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ABSTRACT

BACKGROUND AND PURPOSE: Patients with stroke etiology of large-artery atherosclerosis were thought to have better collateral circulation compared with patients with other stroke etiologies. We aimed to investigate the association between stroke etiology and collateral circulation with a new quantitative collateral assessment method.

MATERIALS AND METHODS: This retrospective study reviewed data from consecutive patients with proximal anterior artery occlusion who underwent CTP before reperfusion therapy. CBF maps were derived from CTP. A new indicator, maximum CBF of collateral vessels within the Sylvian fissure ($cCBF_{max}$), was applied to quantitatively assess the collateral status. The relationship between collateral status and stroke etiology was investigated.

RESULTS: A total of 296 patients were finally analyzed. The median $cCBF_{max}$ was significantly higher in patients with large-artery atherosclerosis than in those without it (92 [interquartile range, 65–123] mL/100 g/min versus 62 [interquartile range, 46–82] mL/100 g/min; $P < .001$). Multivariable analysis revealed that a higher $cCBF_{max}$ score was independently associated with large-artery atherosclerosis etiology (OR, 1.010; 95% CI, 1.002–1.018; $P = .017$) after adjustment. The area under the curve, sensitivity, and specificity of the final model in predicting the etiology of large-artery atherosclerosis were 0.870, 89.7%, and 75.2%, respectively.

CONCLUSIONS: Patients with large-artery atherosclerosis had a more adequate collateral perfusion supply with the new quantitative collateral assessment. The new quantitative collateral measurement might contribute to the prediction of stroke etiology in the acute clinical scenario for patients with acute ischemic stroke.

ABBREVIATIONS: AIS = acute ischemic stroke; AUC = area under the curve; $cCBF_{max}$ = maximum CBF of collateral vessels within the Sylvian fissure; CE = cardioembolism; IQR = interquartile range; LAA = large-artery atherosclerosis; ROC = receiver operating characteristic

Intracranial large-artery occlusion is a common cause of acute ischemic stroke (AIS), which often leads to a poor prognosis.[1,2] Endovascular therapy could greatly improve the recanalization rate of the occluded arteries and has been recommended as a standard therapy for patients with acute proximal large-artery occlusion.[3] The success of endovascular therapy was influenced by the stroke etiology.[4,5] The secondary prevention strategies would also depend on stroke etiologies. Therefore, prediction of stroke etiology might provide potentially pivotal information for neurologists and neurointerventionists to guide management in the acute clinical scenario and enable early initiation of appropriate secondary prevention.

Collateral circulation in patients with AIS can maintain perfusion and may influence the timing of ischemic brain tissue—that is, collateral circulation contributes to improving the prognosis of patients with ischemic stroke. Several clinical trials such as the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) and Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial (EXTEND-IA) revealed that collateral assessment in the acute clinical stage could help select optimal candidates for reperfusion therapy.[6,7] Large-artery atherosclerosis (LAA) and cardioembolism (CE) are the 2 common causes of intracranial large-artery occlusion. It

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has been assumed that atherosclerosis develops chronically, which might lead to better cerebral collateral flow. However, previous studies have presented inconsistent results on the association between stroke etiology and collateral circulation in patients with AIS.[8,9]

Most collateral assessments used in previous research were qualitative collateral grading methods. A qualitative collateral method based on the extent of the reconstitution of the MCA up to the distal end of its occlusion via leptomeningeal collaterals has been proposed before.[10] Recently, we developed a new technique for quantitative assessment of collateral perfusion to the distal end of the occlusion within the Sylvian fissure with CTP.[11] This method was found to be reliable and was also superior to existing qualitative indices of collateral flow.[11] Thus, we aimed to explore the association between stroke etiology and collateral circulation with the new quantitative collateral assessment method.

MATERIALS AND METHODS

Ethics Statement

This protocol was approved by the human ethics committee of the Second Affiliated Hospital of Zhejiang University, School of Medicine. The investigations were conducted according to the principles expressed in the Declaration of Helsinki. Written informed consent was obtained from all patients.

Patients

This retrospective study reviewed our prospectively collected database, Comparison Influence to Prognosis of CTP and MRP in AIS Patients; ClinicalTrials.gov identifier: NCT03367286 (CIPPIS), for consecutive patients with AIS who received intravenous thrombolysis with or without mechanical thrombectomy from May 2009 to July 2018. We then enrolled patients who met the following criteria: 1) They had a diagnosis of AIS confirmed by DWI or CT, 2) underwent CTP within 8 hours after stroke onset, and 3) had occlusion of the MCA-M1 segment with or without the ICA confirmed on reconstructed CTA images from CTP. Patients who had poor image quality due to motion artifacts or incomplete images were excluded. Some of the patients were reported in our previous research based on the database.[11]

Clinical Data

Baseline clinical variables were recorded, including demographics, risk factors (smoking, hypertension, diabetes mellitus, hyperlipidemia, or a history of stroke/TIA or atrial fibrillation), prior antiplatelet use, onset-to-needle time, baseline NIHSS score, and radiologic data. The stroke etiologies were determined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) to categorize the etiology into LAA, CE, undetermined etiology, and another determined cause.[12] The protocol for the work-up of the TOAST criteria is shown in the Online Supplemental Data. The stroke etiology was determined by 2 experienced neurologists according to the TOAST criteria, with rater discrepancies settled by consensus discussion before quantitative collateral measurement.

Baseline Imaging Protocol

All patients underwent baseline CTP on a 64-section CT scanner (Somatom Definition Flash; Siemens), including noncontrast (120 kV, 320 mA, contiguous 5-mm axial sections, matrix of 512 × 512, FOV of 240 × 240 mm^2, 7-second acquisition time, 25 slices) and volumetric perfusion (100 mm in the z-axis, 4-second delay after the start of contrast medium injection, 74.5-second total imaging duration, 80 kV, 120 mA, 1.5-mm section thickness, 32 × 1.2 mm collimation, matrix of 512 × 512, FOV of 240 × 240 mm^2, 2574 slices) scanned in accordance with our stroke imaging protocol.[11]

Imaging Analysis

Pretreatment relative CBF of <30% at CTP was calculated for the baseline infarct core volume.[13] A threshold of time-to-peak of the residual function of >6 seconds was used for volumetric measurement of the pretreatment hypoperfused volume on CTP.[14] The occlusion location was determined on reconstructed CTA derived from CTP. According to the TAN collateral score, collaterals were classified as good if they were seen in ≥50% of the MCA territory and poor in <50% of the territory on CTA.[15] The circle of Willis variants were assessed on CTA according to a previously reported method (type 1: a missing or hypoplastic ipsilateral anterior cerebral artery A1 segment; type 2: a missing or hypoplastic contralateral A1 segment; type 3: a fetal ipsilateral posterior cerebral artery; type 4: an impaired ipsilateral posterior circulation including a missing or hypoplastic ipsilateral the communicating posterior artery or P1 segments).[16]

Quantitative Collateral Assessment

The arterial input function and venous outflow function from the MCA territory and the superior sagittal sinus of the nonischemic hemisphere were automatically selected by MIStar (Version 3.2; Apollo Medical Imaging Technology) and manually adjusted if necessary. Voxel-based quantitative analysis was performed using the MIStar software.

In this study, we performed a quantitative collateral assessment as described previously.[11] To achieve the quantitative collateral assessment, the image sections visualized to contain the visible vessels within the ipsilateral Sylvian fissure on temporally fused MIP CTP images with 10-mm-thick slabs were identified and then outlined by manually drawing the ROI on each image section (Fig 1). For patients without visible vessels within the Sylvian fissure, the ROI was drawn in an area where one would expect to see vessels. Each ROI was then copied to the corresponding CBF map derived from CTP images with a 10-mm-thick MIP. The highest CBF value from all sections was recorded as the maximum CBF of collateral vessels within the Sylvian fissure ($cCBF_{max}$).

Statistical Analysis

Continuous variables were reported as medians with interquartile range (IQR), and categoric variables were reported as proportions. For categoric variables, the χ^2 test was used to compare differences among groups. For continuous variables, the Mann-Whitney *U* test was used to compare the difference between the 2 groups. Receiver operating characteristic (ROC) analyses were performed to assess the discriminative ability, and the area under the curve (AUC) was calculated. Optimal cutoff values were derived from ROC curves, and sensitivity and specificity were calculated on the

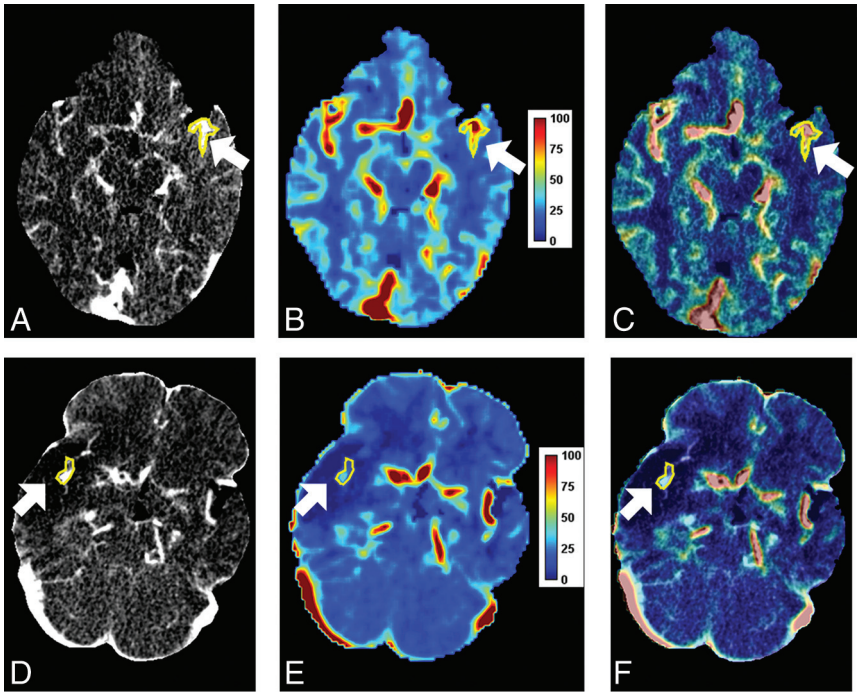

FIG 1. Graphic representation of the quantitative collateral measurement of a patient with LAA with a $cCBF_{max}$ value of 123 mL/100 g/min (*A–C*) and a patient without LAA with a $cCBF_{max}$ value of 51 mL/100 g/min (*D–F*). The patient with LAA had occlusion of the left M1 segment and ICA (*A*). The patient without LAA had occlusion of the right M1 segment of the MCA (*D*). ROIs (*white arrows*) were drawn by outlining the entire visible vessels within the ipsilateral Sylvian fissure on temporally fused MIP CTP images, each ROI was then copied to the corresponding CBF map derived from CTP images with a 10-mm-thick MIP, and the highest CBF value from all sections was recorded as $cCBF_{max}$ (*B* and *E*). The relatively high CBF regions in the ipsilateral Sylvian fissure overlapped well with the collateral vessels (*C* and *F*).

basis of these best cutoff values. The variables with P values $< .1$ on univariable analysis were included in the multivariable models. Multivariable logistic regression with the stepwise method was performed to assess independent predictors of stroke etiology. All statistical analyses were performed using SPSS, Version 22.0 (IBM). $P < .05$ was considered statistically significant.

RESULTS

During the study, 314 patients met the inclusion criteria; then, 18 patients were excluded due to insufficient imaging quality ($n = 14$) and incomplete images ($n = 4$). A total of 296 patients were finally analyzed, with a median age of 73 (IQR, 62–80) years, a median NIHSS score of 14 (IQR, 10–18), and a median onset-to-needle time of 221 (IQR, 149–302) minutes (Online Supplemental Data). According to the TOAST criteria, the stroke etiologies of these patients were CE ($n = 157$), LAA ($n = 58$), undetermined etiology ($n = 80$), and other determined cause ($n = 1$). The median $cCBF_{max}$ was 67 (IQR, 47–91) mL/100 g/min. The median ROI sizes of the patients without visible vessels within the Sylvian fissure were not significantly different compared with those of the patients with visible vessels (1.7 [IQR, 1.2–2.2] mL versus 1.9 [IQR, 1.3–2.5] mL, $P = .576$).

The $cCBF_{max}$ was negatively associated with age ($\rho = -0.262$, $P < .001$), baseline NIHSS score ($\rho = -0.396$, $P < .001$), baseline infarct core volume ($\rho = -0.531$, $P < .001$), and baseline hypoperfusion volume ($\rho = -0.386$, $P < .001$). The median $cCBF_{max}$ was significantly lower in patients with atrial fibrillation than in those without atrial fibrillation (61 [IQR, 42–80] mL/100 g/min versus 71 [IQR, 51–108] mL/100 g/min; $P < .001$) and lower in patients with hypertension than in those without hypertension (63 [IQR, 46–87] mL/100 g/min versus 70 [IQR, 51–96] mL/100 g/min, $P = .046$). There was no significant association between onset-to-imaging time and $cCBF_{max}$ ($\rho = 0.019$, $P = .758$). Similar findings were observed in the LAA group ($\rho = 0.069$, $P = .619$), CE group ($\rho = 0.017$, $P = .838$), or the undetermined etiology group ($\rho = -0.112$, $P = .343$). The locations of the occlusions were significantly associated with median $cCBF_{max}$ scores (57 [IQR, 37–80] mL/100 g/min versus 67 [IQR, 51–87] mL/100 g/min versus 82 [IQR, 54–135] mL/100 g/min for M1+ICA and proximal M1 and distal M1 segments; $P = .001$). We found a trend toward the association between the circle of Willis variants and $cCBF_{max}$ scores ($P = .054$).

In our study, the patients were then dichotomized as the LAA group ($n = 58$) and the non-LAA group ($n = 238$) (Online Supplemental Data). Patients in the LAA group were significantly younger ($P < .001$) and more often male ($P < .001$) and had a higher proportion of smokers ($P < .001$) compared with those in non-LAA group. Patients in LAA group were inclined to have higher rates of diabetes mellitus ($P = .056$). Meanwhile, patients with LAA were found to have lower median baseline NIHSS scores (9 [IQR, 5–13] versus 15 [IQR, 11–18]; $P < .001$) and lower median baseline infarct core volumes (43.1 [IQR, 11.9–78.5] mL versus 59.5 [IQR, 31.4–108.5] mL; $P = .003$), respectively. When collaterals were dichotomized into good and poor according to the TAN score, patients with LAA more often had significantly good collaterals than the patients without LAA (74.1% versus 58.8%, $P = .031$). The sensitivity and specificity of good collaterals determined by the TAN score for predicting LAA were 41.2% and 74.1%, respectively.

Sample illustrations of the quantitative collateral measurement for patients with and without LAA are shown in Fig 1. The median $cCBF_{max}$ score was significantly higher in patients with LAA than in those without it (92 [IQR, 65–123] mL/100 g/min versus 62 [IQR, 46–82] mL/100 g/min; $P < .001$). The ROC analysis revealed an optimal cutoff $cCBF_{max}$ of 89 mL/100 g/min in predicting the LAA etiology from the other etiologies, and the AUC, sensitivity, and specificity were 0.691, 53.4%, and 80.7%, respectively (Fig 2*A*).

Then, age, sex, baseline NIHSS score, smoking, diabetes mellitus, baseline infarct core volume, and $cCBF_{max}$ scores were included

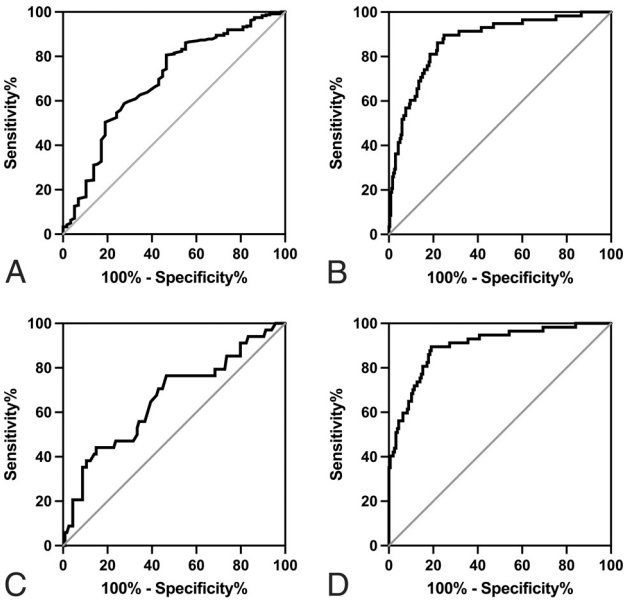

FIG 2. ROC curves (*black line*) of $cCBF_{max}$ in differentiating an LAA etiology from other etiologies (*A*) and from CE (*C*). The ROC curves generated from binary logistic regression models in distinguishing LAA etiology from other etiologies (*B*) and from CE (*D*).

in multivariable stepwise regression analysis. It was revealed that higher $cCBF_{max}$ (OR, 1.010; 95% CI, 1.002–1.018; $P = .017$), younger age (OR, 0.964; 95% CI, 0.940–0.990; $P = .007$), male sex (OR, 10.584; 95% CI, 3.696–30.311; $P < .001$), and lower baseline NIHSS scores (OR, 0.878; 95% CI, 0.821–0.939; $P < .001$) were independently associated with LAA etiology (Online Supplemental Data). The ROC curve generated from the final model in distinguishing the LAA etiology from other etiologies revealed that the AUC, sensitivity, and specificity were 0.870, 89.7% and 75.2%, respectively (Fig 2*B*).

Among patients with the 2 commonly determined etiologies, there were 58 patients with LAA and 157 with CE. The median $cCBF_{max}$ score was significantly higher in patients with LAA than in patients with CE (92 [IQR, 65–123] mL/100 g/min versus 60 [IQR, 44–76] mL/100 g/min; $P < .001$). The optimal cutoff, AUC, sensitivity, and specificity of $cCBF_{max}$ in distinguishing LAA from CE were 89 mL/100 g/min, 0.728, 53.4%, and 87.3%, respectively (Fig 2*C*). Multivariable analysis showed that a higher $cCBF_{max}$ was independently associated with LAA etiology (OR, 1.025; 95% CI, 1.010–1.041; $P = .001$) after adjustment, shown in the Online Supplemental Data. The ROC curve generated from the model in distinguishing LAA from CE showed that AUC, sensitivity, and specificity were 0.921, 88.5%, and 85.6%, respectively (Fig 2*D*).

DISCUSSION

Prediction of stroke etiology is important-but-difficult in the acute stage. In this study, we found that patients with AIS with an LAA etiology might have a more extensive collateral circulation than patients with other etiologies. The new quantitative collateral measurement might contribute to the prediction of stroke etiology in the acute clinical scenario for patients with AIS.

Stroke with an LAA etiology has been associated with better collateral circulation. Guglielmi et al[17] found that patients with ischemic stroke due to cervical carotid atherosclerosis had better collateral circulation graded on a 4-point scale.[9] Hassler et al[9] showed that pre-existing carotid artery stenosis was associated with better collateral status by the TAN score.[8] Most collateral assessment methods used in those previous studies were qualitative-grading collateral methods. A systematic review revealed a wide variation in the methods of grading collateral circulation.[18] Previous studies indicated that quantitative assessment might minimize the observer subjectivity.[19-21]

Recently, we have developed a quantitative parameter of collateral status at CTP ($cCBF_{max}$), which compared favorably with existing qualitative metrics of collateral perfusion.[11] Thus, in the current study, we evaluated the differential value in stroke etiologies with this new quantitative collateral parameter. The proportions of LAA and CE in this study were similar to those in the previous studies.[9,17] A previous histologic study found that the features of the clots in patients with undetermined etiology were more like those of patients with cardiogenic thrombi.[22] Therefore, the patients were further dichotomized into LAA and non-LAA groups in the current study. Then, we found that patients with AIS with an LAA etiology had higher $cCBF_{max}$ values, indicating better collateral supply.

The exact mechanism for the better collateral supply of stroke with an LAA etiology is not totally clear. One possible mechanism might be that atherosclerosis developed chronically, possibly promoting cerebral collateral circulation. Previously, in rat models, it was found that improved cerebral collateral circulation was significantly associated with chronic cerebral hypoperfusion.[23] In patients with carotid artery stenosis, the collateral circulation was associated with carotid stenosis and increased with the degree of stenosis.[8,9] From a pathophysiologic perspective, in patients with carotid artery stenosis, an increased degree of stenosis and repeat arterio-arterial microembolism from carotid plaques might lead to recurrent focal cerebral tissue ischemia.[9,24] It was reported that chronic hypoperfusion was associated with better collateral circulation.[23] Collateral circulation could maintain perfusion, and greater collateral circulation might contribute to a better baseline condition such as a lower baseline NIHSS score and baseline infarct core volume.

Stroke etiology has a crucial role for clinicians involved in acute ischemic stroke management. Different devices and procedures were introduced for patients with different etiologies.[25] Patients with an LAA etiology more often had stent retriever refractoriness and some other complications; those patients were more likely to require adjunctive therapies.[4,5,26-28] Recently, CTP was increasingly performed before reperfusion therapy. On the basis of the CBF maps derived from CTP images, $cCBF_{max}$ could quantitatively assess the collateral status. Our results revealed that $cCBF_{max}$ might help to facilitate prediction of stroke etiology in the acute clinical stage. Therefore, 1 CTP scan could provide the quantitative information of infarct core volume, penumbra volume, and collateral circulation, which might contribute to the selection of the optimal candidates for reperfusion therapy, especially for those beyond the time window.

In our study, we found that the collateral circulation did not change with the time. A previous study found that collateral circulation might show a better response at later time windows—that is, the time window of clinical benefit might be longer if collateral circulation was maintained.[29] Besides, this quantitative collateral method might be helpful for management in patients with stroke with an unknown onset time. Future studies with a large sample size are needed to clarify the relationship between collaterals and time.

This study had some limitations. First, this was a retrospective study, which might have a potential risk of selection bias, though data were prospectively collected using a stroke registry protocol. Second, in this study, we included patients with proximal anterior artery occlusion; thus, the results were inapplicable to the patients with occlusion of small arteries or posterior circulation. Third, we did not include other imaging markers such as clot characteristics, and these might be related to stroke etiology. Further studies with a list of factors are needed to confirm our findings. Finally, the sample size of this study was modest. The prediction of this quantitative collateral method for stroke etiology should be investigated in a large sample size and randomized prospective clinical trials in the future.

CONCLUSIONS

On the basis of CBF maps derived from CTP images, quantitative assessment of $cCBF_{max}$ revealed that patients with LAA had more sufficient collateral perfusion supply to the ischemic brain tissue than patients with other stroke origins, which might contribute to prediction of stroke etiology in the acute clinical scenario and early initiation of appropriate secondary prevention.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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