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DSA-Based Quantitative Assessment of Cerebral Hypoperfusion in Patients with Asymmetric Carotid Stenosis

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Abstract: Digital subtraction angiography (DSA) is often used to evaluate the morphological and pathological changes of cerebral arteries in clinical practice. This study aims to explore the possibility of assessing cerebral hypoperfusion with DSA in patients with carotid stenosis. Thirty patients with a mild to severe stenosis on one side, and a mild stenosis on the other side of the carotid artery were recruited. Frontal, parietal, temporal and occipital lobes were chosen as regions of interest for measuring the quantitative perfusion parameters from their time-density curves (TDCs) of DSA images. The perfusion parameters were compared between the two hemispheres by using paired t-test. In addition, the bilateral asymmetry of these parameters was calculated and its correlation with the bilateral asymmetry in stenosis was analyzed. The parameters included mean transit time (MTT), time of contrast uptake (TU), time taken to the half peak value (1/2TMAX), area under the curve (AUC) were significantly prolonged at the severe stenosis side than those at the mild stenosis side in frontal lobe (P=0.013; P=0.041; P=0.009; P=0.027) and parietal lobe (P=0.008; P=0.041; P=0.002; P=0.012). The asymmetric ratios of MTT and AUC showed statistically significant correlations with stenosis asymmetry in all four lobes. MTT, TU, 1/2TMAX and AUC could reflect the bilateral asymmetry of the cerebral perfusion. These DSA parameters, therefore, may be used for the evaluation of cerebral hypoperfusion caused by carotid stenosis.

Keywords: Cerebral hypoperfusion, carotid stenosis, quantitative functional assessment, DSA.

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1 Introduction

Atherosclerotic stenosis in carotid artery is a major etiology of ischemic stroke [Zaidat, Alexander, Suarez et al. (2004); Taussky, Sangala, Meyer et al. (2011)]. Carotid stenosis can lead to cerebral hypoperfusion, which often cause watershed cerebral infarction. However, the current measurement of carotid stenosis alone cannot adequately reflect the cerebral perfusion [Blaser, Hofmann, Buerger et al. (2002); Jongen, Hendrikse, Moll et al. (2010)]. Identifying cerebral hypoperfusion, therefore, is of vital importance for stroke prevention. Although noninvasive perfusion imaging provides objective data with prognostic value [Turk, Grayev, Rowley et al. (2007); Grand, Tahon, Attye et al. (2013); Axel, Dean, Moss et al. (1984); Summers and Malloy (2011); Miles (2003)], digital subtraction angiography (DSA) is the "gold standard" for in the evaluation of vascular anatomy. Previous studies indicate that time-density curve (TDC) calculated from DSA parametric imaging could represent the dynamic density changes of contrast passing a region of interest (ROI) [Hunter, Hunter and Brown (1985); Bürsch (1983)]. The quantitative parameters extracted from TDC can be used to assess the perfusion status. This method has been developed to color-coded DSA technology recently and it is widely used to analyze perfusion changes in intracranial vascular disease (such as carotid stenosis, carotid cavernous fistula, and moyamoya disease) [Strother, Bender, Deuerling-Zheng et al. (2010); Hung, Liang, Lin et al. (2014); Gölitz, Struffert, Lücking et al. (2013)], arterial stenosis of lower extremity [Hinrichs, Murray, Akin et al. (2017); Jens, Marquering, Koelemay et al. (2015)] and peritherapeutic assessment during cerebrovascular interventional surgery [Levitt, Morton, Haynor et al. (2014); Sato, Shimizu, Inoue et al. (2014)]. Nevertheless, the ROI placements in cases of various vascular disorders mainly focused on main feeding arteries, veins or venous sinuses in previous researches. Certain quantitative parameters extracted from TDC, such as cerebral circulation time (CCT) was verified to reflect hemodynamic changes within the ROIs and had good correlations with CT/MR perfusion parameters [Lin, Hung, Chang et al. (2016); Lin, Hsu, Lin et al. (2016)]. However, the perfusion evaluation in different brain lobes has not been demonstrated on the basis of DSA parametric imaging. The main objective of this study is to investigate the feasibility of using DSA to quantify cerebral perfusion in patients with carotid stenosis. We retrospectively collected 30 patients with asymmetric carotid stenosis and divided them into 3 groups according to their stenosis asymmetry. Eleven quantitative parameters were extracted from the TDCs within ROIs of frontal, parietal, temporal and occipital lobes. The differences of these parameters between two sides of the different lobes within each group were compared and the correlations between the stenosis asymmetry and the asymmetry ratios of these parameters were investigated.

2 Method

2.1 Patients and DSA

The institutional review board of Southeast University approved this retrospective study. The inclusion criterion for this study was having different degrees of stenosis on bilateral internal carotid artery (ICA). After we excluded patients with a pathological condition, beyond the carotid stenosis, that could affect brain perfusion, such as a previous stroke,

AVM or fistula, 30 patients eligible for analysis were retrospectively recruited for the current study. DSA acquisition with a standard, clinically routine protocol was performed using a biplane angiography suite (AXIOM-Artis; Siemens, Erlangen, Germany) in all cases. An 8F angiocatheter was placed in the common carotid artery at the C4 vertebral body level for DSA. A bolus of 8 mL of 60% diluted contrast medium (340 mg I/mL) was injected into the patients at a rate of 5 mL/s using a power injector (LiebelFlarsheim Angiomat Illumena; Cincinnati, OH, USA). The acquisition parameters were 4 frames per second. The degree of stenosis was measured on the lateral views according to the NASCET criteria [Doyle, Stone, Carnicelli et al. (2016)], and it was graded to: mild stenosis (0-29%), moderate stenosis (30-69%), and severe stenosis (>70%). Patients were divided into 3 groups (10 subjects per group): Group 1: bilateral mild stenosis; Group 2: mild stenosis on one side and moderate stenosis on the other side; Group 3: mild stenosis on one side and severe stenosis on the other side. Therefore, the stenosis asymmetry between two sides increased from Group 1 to 3. The H.side represented the side with higher stenotic degree compared to the other side, which was denoted by L.side.

2.2 Image processing

DSA image sequence of the lateral view was extracted and analyzed using MATLAB software (MathWork Inc., Version R2015a). The DSA image size was 512 by 512 pixels and the grayscale value ranged from 0 to 255. Four frames at different time instant are shown in Fig. 1. The regions of interest (ROIs) at the four brain regions, including the frontal lobe, parietal lobe, temporal lobe, and occipital lobe on the image at the end of the arterial phase, respectively. Three ROIs were selected in each lobe as shown in Fig. 2. The ROI placement was standardized to avoid the large blood vessel and inhomogeneous areas. The location and size (5 by 5 pixels) of each ROI were also required to be consistent across the whole DSA image sequence. Two neuroradiologists with 3 years and 5 years of experience, respectively in diagnostic and interventional neuroangiography performed the ROI placements independently.

For each image in the entire DSA dynamic sequence, the average pixel value within ROIs of each lobe was calculated and used to generate the time-density curve (TDC) for each brain region. Then the value of each point on the TDC curve was subtracted by 255. After that, we used the third-order Hermite polynomial interpolation to smooth the time-density curve to obtain the final TDC (Fig. 2).

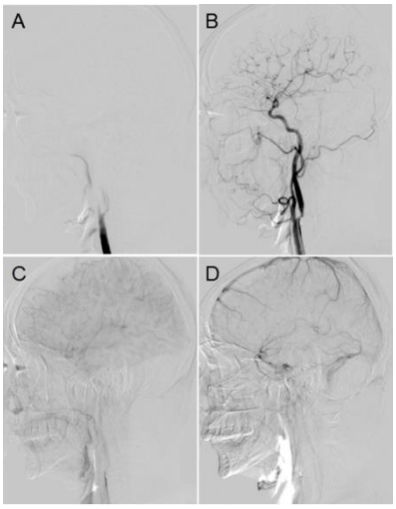

Figure 1: Four frames at different time instant. (A) The start time of contrast appearance. (B) Arterial phase. (C) Venous phase. (D) Venous sinus phase

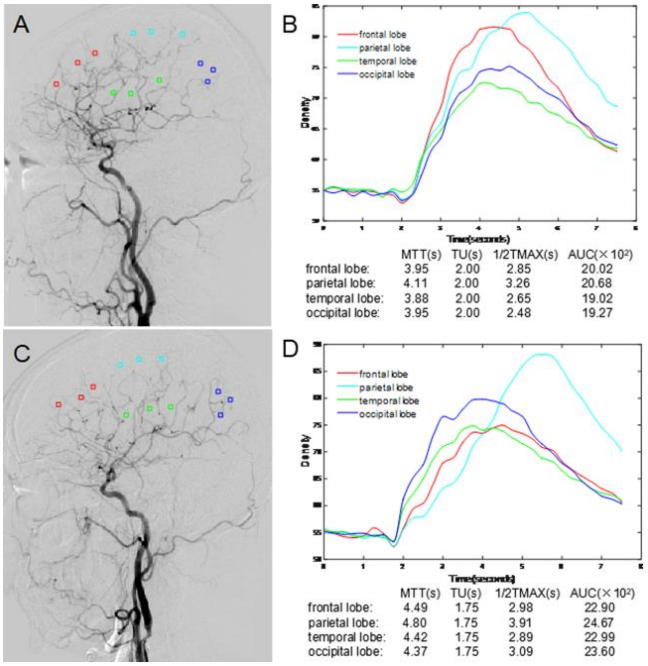

Figure 2: The ROIs selections and and the perfusion parameters values of a patient calculated from TDCs. (A) ROIs placements of the mild stenosis and (B) the corresponding TDCs and the values of MTT, TU, 1/2TMAX, AUC. (C) ROIs placements of the severe stenosis side and (D) the corresponding TDCs and the values of MTT, TU, 1/2TMAX, AUC. Red: frontal lobe. Cyan: parietal lobe. Green: temporal lobe. Blue: occipital lobe

Eleven parameters of TDC were extracted for each region to quantify the perfusion status (Tab. 1). The average of the mean TMAX values for all ROIs in each lobe was defined as the TMAX of the corresponding region and the other 10 parameters of each lobe were calculated in the same way. In order to signify the bilateral asymmetry in cerebral perfusion, the asymmetry ratio of TMAX (AR_{TMAX}) was calculated as: $AR_{TMAX}=TMAX_{H.side}/TMAX_{L.side}$. Accordingly, the asymmetry ratios of the other 10 parameters were also calculated. In addition, the ratio of the stenosis degree in H.side to that in L.side was taken as the asymmetry of stenosis.

Table 1: Description of the perfusion parameters

Parameters	Description
TMAX, seconds	The time from the start of the TDC to the appearance of the highest point; estimation of blood flow velocity
MTT, seconds	The time to half-peak of the integration curve for contrast medium; estimation of blood flow velocity and blood volume
TU, seconds	The time at which each curve takes an upward turn; estimation of blood flow velocity
TD, seconds	The time was calculated as the interval between TU and TMAX; estimation of wash-in rate
1/2TMAX, seconds	The time taken to reach the initial half maximum value; estimation of blood flow velocity
AUC, SI*s	Area under the curve from the start to the end of the TDC; estimation of blood volume
AUC_{before}, SI*s	Area under the curve before reaching the maximal value; estimation of blood volume and wash-in rate
AUC_{before}/AUC	The ratio of the AUC_{before} to the AUC; estimation of blood flow velocity
MS, SI/s	Maximum slope between the initial time and the peak intensity time; estimation of blood flow velocity
AFS, SI/s	The ratio of the increment of density value between TMAX and TU to the TD; estimation of blood flow velocity and wash-in rate
CBF, SI	The ratio of the AUC to MTT; estimation of blood flow

Abbreviations: TMAX, time taken to maximum value; MTT, mean transit time; TU, time of contrast uptake; TD, time of enhancing duration; 1/2TMAX, time taken to half maximum value; SI, signal intensity; AUC, area under the curve; AUC_{before}, area under the curve before maximal value; MS, maximum slope; AFS, average fitting slope; CBF, cerebral blood flow.

2.3 Statistical analyses

All statistical analyses were performed using SPSS 20.0 (IBM Corporation, Somers, NY, USA). The intraclass correlation coefficient (ICC) was calculated to assess the interoperator reliability of the parameter measurements by using two-way mixed model

with measures of absolute agreement. ICC values were classified as almost perfect (1.00-0.8), substantial (0.8-0.6), moderate (0.6-0.4), fair (0.4-0.2), and slight (<0.2, with no significant correlation in DSA perfusion parameters measurements between the two observers if the 95% CI covers zero). All DSA perfusion parameters between the two hemispheres of the patients within each group were compared using paired sample t test. Spearman correlation test was applied to calculate the correlations among the asymmetry ratios of the perfusion parameters and the stenosis asymmetry, in order to find whether the brain perfusion asymmetry change with stenosis asymmetry. Significance level was set at $P<0.05$.

3 Results

3.1 Reproducibility

Four brain lobes included frontal, parietal, temporal and occipital lobes were selected to evaluate cerebral hypoperfusion. Among all the defined perfusion parameters, most of them showed substantial to perfect consistency by using the DSA-based measurement, with ICCs between the two observers ranging from 0.665 to 0.997. On the other hand, TD of frontal, temporal and occipital lobes (ICC=0.512; ICC=0.528; ICC=0.528), AFS of all four lobes (ICC=0.507; ICC=0.530; ICC=0.516; ICC=0.573) as well as MS of the temporal lobe (ICC=0.495), showed moderate agreements (Tab. 2). This result demonstrates that the DSA perfusion parameters calculated from the two groups of ROIs by different observers show good consistency with each other. Therefore, the data used in the following statistical analyses are obtained by taking the average of two observers.

Table 2: Interobserver reliability of the parameters measurements at different lobs

	ICC			
	frontal lobe	parietal lobe	temporal lobe	occipital lobe
TMAX	0.823	0.849	0.747	0.777
MTT	0.996	0.989	0.997	0.994
TU	0.774	0.774	0.616	0.774
TD	0.512	0.665	0.528	0.528
1/2TMAX	0.793	0.871	0.809	0.799
AUC_{before}	0.775	0.754	0.735	0.755
AUC	0.991	0.983	0.987	0.987
AUC_{before}/AUC	0.874	0.842	0.748	0.836
MS	0.801	0.708	0.495	0.665
AFS	0.507	0.530	0.516	0.573
CBF	0.922	0.936	0.806	0.840

Abbreviations: TMAX, time taken to maximum value; MTT, mean transit time; TU, time of contrast uptake; TD, time of enhancing duration; 1/2TMAX, time taken to half maximum value; SI, signal intensity; AUC, area under the curve; AUC_{before}, area under the curve before maximal value; MS, maximum slope; AFS, average fitting slope; CBF,

cerebral blood flow.

3.2 Comparison of perfusion parameters between two hemispheres within each group

The color-coding algorithm was applied to visualization creation in order to better observe the bilateral difference of DSA perfusion parameters of the same patient. An example of the parametric visualization according to the TMAX of the individual pixels is shown in Fig. 3. Compared to the severe stenosis side (Fig. 3(B)), the color-coded composites of the mild stenosis side (Fig. 3(A)) showed a faster contrast filling in the intracranial segment of ICA and more complete contrast filling of the parenchyma.

The comparison of DSA perfusion parameters between H.side and L.side of 4 lobes within each group is partially shown in Tab. 3. Due to the large amount of data and the limitation of space, the comparison of DSA perfusion parameters, we only listed the four parameters which showed significant differences between the groups. In Group 1 and 2, no statistical significance was found among DSA perfusion parameters of frontal, parietal, temporal and occipital lobes. However, in Group 3, significant differences were detected in the following parameters. For the frontal lobe, the values of TMAX , MTT, TU, 1/2TMAX and AUC of the H.sides were significantly larger than those of the L.sides (P=0.023; P=0.013; P=0.041; P=0.009; P=0.027), whereas MS, AFS and CBF demonstrated significantly smaller values (P=0.001; P<0.001; P=0.006). For the parietal lobe, TMAX, MTT, TU, TD, 1/2TMAX and AUC were significantly larger in H.sides (P=0.006; P=0.008; P=0.041; P=0.046; P=0.002; P=0.012), whereas MS and AFS were smaller (P<0.001; P=0.017). For the temporal lobe, only MTT, TU, 1/2TMAX, AUC and AFS of H.sides were found to be significant different compared with L.sides (P=0.007; P=0.041; P=0.020; P=0.014; P=0.042). For the occipital lobe, H.sides showed significantly larger values in TMAX, MTT, TU, TD, 1/2TMAX and AUC (P=0.019; P=0.009; P=0.041; P=0.045; P=0.010; P=0.032; P=0.010). There was no significant difference in AUC_{before} and AUC_{before} /AUC for all the brain sections and for all the 3 groups (results not shown).

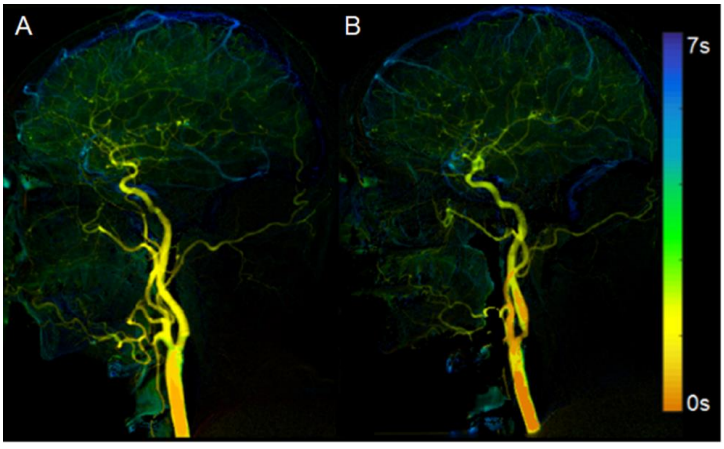

Figure 3: TMAX visualization of bilateral DSA in a patient. (A) the mild stenosis side and (B) the severe stenosis side. Compared with (B), the color-coded composites of (A)

show a faster contrast filling in the intracranial segment of ICA and a more complete contrast filling of the parenchyma

Table 3: Comparison of the perfusion parameters between two hemispheres within each group (mean±SD)

Lobe	Group	Side	MTT	TU	1/2TMAX	AUC(×10^2)
Frontal lobe	Group1	H.side	4.17±0.84	2.13±0.28	3.85±0.68	19.67±4.15
		L.side	3.90±0.51	1.99±0.41	3.54±0.53	18.60±2.83
	Group2	H.side	4.11±0.43	1.91±0.40	3.60±0.72	19.86±2.18
		L.side	4.13±0.64	2.01±0.42	3.57±0.33	19.79±3.29
	Group3	H.side	4.50±0.92*	2.41±0.59*	4.43±1.17*	20.64±4.15*
		L.side	3.70±0.28	2.01±0.27	3.51±0.44	17.68±1.79
Parietal lobe	Group1	H.side	4.24±0.88	2.13±0.28	4.09±0.69	19.84±4.45
		L.side	3.98±0.54	1.99±0.41	3.87±0.55	18.80±3.06
	Group2	H.side	4.21±0.44	1.91±0.40	3.83±0.76	20.15±2.19
		L.side	4.17±0.66	2.01±0.42	3.83±0.59	19.86±3.13
	Group3	H.side	4.62±0.92*	2.41±0.59*	4.65±0.84*	21.24±4.23*
		L.side	3.74±0.29	2.01±0.27	3.68±0.40	17.59±1.83
Temporal lobe	Group1	H.side	4.18±0.84	2.13±0.28	3.49±0.50	20.02±4.25
		L.side	3.88±0.52	1.99±0.41	3.33±0.53	18.57±2.81
	Group2	H.side	4.13±0.45	1.91±0.40	3.41±0.82	20.22±1.90
		L.side	4.12±0.71	1.91±0.54	3.31±0.57	20.16±3.77
	Group3	H.side	4.52±0.89*	2.41±0.59*	4.05±1.01*	21.21±4.25*
		L.side	3.62±0.28	2.01±0.27	3.23±0.38	17.36±1.62
Occipital lobe	Group1	H.side	4.26±0.89	2.13±0.28	3.98±0.80	20.16±4.39
		L.side	3.95±0.54	1.99±0.41	3.77±0.55	18.59±2.95
	Group2	H.side	4.24±0.49	1.91±0.40	3.69±0.72	20.74±2.19
		L.side	4.18±0.68	2.01±0.42	3.66±0.54	20.09±3.49
	Group3	H.side	4.56±0.90*	2.41±0.59*	4.28±0.90*	21.20±4.13*
		L.side	4.17±0.84	2.13±0.28	3.48±0.36	19.67±4.15

Group1: bilateral mild stenosis. Group2: mild stenosis on one side and moderate stenosis on the other side. Group3: mild stenosis on one side and severe stenosis on the other side. H.side: the side with higher stenotic degre. L.side: the contrary side of H.side.
Abbreviations: MTT, mean transit time; TU, time of contrast uptake; 1/2TMAX, time taken to half maximum value; AUC, area under the curve;
*statistical significance (P<0.05, compared to L.side).

3.3 Relationship between perfusion parameters asymmetry and stenosis asymmetry

Since all the patients have bilateral carotid stenosis, we evaluated whether the differences of perfusion parameters between two sides are associated with the asymmetry of stenosis. Here Spearman correlation test was performed between stenosis asymmetry and side-to-

side asymmetry of DSA perfusion parameters in four lobes of all patients. AR_{MTT} and AR_{AUC} had statistically significant correlations with the stenosis asymmetry with the Spearman correlation coefficients of 0.437 and 0.486 for the frontal lobe (P=0.016; P=0.007), 0.488 and 0.474 for the parietal lobe (P=0.006; P=0.008), 0.397 and 0.436 for the temporal lobe (P=0.030; P=0.016), and 0.426 and 0.426 for the occipital lobe (P=0.019; P=0.019), respectively. No correlations were observed in other parameters.

4 Discussion

Conventional DSA of the carotid arteries assists medical diagnosis on cerebrovascular disease while helping make appropriate decision regarding endovascular intervention and treatment efficacy assessment for patients. This imaging characteristic allows relatively precise evaluation of arterial geometry and qualitative assessment of reperfusion in intervention surgeries. However, the clinical evaluation of cerebral hypoperfusion is mostly based on CT/MR perfusion imaging. In this study, we have demonstrated the feasibility of measuring TDCs from DSA images and calculated multiple perfusion parameters to quantify the cerebral hypoperfusion in different brain lobes of patients with asymmetric carotid stenosis. In patients with severe ICA stenosis in one side, there was significant asymmetric change of cerebral perfusion between the two sides, especially in the frontal and parietal lobes.

Certain image processing technologies, such as color-coded DSA, have been developed to assess the perfusion status in arteries and tissues according to TDC obtained from DSA. However, the profile of TDC is easy to be affected by imaging conditions such as the amount, injection rate and concentration of contrast agent, catheter position or even the individual difference and the observers' difference. Therefore, we examined the bilateral carotid artery DSA imaging in this study, which was performed in one operation to avoid the influence caused by observers as much as possible. In order to investigate the perfusion differences caused by different stenotic degrees, thirty patients underwent bilateral carotid artery DSA imaging were enrolled and divided into three groups according to the levels of stenosis asymmetry between two sides. Eleven perfusion parameters were calculated from the TDC data and compared in different brain lobes. The statistical analysis showed that in patients with a severe ICA stenosis at one side, there was a significant asymmetric perfusion between two hemispheres, i.e., the H.side demonstrated a slower contrast filling in the intracranial segment of ICA and a more complete contrast filling of the parenchyma (Fig. 3). The time parameters, including MTT, TU, 1/2TMAX and AUC, were the most sensitive ischemic predictor because of they were all significantly increased in the H.side of all 4 lobes. These results were consistent with the findings from Eastwood et al [Eastwood, Lev, Azhari et al. (2002)], Nagar et al [Nagar, McKinney, Karagulle et al. (2009)], Cheng et al [Cheng, Tian, Zuo et al. (2014)], who also suggested that differences in MTT between two hemispheres may be good indicators of ischemic differences according to the CT perfusion results. Prolonged MTT and increased cerebral blood volume (CBV, i.e., AUC defined in the current study) may indicate a decrease in cerebral perfusion of the lesion side [Dai, Zhao, Zhang et al. (2013); Jeon, Kim, Lee et al. (2012); Kheradmand, Fisher, Paydarfar et al. (2014); Grandin, Duprez, Smith et al. (2001)]. This can be explained by the fact that when the cerebral perfusion pressure declines, the compensatory expansion of the

cerebral vessel and the decrease of the cerebral vascular resistance can lead to the reduction of blood flow velocity and the time parameters prolong accordingly. On the other hand, CBF, which was used to represent cerebral blood flow, was found to decrease in the H.side. However, no statistically significant differences were observed between the bilateral hemispheres except the frontal lobe. The result also supports the validity of the compensatory effect of the cerebrovascular reserve (CVR), which is responsible for keeping relatively stable intracranial blood flow. Thus, small arteries and capillaries expand to maintain the stability of CBF whereas CBV is elevated due to the dilatation of the microvasculature.

Cerebral blood perfusion failure caused by severe stenosis is believed to be the common cause of ischemic cerebrovascular disease. The results of this research indicates that the severe ICA stenosis has a greater impact on frontal and parietal lobes, which suggests that these areas are particularly sensitive to ischemia induced by hypoperfusion. In contrast, AUC_{before} and AUC_{before}/AUC showed no impact on cerebral perfusion. One plausible explanation would be that the measurement of them within the ROIs was beyond the scope of our current frame rate (4 frames/second), which was inadequate to reflect the rising characteristics of the cerebral flow. Declined values of MS and AFS in H.sides suggested the slow blood flow velocity in the severe stenosis side, which were consistent with the time parameters mentioned above. In addition, the asymmetry ratios of MTT and AUC between two sides were correlated with the asymmetry of stenosis and may be indicative of detecting asymmetry in cerebral perfusion.

The limitations of this study should be mentioned. First, the DSA acquisition time is not long enough to cover the whole DSA venous phase. It may reduce the validity of the width (i.e., the time from the start to the end of the TDC), MTT and AUC parameters due to the limited washout flow of contrast agent. Other useful parameters such as cerebral circulation time and full width at half maximum, may be unavailable to be obtained from TDC [Lin, Hsu, Lin et al. (2016); Lin, Chang, Guo et al. (2015)]. Thus, a higher DSA acquisition frame rate is suggested to make sure that contrast bolus flow characteristics are well-recorded. Second, the method proposed in this study is semi-automatic and it is necessary for observers to do manual selection of ROIs. Further improvement will focus on the realization of dividing 4 brain regions automatically. Third, overlapping of vasculature is basically inevitable on a two-dimensional projection during DSA imaging. The flow measurement using 3D distance-concentration functions derived from digital X-ray angiograms may overcome the constraints of two-dimensionality [Ognard, Magro, Caroff et al. (2018); Davis, Royalty, Kowarschik et al. (2013)]. However, it would produce too much radiation exposure on patients. Additionally, hemisphere perfusion can be overevaluated especially when the blood flows from one hemisphere to the other via the collateral circulation on an anterior view. This can accentuate the contrast medium density and might result in different shapes and waveform of TDCs. Fourth, the number of patients recruited into this study is small. Hence, the feasibility of this method was only demonstrated preliminarily. More patients are needed to validate our initial results in the future work. In order to better understand the relationships between these parameters and cerebral blood flow, the most valuable parameter should be determined to simplify the diagnosis of perfusion with DSA-based method. Considering the superiority of DSA in displaying vascular geometry and collateral circulation opening, future work will

evaluate cerebral perfusion comprehensively by combining with the collateral opening status of patients.

5 Conclusions

In conclusion, DSA-based method of perfusion parameters extraction may serve as an adjunctive tool for a more convenient evaluation of cerebral perfusion asymmetry change caused by ICA stenosis. By analyzing TDCs, certain quantitative parameters, including MTT, TU, 1/2TMAX and AUC, are good indicators of detecting asymmetry in cerebral hypoperfusion.

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