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Relationship Between Carotid Artery Angle and Plaque Morphology in Acute Cerebral Infarction Patients

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Background: High-resolution magnetic resonance imaging (HRMRI) can be used to clearly distinguish the luminal structure of the carotid artery (CA); measure the lumen, vessel wall, and total blood vessel area; and accurately describe the morphologic features of plaques.

Methods: This study used HRMRI to investigate the relationship between geometric features and volume and composition of carotid atherosclerotic plaques. Patients ($n = 81$) who had experienced acute cerebral infarction (CI) within 7 ± 3 days before admission to the Neurology Department of Beijing Tiantan Hospital between November 2011 and June 2012 were enrolled in the study. CA HRMRI was performed to analyze the geometry and morphology of plaques in 160 blood vessels.

Results: The median left and right internal carotid artery angles (ICAAs) were 32.79 and 31.00 degrees, respectively. Aside from the nonplanar external CA angle, plaque volume and angles did not differ significantly between the left and right sides. Age ($B = 3.77$; $P = 0.03$) and nonplanar ICAA ($B = 4.70$; $P = 0.01$) were predictors of left but not right carotid plaque volume. ICAA and bifurcation angle did not predict plaque volume.

Conclusions: In this study, CA morphology in acute stroke patients is not associated with plaque volume or composition, but age and nonplanar ICAA can predict left carotid plaque volume.

Key Words: cerebral infarction, high-resolution magnetic resonance imaging, carotid artery angle, stroke subtype

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Cerebral infarction (CI) is a common acute and severe subtype of ischemic stroke. In China, over 2 million new stroke events occur each year, with CI accounting for about two third of these cases.[1] Carotid atherosclerosis (AS) is one of the main causes of CI.[2] Multiple factors contribute to the development of AS, which involves changes in the physical properties of blood vessels. Hemodynamic analyses have revealed complex blood flow dynamics at the bifurcation of the carotid artery (CA), which is consequently susceptible to AS plaque formation[3] with a higher incidence on the left side than on the right side.[4] Studies investigating the relationship between changes in blood flow patterns and the pathophysiology of blood vessels have typically relied on hydrodynamic theory and methodology.[5–8] Carotid AS plaques are thought to induce ischemic cerebrovascular disease via multiple mechanisms.[9] However, few studies have investigated the association between hemodynamics and plaque morphology by measuring carotid artery angle (CAA) or compared plaque formation on the left and right sides of the CA.

The geometry of the CA has been examined by digital subtraction angiography (DSA) and multislice computed tomography angiography.[10–12] High-resolution magnetic resonance imaging (HRMRI) can also be used to clearly distinguish luminal structure; measure the lumen, vessel wall, and total blood vessel area; and accurately describe the morphologic features of plaques.[13,14] In addition, 3-dimensional time-of-flight (3D TOF) can be used to visualize the stereostructure of the CA and measure its geometric parameters.

In the present study, we used HRMRI combined with a previously described postprocessing method[15,16] to reconstruct the CA bifurcation in 3-dimensional (D) and measure CAAs to assess the relationship between CA geometry/morphology and the volume and composition of carotid AS plaques.

METHODS

Study Subjects

This was a single-center prospective study that enrolled all patients with acute CI admitted to the Neurology Department of Beijing Tiantan Hospital between November 2011 and June 2012. The inclusion criteria were as follows: (1) age between 18 and 80 years; (2) disease conformed to the diagnostic criteria for CI of the internal carotid artery (ICA) system; (3) onset of stroke within 7 ± 3 days of admission; (4) intima-media thickness of the CA ≥ 1.5 mm as determined by cervical vascular ultrasonography; (5) the patient had undergone magnetic resonance imaging (MRI); and (6) the patient (or guardian/immediate family members) signed informed consent forms. Exclusion criteria were as follows: (1) the patient had received thrombolytic therapy or other endovascular interventions; (2) cardiogenic embolism was suspected, or else the etiology of CI was unknown; (3) CI was secondary to cerebral hemorrhage, trauma, tumor, abnormal coagulation, aneurysm, or arteriovenous malformation, etc.; and (4) the patient was unable to undergo MRI examination because of claustrophobia, heart valve replacement, or metal denture placement, etc. The study was approved by the Ethics Committee of Beijing Tiantan

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Hospital, Capital Medical University, and all protocols were carried out in accordance with relevant ethics guidelines and regulations. Written, informed consent was obtained from all participants and was approved by the ethics committee.

HRMRI Examination

MRI was performed with a 3.0 T MR scanner (Trio-Tim; Siemens, Erlangen, Germany). The maximum slew rate was 200 T/m/ms, and the maximum gradient strength was 45 mT/m. A 4-channel surface coil (Machnet BV, Eelde, The Netherlands) designed for the CA was used.

The center of the scan was set at the bifurcation of the CA, and axial scanning was performed perpendicular to the blood vessels. Four scanning sequences were used: T1-weighted imaging (WI), T2WI, proton density-weighted imaging (PDWI), and 3D TOF. The field of view of the above sequences was $16\times16\ cm^2$, and the matrix size was 256×256 pixels. The section thickness was 1 mm in 3D TOF and 2 mm in the other sequences. The number of excitations was 1 in 3D TOF and 2 in the other sequences. The spatial resolution was 0.4×0.4 mm in 3D TOF, PDWI, and T1WI and 0.5×0.5 mm in T2WI. The subcutaneous fat signal was suppressed using fat-suppression technology.

Collection and Analysis of Imaging Data

HRMRI of the CA was completed within 7 ± 3 days of CI onset. Using CASCADE software,[17] 2 experienced radiologists (both with >3 y of experience in analyzing CA images) collaborated to perform the measurements and analyses while blinded to the condition of the CA lesions. The measured indicators were CAA size, maximum wall thickness, condition of plaque components, and percentage of all plaque components in the total wall area. Before obtaining plaque component data, images from the 4 sequences were matched to display the same section of the CA using the CA bifurcation as an anatomic marker; images of each section in the 4 sequences were set as synchronous paging.

Based on the signal-to-noise ratio of blood vessels and the degree of clarity of their contours, CA MRI image quality (IQ) was scored according to a 5-point scale (1 = poor and 5 = excellent).[18] Patients were excluded from the analysis if they had an image with IQ ≤ 2 points.

The signal intensity of plaque components was compared with that of adjacent sternocleidomastoid muscle according to previous standards used in multicontrast HRMRI.[19,20] Plaque components such as calcification, lipid-rich necrotic core (LRNC), intraplaque hemorrhage (IPH), loose matrix, and dense fibrous tissue were identified, and their regions-of-interest (ROIs) were delineated on 4 matched sequence images (3D TOF, T1WI, T2WI, and PDWI) (Table 1).

Measurement of CAA

Image postprocessing was performed as previously described[15,16] for in vivo 3D reconstruction of the CA bifurcation and measurement of geometric indicators of blood vessels. The specific steps were as follows.

3D TOF sequence images were selected using CASCADE software. The contours of the common carotid artery (CCA), ICA, and external carotid artery (ECA) on images of each section were accurately traced in different colors by one physician using the ROI plotting tool. The measurements were repeated 2 weeks later, and delineation was performed by the second physician to reduce human error. The outline of each section was automatically reconstructed into a binary image volume; thus, one 3D discrete dynamic outline defined the geometry of the blood vessel lumen, and the left and right sides were independently reconstructed and stored.

TABLE 1. Signal Strength of Plaque Components in Different MR Scanning Sequences

	MR Scanning Sequence			
Plaque Component	**3D TOF**	**T1WI**	**T2WI**	**PDWI**
LRNC	–	–/↑	–/↓	–/↓
IPH	↑	↑	–/↑	–/↑
Ca	↓	↓	↓	↓
Loose matrix	–	↓	↑	↑
Fibrous tissue	↓	–	–	

– indicates isosignal; ↑, high signal; ↓, low signal; 3D TOF, 3-dimensional time-of-flight; Ca, calcification; IPH, intraplaque hemorrhage; LRNC, lipid-rich necrotic core; MR, magnetic resonance; PDWI, proton density-weighted imaging; T1WI, T1-weighted imaging; T2WI, T2-weighted imaging.

The midline and inscribed sphere of all blood vessel branches of the 3D CA bifurcation were automatically generated. Each midline harbored the center of the sphere with the maximum radius plotted in the blood vessel lumen (the maximum diameter of the plotted sphere was approximately equal to the minimum diameter of the blood vessel lumen). The centers of all spheres were connected from the start of the blood vessel midline (ICA0, ECA0, and CCA0) along the midline to the location of the sphere centers toward the distal end (ICA1, ECA1, and CCA1 points). The series of points generated by the above process was reproduced to form 3 linear lines (for the ICA, ECA, and CCA).

To calculate the bifurcation angle (BIFA), the branch direction was defined as the direction of the vector extending from the starting point of bifurcation (CCA0, ICA0, or ECA0) to the distal point of the radius of sphere 1 (CCA1, ICA1, and ECA1, respectively). In the front view of the 3D CA bifurcation, the angle between the ICA and ECA linear lines was the BIFA; the angle between the ICA linear line and reverse extension line of the CCA linear line was the internal carotid artery angle (ICAA); and the angle between the ECA linear line and reverse extension line of the CCA linear line was the external carotid artery angle (ECAA). In the lateral view of the CA bifurcation, the angle between the ICA linear line and reverse extension line of the CCA linear line was the nonplanar ICAA; and the angle between the ECA linear line and reverse extension line of the CCA linear line was the nonplanar ECAA. The ICAA was selected for analysis in this study.[15]

Analysis of Plaque Components

The contours of the vessel wall and lumen were delineated. The ROIs of plaque components (calcification, LRNC, and IPH) were delineated on the 4 matched sequence images (3D TOF, T1WI, T2WI, and PDWI). Consistency of ROI size in all sections of the 4 matched images was ensured by synchronous adjustment of the ROI setup on matched images. The area of different plaque components on each section was measured, and the occurrence of each plaque component was recorded (with or without LRNC). Plaque volume was then calculated. Occluded ICAs and CCAs were omitted from the analysis.

Chinese Ischemic Stroke Subclassification (CISS) of Acute CI Patients

Two attending physicians with >10 years of experience independently determined the CISS of each patient based on

TABLE 2. Baseline Characteristics of Patients According to Sex

Variables	Total	Male	Female	*P*
n (%)	81 (100)	59 (72.8)	22 (27.2)	
Age (mean ± SD) (y)	61.00 ± 11.34	59.03 ± 10.89	66.27 ± 11.07	0.01
Hypertension history [n (%)]	59 (72.8)	41 (50.6)	18 (22.2)	0.27
Diabetes mellitus history [n (%)]	23 (28.4)	15 (18.5)	8 (9.9)	0.34
Coronary heart disease [n (%)]	5 (6.2)	3 (3.7)	2 (2.5)	0.51
Smoking history [n (%)]	50 (61.7)	48 (59.3)	2 (2.5)	< 0.001
Drinking history [n (%)]	38 (46.9)	36 (61.0)	2 (2.5)	< 0.001
Medical history [n (%)]				
Aspirin	1 (1.2)	0	1 (1.2)	0.10
Statins	5 (6.2)	2 (2.5)	3 (3.7)	0.09
Triglyceride [median (Q1, Q3)] (mmol/L)	1.31 (0.96, 2.22)	1.40 (0.92, 2.29)	1.30 (0.98, 1.81)	0.22
Total cholesterol [median (Q1, Q3)] (mmol/L)	4.02 (3.16, 4.70)	4.08 (3.27, 4.66)	3.83 (2.74, 4.89)	0.48
Low-density lipoprotein [median (Q1, Q3)] (mmol/L)	2.14 (1.58, 2.77)	2.11 (1.63, 2.85)	2.24 (1.42, 2.69)	0.10
Total plaque area [median (Q1, Q3)] (mm^2)	60.98 (1.52, 288.99)	64.48 (1.92, 323.40)	40.21 (0.00, 123.84)	0.11

Q1 indicates quartile 1; Q3, quartile 3.

auxiliary examinations including cervical vascular ultrasonography, color ultrasonic cardiography, transcranial Doppler ultrasonography, and DSA. Any discrepancy between the CISS scores assigned by the 2 physicians were resolved by a senior physician.

Statistical Analysis

Statistical analyses were performed using SPSS, v23.0 software (SPSS Inc., Chicago, IL). As all continuous variables except for age showed a skewed distribution, they are expressed as medians with 25th and 75th percentiles, and these values were used for analysis. Age showed a normal distribution and is expressed as mean ± SD. Data for all patients were compared with the nonparametric Wilcoxon signed-rank test, while differences between left and right paired vessels were compared with the *t* test. Categorical variables are described as percentages and were compared with the χ^2 test. Multivariate linear regression analysis was performed to assess the relationship between geometric variables and plaque volume, adjusting for sex, age, hypertension, diabetes, smoking, low-density lipoprotein, cholesterol, ICAA, ECAA, BIFA, nonplanar ICAA, and nonplanar ECAA. The Bonferroni correction was applied when several consecutive analyses were performed. A *P*-value <0.05 was considered statistically significant.

RESULTS

A total of 81 patients with CI (59 males and 22 females) were enrolled in this study, with HRMR images available for 162 blood vessels; 2 images had IQ = 2 points and were therefore excluded from the analysis. Of the 160 remaining cases, the BIFA in 8 images could not be accurately measured because of vascular occlusion or a short or partly obscured bifurcation. In the 152 remaining images, the origin and morphology of the CCA, ICA, and ECA were clearly visible, and the BIFA could be measured. The baseline characteristics of the study population are shown in Table 2.

CISS[21] Subtypes in Acute CI Patients

The following auxiliary examinations were performed on the 81 patients during hospitalization: cervical vascular ultrasonography (n = 79, 97.5%), color ultrasonic cardiography (n = 77, 95.1%), transcranial Doppler ultrasonography (n = 77, 95.1%), and DSA (n = 25, 30.9%). There were 30 cases of artery-to-artery embolism; 16 cases of hypoperfusion/reduced capacity for embolus clearance; 8 cases of occlusion of the perforating artery by a thrombus or plaque; and 27 cases of a mixed type, mainly comprising artery-to-artery embolism and hypoperfusion/reduced capacity for embolus clearance.

TABLE 3. Relationship Between Carotid Plaque Characteristics and Geometric Angles on Both Sides of the Carotid Artery as Determined by Multiple Regression*

	Median (25th, 75th)				95% CI			
	Left	Right	SD	SE Mean	Lower	Upper	Correlation	*P*†
Ca volume (mm^3)	0.00 (0.00, 11.78)	0.00 (0.00, 17.03)	67.94	7.55	−23.05	6.99	0.57	0.29
LRNC volume (mm^3)	1050 (0.00, 58.77)	6.28 (0.00, 81.47)	171.21	19.02	−39.98	35.74	0.43	0.91
IPH volume (mm^3)	0.00 (0.00, 0.00)	0.00 (0.00, 0.87)	62.51	6.95	−23.62	4.03	0.28	0.16
ICAA (deg.)	32.79 (22.86, 41.08)	31.00 (22.91, 41.73)	14.98	1.83	−3.08	4.23	0.36	0.76
ECAA (deg.)	24.53 (16.59, 35.03)	28.30 (18.49, 35.13)	14.96	1.83	−2.92	4.38	0.29	0.69
BIFA (deg.)	58.35 (49.72, 70.53)	57.80 (46.25, 67.86)	18.75	2.27	−2.18	6.90	0.39	0.30
Nonplanar ICAA (deg.)	−3.72 (−11.84, 0.84)	−2.64 (−7.62, 1.65)	12.79	1.56	−5.23	1.00	−0.04	0.18
Nonplanar ECAA (deg.)	−0.95 (−4.09, 3.59)	−4.62 (−9.02, −1.06)	10.59	1.29	1.62	6.78	0.23	0.002

*Adjusted for sex, age, hypertension, diabetes, smoking, low-density lipoprotein, cholesterol, ICAA, ECAA, BIFA, nonplanar ICAA, and nonplanar ECAA.
†Because 2 consecutive statistical procedures were performed, a *P*-value of 0.05/2 = 0.025 was considered as indicating statistical significance.
BIFA indicates bifurcation angle; Ca, calcification; ECAA, external carotid artery angle; ICAA, internal carotid artery angle; IPH, intraplaque hemorrhage; LRNC, lipid-rich necrotic core.

TABLE 4. Relationship Between Plaque Volume and Various Parameters by Linear Regression Analysis

	Left		Right	
Risk Factor	***B* (95% CI)**	***P***	***B* (95% CI)**	***P***
Age	3.77 (0.30-7.24)	0.03	3.36 (−0.86 to 7.57)	0.12
Sex	−39.66 (−152.49 to 73.16)	0.49	−96.51 (−220.51 to 27.49)	0.13
Hypertension	38.59 (−46.24 to 123.43)	0.37	84.52 (−18.77 to 187.81)	0.11
Diabetes	−11.30 (−100.94 to 78.35)	0.80	13.46 (−91.49 to 118.40)	0.80
Smoking	12.26 (−91.10 to 115.62)	0.81	23.68 (−87.31 to 134.68)	0.67
LDL	−0.62 (−2.15 to 0.92)	0.43	−0.18 (−1.99 to 1.62)	0.84
CHO	14.00 (−25.25 to 53.24)	0.48	−23.11 (−64.86 to 18.63)	0.27
ICAA (deg.)	1.16 (−2.56 to 4.88)	0.54	−0.70 (−5.16 to 3.77)	0.76
BIFA (deg.)	−0.62 (−3.59 to 2.35)	0.68	−0.05 (−4.01 to 3.90)	0.98
Nonplanar ICAA (deg.)	4.70 (0.99-8.41)	0.01	−0.69 (−6.64 to 5.27)	0.82

Adjusted for sex, age, hypertension, diabetes, smoking, LDL, ICAA, BIFA, and nonplanar ICAA.
BIFA indicates bifurcation angle; CHO, cholesterol; CI, confidence interval; ICAA, internal carotid artery angle; LDL, low-density lipoprotein.

Analysis of Left and Right Sides of the CA

The median left and right ICAAs were 32.79 and 31.00 degrees, respectively. A comparison of volumes of plaque components (calcification, LRNC, and IPH) and geometric angles (ICAA, ECAA, BIFA, and nonplanar ICAA and ECAA) between the left and right sides showed that only nonplanar ECAA differed significantly between the 2 sides ($P=0.002$; Table 3).

Detection of Carotid AS Plaques

Of the 78 patients in whom ICAA could be measured, 41 had plaques in bilateral carotid arteries (52.6%); 37 (47.4%) had unilateral plaques; and in the remaining 4, plaques were not clearly detected because of vascular occlusion or poor IQ; these cases were excluded from the analysis. Of the 119 cases with plaques, LRNC was detected in 90 (75.6%), IPH in 31 (26.1), and calcification in 70 (58.8%).

We examined the correlation between plaque volume and various parameters including sex, age, hypertension, diabetes, smoking, low-density lipoprotein, cholesterol, and CAAs by linear regression analysis. Only age ($B=3.77$; $P=0.03$) and nonplanar ICAA ($B=4.70$; $P=0.01$) predicted left carotid plaque volume (CPV), but they did not predict right CPV (Table 4).

DISCUSSION

The results of this study demonstrate that besides nonplanar ECAA, plaque characteristics measured by HRMRI (volume and geometric angles) did not differ between left and right CAs; moreover, age and nonplanar ICAA predicted left CPV, but neither of these parameters were predictors of right CPV.

Local hemodynamics play an important role in the occurrence and development of AS. Blood flow shunt and stagnation increase lipid retention time and shear stress at the CA bifurcation, promoting AS plaque formation at this site.[3,22] The anatomy of the CA bifurcation was shown to contribute to local shear stress and influence local blood flow speed and allocation.[6] The percent allocation of blood flow in the ICA and ECA has a major impact on local hemodynamics; a larger ICAA perturbs blood flow at the bifurcation site and increases the areas of low blood flow speed and vessel wall shear stress, thereby increasing the risk of arterial AS development.[15,23] The bifurcation point of the CA is both arched and branched; this geometry creates a unique blood flow environment that promotes plaque formation. BIFA increases with age[24] which could explain our finding that age was a predictor of plaque volume, at least on the left side of the CA.

The median left, and right ICAAs were 32.79 and 31.00 degrees, respectively. The slight discrepancy between these values reflects the variability of human anatomy. However, the difference was not statistically significant, and no differences in ECAA, BIFA, nonplanar ICAA, and plaque volume were observed between the left and right sides. ICAA and BIFA were unrelated to plaque volume. It was previously demonstrated that a larger ICAA increased the risk of stenosis,[25,26] but another study found no relationship between ICAA geometry and degree of CA stenosis,[27] providing indirect evidence that the ICAA does not affect plaque volume, which is consistent with our results. There have been few studies on the relationship between nonplanar ICAA and CPV; we observed that nonplanar ICAA predicted left CPV, but this requires validation in additional studies.

Epidemiologic studies have shown that carotid AS is a risk factor for cerebrovascular disease and is closely associated with the occurrence and development of CI. Our patients all had CI resulting from arterial AS and were grouped according to the CISS. We previously showed that patients with larger CAAs were more susceptible to plaque development.[28] Vulnerable plaques are enriched in lipids; additionally, rupture, hemorrhage, local thrombosis, or detachment of emboli can easily occur under the influence of blood flow, thereby enhancing the probability of CI. Some patients in our study showed a combination of artery-to-artery embolism and hypoperfusion/reduced embolus clearance rate. Although the former plays an important role in the pathogenesis of ischemic stroke caused by carotid plaques, it is not the only pathogenic mechanism; our results indicate that multiple factors contribute to the occurrence of CI.

This study had limitations. First, enrolled patients were relatively stable, and none had massive CI; therefore, our findings may not be representative of all cases of CI and are not applicable to healthy individuals. Second, in some patients, artery-to-artery embolism caused by thrombi that have detached from unstable CA plaques may play a dominant role in the occurrence of ischemic stroke; this could result in the measurement of plaques that are smaller than their actual size after CI onset. Finally, we did not limit plaque thickness or degree of stenosis, which could affect carotid bifurcation geometry through internal remodeling.[22]

CONCLUSIONS

In this study, CA morphology in patients with acute stroke was not associated with plaque volume or composition. Age and nonplanar ICAA predicted left but not right CPV. Thus, HRMRI can provide information on clinically significant changes in AS plaque characteristics in cases of CI, which can aid clinicians in selecting appropriate management strategies.

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