). After grouping patients with MMD based on the presence of fetal-type posterior cerebral arteries, those with fetal-type posterior cerebral arteries showed more intracranial ARV than those without them (figure 2; table 3; p=0.003). Furthermore, no statistical disparity in Suzuki staging was observed between the two groups (table 3).

Table 3 Comparison of the intracranial ARV and Suzuki stage in moyamoya disease with different types of posterior cerebral arteries

Variables	Fetal PCA	Without fetal PCA	P value
Total, n (%)	134 (45.1)	163 (54.9)	
ARV±SD	4.7±2.3	3.9±2.2	0.003*
Suzuki stage, n (%)			0.763
I	0 (0)	0 (0)	
II	0 (0)	2 (1.2)	
III	14 (10.4)	15 (9.2)	
IV	54 (40.3)	72 (44.2)	
V	54 (40.3)	55 (33.7)	
VI	12 (9.0)	19 (11.7)	

*p<0.05.
ARV, arterial residual volumes; PCA, posterior cerebral artery.

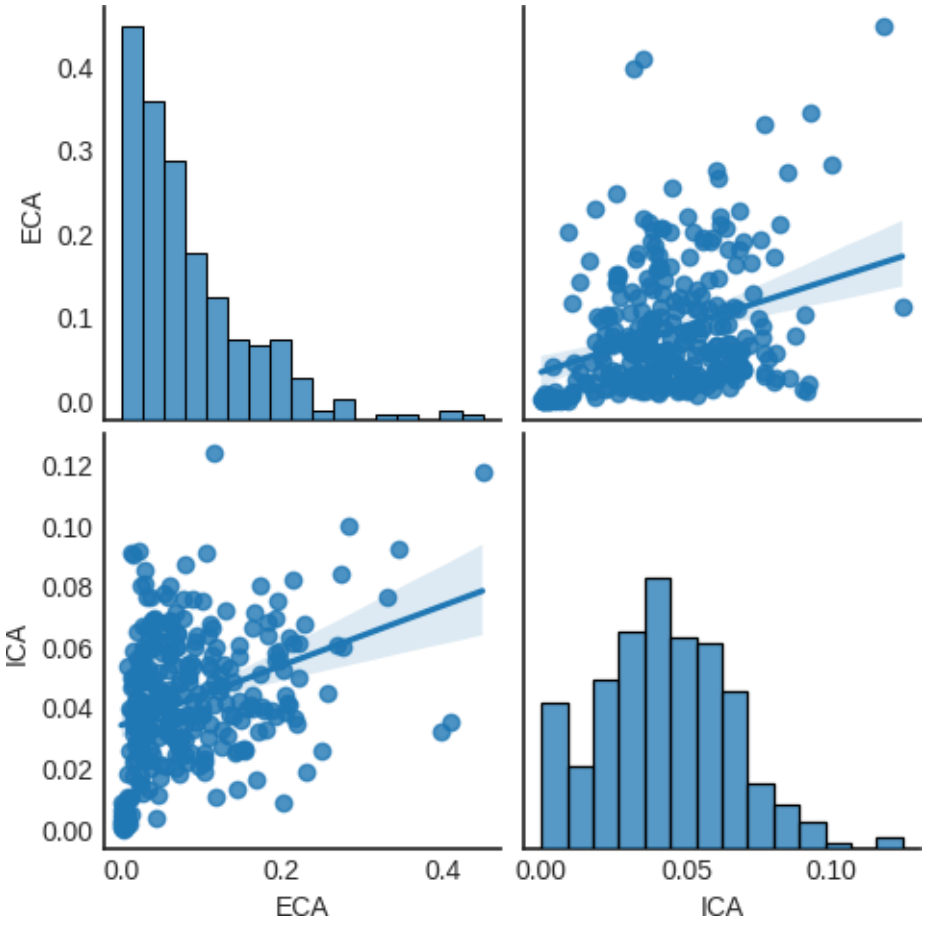

Figure 3 Correlation between the intracranial arterial residual volumes (ARV) and compensation of the external carotid artery in moyamoya disease. Top left: Distribution of compensation of the external carotid artery (ECA); top right and bottom left: Correlation between the intracranial ARV and compensation of the ECA; and bottom right: Distribution of the intracranial ARV. CIs are shown in light blue (with the light blue region representing the region between the 2.5th and 97.5th percentiles of the obtained distribution of correlation values). ICA, internal carotid artery.

Following cerebral revascularisation, the intracranial ARV and the CAR of the ECA showed a strong positive correlation (figure 3; table 2). However, in the subgroup analysis of ischaemic and haemorrhagic MMD, no significant correlations were found between the Suzuki stage or admission mRS scores (online supplemental figure S1 and S2).

As shown in table 4, multiple linear regression analysis revealed that the CAR of the ECA following cerebral revascularisation in patients with MMD remained independent

Table 4 Multiple linear regression analysis of the intracranial ARV, mRS score, Suzuki stage and the CAR of external carotid artery in all participants (n=297)

Variables	Standardised β regression coefficients	95% CI lower-upper	P value
CAR			
Suzuki stage	0.211	0.009 to 0.030	<0.001**
mRS score	−0.480	−0.018 to −0.007	0.375
ARV	0.385	0.921 to 1.669	<0.001**
ARV			
Suzuki stage	−0.318	−0.011 to −0.006	<0.001**
mRS score	0.007	−0.003 to 0.004	0.897
CAR	0.352	0.074 to 0.135	0.001*

*p<0.05, **p<0.01.
ARV, arterial residual volumes; CAR, collateralisation angiogenesis ratio; mRS, modified Rankin Scale.

correlation of the intracranial ARV (β=0.385, 95% CI (0.921 to 1.669), p<0.001) and Suzuki stage (β=0.211, 95% CI (0.009 to 0.030), p<0.001). The mRS score showed a negligible and non-significant positive association with ARV (β=0.007, p=0.897). Conversely, the mRS score, while displaying a negative relationship with CAR (β=−0.480), was not statistically significant (p=0.375).

DISCUSSION

Our research revealed a number of significant elements, such as the relationship between the severity of the disease and the intracranial ARV, the role the fetal-type posterior cerebral artery plays in the compensatory vascular response and the factors influencing the ECA's collateralisation following revascularisation. This study distinctly quantified these associations, providing a more objective evaluation of MMD. However, research on postoperative compensatory blood vessel formation is limited, with most studies focusing on postoperative blood perfusion.[18 19] This quantitative methodology uniquely contributes to previous studies, which predominantly relied on qualitative assessments and provides a comprehensive evaluation of angiogenic phenomena.

The outcomes of our investigation underscore a substantial inverse correlation between the intracranial ARV and the Suzuki stage among patients with MMD. This observation implies that as the severity of the disease increases, the intracranial ARV diminishes.[20] This association confirms the underlying pathological progression of MMD, reaffirming the primary symptoms of arterial stenosis and occlusion. Kim *et al* conducted a DSA examination of 127 children with MMD. They discovered that an increase in the severity of MMD resulted in a decrease in the MCA blood flow volume, accompanied by the formation of basal collaterals.[21] Notably, our study included patients with ischaemic and haemorrhagic MMD, thereby underscoring the universality of this correlation across various clinical presentations.

Furthermore, our findings showed that fetal-type posterior cerebral arteries confer favourable outcomes regarding residual intracranial vessels. Some studies have shown that fetal-type posterior cerebral artery development is more frequently observed in haemorrhagic than ischaemic MMD.[22] This demonstrates a protective role of this anatomical feature, necessitating further investigation to determine the underlying mechanisms.

Our investigation uniquely showed a clear positive association between the collateralisation of the ECA and the intracranial ARV after cerebral revascularisation. Zhao *et al* classified 140 patients with MMD into 2 groups based on their origin: ICA-originated and vertebral artery-originated collaterals and ECA-originated collaterals. These results showed that collaterals originating from the ECAs are associated with advanced Suzuki stages and infarction presentation in MMD.[23] This observation suggests a dynamic interplay between the intracranial and external carotid vasculatures, highlighting the complex nature of revascularisation outcomes. This association remained consistent for ischaemic and haemorrhagic MMD; thus, affirming its stability across distinct clinical subtypes. Our study attempted to bridge existing research gaps by incorporating this inherent diversity, often focusing on isolated clinical phenotypes.

The outcomes of our multiple linear regression analysis provide additional insights into the determinants of the collateralisation of the ECA. Our analysis showed that the emergence of such vessels remains unaffected by Suzuki stage. This independence underscores the complex and multifaceted nature of the angiogenic response after revascularisation.[24] Factors beyond the intracranial ARV and disease severity contribute to the development of compensatory vessels. These factors may encompass genetic predispositions, haemodynamic conditions and complex molecular signalling pathways orchestrating angiogenesis.[25–27]

Acknowledging the inherent limitations of this study is essential. The retrospective design of our analysis introduced biases and limited the ability to establish causal relationships. Moreover, excluding specific patients because of incomplete or suboptimal angiographic data may introduce selection bias. However, our study adopted a thorough and quantitative vascular assessment methodology, providing novel insights into MMD and its revascularisation outcomes.

CONCLUSION

In conclusion, our study is based on a novel quantitative approach for assessing extracranial and intracranial vascularity in patients with MMD. The association among the intracranial ARV, Suzuki stage and the CAR of the ECA provides valuable insights into the complex dynamics of vascular adaptation in MMD. These findings can improve clinical decision-making and enhance patient outcomes by clarifying the determinants of successful revascularisation. Future investigations are warranted to validate and advance our findings, potentially unravelling the underlying mechanisms of vascular competence.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Ethics Committee of Beijing Tiantan Hospital, Capital Medical University, Beijing,

China. KY2022-053-02. Participants gave informed consent to participate in the study before taking part.

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