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Original Article

Application of computed tomography perfusion before and after cerebral revascularization in 30 cases of ischemic cerebrovascular disease

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Abstract: Objective: We discussed the accuracy and reliability of computed tomography perfusion (CTP) before and after revascularization in ischemic cerebrovascular disease (ICVD). Method: Siemens Somatom Sensation 64 CT Scanner was used to collect the images of CTP before and after revascularization in 30 cases of ICVD using our method for delineating region of interest (ROI); the results were interpreted using our method of CTP parameter evaluation alongside statistical analysis of the changes before and after surgery. Results: ROI was delineated for each case, and CTP parameters were detected semi-quantitatively before and after surgery. The CTP imaging coincided with the changes of clinical symptoms before and after surgery. Conclusion: CTP evaluation of cerebral blood flow provides important indications for cerebral revascularization in ICVD. CTP has a high value for outcome evaluation after revascularization for ICVD. An accurate delineation of ROI is a guarantee of accurate CTP. The CTP parameters can be evaluated based on the relative value between the affected side and the healthy side.

Keywords: CT perfusion (CTP), ischemic cerebrovascular disease (ICVD), revascularization

Introduction

Ischemic cerebrovascular disease (ICVD) caused by severe occlusion or stenosis of the major brain-feeding arteries can be alleviated by intracranial-extracranial arterial bypass, which reduces the risk of stroke. However, the presence of anterior and posterior communicating arteries and collateral circulation makes the regional cerebral blood flow pattern highly delicate. Therefore, the degree of vascular stenosis is not directly correlated with cerebral ischemia, and it is a matter of controversy whether a too high or too low regional cerebral blood flow related to the responsible vessels needs surgical correction. Moreover, an evaluation of cerebral blood flow dynamics is necessary to determine whether regional blood flow is improved. Computed tomography perfusion (CTP) is featured by convenience and low cost when used for evaluating the dynamics of cerebral blood flow. It has found wider applications in surgical treatment of ICVD recently. However, some issues relating to the applications of CTP remain unsolved. For example, the delineation of region of interest (ROI) and the judgment criteria for positive perfusion imaging. The results of CTP may be less accurate and reliable because of these uncertainties. It is very likely that the results of CTP imaging may diverge for the same patient detected within the same period. We performed CTP on 30 ICVD cases receiving arterial bypass to evaluate the application value of CTP in surgical treatment of ICVD and to find ways to improve accuracy and reliability of CTP evaluation.

Materials and method

Equipments: Siemens Somatom Sensation 64 CT Scanner (Somaris/5 VA50B).

Table 1. General information of 30 ICVD cases

Case No.	Age (year)	Gender	Diagnosis	Clinical manifestations
1	14	Male	Moyamoya disease	Decrease in muscle strength of the limbs on one side
2	59	Male	Occlusion of internal carotid artery	Decrease in muscle strength of the limbs on one side combined with dysphasia
3	43	Male	Moyamoya disease	Decrease in muscle strength of the limbs on one side
4	37	Female	Moyamoya disease	Hemorrhagic type
5	48	Male	Moyamoya disease	Hemorrhagic type
6	29	Male	Moyamoya disease	Hemianesthesia
7	46	Male	Occlusion of internal carotid artery	Decrease in muscle strength of the limbs on one side
8	60	Male	Occlusion of middle cerebral artery	Decrease in muscle strength of the limbs on one side
9	32	Female	Moyamoya disease	Decrease in muscle strength of the limbs on one side
10	29	Female	Moyamoya disease	Hemorrhagic type
11	47	Male	Occlusion of internal carotid artery	Hemianesthesia
12	50	Male	Severe stenosis of middle cerebral artery	Decrease in muscle strength of the limbs on one side combined with dysphasia
13	39	Male	Occlusion of internal carotid artery	Hemianesthesia
14	41	Female	Occlusion of middle cerebral artery	Decrease in muscle strength of the limbs on one side
15	44	Male	Moyamoya disease	Decrease in muscle strength of the limbs on one side
16	58	Male	Occlusion of internal carotid artery	Decrease in muscle strength of the limbs on one side combined with dysphasia
17	35	Female	Occlusion of internal carotid artery	Decrease in muscle strength of the limbs on one side
18	32	Male	Severe stenosis of middle cerebral artery	Decrease in muscle strength of the limbs on one side
19	25	Female	Occlusion of internal carotid artery	Decrease in muscle strength of the limbs on one side
20	52	Male	Occlusion of middle cerebral artery	Decrease in muscle strength of the limbs on one side
21	46	Female	Moyamoya disease	Hemorrhagic type
22	39	Female	Occlusion of middle cerebral artery	Decrease in muscle strength of the limbs on one side
23	54	Male	Occlusion of internal carotid artery	Decrease in muscle strength of the limbs on one side
24	39	Female	Moyamoya disease	Decrease in muscle strength of the limbs on one side
25	42	Male	Occlusion of middle cerebral artery	Decrease in muscle strength of the limbs on one side combined with dysphasia
26	50	Female	Occlusion of internal carotid artery	Hemianesthesia
27	30	Male	Moyamoya disease	Hemorrhagic type
28	23	Male	Moyamoya disease	Hemianesthesia
29	16	Male	Moyamoya disease	Hemianesthesia
30	50	Male	Occlusion of internal carotid artery	Decrease in muscle strength of the limbs on one side combined with dysphasia

Contrast medium: Iohexol.

Subjects: Thirty cases were included; 13 cases had bilateral moyamoya disease, and 17 cases had other forms of ICVD, which were occlusion or stenosis of intracranial-extracranial blood vessels that supplied the brain. All cases were scored preoperatively using National Institutes of Health Stroke Scale (NIHSS) [1]. There were 8 cases scoring 3, 9 cases scoring 2, 4 cases scoring 1 and 9 cases scoring 0, with total scores of 46; in evaluation at 3 months after surgery using NIHSS, there were 1 case scoring 3, 7 cases scoring 2, 8 cases scoring 1, and 14 cases scoring 0, with total scores of 25; at 6 months after surgery, there were 0 case scoring 3, 4 cases scoring 2 and 19 cases scoring 0, with total scores of 15.

Surgical method

All 30 cases received revascularization procedures, which were superficial temporal artery-middle cerebral artery bypass (STA-MCA bypass) combined with encephalo-duro-myo-synangiosis (EDMS).

Timing of CTP: Within 1 week before surgery, and from the second day to half a year after surgery.

CTP procedures

Plain CT scan of the brain was performed to select the slice of interest for CTP: conventional sequential scanning mode, 120 kV, 260 mAs, slice thickness 5 mm, no interval. CTP: intravenous injection of iohexol was delivered to the elbow (300 mg I/ml, 40 ml) at the rate of 5 ml/s. During injection, in-layer dynamic scan was performed in the basal ganglion for 40 s at the rate of 0.15 s/r. Scan parameters: tube voltage 80 kV, tube current 160 mAs. The probe width was 24 mm, and 4-slice dynamic images with slice thickness of 9.6 mm were acquired.

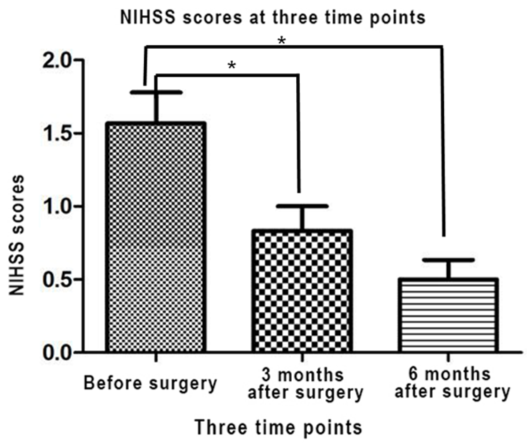


Figure 1. NIHSS scores at three time points in 30 ICVD cases.

The 200 reconstructed dynamic images were uploaded to the workstation and post processed with Perfusion CT software. The contours of the skull and the influence of blood vessels and cerebrospinal fluid were removed from the dynamic images. A circular ROI was delineated in superior sagittal sinus. All ROIs of the images were analyzed, and the CTP parameters were obtained, including cerebral blood flow (CBF) images, cerebral blood volume (CBV) images, and time-to-peak (TTP) images. All these images were colored and used for qualitative analysis after enhancing the contrast. CBF, CBV and TTP of the affected side and the healthy side were measured symmetrically on the images taking the midline as the mirror surface.

Selection of ROI for CTP

Conventional ROIs: For basal ganglia, conventional ROIs were situated in the terminal branches of the anterior cerebral arteries, terminal branches of the middle cerebral arteries and terminal branches of the posterior cerebral arteries, one in each region, respectively. For terminal branches of the anterior cerebral arteries, bilateral frontal lobes were selected; for terminal branches of the middle cerebral arteries, bilateral basal ganglia regions and bilateral temporal lobes were selected; for terminal branches of the posterior cerebral arteries, bilateral occipital lobes were selected. The above ROIs showed left-to-right symmetry with size no less than 1 cm and no bigger than the regions supplied by the detected vessels.

Special ROIs: For patients with focal neurological signs, the corresponding ROIs in the brain were selected; for patients with cerebral infarction caused by the responsible vessels, one ROI was selected at the center and the margin of the infarct area (within 5 mm), respectively, with left-to-right symmetry and size no less than 0.5 cm.

Evaluation of CTP data

The affected and the healthy sides were determined first. For non-moyamoya disease patients, the affected sides were the sides with stenosis or occlusion of the major brain-feeding arteries, and the contralateral sides were the healthy sides. For moyamoya disease patients, the affected sides were located based on the clinical symptoms and the existing infarct loci on CT/MRI.

The low perfusion regions were located by CBF, CBV and TTP.

The ratios of the above parameters of the affected side to the healthy side were calculated. That is, relative CBF (rCBF), relative CBV (rCBV) and relative TTP (rTTP) were measured before and after surgery. If several ROIs were present in the regions supplied by the responsible vessels but only one had low perfusion, then only this ROI was compared before and after surgery.

The ratios of the parameters before and after surgery were subjected to statistical analysis so as to observe the treatment effect.

For each parameter, the absolute value was taken as reference, All evaluations were done independently by two experienced associate chief physicians in Department of Radiology and one experienced chief physician in Department of Neurological surgery.

Statistical analysis

Statistical analyses were performed using Stata 7 software. The parameters before and after surgery were compared by paired-samples t-test in two groups, and whthin three groups we use the analysis of variance (ANOVA).

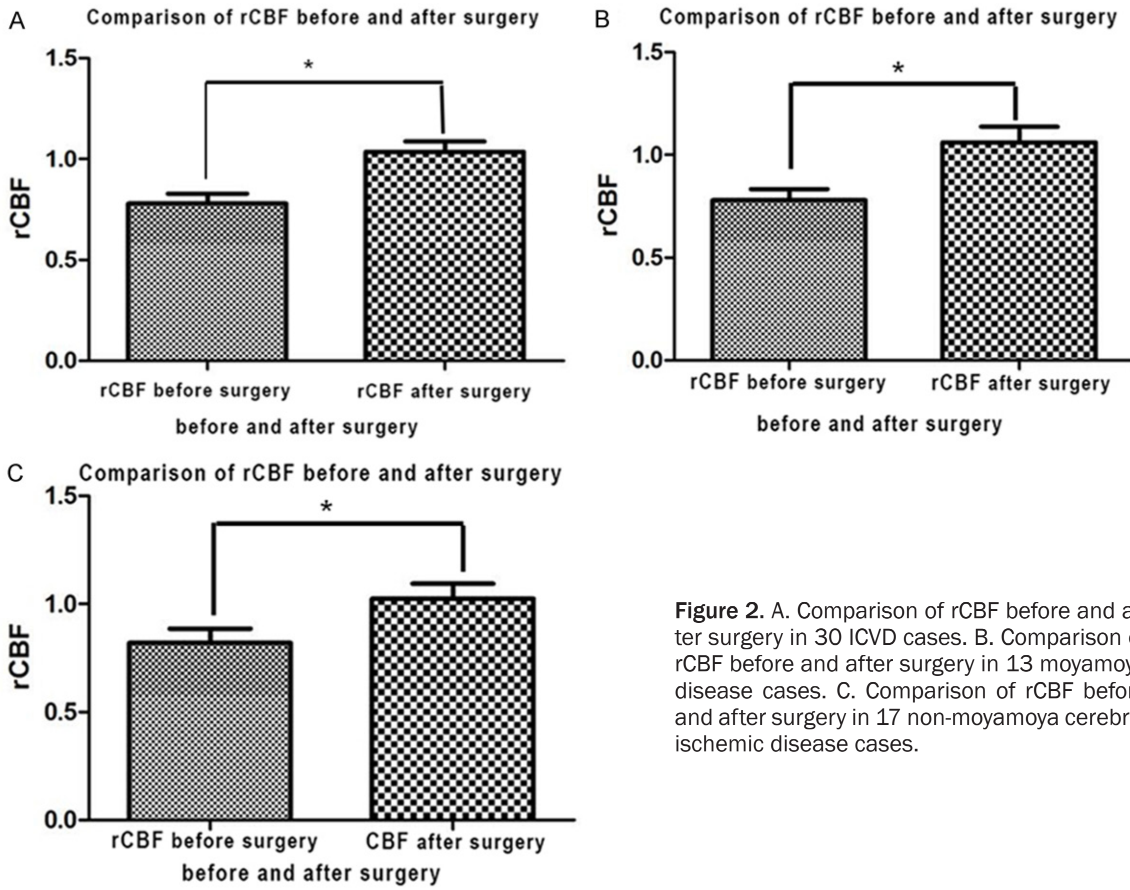


Figure 2. A. Comparison of rCBF before and after surgery in 30 ICVD cases. B. Comparison of rCBF before and after surgery in 13 moyamoya disease cases. C. Comparison of rCBF before and after surgery in 17 non-moyamoya cerebral ischemic disease cases.

Results

General information

Of the 30 included cases, 20 were males and 10 were females, aged 14-60 years (average, 40.167±2.12 years). Thirteen cases had bilateral moyamoya disease; among them, 10 cases had occlusion of internal carotid artery, 5 had stenosis of middle cerebral artery, and 2 had severe stenosis of middle cerebral artery. The general information of the cases is shown in **Table 1**. The total scores were 46 in preoperative NIHSS evaluation, 25 at 3 months after surgery, and 15 at 6 months after surgery; there were statistically significant differences in NIHSS scores before surgery and at 3 months and 6 months after surgery ($P<0.05$); However, no significant differences were observed at 3 months and 6 months after surgery ($P>0.05$) (see **Figure 1**).

The surgery was successfully performed in all cases. Computed tomography angiography (CTA) or digital subtraction angiography (DSA) was performed, confirming that the anastomotic sites were normal. The cases were followed up for 3-26 months (average, 11.73 months) and found to achieve remission. Reexamination with CTP was performed 1 week to 6 months after surgery, and the data of rCBF, rCBV and rTTP were compared before and after surgery. It was found that both rCBF and rCBV increased significantly after surgery ($P<0.05$) (**Figures 2A**, **3A**), while rTTP decreased after surgery ($P>0.05$) (**Figure 4A**). A comparison was made separately for patients with moyamoya disease and those with non-moyamoya cerebral ischemic disease. For the former, rCBF and rCBV increased significantly after surgery ($P<0.05$) (**Figures 2B**, **3B**), whereas rTTP decreased ($P<0.05$) (**Figure 4B**). For the latter, rCBF showed a considerable increase after surgery ($P<0.05$) (**Figure 2C**), and there were no obvious changes of rCBV and rTTP ($P>0.05$) (**Figures 3C**, **4C**).

Case 1: A male patient aged 58 years. He was hospitalized for numbness of the right limbs

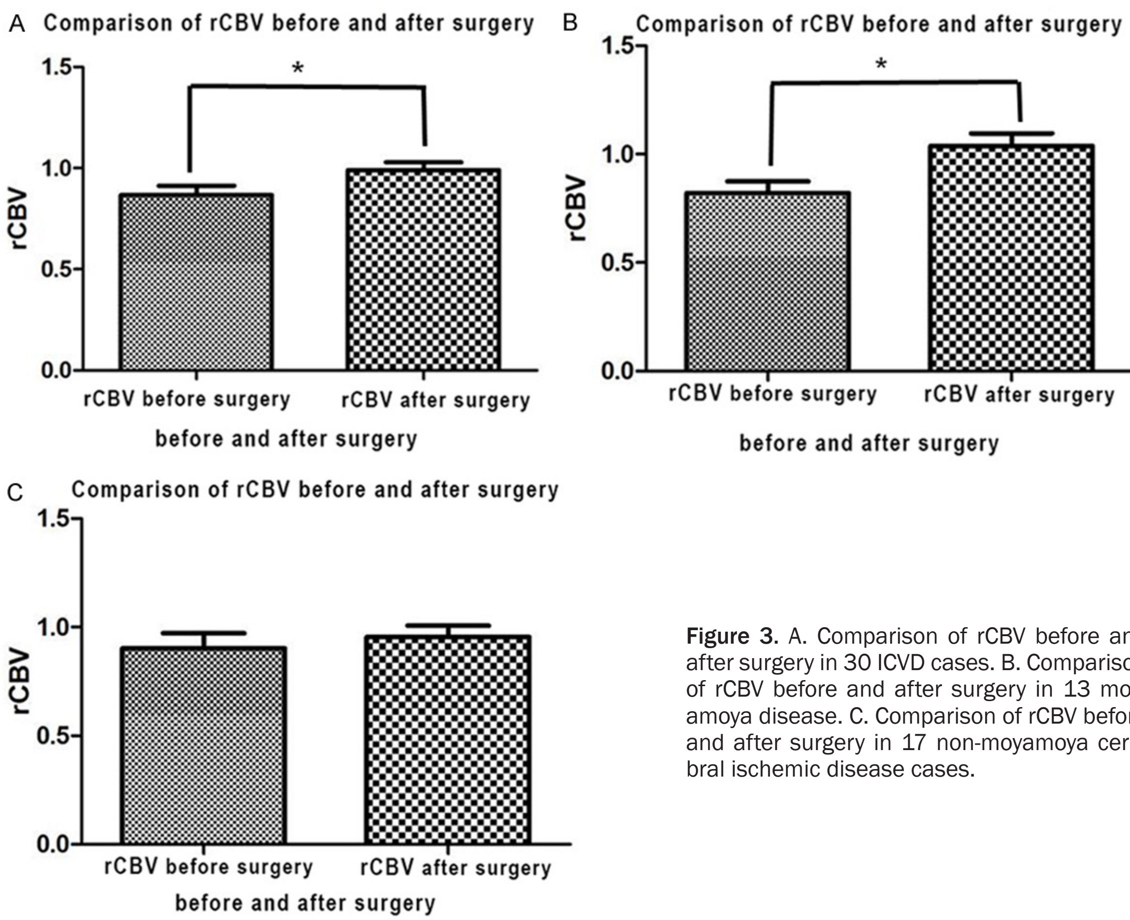


Figure 3. A. Comparison of rCBV before and after surgery in 30 ICVD cases. B. Comparison of rCBV before and after surgery in 13 moyamoya disease. C. Comparison of rCBV before and after surgery in 17 non-moyamoya cerebral ischemic disease cases.

combined with bradyglossia for 2 months and had NIHSS scores of 1. Preoperative MIR revealed lacunar infarction in the left basal ganglia; DSA showed occlusion of the start of left internal carotid artery, and CTP showed decrease in left hemisphere perfusion (**Figure 5**). After STA-MCA bypass + EDMS, this patient achieved remission and had HIHSS scores of 0 at 20 days after surgery. CTP reexamination found an improvement of left hemisphere perfusion (**Figures 6**, **7**).

Discussion

ICVD has a high incidence in Asian countries, especially in China, Japan and Korea. Japan ranks the first in terms of incidence of ICVD, which is still rising in recent years [1, 2]. ICVD is known to have high incidence, high morbidity and high recurrence, and low perfusion caused by stenosis of internal carotid artery and intracranial vessels is considered as the main cause. Since cerebral perfusion directly influences the progression and prognosis of ICVD, it is necessary to detect the dynamics of cerebral blood flow for patients with cerebral artery stenosis so as to decide on the individualized therapy. Because of Willis circle at the base of the brain and the intracranial and extracranial collateral circulation, the cerebral blood flow pattern is highly complex. This makes the preoperative estimation of cerebral perfusion a prerequisite before revascularization. Moreover, for patients that have received cerebral revascularization, the detection of cerebral blood flow dynamics enables an objective and quantitative understanding of lesions after treatment and hence the outcome evaluation of the treatment.

Many techniques are now in use to detect the dynamics of cerebral blood flow pattern, including MR perfusion imaging, positron emission tomography (PET), single photon emission computed tomography (SPECT), Xe-CT and CTP imaging. Each technique has different advan-

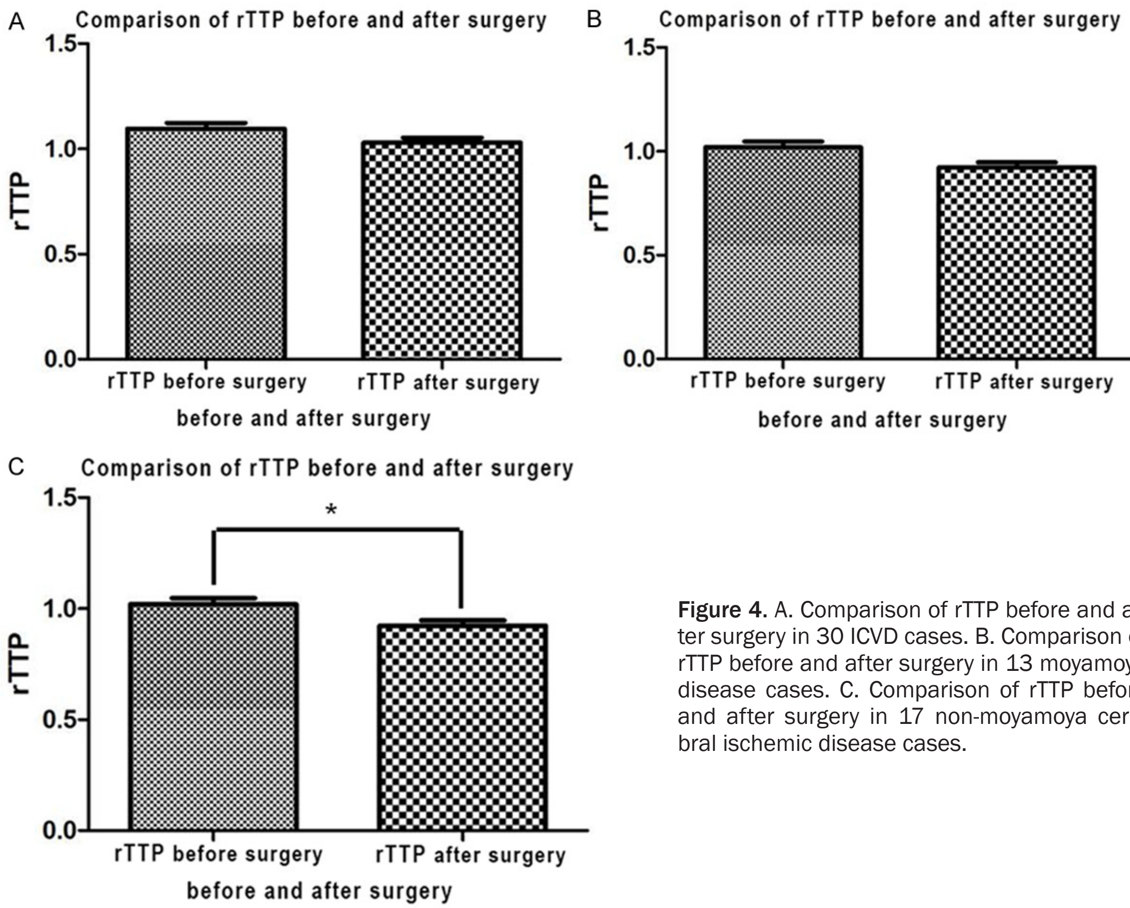


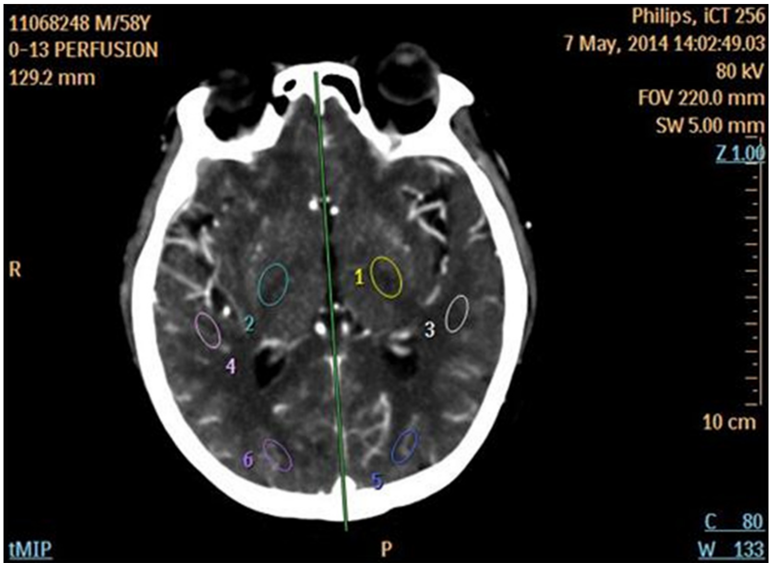
Figure 4. A. Comparison of rTTP before and after surgery in 30 ICVD cases. B. Comparison of rTTP before and after surgery in 13 moyamoya disease cases. C. Comparison of rTTP before and after surgery in 17 non-moyamoya cerebral ischemic disease cases.

tages and defects. The concentration of contrast medium administered by intravenous injection in MR perfusion imaging is not directly proportional to MR signal intensity, which affects the accuracy of MR perfusion imaging. PET is not a conventional imaging technique due to its high cost. SPECT has low spatial resolution and long operating time. Xe-CT is easily affected by patients' respiration and requires complicated procedures [3]. In contrast, CTP imaging is easy and convenient and provides semi-quantitative evaluation. Drewer-Gutland F et al. [4] found that the evaluation criteria for treatment of ICVD should not be mechanical recanalization of the occluded blood vessels, but perfusion. Thus, the application of CTP for evaluation of stroke patients before and after treatment attracts growing attention from radiologists and physicians.

However, CTP requires large radiation dose, and the delineation of ROI varies from one operator to another. CTP results may differ greatly for the same patient [5] with poor reproducibility of measurements. When different measurement methods are used, there is usually a lack of comparability between the researches [1]. In this study, we evaluated the application value of CTP imaging in revascularization for ICVD and explored ways to improve its reliability.

The results are presented as follows according to our analysis.

Most patients had lower CBF and CBV and prolonged TTP in the affected side as compared with the healthy side. This coincided with the clinical manifestations and the results of MR and DSA. Low perfusion was also the indication for cerebral revascularization. KlotzE [6] believed that rCBF was significantly different for areas of reversible and irreversible ischemia, with rCBF = 0.2 considered the threshold for reversible ischemia. According to preoperative data of this study, rCBF was all larger than or equal to 0.20, indicating reversible ischemia. An obvious decline of total NIHSS scores after



Roi Statistics for Slice 13

ROI#	CBV	CBF	MTT	TTP
1	1.73	45.19	2.30	14.73
2	0.82	106.08	0.46	13.67
3	4.43	38.72	6.86	16.90
4	1.22	120.74	0.60	13.79
5	2.65	75.34	2.11	14.94
6	2.42	83.14	1.74	14.66

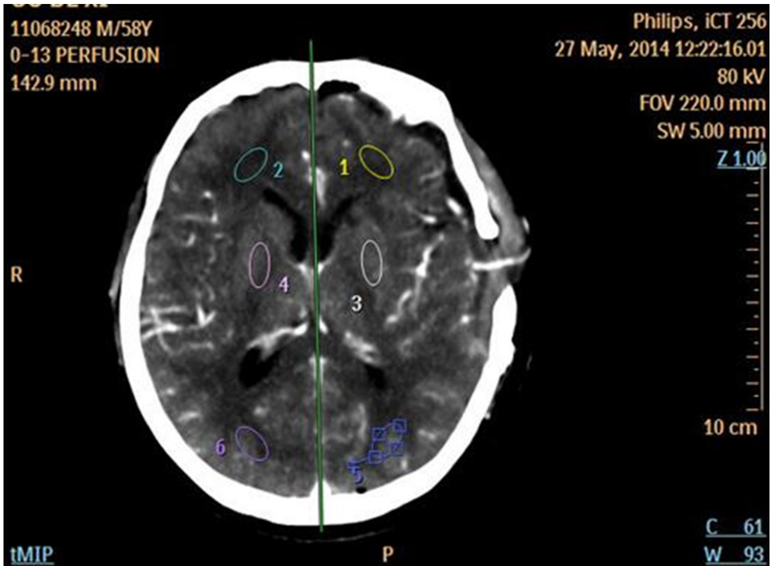
Figure 5. Preoperative CTP revealed a decrease in CBF in left basal ganglia, left temporal lobe and left occipital lobe, with an increase in CBV and prolonging of TTP.

surgery also confirmed the preoperative judgment.

Among the included cases, NIHSS scores at 3 months after surgery were greatly improved (**Figure 1**) as compared with that before surgery. The reason may be that the formation of blood vessel network takes 3-4 months after revascularization for ICVD patients; revascularization does not provide immediate benefits for ICVD patients [7]. Dong Wei Dai et al. [3] found that the frequency of transient ischemic attack at 15-20 days after revascularization decreased considerably in moyamoya disease patients. We found that NIHSS scores at 3 months after surgery decreased markedly, and a further decrease was noted at 6 months, though without significant difference compared with the scores at 3 months. This seemed to suggest that the patients achieved the best recovery 3 months after revascularization.

Both rCBF and rCBV increased significantly after revascularization, which indicated rapid recovery of regional cerebral blood flow. However, rTTP was prolonged after surgery, which was probably due to the inherent features of ICVD itself and the time of reexamination. We found that rCBV was considerably higher in moyamoya disease patients as compared with non-moyamoya ischemic disease patients. For moyamoya disease patients, ischemia was more severe and required longer time to recover with greater deterioration of brain blood flow regulation [3]. These patients had lower rCBV before surgery, and therefore the improvement was more visible after revascularization. For non-moyamoya ischemic disease patients, less change of rCBV after surgery may be due to insignificant preoperative decrease of rCBV. If there is no extensive cerebral infarction in patients with simple proximal arterial occlusion, the regulation of regional cerebral blood flow may not be severe affected. The decrease in CBF can be corrected by dilation of arterioles, and CBF is maintained constant. An obvious shortening of rTTP in moyamoya disease patients in this study can be attributed to better recovery of cerebral blood flow at 3-6 months after revascularization. However, the reexamination was earlier in non-moyamoya ischemic disease patients when more time was needed for forming new blood circulation. This is especially true with STA-MCA bypass. During this period, only part of the damaged vascular bed in previously low perfusion area or infarct area was restored; the increased blood flow entered the above areas largely by collateral circulation. This was a major reason for less significant change of rTTP at early stage after surgery. The above changes of CTP parameters indicated an improvement of regional cerebral perfusion through the bypass, which agreed with the postoperative decline of total NIHSS scores.

Thus, CTP imaging can provide accurate evaluation of surgical indications and treatment outcome for ICVD patients receiving revascularization.



Roi Statistics for Slice 13

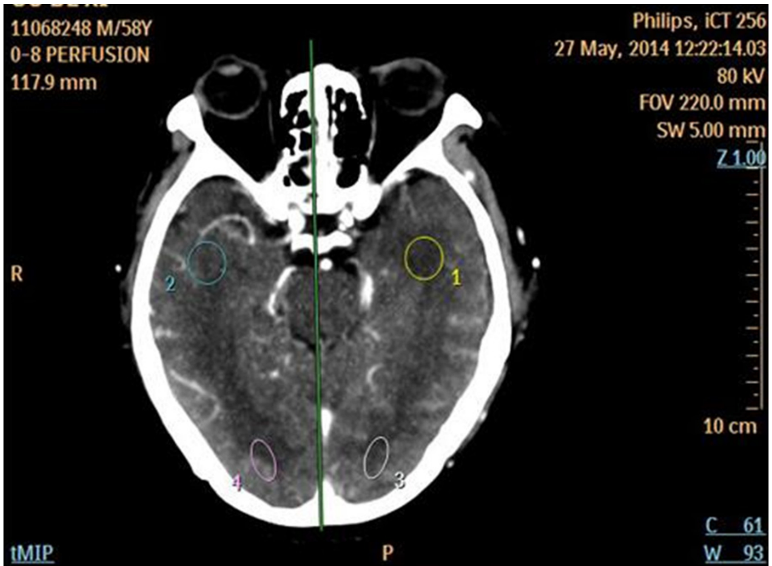
ROI#	CBV	CBF	MTT	TTP
1	1.84	16.52	6.68	21.49
2	3.03	33.90	5.36	19.09
3	7.64	67.17	6.82	19.80
4	3.16	37.25	5.09	18.91
5	5.10	43.12	7.09	20.80
6	3.55	43.13	4.93	18.83

Figure 6. CTP at 20 days after surgery revealed an increase in CBF in left basal ganglia and left occipital lobe, but basically similar CBV and TTP as compared with that before surgery.

CTP is an integration of qualitative and semi-quantitative method. It allows a rough estimation of the ischemic area on the color perfusion maps based on the difference of color as compared with normal brain tissues; for semi-quantitative judgment, the ratios of CBF, CBV and TTP between the affected side and the healthy side are calculated so as to observe any perfusion abnormalities. The quantification based on ratios of the perfusion parameters between the two sides is now widely used [8, 9]. To do the comparisons, we first determined the affected side, which was the site of artery stenosis or occlusion, and the healthy side, which was the contralateral side. For moyamoya disease patients, the affected side was determined based on clinical manifestations and the existing infarct loci on CT/MRI. The low perfusion areas were qualitatively determined by CBF, CBV and TTP maps. Then the ratios between the affected side and the healthy side were calculated, namely, rCBF, rCBV and rTTP, and compared before and after surgery. If several ROIs were present in the regions supplied by the responsible vessels but only one had low perfusion, then only this ROI was compared before and after surgery. As shown by statistical analysis, revascularization was effective for ICVD; Considering the clinical data of the patients, the proposed method for evaluating CTP data was reasonable.

There have been no established quantitative indicators for evaluation of CTP parameters for a single ICVD patient. Some literature defines abnormal CTP parameters as exceeding 95% confidence interval for the corresponding parameters in normal population. But we regard this criterion as lacking operability and prefer a combination of qualitative and semi-quantitative method. That is, the low perfusion area can be qualitatively determined based on CBF, CBV and TTP maps, which is followed by the calculation of rCBF, rCBV and rTTP. The abnormality is defined as decrease (shortening) or increase (prolonging) by 5%.

CTP may be less accurate and lack reproducibility, which is probably due to the selection of ROI. We have no uniform standard for delineating ROI so far. To ensure the optimal reliability, we adopted the following method: Location: a. Keep away from great vessels, skull, ventricular system and cisterns and maintain a safe distance from the surrounding tissues, so as to reduce the partial volume effect; b. For patients with focal neurological signs, besides conventional ROIs in frontal, temporal and occipital lobes and basal ganglia, the ROIs corresponding to these signs should be also delineated. This is crucial for evaluating regional cerebral perfusion; c. Besides the regions supplied by the responsible vessels, ROIs should be also selected at the center and in the periphery of the infarct area for patients with cerebral infarction. Thus, the center of the infarct area and the ischemic penumbra can be better differentiated before surgery, and the changes of CTP parameters be evaluated after surgery; d. ROI



Roi Statistics for Slice 8

ROI#	CBV	CBF	MTT	TTP
1	3.35	33.69	5.97	19.53
2	6.35	63.08	6.04	18.16
3	4.99	57.58	5.20	18.03
4	4.08	36.37	6.73	19.70

Figure 7. CTP at 20 days after surgery revealed an increase in CBF in left temporal lobe and left occipital lobe, a decrease in CBV in left temporal lobe, but basically similar CBV and TTP in the occipital lobe as compared with that before surgery.

may be situated in watershed region. For patients with less significant decrease of perfusion on the affected side, the center of the region supplied by the responsible vessels may suffer from less severe ischemia. However, the periphery of this region adjacent to another blood vessel concentration region may be affected. That is why CTP parameters should be detected in the watershed region.

Size: ROI should be of an appropriate size. A smaller ROI (average 0.35 cm^2) may be affected by mild head movement and result in variations of the measurement. A larger ROI can be affected by partial volume effect, also leading to deviations of measurement of cerebral blood flow [10]. Miles [11] suggested that ROI should cover no less than 50 pixels to reduce quantum noise and partial volume effect. Nabavi et al. [12] made the following assumptions when studying the influence of size and number of ROIs on stability of dynamic CTP imaging: A stable measuring method should yield the same blood flow values for a given tissue regardless of the size and number of ROI. The equation for calculating the size of ROI in dynamic CTP imaging was proposed: ROI (cm^2) = ($N_{pixels} \times 0.29^2$)/100. The relative size of ROI (%) was calculated by dividing the size of ROI of the target area by the size of ROI of the entire brain tissue, i.e., rROI = [$ROI_{target\ area}/ROI_{brain\ tissue}$] × %. Thus, we delineated conventional ROI in the responsible vessels with a size no less than 1 cm, which was no larger than the region supplied by the responsible vessels. Since cerebral infarction varies in size, the ROIs delineated at its center and in the periphery are no less than 0.5 cm.

Shape: We believe that the shape of ROIs will not affect CTP parameters as long as ROIs have reasonable position and size.

ROIs should be selected at the same regions before and after surgery and with the same size.

It is confirmed by the experiment that the proposed method for ROI delineation improves the accuracy and reproducibility of CTP.

The present study has several limitations. First, the sample size was small, and the randomized controlled design was not adopted. We did not carry out a comparison between CTP and other imaging technique for outcome evaluation after revascularization. Therefore, the present study is more of a presentation and analysis of clinical cases. Second, the patients were evaluated by NIHSS at only three time points instead of continuous scoring to cover the whole period of post-operative recovery. CTP reexamination spanned over a period as long as 1 week to 6 months. The results indicated that the treatment effect was better in patients with moyamoya disease than in those with non-moyamoya ischemic disease. But considering the difference in sample size for these two types of patients and different time of CTP reexamination, this conclusion remains to be further consolidated. Finally, although the calculation of ratios of parameters between the affected side and the healthy side can reduce the errors arising from the calculation of absolute values, there was the possibility that the bilateral perfusion decreased simultaneously before surgery or increased simultaneously after surgery. This also caused errors.

To conclude, CTP imaging provides accurate evaluation of surgical indications and treatment outcome for ICVD patients receiving STA-MCA bypass. Accurate calculation of ratios of CTP parameters between the affected side and the healthy side and delineation of ROI are important for reliable CTP imaging.

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Disclosure of conflict of interest

None.

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