Improving Prognostic Evaluation by 4D CTA for Endovascular Treatment in Acute Ischemic Stroke Patients: A Preliminary Study

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Objective: We aim to use 4D CTA with a comprehensive and objective scoring system to assess collateral circulation, and explore the value of prognosis prediction in endovascular treated patients. *Methods:* Thirty-four patients with unilateral anterior circulation large vessels occlusion were reviewed in this study retrospectively. Single-phase CTA (sCTA) and 4D CTA acquired by CT perfusion scanning were analyzed for collateral circulation assessment. The collateral vessels were scored 0-4 according to modified collateral circulation scoring based on 4D CTA. Zero to two points indicated poor collateral circulation; 3-4 points indicated good collateral circulation. Good prognosis was defined as modified Rankin scale score of 0-2. Logistic regression was used to analyze the relationship between collateral circulation and prognosis. *Results:* The mean age was 71.1 ± 11.5 years old. Collateral circulation on 4D CTA was an independent factor for predicting the prognosis (odds ratio = .101; 95% confidence interval: [.101-.924]; $P = .042$), but sCTA could not predict prognosis ($P = .214$). 4D CTA collateral circulation scoring had a good predicting efficacy on clinical prognosis (Area Under Curve (AUC) = .936; 95% confidence interval: [.751-.992], $P < .005$). Patients with good collaterals (4D CTA scores of 3-4) could obtain benefit from endovascular treatment ($P = .029$) compared with patients with poor collaterals ($P = 1.000$). *Conclusions:* 4D CTA could be applied to effectively evaluate cerebral collateral status. The accurate assessment of collateral circulation based on 4D CTA would be helpful to make medical decisions, especially for those patients who would undergo endovascular interventional treatment.

Key Words: Acute stroke—collateral circulation—vascular lesions—computed tomography angiography

Introduction

Acute ischemic stroke is a kind of common and frequently-occurring disease.[1] Previous studies have shown that good collateral circulation would reduce cerebral infarction volume, maintain cerebral blood perfusion, improve prognosis, and reduce the risk of recurrence.[2-4] Therefore, a comprehensive and accurate assessment of collateral circulation status is of great value for choosing of clinical treatments and the prediction of recovery.

Digital subtraction angiography (DSA) is a gold standard for the assessment of intracranial vascular stenosis and collateral circulation, however, it is not suitable for routine examination because of the invasive property.[3,5] Currently, many noninvasive methods have been applied to evaluate collateral circulation, including time of flight

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magnetic resonance angiography (TOF-MRA), conventional single-phase CT angiography (sCTA), and one-stop CT angiography (CTA)-CT perfusion (CTP).[6,7] For patients with acute ischemic stroke, CTA has higher sensitivity and positive predictive value and more conveniently than MRA in evaluating vascular occlusion and collateral circulation.[8] In addition, MRA is unable to evaluate the distal leptomeningeal vessels and angiogenesis.[9] Conventional sCTA is widely applied now, but it will lose partial vascular information due to the injection rate of contrast agent and image acquisition time.[3,10]

4D CTA acquired by CT perfusion scanning was able to provide the whole brain perfusion images and dynamic angiographic information simultaneously. Compared with the above-mentioned methods, 4D CTA could comprehensively evaluate the vascular status and cerebral hemodynamics, herein, 4D CTA could be similar to DSA in evaluating the collateral circulation.[11]

In this study, we used a 4D CTA-based modified collateral circulation scoring system, a comprehensive and objective method, to evaluate the extent of collateral status in acute stroke patients. The aim of this study was to disclose whether this scoring system could predict the clinical prognosis of acute ischemic stroke patients who underwent endovascular procedures.

Materials and Methods

Study Population

The study was approved by the local institutional research ethics board, and informed consent was waived as the patients' data were evaluated retrospectively and anonymously.

Acute ischemic stroke patients who were admitted and underwent endovascular procedures in our hospital from June 2017 to July 2018 were retrospectively reviewed. Inclusion Criteria: (1) age ≥18 years; (2) endovascular treatment (EVT) was performed within 24 hours after symptom onset; (3) patients with occlusion of middle cerebral artery (MCA) M1/M2 segment and/or internal carotid artery; (4) the admission one-stop 4D CTA-CTP imaging data and the follow-up clinical data were complete. Exclusion Criteria: (1) Noncontrast CT (NCCT) scan indicated intracranial hemorrhage; (2) previously suffered from massive cerebral infarction in ipsilateral cerebral hemisphere (infarct size was equal or more than two thirds of the blood supply area of the middle cerebral artery; (3) the modified Rankin scale scores (mRS) before the onset is greater than 2; (4) severe motion artifacts.

Imaging Acquisition

After admission, NCCT was used to exclude intracranial hemorrhage. ASPECTS scoring based on NCCT was used for evaluating the early ischemic changes of brain parenchyma. For NCCT, following parameters were used: 80 kV; 200 mAs; detector .5 × 80/volume scan. Subsequently, one-stop whole brain dynamic volume CTA-CTP examination was performed using a 320 × .5 mm detector rows CT (Aquilion ONE, Canon Medical Systems), with covering 160 mm of volume each rotation. 18G venous indwelling needle was embedded in cubital vein. Intravenous infusion of 40-50 mL of nonionic iodinated contrast medium (Iopamidol, Braccosine, Shanghai, China; Omnipaque, GE healthcare, Shanghai, China) according to iodine concentration per body weight (.6 ml/kg) was injected followed by 30 ml saline with a 2-channel high pressure injector. Dynamic volume perfusion scanning was performed 7 seconds later after contrast injection. The one-stop scanning parameters were as following: 80 kV, 100 mAs, coverage of 160 mm, and layer thickness of .5 mm. IRE iterative reconstruction was used.

Ninteen phases with total of 6080 frames of whole brain dynamic volume data were collected. The original data of 6080 images (320 images of each volume with layer thickness of .5 mm) were transferred to the workstation (Vitrea; Canon) for postprocessing, and the 4D CTA images were acquired based on the original images. Meanwhile, arterial phase was selected from the 19 phases to generate images of single-phase CTA for each patient.

Collateral Circulation Scoring

Collateral Circulation Scoring on sCTA

On sCTA, the collaterals were graded with a 4-point grading system proposed by Tan et al.[12] In short, collateral scores were determined according to the following rules: 0 score indicated absent collateral flow compared to the normal side; 1 score indicated poor collateral flow (<50% flow compared to the normal side); 2 scores indicated intermediate collateral flow (between 50% and 100% flow compared to the normal side); 3 scores indicated good collateral flow (100% flow compared to the normal side). Patients were divided into poor collateral circulation group (0-1 scores) and good collateral circulation group (2-3 scores).

Modified Collateral Circulation Scoring System on 4D CTA

On 4D CTA, 19 phases were used to obtain information about extent of collateral circulation. In this study, a more appropriate grading system simulated modified ASITN/SIR collateral circulation scoring system combined with the grading system of Tan et al.[12,13] The collateral vessels were scaled into 0-4 along the time shaft: 0 score indicated no or few collateral vessels (<50% flow of the normal side) in ischemic area in any phase; 1 score indicated partial collateral vessels (between 50% and 100% flow of the normal side) were revealed until late venous phase; 2 scores indicated partial collateral vessels (between 50%

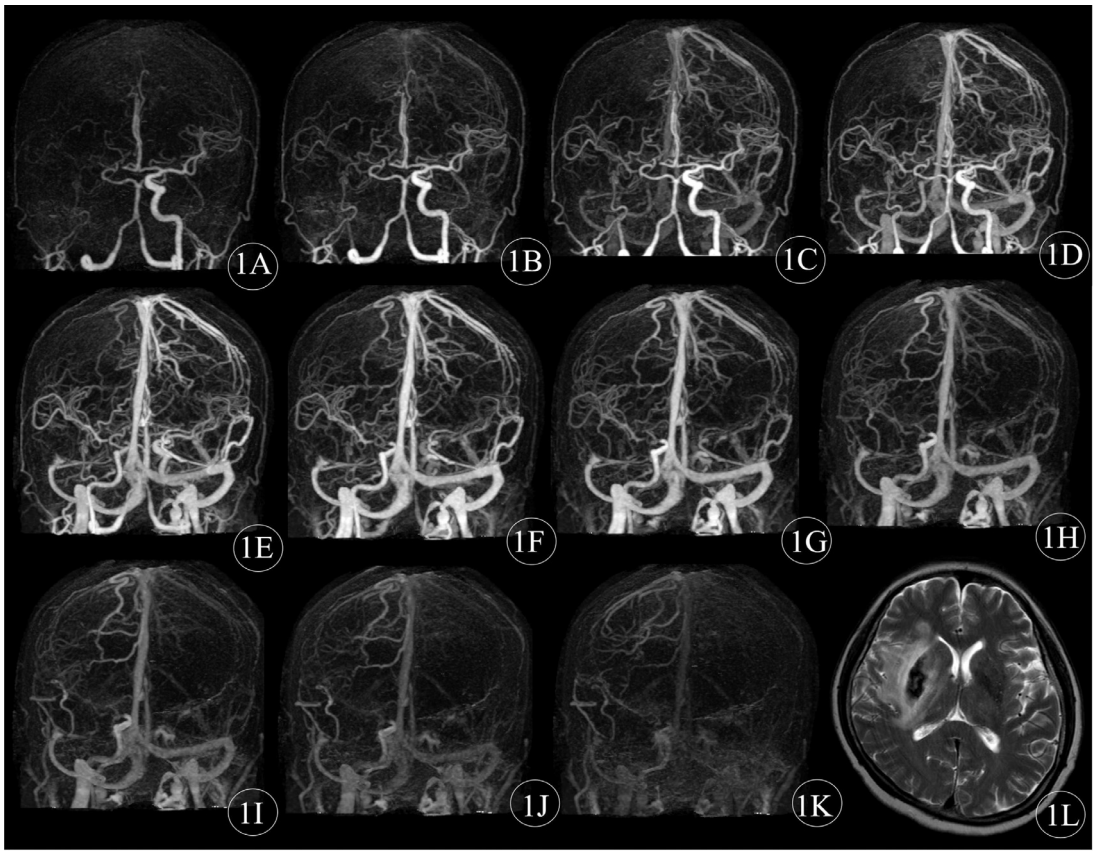

Figure 1. *Good collateral case. One 68-year-old female patient suddenly suffered from deviated mouth, inarticulate speech and inability to lift left upper limb for 6 hours. She had an initial NIHSS score of 15 and a mRS score of 1 after 3 months. 4D CTA (1A-1B) showed occlusion of the whole right internal carotid artery (ICA) and right middle cerebral artery (MCA), but on delayed phase images (1C – 1H), the majority of the right ICA was well developed. Thus, the patient got a 4D CTA collateral circulation score of 3, and a sCTA (1B) collateral circulation score of 1. The T2WI on day 6 (1L) showed acute infarct lesions with hemorrhage.*

and 100% flow of the normal side) were found before venous phase; 3 scores indicated complete collateral circulation (≥100% flow of the normal side) was found in the late venous phase (no matter partial collateral vessels was found before venous phase or not) (Fig 1); 4 scores indicated complete collateral circulation (≥100% flow of the normal side) was found before venous phase. According to the time density curve, venous phase was defined as the peak of the venous curve, late venous phase was defined as the phases after the peak of the venous curve (Fig 2). All the patients were divided into 2 groups according to collateral circulation scores, namely, poor collateral circulation (0-2 scores), and good collateral circulation (3-4 scores).

Endovascular Procedures

In general, all procedures were performed under conscious sedation via the right femoral artery approach. Thrombectomy with Solitaire AB (Medtronic, Dublin, Ireland) retrievable stents was our first-line choice. An 8-French guide catheter was firstly placed in the ipsilateral internal carotid artery. And then, a microcatheter (usually

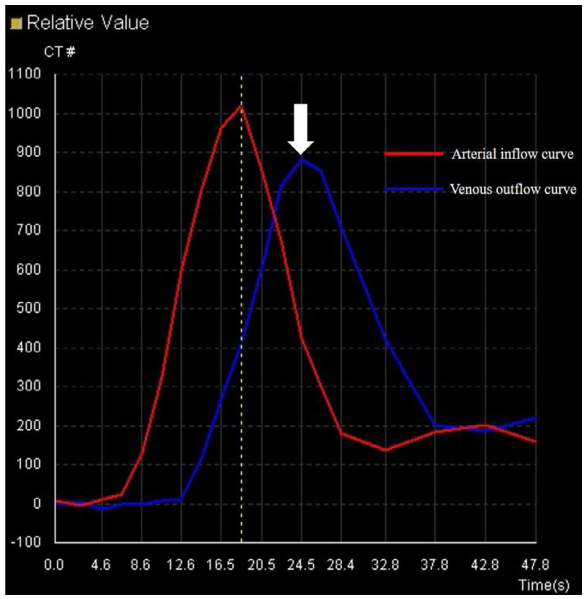

Figure 2. *The graph shows the time-density dynamic distribution curve. The horizontal axis is the time axis, the vertical axis is the CT value. The peak value of the venous curve indicated by the white arrow is the venous phase, and the area after the peak of the venous curve is the late venous.*

with Rebar 18, Medtronic) was navigated to the clot. After that, a Solitaire device was delivered through the microcatheter to cover the thrombus. A control angiogram was performed to confirm the flow status, and the retriever stent was released for about 5 minutes, then, the stent and the microcatheter were taken out together, and a control angiogram was performed to determine whether successful recanalization (defined as modified Thrombolysis In Cerebral Ischemia [mTICI] grade ≥ 2b) was achieved. If necessary, the same procedure would be repeated 2-3 times. In some cases, a large-bore aspiration catheter (ACE, Penumbra, CA), a rescue strategy with balloon angioplasty or Solitaire stent would be performed to achieve better perfusion.

Clinical and Imaging Evaluation

National Institutes of Health Stroke Scale (NIHSS) score at baseline was collected. The mRS score was used to evaluate the patients' functional outcome. The mRS scores equal or less than 2 indicated good prognosis, while the mRS scores ranged from 3 to 6 indicated poor prognosis. If patients died during follow-up, the score was recorded as 6.

The low density area on CT or high signal area on MR T2WI or DWI after 3-7 days was considered as the final infarction volume.

Statistical Analysis

SPSS 22.0 software was used for statistical analysis. Firstly, the normality test was performed on the measurement data. The data consistent with normal distribution was expressed as mean ± standard deviation, and the independent sample *t* test was used for comparison; the data inconsistent with normal distribution was expressed as median and quartile, and Mann-Whitney *U* test was used for comparison. The count data was expressed as frequency and percentage, and Person chi-square test was used. When the *P* value was less than .05 in univariate analysis, the corresponding data was entered into the multivariate logistic regression model, which was used for screening the affecting factors of poor prognosis. The receiver operating characteristic curve was used for evaluating the collateral circulation scoring predicting the sensitivity and specificity of poor outcome. This study is a 2-tailed test, and *P* less than .05 was considered statistically significant.

Result

Study Population

Totally 34 patients were enrolled in this study including 19 males (55.9%) and 15 females (44.1%). The patients aged from 41 to 95 years old, with the mean age of (71.1 ± 11.5) years old. The mean baseline ASPECTS was 6.6 ± 2.5. The median of baseline NIHSS score was 12.0 (interquartile range [IQR], 7.0-16.3). The median time from symptom onset to imaging was 170 minutes (IQR, 86.5-275.5). All the 34 patients underwent endovascular interventional treatment, and 28 of them obtained successful vascular recanalization (the TICI classification was grade 2b to grade 3). The follow-up imaging examination showed that the median of infarction volume was 50.2 cm^3 (IQR, 5.7-98.5) (Table 1).

Association of Collateral Scores With Radiological and Clinical Outcome

In univariate analysis, patients with good prognosis showed the low baseline NIHSS scores, and significant higher 4D CTA collateral circulation scores (median = 3, $P < .001$) in comparison with those of poor outcome. In contrast, collateral status on sCTA between these 2 groups did not reach statistic significance (Table 1). In multivariate logistic regression analysis, 4D CTA collateral circulation score (odds ratio, .101, 95% confidence interval, .101-.924, P=.042) was an independent predictive factor of prognosis (Table 2). The receiver operating characteristic curve revealed that the sensitivity of 4D CTA collateral circulation score in predicting clinical prognosis was 76.9%, and the specificity was 90.0%. The area under curve was .936 (confidence interval: .751-.992, $P < .005$).

Clinical and Imaging Outcomes According to Collateral Circulation Scoring on 4D CTA and sCTA

The collateral circulation score was independently evaluated by 2 trained radiologists. Intraclass correlation coefficient for interrater agreement of sCTA collateral score and 4D CTA collateral score were .820 and .885, respectively. They reached an agreement through consultation when the evaluation results were inconsistent.

The patients were divided into 2 groups according to the collateral circulation score on sCTA, including 9 cases (26.5%) with good collateral circulation (the collateral circulation scores of 2-3) and 25 cases (73.5%) with poor collateral circulation (the collateral circulation scores of 0-1). The patients with higher collateral circulation score had higher ASPECTS score and better prognosis when compared with those with low collateral circulation score ($P < .05$), but other data did not reach statistic significance.

On 4D CTA, the patients were divided into 2 groups according to the collateral circulation score, including 15 cases (44.1%) with good collateral status (the collateral circulation scores of 3-4) and 19 cases (55.9%) with poor collateral status (the collateral circulation scores of 0-2). The patients with higher collateral circulation score had lower baseline NIHSS scores, smaller baseline infarct volume, higher ASPECTS scores, and longer interval from symptom onset to imaging examination when compared with

Table 1. *Univariate comparison for baseline clinical and imaging data*

	Total	Good outcome (mRS score, 0-2)	Poor outcome (mRS score, 3-6)	*P*
	(n = 34)	(n = 14)	(n = 20)	
Age (mean ± SD), years	71.1 ± 11.5	67.1 ± 12.2	73.0 ± 11.2	.156
Female, n (%)	15 (44.1)	6 (42.9)	9 (45.0)	.901
Hypertension, n (%)	25 (73.5)	9 (64.3)	16 (80.0)	.307
Diabetes mellitus, n (%)	9 (26.4)	2 (14.3)	7 (35.0)	.178
Atrial fibrillation, n (%)	17 (50.0)	7 (50.0)	10 (50.0)	1.000
Hyperlipidemia, n (%)	16 (47.1)	7 (50.0)	9 (45.0)	.774
Myocardial infarction, n (%)	11 (32.3)	6 (42.9)	5 (25.0)	.273
Smoking, n (%)	9 (26.5)	2 (14.3)	7 (35.0)	.341
Peripheral vascular disease, n (%)	2 (5.9)	1 (7.1)	1 (5.0)	.794
Previous ischemic stroke, n (%)	5 (14.7)	1 (7.1)	4 (20.0)	.298
Previous antiplatelet use, n (%)	4 (11.8)	0 (.0)	4 (20.0)	.075
Site of occlusion, n (%)				.201
ICA	15 (44.1)	8 (57.1)	7 (35.0)	
MCA	19 (55.8)	6 (42.9)	13 (65.0)	
Recanalization, n (%)	28 (82.4)	14 (100.0)	14 (70.0)	.072
Time (onset to imaging) (median) (IQR)(min)	170.0 (86.5-275.5)	202.5 (90.0-263.3)	125.0 (65.0-286.5)	.089
Final infarct volume (median) (IQR) (cm^3)	50.2 (5.7-98.5)	5.2 (2.0-27.0)	80.1 (51.9-163.5)	.000
Baseline ASPECTS (mean ± SD)	6.6 ± 2.5	7.9 ± 1.7	5.6 ± 2.5	.005
Baseline NIHSS (median)(IQR)	12.0 (7.0-16.3)	9.0 (5.8-12.8)	15.5 (9.3-18.8)	.005
4D CTA collateral scores (median) (IQR)	2.0 (1.0-3.0)	3.0 (3.0-4.0)	1.0 (1.0-2.0)	.000
sCTA collateral scores (median) (IQR)	1.0 (.0-2.0)	1.0 (1.0-2.0)	.0 (.0-1.3)	.214

ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; SD, standard deviation; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; MCA, middle cerebral artery.

those with low collateral circulation score (all, $P < .05$). Meanwhile, the patients with higher collateral circulation score had a higher proportion of good prognosis (80.0% versus 10.5%, $P < .001$). Within the group of good collaterals, the proportion of good outcome was higher in the patients who had effective vascular recanalization than those who did not (92.3% versus .0%, $P = .029$), whereas, within the group of poor collaterals, there was no statistic difference of outcome between the patients with and without effective recanalization (13.3% versus 0%, $P = 1.000$) (Fig 3).

Interestingly, 6 patients were defined poor collateral circulation on sCTA, but good collateral on 4D CTA. Among these 6 people, 5 (83.3%) of them had good outcome (mRS score < 3) (Table 3; Fig 1).

Table 2. *Multivariate analysis of predictors of poor functional outcome*

	OR	95%CI	*P*
Final infarct volume	1.065	.963-1.179	.222
Baseline ASPECTS	.655	.373-4.806	.655
Baseline NIHSS	1.235	.901-1.692	.189
Collateral scores on 4D CTA	.101	.011-.924	.042

ASPECTS, Alberta Stroke Program Early CT Score; CI, confidence interval; OR, odd ratio; NIHSS: National Institutes of Health Stroke Scale.

Discussion

Previous studies have reported that patients with good collateral circulation obtained more benefits from EVT than those with poor collateral circulation, and our results

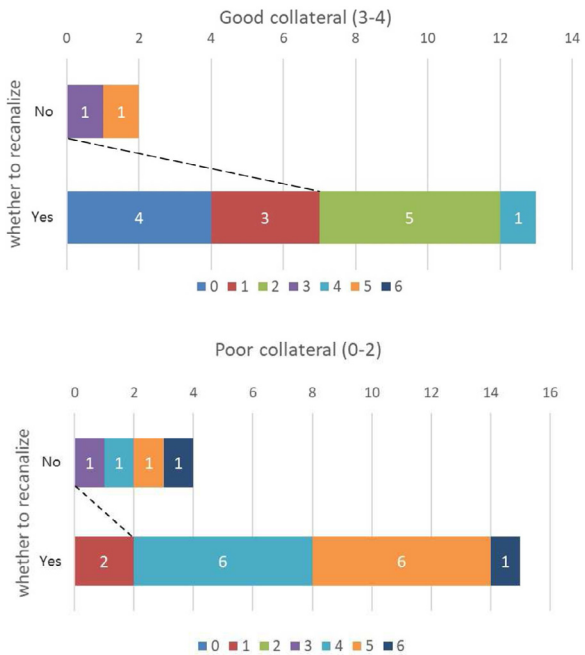

Figure 3. *Clinical outcome measured on mRS stratified by 4D CTA collateral score and recanalization.*

Table 3. *Clinical and radiological outcomes stratified by collateral score*

	4D CTA			sCTA		
	Poor collaterals (score, 0-2) (n = 19)	Good collaterals (score, 3-4) (n = 15)	*P*	Poor collaterals (socre,0-1) (n = 25)	Good collaterals (score, 2-3) (n = 9)	*P*
Final infarct volume (median) (IQR) (cm^3)	85.1 (50.4-163.7)	13.6 (3.7-45.2)	.002	44.4 (4.9-80.1)	71.7 (33.1-174.4)	.089
Time (Onset to imaging) (median) (IQR) (min)	120.0 (63.0-230.0)	241.0 (90.0-300.0)	.040	162.0 (72.0-263.0)	178.0 (105.0-330.0)	.241
Baseline NIHSS (median) (IQR)	16.0 (9.0-19.0)	11.0 (6.0-12.0)	.013	11.0 (7.0-16.0)	15.0 (9.0-19.5)	.177
Baseline ASPECTS (mean ± SD)	5.4 ± 2.5	7.9 ± 1.6	.003	7.3 ± 2.3	4.6 ± 1.9	.003
Good outcome at 3 months, n (%)	2 (10.5%)	12 (80.0%)	<.001	7 (28.0%)	7 (77.8%)	.017
Recanalization, n (%)	15 (78.9%)	13 (86.7%)	.558	21 (84.0%)	7 (77.8%)	.675

ASPECTS, Alberta Stroke Program Early CT Score; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation.

are in agreement with these reports.[14,15] But we scored the collateral circulation based on both 4D CTA and sCTA. Interestingly, we found that good collateral circulation on 4D CTA rather than sCTA was an independent predictive factor for prognosis in the patients with acute anterior circulation vascular occlusion who underwent EVT.

Our result illustrated that 4D CTA could evaluate collateral circulation more accurately. In our series, collateral status assessed with 4D CTA was different from that with sCTA. The collateral circulations in 6 patients were defined poor on sCTA, but good on 4D CTA. Among these 6 patients, 5 (83.3%) had good outcome. Compared with sCTA, 4D CTA is a better indicator in prognosis and collateral condition. This was due to pathophysiology status, the display of collateral vessels was usually delayed (after artery phase), and sCTA shows vessels only in arterial phase, so sCTA may underestimate the degree of collateral circulation.[16] The temporal resolution and spatial resolution of 4D CTA were high enough to visualize the angiographic information dynamically from arterial phase to venous phase, and clearly show the collateral blood flow, thus achieving the DSA-like effect.[11] We evaluated the collateral blood vessels using 4D CTA-based modified ASITN/SIR collateral circulation scoring system similar to DSA collateral circulation scoring system. Furthermore, the 4D CTA images were directly from CTP original data, which provided additional cerebral hemodynamic information without additional scan.[17] Hence, 4D CTA-based collateral grading system comprehensively evaluated the range of collateral vessels, and benefitted the patients.

Previous studies showed small infarction core, good collateral circulation, and rapid EVT could improve the functional prognosis of the acute ischemic patients.[4,14,18,19] In agreement with these studies, our results indicated that the status of collateral vessels on 4D CTA was correlated with the prognosis of stroke patients undergoing endovascular interventional treatment, and it was an independent predictive factor of prognosis. We had baseline ASPECTS of 7.9 ± 1.7 for good outcome group and 5.6 ± 2.5 for poor outcome group. That means the primarily infarct size is no larger than 50 ml for the good outcome group and no larger than 70 ml for the poor outcome group, but the patients with good collateral status obtained more benefits from vascular recanalization than those with poor collateral status. However, 3 patients with good collateral circulation had poor prognosis in our study, the results may be related to multiple factors, such as age and previous medical history. Two of these 3 patients (84 years old and 75 years old) had no successful vascular recanalization, and 1 patient had a history of aplastic anemia (61 years old).

Furthermore, we found that patients with good collateral circulation had longer interval from symptom onset to imaging, and this may be induced by several reasons. Patients with good collateral circulation would have mild symptoms and late brain tissue infarct. Prolonged survival time of some brain tissues is attributed to the compensatory effect of collateral vessels, which could prevent or delay permanent ischemic neuronal damage.[20,21] Recent studies had demonstrated that the time window of EVT could be extended to 16 hours and 24 hours, respectively.[18,22] Based on the results of our study, we believe that the treatment time window of acute ischemic stroke patients may change individually due to their underlying ischemic compensatory conditions (including collateral blood flow). Therefore, confirming the status of collateral vessels with our collateral grading system could help to determine the treatment strategies, especially for those patients who could undergo endovascular interventional treatment.

There are some limitations in this study. Firstly, the sample size of this study is small. As this is a preliminary and single-center study, the sample size for enrollment is small. We did not find statistic difference on collateral status between patients with good and poor outcomes shown by sCTA, this result may be somehow due to the small sample size. We need a larger population in the future to clarify the advantages of 4D CTA in the

assessment of collateral circulation. Secondly, follow-up with CT or MRI may lead to the heterogeneity of volume measurement. Thirdly, DSA is the gold standard, but we did not use DSA to validate the modified collateral circulation scoring system. One of the reasons is all the patients included in this study were the patients with acute ischemic stroke. Due to the limited treatment time window, intravascular therapy was performed immediately and directly to the target after the identification of the responsible vessels based on multimodality CT examination. We did not use DSA to check the whole-brain vascular status. Another reason is that the collateral grading is generally used for prognosis evaluation, while in this study, DSA was used for intravascular therapy, that is why we did not use DSA to validate scoring system on 4D CTA.

Conclusion

4D CTA is better than sCTA and 4D CTA-based modified collateral circulation scoring system in this study could help to predict the clinical prognosis of patients with acute ischemic stroke and may help to make medical decisions, especially for the patients who would undergo endovascular interventional treatment. The treatment time window may be extended individually for patients with good collateral vessels, who may obtain more benefits from EVT.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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None.

Author Contributions

RYC collected studies, collected, cleaned, and analyzed the data, and drafted and revised the paper. PQ collected studies, collected and cleaned the data, and drafted and revised paper.

YHL monitored the data collection and analyzed the data. XXM and ZYS revised the draft paper. JC designed the study, monitored the studies collection and data collection, analyzed the paper, and drafted and revised the paper. She is the guarantor.

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