

ORIGINAL RESEARCH

# Antegrade Blood Flow on 4-Dimensional Computed Tomography Angiography Predict Stroke Subtype in Patients With Acute Large Artery Occlusion

Meixia Zhang, MD\*; Zhicai Chen, MD\*; Jinjin Xu, MD; Xiaoxian Gong, MD; Feina Shi, MD; Min Lou , MD, PhD

**BACKGROUND:** The purpose of this study was to determine whether the presence of antegrade blood flow was related to stroke subtype in patients with acute intracranial large artery occlusion.

**METHODS AND RESULTS:** The prospectively collected data for consecutive patients who had occlusion of the unilateral M1 segment of the middle cerebral artery with or without internal carotid artery and received reperfusion therapy were retrospectively reviewed. Stroke causes were determined according to the Trial of ORG 10172 in Acute Stroke Treatment standard. We defined antegrade flow as early opacification at the distal interface of the clot with subsequent distal extension on 4-dimensional computed tomography angiography. A total of 387 large artery occlusion patients were analyzed (229 men and 158 women; mean age, 71±14 years), including 77 (19.9%) with large artery atherosclerosis (LAA), 206 (53.2%) with cardioembolism, and 104 (26.9%) with undetermined causes. Antegrade flow was found in 206 (53.2%) patients, and 181 (46.8%) presented with retrograde flow. The rate of antegrade flow was much higher in patients with LAA than in those with cardioembolism (85.7% versus 42.2%,  $P<0.001$ ). Multivariable logistic regression revealed that presence of antegrade flow was significantly associated with cause of LAA after adjusting for confounding factors, when setting cardioembolism as reference (odds ratio, 5.650; 95% confidence interval, 2.451–13.158;  $P<0.001$ ). The sensitivity, specificity, and positive and negative predictive values of the antegrade flow for predicting LAA were 43.1%, 91.5%, 85.7%, and 57.8%, respectively.

**CONCLUSIONS:** Using 4-dimensional computed tomography angiography, antegrade flow can be identified in more than half of acute anterior large artery occlusion patients and occurs more frequently in those with LAA as the cause of stroke.

**Key Words:** acute ischemic stroke ■ antegrade flow ■ computed tomography angiography ■ large artery occlusion ■ stroke cause

Intracranial large artery occlusion (LAO), which accounts for about one third of acute ischemic strokes (AISs), may cause severe disability and high mortality rates.<sup>1,2</sup> Endovascular therapy is the recommended treatment for patients with acute LAO patients, whereas clinical outcomes vary among individuals. Different devices and combined therapy have been introduced when treating patients with different causes. For example, presence of a truncal-site occlusion, indicating large artery atherosclerosis (LAA),

was associated with a lower chance of stent retriever success, and adjunctive therapies, such as stent placement, were more frequently required.<sup>3</sup> Rapid identification of the cause is thus crucial for emergent management.

On angiography, in some patients with acute LAO, slow opacification of antegrade contrast from the distal occlusion site, called antegrade blood flow, can still be observed by dynamic computed tomography angiography and digital subtraction angiography, but

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## CLINICAL PERSPECTIVE

### What Is New?

- More than half of the patients with acute ischemic stroke demonstrated antegrade flow permeating through complete arterial occlusion in the peak phase of 4-dimensional computed tomography angiography reconstructed from perfusion computed tomography.
- Presence of antegrade flow was significantly associated with large artery atherosclerosis as the cause of stroke.
- Rate of antegrade flow was much higher in patients with the large artery atherosclerosis subtype than in those with cardioembolism.

### What Are the Clinical Implications?

- Evaluating the antegrade flow on 4-dimensional computed tomography angiography images could help rapidly identify stroke subtype and provide alternatives to assist the decisionmaking about reperfusion therapy.

## Nonstandard Abbreviations and Acronyms

<b>4D-CTA</b>	4-dimensional computed tomography angiography
<b>AIS</b>	acute ischemic stroke
<b>CTA</b>	computed tomography angiography
<b>CTP</b>	computed tomography perfusion
<b>LAA</b>	large artery atherosclerosis
<b>LAO</b>	large artery occlusion
<b>NIHSS</b>	National Institutes of Health Stroke Scale

not traditional single-phase computed tomography angiography (CTA), which is actually different from retrograde collateral flow. Four-dimensional CTA (4D-CTA) reconstructed from perfusion computed tomography (CTP) was recently found to differentiate antegrade blood flow from retrograde collateral flow with high sensitivity and specificity.<sup>4</sup> Although studies have demonstrated the association between antegrade blood flow and increased chance of early vessel recanalization, it is not clear whether antegrade blood flow could indicate the stroke cause. Theoretically, the clot burden of LAA is often less than that of cardioembolism,<sup>5</sup> which makes it easier for contrast to penetrate through and form antegrade blood flow. Therefore, we hypothesized that the rate of antegrade blood flow would be higher in LAA patients, and therefore we tested it in acute LAO patients on 4D-CTA reconstructed from CTP.

## METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Study Design

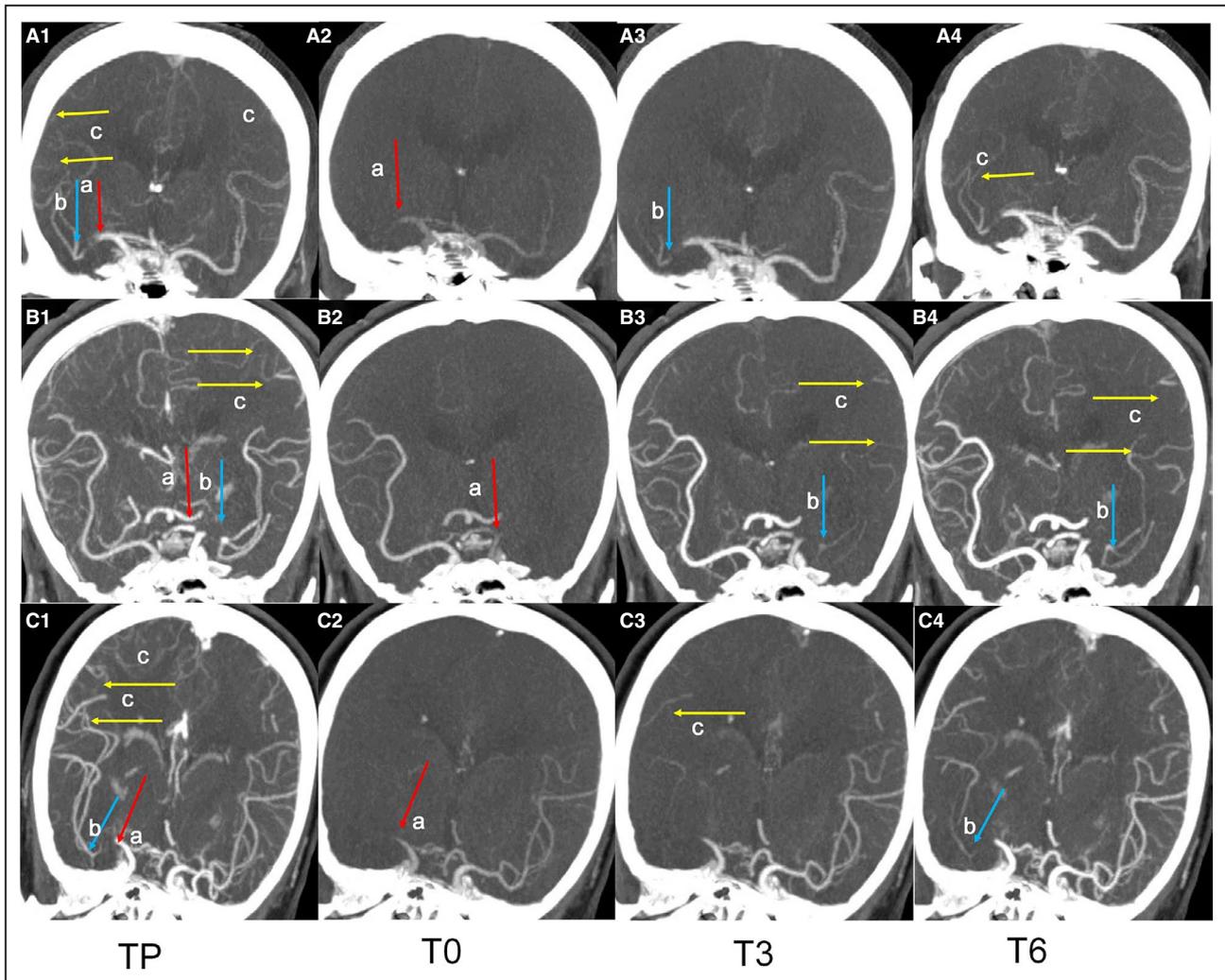
In this study we retrospectively reviewed our prospectively collected cohort for consecutive patients with AIS who received reperfusion therapy (intravenous thrombolysis with or without endovascular treatment) between June 2009 and April 2019. Patients with acute ischemic stroke underwent CT perfusion and noncontrast CT imaging before receiving reperfusion therapy, which was administered within 8 hours after the onset of stroke or last-known-well. Our study protocol was approved by the human ethics committee of The Second Affiliated Hospital of Zhejiang University. The clinical investigation was conducted according to the principles expressed in the Declaration of Helsinki. Written informed consent was obtained from all patients.

### Study Subjects and Clinical Data

We enrolled patients who: (1) underwent CTP within 8 hours after stroke onset or when last seen normal before reperfusion therapy, with CTP source images used to reconstruct 4D-CTA; (2) had unilateral occlusion of the M1 segment of the middle cerebral artery with or without internal carotid artery, which was confirmed during the peak artery phase of 4D-CTA; and (3) had AIS with cardioembolism, or LAA, or undetermined cause. Patients were excluded if they had poor-quality images because of motion artifacts, incomplete images, no blood flow beyond the occlusion site on imaging, or bilateral occlusion of the M1 segment of the middle cerebral artery.

Baseline clinical variables were recorded, including demographics (age and sex), risk factors (smoking, hypertension, diabetes mellitus, hyperlipidemia, homocysteinemia, coronary heart disease, a history of stroke/transient ischemic attack history, or atrial fibrillation), use of antiaggregants or anticoagulants, time from onset to imaging, baseline National Institutes of Health Stroke Scale (NIHSS) score, and laboratory and radiologic data.

Stroke causes were determined according to the Trial of Org 10172 in Acute Stroke Treatment.<sup>6</sup> Patients with cardiac disease with a potential for embolism and no evidence of stenosis >50% on relevant intracranial or extracranial large arteries were considered cardioembolism cases. LAA needed to have relevant artery of either significant (>50%) stenosis or occlusion presumably due to atherosclerosis, and no potential sources of cardiogenic embolism. Patients with both



**Figure.** Representative images of antegrade and retrograde flow.

From left to right, images show peak phase of 4D-CTA (TP), the moment at which point “a” appears (T0), 3 seconds after T0 (T3), and 6 seconds after T0 (T6), respectively, for 3 patients. For each peak phase of 4D-CTA (A1, B1, and C1), point “a” is set as the proximal occlusion site, point “b” as the distal occlusion site, and point “c” as the surrounding pial collaterals. Antegrade flow was defined when opacification of point “b” (A3) was earlier than point “c” (A4) in a patient with right occlusion of the M1 segment of middle cerebral artery, or when opacification of point “b” appeared at the same time as point “c” (B3 and B4) in a patient with left middle cerebral artery M1 occlusion. Retrograde flow was then defined when opacification of point “b” (C4) was later than point “c” (C3) in a patient with right occlusion of the M1 segment of the middle cerebral artery. 4D-CTA, 4-dimensional computed tomography angiography.

evidence of stenosis >50% and potential sources of cardiogenic embolism and those having neither of these were considered to have an undetermined cause.

### Image Parameters

CTP was performed on a 64-slice CT scanner (SOMATOM Definition Flash; Siemens Healthcare Sector, Forchheim, Germany), including noncontrast CT scan (120 kV, 320 mA, contiguous 5-mm axial slices, acquisition time 7 seconds) and volume CTP (100 mm for the z axis, 4-second delay after start of contrast medium injection, 74.5-second total imaging duration, 80 kV, 120 mA, slice thickness 1.5 mm,

collimation 32×1.2 mm). Volume CTP consisted of 26 consecutive spiral acquisitions of the brain. The 26 scans were divided into 4 categories: (1) 2 scans with a 3-second cycle time; (2) 15 scans with a 1.5-second cycle time; (3) 4 scans with a 3-second cycle time; and (4) 5 scans with a 6-second cycle time. Axial slice coverage was 150 mm. A 60-mL bolus of contrast medium (Iopamidol; Braccosine, Shanghai, China) in a single injection was used at a flow rate of 6 mL/s, followed by a 20-mL saline chaser at 6 mL/s.

### Imaging Assessment

Acute arterial occlusion was determined by the invisibility of the artery in the peak phase of 4D-CTA with

**Table 1. Comparison of Characteristics Between Antegrade and Retrograde Flow Groups**

	Retrograde Flow Group (n=181)	Antegrade Flow Group (n=206)	P Value
Female, %	81 (44.8)	77 (37.4)	0.141
Age, y	72±13	68±14	0.003
Coronary heart disease, %	24 (13.3)	19 (9.2)	0.207
Smoking, %	42 (23.2)	69 (33.5)	0.026
Atrial fibrillation, %	115 (63.5)	84 (40.8)	<0.001
Previous stroke or TIA history, %	29 (16.0)	42 (20.4)	0.268
Hypertension, %	113 (62.4)	124 (60.2)	0.652
Diabetes mellitus, %	25 (13.8)	49 (23.8)	0.013
Homocysteinemia, %	24 (13.3)	34 (16.5)	0.372
Hyperlipidemia, %	61 (33.7)	83 (40.3)	0.181
Antiaggregants, %	38 (21.0)	43 (20.9)	0.977
Anticoagulants, %* (n=372)	17 (9.8)	16 (8.0)	0.546
Cause of stroke			<0.001
Cardioembolism, %	119 (65.7)	87 (42.2)	
Large arterial atherosclerosis, %	11 (6.1)	66 (32.0)	
Undetermined cause, %	51 (28.2)	53 (25.7)	
Baseline systolic blood pressure, mm Hg	149±19	152±21	0.372
Baseline diastolic blood pressure, mm Hg	82±13	83±14	0.460
Baseline blood glucose, mmol/L	7.46±2.97	7.64±2.70	0.567
Baseline NIHSS score (IQR)	14 (12–18)	13 (8–17)	0.001
ICA occlusion, %	46 (25.4)	50 (24.3)	0.795
Regional leptomeningeal collateral score (IQR) <sup>†</sup> (n=375)	11 (7–14)	12 (8–16)	0.002
Baseline infarct core volume, mL (IQR) <sup>‡</sup> (n=376)	55 (27–91)	42 (19–80)	0.011
Baseline hypoperfusion volume, mL (IQR) <sup>‡†</sup> (n=376)	123 (80–167)	111 (67–162)	0.183
Endovascular thrombectomy, %	108 (59.7)	93 (45.1)	0.004
Onset to imaging time, min	207 (110–313)	208 (136–314)	0.549
Wake-up stroke, %	41 (22.7)	42 (20.4)	0.588

Sample sizes: n=387, unless noted otherwise. ICA indicates internal carotid artery; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.

\*Fifteen patients without anticoagulant data.

<sup>†</sup>Twelve patients without collaterals data because of reconstruction failure.

<sup>‡</sup>Eleven patients without infarct core and hypoperfusion volume data because of reconstruction failure.

corresponding symptoms compatible with the involved artery. The proximal artery was selected in the contralateral hemisphere to generate the arterial input function curve to determine the peak phase. Thick-slab reformatted 4D-CTA images were reconstructed from axial, coronal, and sagittal CTP source images using a GE Advantage Windows workstation (GE Medical Systems, Milwaukee, Wisconsin). Two neurologists (M.Z. and X.G.), blinded to patients' clinical information, independently assessed the direction of blood flow on 4D-CTA.

Due to the partial volume effects on CTA, the residual flow within the clot could not be clearly visualized.<sup>7</sup> Theoretically, due to the short distance, when residual flow goes through the clot, contrast would appear quickly at the distal interface of the clot. In contrast, flows from good collaterals usually proceed

for a relatively long distance to the distal end of the clot, thus the contrast would appear late. We then defined the antegrade flow as early opacification at the distal interface of clot with subsequent distal extension, and the retrograde flow as earlier opacification in the surrounding area than that at the distal end of the occluded vessel segment on 4D-CTA imaging (Figure).

Volumetric analysis was performed using MIStar software (Apollo Medical Imaging Technology, Melbourne, Australia). Previously validated thresholds were applied to measure the volume of acute hypoperfusion lesion ( $T_{max} >6$  seconds) and acute infarct core (relative cerebral blood flow <30%).<sup>8</sup>

The regional leptomeningeal collateral score (20 points) was based on scoring extent of contrast opacification in 6 Alberta Stroke Programme Early CT Score

cortical regions (M1–6), the parasagittal anterior cerebral artery territory, and the basal ganglia at the arterial peak phase of 4D-CTA.<sup>9</sup>

## Statistical Analysis

The kappa-statistic value was used to assess intra- and interobserver variability for evaluating antegrade flow and retrograde flow. Clinical characteristics and imaging profiles were summarized as mean±standard deviation or median (25th–75th percentile) for quantitative variables and as proportions for categorical variables. The chi-square test was used to compare dichotomous variables between 2 groups, whereas an independent-sample 2-tailed Student *t* test or Mann–Whitney *U* test was used for continuous variables, depending on normality of the distribution. The Kruskal–Wallis test was used to compare differences among 3 groups. Diagnostic parameters, including sensitivity, specificity, and positive and negative predictive values, were calculated to assess the prognosis of the antegrade blood flow in differentiating LAA from other causes. We performed a multivariable logistic regression analysis for LAA cause and a binary logistic regression for the presence of antegrade flow using a direct entry model to assess the odds ratios (ORs) and corresponding 95% CIs. Those variables with *P*<0.10 on univariate analysis were included in the binary logistic regression and multivariable logistic regression analyses. Candidate explanatory variables were identified as: (1) those with *P*<0.10 on univariate analysis, and (2) those assessed before reperfusion therapy. All statistical analyses were performed using SPSS version 22.0 (IBM, Armonk, New York). *P*<0.05 was considered statistically significant.

## RESULTS

### Overall Characteristics

Among the 403 patients meeting the inclusion criteria, 6 had incomplete CTP raw images or reconstructed images of poor quality, 6 had bilateral occlusion of the M1 segment of the M1 middle cerebral artery, and 4 had no blood flow beyond the occlusion site on the images. A total of 387 patients were assessed in the final analysis. Patients' mean age was 71±14 years; there were 229 men (59.2%) and 158 (40.8%) women. Median NIHSS score on admission was 14 (interquartile range, 10–18). Seventy-seven patients (19.9%) had an LAA subtype, 206 (53.2%) had cardioembolism, and 104 (26.9%) had an undetermined cause.

Intra- and interobserver kappa values for detection of blood flow were 0.849 (95% CI, 0.74–0.96; *P*<0.001) and 0.827 (95% CI, 0.71–0.94; *P*<0.001), respectively.

There were 206 (53.2%) patients with antegrade flow and 181 (46.8%) with retrograde flow.

### Comparison Between Antegrade Flow and Retrograde Flow

As shown in Table 1, patients with antegrade flow were younger, had higher rates of smoking and diabetes mellitus, lower rate of atrial fibrillation, higher rate of LAA, lower baseline NIHSS score, higher regional leptomeningeal collateral score, lower baseline infarct core volume, and lower rate of endovascular thrombectomy, compared with patients with retrograde flow.

Binary logistic regression showed that large arterial atherosclerosis was significantly associated with the presence of antegrade flow (OR, 4.453; 95% CI, 1.752–11.317; *P*=0.002), when setting cardioembolism as reference, after adjusting for age, smoking, diabetes mellitus, atrial fibrillation, baseline NIHSS score, and leptomeningeal collateral score (Table 2).

### Stroke Subtype and Antegrade Flow

As shown in Table 3, patients with the LAA subtype were younger and less frequently female, and had a lower rate of coronary heart disease and atrial fibrillation, higher rate of smoking and diabetes mellitus, lower NIHSS score, higher regional leptomeningeal collateral score, smaller baseline infarct core volume, and longer duration from onset to imaging time, compared with patients with cardioembolism. Moreover, the rate of antegrade flow was much higher in patients with the LAA subtype than in those with cardioembolism (85.7% versus 42.2%, *P*<0.001).

Multivariable logistic regression revealed that, when setting cardioembolism as reference, the presence of antegrade flow was significantly associated with LAA

**Table 2. Binary Logistic Regression for Presence of Antegrade Flow**

	OR	95% CI	P Value
Age, y	0.993	0.976–1.011	0.437
Smoking, %	1.396	0.830–2.349	0.209
Atrial fibrillation, %	0.798	0.428–1.486	0.477
Diabetes mellitus	1.713	0.935–3.140	0.081
Regional leptomeningeal collateral score	1.044	0.997–1.093	0.064
Cause of stroke (set "cardioembolism" as reference)			
Large arterial atherosclerosis	4.453	1.752–11.317	0.002
Undetermined cause	1.106	0.590–2.073	0.754
Baseline NIHSS score	0.971	0.935–1.008	0.118

Sample sizes: n=387. NIHSS indicates National Institutes of Health Stroke Scale.

**Table 3. Comparison of Characteristics Among Different Stroke Subtypes**

	Cardioembolism (n=206)	Large Arterial Atherosclerosis (n=77)	P1 Value	Undetermined Cause (n=104)	P Value
Female, %	103 (50.0)	16 (20.8)	<0.001	39 (37.5)	<0.001
Age, y	73±12	63±13	<0.001	67±15	<0.001
Coronary heart disease, %	31 (15.0)	4 (5.2)	0.025	8 (7.7)	0.027
Smoking, %	42 (20.4)	36 (46.8)	<0.001	33 (31.7)	<0.001
Atrial fibrillation, %	176 (85.4)	0 (0)	<0.001	23 (22.1)	<0.001
Previous stroke or transient ischemic attack history, %	40 (19.4)	16 (20.8)	0.798	15 (14.4)	0.465
Hypertension, %	126 (61.2)	50 (64.9)	0.561	61 (58.7)	0.692
Diabetes mellitus, %	31 (15.0)	27 (35.1)	<0.001	16 (15.4)	<0.001
Homocysteinemia, %	25 (12.1)	10 (13.0)	0.847	23 (22.1)	0.058
Hyperlipidemia, %	71 (34.5)	34 (44.2)	0.133	39 (37.5)	0.323
Antiaggregants, %	50 (24.3)	14 (18.2)	0.276	17 (16.3)	0.216
Baseline systolic blood pressure, mm Hg	151±21	151±19	0.832	149±21	0.603
Baseline diastolic blood pressure, mm Hg	83±14	83±13	0.938	83±11	0.997
Baseline blood glucose, mmol/L	7.7±3.2	7.6±2.3	0.830	7.3±2.3	0.665
Baseline NIHSS score (IQR)	15 (12–18)	10 (5–14)	<0.001	14 (10–17)	<0.001
ICA occlusion, %	47 (22.8)	24 (31.2)	0.149	25 (24.0)	0.343
Antegrade flow, %	87 (42.2)	66 (85.7)	<0.001	53 (51.0)	<0.001
Regional leptomeningeal collateral score (IQR)* (n=375)	11 (7–15)	14 (10–18)	0.011	11 (7–15)	0.001
Baseline infarct core volume, mL (IQR)† (n=376)	54 (27–92)	38 (18–67)	0.002	44 (19–86)	0.008
Baseline hypoperfusion volume, mL (IQR)† (n=376)	122 (79–164)	111 (74–154)	0.374	108 (60–174)	0.549
Endovascular thrombectomy, %	116 (56.3)	30 (39.0)	0.009	55 (52.9)	0.033
Onset to imaging time, min	180 (106–276)	229 (152–324)	0.005	239 (152–364)	0.001
Wake-up stroke, %	38 (18.4)	15 (19.5)	0.843	30 (28.8)	0.097

Sample sizes: n=387, unless noted otherwise. P1 value is obtained when comparing cardioembolism and large arterial atherosclerosis groups, and P value is obtained when comparing cardioembolism, large arterial atherosclerosis, and undetermined cause simultaneously. ICA indicates internal carotid artery; IQR, interquartile range; and NIHSS, National Institutes of Health Stroke Scale.

\*Twelve patients could not analyze the collaterals because of reconstruction failure.

†Eleven patients could not analyze the infarct core and hypoperfusion volume because of reconstruction failure.

cause (OR, 5.650; 95% CI, 2.451–13.158;  $P<0.001$ ) after adjusting for baseline infarct core volume, time from onset to imaging, coronary heart disease, wake-up stroke, and homocysteinemia. Other factors associated with cause of LAA included age, female sex, smoking, diabetes mellitus, baseline NIHSS score, and regional leptomeningeal collateral score (Table 4).

Among those with causes identified, there were 206 cardioembolism patients and 77 LAA patients. The sensitivity, specificity, and positive and negative predictive values of the antegrade flow for predicting LAA were 43.1%, 91.5%, 85.7% and 57.8%, respectively.

## DISCUSSION

Our study has delineated 2 major findings: (1) more than half of acute AIS patients demonstrated antegrade

flow permeating through complete arterial occlusion in the peak phase of 4D-CTA reconstructed from CTP; and (2) the rate of antegrade flow was much higher in patients with the LAA subtype than in those with cardioembolism. To our knowledge, this study is the first to analyze the relationship between blood flow and cause of stroke.

The reported rate of antegrade flow ranged from 19.3% to 25.8% in previous studies,<sup>4,5</sup> lower than that in our study (53.2%). This discrepancy may result from the different screening approaches used, as multiphase CTA was used in the earlier studies to identify complete occlusion, which was more likely to exclude patients with antegrade flow than the peak phase of CTP in the current study. Using traditional CTA, 57.4% of patients were found to have permeable thrombi,<sup>10</sup> presenting as anterograde flow,<sup>5</sup> similar to

**Table 4. Multivariable Logistic Regression for Large Artery Atherosclerosis**

	OR	95% CI	P Value
Set "cardioembolism" as reference			
Age, y	0.954	0.930–0.980	<0.001
Baseline NIHSS	0.872	0.815–0.933	<0.001
Regional leptomeningeal collateral score	1.096	1.006–1.195	0.036
Baseline infarct core volume, mL	1.005	0.996–1.014	0.273
Onset to imaging time, min	1.003	1.000–1.006	0.060
Female	0.357	0.149–0.858	0.021
Coronary heart disease	0.414	0.167–1.613	0.204
Smoking	2.347	1.041–5.291	0.040
Diabetes mellitus	4.237	1.835–9.804	0.001
Homocysteinemia	0.810	0.301–2.183	0.678
Presence of antegrade flow	5.650	2.451–13.158	<0.001
Wake-up stroke	0.353	0.098–1.271	0.111

Sample size: n=387. NIHSS indicates National Institutes of Health Stroke Scale.

the rate of antegrade flow seen in the present study. Indeed, leptomeningeal collateral pathways usually emphasize the retrograde filling of pial arteries to the distal end of an occlusion. However, measurement of the leptomeningeal collateral scale on CTA always focuses on the anatomic extent of opacification of large arterial branches, but not the filling flow itself.<sup>11</sup> Thus, to some extent, such assessment of leptomeningeal collaterals is not a true reflection of collateral status. In this study, our definition of antegrade or retrograde flow was highly repeatable and easier to evaluate, and it is of interest that only 46.8% of patients had totally true retrograde filling to the distal end of the thrombus.

The rate of anterograde blood flow was higher in LAA patients, which may be explained by the structural differences of the clots. A recent histopathologic study showed that clotting due to LAA had a higher proportion of erythrocytes and lower proportion of fibrin/platelets.<sup>12</sup> Experimental studies showed that fibrin/platelets-enriched white thrombi retracted more than erythrocytes-enriched red thrombi, resulting in reduced permeability to the bulk flow of thrombolytic agents.<sup>13,14</sup> Therefore, LAA clots may allow contrast/blood to penetrate and distribute homogeneously, appearing as anterograde flow. Furthermore, median thrombus length in patients with antegrade flow was much shorter than in patients with retrograde flow,<sup>5</sup> whereas preclinical studies have shown that the shorter thrombus was related to the LAA stroke subtype.<sup>10</sup>

Different devices and combined therapies have been introduced to treat AIS with specific causes.<sup>15</sup> Rescue therapy or intra-arterial tirofiban plus recombinant tissue plasminogen activator/mechanical

thrombectomy has been reported to improve reperfusion rate for intracranial large artery occlusion with underlying atherosclerosis.<sup>16,17</sup> Thus, the precise assessment of LAO subtype before endovascular procedures may result in different therapeutic strategies and promote better operative planning. Although previous studies have reported that susceptibility vessel sign on T2-weighted magnetic resonance angiography<sup>18</sup> and longer length of delayed-contrast filling of clot on 4D-CTA<sup>19</sup> were imaging markers of stroke causes in AIS patients, our study is the first to use antegrade flow on 4D-CTA images to distinguish the LAA subtype from cardioembolism. The specificity and positive predictive values of the antegrade flow for predicting LAA were 91.5%, and 85.7%, respectively, which indicates that the cause of acute LAO patients with retrograde flow was less likely to be the LAA subtype. In addition, 4D-CTA reconstructed from CTP only took 74.5 seconds of scanning time plus several minutes for reconstruction, without additional radiation or contrast administration. Therefore, evaluating the antegrade flow on 4D-CTA images would provide alternatives to assist in the decisionmaking associated with reperfusion therapy. In addition, early prediction of AIS can bring forward secondary prevention strategy, which is also of great importance in AIS treatment.

Age and baseline NIHSS were also significantly associated with cause of LAA, which is consistent with previous studies. In our study, LAA patients were younger, which was also the case in the study by Rebellos et al, who investigated causes of stroke and collaterals. They found that atrial fibrillation patients were older<sup>20</sup> than patients with cervical atherosclerotic steno-occlusive disease. Actually, a previous study reported that cardiac embolism played a greater role in the cause of stroke in the elderly.<sup>21</sup> In addition, stroke due to LAA usually demonstrated smaller infarct core volumes,<sup>22</sup> which also explains the lower NIHSS in these patients.

Our study has limitations. First, although we prospectively collected data using a stroke registry and CTP protocol, our study had a retrospective design and only included patients with reperfusion therapy, and thus there may have been selection bias. Second, we only included patients with M1 segment middle cerebral artery occlusion with or without involvement of internal carotid artery to reduce heterogeneity. Given the modest sample size at a single center, further confirmation and extension of our findings will be needed in larger and multicenter cohorts.

## CONCLUSIONS

Using 4D-CTA, antegrade flow could be identified in >50% of acute anterior LAO patients and was seen more frequently in those with LAA.

## ARTICLE INFORMATION

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### Disclosures

None.

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