ORIGINAL RESEARCH

Associations Between Features of Nonstenosing Carotid Plaque on Computed Tomographic Angiography and Ischemic Stroke Subtypes

Ashley Knight-Greenfield, MD; Joel Jose Quitlong Nario, BS; Amar Vora, MD; Hediyeh Baradaran, MD; Alex Merkler, MD; Babak B. Navi, MD, MS; Hooman Kamel, MD; Ajay Gupta, MD, MS

***Background*—**Thromboembolism from nonstenosing carotid plaques may be an underrecognized cause of embolic strokes of undetermined source (ESUS). We evaluated the association between features of nonstenosing atherosclerotic plaque on computed tomographic angiography and ESUS.

***Methods and Results*—**We identified consecutive acute ischemic stroke patients from 2011 to 2015 who had unilateral anterior territory infarction on brain magnetic resonance imaging and a neck computed tomographic angiography. We included ESUS cases and as controls, cardioembolic strokes. Patients with ≥50% internal carotid artery atherosclerotic stenosis ipsilateral to the stroke were excluded from this analysis. Reviewers blinded to infarct location and stroke cause retrospectively evaluated computed tomographic angiography studies for specific plaque features including thickness of the total, soft, and calcified plaque; presence of ulceration; and perivascular fat attenuation. Paired *t* tests and McNemar's test for paired data were used to compare plaque features ipsilateral versus contralateral to the side of infarction. Ninety-one patients with ESUS or cardioembolic stroke were included in this study. Total plaque thickness was greater on the infarcted side (2.1±2.0 mm) than the contralateral side (1.2±1.5 mm) (*P*=0.006) among ESUS cases, but not among cardioembolic cases (1.9±1.6 mm versus 1.8±1.6 mm) (*P*=0.32).

***Conclusions*—**Among ESUS cases, total plaque thickness was greater ipsilateral to the side of infarction than on the contralateral, stroke-free side. No such side-to-side differences were apparent in cardioembolic strokes. Our findings suggest that nonstenosing large-artery atherosclerotic plaques represent one underlying mechanism of ESUS. **(*J Am Heart Assoc*. 2019;8:e014818. DOI: 10.1161/JAHA.119.014818.)**

Key Words: acute stroke • carotid artery • computed tomography angiography • plaque

Ischemic stroke is a major cause of death and disability, and nearly one third of such strokes have no known cause, even after a full diagnostic evaluation. Such cryptogenic strokes pose a significant treatment dilemma, as the prevention of recurrent ischemic stroke relies heavily on identifying cause. Increasingly, such strokes have been classified as embolic strokes of undetermined source (ESUS), with imaging studies confirming the presence of a nonlacunar infarction without hemodynamically significant stenosis in a proximal artery, and no identifiable cardioembolic source.[1]

Extracranial internal carotid artery (ICA) atherosclerotic disease is a known risk factor for acute stroke, with established guidelines focused on the management of ≥50% stenosis.[2,3] However, recent studies have suggested that certain vulnerable plaques with features that can be readily identified on standard imaging may present a risk factor for acute embolic infarction despite not causing any hemodynamically significant stenosis. As such, there has been recent interest in high-risk nonstenosing plaques as a potential culprit for a substantial proportion of strokes classified as ESUS.[4–11]

While several high-risk plaque features have been examined by computed tomographic angiography (CTA) in patients with stenotic lesions, it is uncertain which features are most strongly associated with stroke in patients with nonstenotic plaques.[12–16] Furthermore, there are few data comparing plaque features between stroke subtypes, particularly the ESUS subgroup in comparison to other embolic stroke causes, such as strokes secondary to cardioembolism.

From the Department of Radiology, Weill Cornell Medicine, New York, NY (A.-K.G., J.J.Q., A.V., A.M., B.B.N., H.K., A.G.); Department of Radiology, University of Utah, Salt Lake City, UT (H.B.); Feil Family Brain and Mind Research Institute, New York, NY (A.M., B.B.N., H.K., A.G.).

Correspondence to: Ajay Gupta, MD, MS, Weill Cornell Medicine, Department of Radiology and Feil Family Brain and Mind Research Institute, 525 East 68th St, New York, NY 10065. E-mail: ajg9004@med.cornell.edu

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Clinical Perspective

What Is New?

- This is the first study evaluating multiple carotid plaque features in embolic strokes of undetermined source patients using cardioembolic stroke cases as a control.
- Among multiple internal carotid artery plaque features analyzed, we found that embolic strokes of undetermined source patients had greater total plaque thickness on the side ipsilateral to their brain infarct as compared with the contralateral, infarct-free side.
- This relationship did not hold for patients with a known cardioembolic source of infarction.

What Are the Clinical Implications?

- Our findings suggest that increased plaque thickness is a mechanism for stroke in a subgroup of embolic strokes of undetermined source patients.
- By further defining this subgroup, we may be able to identify patients who could potentially benefit from trials of aggressive therapy aimed at plaque reduction.

We evaluated multiple plaque features on CTA in patients with acute ischemic stroke and no hemodynamically significant stenosis. We performed a within-subject analysis in which we compared plaque features of the ipsilateral versus contralateral side of ischemic stroke. We hypothesized that certain plaque features are more likely to be associated with ipsilateral strokes in patients with ESUS, whereas these features would not be associated with infarct side for cardioembolic cases.

Methods

Study Design

We performed a within-subject analysis comparing the prevalence of high-risk nonstenosing plaque on the side ipsilateral to acute infarction versus the contralateral side (control side) among ESUS patients enrolled in CAESAR (Cornell Acute Stroke Academic Registry). We also performed the same analysis on patients with strokes of cardioembolic cause, who were included as a negative control group because they were not expected to have side-to-side differences in high-risk plaque prevalence. Strokes secondary to small-vessel occlusion or other causes were excluded because of small sample sizes and heterogeneity in this group.

The institutional review board at Weill Cornell Medicine approved this study and waived the informed consent requirement. Deidentified data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient Population

All patients hospitalized at New York-Presbyterian Hospital/Weill Cornell Medical Center for acute ischemic stroke are prospectively enrolled in the American Heart Association's Get With The Guidelines–Stroke registry. Trained hospital analysts prospectively collect data on demographics, vascular risk factors and comorbidities, stroke severity, and in-hospital treatments and outcomes. CAESAR combines the Get With The Guidelines data plus additional retrospectively collected clinical, laboratory, and radiographic data. Patients' medical records from the stroke hospitalization are reviewed by a panel of at least 3 neurologists who adjudicate the cause of stroke per the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification[17] and per the recently proposed definitions for ESUS.[11] For this analysis, we included consecutive cardioembolic and ESUS patients who were admitted to the hospital between 2011 and 2015, had a magnetic resonance imaging study of the brain demonstrating a unilateral acute infarction in the anterior circulation, and had a CTA with <50% ICA stenosis bilaterally. Patients with apparent severe aortic arch atherosclerosis or common carotid artery stenosis were excluded.

Table 1. Plaque Feature Definitions

Plaque Feature	Definition	Value Recorded
Total plaque thickness	Maximum thickness of plaque on CTA axial sections	mm
Soft plaque thickness	Maximum thickness of noncalcified plaque component on CTA axial sections	mm
Calcified plaque thickness	Maximum thickness of calcified plaque component on CTA axial sections	mm
Distal CCA wall thickness	Measured at its thickest point on the distal wall of the CCA, where there is no evidence of plaque	mm
Perivascular fat attenuation	2 ROIs drawn in the perivascular fat at the level of greatest total plaque thickness on CTA axial sections. If no plaque on 1 side, measured at same level as on the side with plaque. If no plaque on either side, measured at the bifurcation.	Hounsfield Units
Ulceration	Extension of contrast by >1.5 mm beyond vascular lumen	Yes/no

CCA indicates common carotid artery; CTA, computed tomographic angiography; ROI, region of interest.

Measurements

ICA plaque features at the carotid bifurcation were retrospectively characterized on helical axial CTA images (0.625 mm) and measured by a single radiologist according to definitions based on previous studies (Table 1).[10,16,18–20] The reader was blinded to the clinical information and brain magnetic resonance imaging study findings. The degree of stenosis was measured on both ICAs according to the NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria.[21,22] The vessel was then evaluated 2 cm proximal and distal to the bifurcation, and the axial slice with the largest total plaque thickness was measured perpendicular to the long axis of the vessel.[10] Soft plaque thickness and calcified plaque thickness were measured in the same fashion. Distal common carotid artery wall thickness was defined as the maximal thickness of the distal common carotid artery where no plaque was present.[18] Ulceration was defined as focally defined contrast extending beyond the vascular lumen by ≥1.5 mm.[16,19] Lastly, we measured the perivascular fat attenuation similar to prior studies, although, given our focus on nonstenosing plaque, measurements were made at the level of greatest plaque thickness rather than maximal stenosis (Figure).[20] We have previously demonstrated reproducibility of perivascular fat attenuation and plaque thickness measurements, with excellent interrater reliability.[13,20]

The magnetic resonance imaging studies were reviewed independently, and the reader was blinded to carotid CTA imaging. The presence of acute infarction was determined based on diffusion-weighted imaging.

Statistical Analysis

We compared the mean total plaque thickness on the side ipsilateral and contralateral to the acute infarct using a 2-tailed paired *t* test. We performed the same analysis on the secondary variables of soft plaque thickness, calcified plaque thickness, distal common carotid artery wall thickness, and perivascular fat attenuation. We assessed side-to-side differences in the prevalence of plaque ulceration using McNemar's test for paired observations. We performed the above analyses separately in ESUS cases and cardioembolic cases. In sensitivity analyses, we evaluated only ESUS cases with cortical infarcts, and we excluded ESUS patients who developed atrial fibrillation after discharge.

Results

Patient Characteristics

From 138 patients with available CTA and magnetic resonance imaging study data, 91 fit the inclusion criteria, of whom 36 had ESUS and 55 had cardioembolic stroke (Table 2). The mean age of ESUS patients was 65±17 years, with a mean National Institutes of Health stroke scale upon arrival to the emergency room of 9.0±7.0. The mean age of cardioembolic patients was 70.0±12.7 years, with mean National Institutes of Health stroke scale of 11.5±7.8. Cardioembolic patients were significantly more likely to have heart failure and thrombolysis administered, and ESUS patients were more likely to undergo transesophageal echocardiogram.

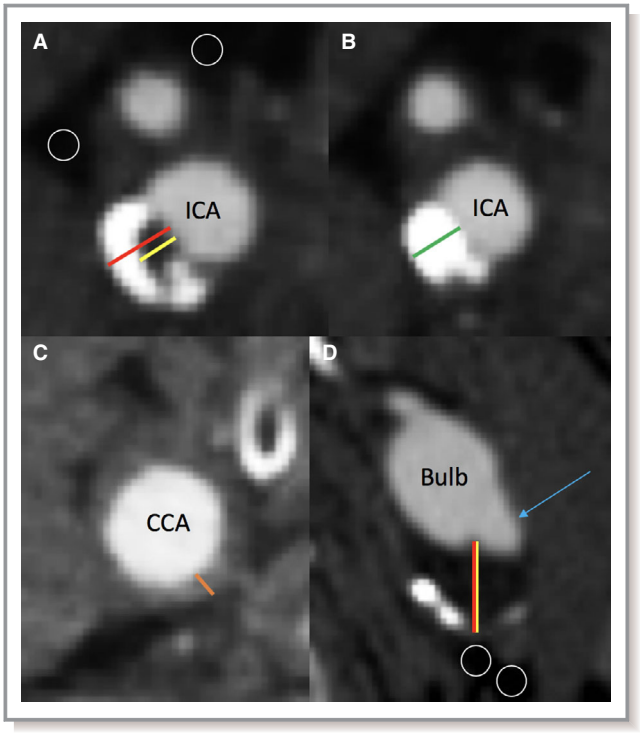

Figure. Methods of plaque assessment. Four axial slices at the level of the carotid bifurcation demonstrating methods of plaque feature assessment. **A** through **C**, Measurements from a single patient with mixed calcified and atherosclerotic plaque. Maximal total plaque thickness (red line) and maximum soft plaque thickness (yellow line) are measured at the same level in this patient. Maximum calcified plaque thickness (green line) is measured at a different level. This patient also has thickening of the distal common carotid artery wall (orange line). **D**, Measurements from a patient with predominantly soft plaque, in which the maximal plaque thickness (red line) and soft plaque thickness (yellow line) are equal, and on the same slice. This patient also has ulceration (blue arrow). The white circles demonstrate the perivascular fat attenuation measurements, taken at the level of maximal plaque thickness in both patients. CCA indicates common carotid artery; ICA, internal carotid artery; Bulb, carotid bulb.

Plaque Features in ESUS Patients

Among ESUS patients, mean stenosis, as measured by the NASCET criteria, was 4.3±11% ipsilateral to the side of

Table 2. Baseline Characteristics of Patients

Stroke Subtype	ESUS, n=36 (40%)	Cardioembolic, n=55 (60%)	*P* Value
Race			
White	33 (92)	42 (76)	0.164
Black	1 (3)	6 (11)	0.164
Other	2 (5)	7 (13)	0.164
Sex			
Female	23 (64)	38 (69)	0.606
Male	13 (36)	17 (31)	0.606
Clinical features			
Chronic kidney disease	0	0	. . .
Heart failure	0	7 (13)	0.026
Coronary artery disease	2 (5.6)	9 (16)	0.122
Diabetes mellitus	9 (25)	10 (18)	0.434
Hypertension	21 (58)	35 (64)	0.611
Prior stroke	5 (14)	11 (20)	0.454
Peripheral vascular disease	0	2 (3.6)	0.247
Active tobacco use	3 (8.3)	6 (11)	0.687
Valvular disease	0	0	. . .
Thrombolysis administered	4 (11)	16 (29)	0.043
Transesophageal echocardiogram	16 (44)	8 (15)	0.002

ESUS indicates embolic stroke of undetermined source.

infarction, and 1.4±8.2% on the contralateral side. Among all ESUS patients, total plaque thickness was significantly higher on the side ipsilateral to the infarction (2.1±2.0 mm) compared with the contralateral, infarct-free side (1.2±1.5 mm) (*P*=0.006) (Table 3). These results were the same in a subsequent sensitivity analysis limited to only ESUS cases with cortical infarcts and excluding ESUS cases with postdischarge atrial fibrillation. In analyses of secondary variables, calcified plaque thickness, perivascular fat attenuation, distal common carotid artery wall thickness, and the prevalence of ulceration were not significantly different between the ipsilateral and contralateral sides. Soft plaque was nonsignificantly thicker on the ipsilateral side (1.7±2.1 mm) than on the contralateral side (1.1±1.4 mm) (*P*=0.07).

Plaque Features in Cardioembolic Stroke Patients

Among patients with cardioembolic stroke, total plaque thickness was similar on the side ipsilateral to infarction (1.9±1.6 mm) compared with the contralateral, infarct-free side (1.8±1.6 mm) (*P*=0.32). There were also no side-to-side differences in any of the secondary plaque features we assessed. Mean stenosis ipsilateral to the infarction side was 1.8±7.6%, and 3.9±11% contralateral to the infarction side.

Table 3. Associations Between Plaque Features and Ipsilateral Infarction

Plaque Feature	Ipsilateral to Infarct*	Contralateral to Infarct	*P* Value
ESUS cases			
Total plaque thickness	2.12±2.01	1.24±1.49	0.006
Soft plaque thickness	1.73±2.15	1.09±1.41	0.065
Calcified plaque thickness	0.93±1.02	0.79±0.97	0.419
Perivascular fat attenuation	−53.5±41.8	−52.1±20.2	0.853
Distal CCA thickness	1.14±0.73	1.12±0.72	0.750
Prevalence of ulceration	28	14	0.267
Cardioembolic cases			
Total plaque thickness	1.94±1.59	1.77±1.58	0.318
Soft plaque thickness	1.42±1.43	1.00±1.17	0.062
Calcified plaque thickness	1.37±1.38	1.93±4.24	0.270
Perivascular fat attenuation	−54.1±19.5	−52.9±17.4	0.654
Distal CCA thickness	1.30±0.73	1.24±0.80	0.596
Prevalence of ulceration	20	7.2	0.065

CCA indicates common carotid artery; ESUS, embolic stroke of undetermined source.
*Data are presented as mean±SD, except for prevalence of ulceration, which is reported as a percentage.

Discussion

In a prospective, single-center registry, we studied the association between features of nonstenosing carotid plaque on CTA and ipsilateral ischemic stroke. We found that ESUS patients had greater carotid plaque thickness on the side ipsilateral to their brain infarct as compared with their contralateral, infarct-free side. No such association was found in cardioembolic stroke patients, who we assessed as a negative control group because they already had an explanation for their infarct. These findings suggest that nonstenosing plaque identifiable on CTA may be the mechanism underlying a subset of ESUS cases.

We and others have previously reported associations between nonstenosing plaque on CTA or magnetic resonance angiography and ipsilateral infarction in patients with ESUS.[4,8–10] Prior studies using CTA have assessed only a single plaque feature and have not included a negative control group with a defined cause of stroke, such as cardioembolic stroke patients.[10] We have previously found an association between intraplaque hemorrhage on magnetic resonance angiography and ipsilateral infarction in ESUS patients, and no

such association in cardioembolic strokes.[8] However, magnetic resonance angiography may not be universally available, and CTA has advantages in the evaluation of acute ischemic stroke. In this context, our study adds novel information that indicates that nonstenosing plaque may be one mechanism underlying ESUS, and that such plaques can be readily detectable on routine CTA studies.

Among the individual components of nonstenosing plaque, we found a nonsignificant association in ESUS patients between soft plaque and ipsilateral infarction, and no association at all between calcified plaque and ipsilateral infarction. This is consistent with previous studies of patients with >50% stenosis.[14,23,24] We did not find any association with other plaque features, such as ulceration. Since only a subgroup of ESUS patients had plaque ulceration, our sample size may have limited our ability to detect differences in the prevalence of ulceration ipsilateral versus contralateral to the side of infarction in ESUS patients. In the future, larger studies are warranted, which may reveal associations with additional plaque features.

Our findings may have implications for therapeutic strategies to prevent recurrent stroke. The standard set of preventive therapies currently recommended after ESUS includes antiplatelet therapy, statin therapy, and blood pressure control. Recent attempts to improve outcomes by using anticoagulant therapy in the overall ESUS population were unsuccessful.[25,26] Such results suggest the need for more tailored therapy according to the likely mechanism of ESUS. Our findings suggest that for a subset of patients, specific measures directed at stabilizing atherosclerotic plaque, such as intensive low-density lipoprotein lowering and potentially mild immunosuppressive medications,[27] may ultimately be helpful. Such strategies will need to be tested in randomized clinical trials.

There are limitations to this study. First, our sample of ESUS cases is from a single institution, our work was performed without prespecified power analyses, and we lacked the sample size needed to perform meaningful receiver operating characteristics analysis. Future larger studies will be needed to determine the degree of side-to-side asymmetry in plaque thickness that might best identify ESUS cases that are caused by artery-to-artery embolism. Second, our study looked at the association between plaque features on CTA after a stroke, rather than before. We believe that this is a clinically relevant approach for improving secondary stroke prevention efforts. However, to broaden the relevance of these findings to stroke-free individuals, it will be important for future studies to assess the relationship between plaque thickness and risk of first-time stroke.

Despite these limitations, our study suggests that quantitative analysis of routine CTA studies may allow elucidation of underlying embolic sources in ESUS cases. Future investigations are required to determine optimal thresholds of plaque thickness on CTA for identifying a subgroup of ESUS patients who could be enrolled in trials of aggressive therapy directed at plaque reduction, including high-intensity lipid lowering and ultrapotent antiplatelet therapy.

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Disclosures

Dr Kamel serves on an end point adjudication committee for a clinical trial of a diabetes mellitus medication made by Boehringer-Ingelheim. The remaining authors have no disclosures to report.

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