



# Relationship between CT angiography-derived collateral status and CT perfusion-derived tissue viability

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**AIM:** To explore the relationship between computed tomography (CT) angiography (CTA)-derived collateral status and CT perfusion (CTP)-derived tissue viability.

**MATERIALS AND METHODS:** Patients having middle cerebral artery (MCA) M1/M2 segment and/or internal carotid artery (ICA) occlusion and within 12 hours of onset were included. Collateral was graded from 0 to 3 on maximum intensity projection (MIP) images of CTA. The area with relative cerebral blood flow (rCBF) <30% or time-to-maximum (Tmax) >10 or >12 or >14 seconds was defined as the infarct core, and Tmax >6 seconds as the penumbra. Kruskal–Wallis and Spearman's correlation tests were performed to assess the correlation between collateral grade and infarct size or mismatch ratio.

**RESULTS:** Eighty-three patients were enrolled and 52 of them met the inclusion criteria. Infarct size defined by rCBF <30% or Tmax >10 or >12 or >14 seconds and mismatch ratios were significantly different among the four groups. The correlation between collateral grades and infarct core using rCBF <30% ( $\rho = -0.814$ ,  $p < 0.01$ ) was better than that defined by Tmax >10s, >12s or >14s. Mismatch ratio for the infarct core defined by rCBF <30% ( $\rho = 0.945$ ,  $p < 0.01$ ) had the best correlation with collateral grades.

**CONCLUSION:** Patients with good collaterals show a smaller infarct core and higher mismatch ratio. Infarct size defined by rCBF <30% and mismatch ratio defined by rCBF <30% and Tmax >6 seconds appear to be more correlated with collaterals in AIS patients.

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## Introduction

The cerebral collateral circulation plays an important role to reconstruct blood supply to ischaemic brain tissue. When a localised major blood vessel is blocked, the contralateral

blood flow through the circle of Willis carries blood around the blockages, and anastomosis with smaller vessels will open up.<sup>1</sup> The collateral supply improves the success rate of vascular recanalisation therapy and reduces the infarct volume and the risk of haemorrhagic transformation.

The grading of collateral vessels on computed tomography (CT) angiography (CTA) makes the selection of patients for intra-arterial treatment (IAT) more effective.<sup>2</sup> The Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimising CT to Recanalisation Times (ESCAPE) trial demonstrated

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that endovascular treatment was more effective in patients with moderate to good collaterals on CTA.<sup>3</sup> CT perfusion (CTP) mismatch predicts penumbra and infarct core intuitively and accurately. The Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial (EXTEND-IA) trial used CTP to screen patients for early endovascular therapy.<sup>4</sup> A comprehensive understanding of CTA and CTP information in acute settings may facilitate the triage of acute ischaemic stroke (AIS) patients who may still benefit from intra-arterial treatment, such as mechanical thrombectomy, beyond 4.5 hours.

The objective of the present study was to determine whether CTA-derived collateral status and CTP-derived tissue viability could provide correlative and effective ischaemic information for clinical mechanical thrombectomy or thrombolysis. An additional aim was to explore which CTP parameters defined infarct core and penumbra better associated with their collateral status.

## Materials and methods

### Patients

“One-stop” multi-modal CT examinations, including unenhanced CT (NCCT), CTP, and CTA, were performed for consecutively enrolled stroke patients who were admitted via the emergency “green expressway” from August 2016 to March 2017. The inclusion criteria were as follows (1) time from witnessed symptom onset to first CT scan <12 hours; (2) CTP suggested the presence of ischaemic hypoperfusion; (3) and M1/M2 segment of middle cerebral artery (MCA) and/or internal carotid artery (ICA) occlusion seen on CTA.

Patients were excluded because of inability to complete the imaging examination, poor image quality, and patients with arterial stenosis but no visible occlusion. Patient age, sex, risk factors (diabetes mellitus, hypertension, coronary artery disease, atrial fibrillation, etc.), time from symptom onset, and therapy were recorded. Informed consent was obtained from all enrolled patients, and the study was approved by the institutional ethics board.

### CT examination protocol

All CT examinations were conducted using a 256-row Brilliance iCT machine (Philips Healthcare, Cleveland, OH, USA). At emergency admission, all patients had NCCT, head/neck CTA, and CTP examinations. NCCT was performed first to locate possible ischaemic hypodensity/oedema and ascertain the scan range. For the CTP protocol, the head coverage was 80 mm in z-axis direction and the collimation was 0.625 mm with an axial image reconstruction of 5 mm per section. The tube voltage was 80 kV and tube current was 150 mAs. Fifty millilitres of iodinated contrast agent (iodixanol 320 mg iodine/ml; Visipaque 320, GE Healthcare, Cork, Ireland) was injected at 5 ml/s followed by a saline flush of 50 ml at 5 ml/s. The scanning began after a delay of 5 seconds from contrast medium injection. Total scan time was 60 seconds at an image sampling rate of 2 seconds. CTA

acquisition was obtained using spiral scanning at a pitch of 0.7 (120 kV, 250 mAs, 1-second rotation time). CTA covered from the aortic arch to the top of the brain. A total volume of 50 ml contrast agent was injected at 4 ml/s followed by a saline flush of 45 ml at 5 ml/s.

### CTP image analysis

CTP was used to calculate perfusion parameters and to assess blood perfusion quantitatively in the ischaemic brain tissue. The CTP source images were post-processed using the perfusion based on a delay-insensitive deconvolution algorithm (CT Kinetics, Shanghai, GE Healthcare, China). The image section with the maximum ischaemic area was selected to analyse CTP parameters including cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time-to-maximum (Tmax). Relative CBF to the contralateral hemisphere (rCBF) <30%,<sup>5</sup> or Tmax >10, >12 or >14 seconds were used to detect which threshold was best for delineating infarct core, and used Tmax >6 seconds as the hypoperfused lesion.<sup>6</sup> The mismatch ratio was defined as the ratio of the penumbra/infarct core area. The software’s automatic segmentation defined the penumbra as the green area and infarct as the red area.

### Collateral assessment on CTA

The CTA images were reviewed on a picture archiving and communication system (PACS) workstation (Neusoft, Shenyang, China) by one junior radiologist (3 years of experience) and one senior radiologist (10 years of experience) independently. If they had different views, another reading session was performed to reach an agreement; observers were blinded to patient information. The CTA axial source images and sagittal and coronal multiple planar reconstruction (MPR) were used to determine the site of the vascular occlusion. Collateral circulation was graded using a four-point scale on axial maximum intensity projection images (MIP) of CTA (at 7 mm per section) as follows: grade 0: absent collaterals; grade 1: collaterals filling in ≤50% of the occluded territory; grade 2: collaterals filling in >50%, but <100 % of the occluded territory; grade 3: collaterals filling in 100% of the occluded territory.<sup>7</sup>

### Statistical analysis

All patients were divided into four groups according to the four grades of collateral circulation. All statistical analyses were performed using SPSS (version 19; IBM, Armonk, NY, USA). Normality test was assessed using the Shapiro–Wilk test. Normally distributed variables were reported as mean ± standard deviation (SD); and abnormally distributed variables were presented as median and interquartile ranges (IQR). The Kruskal–Wallis test was used to investigate the association between collateral grades and CTP outcomes followed by all pairwise multiple comparisons. The correlation strength between CTA collaterals and CTP outcomes was reported as Spearman correlation coefficients ( $\rho$ ). The statistical significance level was set at  $p < 0.05$ .

## Results

Data from 83 ischaemic stroke patients who underwent multimodal CT imaging including NCCT, CTA, and CTP were collected. Thirty-one patients were excluded, among which 15 patients were excluded because the time from witnessed symptom to admission was >12 hours, six patients due to arterial stenosis but no visible occlusion, 10 patients due to posterior circulation infarction or distal MCA occlusion. Finally, 52 patients met the inclusion criteria (28 male and 24 female patients with a mean age of  $68.3 \pm 14.2$  years; Table 1). The mean time elapsed from symptom onset to CT scan was  $246.6 \pm 148.1$  minutes. M1 segment occlusion of the MCA was diagnosed in 30 patients (57.7%) and M2 segment occlusion in 13 patients (25%). ICA occlusion appeared in nine patients (17.3%), and four (7.7%) of them

**Table 1**  
Patients characteristics.

	All patients (n=52)
Age, years, mean±SD	68.3±14.2
Female sex, n (%)	24 (46.2%)
Time from symptom onset to CTP, min, mean±SD	246.6±148.1
Risk factors, n (%)	
Diabetes mellitus	10 (19.2%)
Hypertension	35 (67.3%)
Coronary artery disease	5 (9.6%)
Atrial fibrillation	11 (21.2%)
Undetermined	5 (9.6%)
Recanalisation therapy, n (%)	
IV tPA	23 (44.2%)
Endovascular	3 (5.8%)
No treatment	26 (50.0%)
Infarct size, mm <sup>2</sup> , median (IQR)	
rCBF <30%	1,827 (2089.4)
Tmax >10 s	1,819.75 (1925.8)
Tmax >12 s	1,379.5 (1558.8)
Tmax >14 s	704 (1296.5)
Mismatch ratio (rCBF <30%, Tmax >6 s) <sup>a</sup> , median (IQR)	0.9 (0.7)
Mismatch ratio (Tmax >10 s, Tmax >6 s) <sup>a</sup> , median (IQR)	1.4 (1.8)
Mismatch ratio (Tmax >12 s, Tmax >6 s) <sup>a</sup> , median (IQR)	2.3 (5.6)
Mismatch ratio (Tmax >14 s, Tmax >6 s) <sup>a</sup> , median (IQR)	3.9 (15)
Site of occlusion, n (%)	
M1	30 (57.7%)
M2	13 (25%)
M1+ICA	4 (7.7%)
ICA	5 (9.6%)
Collateralisation, n (%)	
Grade 0	8 (15.4%)
Grade 1	16 (30.8%)
Grade 2	15 (28.8%)
Grade 3	13 (25%)

CTP, computed tomography perfusion; IQR, interquartile range; rCBF, relative cerebral blood flow; Tmax, time-to-maximum; IV tPA, intravenous tissue-type plasminogen activator; SD, standard deviation; IQR, interquartile range; ICA, internal cerebral artery; M1, main trunk of the middle cerebral artery; M2, secondary trunk of the middle cerebral artery.

<sup>a</sup> Mismatch ratio (threshold of infarct core, threshold of hypoperfused lesion).

had concurrent M1 occlusion. Patient characteristics are presented in Table 1.

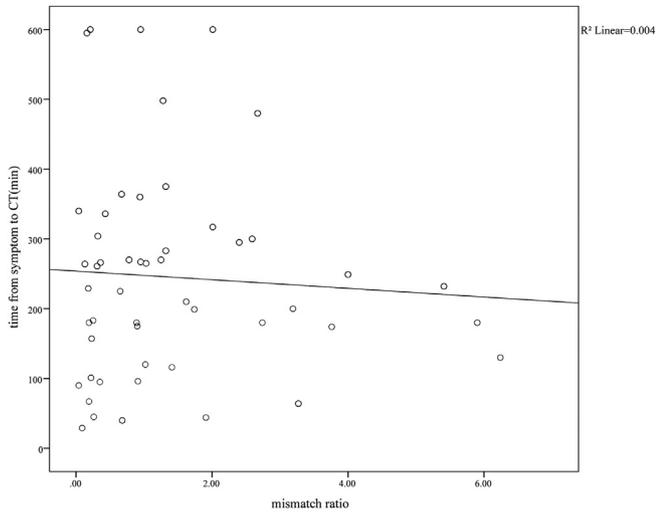
There was no significant difference in age and time from symptom to CT among the four groups ( $p=0.540$  for age and  $p=0.359$  for time). The occlusion sites and risk factors did not differ among groups. The relationship between the time from symptom onset to CT and CTP mismatch ratio showed no sign of specific trend (Fig 1). The correlation between CTA collateral grades and CTP-derived infarct core or mismatch ratio is shown in Table 2. The closer the Spearman correlation coefficient ( $\rho$ ) was to 1 or  $-1$ , the stronger the correlation was. CTA collateral grade was negatively correlated with CTP infarct size, and the correlation between collateral grades and infarct of rCBF <30% was the strongest ( $\rho=-0.814$ ,  $p<0.01$ , Fig 2a), followed by Tmax >14 seconds, and the infarct size of Tmax >10 seconds had the weakest correlation. CTA collateral grade was positively correlated with mismatch ratio, and the correlation between collateral grades and mismatch ratio (defined with the dual threshold: rCBF <30% and Tmax >6 seconds) was the strongest ( $\rho=0.945$ ,  $p<0.01$ , Fig 2b) compared to the other ratios. CTP mismatch ratio defined with Tmax >14 seconds and Tmax >6 seconds was more correlated with collateral scores than that defined with Tmax >10 or >12 and >6 seconds. The NCCT images and CTP maps (CBF, CBV, MTT, Tmax, and perfusion mismatch) under the collateral grades from 0 to 3 on the corresponding CTA-MIP are illustrated in Fig 3.

Patients with high collateral score (grades 2–3) had a smaller infarct size and a larger mismatch ratio, compared to those with poor collaterals (grades 0–1). Fig 4 demonstrates CTA images of the occluded vessel, the collaterals region, an adjacent appropriate CT perfusion image, and a follow-up NCCT image after 7 days. Pairwise multiple comparisons revealed a significant difference in the mismatch ratio between the collateral groups of grade 1 and grade 2.

## Discussion

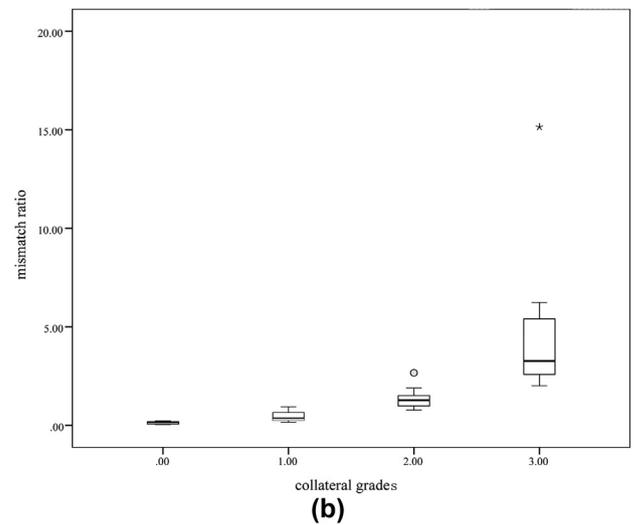
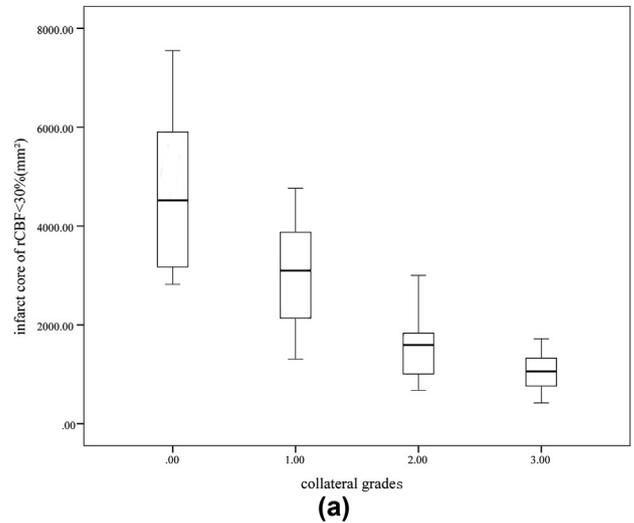
The results of the present study found that patients with high collateral grade had smaller infarct sizes and greater mismatch ratios. The mismatch ratio and infarct size defined by the dual threshold of rCBF <30% and Tmax >6 seconds correlated better with collateral status, as compared to those using Tmax >10 or >12 or >14 seconds as infarct core; however, the correlation between time from symptom onset and mismatch ratio was not found.

The first key point of this study, in addition to the “time is brain”, is the “perfusion and collaterals are brain”. The present observations indicated that patients who had good collateral flow could still preserve a considerable penumbra volume, even if time from symptom onset was beyond 4.5 hours. The imaging-based triage of AIS patients extends the time window in selected patients, especially for endovascular thrombectomy. The study of Copen *et al.*<sup>8</sup> found that the diffusion–perfusion magnetic resonance imaging (MRI) mismatch persisted for >9 hours after stroke onset in some



**Figure 1** The relationship between time from symptom onset to CT and mismatch ratio (rCBF <30% as the infarct core and Tmax >6 seconds as the hypoperfused lesion). There was no clear relation between time from symptom to CT and mismatch ratio.

patients who had proximal arterial occlusion. Other MRI perfusion studies also reported that patients beyond 9 hours after stroke onset still preserved moderate ischaemic penumbra.<sup>9,10</sup> To further elucidate the “penumbra over time” hypothesis, patients who underwent CTP within 12 hours of the onset of symptoms were investigated. Indeed, the results showed that there was no correlation between time from symptom onset and mismatch ratio. In contrast, some patients arriving within 4.5 hours may have a very small treatable penumbra and large infarct, if the collateral route has already failed. These studies suggest that clinical treatment decisions cannot be solely based on the length of onset time. The DEFUSE-3<sup>11</sup> and DAWN<sup>12</sup> trials broadened the time window for endovascular treatment to 16 hours and even 24 hours. The favourable clinical outcomes demonstrated the feasibility of imaging methods instead of “time window” for screening patients for endovascular treatment; however, the current AIS treatment guideline has not extend the time window for intravenous or intra-arterial thrombolysis because of the risk of thrombolysis-related haemorrhagic transformation.<sup>13,14</sup> In the future, more imaging-based selection of treatable patients may



**Figure 2** Correlation between collateral grade and infarct core defined by rCBF <30% (a) and the corresponding mismatch ratio (b). Data represent median and interquartile range. There was significant difference in infarct size or mismatch ratio for the different collateral grades ( $p < 0.01$  for both). The infarct size was negatively correlated with collateral grades, and the mismatch ratio was positively correlated with the grades.

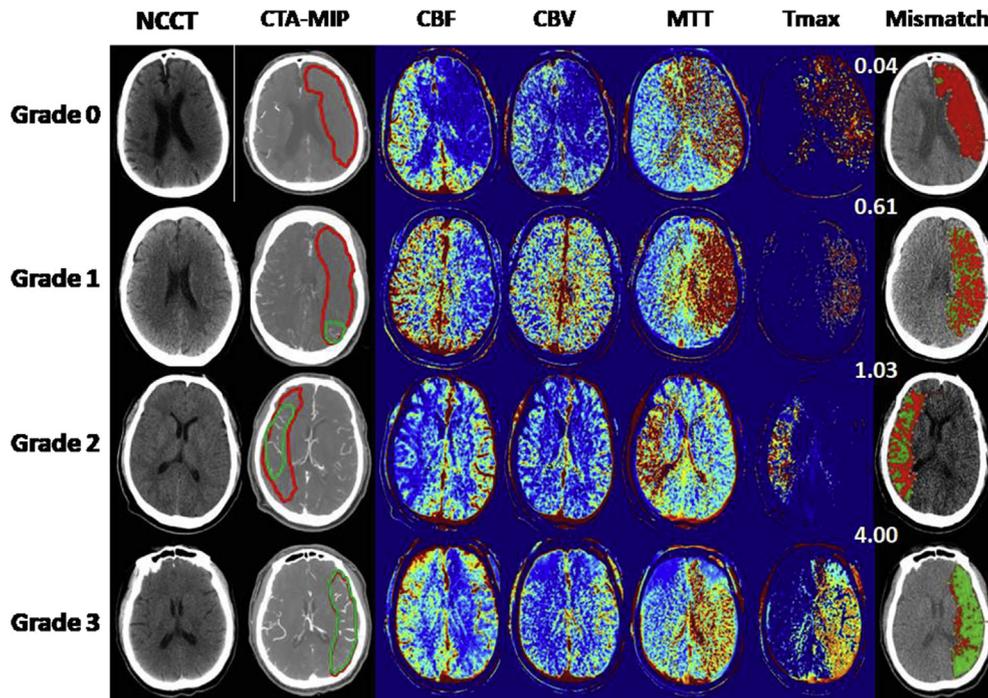
become a focus to extend the time window for the guideline.

**Table 2**

Correlation of computed tomography (CT) angiography (CTA) with CT perfusion (CTP)-derived infarct core and mismatch ratio.

Collateral grades	Infarct core (mm <sup>2</sup> ), median (IQR)				mismatch ratio, median (IQR)			
	rCBF <30%	Tmax >10 s	Tmax >12 s	Tmax >14 s	rCBF <30%, Tmax >6 s	Tmax >10 s, Tmax >6 s	Tmax >12 s, Tmax >6 s	Tmax >14 s, Tmax >6 s
Grade 0 (n=8)	4,518.1 (2,366.8)	2,475.3 (1,071.5)	2,030.8 (1,093.7)	1,784.8 (998.3)	0.2 (0.1)	1.0 (0.3)	1.5 (0.6)	1.8 (0.7)
Grade 1 (n=16)	3,098.8 (1,596.2)	2,251.1 (1,528.5)	1,757.6 (1,287.9)	1,200.6 (1,014.5)	0.4 (0.4)	0.9 (0.9)	1.4 (1.9)	2.5 (3.2)
Grade 2 (n=15)	1592.3 (829.0)	670.3 (1,706.3)	616.8 (1,334.0)	243 (1,015.5)	1.3 (0.5)	1.9 (5.7)	3.5 (10.8)	15.1 (20.5)
Grade 3 (n=13)	941.4 (552.4)	956.8 (1,571.4)	453.1 (1341.7)	75.9 (277.8)	3.5 (2.8)	2.9 (13.5)	9.2 (63.7)	63.5 (155.0)
p-Value	<0.001	0.021	0.003	<0.001	<0.001	0.004	<0.001	<0.001
Correlation (ρ)	-0.814	-0.402	-0.496	-0.690	0.945	0.490	0.586	0.743

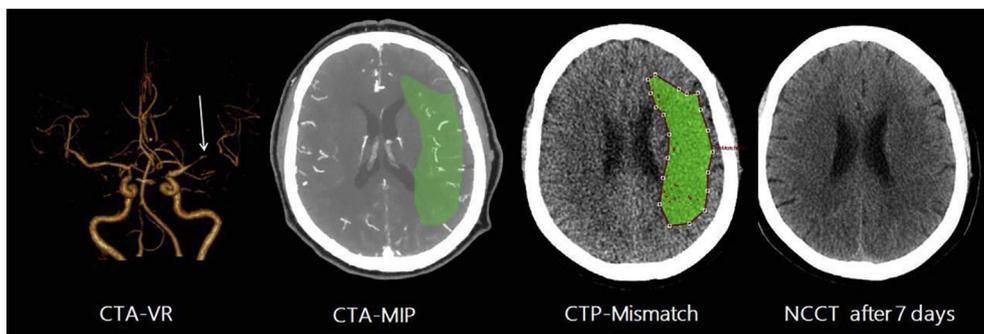
IQR, interquartile range; rCBF, relative cerebral blood flow; Tmax, time-to-maximum.



**Figure 3** Images of NCCT, CTA, and CTP for each grade of patient. For the CTA-MIPs, the area within the red outline was the occluded territory, and there were collaterals filling within the green outline. Grade 0: absent collaterals, Grade 1: collaterals filling in  $\leq 50\%$  of the occluded territory, Grade 2: collaterals filling in  $>50\%$ , but  $<100\%$  of the occluded territory, Grade 3: collaterals filling in  $100\%$  of the occluded territory. For the CTP mismatch maps, the penumbra (green) was defined by  $T_{max} > 6$  seconds, and the infarct core (red) was defined by  $rCBF < 30\%$ . The mismatch ratios were showed in the top right corner.

The importance of imaging-based triage of AIS patients has become a focus for endovascular clot retrieval; however, specific CTP parameters within 12 hours of stroke have not been fully explored to characterise collateral potency via its relation to the penumbra mismatch profile. CTP parameters such as time to peak (TTP) and  $T_{max}$  have already been used in some clinical studies. One study reported that  $T_{max} > 16$ ,  $> 12.5$ , and  $> 9.5$  seconds might delineate infarct region when reperused within 90 minutes, 90–180 minutes from CTP, and no acute reperfusion, respectively.<sup>15</sup> Different from the ultra-early stage of the stroke in their study, the present study investigated  $T_{max} > 10$  or  $> 12$  or  $> 14$  seconds as the threshold to define infarct core within 12 hours of stroke

onset. In the present study, the correlation between collateral grades and infarct core defined by all  $T_{max}$  thresholds was weaker than that defined by  $rCBF < 30\%$ .  $T_{max} > 14$  seconds better defined the infarct core and the corresponding mismatch ratio than  $T_{max} > 10$  or  $> 12$  seconds.  $T_{max}$  primarily reflects macrovascular characteristics,<sup>16</sup> but more severe  $T_{max}$  delays may associate with microvascular integrity supplied by collateral circulation.<sup>17</sup> Bruce *et al.* demonstrated that CTP-derived  $rCBF$  was the optimal parameter for identifying infarct core, and the similar results were confirmed in the diffusion-weighted imaging (DWI) lesion.<sup>5</sup> A meta-analysis reported that CBF had the best diagnostic characteristics for AIS (sensitivity:



**Figure 4** Volume rendering (VR) image of CTA showed the M1 of MCA occlusion (arrow). The green area on CTP defined by  $T_{max} > 6$  seconds represented ischaemic hypo-perfusion. CTA-MIP showed collaterals filling in  $100\%$  of the occluded territory. Very little small lacunar infarcts defined by  $rCBF < 30\%$  (red) were observed on CTP mismatch image, which matching the result of NCCT after 7 days.

47.3%; specificity: 91%).<sup>18</sup> This is consistent with the present study that infarct core defined by rCBF <30% was strongly and better correlated with collateral status.

Liu et al.<sup>19</sup> reported that the combined collateral grading system of both CTA and CTP showed excellent consistency as compared to digital subtraction angiography (DSA) findings ( $\kappa$ -coefficient: 0.770) in AIS patients. Based on the premise that the diagnostic results of the two methods of CTP and CTA have good correlation, the joint diagnosis has scientific guiding significance. The present study proved this point. In the grade 0 group, three patients had thrombolytic haemorrhagic transformation with small or moderate mismatch ratio. The benefit of IAT was great in patients with good collaterals on CTA, whereas patients with absent or poor collaterals had poor outcomes when treated with IAT.<sup>2</sup> The advanced CT imaging assessment of mismatch ratio and collateral perfusion can provide valuable functional information about the penumbral reserve at critical condition, thus making more patients benefit from endovascular treatment.

There were several limitations to the present study. Firstly, the CTA collateral grading system used for collateral assessment was based on conventional angiography. A comparison was made between CTA collateral grading scale and DSA ASTIN-ASN system ( $\kappa$ -coefficient: 0.679), showing good consistency.<sup>19</sup> Secondly, the sample size was small ( $n=52$ ) and only three patients underwent endovascular treatment. Moreover, for now only the imaging data were investigated; in the future, clinical and follow-up evaluations will be added.

In conclusion, the present study found that CTP mismatch ratio had no clear relationship with time from symptom onset. Patients with good collaterals showed a smaller infarct core and higher mismatch ratio. Infarct size defined by rCBF <30% and mismatch ratio defined by rCBF <30% and Tmax >6 seconds appear to be strongly and better correlated with collateral grades in acute ischaemic stroke patients. The diagnostic results of CTP and CTA are correlative and complementary, and can provide both vascular and functional information for clinical decision-making.

## Conflict of interest

The authors declare no conflict of interest.

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