Characteristics of donor vessels and cerebral blood flow in the chronic phase after combined revascularization surgery for moyamoya disease

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Abstract

This study aimed to analyze whether the development of donor vessels after combined revascularization surgery for moyamoya disease (MMD) was related to cerebral blood flow (CBF) changes. We retrospectively reviewed the charts of 11 adult (12 hemispheres) and 13 pediatric (19 hemispheres) patients who underwent combined revascularization in our department. The total vessel cross-sectional area (TVA) was the sum of the cross-sectional areas of the superficial temporal, middle meningeal, and deep temporal arteries imaged using time-of-flight magnetic resonance angiography. The ipsilateral relative CBF (RCBF) on the brain surface in the craniotomy area was calculated by single-photon emission computed tomography. The preoperative and postoperative ratios of the TVA and RCBF were defined as ΔTVA and ΔRCBF, respectively. Finally, we investigated the correlation between ΔTVA and ΔRCBF in adults and children.

The TVA and RCBF showed a significant increase after surgery regardless of the age group. However, there was no significant correlation between ΔTVA and ΔRCBF in either the adult or pediatric groups. The adult group had significantly higher ΔRCBF values than the pediatric group ($p < 0.01$, $r = -0.44$), but the pediatric group had higher ΔTVA values than the adult group ($p = 0.06$). An increase in CBF was detected around the craniotomy area during the chronic phase after combined revascularization for MMD. However, there was no correlation between the increase in CBF and the measurable total donor vessel area changes.

Introduction

Moyamoya disease (MMD) causes compensatory development of abnormal microvascular networks in the base of the brain with stenosis of the terminal internal carotid artery, which can lead to fatal ischemic and hemorrhagic stroke [1, 2]. Accurate diagnosis and appropriate intervention during the early stage of MMD onset are essential to improve its long-term prognosis. Superficial temporal artery (STA)–middle cerebral artery (MCA) anastomosis and indirect revascularization are considered standard surgical procedures for ischemic MMD [3]. These procedures are expected to improve cerebral blood flow (CBF) disorder and reduce the risk of ischemic stroke [4]. Furthermore, continuous, long-term postoperative follow-up is important to maintain a good prognosis [5, 6, 7].

The development of donor vessels, as assessed by magnetic resonance angiography (MRA), is generally seen as a positive result leading to improved cerebral circulation and metabolism [3]. Similarly, changes in postoperative CBF observed by single-photon emission computed tomography (SPECT) have been reported to be useful for optimal postoperative clinical management and the diagnosis of improved cerebral circulation metabolism [4, 8]. However, as far as we know, there are no reports explaining the correlation between donor vessel development and the increase in CBF, and little research has been done on cerebral hemodynamics in the postoperative chronic phase.

In this study, changes in donor vessels were analyzed based on the total vessel cross-sectional area (TVA) by time-of-flight magnetic resonance angiography (TOF-MRA), and changes in CBF were analyzed based on the relative CBF (RCBF) by SPECT. Furthermore, by evaluating their correlation, we could confirm if the development of donor vessels was related to changes in CBF.

Materials And Methods

Patients

This retrospective observational study enrolled 72 patients (112 hemispheres) who underwent compound revascularization for ischemic MMD at Nagoya University Hospital between April 2014 and May 2020 and underwent follow-up examination > 6 months after surgery. All patients who met the radiological diagnostic criteria for MMD promulgated by the Moyamoya Disease Research Committee accredited by the Ministry of Health, Labor, and Welfare were included [3], and patients with moyamoya syndrome. Patients with vessel stenosis due to atherosclerosis were excluded. Cases in which the donor STA could not be identified in postoperative TOF-MRA were also excluded.

All patients underwent resting cerebral perfusion SPECT (with *N*-isopropyl-*p*-iodine-123-iodoamphetamine [^{123}I-IMP] or technetium-99m ethyl cysteinate dimer [^{99m}Tc-ECD]) and TOF-MRA preoperatively and at > 6 months postoperatively (Fig. 1). The research protocol was approved by the Institutional Review Board of Nagoya University Hospital, and opt-out consent was used in patients from whom written consent could not be obtained.

Indications and procedures for combined cerebral revascularization

The indications for surgical intervention were determined based on the guidelines established by Fukui [3]. The specific indications are ischemic symptoms (such as transient ischemic attack [TIA]) and hemodynamic compromise, as evidenced by CBF evaluation. Combined cerebral revascularization comprised direct and indirect bypass. The procedure selected for the direct bypass was STA-MCA anastomosis. Indirect bypass consisted of placing vascularized pedicles using the temporalis muscle, dura mater, epicranial aponeurosis, and periosteum. The surgical procedure has been described in detail in a previous study [9]. The patency of anastomosis was confirmed by intraoperative indocyanine green imaging and Doppler ultrasound.

Evaluation index of direct and indirect donor vessel development by MRA

Donor vessels were captured using TOF-MRA horizontal section images. The STA was captured in the anterior surface of the auricle before branching to the frontal and parietal branch, the deep temporal artery (DTA) was captured in the temporalis transition, and the MMA was captured in the foramen spinosum. Furthermore, the blood vessel's cross-sectional area was measured from each donor vessel's diameter (square of blood vessel radius · 3.14). Additionally, the TVA was calculated as the total cross-sectional area of all donor vessels. The full width at half maximum (FWHM) was used when measuring blood vessel diameter (Fig. 2) [10, 11]. Finally, the preoperative and postoperative change ratio of the donor vessels was used as an index of the development of vessels (ΔTVA). TOF-MRA images were obtained using clinical 3.0T scanners (Magnetom-Skyra, Magnetom-Verio, Magnetom-Prisma; Siemens AG, Erlangen, Germany) with 32-channel head coils, using uniform imaging parameters as follows: 3D gradient echo, TR = 33 ms, TE = 3.7 ms, flip angle = 16°, averaging = 1, three slabs, thickness = 0.65 mm, field of view = 20 cm, matrix = 448 ´ 250.

Evaluation index of CBF by SPECT

CBF was measured by SPECT, following a previously described method [12] with ^{123}I-IMP and ^{99m}Tc-ECD. The nuclide used for SPECT must be matched before and after surgery for each patient. The region of interest (ROI) was set in the cerebral cortex as a 1-cm-thick band immediately below the craniotomy area where the donor vessels gather (craniotomy ROI). Furthermore, RCBF was calculated with measured CBF as the ipsilateral cerebellum ratio (Fig. 3). Finally, the preoperative and postoperative change ratios were calculated and used as an evaluation index for the ΔRCBF.

Comparison of characteristics in preoperative and postoperative changes in MRA and SPECT

We investigated the correlation between ΔTVA and ΔRCBF in the adult and pediatric groups. We also investigated whether ΔTVA and ΔRBFR are associated with clinical factors in patients.

Statistical procedures

All statistical analyses were performed using SPSS version 27 (IBM Corp., Armonk, NY, USA). Data are expressed as mean ± standard deviation. Changes in values at two-time points were evaluated using Wilcoxon signed-rank test. The difference between the values in the two groups was assessed using Spearman's rank correlation analysis. Significance was set to $p < 0.05$ in all statistical analyses.

Results

Patient characteristics

We enrolled 24 patients (adults, n = 11, 12 hemispheres; children, n = 13, 19 hemispheres) with ischemic MMD who had undergone follow-up > 6 months after surgery. The demographic and clinical characteristics of the patients are summarized in Table 1. One adult patient had moyamoya syndrome with Basedow disease (two hemispheres). No obvious cerebral infarction or hemorrhage was observed in any of the patients' hemispheres until postoperative imaging.

Table 1
Patients’ demographic and clinical information

	Adult (n = 11, 12 hemispheres)	Children (n = 13; 19 hemispheres)
Male/female, hemispheres	1:11	3:16
Side (left), n/n (%)	5/12 (41.7)	7/19 (36.8)
Age (years), mean ± SD[a] [range]	31.4 ± 12.6 [15–49]	8.3 ± 3.2 [3–14]
Postoperative imaging period (months), mean ± SD	13.4 ± 5.2	12.4 ± 4.3
Onset type, n/n (%)		
TIA[b]	11/12 (91.7)	13/19 (68.4)
Infarction	1/12 (8.3)	6/19 (31.6)

[a] SD, standard deviation; [b] TIA, transient ischemic attack

Development of TVA

The median preoperative TVA was 3.65 (interquartile range [IQR], 3.46–4.25) in adults and 2.99 (IQR, 2.66–3.29) in children. The median postoperative TVA was 6.14 (IQR, 4.93–7.1) in adults and 5.46 (IQR, 4.57–6.36) in children. The TVA was significantly developed postoperatively, regardless of the age group ($p < 0.05$) (Fig. 4A).

Increased RCBF

The median preoperative RCBF was 0.83 (IQR, 0.78–0.91) in adults and 1.08 (IQR, 0.98–1.14) in children. The median postoperative RCBF was 0.97 (IQR, 0.85–1.00) in adults and 1.1 (IQR, 1.01–1.20) in children. RCBF was significantly developed postoperatively, compared with preoperatively in adults ($p < 0.05$), but it was not statistically superior in children (Fig. 4B).

Relationship between ΔTVA and ΔRCBF

ΔTVA was not correlated with ΔRCBF in either the adult or pediatric group ($p > 0.05$) (Fig. 5). In addition, ΔTVA and ΔRCBF were not correlated with sex, hemisphere side, preoperative symptom type, or improvement of TIA frequency ($p > 0.05$). When divided into adult and pediatric groups, the adult group tended to have significantly higher ΔRCBF ($p < 0.01$, $r = -0.44$), whereas the pediatric group tended to have higher ΔTVA ($p = 0.06$).

Discussion

This study focused on the chronic phase after combined cerebral revascularization for MMD. The sum of the donor vessel cross-sectional areas of the STA, MMA, and DTA was evaluated as TVA using TOF-MRA, and RCBF was evaluated by SPECT. In addition, the preoperative and postoperative change ratios were defined as ΔTVA and ΔRCBF, respectively. The TVA and RCBF significantly increased postoperatively, but no significant correlation was found between ΔTVA and ΔRCBF. In addition, when divided into adult and pediatric groups, ΔRCBF tended to be significantly higher in the adult group, whereas ΔTVA tended to be higher in the pediatric group.

Evaluation of donor vessel cross-sectional area by TOF-MRA

TOF-MRA has long been the focus of attention as an alternative to digital subtraction angiography (DSA) for assessing donor vessel development [13]. In recent years, Uchino et al. reported that postoperative STA and DTA dilation correlates with DSA gradual revascularization assessment [14]. In addition, one report suggested that if MMA is preserved intraoperatively without sacrifice, the resulting increase in MMA diameter after surgery may reinforce the development of indirect pathways [15]. The significant development of donor vessels after surgery in these reports is consistent with our results. Therefore, the development of donor vessels observed using TOF-MRA is considered a beneficial finding that predicts the enhancement of revascularization.

However, it should be noted that previous reports evaluated donor vessel development by vessel diameter. This is because the blood flow through the blood vessels depends on the blood flow velocity and cross-sectional area of the blood vessel. We adopted the vessel cross-sectional area rather than the vessel diameter to estimate the blood flow through the vessel more accurately. In fact, an algorithm for evaluating CBF using the cross-sectional area of blood vessels has been proposed [16], and a report that used the algorithm with magnetic resonance imaging suggested that CBF decreases with age [17].

Meanwhile, FWHM has the advantages of minimizing interobserver variation caused by window-level adjustments and improving measurement reproducibility. FWHM has been previously reported as an effective tool for assessing the residual components of aneurysms after coiling treatment [10]. In addition, if the vessel cross-section is oval during the vessel diameter measurement, the minor diameter is measured to avoid overestimating the actual radius.

Evaluation of CBF by SPECT

The CBF quantitative value by SPECT is an established evaluation method of cerebral circulation metabolism, but the fluctuation between patients is large [18]. Since RCBF calculates relative values based on the cerebellum of the same patient, it is expected to reduce evaluation errors. In previous reports, RCBF has been adopted as an effective semiquantitative parameter for understanding postoperative cerebral hemodynamics [12, 19].

Donor vessel development and increased CBF are not correlated

We hypothesized that TVA and RCBF reflect revascularization effects and correlate with their tendency to strengthen. However, contrary to expectations, there was no correlation between ΔTVA and ΔRCBF. To explain this result, we present three possible factors.

First, microvessels that were not evaluated as donor vessels may have enhanced CBF in the postoperative craniotomy area. The unique microvascular hyperplasia of the cerebral cortex of patients with MMD has been implicated in the development of collateral circulation that compensates for ischemia [20]. Furthermore, angiogenic activity in the craniotomy area has been reported to be activated by the intervention of revascularization [21]. These reports reinforce the first hypothesis. Second, the development of the donor vessels may have the effect of strengthening the external carotid (EC) blood flow system, which, in contrast, reduces the internal carotid (IC) blood flow system. This phenomenon is a dynamic change in the blood flow system characteristic of MMD and is called IC-EC conversion [22]. Similar to the first hypothesis, interventions in revascularization surgery have been reported to promote IC-EC conversion [12, 23]. In this study, ΔTVA increase was detected as strengthening the EC blood flow system. However, ΔRCBF may decrease with the weakening of the IC blood flow system under the influence of IC-EC conversion. Therefore, IC-EC conversion may have disrupted the correlation between ΔTVA and ΔRCBF. Finally, RCBF may reflect diminished cerebellar blood flow opposite the supratentorial lesion, called crossed cerebellar diaschisis (CCD) [24]. Of the 24 patients (31 hemispheres) included in this study, 18 (25 hemispheres) had contralateral lesions. Therefore, if CCD lowers the cerebellar blood flow on the subject side, it will affect the calculation of RCBF.

These hypotheses warn of the difficulty of postoperative cerebral circulation metabolism assessment in patients with MMD. Furthermore, it may be important to use a combination of multiple parameters to verify cerebral circulation metabolism more accurately. According to a report in China, CBV in the MCA region decreased significantly 3–14 months after surgery [25].

Limitations

This study has some limitations. First, this was a retrospective cohort study conducted in a single center and with small sample size. Therefore, the results should be carefully interpreted. Second, the study included cases where a decrease in preoperative RCBF was not apparent. A correlation may be confirmed between ΔTVA and ΔRCBF by extracting and verifying cases with a marked decrease in RCBF. Third, in TOF-MRA images, the brightness of the vessel lumen depends on blood flow velocity, but the brightness has not been evaluated. Therefore, to determine donor blood flow more accurately, the brightness of the vessel lumen should be investigated using TOF-MRA. Finally, the postoperative chronic phase was defined as after 6 months without an upper limit. However, there is little evidence that donor vessel development and cerebral blood flow remain stable after 6 months. Thus, individual differences in strengthening TVA and RCBF that occur after 6 months were not considered.

Conclusions

TVA and RCBF were reinforced in the postoperative chronic phase. However, there was no correlation between ΔTVA and ΔRCB, and there was no evidence that the development of donor vessels directly affected changes in CBF.

Declarations

Ethical Approval and Consent to participate

The research protocol was approved by the Institutional Review Board of Nagoya University Hospital. And this study used opt-out consent for patients from whom written consent could not be obtained.

Human and Animal Ethics

Not applicable

Consent for publication

The authors affirm that human research participants provided informed consent for publication of the images in Figure(s) 1a-h, 2a, 2b, and 3a-e.

Availability of supporting data

The data and materials that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

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Authors' contributions

All authors contributed to the inspiration and design of the study. Data collection, analysis, and interpretation were performed by Takashi Mamiya, Yoshio Araki, and Toshiaki Taoka. The manuscript was written by Takashi Mamiya. All authors read and approved the final manuscript.

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Figures

Figure 1

Preoperative (A-D) and 10-month postoperative (E-H) time-of-flight magnetic resonance angiography (TOF-MRA) and single-photon emission computerized tomography (SPECT) images of a 15-year-old girl with transient ischemic attack.

TOF-MRA: (A, E) superficial temporal artery (short arrow), (B, F) deep temporal artery (long arrow), and (C, G) middle meningeal artery (arrowhead). SPECT: (D, H) cerebral blood flow map.

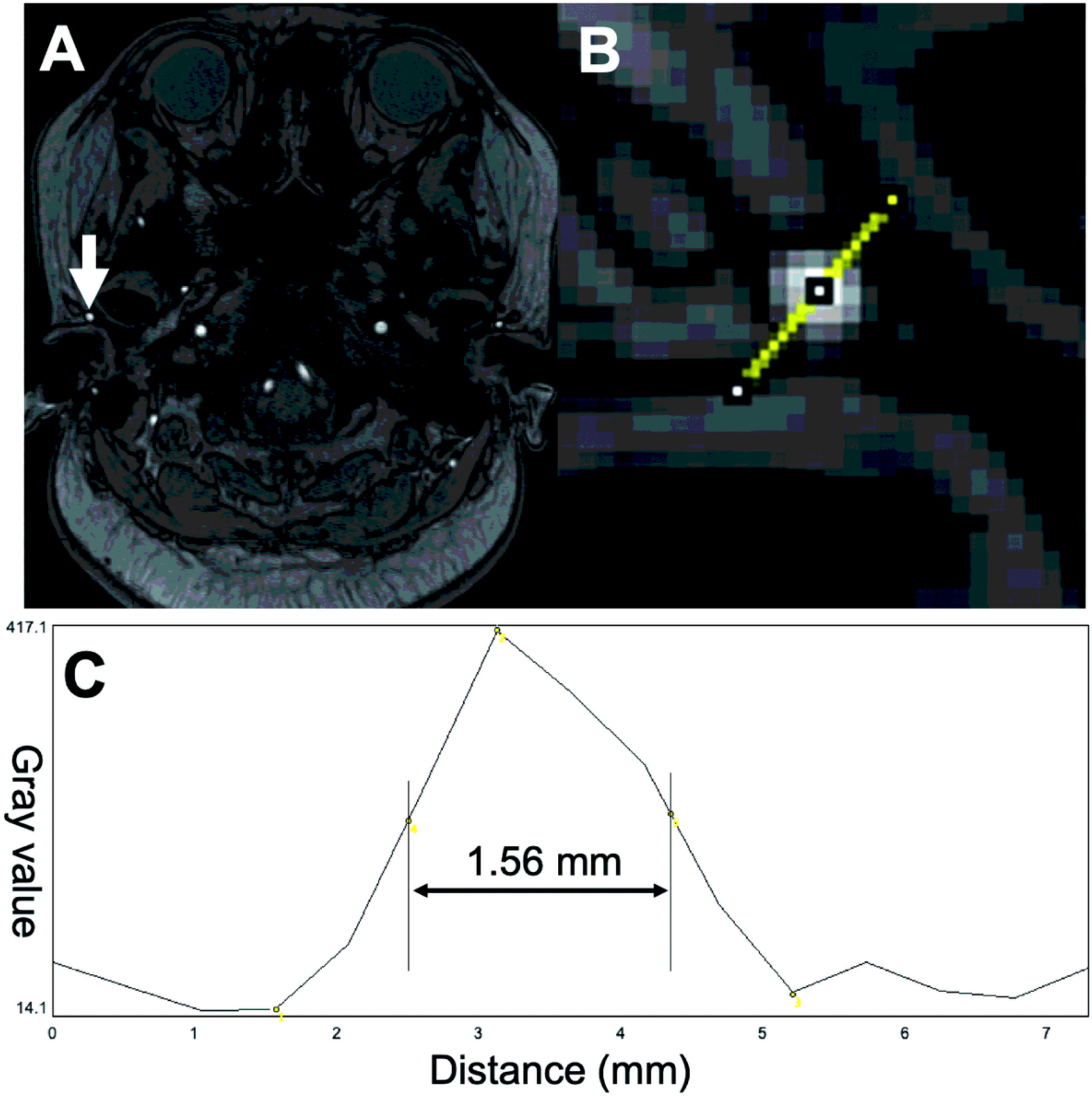

Figure 2

Measurement method of the right superficial temporal artery (STA) blood vessel diameter based on full width at half maximum (FWHM). In the axial time-of-flight magnetic resonance angiography image, (A) the right STA was identified as a cross-section (white arrow), (B) the short diameter line (yellow line) of the blood vessel cross-section was set, and (C) the signal intensity profile was obtained from image B; then, the FWHM indicated by the dimension line was determined from the intensity of half of the maximum gray-value change consisting of the center and the edge of the vessel cross-section.

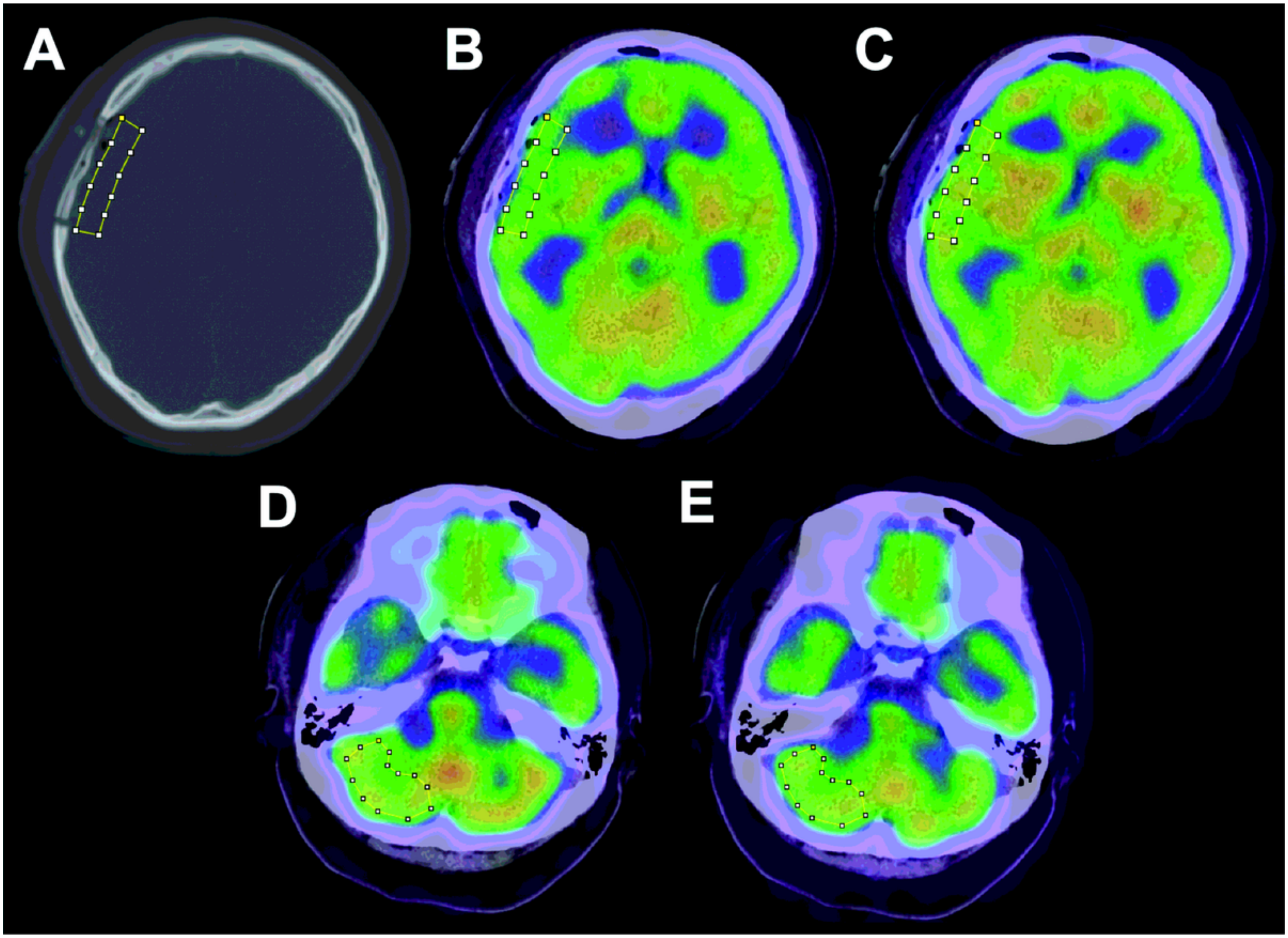

Figure 3

(A) The surgical craniotomy range was clearly identified using single-photon emission computerized tomography/computed tomography. A region of interest (ROI) immediately below the craniotomy area measuring 1 cm thick (craniotomy ROI) was set preoperatively (B) and postoperatively (C). A cerebellar ROI was set preoperatively (D) and postoperatively (E).

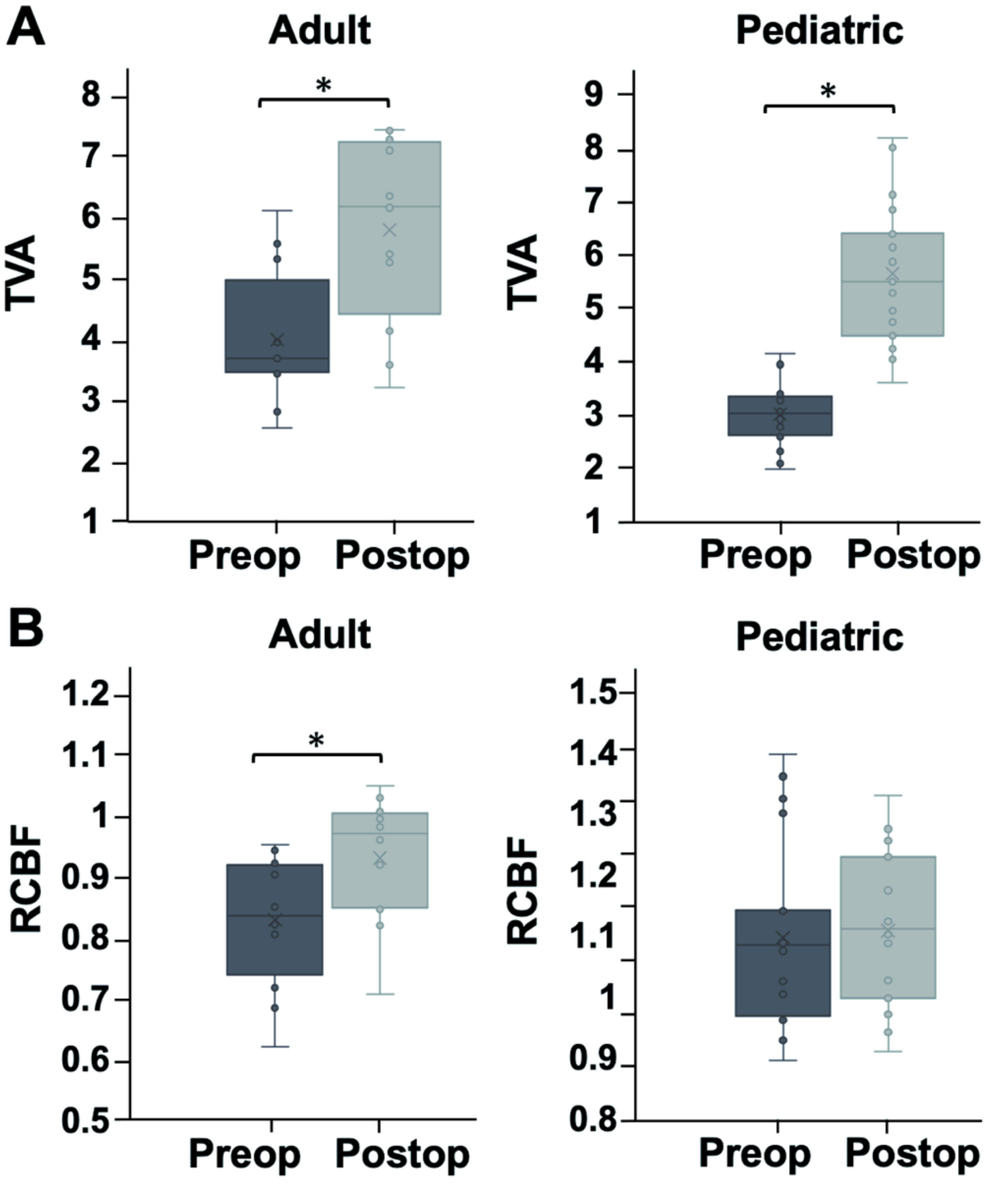

Figure 4

Box plots of preoperative and postoperative TVA (A) and RCBF (B) in adults (left) and children (right). *p < 0.05. TVA, total vessel cross-sectional area; RCBF, relative cerebral blood flow; Pre-op, preoperative; Post-op, postoperative.

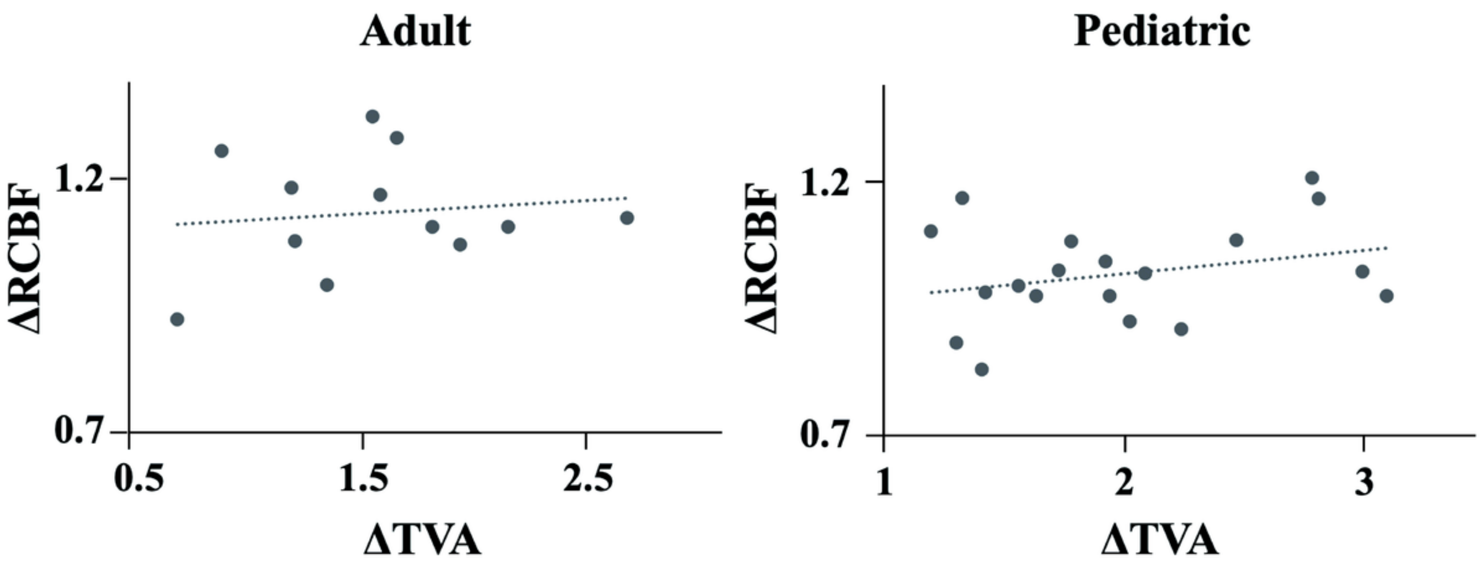

Figure 5

Scatter plot showing the corresponding ΔRCBF and ΔTVA values in adults (left) and children (right). No significant correlation was found between ΔRCBF and ΔTVA ($p > 0.05$). ΔRCBF, change in relative cerebral blood flow; ΔTVA, change in total vessel cross-sectional area.